

Original Article

Smoking, preexisting heart disease, tumor proximity to the heart, and high radiotherapy dose are associated with radiation-induced heart disease after IMRT

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Received August 3, 2026; Accepted September 15, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Objectives: To identify factors associated with radiation-induced heart disease (RIHD) after intensity-modulated radiotherapy (IMRT) for non-cardiac malignancies and assess the value of combined dynamic electrocardiography (DCG), cardiac troponin I (cTnI), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) monitoring. Methods: This retrospective study included 160 patients who underwent IMRT between January 2024 and January 2025 and completed 12 months of follow-up. Patients were classified into RIHD (n=50) and control (n=110) groups. DCG and cardiac biomarkers were assessed before radiotherapy and at 3, 6, and 12 months. Multivariable logistic regression identified factors associated with RIHD. Results: RIHD occurred in 31.25% of patients. Smoking (OR=3.42, 95% CI: 1.55-7.55, $P=0.002$), previous heart disease (OR=3.68, 95% CI: 1.72-7.90, $P=0.001$), tumor location near the heart (OR=2.16, 95% CI: 1.05-4.45, $P=0.036$), and radiotherapy dose ≥ 55 Gy (OR=2.57, 95% CI: 1.08-6.11, $P=0.033$) were independently associated with RIHD, whereas surgery was associated with lower odds (OR=0.43, 95% CI: 0.21-0.88, $P=0.021$). cTnI and NT-proBNP were higher in the RIHD group at all post-radiotherapy assessments (all $P<0.001$), whereas conventional myocardial enzymes did not differ. Among RIHD patients, DCG abnormalities increased from 14.00% at baseline to 68.00% at 12 months ($Q=54.692$, $P<0.001$). Combined DCG/cTnI/NT-proBNP assessment yielded a 92.00% positive detection rate versus 78.00% for DCG and 72.00% for biomarkers alone (adjusted $P=0.023$ and 0.004). Conclusions: Baseline cardiovascular risk, tumor proximity to the heart, and higher radiotherapy dose were associated with RIHD. Combined longitudinal monitoring may increase abnormal-signal detection among confirmed RIHD cases, although its diagnostic performance requires validation.

Keywords: Radiation-induced heart disease, intensity-modulated radiotherapy, dynamic electrocardiography, cardiac troponin I, N-terminal pro-B-type natriuretic peptide, risk factors

Introduction

Radiation-induced heart disease (RIHD) encompasses a spectrum of structural and functional cardiac abnormalities caused by exposure of cardiac tissues to ionizing radiation. It may involve the myocardium, pericardium, coronary arteries, cardiac valves, and conduction system, with clinical manifestations including myocardial injury, pericardial disease, arrhythmias, and conduction disturbances [1]. Previous studies reported that the incidence of RIHD or related early cardiac abnormalities may reach approximately 20%-68% within 3 months after radiotherapy, compromising patients' quality of life and long-term prognosis [2]. The clinical manifestations of RIHD are het-

erogeneous and may include pericarditis, myocardial dysfunction, coronary artery disease, valvular disease, arrhythmias, and conduction block [3]. Some patients remain asymptomatic during the early stages despite the presence of myocardial injury or electrophysiological abnormalities, making early detection and timely intervention challenging [4]. With the widespread use of radiotherapy as part of multimodal cancer treatment, early identification of RIHD, assessment of individual susceptibility, and implementation of longitudinal cardiac monitoring have become important issues in the field of cardio-oncology.

The development of RIHD depends not only on the prescribed radiation dose but also by tumor

location, the actual cardiac radiation exposure, fractionation schedules, concomitant anticancer therapies, and pre-existing cardiovascular risk factors [5]. A history of heart disease, smoking, hypertension, and diabetes may further increase the risk of cardiovascular events after radiotherapy [6]. Therefore, individual risk cannot be accurately estimated solely on the basis of tumor type or total radiation dose. Comprehensive cardiovascular risk assessment before radiotherapy and dynamic monitoring during and after treatment are clinically important.

The European Society of Cardiology cardio-oncology guidelines recommend risk-stratified surveillance according to patients' baseline cardiovascular risk, anticancer treatment regimens, and cardiac radiation exposure [7]. Dynamic electrocardiography (DCG) provides continuous recording of cardiac electrical activity during daily activities and rest and may improve the detection of transient arrhythmias, ST-T abnormalities, and conduction disturbances [8]. Cardiac troponin I (cTnI) is a relatively specific biomarker of myocardial injury, whereas N-terminal pro-B-type natriuretic peptide (NT-proBNP) reflects myocardial wall stress and cardiac hemodynamic burden. Current evidence suggests that cardiac troponins and natriuretic peptides may facilitate the identification of early or subclinical cardiac injury during cancer treatment [9]. However, findings remain inconsistent across tumor types, radiation doses, and assessment time points, and the predictive performance of any single marker appears to be limited.

Previous studies of RIHD have predominantly focused on individual malignancies, such as lung cancer, breast cancer, or lymphoma. Some studies have also had relatively short follow-up periods and have mainly examined acute changes during radiotherapy. Consequently, the combined evaluation of DCG abnormalities, cardiac biomarker changes, and individual clinical risk factors at different post-radiotherapy time points remains insufficient. In addition, conventional myocardial enzymes have limited cardiac specificity and sensitivity for detecting early injury. Further research is therefore required to determine whether integrating DCG, cTnI, NT-proBNP, and clinical and radiotherapy-related factors can improve the

early identification and risk stratification of RIHD.

Accordingly, this retrospective study included patients with non-cardiac malignancies who underwent intensity-modulated radiotherapy (IMRT). Clinical characteristics, underlying diseases, tumor location, and treatment-related factors were compared between patients who developed RIHD and those who did not. Longitudinal changes in DCG findings, cTnI, NT-proBNP, and conventional myocardial enzymes were evaluated before radiotherapy and at 3, 6, and 12 months after treatment. Multivariable logistic regression analysis was subsequently performed to identify factors independently associated with RIHD. This study aimed to provide evidence supporting the early identification, longitudinal surveillance, and individualized risk management of cardiac injury following IMRT in patients with non-cardiac malignancies.

Unlike previous studies focusing on a single tumor type or an individual cardiac assessment modality, the present study simultaneously evaluated clinical and radiotherapy-related factors, serial DCG findings, cTnI, NT-proBNP, and conventional myocardial enzymes during 12 months of follow-up. This integrated longitudinal assessment represents the principal innovation of the study and may provide clinically relevant information for identifying patients who require closer cardiac surveillance after IMRT.

