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Association of Radiation-Induced Heart Disease with Long-Term Prognosis Assessed by Two-Dimensional Speckle-Tracking Echocardiography

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ABSTRACT

Background: Echocardiographic global longitudinal strain (GLS) is a sensitive metric for the detection of radiation-induced heart disease (RIHD). Compared with the traditional contraction index, the GLS is more sensitive to asymptomatic myocardial damage. However, the association between RIHD and long-term prognosis remains unknown.

Purpose: This study aimed to explore the relationships between RIHD as assessed by the GLS and long-term prognosis, as well as the risk factors influencing adverse outcomes.

Methods: In a prospective cohort study, 78 patients with malignant tumors admitted to the Department of Radiation Oncology at Peking University Third Hospital between January 2020 and December 2021 were enrolled. All patients underwent radiotherapy. The incidence of RIHD was evaluated at 2 months, and adverse cardiovascular events (MACEs) and all-cause deaths were recorded via telephone follow-up 1 year posttreatment.

Results: RIHD, detected via GLS, was observed in 39 patients (55.7%), with a mean GLS of -12.13 ± 2.99. Adverse events occurred in 37.1% of patients (21 deaths, 2 cases of heart failure, 2 cases of atrial fibrillation, and 1 case of pericardial effusion). RIHD significantly increased the likelihood of adverse events (76.9% vs. 43.2%, P = 0.006). Independent risk factors for adverse events included hypertension (OR: 4.940, 95% CI: 1.361–17.926, P < 0.05), anthracycline therapy (OR: 4.790, 95% CI: 1.253–18.310, P < 0.05), and RIHD (OR: 3.045, 95% CI: 0.953–9.729, P = 0.06).

Conclusions: RIHD is associated with long-term adverse events. RIHD, hypertension, and anthracycline therapy may be valuable for estimating patient prognosis and should be further studied as a strategy for risk stratification of patients receiving radiotherapy.

Keywords: Radiation-Induced Heart Disease; Stereotactic Body Radiotherapy; Two-Dimensional Speckle Tracking Echocardiography; Cardiotoxicity; Radiotherapy

Abbreviations: 2D-STE: Two-Dimensional Speckle Tracking Echocardiography; A: Latediastolic Transmitral Velocity; ACEI: ACEI; ALT: Alanine Transaminase; ARB: Angiotensin Receptor Blocker; AST:AST;BMI: Body Mass Index; CK:CK; CKMB: Creatine Kinase-MB; Cr: Creatinine; E: Earlydiastolic Transmitral Velocity; ECG: Electrocardiogram; GCS: Global Circumferential Strain; GLS: Globallongitudinal Strain; GRS: Global Radial Strain; GTV: Gross Tumor Volume; HDL-C: High Density Lipoprotein Cholesterol; HGB: Hemoglobin; LAA: Left Atrial Area; LAD: Left Atrial Diameter; LAP: Left Atrial Pressure; LDL-C: Low Density Lipoprotein Cholesterol; LVEDD: Left Ventricular End-Diastolic Dimension; LVEF: Left Ventricular Ejection Fraction; LVESD: Left Ventricular End-Systolic Dimension; MACE: Major Adverse Cardiovascular Event; NSCLC: Non-Small Cell Lung Cancer; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; OR: Odds Ratio; PLT: Platelet; PTV: Planned Target Volume; RBC: Red Blood Cell; RIHD: Radiation-Induced Heart Damage; SBRT: Stereotactic Body Radiotherapy; Sm: Systolic Mitral Annular Velocity; TC: Total Cholesterol; TG: Triglyceride; Tn: Ttroponin T; UA: Uric Acid; US-CRP: Ultrasensitive C-Reaction Protein; WBC: White Blood Cell; CT: Computerized Tomography; MACEs: Major Adverse Cardiovascular Events; HF: Heart Failure

Introduction

Cancer remains the leading cause of death worldwide. While multimodal cancer treatment, including radiotherapy, has significantly improved patient survival rates, the accompanying cardiotoxicity has become one of the main noncancer causes of death in cancer survivors [1,2]. Early-stage cardiotoxicity is often asymptomatic; therefore, the priority of research has shifted from improving the overall survival rate of patients to early diagnosis and reducing radiation-related damage. RIHD includes a range of cardiovascular complications, including pericarditis, cardiomyopathy, coronary artery disease, valvular disease, and cardiac conduction abnormalities [3]. The cardiotoxicity associated with radiotherapy can persist for many years and can affect mortality [4]. Early recognition can decrease morbidity and mortality. A growing body of work has shown that, compared with traditional indicators such as the left ventricular ejection fraction (LVEF), global longitudinal strain (GLS) has greater sensitivity and prognostic value for the early detection of RIHD [5-9]. However, current studies have focused mainly on breast cancer and lymphoma and have analyzed the early diagnosis of RIHD by the GLS. Limited data exist regarding the relationship between early RIHD and long-term prognosis in patients with thoracic malignancies receiving stereotactic body radiotherapy (SRBT). This study aimed to clarify the relationship between RIHD and long-term prognosis and to explore the risk factors influencing long-term prognosis. We present the 1-year follow-up analysis of a prospective cohort study.

Materials and Methods

Aim

This study aimed to investigate the correlation between RIHD, as assessed by the GLS, and long-term prognosis, as well as to identify risk factors influencing adverse outcomes.

