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# A randomized trial of early cardiotoxicity in breast cancer patients receiving postoperative IMRT with or without serial cardiac dose constraints

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## Abstract

Optimal cardiac dose constraints in breast cancer (BC) patients undergoing postoperative intensity-modulated radiation therapy (IMRT) are unclear, although as low as possible is recommended. This trial proposes serial cardiac dose constraint to optimize cardiac safety. Postoperative BC patients eligible for anthracycline/taxanes-based chemotherapy or HER2-targeted therapy were randomized to cardiac safety arm with prespecified mean heart dose (MHD) (≤6 Gy), V30 (≤20%), and V10 (≤50%) constraints, or to a control arm with in-house protocol (mainly MHD ≤8 Gy). The primary endpoint was cumulative incidence of newly onset cardiac events within 1-year post-RT. An exploratory analysis examined the relationship between whole heart dose metrics and those of substructures. Of 199 participants, 93 were in the cardiac safety and 106 in the control arm. The cardiac safety group showed lower MHD, V10, and V30. The 1-year cardiac event incidence was slightly lower in the cardiac safety group (19.4%) compared to controls (24.9%). The LVEF and diastolic dysfunction rates were 0% and 5.4% in the study arm, and 1.9% and 8.8% in the control arm, respectively. The LAD, LV, and RV received the highest doses for left-sided patients. For right-sided patients, RA, RCA, and RV were most irradiated. The MHD, V10, and Dmax of heart significantly correlated with all substructure doses in either laterality. Our study supports the early cardiac safety profile using IMRT in BC patients receiving cardiac-toxic systemic therapy, with serial cardiac dose constraints. Combined constraints on MHD and dose-volume parameters are representative of the cardiac substructure dose.

**KEYWORDS**

breast cancer, cardiac dose constraints, cardiac substructures, early cardiac toxicity, IMRT

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**What's New?**

Radiation-induced heart disease can offset the survival benefits of postoperative radiotherapy in breast cancer patients. Optimal cardiac dose constraints in breast cancer patients undergoing postoperative intensity-modulated radiation therapy however remain unclear. In this trial, the authors propose serial dose-volume constraints to optimize early cardiac safety. Moreover, they report on the dose distribution to cardiac substructures based on individual intensity-modulated radiation therapy planning. The combined constraints on mean heart dose and dose-volume parameters were representative of the doses received by cardiac substructures. The findings support a new effective approach for monitoring cardiac radiation doses in clinical practice.

## 1 | INTRODUCTION

Postoperative radiotherapy (RT) plays an indispensable role in reducing recurrence and improving survival in breast cancer (BC) patients.[1,2] However, evidence has shown that radiation-induced heart disease (RIHD) would offset the survival benefits at different extents.[3,4] Unlike systemic treatments that are administered with fixed doses, radiation dose to the heart depends on predefined constraints and techniques. Mean heart dose (MHD) is the most commonly used parameter to evaluate cardiac exposure and its relationship with cardiac toxicity.[5] The state-of-the-art techniques have significantly reduced MHD in BC patients,[6–8] while cardiac dose distribution varies greatly with intensity-modulated radiation therapy (IMRT), therefore serial dose-volume metrics are needed to define a comprehensive cardiac dose constraint.[9–11] However, the majority of studies on cardiac dosimetry in BC patients is based on 3D-conformal RT.

Our prior studies demonstrated that limiting MHD to ≤8Gy reduced left ventricular ejection fraction (LVEF) dysfunction following RT in left-sided patients, from 24.4% in the retrospective cohort to 2.7% in the prospective cohort. The decrease of MHD and serial dose-volume parameters (D10-D30, D50-D55, and V5-V20) was significantly associated with reduced LVEF dysfunction.[12,13] Based on these findings, we initiated this randomized trial to evaluate whether implementing additional serial dose-volume constraints can reduce the rate of cardiac events compared to the current in-house protocols of participating centers using the IMRT technique.

There is growing evidence suggesting that specific cardiac substructure represents different sensitivity to ionizing radiation.[9,14,15] The radiation dose to different cardiac substructures depends on laterality, anatomical variation, and target volumes, and the knowledge of the corresponding dose constraints is limited.[14] Considering these challenges, we conducted an exploratory analysis to examine the relationship between whole heart dose-volume metrics and those of the substructures, to determine whether whole heart dose-volume parameters could serve as an alternative strategy to cardiac substructure dose constraints.

## 2 | METHODS

### 2.1 | Study design and participants

This study included BC patients who met the following criteria: planned postoperative RT, completed anthracycline/taxanes-based chemotherapy, and/or received HER2-targeted therapy, LVEF over 50% at diagnosis and before RT. Patients with distant metastasis or a history of other malignant tumors, serious heart diseases (such as coronary artery disease, heart failure, arrhythmia, valvular heart disease, cardiomyopathy, congenital heart defects, pericardial disease, or aortic aneurysms), severe organic or functional diseases, autoimmune diseases that could hinder postoperative RT or follow-up, and history of previous thoracic RT were excluded. Patients with asymptomatic cardiovascular diseases that do not require clinical intervention can be included.

### 2.2 | Randomization

The process of randomization was carried out at Ruijin Hospital in Shanghai, China, by independent personnel. Simple randomization was used without stratification, and a computer-generated random number table was used to assign even numbers to the cardiac safety group and odd numbers to the control group. Eligible patients were randomly assigned to either the cardiac safety or control group in a 1:1 ratio.

### 2.3 | Procedures

The cardiac safety group required dose constraints of MHD ≤6 Gy, V30 ≤ 20%, and V10 ≤ 50% regardless of laterality and regional nodal irradiation (RNI). The control group followed each participating center's protocol (mainly MHD ≤8 Gy).[16,17] The delineation of the whole heart and cardiac substructures of the left atrium (LA), left ventricle (LV), right atrium (RA), right ventricle (RV), left anterior descending coronary artery (LAD), and right coronary artery (RCA) adhered to the

heart atlas published by Feng et al.[18] Due to the nature of the intervention, blinding of clinicians and patients was not possible.

