Original Article

Analysis of the value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and other parameters related to right heart function in detecting acute radiation-induced right heart injury

Jinqiu Li[1]^, Likun Wang[2], Hongqiang Liu[2]^, Zhilin Zhang[1], Shanglin Dong[2], Yunbo Zhang[3], Xiaochun Wu[4], Cong Wang[1], Xin Ji[1], Huan Ma[1], Chengbo Ren[1]

[1]Department of Radiotherapy, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China; [2]Department of Ultrasonography, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China; [3]Department of Oncology, Zibo Bashan Wanjie Hospital, Zibo, China; [4]Health Management Center, Inner Mongolia People's Hospital, Hohhot, China

Contributions: (I) Conception and design: H Liu, J Li; (II) Administrative support: Z Zhang; (III) Provision of study materials or patients: C Wang, Y Zhang, C Ren; (IV) Collection and assembly of data: L Wang, X Wu, X Ji; (V) Data analysis and interpretation: H Ma, S Dong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hongqiang Liu. Department of Ultrasonography, The First Affiliated Hospital of Hebei North University, No.14 Changqing Road, Zhangjiakou 075000, China. Email: lhq820203@126.com.

Background: The aim of the present study was to investigate the value of parameters related to right heart function combined with N-terminal pro-B-type natriuretic peptide (NT-proBNP) in acute radiation-induced right heart injury.

Methods: Seventy patients who received chest radiotherapy (RT) in the RT department of our hospital between September 2015 and March 2019 were included in the study.

Results: Of the included 70 patients, 19, 32, 4, and 15 had thoracic esophageal cancer, central lung cancer, thymoma, and left breast cancer, respectively. The Tei index, tricuspid annular displacement, right ventricular ejection fraction, and NT-proBNP of the 70 patients were measured 1 week before RT, at weeks 2 and 4 during RT, and 4 weeks after RT. Differences in the Tei index, the tricuspid annular displacement, and NT-proBNP were significant ($P<0.01$, $P<0.05$, and $P<0.05$, respectively). The Tei index significantly increased in the second week of RT. Tricuspid annular displacement decreased significantly 4 weeks after RT. NT-proBNP reached its peak value in the fourth week of RT. However, there was no significant difference in right ventricular ejection fraction ($P>0.05$).

Conclusions: The Tei index of the right ventricle can be used as a sensitive indicator for the early detection of right heart injury after RT for thoracic tumors. Additionally, tricuspid annular displacement can be used as an index for the early detection of right ventricular damage after RT for thoracic tumors. However, right ventricular ejection fraction showed no significant change in the early stage of right heart damage after RT. Finally, it is important to consider NT-proBNP for the detection of acute radiation-induced heart injury. In acute radiation-induced right heart injury, the combined application of right ventricular Tei index, tricuspid annular displacement, and NT-proBNP is clinically relevant.

Keywords: Acute radiation-induced right heart injury; Tei index; tricuspid annular displacement; N-terminal pro-B-type natriuretic peptide (NT-proBNP)

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^ ORCID: Hongqiang Liu, 0000-0002-5147-1887; Jinqiu Li, 0000-0002-2159-021X.