Patients

This prospective single-center cohort study enrolled 78 patients with thoracic malignancies admitted to the Department of Oncology at Peking University Third Hospital from January 1, 2020, to May 31, 2021. Eight patients were lost to follow-up. Thus, this study ultimately included 70 patients. There were 39 males and 31 females, with a mean age of 68.0 (50.25, 74.00) years. There were 46 patients with lung cancer and 24 patients with lung metastatic tumors (1 patient with hepatoma, 1 patient with cervical carcinoma, 7 patients with osteosarcoma, 6 patients with colorectal carcinoma, 1 patient with breast carcinoma, 3 patients with soft tissue sarcoma, 1 patient with neuroendocrine tumor, 3 patients with gastric carcinoma, and 1 patient with endometrial stromal sarcoma). The inclusion criteria were as follows:

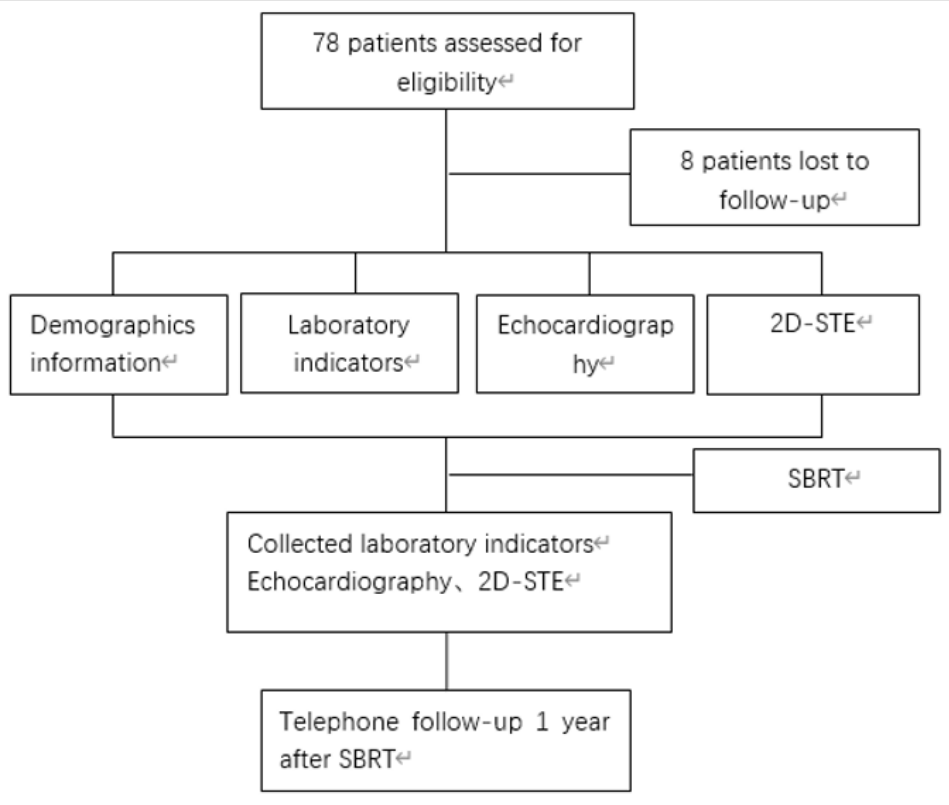
1. Baseline LVEF >50% and
2. Underwent pulmonary SBRT and cardiac radiation exposure.

The exclusion criteria were as follows:

1. Unclear echocardiogram images,
2. Inability to undergo cardiac strain analysis,
3. History of chest radiotherapy,
4. Coronary heart disease,
5. Heart failure (NYHA III-IV),
6. Valvular heart disease (moderate to severe valvular regurgitation and/or stenosis),
7. Arrhythmias requiring intervention (medication, radiofrequency ablation, or pacemaker treatment),
8. Congenital heart disease,
9. Cardiomyopathy,
10. Pericardial effusion,
11. Pulmonary hypertension (pulmonary systolic pressure ≥50 mmHg),
12. Severe liver and kidney dysfunction (aminotransferase ≥3 times the upper limit of normal, creatinine ≥130 mmol/L), and
13. Participation in other clinical studies of drug intervention. Our study was performed in accordance with all ethical requirements (Research Ethics Management System of Peking University Third Hospital). All patients provided written informed consent.

Procedures

As shown in Figure 1, patients who received radiotherapy generally received baseline information collection, blood tests, and electrocardiography on visit days. Information on demographics, including age, sex, BMI, blood pressure, tumor type, and whether the patient received other treatments, was collected from the outpatient system, inpatient system or face-to-face inquiry at Peking University Third Hospital. All blood tests and electrocardiography data were collected again 2 months after SBRT. The laboratory measurements included mainly myocardial enzymes, troponin T, and NT-proBNP. All blood samples met the quality inspection standards. Twelve months after SBRT, we obtained the incidence of adverse cardiovascular events through telephone follow-up.



Note: SBRT, stereotactic body radiotherapy; 2D-STE, two-dimensional speckle tracking echocardiography

Figure 1: Enrollment, screening, and follow-up.

Radiotherapy

The detailed operation process of SBRT was as follows: computerized tomography (CT) localization of radiotherapy was performed before radiotherapy, and the gross tumor volume (GTV) was delineated according to the CT localization. On the basis of the GTV, the planned target volume (PTV) was adjusted to 3~5 mm according to the specific conditions of the patients. The Multiplan4.6 planning system was used to make a treatment plan. After plan completion, the plan was first verified, and then SBRT robotic therapy was performed. An X sight-spine tracking system or synchronous respiratory tracking mode was used in the treatment, and a six-dimensional bed system was used to control the patient's body position and lesion location. The radiotherapy data of patients, including the radiotherapy location; minimum cardiac dose; average cardiac dose; maximum cardiac dose; and volume percentage of cardiac doses ≥5 Gy (V5), ≥10 Gy (V10), ≥20 Gy (V20) and ≥30 Gy (V30), were obtained through the CyberKnife treatment planning system of the Oncology Radiotherapy Department of Peking University Third Hospital.

Echocardiographic Assessment

A GE Vivid E9 color Doppler ultrasonic diagnostic instrument was used to create a new medical record. The patient's medical record number and name were input, the electrocardiogram (ECG) was connected, curve stability was ensured, and the frame rate of the two-dimensional image was >40 frames/second. Dynamic images of the apical three-chamber heart, four-chamber heart, and two-chamber heart with three to five cardiac cycles were acquired and stored. The two-dimensional image section was stable, including complete left ventricular wall information and endocardial visibility, and the aortic valve was clearly visible on the apical three-chamber section. The maximum heart rate difference among all the images collected was less than 5 beats/minute. The stored images were copied onto a mobile hard disk, and the stored images (DICOM format) were analyzed via offline two-dimensional speck-tracking strain imaging via TomTec (TomTec Imaging Systems GmbH, Unterschleisheim, Germany) (Figure 2). To reduce surveyor error, all ultrasonic image analyses were performed by the same surveyor before radiotherapy and 2 months after radiotherapy; additionally, the ultrasonic image collectors and image analysts were blinded.