Target volume delineation adhered to the Breast Cancer Atlas of the Radiation Therapy Oncology Group.[19] Both conventional (50–50.4 Gy in 25–28 fractions) and the hypofractionated (40–42.5 Gy in 15–16 fractions) regimens were permitted. All patients were treated using a fixed-beam IMRT technique. As described in our previous study, approximately 8–12 fixed-jaw beams were used according to the patient's anatomy, in which 6–8 tangential beams cover the chest wall or whole breast, and left-sided internal mammary, and 3–4 anterior/posterior-oblique beams for the supra/infraclavicular region.[17,20] For the linear accelerator without an X-jaw, we fixed the beam by restricting the field size. During the optimization, priority was given to the planning target volume (PTV), heart, and lung dose constraints over other organs at risk. Compared with the control group, more effort was made to optimize the dose to the heart in the cardiac safety group. For the cardiac safety group, the objective of the heart and the corresponding priority value were iteratively fine-tuned until it met the clinical goals. The dose-volume constraints for the PTV and other organs at risk were kept the same in both the control group and the cardiac safety group. To adjust for the radiobiological effect, mean doses to the whole heart and cardiac substructures were converted to EQD2 doses ($Hmean_{EQD2}$) using an $\alpha/\beta$ ratio of 3 Gy between conventional and hypofractionated regimens.[21–23]

Systemic treatment strategies and follow-up plans were outlined in multidisciplinary meetings, as previously described.[24] HER2-targeted therapy and endocrine therapy were permitted during RT. The staging adhered to the 7th edition AJCC staging system and recorded the maximal disease stage in patients receiving neoadjuvant therapy.

### 2.4 | Assessment of cardiac events

The primary endpoint was the cumulative occurrence of newly onset cardiac events within 1 year after RT. Secondary endpoints included cardiac events occurring thereafter, and overall survival. Cardiac assessments are performed at baseline (within 4 weeks before the start of RT) and every 3 months for the first 2 years, every 6 months from 3 to 5 years, and annually thereafter, including echocardiogram and cardiac biomarkers. The cardio-oncology team managed reported cardiac events.

Newly onset cardiac events were defined as the development of any clinical or subclinical cardiac dysfunction after the completion of RT. Clinical cardiac events include clinical diagnoses such as coronary artery disease (e.g., angina pectoris, myocardial infarction), severe arrhythmia, heart failure, moderate/severe valvular stenosis/insufficiency, and moderate/severe constrictive pericarditis. Subclinical cardiac events refer to abnormalities detected on echocardiograms or via cardiac biomarkers without symptoms.[25,26] LVEF and diastolic function were evaluated by echocardiogram. LVEF dysfunction was defined as LVEF <50% with ≥10% reduction from baseline. Diastolic dysfunction melt two or more of the following criteria: (1) average E/Em >14 (E/Em-lateral wall >13 or E/Em-septal >15); (2) Em-lateral wall <10 cm/s or Em-septal <7 cm/s; (3) Tricuspid regurgitation velocity >2.8 m/s. For biomarkers, NT-proBNP >100 pg/ml or cTnI ≥30 pg/ml were considered abnormal.[13,27,28] Persistent cardiac dysfunction is defined as an abnormality on at least two consecutive assessments.

### 2.5 | Statistics

In our previous prospective study,[13] cumulative systolic and diastolic dysfunction occurred in 5% and 37.9% of patients receiving left-sided RT and concurrent trastuzumab. Considering the consecutive decrease in cardiac dose over the years and the current study enrolling patients with both left and right-sided BC with or without anti-HER2 therapy, we hypothesized that the cumulative incidence of newly onset cardiac events within 1 year after completion of RT would decrease from 25% in the control group to 5% in the cardiac safety group. To achieve 80% power with a two-tailed alpha of 0.05 or less, 100 eligible patients per group were required. Estimating a 10% loss to follow-up, the total sample size was set to 220 patients.

An intention-to-treat approach includes all participants regardless of adherence. Chi-squared and *t*-tests/Mann–Whitney *U* tests assessed categorical and continuous variables, respectively. Kaplan–Meier methods estimated cumulative risk, with group comparisons via log-rank test. Cox proportional hazard models analyzed intervention effects and risk factors as hazard ratios (HRs) with 95% confidence intervals (CIs). Cardiac function parameters change over time were analyzed using repeated measures ANOVA. Heart dosimetry correlations were evaluated using Spearmans' analysis, presented in a non-square correlation matrix plot. Statistical significance was defined as two-sided $p < .05$. Variables with $p < .2$ on univariate analysis were included in the multivariate analysis. Analyses utilized SPSS version 25.0 (IBM Corporation, USA), R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism 6 (GraphPad Software, La Jolla, CA).

## 3 | RESULTS

### 3.1 | Patient, tumor, and treatment characteristics

Between June 2017 and August 2019, 220 patients were enrolled and randomized into the cardiac safety group ($N = 110$) or control group ($N = 110$). After excluding 17 patients from the cardiac safety group and four from the control group, 199 patients were analyzed (93 cardiac safety, 106 control). Figure 1 summarizes patient flow and group assignments.

Patient demographics, tumor characteristics, and treatment details were balanced between groups (Table 1). The median age was 52 years. Pre-existing cardiac conditions were found in 24 (25.8%) cardiac safety patients and 25 (23.6%) control patients, respectively. The number of left-sided BC was 54 (58.1%) in the cardiac safety group and 65 (61.3%) in the control group. Left-sided internal mammary nodal radiotherapy (IMN-RT) was given to 42 (45.2%) cardiac safety and 53 (50%) control patients.

