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Evaluation of cardiotoxicity following breast cancer irradiation in an Asian cohort in real-world settings

Wen-Chi Yang [a,b,c], Yu-Hsuan Chen [b], Chia-Chun Wang [a,b,c], Shih-Fan Lai [a,b], Szu-Huai Lu [b], Li-Ting Ho [f,g], Chiun-Sheng Huang [d], Sung-Hsin Kuo [a,b,c,e,*]

[a] Department of Radiation Oncology, National Taiwan University Cancer Center, National Taiwan University College of Medicine, Taipei, Taiwan
[b] Division of Radiation Oncology, Department of Oncology, National Taiwan University College of Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Graduate Institute of Oncology, National Taiwan University College of Medicine, National Taiwan University, Taipei, Taiwan
[d] Department of Surgery, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[e] Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan
[f] Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan
[g] Cardiovascular Center, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

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ABSTRACT

Background: Adjuvant radiotherapy (RT) for early-stage breast cancer is associated with increased major cardiovascular (CV) events. This study investigates cardiac toxicity in an Asian breast cancer cohort, focusing on the interplay between RT, cardiovascular risk factors, and systemic treatments, a topic less explored in regions with lower cardiovascular disease (CVD) prevalence.

Methods: Patients with breast cancer who underwent adjuvant RT between January 2004 and November 2014 were included in this single-institutional retrospective study. Patients were categorized by CVD risk factors, including obesity, smoking history, prior CVD incidents, chronic kidney disease (CKD), diabetes mellitus, hypertension, and dyslipidemia. The primary outcome was the incidence of major CV events, defined as conditions requiring intervention, including heart failure, arrhythmia, and ischemic heart disease. Kaplan–Meier methods, log-rank tests, and Cox regression models were used for statistical analysis.

Results: Among the 975 patients, the 10-year cumulative incidence of major CV events was 3.7 %, with no significant difference ($p = 0.892$) between right-sided (3.8 %) and left-sided RT (3.4 %). Patients with low, intermediate, and high CVD risk factors had 10-year cumulative incidences of 0.7 %, 2.5 %, and 13.7 %, respectively. Multivariate analysis revealed that hypertension, CKD, and previous CVD were significantly associated with major CV events. In patients without CVD risk factors, the 10-year incidence of CV events was higher in those undergoing left-sided RT compared to right-sided RT (1.3 % vs. 0.0 %, $p = 0.032$).

Conclusions: Major CV events incidences following RT in this Asian cohort with low baseline CVD risk were modest. However, the impact was more pronounced in patients without baseline CVD risk factors, emphasizing the need for personalized risk assessment in RT planning.

1. Introduction

Adjuvant radiotherapy (RT) is used to treat patients with early-stage breast cancer (BC) who have undergone breast-conserving surgery or mastectomy to reduce recurrence but have high-risk characteristics [1,2]; thus, RT has become an essential treatment for BC. The Danish Breast Cancer Cooperative Group 82b and 82c trials demonstrated that postmastectomy RT increased the survival of patients with high-risk BC but did not increase the risk of ischemic heart disease (IHD) at 12 years compared with those who did not undergo postmastectomy RT [3]. Furthermore, morbidity and mortality from IHD were similar between patients who underwent right-sided or left-sided RT [3]. However, RT increases the risk of coronary heart disease and cardiac mortality in patients with BC from database analyses [4–6]. This risk difference becomes more pronounced with extended follow-up periods, surpassing 20 years. A linear correlation between the mean heart dose in breast RT and the development of major coronary events was observed in a population-based case-control study [7]. RT-induced cardiotoxicity

* Corresponding author. Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan. (zip code 100)
E-mail address: shkuo101@ntu.edu.tw (S.-H. Kuo).

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manifests in acute phases as pericarditis, pericardial effusion, and arrhythmias. Additionally, these adverse events may lead to late complications of cardiac disorders, such as heart failure, valvular dysfunction, and conduction abnormalities [8], particularly in patients receiving internal mammary node irradiation (IMNI) [9].

Radiation oncologists attempt to minimize cardiac exposure during left-sided RT for BC using innovative techniques such as deep inspiration breath-hold (DIBH) and proton therapy [10]. Heart-sparing RT reduces cardiotoxicity but is more expensive and labor-intensive than conventional therapies. Moreover, advances in systemic therapies increase survival but impose an economic burden on patients [11]. Nonetheless, whether these advanced RT techniques can be used in resource-limited settings is unknown [12].

Most cohort studies on breast RT-induced cardiotoxicity were published in Western countries, leaving a significant gap in determining the incidence of cardiovascular (CV) events following RT in low-risk Asian patient groups [13]. Evaluating the cost-effectiveness of RT techniques is essential in Asian countries, where the risk of CV events is lower than that in Western countries. Moreover, although smoking can increase the risk of radiation-induced IHD in BC survivors [9], it is unknown whether RT can increase the incidence of CV events in BC patients from a nearly non-smoking population.

This study evaluated cardiotoxicity in an Asian BC cohort undergoing breast or chest wall RT with regional nodal irradiation in real-world settings. The study evaluated the incidence of CV events in low-risk patients and the association between RT, underlying cardiovascular disease (CVD) risk factors, and medications. The results can help identify subgroups that could benefit from heart-sparing RT.