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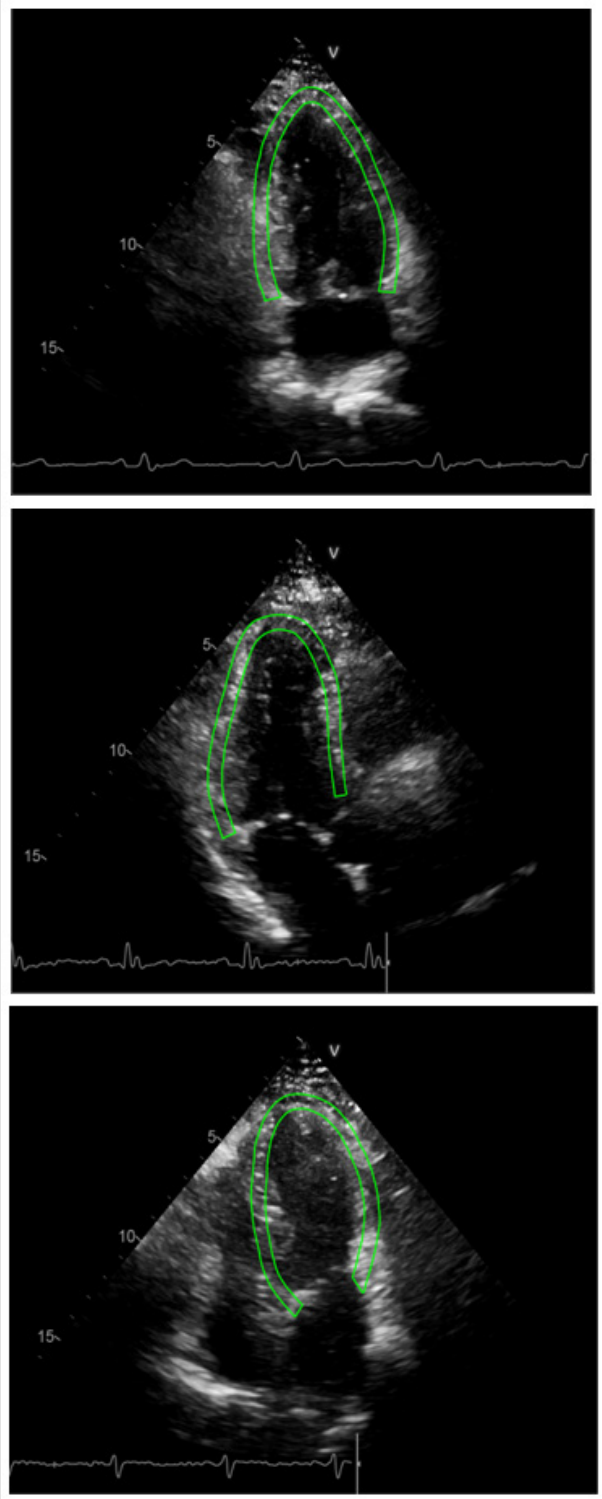

Note: At the end of ventricular diastole, one point was placed at the midpoint of the mitral ring, and one point was placed at the apex of the left ventricle. The software semiautomatically mapped the endocardial and epicardial membranes to obtain areas of interest for strain analysis. If necessary, the delineation lines could be moved manually.

Figure 2: Two-chamber, three-chamber, and four-chamber semiautomatic sketch images.

Definitions of Clinical Outcomes

Asymptomatic cancer therapy-related cardiac dysfunction (CTRCD) is much more common during cancer therapy than symptomatic heart failure (HF). Early-stage RIHD was defined as a decrease in the GLS of 15% or more relative to baseline [10]. The incidence of adverse events was assessed again 12 months later, and these events included major adverse cardiovascular events (MACEs), such as hospitalization or death due to unstable angina, arrhythmias requiring intervention, acute myocardial infarction, heart failure (NYHA grade III-IV), valvular heart disease, acute pericarditis and all-cause death. Disease diagnosis was based on the patient's clinical symptoms, markers of heart injury, and ECG and echocardiogram results. The above results were obtained through telephone follow-up and medical records from our hospital and other hospitals.

Statistics

SPSS 27.0 software was used for statistical analysis and descriptive analysis of the data. The one-sample Kolmogorov–Smirnov test was used to test for normality of the measurement data. Normally distributed measurement data are expressed as the means ± standard deviation, nonnormally distributed measurement data are expressed as the medians (25%, 75%), and count data are expressed as the frequencies (percentage). Independent sample t tests were used to compare normally distributed measurement data between groups. The Mann–Whitney U test was used to compare nonnormally distributed measurement data between groups. The chi-square test was used to compare counting data between groups. A binary logistic regression model was used for univariate analysis and multivariate analysis, and the results are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results

Baseline Characteristics

The 70 patients included in our study were divided into the adverse events group and the nonadverse events group. The incidence of long-term adverse events was 37.1% (all-cause deaths: 21 patients; heart failure: 2 patients; atrial fibrillation: 2 patients; and pericardial effusion: 1 patient). All adverse events occurred two months after SBRT. The general population characteristics (Table 1) were as follows: mean patient age, 68.0 (50.25, 74.00) years; 39 male patients (55.7%); 65.7% of patients had lung cancer; and 34.3% patients had metastatic lung cancer. The remaining indicators are shown in Table 1.

Table 1: Demographic data.