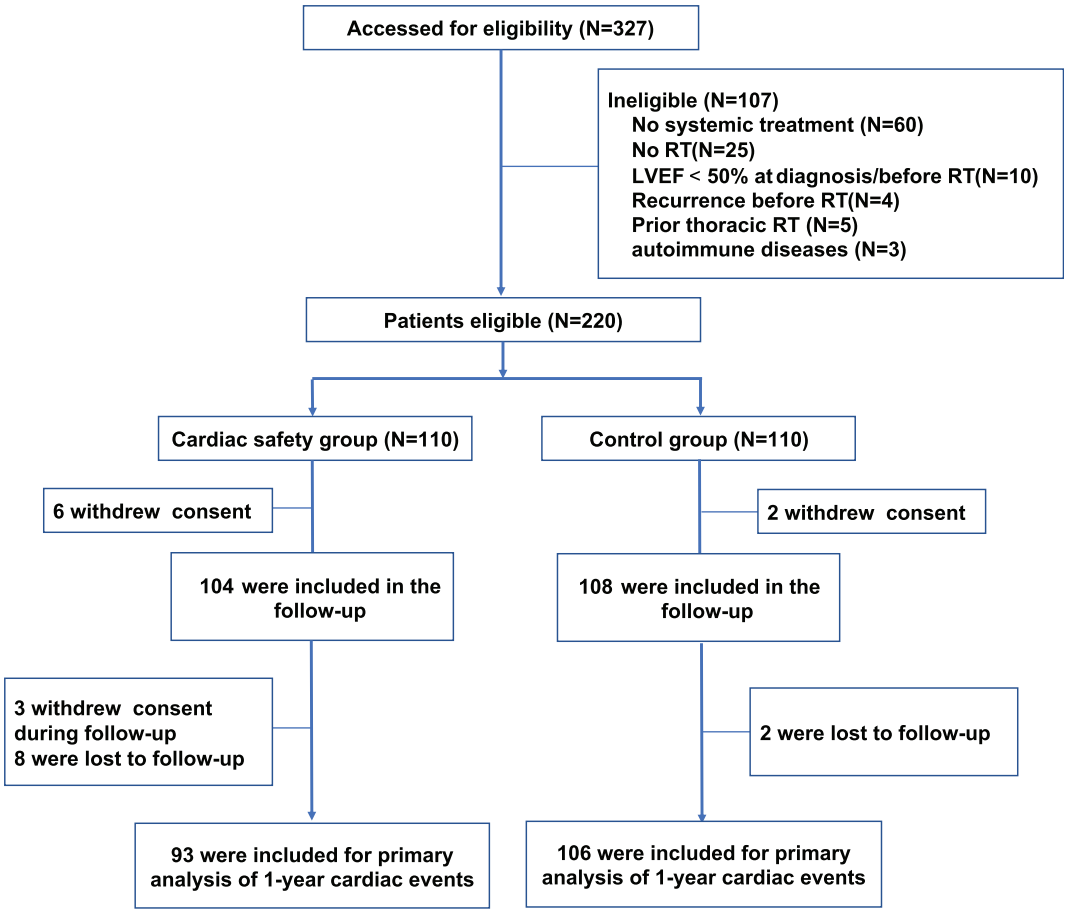


**FIGURE 1** The CONSORT diagram and trial profile.

The median follow-up was 70.2 months (range, 12.9–81.5). There were five breast cancer-related deaths in the cardiac safety group, as well as one breast cancer-related death and one death due to acute myeloid leukemia in the control group. The estimated 5-year of overall survival was 98.5% (95% CI 96.7%—100%). One patient in the cardiac safety group and two patients in the control group developed clinical cardiac events at 18, 51.7, and 7 months after RT, respectively. All three had right-sided tumors, recovered after the intervention, and remained asymptomatic until the last clinical visit (details provided in Table S1). All 199 patients completed 1-year cardiac assessments at 4 time points following the completion of RT. This article reports the primary endpoint of newly onset cardiac events within 1 year after RT.

## 3.2 | One-year cardiac events

The cumulative cardiac events incidence was 19.4% (95% CI 11.4%–27.4%) for the cardiac safety group and 24.9% (95% CI 16.5%–33.3%) for the control group ($p = .835$) (Table 2).

The cardiac safety group had no LVEF dysfunction versus 1.9% in the control group. Diastolic dysfunction occurred in 5.4% and 8.8% while persistent dysfunction occurred in 1.9% and 1.3% of cardiac safety and control groups, respectively. Abnormal NT-proBNP occurred in 15.5% and 18.1%, with persistent abnormality in 3.2% and 5.7%, of cardiac safety and control groups, respectively. One patient per group experienced cTnI abnormality. Despite lower cardiac dysfunction rates in the cardiac safety group, differences were not statistically significant (Table 2).

In the 1-year following RT, the control group had a significantly greater maximum LVEF reduction from baseline compared to the cardiac safety group (−3.08% ± 3.86% vs. −1.94% ± 3.66%, $p = .034$). At 12 months, all patients had LVEF above 50%, while diastolic dysfunction occurred in four cardiac safety and two control patients. There were no significant inter-group differences in cardiac parameters at baseline or follow-up (Table S2), except for the 6-month NT-proBNP, which was higher in the control group (65.09 ± 59.88 pg/ml vs. 57.95 ± 58.59 pg/ml, $p = .008$). In the entire cohort, there existed a fluctuation of diastolic function parameters and NT-proBNP value over time (Table S3).

## 3.3 | Comparisons of cardiac radiation dosimetry between groups

RT planning met the prespecified cardiac dose constraints in 96.8% of the cardiac safety group and 82.1% of the control group. In general, the cardiac safety group demonstrated lower MHD (345.9 ± 217.6 cGy vs. 373.5 ± 229.6 cGy), $Hmean_{EQD2}$ (325.4 ± 199.5 cGy