Materials and methods

Patient selection

This was a single-center retrospective cohort study. Clinical data were consecutively collected from patients with non-cardiac malignancies who underwent intensity-modulated radiotherapy (IMRT) at our institution between January 2024 and January 2025. All patients were followed for 12 months after completion of radiotherapy, with assessments performed at 3, 6, and 12 months. Potentially eligible patients were identified by searching the electronic medical record and radiotherapy planning systems for adults with pathologically or cytologically confirmed non-cardiac malignancies who underwent IMRT between January 2024 and January 2025. Patient records were

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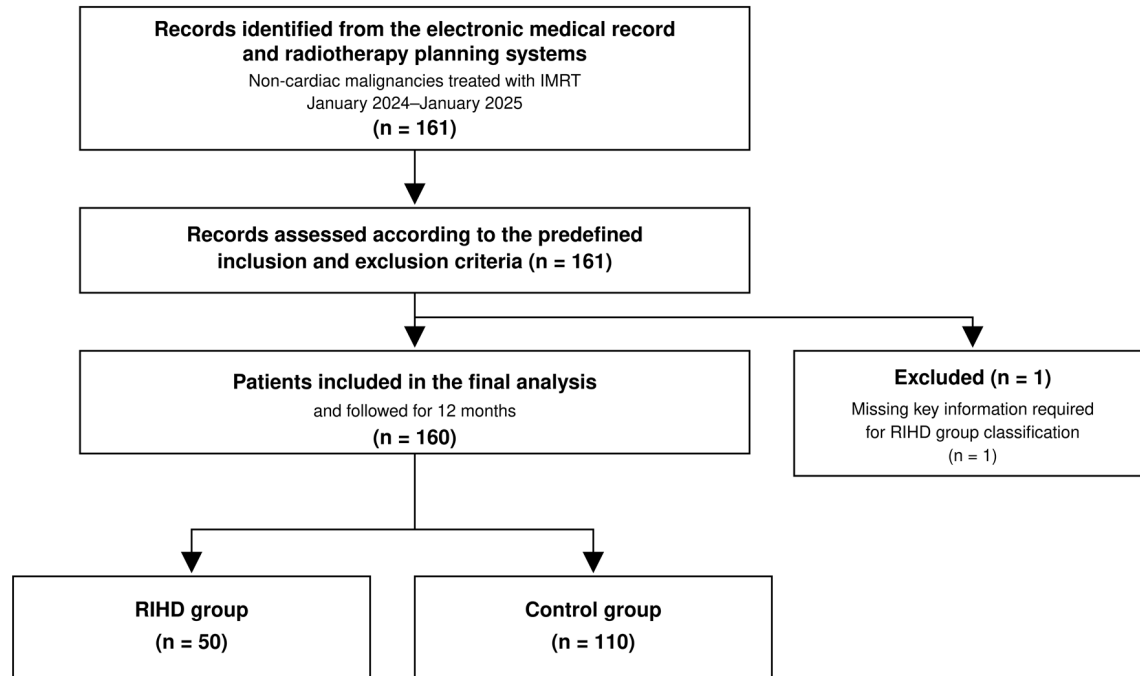


Figure 1. Flow diagram of patient screening and group allocation.

consecutively screened according to the pre-defined inclusion and exclusion criteria.

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) a pathologically or cytologically confirmed primary non-cardiac malignancy; (3) completion of IMRT, with complete records of the radiotherapy plan, prescribed dose, and actual number of fractions; (4) availability of clinical follow-up data before radiotherapy and at 3, 6, and 12 months after radiotherapy; (5) availability of relevant data on dynamic electrocardiography (DCG), cardiac troponin I (cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and conventional myocardial enzymes; (6) complete essential clinical data; (7) a Karnofsky Performance Status (KPS) score of ≥ 70 and an expected survival of ≥ 12 months; and (8) completion of baseline cardiac assessments within 7 days before IMRT.

The exclusion criteria were as follows: (1) a primary cardiac tumor or confirmed cardiac metastasis; (2) a history of thoracic or mediastinal radiotherapy; (3) acute coronary syndrome, acute myocarditis, decompensated heart failure, or another severe acute cardiovascular event within 3 months before radiotherapy; (4) severe hepatic or renal dysfunction,

severe infection, hematologic disease, or immune system disease; (5) a follow-up duration of less than 12 months or missing key data that precluded assessment of the primary outcome; and (6) pregnancy or lactation.

A total of 160 patients were ultimately included. According to whether radiation-induced heart disease (RIHD) occurred during follow-up, the patients were classified into the RIHD group ($n=50$) and the control group ($n=110$). The patient screening and group allocation process is shown in **Figure 1**.

The study protocol was approved by the Medical Ethics Committee of Wuhan No. 1 Hospital, Wuhan, China (Approval No. 2026-104). Because of the retrospective nature of the study, the requirement for written informed consent was waived by the ethics committee. All patient data were anonymized before analysis, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Data extraction and validation

Patient data were obtained from the electronic medical record system, radiotherapy planning

system, laboratory information system, and electrocardiographic examination system. General characteristics included age, sex, height, weight, and body mass index (BMI). Lifestyle-related variables included smoking and alcohol consumption histories. Pre-existing medical conditions included hypertension, diabetes mellitus, coronary artery disease, arrhythmia, and a history of heart disease. Tumor-related variables included tumor type, tumor location, lesion laterality, and tumor proximity to the heart. Treatment-related variables included surgical history, chemotherapy history, concurrent or sequential chemotherapy, targeted therapy or immunotherapy, total radiotherapy dose, dose per fraction, and the actual number of radiotherapy fractions delivered.

Radiotherapy procedure

All patients received intensity-modulated radiotherapy (IMRT). Patients were placed in the supine position and immobilized using a thermoplastic mask or vacuum cushion. Computed tomography simulation was performed, and the acquired images were transferred to the radiotherapy treatment-planning system. Based on tumor type, imaging findings, and treatment intent, radiation oncologists delineated the gross tumor volume, clinical target volume, planning target volume, and organs at risk. Medical physicists subsequently performed treatment planning, dose optimization, and pretreatment quality assurance [10].

Radiotherapy was delivered using a linear accelerator. The prescribed dose and fractionation schedule were individualized according to tumor type, clinical stage, treatment intent, and patient tolerance. The total radiotherapy dose, dose per fraction, and actual number of completed fractions were recorded for each patient. Radiation doses to individual cardiac substructures were not routinely included in the present analysis.

Dynamic electrocardiography

Patients underwent 24-hour dynamic electrocardiography before radiotherapy and at 3, 6, and 12 months after radiotherapy. Cardiac electrical activity during daily activities and rest was continuously recorded using a dynamic electrocardiographic monitoring system. The recordings were initially analyzed using auto-

mated software and were subsequently reviewed independently by two physicians experienced in electrocardiographic interpretation.

The evaluated abnormalities included ST-T changes, arrhythmias, bundle branch block, atrioventricular block, and new-onset atrial fibrillation or atrial flutter. An overall abnormal DCG finding was defined as the new onset or clinically meaningful worsening of any of the aforementioned abnormalities compared with the pre-radiotherapy assessment. A single patient could have more than one type of electrocardiographic abnormality. Because DCG data were incomplete at some follow-up time points in the control group, longitudinal changes in DCG abnormalities were analyzed only among patients in the RIHD group who had complete data at all four assessment time points.