	(n=70)
Age (years)	68.0 (50.25, 74.00)
Male, n (%)	39 (55.7)
BMI (kg/m^2)	23.63 ± 3.52
Systolic pressure (mmHg)	128.36 ± 13.06
Diastolic blood pressure (mmHg)	76.94 ± 15.73
Heart rate (times/minute)	76.94 ± 15.73
Tumor type:	
Lung cancer, n (%)	46 (65.7)
Lung metastasis, n (%)	24 (34.3)
Risk factors for coronary heart disease:	
Coronary heart disease, n (%)	11 (15.7)
Hypertension, n (%)	28 (40.0)
Diabetes mellitus, n (%)	13 (18.6)
Hyperlipidemia, n (%)	33 (47.1)
Smoking, n (%)	15 (21.4)
Drug combination:	
Chemotherapy agents, n (%)	40 (57.1)
Anthracyclines, n (%)	22 (31.4)
Targeted drugs, n (%)	35 (50.0)
Immune checkpoint inhibitor, n (%)	13 (18.6)
Beta blockers, n (%)	9 (12.9)
ACEI/ARB, n (%)	11 (15.7)
CCB, n (%)	14 (20.0)
Statins, n (%)	13 (18.6)

Description of Patients with/without Adverse Events

There were no significant differences in age, sex, BMI, blood pressure, heart rate, tumor type, history of diabetes, history of hyperlipidemia, smoking status, tumor stage, chemotherapy, immunotherapy, drug combination, or targeted therapy between the two groups (P>0.05). The adverse events group had a significantly greater incidence of hypertension and anthracyclines than did the nonadverse events group (57.7% vs. 29.5%, P=0.02; 46.2% vs. 22.7%, P=0.041) (Table 2).

Table 2: Comparison of general information between the adverse events group and the nonadverse events group.

	Adverse events group (n=26)	Nonadverse events group (n=44)	*p value*
Age (years)	69.0 (52.00, 75.00)	67.0 (49.50, 73.00)	0.268
Male, n (%)	17 (42.5)	31 (48.4)	0.066
BMI (kg/m^2)	23.6 ±4.4	23.7 ±4.7	0.559
Systolic pressure (mmHg)	125.6 ±10.6	125.8 ±13.6	0.437
Diastolic blood pressure (mmHg)	75.3 ±8.7	74.9 ±8.4	0.905
Heart rate (times/minute)	83.5 ±17.3	78.2 ±13.9	0.088
Tumor type			0.216
Lung cancer, n (%)	17 (65.4)	29 (65.9)	
Lung metastasis, n (%)	9 (34.6)	15 (34.1)	
Cardiovascular risk factors			
Hypertension, n (%)	15 (57.7)	13 (29.5)	0.02*
Diabetes mellitus, n (%)	7 (26.9)	6 (13.6)	0.167
Hyperlipidemia, n (%)	9 (34.6)	24 (54.5)	0.107
Smoking, n (%)	4 (15.4)	11 (25.0)	0.343
Tumor staging			0.368
I	5 (19.2)	16 (36.4)	
II	0 (0)	1 (2.3)	
III	2 (7.7)	2 (4.5)	
IV	19 (73.1)	25 (56.8)	
Concomitant therapy			
Chemotherapy agents, n (%)	15 (57.7)	25 (56.8)	0.943
Anthracyclines, n (%)	12 (46.2)	10 (22.7)	0.041*
Immunotherapy, n (%)	6 (23.1)	7 (15.9)	0.456
Targeted therapy, n (%)	15 (57.7)	20 (45.5)	0.322
Drug combination			
Beta blockers, n (%)	5 (19.2)	4 (9.1)	0.221
ACEI/ARB, n (%)	4 (15.4)	7 (15.9)	0.954
CCB, n (%)	6 (23.1)	8 (18.8)	0.621
Statins, n (%)	4 (15.4)	9 (20.5)	0.598

Note: Measurement data conforming to a normal distribution are expressed as the means ± standard deviation, and an independent sample t test was used for data analysis. Nonnormally distributed data are represented as the medians (25, 75), and a nonparametric test was used for data analysis. Count data are expressed as the frequencies (percentages), and the chi-square test was used for data analysis. BMI: body mass index; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker.

Clinical Biochemical Data

These data included routine blood measurements at baseline and 2 months after radiotherapy (WBC, RBC, HGB, and PLT), liver function measurements (ALT and AST), renal function measurements (Cr), fasting blood glucose (Glu), lipid levels (TC, TG, LDL-C, and HDL-C), uric acid (UA), US-CRP, and markers of cardiac injury (CK, CKMB, TNT and NT-proBNP). The clinical biochemical data at baseline of the two groups were compared. There were no significant differences in the biochemical data (P>0.05) (Table 3).

Table 3: Changes in clinical biochemical indices and comparisons between the adverse events group and the nonadverse events group.

	Total population (baseline)	Total population (2-months after SBRT)	Adverse events group (n=26)	Nonadverse events group (n=44)
WBC (10^9/L)	5.96（4.70,7.49）	5.93(4.62,6.81)	6.20 (4.74, 8.63)	5.93 (4.57, 7.01)
RBC (10^9/L)	4.27 (3.86,4.72)	4.27(3.78,4.58)	4.36 (3.93, 5.06)	4.20(43.86, 4.59)
HGB (g/L)	129.00 (115.75,139.00)	131(114,138.5)	132.00 (115.00, 149.25)	128.50 (116.0, 136.75)
PLT (10^9/L)	207.50 (174.50,253.50)	195(171.00,236.50)	205.50(171.50, 255.75)	213.00 (175.75, 252.75)
ALT (U/L)	16.50(12.00,27.00)	16.00(11.50,29.50)	28.00 (11.75, 28.75)	16.50 (12.50, 27.00)
AST (U/L)	22.50(17.00,30.25)	21.00(16.50，30.50)	28.00 (11.75, 28.75)	16.50 (12.50, 27.00)
Cr (mmol/L)m	71.00(61.75,85.25)	72.00(62.00,84.50)	25.50(17.75,31.50)	20.50 (17.00,29.75)
Glu (mmol/L)	5.55(5.10,6.30)	5.40（5.10,6.25）	5.50 (5.20, 6.10)	5.80(5.10, 6.30)
TC (mmol/L)	4.51(3.71,5.13)	4.47（3.55,4.98）	4.71 (4.17, 5.22)	4.32 (3.65, 5.10)
TG (mmol/L)	1.48(1.03,2.31)	1.36（0.90,2.04）	1.71 (1.05, 2.42)	1.36 (1.00, 1.97)
LDL-C (mmol/L)	2.61(2.03,3.13)	2.62（1.96,3.23）	2.90 (2.3, 3.3)	2.59 (2.02, 3.18)
HDL-C (mmol/L)	1.10(0.99,1.33)	1.10(0.92,1.30)	1.12 (0.92, 1.39)	1.10 (1.02, 1.32)
US-CRP (mg/L)	2.21(0.60,9.07)	2.52(0.91,10.96)	3.12 (0.60,17.51)	1.90 (0.60, 6.34)
CK (U/L)	73.00(48.00,96.50)	72.00(54.50,111.50)	65.00 (44.75, 102.25)	74.50 (53.50, 96.25)
CKMB (U/L)	8.00(7.00，11.00)	8.00（7.00,11.50）	9.00 (7.0, 11.50)	8.00 (6.25, 11.00)
TnT (ng/ml)	0.009(0.006,0.014)	0.009(0.006,0.013)	0.008 (0.005, 0.014)	0.01 (0.006, 0.014)
NT-proBNP (pg/ml)	86.50(27.75,140.75)	85.50(32.75,176.00)	85.50 (31.25, 159.50)	86.50 (27.75, 140.00)