**TABLE 1** Patient demographics, tumor characteristics, and treatment details at randomization.

| Parameters | Entire cohort ($N = 199$) | Cardiac safety group ($N = 93$) | Control group ($N = 106$) | $p^*$ |
|---|---|---|---|---|
| Age (years), median (IQR) | 52 (41–60) | 53 (41–61) | 50 (41–59) | 0.69 |
| BMI (kg/m$^2$), median (IQR) | 22.9 (20.8–24.9) | 22.6 (20.2–25.4) | 23 (21.2–24.7) | 0.32 |
| Cardiac conditions | 49 (24.6%) | 24 (25.8%) | 25 (23.6%) | 0.717 |
| Cardiovascular disease | | | | |
| No | 183 (92%) | 86 (92.5%) | 97 (91.5%) | 0.80 |
| Yes | 16 (8%) | 7 (7.5%) | 9 (8.5%) | |
| Hypertension | | | | |
| No | 164 (82.4) | 76 (81.7) | 88 (83) | 0.81 |
| Yes | 35 (17.6) | 17 (18.3) | 18 (17) | |
| Diabetes | | | | |
| No | 193 (97) | 89 (95.7) | 104 (98.1) | 0.32 |
| Yes | 6 (3) | 4 (4.3) | 2 (1.9) | |
| Hyperlipidemia | | | | |
| No | 192 (96.5) | 91 (97.8) | 101 (95.3) | |
| Yes | 7 (3.5) | 2 (2.2) | 5 (4.7) | |
| Menopausal status | | | | |
| Pre-menopause | 99 (49.7%) | 44 (47.3%) | 55 (51.9%) | 0.52 |
| Post-menopause | 100 (50.3%) | 49 (52.7%) | 51 (48.1%) | |
| Side of primary tumor | | | | |
| Left | 119 (59.8%) | 54 (58.1%) | 65 (61.3%) | 0.64 |
| Right | 80 (40.2%) | 39 (41.9%) | 41 (38.7%) | |
| Quadrants | | | | |
| Others | 128 (64.3%) | 54 (58.1%) | 74 (69.8%) | 0.084 |
| Inner/Central | 71 (35.7%) | 39 (41.9%) | 32 (30.2%) | |
| Stage | | | | |
| I | 51 (25.6%) | 23 (24.7%) | 28 (26.4%) | 0.079 |
| II | 94 (47.2%) | 51 (54.8%) | 43 (40.6%) | |
| III | 54 (27.1%) | 19 (20.4%) | 35 (33%) | |
| T stage | | | | |
| 1 | 99 (49.7%) | 45 (48.4%) | 54 (50.9%) | 0.72 |
| 2 | 85 (42.7%) | 40 (43%) | 45 (42.5%) | |
| 3 | 11 (5.5%) | 5 (5.4%) | 6 (5.7%) | |
| 4 | 4 (2%) | 3 (3.2%) | 1 (0.9%) | |
| N stage | | | | |
| 0 | 82 (41.2%) | 42 (45.2%) | 40 (37.7%) | 0.059 |
| 1 | 64 (32.2%) | 33 (35.5%) | 31 (29.2%) | |
| 2 | 33 (16.6%) | 14 (15.1%) | 19 (17.9%) | |
| 3 | 20 (10.1%) | 4 (4.3%) | 16 (15.1%) | |
| Histological grade | | | | |
| 1–2 | 95 (47.7%) | 47 (50.6%) | 48 (45.3%) | 0.66 |
| 3 | 89 (44.7%) | 41 (44.1%) | 48 (45.3%) | |
| Unknown | 15 (7.5%) | 5 (5.4%) | 10 (9.4%) | |
| HR status | | | | |
| Negative | 69 (34.7%) | 31 (33.3%) | 38 (35.8%) | 0.71 |
| Positive | 130 (65.3%) | 62 (66.7%) | 68 (64.2%) | |

(Continues)

**TABLE 1** (Continued)

| Parameters | Entire cohort ($N = 199$) | Cardiac safety group ($N = 93$) | Control group ($N = 106$) | $p^*$ |
|---|---|---|---|---|
| HER2 status | | | | |
| Negative | 135 (67.8) | 67 (72%) | 68 (64.2%) | 0.23 |
| Positive | 64 (32.2) | 26 (28%) | 38 (35.8%) | |
| Ki-67, median (IQR) | 40 (20–60) | 40 (20–60) | 30 (20–60) | 0.062 |
| Primary surgery | | | | |
| Mastectomy | 99 (49.7%) | 47 (50.5%) | 52 (49.1%) | 0.84 |
| BCS | 100 (50.3%) | 46 (49.5%) | 54 (50.9%) | |
| ALND | | | | |
| No | 91 (45.7%) | 41 (44.1%) | 50 (47.2%) | 0.66 |
| Yes | 108 (54.3%) | 52 (55.9%) | 56 (52.8%) | |
| RT regimen | | | | |
| Hypofractionated | 42 (21.1%) | 24 (25.8%) | 18 (17.0%) | 0.16 |
| Conventional fractionation | 157 (78.9%) | 69 (74.2%) | 88 (83%) | |
| RNI | | | | |
| No | 78 (39.2%) | 38 (40.9%) | 40 (37.7%) | 0.65 |
| Yes | 121 (60.8%) | 55 (59.1%) | 66 (62.3%) | |
| IMN-RT | | | | |
| No | 104 (52.3%) | 51 (54.8%) | 53 (50%) | 0.50 |
| Yes | 95 (47.7%) | 42 (45.2%) | 53 (50%) | |
| Tumor bed boost in BCS | | | | |
| No | 4 (4%) | 1 (2.2%) | 3 (5.6%) | 0.62 |
| Yes | 96 (96%) | 45 (97.8%) | 51 (94.4%) | |
| Chemotherapy | | | | |
| Neoadjuvant | 14 (7%) | 4 (4.3%) | 10 (9.4%) | 0.13 |
| Neoadjuvant + Adjuvant | 11 (5.5%) | 3 (3.2%) | 8 (7.5%) | |
| Adjuvant | 174 (87.4%) | 86 (92.5%) | 88 (83%) | |
| Chemotherapy regimens | | | | |
| Anthracyclines | 12 (6%) | 4 (4.3%) | 8 (7.5%) | 0.071 |
| Taxanes | 44 (22.1%) | 27 (29%) | 17 (16%) | |
| Anthracyclines + Taxanes | 143 (71.9%) | 62 (66.7%) | 81 (76.4%) | |
| Cycles of Chemotherapy, median (IQR) | 8 (6–8) | 8 (6–8) | 8 (6–8) | |
| HER2-targeted therapy in HER2-positive tumor | | | | |
| No | 2 (3.1%) | 1 (3.8%) | 1 (2.6%) | 1 |
| Yes | 62 (96.9%) | 25 (96.2%) | 37 (97.6%) | |
| Endocrine therapy in HR-positive tumor | | | | |
| No | 0 (0%) | 0 (0%) | 0 (0%) | 0.71 |
| Yes | 130 (100%) | 62 (100%) | 68 (100%) | |

*Note*: *$p$ value is from the comparisons between the cardiac safety group and the control group.
Abbreviations: ALND, axillary lymph node dissection; BCS, breast conserving surgery; BMI, body mass index; HER2, human epidermal growth factor receptor-2; HR, hormonal receptor; IMN-RT, internal mammary nodal radiotherapy; IQR, interquartile range; RNI, regional nodal irradiation; RT, radiotherapy.

vs. 350.3 ± 209.6 cGy), V10 (6.2 ± 5.7% vs. 7 ± 6.3%), and V30 (2.9 ± 3% vs. 3.3 ± 3.4%) although without statistical significance (Table 3). Mean doses and $Hmean_{EQD2}$ of cardiac substructures were also lower in the cardiac safety group, with no statistical significance either (Table 3).