Measurement of serum markers of myocardial injury

Fasting venous blood samples of 3-5 mL were collected in the morning before radiotherapy and at 3, 6, and 12 months after radiotherapy. Serum was separated by centrifugation in accordance with the standard procedures of the hospital laboratory.

Cardiac troponin I (cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), creatine kinase (CK), and lactate dehydrogenase (LDH) were measured using automated laboratory analyzers. cTnI and NT-proBNP were measured using chemiluminescent immunoassays, whereas CK-MB, CK, and LDH were measured using routine biochemical methods. All assays were performed after satisfactory completion of internal laboratory quality-control procedures. Abnormal results were defined as values exceeding the contemporaneous upper reference limits established by the hospital laboratory.

Outcome measures

Clinical and treatment-related variables were collected at baseline. DCG findings and serum cTnI, NT-proBNP, CK-MB, CK, and LDH levels were assessed before radiotherapy and at 3, 6, and 12 months after radiotherapy. The primary outcome was the occurrence of RIHD

within 12 months after radiotherapy. Secondary outcomes included longitudinal changes in DCG findings and cardiac biomarkers, the positive detection rates of individual and combined assessments among patients with confirmed RIHD, and clinical and treatment-related factors associated with RIHD.

RIHD was defined as a newly developed cardiac structural or functional abnormality, or a clinically meaningful worsening of a pre-existing abnormality after radiotherapy, including pericardial disease, ischemic heart disease, myocardial dysfunction or heart failure, clinically significant arrhythmia, or conduction disturbance, which was considered to be associated with radiotherapy after comprehensive clinical evaluation [7].

The diagnosis of RIHD was based on clinical symptoms, medical history, standard electrocardiography or dynamic electrocardiography (DCG), echocardiography, and additional cardiac imaging findings when necessary. Tumor progression, severe infection, acute coronary syndrome, and other identifiable causes were excluded. An isolated abnormality in DCG findings or cardiac biomarkers without supporting clinical or imaging evidence was not considered sufficient for the diagnosis of RIHD. Two cardiologists independently assessed each case. Any disagreement was resolved through discussion with a third cardiologist.

Definitions of individual and combined positive findings

Among the 50 patients who were ultimately diagnosed with RIHD during follow-up, the positive detection rates of DCG, the combined cTnI/NT-proBNP assessment, and the combined assessment of DCG, cTnI, and NT-proBNP were calculated.

DCG was considered positive when any new electrocardiographic abnormality or clinically meaningful worsening of a pre-existing abnormality was detected. The cTnI/NT-proBNP assessment was considered positive when either cTnI or NT-proBNP exceeded the upper reference limit of the hospital laboratory. The combined assessment was based on a parallel-testing strategy and was considered positive when any of the following was present: an abnormal DCG finding, an elevated cTnI level, or an elevated NT-proBNP level.

The positive detection rate was calculated as the number of RIHD patients with a positive test result divided by the total number of patients with confirmed RIHD. This analysis compared only the proportions of positive findings among confirmed RIHD cases and was not interpreted as an assessment of sensitivity, specificity, or overall diagnostic performance.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0. Continuous variables were initially assessed for normality. Normally distributed variables were presented as the mean $\pm$ standard deviation and were compared between groups using the independent-samples t-test. Non-normally distributed variables were presented as the median (interquartile range [IQR]) and were compared using the Mann-Whitney U-test. Categorical variables were presented as numbers and percentages and were compared using Pearson's chi-square test. Fisher's exact test or the Monte Carlo exact method was used when expected cell counts were small.

Longitudinal changes in cTnI, NT-proBNP, CK-MB, CK, and LDH levels before radiotherapy and at 3, 6, and 12 months after radiotherapy were analyzed using linear mixed-effects models. Each laboratory value was entered separately as the dependent variable. Group, time, and the group-by-time interaction were included as fixed effects, whereas patient identification number was included as a random effect to account for within-patient correlations among repeated measurements. NT-proBNP and other markedly right-skewed variables were natural logarithm-transformed before inclusion in the models. The F statistics and P values for the main effects of group and time and for the group-by-time interaction were reported. When a statistically significant interaction was identified, simple-effects analyses based on estimated marginal means were performed to compare the RIHD and control groups at each time point and to compare different time points within each group. Bonferroni correction was applied to multiple comparisons.

Changes in the overall proportion of abnormal DCG findings across different time points in the RIHD group were evaluated using Cochran's Q test. Because the numbers of

some specific DCG abnormalities were small, these subtypes were analyzed descriptively. The positive detection rates of DCG, the cTnI/NT-proBNP assessment, and the combined assessment among patients with confirmed RIHD were compared using paired McNemar tests.

Binary logistic regression analysis was performed with RIHD status as the dependent variable, coded as 0 for no RIHD and 1 for RIHD. Variables with $P < 0.05$ by univariable analyses and with clinical relevance to RIHD were considered candidate variables, including sex, smoking history, alcohol consumption history, hypertension, coronary artery disease, previous heart disease, tumor location near the heart, surgery, total radiotherapy dose, total radiotherapy dose ≥ 55 Gy, and number of radiotherapy fractions. Tumor type was not entered into the regression model because of sparse data in several categories. To reduce multicollinearity, coronary artery disease and previous heart disease were not entered simultaneously. Similarly, total radiotherapy dose, total dose ≥ 55 Gy, and number of radiotherapy fractions were not included simultaneously in the same model. Independent factors associated with RIHD were identified using forward stepwise likelihood-ratio selection. The final model included smoking history, previous heart disease, tumor location near the heart, surgery, and total radiotherapy dose ≥ 55 Gy. The results are presented as regression coefficients (β), standard errors, Wald chi-square statistics, odds ratios (ORs), 95% confidence intervals (CIs), and P values.

Available-case analysis was used for baseline variables, whereas complete-case analysis was used for the multivariable model. Missing values were not imputed. All statistical tests were two-sided, and $P < 0.05$ was considered significant.

Results

Comparison of baseline characteristics between the two groups

A total of 160 patients were included in the study, comprising 110 patients in the control group and 50 patients in the RIHD group. No significant differences were observed between the two groups in age, height, body weight, or

BMI (all $P > 0.05$). The proportion of male patients was higher in the RIHD group than in the control group (70.00% vs. 52.73%; $\chi^2 = 4.214$, $P = 0.04$). The proportions of patients with a history of smoking and alcohol consumption were also higher in the RIHD group than in the control group (76.00% vs. 39.09% and 32.00% vs. 11.82%, respectively $P < 0.001$, $P = 0.002$).

Regarding pre-existing medical conditions, the proportions of patients with hypertension, coronary artery disease, and a history of heart disease were significantly higher in the RIHD group than in the control group (56.00% vs. 38.18%, 42.00% vs. 21.82%, and 58.00% vs. 21.82%, respectively; $P = 0.035$, $P = 0.008$, $P < 0.001$). No significant differences were observed between the two groups in the proportions of patients with diabetes mellitus or a history of arrhythmia ($P = 0.063$ and $P = 0.068$, respectively).