Note: Measurement data conforming to a normal distribution are expressed as the means ± standard deviation, and an independent sample t test was used for data analysis. Count data are expressed as the frequencies (percentages), and data analysis was performed with the chi-square test; *indicates P<0.05; other abbreviations are listed in Table 1.

Stereotactic Radiotherapy Data

The radiotherapy location and cardiac dose-related index data (minimum cardiac dose, mean cardiac dose, maximum cardiac dose, V5, V10, V20 and V30) of the two groups were analyzed. There were no significant differences in the stereotactic radiotherapy data (P>0.05) (Table 4).

Table 4: Comparison of stereotactic radiotherapy data between the adverse and nonadverse events groups.

	Adverse events group (n=26)	Nonadverse events group (n=44)	*P value*
Radiotherapy location			0.510
Upper lobe of the left lung, n (%)	10 (38.5)	14 (31.8)	
Lower lobe of the left lung, n (%)	5 (19.2)	12 (27.3)	
Upper lobe of the right lung, n (%)	8 (30.8)	8 (18.2)	
Middle lobe of the right lung, n (%)	2 (7.7)	2 (4.5)	
Lower lobe of the right lung, n (%)	1 (3.8)	3 (6.8)	
Multiple lung lobes, n (%)	0 (0)	2 (4.5)	
Thoracic vertebra, n (%)	0 (0)	3 (6.8)	
Prescribed dose (Gy)	40 (36, 45)	36 (36, 45)	0.93
Number of separation (n)	3 (3, 5)	3 (3, 3)	0.006
Minimum cardiac dose (cGy)	20.72 (1.01, 77.06)	26.21 (0.85, 56.93)	0.846
Mean cardiac dose (cGy)	144.13 (8.38, 456.38)	154.45 (6.77, 526.96)	0.98
Maximum cardiac dose (cGy)	1602.89 (37.98, 3631.10)	1244.76 (124.30, 2483.43)	0.437
V5 (%)	39.05 (14.75, 69.93)	44.80 (6.90, 79.83)	0.879
V10 (%)	9.75 (1.45, 36.63)	17.10 (1.00, 53.88)	0.674

V20 (%)	0.85 (0.00, 8.93)	0.40 (11.83, 0.00)	0.8
V30 (%)	0 (0.00, 2.33)	0 (0, 0.68)	0.446

Note: The normally distributed measurement data are expressed as the means ± standard deviation, and the independent sample t test was used for data analysis. Nonnormally distributed data are represented as the medians (25, 75), and nonparametric tests were used for data analysis. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; PLT: platelet; ALT: alanine transaminase; AST: aspartate transaminase; Cr: creatinine; Glu: glucose; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; UA: uric acid; US-CRP: ultrasensitive C-reactive protein; CK: creatine kinase; CKMB: creatine kinase isoenzyme-MB; TnT: troponin T; NT-pro BNP: N-terminal pro-B-type natriuretic peptide, *indicates P<0.05; p value indicates statistical significance of the differences between the adverse events group and nonadverse events group.

Echocardiogram Indices and Two-Dimensional Speckle Tracking Echocardiogram Data

These data included echocardiogram indices and two-dimensional speckle tracking echocardiogram data at baseline and 2 months after radiotherapy. Overall, 39% of the patients developed RIHD, and the GLS for patients with RIHD was -12.13±2.99 (Table 5). There were no significant differences in the baseline echocardiogram data (structural indices, systolic function indices or diastolic function indices) between the two groups (P>0.05). The adverse events group had significantly greater levels of RIHD than did the nonadverse events group (76.90% vs. 43.20%, P=0.006) (Table 6).

Table 5: Comparison of 2D-STE indices between the RIHD and non-RIHD groups.

	Non-RIHD	RIHD
GLS	-16.01 ±2.45	-12.13 ±2.99
GCS	-14.74 ±5.19	-12.14 ±4.48
GRS	20.06 ±15.63	24.34 ±11.93

Note: Nonnormally distributed data are presented as the medians (25, 75), and a nonparametric test was used for data analysis. Count data are expressed as the frequencies (percentages), and data analysis was performed with the chi-square test. V5, V10, V20 and V30: percentages of heart volume receiving doses ≥5 Gy, ≥10 Gy, ≥20 Gy and ≥30 Gy, respectively; BED: equivalent biological dose; EQD2: equivalent dose of 2 Gy fractional radiation; *indicates P<0.05.

Table 6: Changes in echocardiographic indices and comparisons between the adverse events group and the nonadverse events group.