### 3.4 | Radiation dosimetry of cardiac substructures

In patients treated with left-sided IMN-RT, the LAD received the highest mean dose (2430.8 cGy), followed by the LV (668 cGy) and RV (608 cGy) (Figure 2A). Substructure dose distribution was

**TABLE 2** One-year cumulative incidence of cardiac events after RT.

| | Entire cohort | | | Cardiac safety group | | | Control group | | | Log-rank test $p^*$ | HR (95% CI) | $p^*$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Events (N) | Incidence | 95% CI | Events (N) | Incidence | 95% CI | Events (N) | Incidence | 95% CI | | | |
| Any cardiac events | 51 | 23% | 17.1%–28.8% | 23 | 19.4% | 11.4%–27.4% | 28 | 24.9% | 16.5%–33.3% | 0.835 | 0.943 (0.54–1.64) | 0.835 |
| Clinical cardiac events | 1 | 0.5% | / | 0 | 0 | / | 1 | 0.9% | / | / | / | / |
| LVEF dysfunction | 2 | 1% | 0%–2.4% | 0 | 0% | 0% | 2 | 1.9% | 0%–4.4% | 0.184 | 0.02 (0–1549.5) | 0.485 |
| Diastolic dysfunction | 16 | 7.1% | 3.6%–10.6% | 7 | 5.4% | 0.9%–9.9% | 9 | 8.8% | 3.3%–14.3% | 0.813 | 0.89 (0.33–2.39) | 0.813 |
| Persistent diastolic dysfunction | 6 | 0.8% | 0–2.4% | 3 | 1.9% | 0.2%–3.6% | 3 | 1.3% | 0%–2.6% | 0.400 | 2.13 (0.35–12.78) | 0.411 |
| NT-proBNP abnormality | 38 | 16.9% | 11.6%–22.1% | 17 | 15.5% | 8.1%–22.9% | 21 | 18.1% | 10.5%–25.7% | 0.875 | 0.95 (0.50–1.81) | 0.876 |
| Persistent NT-proBNP abnormality | 9 | 4.5% | 1.6%–7.4% | 3 | 3.2% | 0.7%–5.7% | 6 | 5.7% | 1.2%–10.2% | 0.416 | 0.57 (0.14–2.27) | 0.422 |
| cTnI abnormality | 2 | 1% | 0%–2.4% | 1 | 1.1% | 0%–3.3% | 1 | 1% | 0%–2.8% | 0.94 | 1.11 (0.7–17.79) | 0.94 |

*Note*: *$p$ values were from the comparisons between the cardiac safety group and the control group.
Abbreviations: 95% CI, 95% confidence intervals; HR, hazard ratios; LVEF, left ventricular ejection fraction.

comparable between left-sided patients with and without IMN-RT (Figure 2B). Overall, right-sided patients showed significantly lower substructure doses and less variation compared to left-sided patients (Figure 2C and Table S4), the most irradiated substructures were the RA (244 cGy), RCA (219.3 cGy), LAD (202.6 cGy), and RV (158.1 cGy).

In left-sided IMN-RT patients, MHD, Dmax, and V10-30 of the heart were strongly correlated with the LAD, LV, and RV doses (all $p < .05$) (Figure S1B). In left-sided patients without IMN-RT, there was a significant correlation between MHD, Dmax, and V5-20 of the heart and dose to all substructures ($p < .05$) (Figure S1C). In right-sided patients, MHD, Dmax, and V5-10 of the heart were correlated with dose to all substructures (Figure S1D).

Over the study period, the heart and substructure dose decreased yearly (Figure 3 and Table S5), with most prominent in left-sided patients without IMN-RT. For left-sided IMN-RT, the decrease was limited to V5 of heart, LV, and LA (Figure 3A–D and Table S5). For right-sided patients, dose reduction primarily occurred in MHD, Dmax, and V5-10 for the heart, RA, and RCA (Figure 3E–H).

### 3.5 | Risk factors for early cardiac toxicity

In multivariable analysis, hypertension was an independent risk factor for cardiac events (HR = 2.99, 95% CI 1.49–5.99, $p = .002$) and persistent diastolic dysfunction (HR = 28.61, 95% CI 1.56–523.53, $p = .024$). Cardiovascular disease (HR = 7.60, 95% CI 1.46–39.67, $p = .016$) and left laterality (HR = 9.40, 95% CI 1.1–82.9, 0.044) were independent risk factors for persistent NT-proBNP abnormality (Table S6).

## 4 | DISCUSSION

In this randomized trial, we introduce a serial dose-volume constraint for BC patients undergoing postoperative IMRT. For the entire cohort, early cardiac safety was favorable, with no RT-induced clinical cardiac events, and most subclinical cardiac dysfunctions recovered within 12 months after RT. This study is the first to report on dose distribution to cardiac substructures based on individual IMRT planning. Dosimetric analyses showed a distinct pattern of dose distribution in cardiac substructure between left-sided versus right-sided patients. Correlations between whole heart and substructure doses varied with tumor laterality and receipt of IMN-RT.