Introduction

The treatment of malignant tumors is associated with specific and different levels of injury to the cardiovascular system that includes direct and indirect injuries. Currently, radiotherapy (RT) is one of the main treatment modalities, and is used in over 50% of all cancer patients, either alone or more commonly in combination with surgery and chemotherapy, to treat a wide range of cancers (1). Based on findings from recent research, the risk of mortality among cancer survivors from cardiovascular disease is much higher than that from cancer (2). For thoracic RT physicians, it is important to understand how heart injuries caused by RT are associated with death as a result of cardiovascular disease. Heart injury due to RT is caused by complex interactions between cytokines, growth factors, and chemokines. It can cause pathological changes, including inflammatory changes, thrombosis, and endothelial cell dysfunction. The clinical manifestations are cardiac insufficiency, myocardial lesions, pericardial injury, conduction disturbance, valvular disease, and coronary atherosclerotic heart disease (3). The majority of heart injuries as a result of RT only clinically manifest after years or decades, but some may appear immediately, so early intervention makes sense. Previous research has mainly focused on myocardial lesions and pericardial injury; there are few studies on right ventricular dysfunction (4). However, in recent years, with the deepening understanding of the cardiovascular disease, it is found that in critical illness, right ventricular dysfunction (RVD) is more universal compared with left heart damage. If the RVD suffered serious or failed to correct, it will into a vicious cycle of deterioration of autonomous, so cause severe hemodynamic fluctuations and consequences (5). So the damage to right ventricular function has received increasing attention. Therefore, this study focused on the acute RVD of Radiation-Induced Heart Disease (RIHD). The two indicators of NT-proBNP and Tei index of echocardiography were selected. NT-proBNP is decomposed by BNP, is commonly used in heart failure. BNP is mainly synthesized and secreted by cardiomyocytes, with diuretic, sodium, vasodilator effect. When the ventricle is stimulated by pressure and capacity load, the level of NT-proBNP in the body is significantly increased (6). The right ventricular Tei index is the myocardial work index of the right ventricle. Echocardiography was used to measure the right ventricular isovolumetric systolic time (IVCT), isovolumetric diastolic time (IVRT) and ejection time (ET), which were calculated by the formula Tei index = (IVCT + IVRT)/ET. Tei index is a reliable index to evaluate the systolic and diastolic functions of the right ventricle, which is not affected by cardiac load (7). They have wide clinical application, mature technology and strong reproducibility. The aim of present study was to explore the value of these two indicators in the diagnosis of the acute RVD of RIHD. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-1014).

Methods

Seventy patients were enrolled in the present study. They all received chest RT in the RT department of our hospital between September 2015 and March 2019. The Tei index, tricuspid annular displacement, right ventricular ejection fraction, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) of the 70 patients were measured 1 week before RT, at weeks 2 and 4 during RT, and 4 weeks after RT. The electrocardiogram equipment in our unit is a little old, so we did not choose the electrocardiogram index.

Inclusion criteria

All patients with malignant tumors, which were confirmed pathologically before treatment, were included. Additionally, the following inclusion criteria had to be met: had an Eastern Cooperative Oncology Group score of 0–2, underwent complete chest radiation program, had satisfactory images from echocardiography examination at all-time points, and had complete NT-proBNP examination data at each time point.

Exclusion criteria

Patients were excluded if they had chronic or acute cardiopathy before RT and/or if they had been treated using chest radiation.

RT method

After fixing the body's position with thermoplastic film, the Philips Bigbore (Philips, Amsterdam, the Netherlands) large-aperture computed tomography (CT) machine guided location scan. Doctors contoured the target volume in the Elekta Focal workstation (Elekta, Stockholm, Sweden), formulated the RT plan in the Elekta Focal XIO (Elekta, Stockholm, Sweden) system. Elekta Synergy 6-MV

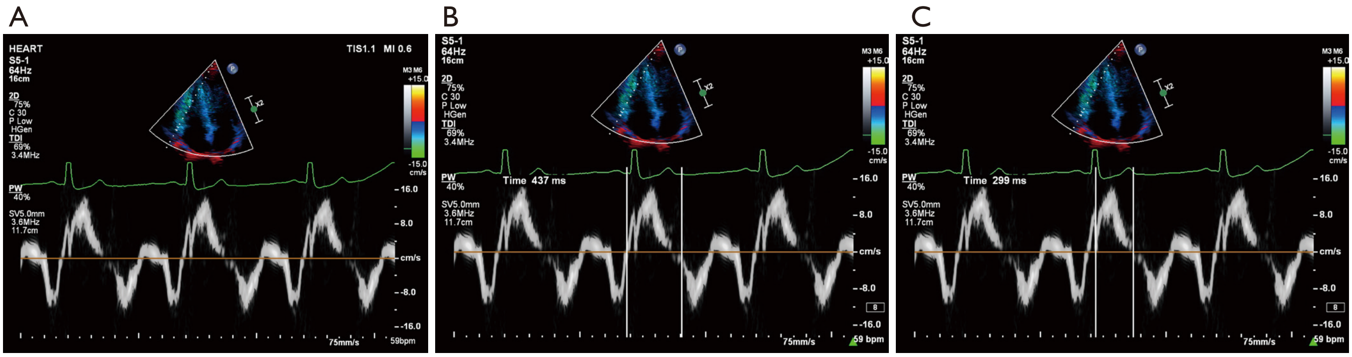

Figure 1 Measurement of Tei index. (A) Tricuspid annulus tissue Doppler spectrum. (B) Tricuspid valve opening to closure time (a). (C) Right ventricular ejection time.