With respect to tumor-related characteristics, neither the overall distribution of tumor location nor the proportion of left-sided tumors differed significantly between the two groups ($P = 0.221$ and $P = 0.146$, respectively). However, tumors located near the heart were more common in the RIHD group than in the control group (46.00% vs. 28.18%; $P = 0.023$). The detailed results are presented in **Table 1**.

Comparison of tumor type and tumor stage distributions between the two groups

Lung cancer was the most common tumor type, occurring in 51 patients (31.9%), followed by breast cancer in 31 patients (19.3%), colorectal cancer in 15 patients (9.3%), and esophageal or gastric cardia cancer in 12 patients (7.5%). Cervical cancer and head and neck tumors were each identified in 9 patients (5.6%). Among the 160 patients with complete group allocation data, the distribution of tumor types differed significantly between the RIHD and control groups ($\chi^2 = 39.728$, $P < 0.001$).

Regarding tumor stage, 11 patients (6.8%) had stage I disease, 29 (18.1%) had stage II disease, 23 (14.3%) had stage III disease, and 57 (35.6%) had stage IV disease. Three patients (1.9%) were staged using a non-TNM classification system. In addition, 21 patients (13.0%)

Table 1. Comparison of baseline characteristics between the two groups

Variable	Control group (n=110)	RIHD group (n=50)	Statistic	P value
Age (years)	67.16 ± 9.50	69.78 ± 9.07	t=1.638	0.103
Height (m)	1.65 ± 0.08	1.67 ± 0.07	t=1.196	0.233
Weight (kg)	60.76 ± 12.00	60.87 ± 12.76	t=0.053	0.958
BMI (kg/m ²)	22.30 ± 4.79	21.82 ± 4.53	t=0.591	0.555
Male sex, n (%)	58 (52.73)	35 (70.00)	χ ² =4.214	0.040
Female sex, n (%)	52 (47.27)	15 (30.00)		
Smoking history, n (%)	43 (39.09)	38 (76.00)	χ ² =18.734	<0.001
Alcohol consumption history, n (%)	13 (11.82)	16 (32.00)	χ ² =9.435	0.002
Hypertension, n (%)	42 (38.18)	28 (56.00)	χ ² =4.435	0.035
Diabetes mellitus, n (%)	17 (15.45)	14 (28.00)	χ ² =3.463	0.063
Coronary artery disease, n (%)	24 (21.82)	21 (42.00)	χ ² =6.926	0.008
History of arrhythmia, n (%)	9 (8.18)	9 (18.00)	χ ² =3.319	0.068
History of heart disease, n (%)	24 (21.82)	29 (58.00)	χ ² =20.314	<0.001
Tumor location: left, n (%)	30 (27.52)	17 (34.00)	χ ² =4.403	0.221
Tumor location: right, n (%)	37 (33.94)	16 (32.00)		
Tumor location: central, n (%)	33 (30.28)	9 (18.00)		
Tumor location: near the mediastinum, n (%)	9 (8.26)	8 (16.00)		
Left-sided tumor, n (%)	32 (29.09)	20 (40.00)	χ ² =2.118	0.146
Tumor near the heart, n (%)	31 (28.18)	23 (46.00)	χ ² =5.142	0.023

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables as n (%). BMI was calculated using available data. Tumor location was missing for one patient in the control group; the corresponding percentages were calculated using 109 patients. P<0.05 was considered statistically significant.

had TNM information recorded but could not be accurately assigned to a specific clinical stage, while staging information was missing or indeterminate in 16 patients (9.9%). No significant difference in tumor stage distribution was observed between the RIHD and control groups (χ²=8.579, P=0.198; **Table 2**).

Comparison of treatment-related baseline characteristics between the two groups

No significant differences were observed between the two groups in the proportions of patients with a history of chemotherapy, targeted therapy or immunotherapy, concurrent chemotherapy, or sequential chemotherapy (all P>0.05). The proportion of patients who underwent surgery was lower in the RIHD group than in the control group (38.00% vs. 62.73%; P=0.005).

The total radiotherapy dose was higher in the RIHD group than in the control group (48.37 ± 11.86 Gy vs. 41.06 ± 13.34 Gy; P=0.001). The proportion of patients receiving a total radio-

therapy dose of ≥55 Gy was also higher in the RIHD group than in the control group (26.00% vs. 11.82%; χ²=4.731, P=0.030). In addition, the RIHD group received a greater number of radiotherapy fractions than the control group (21.10 ± 7.40 vs. 18.31 ± 7.39 fractions; P=0.030). No significant difference was found in the dose per fraction between the two groups (P=0.659). All patients received IMRT. The detailed results are presented in **Table 3**.

Comparison of cTnI and NT-proBNP levels between the two groups at different time points

Before radiotherapy, neither cTnI nor NT-proBNP differed significantly between the control and RIHD groups (P=0.234 and P=0.056, respectively). At 3, 6, and 12 months after radiotherapy, both cTnI and NT-proBNP levels were significantly higher in the RIHD group than in the control group at the corresponding time points (all P<0.001). In the RIHD group, the median cTnI level was highest at 3 months after radiotherapy and subsequently decreased, whereas the median NT-proBNP

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Table 2. Comparison of tumor type and tumor stage distributions between the two groups

Variable	Category	Overall (n=160)	RIHD group (n=50)	Control group (n=110)	χ^2 value	P value
Tumor type	Lung cancer	51 (31.9)	25 (50.0)	26 (23.6)	39.728	<0.001
	Breast cancer	31 (19.4)	6 (12.0)	25 (22.7)		
	Colorectal cancer	15 (9.4)	0 (0.0)	15 (13.6)		
	Esophageal/gastric cardia cancer	12 (7.5)	10 (20.0)	2 (1.8)		
	Cervical cancer	9 (5.6)	1 (2.0)	8 (7.3)		
	Head and neck tumor	9 (5.6)	2 (4.0)	7 (6.4)		
	Hepatobiliary and pancreatic tumor	8 (5.0)	1 (2.0)	7 (6.4)		
	Gastric/remnant gastric cancer	7 (4.4)	3 (6.0)	4 (3.6)		
	Urinary system tumor	4 (2.5)	0 (0.0)	4 (3.6)		
	Thymic/mediastinal tumor	3 (1.9)	0 (0.0)	3 (2.7)		
	Endometrial cancer	2 (1.3)	0 (0.0)	2 (1.8)		
	Other	9 (5.6)	2 (4.0)	7 (6.4)		
Tumor stage	Stage I	11 (6.9)	1 (2.0)	10 (9.1)	8.579	0.198
	Stage II	29 (18.1)	6 (12.0)	23 (20.9)		
	Stage III	23 (14.4)	9 (18.0)	14 (12.7)		
	Stage IV	57 (35.6)	23 (46.0)	34 (30.9)		
	Non-TNM classification	3 (1.9)	0 (0.0)	3 (2.7)		
	TNM data recorded, but clinical stage undetermined	21 (13.1)	7 (14.0)	14 (12.7)		
	Missing/indeterminate	16 (10.0)	4 (8.0)	12 (10.9)		
	Total	160 (100.0)	50 (100.0)	110 (100.0)		

Note: Data are presented as n (%). All analyses included the 160 patients with complete group allocation data (RIHD group, n=50; control group, n=110). P values were estimated using the Monte Carlo exact method because some expected cell counts were small.