	Total population (baseline)	Total population (2-months after SBRT)	Adverse events group (n=26)	Nonadverse events group (n=44)	*P value*
LAD (mm)	34.53 ±5.98	34.50±5.68	35.62 ± 5.04	33.88 ± 6.45	0.242
LAA $(cm)^2$	18.00(15.00,21.00)	18.00(16.00,21.00)	17.7 (15.00, 22.25)	18.0 (15.00, 21.00)	0.909
IVST (mm)	8.20(7.30,8.90)	8.00(7.30,8.50)	8.0 (7.23, 8.57)	7.75 (7.18, 8.53)	0.963
LVEDD (mm)	46.69 ±4.51	46.25±4.60	47.50 ± 3.77	46.22 ± 4.88	0.252
LVESD (mm)	28.00(26.00,30.00)	28.15(26.00,30.13)	28.15 (27.00, 30.13)	28.0 (26.00, 30.15)	0.46
LVEF (%)	69.00(66.00,72.00)	70.00(66.75,72.00)	70.0 (68.00, 71.25)	68.0 (66.00, 72.00)	0.208
LVM (g)	122.61 ±33.29	119.99±30.55	126.84 ± 30.89	120.11 ± 34.74	0.334
E(m/s)	0.69(0.53,0.85)	0.70(0.57,0.80)	0.71 (0.53, 0.88)	0.68 (0.55, 0.80)	0.662
A (m/s)	0..84(0.70,0.93)	0.85(0.71,0.99)	0.86 (0.75, 0.95)	0.79 (0.63, 0.93)	0.213
E/A	0.80(0.66,1.00)	0.80(0.67,0.98)	0.84 (0.69, 0.89)	0.80 (0.63, 1.17)	0.618
Sm (cm/s)	10.00(8.000,12.00)	10.00(8.00,12.00)	10.00 (9.00, 12.00)	10.00 (8.00, 12.00)	0.41
Em (cm/s)	10.00(8.00,12.00)	10.50(8.75,12.00)	9.50 (7.75, 12.00)	10.50 (8.00, 12.75)	0.471
E/Em	6.00(5.00,8.00)	6.00(5.00,8.00)	6.00 (4.75, 10.00)	6.00 (5.00, 7.75)	0.523
LAP (mmHg)	9.00 (8.00,11.00)	9.00(8.00,11.00)	9.00 (8.00, 10.75)	9.00 (8.00, 14.00)	0.388
GLS	-16.49 ±1.90	-13.87 ±3.36	-16.71 ± 1.41	-16.35 ± 2.14	0.458
GRS	19.76 ±12.91	22.44 ±13.75	21.82 ± 14.22	18.54 ± 12.07	0.308
GCS	-14.50 ±5.20	-13.29 ±4.95	-15.51 ± 4.46	18.54 ± 12.07	0.212
RIHD (n)	0	39(55.7%)	20 (76.90)	19 (43.20)	0.006*

Note: 2D-STE: two-dimensional speckle tracking echocardiography; RIHD: radiation-induced heart disease; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain.

Univariate Logistic Regression Analysis of Long-Term Prognosis

The indices from baseline that might be associated with adverse events were included in the univariate analysis, including radiotherapy-related indicators (minimum cardiac dose, mean cardiac dose, maximum cardiac dose, V5, V10, V20, V30), antitumour drugs (chemotherapy, anthracyclines, targeted therapy, and immunotherapy), hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, smoking history, ACEI/ARB, beta blockers, statins, CCB, blood tests (TnT, NT-proBNP, GLU, US-CRP, CK, CK-MB), and echocardiogram data (LVEF, E/A, LVM, E/Em, and LAP, RIHD). Binary logistic regression analysis was performed with adverse events as the dependent variable, and the entry criterion was P<0.05. The exclusion criterion was P>0.1. The results revealed that hypertension (OR: 3.252, 95% CI: 1.182–8.948, P=0.022), anthracyclines (OR: 2.914, 95% CI: 1.025–8.285, P=0.045), US-CRP (OR: 1.034, 95% CI: 1.000–1.068, P=0.049) were associated with the occurrence of adverse events (Table 7).

Table 7: Logistic regression analysis of adverse events and nonadverse events.

Variable	Regression coefficient	Standard error	OR (95% CI)	*P value*
Minimum cardiac dose	0.003	0.005	1.003 (0.994, 1.012)	0.494
Mean cardiac dose	0	0.001	1.000 (0.999, 1.002)	0.673
Maximum cardiac dose	0	0	1.000 (1.000, 1.001)	0.17
V5	-0.003	0.003	0.997 (0.990, 1.003)	0.273
V10	-0.005	0.005	0.995 (0.984, 1.005)	0.322
V20	-0.009	0.012	0.991 (0.968, 1.015)	0.445
V30	-0.012	0.018	0.988 (0.954, 1.023)	0.484
Concomitant therapy				
Chemotherapy agents	0.036	0.5	1.036 (0.389, 2.762)	0.943
Anthracyclines	1.07	0.533	2.914 (1.025, 8.285)	0.045
Immunotherapy	0.461	0.622	1.586 (0.469, 5.363)	0.458
Targeted therapy	0.492	0.499	1.636 (0.615, 4.353)	0.324
Drug combination				
Beta blockers	0.842	0.723	2.321 (0.562, 9.583)	0.244
ACEI/ARB	-0.04	0.682	0.961(0.539, 8.512)	0.954
CCB	0.272	0.608	1.312 (0.398, 4.325)	0.655
Statins	-0.347	0.66	0.707 (1.194, 2.576)	0.599
Traditional cardiovascular risk factors				
Coronary heart disease	0.95	0.665	2.340 (0.635, 8.616)	0.201
Hypertension	1.179	0.516	3.252 (1.182, 8.948)	0.022 *
Diabetes mellitus	0.847	0.623	2.333 (0.688, 7.916)	0.174
Hyperlipidemia	-0.818	0.511	0.441 (0.162, 1.202)	0.11
Smoking	-0.606	0.645	0.545 (0.154, 1.933)	0.348
Echocardiogram data				
LVEF	0.086	0.061	1.089 (0.966, 1.229)	0.163
LVM	0.006	0.008	1.006 (0.991, 1.021)	0.412
E/A	-0.63	0.761	0.533 (0.120,2.366)	0.408
E/Em	0.108	0.084	1.114 (0.945, 1.312)	0.199
LAP	0.097	0.068	1.102 (0.965, 1.259)	0.153
Blood test:				
TnT	-13.304	33.719	0.000 (0.000, 8.388 e+22)	0.693
GLU	-0.052	0.118	0.949 (0.753, 1.197)	0.66
US-CRP	0.033	0.017	1.034 (1.000, 1.068)	0.049*
CK	0	0.003	1.000 (0.994, 1.005)	0.905
CK-MB	-0.011	0.033	0.989 (0.927, 1.055)	0.732
NT-proBNP	-0.001	0.001	0.999 (0.997, 1.002)	0.626