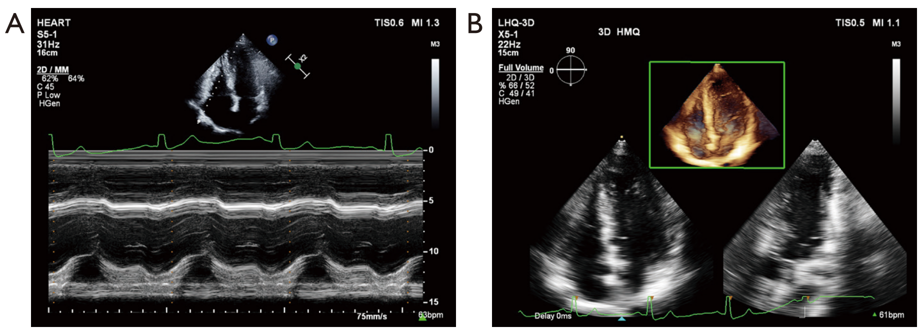

Figure 2 Tricuspid valve ring displacement. (A) Tricuspid annulus displacement image. The yellow mark indicates tricuspid valve displacement. (B) Measurement of the tricuspid annulus displacement image. The green marks represent the 3D sampling box.

Compact linear accelerator (Elekta, Stockholm, Sweden) was used to execute the conventional fractionated RT. The total dose of RT was 48–66 Gy, 1.8–2.2 Gy/fraction, once daily, 5 times weekly; the prescription limit dose for the heart as organ at risk was V_{30}<40%.

Echocardiography examination

The examination time nodes were 1 week before RT, 2 and 4 weeks during RT, and 4 weeks after RT. At the different points, 3 measurements were taken, and the average value was recorded. Echocardiography was performed using Philips EPIQ7C color Doppler echocardiography (Philips, Amsterdam, the Netherlands), with cardiac volume probe X5-1 and a frequency of 1–5 MHz. To acquire the right ventricular Tei index, the following steps were used: (I) the apical 4-chamber section was displayed to show a clear position; (II) the sampling volume was placed at the position of the anterior tricuspid annulus; (III) the Tissue Doppler Imaging (TDI) mode was started; (IV) the patient was instructed to hold his/her breath; (V) a clear tricuspid annulus tissue Doppler spectrum was obtained (*Figure 1A*); (I) the tricuspid valve's opening to closure time (a) was measured (*Figure 1B*); and (VII) the right ventricular ejection time (b) in the same cycle was measured (*Figure 1C*). The Tei index was calculated using the following formula: (a–b)/b (7). The tricuspid annulus displacement acquisition method comprised the following steps: (I) the apical 4-chamber section was displayed to show a clear posture; (II) the M-mode ultrasonic sampling line was placed in the position of the anterior tricuspid annulus; (III) the patient was instructed to hold his/her breath; and (IV) a clear tricuspid annulus displacement image was obtained (*Figure 2A*). Displacement data were obtained by measuring the vertical distance from the lowest to the highest point of displacement (*Figure 2B*). The right ventricular ejection fraction acquisition method was as follows: (I) to obtain detailed and reliable analysis data, the acquisition time was