### 4.1 | Cardiac events

In this study, we conducted an intensive monitoring of LVEF, diastolic function, and cardiac biomarkers over four follow-up visits within the first year following RT. This possibly explains the high overall cardiac event incidence in our study. Specific dysfunction are usually reported separately. Our previous prospective study found that 27% (31 out of 115) of BC patients developed diastolic dysfunction within 6 months

**TABLE 3** Whole Heart Dose-Volume Parameters and Mean Doses to Cardiac Substructures.

| | Entire cohort | Cardiac safety group | Control group | *p** |
|---|---|---|---|---|
| Entire cohort (N) | 199 | 93 | 106 | |
| Whole Heart (cGy) | | | | |
| Mean dose (cGy) | 360.6 ± 223.9 | 345.9 ± 217.6 | 373.5 ± 229.6 | 0.392 |
| V5 (%) | 12.5 ± 10 | 11.8 ± 9.6 | 13.1 ± 10.3 | 0.363 |
| V10 (%) | 6.7 ± 6 | 6.2 ± 5.7 | 7 ± 6.3 | 0.349 |
| V20 (%) | 4.2 ± 4.2 | 3.9 ± 3.9 | 4.5 ± 4.4 | 0.367 |
| V30 (%) | 3.1 ± 3.2 | 2.9 ± 3 | 3.3 ± 3.4 | 0.358 |
| Mean dose of cardiac substructures | | | | |
| LA (cGy) | 138 ± 115.8 | 132.3 ± 119.8 | 143 ± 112.6 | 0.522 |
| LV (cGy) | 417.9 ± 339.2 | 401.8 ± 328.8 | 432 ± 349.1 | 0.537 |
| RA (cGy) | 168.1 ± 161.7 | 154.7 ± 145.4 | 179.9 ± 174.7 | 0.279 |
| RV (cGy) | 380.1 ± 286.1 | 355.5 ± 280.1 | 401.6 ± 290.9 | 0.263 |
| LAD (cGy) | 1453.9 ± 1293.3 | 1406.3 ± 1278.1 | 1495.4 ± 1311.3 | 0.632 |
| RCA (cGy) | 198.4 ± 201.6 | 177.3 ± 126.4 | 216.9 ± 248.7 | 0.172 |
| $Hmean_{EQD2}$ of the whole heart and cardiac substructures | | | | |
| Whole Heart (cGy) | 338.7 ± 204.8 | 325.4 ± 199.5 | 350.3 ± 209.6 | 0.399 |
| LA (cGy) | 134 ± 108.9 | 128.3 ± 112.9 | 138.9 ± 105.6 | 0.502 |
| LV (cGy) | 383.7 ± 305.5 | 369.8 ± 297.2 | 395.9 ± 313.6 | 0.552 |
| RA (cGy) | 161.5 ± 148.4 | 149.1 ± 134.2 | 172.5 ± 159.7 | 0.273 |
| RV (cGy) | 354 ± 254.8 | 331.9 ± 248.8 | 373.2 ± 259.6 | 0.26 |
| LAD (cGy) | 1151.8 ± 994.3 | 1117.1 ± 982.4 | 1182.1 ± 1008.4 | 0.65 |
| RCA (cGy) | 189.6 ± 172 | 171.3 ± 117.4 | 205.6 ± 207.7 | 0.165 |
| Subgroup treated with left-sided IMN-RT (N) | 60 | 23 | 37 | |
| Whole heart (cGy) | | | | |
| Mean dose (cGy) | 551.2 ± 159.5 | 536.1 ± 161.5 | 561.2 ± 159.7 | 0.562 |
| V5 (%) | 20.5 ± 8.8 | 19.1 ± 8.3 | 21.4 ± 9.1 | 0.343 |
| V10 (%) | 11.8 ± 5 | 10.8 ± 4.6 | 12.5 ± 5.1 | 0.198 |
| V20 (%) | 7.6 ± 3.6 | 7.1 ± 3.6 | 7.9 ± 3.6 | 0.437 |
| V30 (%) | 5.5 ± 3 | 5.2 ± 3 | 5.7 ± 3.1 | 0.575 |
| Mean dose of cardiac substructures | | | | |
| LA (cGy) | 191.1 ± 139.4 | 179.9 ± 130.5 | 198.4 ± 146.4 | 0.624 |
| LV (cGy) | 668 ± 257.7 | 653.9 ± 247.5 | 677.4 ± 267.3 | 0.737 |
| RA (cGy) | 150.1 ± 169.6 | 133.9 ± 161.1 | 160.7 ± 176.4 | 0.561 |
| RV (cGy) | 608.5 ± 263.6 | 593.8 ± 307.4 | 618.2 ± 234.8 | 0.733 |
| LAD (cGy) | 2430.8 ± 1001.5 | 2419.8 ± 1038.5 | 2438.1 ± 991.8 | 0.947 |
| RCA (cGy) | 230.8 ± 311.5 | 176.1 ± 122.6 | 266.8 ± 386.8 | 0.282 |
| $Hmean_{EQD2}$ of the whole heart and cardiac substructures | | | | |
| Whole Heart (cGy) | 513.4 ± 142.9 | 500.2 ± 144.7 | 522 ± 143.1 | 0.574 |
| LA (cGy) | 184.4 ± 129.6 | 173.9 ± 122.8 | 191.2 ± 135.2 | 0.624 |
| LV (cGy) | 611.5 ± 227.1 | 600.2 ± 219.8 | 619 ± 234.7 | 0.761 |
| RA (cGy) | 144.3 ± 153.1 | 129.1 ± 145.4 | 154.3 ± 159.2 | 0.544 |
| RV (cGy) | 560.1 ± 227.3 | 545.8 ± 262.8 | 569.5 ± 204.2 | 0.702 |
| LAD (cGy) | 1912.8 ± 739.8 | 1907.5 ± 756.3 | 1916.2 ± 739.9 | 0.966 |
| RCA (cGy) | 216.5 ± 255.4 | 170.6 ± 113.3 | 246.7 ± 314.1 | 0.271 |

*Note*: **p* values were from comparisons between the cardiac safety group and the control group.
Abbreviations: LA, left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; N, number of patients; RA, right atrium; RCA, right coronary artery; RV, right ventricle.