Note: Normally distributed data are expressed as the means ± standard deviation, and an independent sample t test was used for data analysis. Non-normally distributed data are represented as the medians (25, 75), and a nonparametric test was used for data analysis. Count data are expressed as the frequencies (percentages), and data analysis was performed with the chi-square test. LAD: left atrial diameter; LAA: left atrial area; IVST: interventricular septum thickness; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; E: early diastolic transmitral velocity; A: late diastolic transmitral velocity; Sm: systolic mitral annular velocity; Em: early diastolic mitral annular velocity; LAP: left atrial pressure; RIHD: radiation-induced heart disease; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain; *indicates P<0.05; p value indicates a statistically significant difference between the adverse events group and the nonadverse events group.

Multivariate Logistic Regression Analysis of Long-Term Prognosis

Hypertension (OR: 4.940, 95% CI: 1.361–17.926, P<0.05), anthracycline exposure (OR: 4.790, 95% CI: 1.253–18.310, P<0.05), and RIHD (OR: 3.045, 95% CI: 0.953–9.729, P=0.06) were independently associated with an increased risk of adverse events (Figure 3).

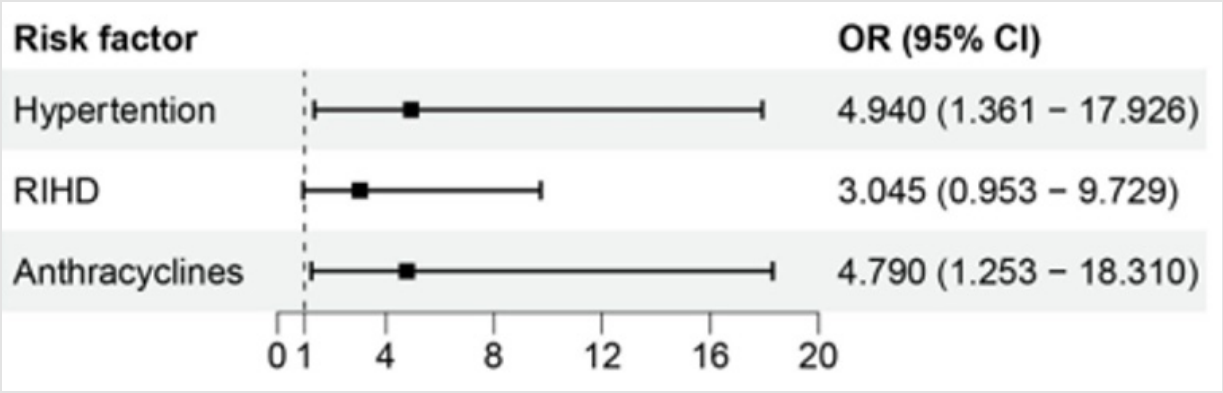

Figure 3: Multivariate regression analysis of adverse events and nonadverse events. OR: odds ratio; CI: confidence interval.

Discussion

Radiotherapy is widely used in daily oncology practice. However, its accompanying side effects pose a particular challenge when considering the balance of heart protection and radiation efficacy [10-13]. The innovation of this prospective cohort study is that it combined the incidence of RIHD with the incidence of MACEs 1 year after radiation therapy and further explored the risk factors to administer cardioprotective measures and ensure a better prognosis for cancer survivors.

Our results were as follows:

1. RIHD was significantly associated with the incidence of MACEs, and
2. Hypertension, anthracyclines and RIHD were independently associated with adverse events.

Radiotherapy can damage various tissues of the heart through endothelial cell injury, the inflammatory response and oxidative stress [14-16]. RIHD, which is more common than symptomatic cardiac events, can be graded by the left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), and biomarkers. In this study, two months after radiotherapy, 39 patients developed RIHD, which was diagnosed by the GLS, without significant changes in the LVEF or biomarkers. Consistent with previous studies, the LVEF did not decrease significantly after radiotherapy for most patients [9,17], further demonstrating the limitations of the traditional LVEF indicator in assessing early or asymptomatic RIHD. In our study, patients with RIHD had a significantly greater probability of experiencing adverse events (P<0.05). In further multivariate logistic regression analyses, our study indicated that patients with RIHD had a greater risk of poor outcomes (OR: 3.045, 95% CI: 0.953–9.729; P=0.06).

These findings suggest that the GLS has the potential to predict long-term cardiac dysfunction. Similarly, Siddharth J. Trivedi et al. reported that subclinical cardiac insufficiency indicated by the GLS was still present one year after radiotherapy [7]. In prospective studies of breast cancer, Tuohinen S. S., Skytta T., and Huhtala H. et al. reported that early GLS changes may be associated with long-term adverse cardiovascular events [18]. When the heart muscle is damaged or the membrane permeability is abnormal, myocardial enzymes are released into the blood, increasing their concentration. To date, multiple studies have evaluated changes in troponin levels following radiotherapy, with promising results. In a prospective observational

study of 45 patients who underwent left breast cancer radiotherapy, Vera Cirnigliaro et al. reported that 26% of patients had a significant increase in hypersensitive troponin (hsTnT) one week after radiotherapy, but no cardiac events were recorded during follow-up [19]. In a prospective study of 58 patients who underwent radiotherapy for left-sided breast cancer, Skytta et al. reported that 21% of patients had elevated levels of hypersensitive TnT and that the cardiac radiation doses for the whole heart and left ventricle were greater in patients with a 30% increase in hypersensitive TnT [20]. Similarly, in this study, we also analyzed the associations between myocardial enzymes and patient prognosis, but the results were not statistically significant. First, there was a significant correlation between cardiac injury and heart exposure to radiation.