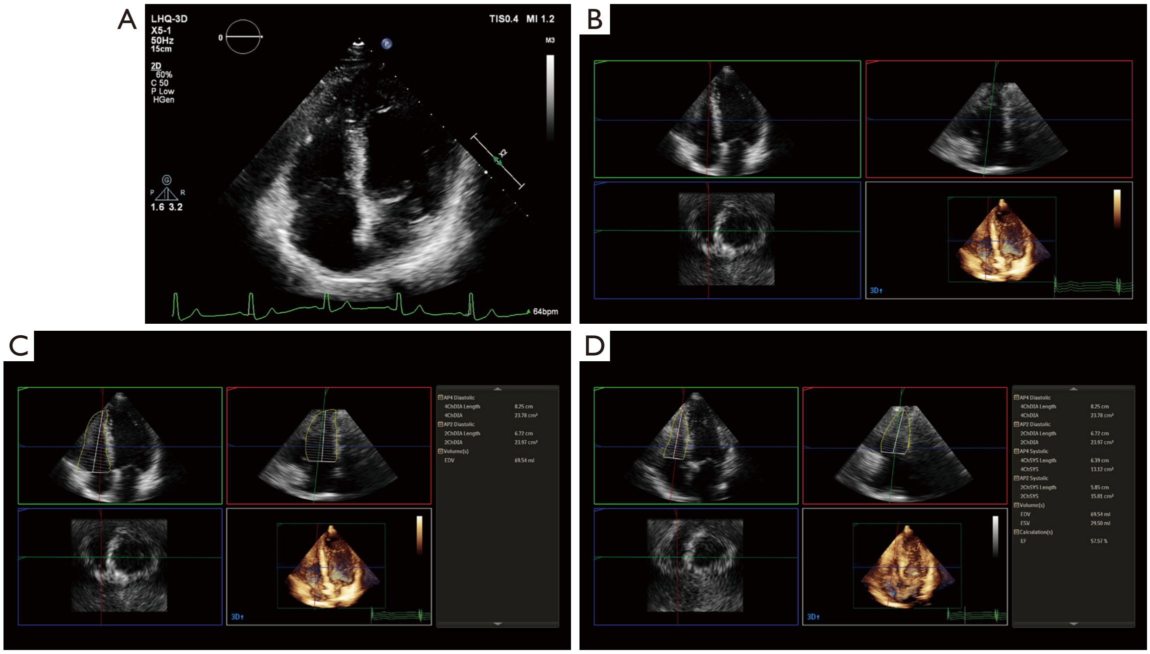

Figure 3 Method of collecting right ventricular ejection fraction. (A) HM mode. Real-time 3D dynamic map and storing images. (B) HM mode-adjusted baseline value for the right ventricle measurement. (C) HM mode. End-diastolic volume of the right ventricle measurement. (D) HM mode. End-systolic volume of the right ventricle measurement. HM, Heart Mode.

set to more than 4 cardiac cycles; (II) the apical 4-chamber section was taken to show a clear image; (III) the Heart Mode (HM) mode was started; (IV) the patient was instructed to hold his/her breath; (V) a clear real-time 3D dynamic map was obtained (*Figure 3A*); (VI) the 3DQA key was pressed to analyze the image; (VII) the end-diastolic analysis image was determined first; (VIII) the cross-reference lines of the A, B, and C planes were translated and crossed and adjusted to the standard apical 4-chamber, right ventricular apical 2-chamber, and right ventricular short-axis sections; (IX) the A-plane red line and B-plane green line were dragged to pass through the middle and apex of the tricuspid orifice (*Figure 3B*); (X) "Next" was clicked to enter the interface by adding end-diastolic reference points; (XI) because the right ventricular cavity was irregular, the end-diastolic volume of the right ventricle had to be measured manually (*Figure 3C*); (XII) the end-systolic volume of the right ventricle was also measured based on the steps outlined in the software, and the right ventricular ejection fraction was obtained (*Figure 3D*).

NT-proBNP detection

We used the Hitachi 7600-110 (HITACHI, Tokyo, Japan) automatic electrochemical luminescence analyzer and the NT-proBNP kit. Three milliliters of early morning fasting blood was collected and was allowed to stand for 30 min at 24–37 °C. The serum was then separated after solidification and assessed by electrochemical luminescence. The steps for the detection process strictly followed the relevant operating procedures and standards; therefore, quality control was ensured.

Statistical methods

Statistical analysis was performed using SPSS (version 26.0, IBM, Armonk, NY, USA). Count data were expressed as rates, and measurement data were expressed means ± standard deviations. Analysis of variance was used for repeated measurement data, regardless of interactions between the groups. One-way ANOVA was used for comparison between groups. $P<0.05$ was considered statistically significant.

Ethics

All procedures performed in this study involving human participants were in accordance with the Declaration

Table 1 Clinical and demographic data of the enrolled participants

Characteristics	Unit	Frequency/ratio	P value
Sex	Male	49 (70.00%)	>0.05
	Female	21 (30.00%)	
Age (years)	<40	1 (1.43%)	>0.05
	41–60	28 (40.00%)	
	>60	41 (58.57%)	
Disease	Left central lung cancer	32 (45.72%)	>0.05
	Thoracic esophageal cancer	19 (27.14%)	
	Left breast cancer	15 (21.43%)	
	Thymoma	4 (5.17%)	
Radiotherapy dose	≤50 Gy	17 (24.29%)	>0.05
	>50 Gy	53 (75.71%)	

Table 2 Changes in the Tei index before and after radiotherapy

No. cases	Time 1	Time 2	Time 3	Time 4	F-value	P value
70	0.406±0.024	0.420±0.032	0.421±0.030	0.424±0.023	11.138	<0.01

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. RT, radiotherapy.