Table 3. Comparison of treatment-related baseline characteristics between the two groups

Variable	Control group (n=110)	RIHD group (n=50)	Statistic	P value
History of chemotherapy, n (%)	68 (61.82)	34 (68.00)	$\chi^2=0.568$	0.451
History of targeted therapy/immunotherapy, n (%)	30 (27.27)	16 (32.00)	$\chi^2=0.375$	0.540
Surgery, n (%)	69 (62.73)	19 (38.00)	$\chi^2=7.869$	0.005
Concurrent chemotherapy, n (%)	16 (14.55)	11 (22.00)	$\chi^2=1.502$	0.220
Sequential chemotherapy, n (%)	40 (36.36)	13 (26.00)	$\chi^2=1.475$	0.225
Total radiotherapy dose (Gy)	41.06 ± 13.34	48.37 ± 11.86	t=3.280	0.001
Total dose ≥55 Gy, n (%)	13 (11.82)	13 (26.00)	$\chi^2=4.731$	0.030
Dose per fraction (Gy)	2.39 ± 0.70	2.45 ± 0.90	t=0.442	0.659
Number of radiotherapy fractions	18.31 ± 7.39	21.10 ± 7.40	t=2.184	0.030
Radiotherapy modality: IMRT, n (%)	110 (100.00)	50 (100.00)	-	-

Note: Categorical variables are presented as n (%), and continuous variables as mean ± standard deviation. P<0.05 was considered significant. IMRT, intensity-modulated radiotherapy.

level reached its highest value at 6 months and declined at 12 months. The detailed results are presented in **Table 4**.

Comparison of myocardial enzyme levels between the two groups at different time points

No significant differences in CK-MB, CK, or LDH levels were observed between the control and

RIHD groups before radiotherapy or at 3, 6, and 12 months after radiotherapy (all P>0.05). These parameters showed only minor fluctuations during follow-up in both groups, without persistent or marked increases. Compared to cTnI and NT-proBNP, conventional myocardial enzyme markers appeared to be less responsive to early subclinical myocardial injury following IMRT, suggesting that they may be

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Table 4. Comparison of cardiac biomarker levels between the two groups at different time points

Marker	Time point	Control group (n=110)	RIHD group (n=50)	U/t	P value
cTnI (ng/L)	Before radiotherapy	2.0 (1.0, 4.5)	2.0 (1.0, 4.8)	2721.5	0.234
	3 months after radiotherapy	3.0 (1.0, 5.8)	21.0 (3.8, 90.6)	1075.500	<0.001
	6 months after radiotherapy	1.0 (1.0, 12.0)	13.0 (3.0, 41.0)	1348.000	<0.001
	12 months after radiotherapy	1.0 (1.0, 2.0)	2.0 (1.4, 15.0)	1594.500	<0.001
NT-proBNP (pg/mL)	Before radiotherapy	95.0 (53.0, 169.0)	130.5 (72.8, 261.8)	2230.5	0.056
	3 months after radiotherapy	106.5 (76.3, 253.8)	469.0 (85.0, 1416.3)	1689.0	<0.001
	6 months after radiotherapy	112.5 (73.5, 154.5)	642.0 (140.5, 1780.0)	1160.5	<0.001
	12 months after radiotherapy	96.0 (80.5, 153.0)	421.5 (109.0, 1174.8)	1398.0	<0.001
CK-MB (U/L)	Before radiotherapy	12.64 ± 3.91	13.07 ± 4.26	0.607	0.545
	3 months after radiotherapy	12.78 ± 4.02	13.31 ± 4.39	0.726	0.470
	6 months after radiotherapy	12.91 ± 4.15	13.58 ± 4.61	0.879	0.382
	12 months after radiotherapy	13.05 ± 4.27	13.84 ± 4.83	0.993	0.323
CK (U/L)	Before radiotherapy	87.42 ± 28.16	86.93 ± 29.38	-0.099	0.921
	3 months after radiotherapy	87.95 ± 28.74	88.21 ± 29.92	0.052	0.959
	6 months after radiotherapy	88.63 ± 29.21	89.37 ± 30.54	0.144	0.886
	12 months after radiotherapy	89.14 ± 29.88	90.16 ± 31.22	0.194	0.847
LDH (U/L)	Before radiotherapy	182.36 ± 41.98	183.14 ± 44.17	0.105	0.917
	3 months after radiotherapy	183.12 ± 42.42	184.01 ± 44.63	0.119	0.906
	6 months after radiotherapy	184.03 ± 42.96	185.28 ± 45.16	0.165	0.870
	12 months after radiotherapy	184.78 ± 43.51	186.47 ± 45.72	0.220	0.826

Note: Data are presented as median (Q1, Q3) for cTnI and NT-proBNP and as mean ± standard deviation for CK-MB, CK, and LDH. Between-group comparisons were performed using the Mann-Whitney U test for cTnI and NT-proBNP and independent-samples t tests for CK-MB, CK, and LDH. cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK-MB, creatine kinase-MB; CK, creatine kinase; LDH, lactate dehydrogenase.

more appropriate as supplementary monitoring indicators rather than primary markers for the early identification of cardiac injury. The detailed results are presented in **Table 4**.

Changes in DCG abnormalities in the RIHD group at different follow-up time points

Before radiotherapy, the overall prevalence of abnormal dynamic electrocardiographic findings in the RIHD group was 14.00% (7/50). The prevalence increased progressively during follow-up, reaching 30.00% (15/50), 50.00% (25/50), and 68.00% (34/50) at 3, 6, and 12 months after radiotherapy, respectively. Cochran's Q test showed a statistically significant difference in the overall prevalence of DCG abnormalities across the four assessment time points ($Q=54.692$, $P<0.001$).

Among the specific types of abnormalities, ST-T changes and arrhythmias were the most common and showed a progressive increase over time. At 12 months after radiotherapy, the prevalence of ST-T changes and arrhythmias had increased to 36.00% and 30.00%, respec-

tively. Bundle branch block, atrioventricular block, and new-onset atrial fibrillation or atrial flutter were less common but also increased to varying degrees during follow-up. Because the numbers of patients with some specific electrocardiographic abnormalities were small, these subtypes were analyzed descriptively and were not included in the primary inferential comparisons. The detailed results are presented in **Table 5**.