Moreover, the cardiac radiation dose of SBRT was relatively small. According to the current research results, the sensitivity of hsTnT was greater than that of TnT, but unfortunately, this index was not included in our study.

BNP is synthesized by ventricular myocytes. When the heart is damaged and the ventricular load is aggravated, ventricular wall tension increases, and BNP synthesis and release increase. Serum NT-proBNP is a laboratory indicator that is proportional to BNP. In our study, no association was found between NT-proBNP and adverse cardiovascular events. In the present study, the relationships between BNP or NT-proBNP and RIHD remain unclear [20,21]. In a prospective study of 43 patients with left breast cancer, I. Palumbo et al. performed BNP, ECG, and echocardiographic measurements before radiotherapy and 1, 6, and 12 months after radiotherapy. BNPn [the ratio between the BNP value at each time point (T1, T6, T12) and the baseline BNP (T0)] was significantly correlated with V20, V25, V30, V45, the average dose and MHD. However, the LVEF remained unchanged in this study, and there was no other evidence of heart failure; thus, the increase in BNP may have been caused by cardiomyocyte stress. Therefore, radiotherapy affects the heart before cardiotoxic symptoms appear, but whether BNP or NT-proBNP can be used as an early indicator of asymptomatic RIHD needs further verification. Current studies have focused mainly on cardiac toxicity correlated with conventionally fractionated radiotherapy, where large volumes of the heart are often exposed to rather low radiation doses [22].

RTOG 0617, a phase III randomized trial investigating the relationship between cardiac dose and overall survival in advanced non-small cell lung cancer patients, reported an absolute decrease of approximately 10% in 12-month survival after radiotherapy in patients treated with a higher dose (74 Gy) than in those treated with a lower dose (60 Gy) [23]. In a 2019 retrospective study involving 748 patients with locally advanced NSCLC who received continuous chest radiotherapy, Katelyn M. Atkins et al. reported that the cardiac radiation dose is a modifiable cardiac risk factor for MACEs and all-cause death [24]. In 2021, Katelyn M. Atkins et al. further analyzed the correlation between the cardiac substructural radiation dose and MACEs and all-cause death in non-small cell lung cancer patients and concluded that, after adjusting for baseline CHD status and other prognostic factors, a left anterior descending branch coronary artery V15Gy ≥10% was associated with MACEs and all-cause death [25]. There are few studies on heart damage caused by SBRT, and the published research results are ambiguous. Some studies have shown a correlation between heart damage and radiation dose [26,27], whereas others have reported no statistical link between the two [28,29]. In this study, we did not find an association between cardiac radiation dose indicators and poor prognosis. SBRT is characterized by high-dose-per-fraction treatments with very steep dose fall-offs, resulting in high doses to a small volume of the heart.

For this reason, compared with studying the dose to the whole heart, exploring the dose to individual cardiac substructures is more valuable. Thus, longer follow-up, larger patient samples, prospective study designs and contouring of individual cardiac substructures are essential to explore cardiac doses and patient outcomes after SBRT. Chemotherapy combined with radiotherapy can cause significant cardiac injury and increase the incidence of long-term adverse events. As first-line chemotherapy regimens, anthracyclines exert antitumour effects by inhibiting DNA replication and transcription [30]. The main side effects of anthracyclines include arrhythmia, heart failure, and myocardial damage, as well as hair loss, thrombocytopenia, and anemia. Notably, cardiac insufficiency has become the leading cause of chemotherapy-related death in postmenopausal patients with breast cancer [31]. In a case-control trial published in 2017, Frederika A. van Nimwegen et al. found that, in 91 patients with Hodgkin's lymphoma, anthracyclines were associated with a threefold increase in the incidence of heart failure [32]. Similarly, in a prospective cohort of 323 breast cancer patients treated with anthracyclines, Biniyam G. Demissei et al. reported that significant increases in the levels of markers of cardiovascular injury, such as hsTnT and NT-proBNP, were detected in patients receiving anthracyclines, confirming that anthracyclines further increase cardiovascular risk [33]. This finding is consistent with our findings; thus, in patients with malignancies treated with multiple therapies, this cardiac damage is compounded, affecting long-term outcomes and obscuring treatment benefits.

As with the general population, traditional cardiovascular risk factors can also increase the incidence of MACEs and mortality. According to our study, hypertension may be a significant factor predisposing patients to radiation-induced cardiotoxicity. This finding was also confirmed in previous studies. In a 2013 case–control trial of 2168 patients with breast cancer, Sarah C. Darby et al. reported that women with preexisting heart risk factors were at greater risk for RT [34]. Therefore, for patients with one or more traditional cardiovascular risk factors, it is necessary to actively control related risk factors and follow up on cardiovascular events after radiotherapy; moreover, the cardiac dose should be minimized during RT. In conclusion, early RIHD provides predictive information about adverse events and should be included in the risk stratification of cardiotoxicity associated with radiotherapy. Furthermore, more attention should be given to

RIHD and related cardiovascular risk factors in clinical management. Therefore, comprehensive identification and management of cancer patients will be the focus of cancer treatment in the future.

Limitations

First, the study was a prospective, single-center-based cohort study, which might have reduced the external validity of our results. Second, the small sample size may have potentially caused a certain β error. Third, owing to the short follow-up time, the incidence of adverse events beyond the follow-up time was lost.

Conclusion

One of the significant findings was that RIHD was associated with adverse cardiovascular events in the long term, especially in patients with multiple cardiovascular risk factors. Early intervention by recognizing risk factors and comprehensive management of malignancies are beneficial to patient prognosis. Therefore, the comprehensive management of cancer patients requires the involvement of cardiologists.

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Drafting of the article: Yi Qiao.

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