Table 3 Paired comparison of the changes in the Tei index before and after radiotherapy at the different time points

	Time 1			Time 2		Time 3
	Time 2	Time 3	Time 4	Time 3	Time 4	Time 4
P	0.00	0.00	0.00	0.75	0.32	0.29

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. P values for comparisons are shown. RT, radiotherapy.

of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (No. 2020275), and consent was obtained from all patients prior to enrollment.

Results

In total, 70 patients with a mean age of 59.48±9.45 years received chest RT in the RT department of the First Affiliated Hospital of Hebei North University between September 2015 and March 2019 (*Table 1*). Of these, 19 (27.14%) patients had thoracic esophageal cancer, 32 (45.71%) had central lung cancer, 4 (5.71%) had thymoma, and 15 (21.43%) had left breast cancer.

Changes in the Tei index

There were significant differences in the Tei index at weeks 2 and 4 during RT, and 4 weeks after RT compared with 1week before RT (P<0.01) (*Table 2*). However, there was no significant difference between 1 week before RT, 2 and 4 weeks during RT, and 4 weeks after RT (*Table 3*). The Tei index increased significantly 2 weeks before RT and then stabilized (*Figure 4*).

Changes in tricuspid annulus displacement

There were significant differences in tricuspid annulus displacement at the different time points when compared with before RT (*Table 4*). However, the difference at week 2

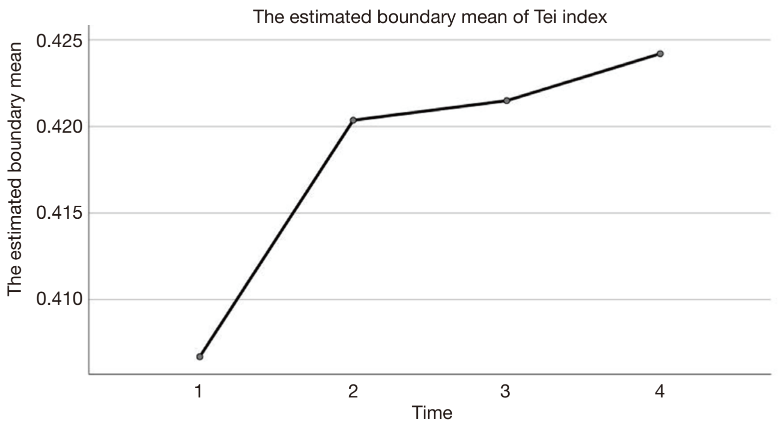

Figure 4 Changes in the Tei index before and after radiotherapy.

Table 4 Changes in tricuspid annulus displacement before and after radiotherapy

No. cases	Time 1	Time 2	Time 3	Time 4	F-value	P value
70	21.8±2.5	21.6±2.2	21.2±2.1	20.9±1.2	3.291	0.026

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. RT, radiotherapy.

Table 5 Paired comparison of the changes in tricuspid annulus displacement before and after radiotherapy

	Time 1			Time 2		Time 3
	Time 2	Time 3	Time 4	Time 3	Time 4	Time 4
P	0.246	0.044	0.004	0.035	0.003	0.028

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. P values for comparisons are shown. RT, radiotherapy.

of RT was not significant (P>0.05), while all other differences were significant (P<0.05). There were significant differences in tricuspid annulus displacement between weeks 2 and 4 during RT (P<0.01). Furthermore, when tricuspid annulus displacement at week 4 of RT was compared with the values 4 weeks after RT (P<0.05), significant differences were observed (*Table 5*). Tricuspid annulus displacement decreased slowly 2 weeks before RT, and then decreased at a faster rate (*Figure 5*).

Changes in right ventricular ejection fraction

There were no significant differences in right ventricular ejection fraction at the different time points when compared with before RT (*Table 6*). Except of the comparison between weeks 2and 4 of RT (P<0.05) (*Table 7*). There was a trend toward right ventricular ejection fraction slowly decreasing after RT (*Figure 6*).