Multivariable stepwise logistic regression analysis of factors associated with RIHD

The occurrence of radiation-induced heart disease (RIHD) after intensity-modulated radiotherapy (IMRT) in patients with non-cardiac malignancies was used as the dependent variable, with absence of RIHD coded as 0 and presence as 1. Variables that were significant in the univariable analyses were entered as candidate independent variables, including sex, smoking history, alcohol consumption history, hypertension, coronary artery disease, previous heart disease, tumor location near the heart, surgical treatment, total radiothera-

Table 5. Changes in DCG abnormalities in the RIHD group at different follow-up time points [n (%)]

DCG abnormality	Before radiotherapy (n=50)	3 months after radiotherapy	6 months after radiotherapy	12 months after radiotherapy	Q value	P value
Overall DCG abnormality	7 (14.00)	15 (30.00)	25 (50.00)	34 (68.00)	54.692	<0.001
ST-T changes	4 (8.00)	8 (16.00)	13 (26.00)	18 (36.00)	-	-
Arrhythmia	3 (6.00)	7 (14.00)	11 (22.00)	15 (30.00)	-	-
Bundle branch block	1 (2.00)	3 (6.00)	5 (10.00)	8 (16.00)	-	-
Atrioventricular block	1 (2.00)	2 (4.00)	4 (8.00)	6 (12.00)	-	-
New-onset atrial fibrillation/atrial flutter	0 (0.00)	1 (2.00)	2 (4.00)	4 (8.00)	-	-

Note: A patient could have more than one type of DCG abnormality; therefore, the sum of the subtype counts may exceed the number of patients with any DCG abnormality. Overall DCG abnormalities were compared using Cochran's Q test. Specific abnormality subtypes were analyzed descriptively because of the small number of events. DCG, dynamic electrocardiography.

Table 6. Coding of variables included in the multivariable logistic regression analysis

Variable	Coding
RIHD occurrence	No = 0; yes = 1
Sex	Female = 0; male = 1
Smoking history	No = 0; yes = 1
Alcohol consumption history	No = 0; yes = 1
Hypertension	No = 0; yes = 1
History of heart disease	No = 0; yes = 1
Tumor near the heart	No = 0; yes = 1
Surgery	No = 0; yes = 1
Total radiotherapy dose ≥ 55 Gy	No = 0; yes = 1

Note: RIHD, radiation-induced heart disease.

py dose, total radiotherapy dose ≥ 55 Gy, and number of radiotherapy fractions. Multivariable logistic regression analysis was performed using a forward stepwise selection procedure. The coding of the independent variables is presented in **Table 6**.

Because coronary artery disease overlapped conceptually with previous heart disease, and because total radiotherapy dose, total radiotherapy dose ≥ 55 Gy, and number of radiotherapy fractions were potentially highly correlated, these variables were not entered simultaneously into the same model to minimize multicollinearity. The final model therefore retained previous heart disease and total radiotherapy dose ≥ 55 Gy, while coronary artery disease, total radiotherapy dose as a continuous variable, and number of radiotherapy fractions were excluded.

Multivariable stepwise logistic regression analysis showed that smoking history, previous heart disease, tumor location near the heart,

and total radiotherapy dose ≥ 55 Gy were independently associated with higher odds of RIHD after IMRT in patients with non-cardiac malignancies (all $P < 0.05$). Patients with a smoking history had 3.42-fold higher odds of developing RIHD than those without a smoking history (OR=3.42, 95% CI: 1.55-7.55). Patients with previous heart disease had 3.68-fold higher odds of RIHD than those without previous heart disease (OR=3.68, 95% CI: 1.72-7.90). Tumors located near the heart were associated with 2.16-fold higher odds of RIHD compared to tumors located farther from the heart (OR=2.16, 95% CI: 1.05-4.45). A total radiotherapy dose of ≥ 55 Gy was associated with 2.57-fold higher odds of RIHD than a total dose of < 55 Gy (OR=2.57, 95% CI: 1.08-6.11).

In contrast, surgical treatment was associated with lower odds of RIHD (OR=0.43, 95% CI: 0.21-0.88; $P=0.021$). Sex, alcohol consumption history, hypertension, and other variables did not remain in the final model after adjustment for the other covariates. The detailed results are presented in **Table 7**.

Comparison of the positive detection rates of DCG, cTnI/NT-proBNP, and their combined assessment in patients with RIHD

The analysis included 50 patients who were ultimately diagnosed with RIHD during the follow-up period. DCG alone was positive in 39 patients, corresponding to a positive detection rate of 78.00%. The combined cTnI/NT-proBNP assessment was positive in 36 patients, with a positive detection rate of 72.00%. The combined assessment of DCG, cTnI, and NT-proBNP was positive in 46 patients, yielding a positive detection rate of 92.00%.

Risk factors for radiation-induced heart disease after IMRT

Table 7. Multivariable stepwise logistic regression analysis of factors associated with RIHD after IMRT

Variable	β	SE	Wald χ^2	OR	95% CI	P value
Smoking history	1.230	0.404	9.267	3.42	1.55-7.55	0.002
History of heart disease	1.303	0.389	11.219	3.68	1.72-7.90	0.001
Tumor near the heart	0.770	0.369	4.355	2.16	1.05-4.45	0.036
Total radiotherapy dose ≥ 55 Gy	0.944	0.441	4.583	2.57	1.08-6.11	0.033
Surgery	-0.844	0.366	5.318	0.43	0.21-0.88	0.021
Constant	-2.106	0.486	18.774	0.12	-	<0.001

Note: β , regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; RIHD, radiation-induced heart disease; IMRT, intensity-modulated radiotherapy. An OR >1 indicates higher odds of RIHD, whereas an OR <1 indicates an association with lower odds of RIHD.

Table 8. Comparison of positive detection rates for DCG, combined cTnI/NT-proBNP assessment, and combined DCG/cTnI/NT-proBNP assessment in patients with RIHD

Assessment method	Positive, n	Negative, n	Positive detection rate, n (%)
DCG	39	11	39 (78.00)
Combined cTnI/NT-proBNP assessment	36	14	36 (72.00)
Combined assessment of DCG, cTnI, and NT-proBNP	46	4	46 (92.00)

Note: For the combined assessment, a result was considered positive when any of the following was present: an abnormal DCG finding, an elevated cTnI level, or an elevated NT-proBNP level. The combined and individual assessments were compared using paired McNemar tests. DCG, dynamic electrocardiography; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RIHD, radiation-induced heart disease.

The positive detection rate of the combined DCG, cTnI, and NT-proBNP assessment was higher than those of DCG alone and the combined cTnI/NT-proBNP assessment. Paired McNemar tests showed that the difference between the combined assessment and DCG alone was statistically significant ($\chi^2=5.143$, $P=0.023$). The difference between the combined assessment and the cTnI/NT-proBNP assessment was also statistically significant ($\chi^2=8.100$, $P=0.004$). No significant difference was observed between DCG alone and the cTnI/NT-proBNP assessment ($P>0.05$). The detailed results are presented in **Table 8**.