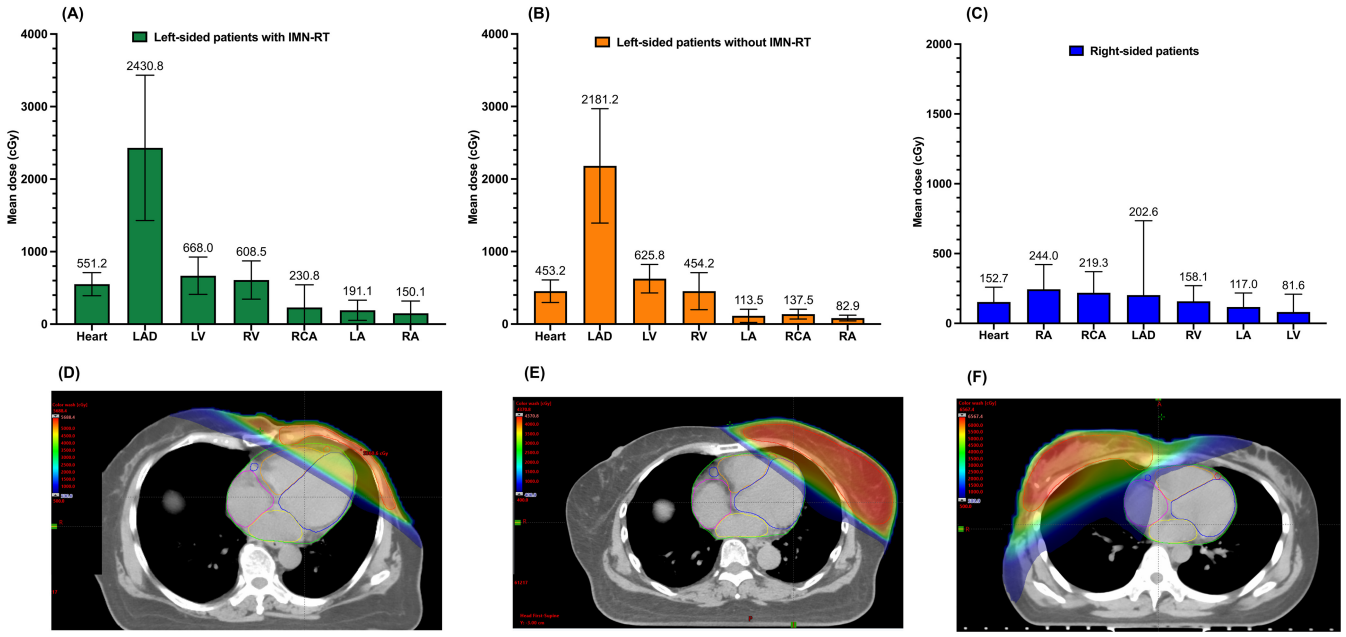


**FIGURE 2** Distribution of radiation dose to the whole heart and cardiac substructures. The mean dose of the whole heart and cardiac substructures in left-side patients with IMN-RT (A), left-side patients without IMN-RT (B), and right-sided patients (C). The isodose distribution at the four-chamber heart level on the planning CT images for left-side patients with IMN-RT (D), left-side patients without IMN-RT (E), and right-sided patients (F).

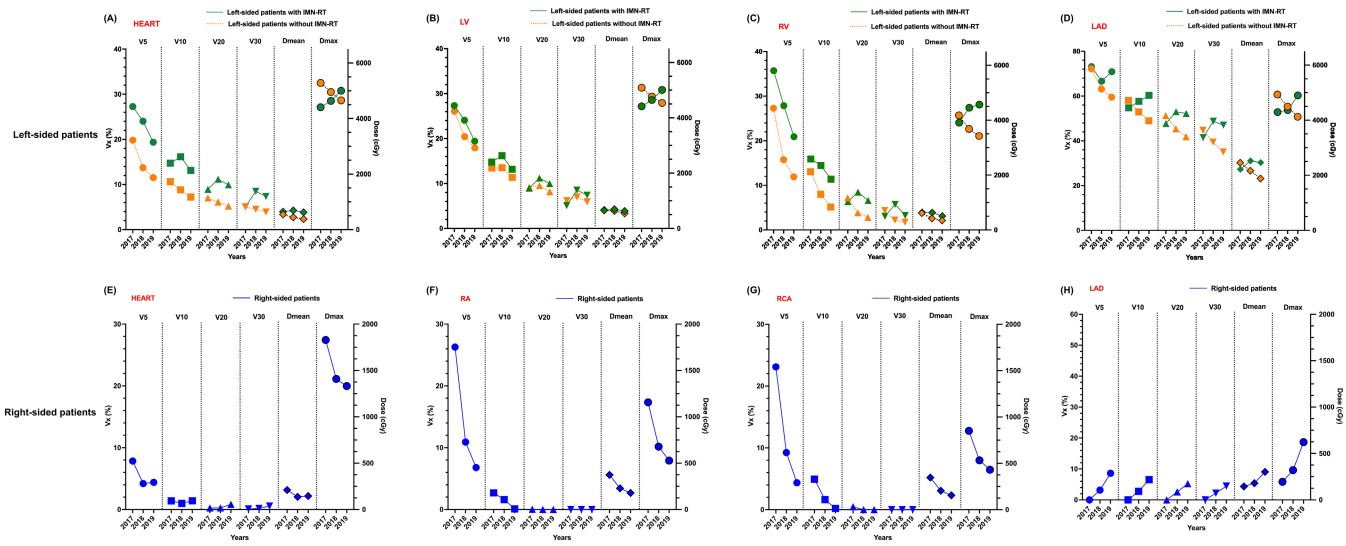


**FIGURE 3** Changes in dose-volume parameters of the whole heart and highly irradiated cardiac substructures over the study period in left-sided patients with or without IMN-RT (A–D) and in right-sided patients (E– H).

post-RT.[13] A cross-sectional analysis found abnormal LVEF in 14% of patients and diastolic dysfunction in 39% following RT, assessed at a median of 7 years post-diagnosis.[29] In comparison to these reports, separate LVEF, diastolic, and persistent diastolic dysfunction rates in our study were lower, at 1%, 7.1%, and 0.8%, respectively. The most observed subclinical cardiac event in our study was transient NT-proBNP abnormality, with only 4% of patients exhibiting NT-proBNP >150 pg/ml at 12 months after RT. As all the events were subclinical, most of which recovered within 1-year post-RT without medical intervention, our dosimetric approach can be considered safe. As with most early cardiac toxicity studies, longer-term follow-up is needed.