Changes in the NP-proBNP measurement value

There were significant differences in the NT-proBNP measurement value at the different time points when compared with those before RT (P=0.04). The detection value was the highest at 4 weeks during RT, but decreased 4 weeks after RT (*Table 8*).

Discussion

RT plays a major role in the treatment of cancer and is preferred over surgery in clinical practice (8,9). The cure rate for advanced cancer is 33%; for RT treatment, the cure rate is 18% (10-12). In recent years, the cure rate of RT has been further improved. Li *et al.* reported that in

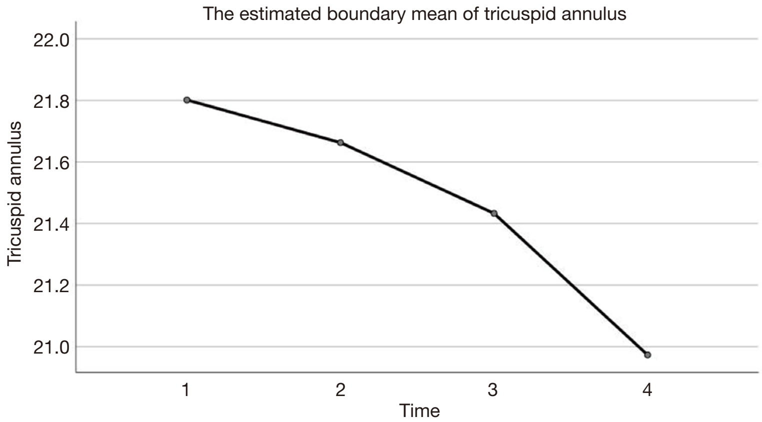

Figure 5 Changes in tricuspid annulus displacement before and after radiotherapy.

Table 6 Changes in right ventricular ejection fraction before and after radiotherapy

No. cases	Time 1	Time 2	Time 3	Time 4	F-value	P value
70	48.0±4.6	47.8±4.1	21.2±2.1	47.6±4.2	1.903	0.079

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. RT, radiotherapy.

Table 7 Paired comparison of the changes in right ventricular ejection fraction before and after radiotherapy

	Time 1			Time 2		Time 3
	Time 2	Time 3	Time 4	Time 3	Time 4	Time 4
P	0.502	0.242	0.332	0.022	0.437	0.797

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. P values for comparisons are shown. RT, radiotherapy.

the curable tumors, the contribution rate of radiotherapy is about 40% (13). As RT is more routinely used, it is important to monitor adverse reactions, especially for radiation-induced heart disease (RIHD) (14). The risk of heart disease is increased among patients with advanced cancer who receive RT (15). Anti-tumor therapy is often associated with chemotherapy, targeted drugs and radiotherapy for cardiovascular damage. Chemotherapy and targeted drug related cardiovascular damage are common acute adverse reactions, in a dose-dependent manner. Left ventricular ejection fraction (LVEF) detection by echocardiography is commonly used, and the most important is that it can be recovered after drug withdrawal. RIHD is mainly a chronic injury, and the damage to the cardiovascular system caused by radiation is dose-dependent and irreversible. The manifestations of RIHD include pericarditis, myocardial fibrosis or pancarditis, asymptomatic cardiac hypofunction, angina pectoris and myocardial infarction, electrocardiogram abnormalities, valve dysfunction and other types. RIHD can also have serious clinical consequences, particularly among elderly patients. According to the findings from studies conducted over the 2017–2020, cardiovascular diseases caused by RIHD do not only appear after an extended duration but also within a short time. A study from the SEER database, which was followed for 105 months, showed that cardiovascular disease was the leading cumulative cause of death in breast cancer patients, surpassing breast cancer itself (16). Due to the long-term latency specification of RIHD, the diagnosis and treatment of acute-stage RIHD has attracted more attention (17). In order to lower the risk of radiation-induced injuries research on RIHD is increasing. Results from animal experiments showed that RT causes injury in heart structures, and these injuries