Discussion

This study included 160 patients with non-cardiac malignancies who underwent intensity-modulated radiotherapy (IMRT), of whom 50 developed radiation-induced heart disease (RIHD) within 12 months after radiotherapy, corresponding to an incidence of 31.25%. The findings showed that the occurrence of RIHD was associated not only with the intensity of radiotherapy and the anatomical location of the tumor, but also with patients' baseline cardiovascular status and lifestyle factors. Multivariable logistic regression analysis identi-

fied smoking history, pre-existing heart disease, tumor location near the heart, and a total radiotherapy dose of ≥ 55 Gy as independent risk factors for RIHD, whereas surgical treatment was associated with lower odds of RIHD. In addition, cTnI and NT-proBNP levels and the prevalence of abnormal dynamic electrocardiographic findings showed significant post-radiotherapy increases. The combined assessment of DCG, cTnI, and NT-proBNP yielded a higher positive detection rate among patients with confirmed RIHD than either assessment alone. Collectively, these findings suggest that RIHD may result from the combined effects of baseline cardiovascular susceptibility, radiation exposure, and treatment-related factors, highlighting the importance of pretreatment risk stratification and longitudinal post-treatment monitoring. Overall, the consistency of the present findings with previous studies on baseline cardiovascular susceptibility, radiation-related cardiac risk, biomarker changes, and electrocardiographic abnormalities supports their biological plausibility. Differences from some previous reports may be related to heterogeneity in tumor type, baseline cardiovascular risk, actual cardiac radiation exposure, concomitant anticancer treatments, bio-

marker assay platforms, and follow-up time points.

Patients with a smoking history and those with pre-existing heart disease had 3.42- and 3.68-fold higher odds of RIHD, respectively, than patients without the corresponding histories. Smoking promotes endothelial dysfunction, oxidative stress, and chronic inflammation and accelerates the progression of atherosclerosis. Pre-existing heart disease may indicate underlying structural or functional cardiac abnormalities before radiotherapy, reduced cardiovascular reserve, and increased susceptibility to radiation-associated cardiac injury. The 2022 European Society of Cardiology guidelines on cardio-oncology emphasize that pre-existing cardiovascular disease, traditional cardiovascular risk factors, and the planned anticancer treatment should be comprehensively evaluated before treatment, and that individualized monitoring strategies should be established accordingly [11]. Bergom et al. also noted that the risk of radiation-associated cardiotoxicity is not determined solely by radiation dose; age, smoking, hypertension, or diabetes mellitus, and pre-existing cardiovascular disease may all influence the absolute cardiovascular risk after radiotherapy [12]. Therefore, cardiovascular risk factors should be more rigorously controlled before radiotherapy in patients with a smoking history or pre-existing heart disease, and closer electrocardiographic, biomarker, and cardiac imaging surveillance should be considered during and after treatment.

The present study also showed that tumor location near the heart and a total radiotherapy dose of ≥ 55 Gy were associated with 2.16- and 2.57-fold higher odds of RIHD, respectively, suggesting that tumor anatomy and radiotherapy intensity may be important treatment-related determinants of RIHD. When a tumor or planning target volume is located close to the heart, the myocardium, coronary arteries, atria, cardiac valves, and conduction system may receive varying degrees of radiation exposure even when IMRT is used. In patients with breast cancer, Darby et al. reported that the incidence of major coronary events increased with increasing mean heart dose, with an approximately 7.4% increase in risk for each additional 1 Gy, and

that patients with pre-existing cardiovascular risk factors had a higher absolute risk [13]. The direction of the association observed in the present study is consistent with the previously reported radiation dose-cardiac risk relationship. However, the dose evaluated in this study was the prescribed total tumor dose rather than the mean heart dose or cardiac dose-volume parameters. Therefore, a total radiotherapy dose of ≥ 55 Gy should not be interpreted as indicating that the heart itself received ≥ 55 Gy, nor can these data be used to establish a precise cardiac dose-response relationship. Future studies should include the mean heart dose, cardiac V5, V30, and V40, as well as radiation doses to the coronary arteries, atria, and cardiac conduction system, to more accurately clarify the relationship between actual cardiac exposure and RIHD.

Surgical treatment was associated with lower odds of RIHD in this study; however, this finding should be interpreted cautiously. Surgery itself has no established direct cardioprotective effect, and the observed association may reflect residual confounding by tumor stage, general condition, treatment intent, and subsequent radiotherapy intensity. Patients eligible for curative surgery often have earlier-stage disease, better performance status, a smaller tumor burden, and potentially smaller radiotherapy target volumes. In contrast, patients who do not undergo surgery may be more likely to receive definitive or palliative chemoradiotherapy, which may expose the heart and its substructures to higher radiation doses. Therefore, this finding should not be interpreted as evidence that surgery prevents RIHD, but rather as an association that requires confirmation in further studies.

Before radiotherapy, cTnI and NT-proBNP levels did not differ significantly between the two groups. At 3, 6, and 12 months after radiotherapy, both biomarkers were significantly higher in the RIHD group than in the control group; however, their median values fluctuated during follow-up rather than showing a consistent progressive increase. cTnI primarily reflects myocardial cell injury, whereas NT-proBNP reflects ventricular wall stress and changes in cardiac volume or pressure load. Thus, these biomarkers may reflect different pathological components of early or subclinical

cardiac injury. In a study of 202 patients undergoing thoracic radiotherapy, Tao et al. found that a higher mean heart dose and elevated hs-cTnT and NT-proBNP levels were associated with an increased risk of post-radiotherapy electrocardiographic changes, and that changes in some biomarkers may precede overt electrocardiographic abnormalities [14]. Beukema et al. reported in a prospective cohort of 87 patients with esophageal cancer that, hs-cTnT levels at the end of treatment were associated with the mean heart dose and that longitudinal changes in hs-cTnT and NT-proBNP differed between patients who subsequently developed new cardiac events and those who did not [15]. These findings are broadly consistent with the post-radiotherapy increases in cTnI and NT-proBNP observed in the RIHD group in the present study and support the value of serial cardiac biomarker monitoring for the early identification of RIHD.

Nevertheless, previous findings regarding cardiac troponins and natriuretic peptides in RIHD have not been entirely consistent. In a prospective study of patients receiving thoracic radiotherapy with relatively high cardiac exposure, Gomez et al. found that only a small proportion of patients had mildly elevated troponin levels at the end of treatment, which returned to undetectable levels at the first follow-up visit. Although NT-proBNP levels changed to some extent, no stable association with the mean heart dose was identified [16]. A meta-analysis by Michel et al. also suggested that troponins and BNP/NT-proBNP may help identify cancer therapy-related cardiotoxicity. However, substantial heterogeneity exists across tumor types, anticancer regimens, biomarker assays, and measurement time points, and the predictive performance of any single biomarker remains limited [17]. Differences between the present findings and those of some previous studies may be attributable to variations in tumor type, baseline cardiovascular risk, radiation exposure, the use of concomitant chemotherapy or targeted therapy, follow-up duration, and the cTnI assay platform. Therefore, cTnI and NT-proBNP may be more appropriately used as serial monitoring indicators than as stand-alone diagnostic markers. Their results should also be interpreted in the context of renal function, age, atrial fibrillation, volume status, and other cardiac conditions.