## 4.2 | Cardiac substructures dosimetry

Our result showed distinct dose distribution to different substructures between left- and right-sided patients. Left-sided RT predominantly affected the LAD, LV, and RV, while right-sided treatment more

uniformly impacted the RA, RCA, LAD, and RV. Milo et al.[30] also found the highest RT doses to the LV and LAD for left-sided RT and the RA and RCA for right-sided RT. Previous substructure studies often emphasized the LV and LAD due to their greater radiation exposure associated with classical tangents and its correlation with RIHD.[31–33] Endothelial cells are highly radiosensitive, damage to them is an early event preceding most cardiac injuries,[34–36] which is less associated with certain substructures. In line with this, a meta-analysis from Darby et al. and subsequent research highlighted the importance of minimizing exposure to all cardiac substructures instead of defining a threshold dose.[5,7,37]

State-of-the-art RT techniques have narrowed cardiac event incidence gaps between left- and right-sided BC patients.[37,38] In a nested case–control study of 116 BC patients, right-sided patients had a higher arrhythmia propensity associated with increasing RA doses.[39] Wang et al.[40] identified a borderline significant relationship between arrhythmia and doses to the RA, LA, and whole heart. Errahmani et al.[41] observed that the sinoatrial (SA) and atrioventricular (AV) node doses exceeding 1 Gy were common among right-sided BC patients, suggesting the RA could serve as a surrogate to evaluate SA node exposure, which might explain the high rate of arrhythmia in these patients. In a recent review, Tadic et al.[42] emphasized RV's role in radiation-induced cardiac toxicity. Therefore, we recommend a comprehensive protective strategy to include the RV for left-sided patients and the RA, RCA, LAD, and RV for right-sided patients. Within this framework, strategies to significantly decrease overall cardiac dose such as proton therapy are expected to benefit BC patients regardless of the laterality.[6,43,44]

Previous studies have indicated that MHD per se is not representative of LAD and LV doses.[9,10,45] Our study confirms that MHD did not uniformly reflect substructure doses, with significant variability based on laterality and IMN-RT. Despite our study's focus on limiting only the whole heart dose-volume in the study group, we observed almost proportional reductions in the doses to both whole heart and substructure throughout the study period. These findings imply that in clinical practice, comprehensive constraints on MHD and whole heart dose-volume parameters could serve as clinical goals instead of substructure-specific dose limits, which will efficiently decrease the complexity of treatment planning optimization. Whole heart dose volumes can also serve as surrogates for RT plan evaluation and comparison in different clinical studies to approximate substructure dose evaluation.

### 4.3 | Cardiac dosimetry and early toxicity

Heart dose in BC RT has significantly decreased over the years, while patient's baseline and systemic therapy-related cardiovascular risk factors playing an increasing role in RIHD development. Our study found hypertension and pre-existed cardiovascular disease are independent predictors of subclinical cardiac events, consistent with previous reports.[46,47] No significant difference existed in 1-year cardiac event incidence between the two study arms. This may be explained by the fact that radiation doses to the whole heart and substructures were well below the pre-specified cardiac constraints, even in the control arm.

To assess the impact of cardiac dosimetry on early cardiac toxicity, we compared the rate of LVEF and diastolic dysfunction between the current and our published prospective study in 2015.[13] Current study shows a marked decrease in both LVEF dysfunction (1% vs. 2.8%) and diastolic dysfunction (7.1% vs. 26.9%) (Table S7). A proportional decline in MHD and heart dose-volume parameters, particularly in mid-to-high dose regions for left-sided and low-dose regions for right-sided patients, was also observed in the current study (Table S8). These findings support the relationships between early cardiac events and overall heart dose. Leveraging this, we tightened cardiac dose-volume constraints for a subsequent randomized trial (NCT03829553) comparing hypofractionated and conventional-fractionated IMRT with RNI including IMN, reducing V10 from 50% to 20% and V30 from 20% to 10%, anticipating lower cardiac event rates.[48]

### 4.4 | Limitations

Cardiac doses were below estimates, which limits the ability to extrapolate the impact of cardiac constraints on early toxicity. Nevertheless, by comparing the current study with our previous one, a strong correlation between LVEF, diastolic dysfunction, and dose-volume metrics was established. Long-term follow-up is important not only to establish the implications of early subclinical cardiac dysfunctions, but also the relationship between cardiac dysfunctions and specific substructural doses. Finally, the cardiac monitoring strategy in our study is more intensive than most practical recommendations, which also warrants further discussion.

## 5 | CONCLUSIONS

With comprehensive constraints on MHD and dose-volume metrics, IMRT ensures early cardiac safety in postoperative RT for BC patients. Cardiac substructure dose distributions were distinct between left and right-sided RT. MHD and whole heart dose-volume metrics could represent the dose distribution to critical cardiac substructures.

### AUTHOR CONTRIBUTIONS

**Lu Cao:** Conceptualization; methodology; formal analysis; funding acquisition; writing – original draft. **Dan Ou:** Methodology; data curation; project administration; writing – original draft; conceptualization. **Wei-Xiang Qi:** Data curation; formal analysis; writing – original draft. **Cheng Xu:** Methodology; project administration; investigation. **Ming Ye:** Methodology; project administration; data curation; investigation. **Yue-Hua Fang:** Methodology; formal analysis. **Mei Shi:** Project administration; data curation; investigation. **Xiao-Bo Huang:** Project administration; data curation; investigation. **Qing Lin:** Data curation; project administration; investigation. **Tong Liu:** Formal analysis;

methodology; writing – review and editing. **Gang Cai:** Data curation; project administration; investigation. **Rong Cai:** Data curation; project administration; investigation. **Mei Chen:** Methodology; formal analysis. **Yi-Bin Zhang:** Data curation; methodology; project administration. **Xiu-Xiu Su:** Methodology; formal analysis. **Xiao-Fang Qian:** Data curation. **Kun-Wei Shen:** Methodology. **Jia-Yi Chen:** Conceptualization; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

All data and materials supporting the conclusions of this article are available in the figures, tables, and Supplementary material, which are available to authorized users. Further information is available from the corresponding author upon request.

## ETHICS STATEMENT

This trial was conducted at five tertiary hospitals in China, with the ethics approval of each participating center. All patients provided written informed consent. The trial was registered on ClinicalTrials.gov (NCT02942615).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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