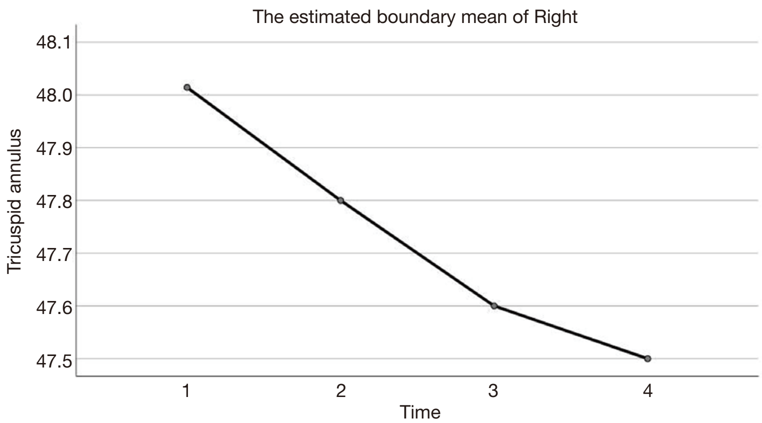

Figure 6 Changes in the right ventricular ejection fraction before and after radiotherapy.

Table 8 Changes in N-terminal pro-B-type natriuretic peptide (pg/L) before and after radiotherapy

Cases	Time 1	Time 2	Time 3	Time 4	F-value	P value
70	420.59±96.67	470.86±139.43	820.66±311.45	590.54±176.66	55.26	0.00

Time 1, before RT; time 2, week 2 during RT; time 3, week 4 during RT; time 4, 4 weeks after RT. RT, radiotherapy.

are time-dependent (18-20). Radioactive rays can damage the vascular endothelial cell and microcirculation system, causing myocardial ischemia, inflammatory cell infiltration, and lamellar or focal myocardial fibrosis; additionally, they can damage the heart structure and function (21,22). According to a previously published study, 1 month after the cure of acute-stage RIHD, pathological changes may include inflammatory cell infiltration, myocardial cell edema, and fibrin exudation (23). There are no global medical guidelines for the monitoring of cardiotoxicity related to cancer treatment. The American Society of Clinical Oncology, European Society of Cardiology, European Society for Medical Oncology, and other authoritative medical organizations published an article on cardiac monitoring during tumor treatment with different rules (24). In the article, echocardiography and BNP were also recommended as monitoring tools (24). Acute radiation damage and damage to the left ventricular function have also been evaluated in previous studies (25). Due to the uniqueness of the anatomy of the right heart, there is no effective and reliable method at present of detection of right heart injury (26). The right side of the heart can withstand increased pressure better than an increase in volume, especially when there is a sudden increase in pressure, as well as in cases of right ventricular failure. Currently, there is no extensive study on right ventricular failure that focuses on Echocardiography (ECHO), magnetic resonance imaging, and Emission Computed Tomography (ECT), as well as BNP and NT-proBNP. Existing methods mainly focus on acute right heart failure and pulmonary arterial hypertension (27). Shen *et al.* highlighted that the Tei index can be used to evaluate the independence of right ventricular systolic function in the diagnosis and treatment of right heart failure (28). It is not affected by the geometric features of the heart, heart rate, and right ventricular anterior and posterior load, and it has no relationship with the degree of tricuspid regurgitation. Shen *et al.* also noted that during injury, diastolic function injuries appears earlier than systolic function injuries, right ventricular dilatation, and hypertrophy. Therefore, the treatment of right ventricular diastolic function injury is important for patients. According to the Wei *et al.*'s study on the Tei index and heart injury in patients with cancer after chest RT, the Tei index of the left/right heart was found to be significantly higher after treatment (29). After comprehensive analysis, it was determined that the change in Tei index was related to the degree of heart injury, and this can be used to evaluate heart injury after chest RT. NT-proBNP is secreted by cardiomyocytes and functions as a diuretic, natriuretic, vasodilator, and an antagonist for the renin-angiotensin-aldosterone system. When blood volume is increased and fluid is retained, increased secretion of NT-proBNP is stimulated by stretching the ventricle. NT-proBNP and BNP tests are already used in the treatment of acute cerebrovascular disease, acute lung disease, and acute organophosphorus, carbon monoxide, and paraquat poisoning. NT-proBNP and BNP tests are already used in the diagnosis, treatment, and assessment of the severity of acute cerebrovascular disease, acute lung disease, and acute organophosphorus, carbon monoxide, and paraquat poisoning (30,31). This value is positively correlated with the degree of myocardial damage and the fatality rate. According to Li *et al.*, the plasma BNP level can be used to evaluate the severity of right ventricular dysfunction, and it can indirectly indicate the severity of respiratory failure (32).