In contrast to cTnI and NT-proBNP, CK-MB, CK, and LDH did not show marked or sustained increases before radiotherapy or at 3, 6, or 12 months after treatment. Conventional myocardial enzymes may be more suitable for detecting substantial myocardial necrosis or tissue injury, whereas early RIHD following modern IMRT may be characterized by mild myocardial injury, microvascular dysfunction, altered cardiac loading conditions, or electrophysiologic abnormalities. Consequently, these enzymes may have limited sensitivity for subclinical injury [18, 19]. The present findings suggest that CK-MB, CK, and LDH may serve as supplementary monitoring indicators but should not replace cardiac troponins, natriuretic peptides, electrocardiographic monitoring, or cardiac imaging in the early assessment of RIHD. Because these biomarkers were not analyzed in relation to cardiac radiation dose, echocardiographic strain parameters, or long-term clinical cardiac events, their actual predictive value should be further evaluated in prospective studies.

The overall prevalence of abnormal DCG findings in the RIHD group increased from 14.00% before radiotherapy to 30.00%, 50.00%, and 68.00% at 3, 6, and 12 months after radiotherapy, respectively. ST-T changes and arrhythmias were the most frequently observed abnormalities. Radiation may affect myocardial repolarization and conduction-system function through microvascular injury, endothelial dysfunction, local ischemia, inflammation, and fibrosis, thereby contributing to ST-T abnormalities, atrial or ventricular arrhythmias, and conduction block. Tao et al. reported that the mean heart dose and elevated cardiac biomarkers were associated with electrocardiographic changes after thoracic radiotherapy [9]. In patients with lung cancer, Kim et al. further showed that the maximum radiation dose to the sinoatrial node was associated with the risk of new-onset atrial fibrillation and mortality, suggesting that radiation exposure to individual cardiac conduction structures may explain some radiotherapy-associated arrhythmias more effectively than the mean heart dose alone [20]. In the present study, the prevalence of bundle branch block, atrioventricular block, and new-onset atrial fibrillation or atrial flutter also increased during

follow-up, which is broadly consistent with these previous findings.

However, radiation doses to the sinoatrial node, atrioventricular node, atria, and other components of the conduction system were not collected in the present study. Therefore, no direct causal relationship can be established between irradiation of a specific conduction structure and the corresponding DCG abnormality. Moreover, longitudinal DCG changes were analyzed only in RIHD patients with complete data at all four time points because follow-up DCG data were incomplete in the control group. Consequently, the potential effects of aging, baseline heart disease, medications, and anticancer treatment on electrocardiographic abnormalities cannot be fully excluded. Future studies should perform DCG monitoring at standardized time points in both RIHD and non-RIHD groups and correlate specific electrocardiographic abnormalities with radiation doses to the heart and individual conduction-system substructures.

In the present study, the positive detection rates of DCG alone, the combined cTnI/NT-proBNP assessment, and the combined assessment of all three measures among patients with confirmed RIHD were 78.00%, 72.00%, and 92.00%, respectively. The higher positive detection rate observed with the combined assessment may be explained by the fact that electrophysiologic abnormalities and cardiac biomarkers reflect different pathological processes. Some patients may initially develop elevated cTnI or NT-proBNP levels without a definite DCG abnormality, whereas others may predominantly present with arrhythmias, ST-T changes, or conduction disturbances while their cTnI and NT-proBNP levels remain normal or borderline. Combined monitoring may therefore increase the likelihood of detecting abnormal signals in patients with RIHD and reduce the number of abnormalities missed when relying on a single assessment.

Nevertheless, only the 50 patients with confirmed RIHD were included in the comparison of positive detection rates, and false-positive results in the 110 control patients were not evaluated. Therefore, the 92.00% value should be interpreted only as the positive detection rate among confirmed RIHD cases and not as

diagnostic sensitivity. Similarly, these data do not establish the specificity, positive predictive value, negative predictive value, or overall diagnostic performance of the combined assessment. Future studies should construct complete contingency tables using the entire study population, calculate sensitivity, specificity, positive and negative predictive values, and the area under the receiver operating characteristic curve, and assess the stability and clinical applicability of the combined approach through internal and external validation.

This study has several limitations. First, it was a single-center retrospective study with a relatively limited sample size, and selection and information biases may have been present. Second, multiple types of non-cardiac malignancies were included, resulting in heterogeneity in tumor location, clinical stage, treatment intent, radiotherapy target volume, and concomitant treatment regimens. Third, the mean heart dose, cardiac V5, V30, and V40, and radiation doses to the coronary arteries, atria, and conduction-system substructures were not available; therefore, the dose-response relationship between actual cardiac exposure and different RIHD phenotypes could not be accurately evaluated. Fourth, incomplete DCG data at some follow-up time points in the control group limited direct longitudinal comparisons of electrocardiographic abnormalities between the groups. Fifth, cTnI and NT-proBNP may be influenced by age, renal function, atrial fibrillation, volume status, and other treatment-related factors, and not all potential confounders were adequately adjusted for. Sixth, the follow-up duration was limited to 12 months and mainly reflected early or subclinical cardiac injury; long-term outcomes such as coronary artery disease, valvular disease, myocardial fibrosis, and chronic heart failure could not be evaluated. Finally, the current logistic regression model was not evaluated for discrimination or calibration and did not undergo internal or external validation. Its value for individualized risk prediction therefore remains to be established.

In conclusion, the occurrence of RIHD after IMRT in patients with non-cardiac malignancies was closely associated with smoking history, pre-existing heart disease, tumor location near the heart, and a higher total radiotherapy dose.

cTnI and NT-proBNP levels became abnormal and DCG abnormalities gradually emerged after radiotherapy, whereas conventional myocardial enzymes appeared to have limited value for identifying early subclinical cardiac injury. The combined assessment of DCG, cTnI, and NT-proBNP may increase the likelihood of detecting abnormal signals in patients with RIHD, although its complete diagnostic performance requires further investigation. In clinical practice, individualized risk stratification and follow-up management should integrate baseline cardiovascular risk, tumor location, actual cardiac radiation exposure, and longitudinal monitoring findings. In addition, requiring complete 12-month follow-up may have introduced attrition or survivor bias by excluding patients who died or were lost to follow-up earlier. The use of multiple exploratory comparisons and stepwise regression with a limited number of RIHD events may also have increased the risks of type I error and model overfitting.

Acknowledgements

This work was supported by 2024 Wuhan Natural Science Foundation Exploration Program (No. 2024040801020364).

Disclosure of conflict of interest

None.

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