Xu *et al.* conducted a study on the relationship between the evaluation index of right ventricular function in patients with heart failure with a reduced ejection fraction and NT-proBNP (33). In their study, they measure the changes in the diameter of the left and right ventricles in different cardiac cycles and the hemodynamic index. After analyzing the correlation and partial correlation, echocardiography was used to evaluate whether there was an obvious relationship between the indicators of left ventricular function and NT-proBNP. However, using 2D speckle tracking technology and tissue Doppler imaging, it was determined that there was a relationship between multiple right heart function indexes and NT-proBNP. The long-axis strain index of the right ventricular free wall and the overall long-axis strain index of the right ventricle were the most closely related to NT-proBNP. Additionally, in research on NT-proBNP in patients with heart failure with preserved ejection fraction, serum NT-proBNP appeared to be one of the most important signals for the diagnosis of heart failure with preserved ejection fraction (34). Furthermore, it can also impact the severity of heart failure.

With further research on RIHD, injury to the right heart function will be paid more attention. In order to satisfy the current needs of clinical diagnosis and treatment, there are continual efforts to identify methods with a high sensitivity index, good reproducibility and maneuverability, and easy handling. If these can be achieved, improvements to prior studies can be made. In the present study, we found that, in patients with acute RIHD, right heart damage was caused by RT used for the treatment of chest tumors; Tei index values during weeks 2 and 4 of RT and 4 weeks after RT were higher than those before RT. This increase was the most significant during week 2 of RT, indicating that the Tei index could detect changes in right ventricular function in the early stage of RT. The response of tricuspid annulus displacement to the change in right ventricular function occurred later than that of the Tei index, but the change was more significant than the Tei index after 2 weeks of RT. Therefore, the combination of the both could improve the accuracy of the detection of myocardial injury after RT. During and within 4 weeks after RT, we found that there was no significant change in the ejection fraction of the right ventricle; therefore, its role as an index for the diagnosis of myocardial injury in the early stage of RT was limited. As a result of the structure of the right ventricle, it is difficult to accurately measure the ejection fraction of the right ventricle; real-time 3D ultrasound is used to accurately measure the volume of the right ventricle, and the results are reliable. We also found that NT-proBNP increased after RT, with a peak at 4 weeks after RT; this decreased gradually at 4 weeks after RT. Statistical analysis confirmed that the Tei index and tricuspid valve displacement combined with NT-proBNP are sensitive and reliable for the diagnosis of acute radiation-induced right ventricular function injury. Echocardiography can be used to easily obtain the Tei index and tricuspid valve displacement, and it has better repeatability. Serum NT-proBNP has a longer half-life *in vivo*, less variation, and better stability than BNP *in vitro*, reliable detection accuracy, and allows for convenient sample collection. Additionally, the cost of echocardiography and the assessment of serum NT-proBNP levels are relatively low. The clinical application of this method has shown that it improves diagnostic accuracy.

The present study has several limitations. First, the sample size was relatively small, and this might have impacted the validity of our findings. Future studies should enroll larger sample sizes and extend the follow-up time to evaluate the long-term damage of radiation on the Tei index and tricuspid valve displacement after RT. Second, patients' underlying medical conditions, such as diabetes or high blood pressure, may have affected the results of the study. In future studies, more suitable populations will need to be screened.

In conclusion, we found that the Tei index is a sensitive index that reflects right heart injury in the early stage of chest RT. Tricuspid valve displacement and serum NT-proBNP detection also have important clinical significance in the detection of right heart injury in the early stage of chest RT. The combination of these indexes might improve the accuracy and reliability of right heart injury in the early stages of chest RT. Based on the findings of the present study, we suggest that, during RT for chest tumors, routine cardiac ultrasound examination should be performed at weeks 2 and4, and 4 weeks after RT. The Tei index of the right heart and tricuspid annulus displacement of the right ventricle should be monitored, and NT-proBNP assay should be performed for the timely detection of early RIHD.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-21-1014

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1014).The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (No. 2020275), and consent was obtained from all patients prior to enrollment. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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