2. Material and methods

2.1. Patients

This single-institutional retrospective cohort study was approved by the Institutional Review Board (IRB) of the Research Ethical Committee of National Taiwan University Hospital (NTUH) (NTUH IRB number: 202404020RINB). All patient data have been anonymized to protect privacy and confidentiality. Patients with localized BC who underwent adjuvant RT for the whole breast or chest wall and regional nodes from January 2004 to November 2014 at NTUH were included in this study. Patients with bilateral BC who received bilateral irradiation, those without pathological reports, and those with incomplete or unclear RT records were excluded from the study. In this study, the clinical characteristics, treatment details, cardiovascular risk factors, and outcomes were retrospectively and manually extracted from electronic medical records (EMRs) and RT planning systems. Nevertheless, before 2014, no prospective registration data for breast cancer existed in our institution. Data on patient age, histological type and grade, tumor size, nodal stage, and treatment characteristics (breast and axilla surgery type, regional nodal irradiation, and types of adjuvant systemic therapy) were collected and analyzed. Patients were scheduled for oncology clinic visits every 3–6 months during the first 3–5 years and every 6–12 months thereafter, according to institutional practice, consistent with the National Comprehensive Cancer Network (NCCN) guidelines. Cardiology assessments, including echocardiography and electrocardiography, were performed when clinically indicated rather than using a fixed protocol.

2.2. CVD risk assessment

CVD risk was assessed by evaluating obesity (body mass index [BMI]>27 kg/m^2), smoking history, prior CVD incidents, including myocardial infarction, stroke, angina, or clinically significant arrhythmia such as atrial fibrillation/flutter, Grade ≥ 2 atrioventricular block, marked QT-prolongation, or rhythm control by device implantation, chronic kidney disease (CKD), diabetes mellitus (DM) (HbA1c $\geq$6.5 % or antidiabetic medication use), hypertension (HTN) (systolic $\geq$140 mmHg and/or diastolic $\geq$90 mmHg, or antihypertensive medication use), and dyslipidemia (LDL $\geq$130 mg/dL, HDL $<$40 mg/dL for males or $<$50 mg/dL for females, or lipid-lowering medication use).

Additionally, we analyzed data from patients who were prescribed medications that could potentially cause cardiotoxicity, including trastuzumab and doxorubicin. Patients were categorized into three subgroups based on the number of risk factors for CVD: low risk (no risk factors), intermediate risk (one risk factor), and high risk (two or more risk factors).

2.3. Radiotherapy techniques and doses

Computed Tomography (CT) simulations were performed, followed by conventional RT targeting regional nodes and the ipsilateral whole breast or chest wall, with a total dose of 5000 cGy in 25 fractions. The patients who underwent partial mastectomy received a tumor bed boost ranging from 1000 cGy to 1600 cGy using an en face electron beam (9–15 MeV) technique (200 cGy per fraction). We routinely utilized forward field-in-field (FiF) intensity-modulated radiation therapy (IMRT) techniques to treat both the left- and right-sided whole breast or chest wall of patients with breast cancer. Wedges were rarely used for left- or right-sided breast or chest wall irradiation. To obtain the best dosage uniformity, tangential fields using the FiF IMRT approach were used for primary full breast or chest wall treatment, which provided superior dose homogeneity compared to wedge-based 3D conformal RT. For the irradiation of the axilla and supraclavicular fossa (SCF), an anterior-posterior (AP) beam arrangement using 3D conformal planning was most commonly implemented, although anterior/posteroanterior (AP/PA) beams are occasionally adopted to enhance target coverage. For IMNI, an anterior electron beam, a wide tangential photon field integrated within the breast treatment fields, or a combination of photon and electron fields were employed, depending on the clinical requirements and anatomical considerations.

The representative beam arrangement and isodose curve in a patient with breast cancer treated with the left chest wall using tangential FiF IMRT techniques and with the left SCF using 3D conformal planning are shown in Supplementary Figure 1. None of our patients underwent multi-field inverse IMRT or volumetric modulated arc therapy (VMAT), as these advanced techniques, although recognized for improved heart sparing, were not standard practices during the study period (2004–2014).

2.4. Evaluation of the incidence of major CV events

Major CV events were defined as CV conditions requiring intervention. Specifically, heart failure was characterized by the presence of dyspnea, orthopnea, edema, or a reduction in left ventricular ejection fraction (LVEF) to less than 45 % (LVEF $<$45 %). Arrhythmia was defined as symptomatic irregular heartbeats, including palpitations, shortness of breath, or fainting, accompanied by electrocardiographic abnormalities. Patients necessitating medications, ablation, or pacemaker implantation for conduction abnormalities were also included in the analysis. IHD was defined as abnormal findings in coronary angiography or coronary CT accompanied by the use of aspirin or antiplatelet drugs. The latter group included patients diagnosed with myocardial infarction, those who underwent coronary stent placement, and those who underwent coronary bypass surgery. Patients with CVD incidents were considered those diagnosed with CVD before RT. These CV events and procedures were identified from the institutional integrated EMR, which captures both inpatient and outpatient care across the main hospital and its affiliated branches, and from information reported during scheduled oncology follow-up visits. Source documents included cardiology consultation notes, echocardiography and electrocardiography reports, catheterization laboratory and operative reports, radiology reports (coronary CT/angiography), discharge summaries,

and relevant medication records (e.g., initiation of antiplatelet therapy for IHD). All identified CV events were centrally reviewed by a cardiologist to ensure consistency in diagnostic criteria and reporting. The time to occurrence of CV events was calculated from the initiation of RT to the occurrence of major CV events.

2.5. Statistical analysis

In this study, analyses were conducted using the follow-up data available on January 31, 2024. We employed the Kaplan–Meier method to calculate the incidences of CV events and assessed disparities between CV events and baseline patient or treatment characteristics using the log-rank test. The effects of age, RT site, IMNI, surgery type, systemic treatment, smoking, and CVD risk factors on the incidence of CV events were analyzed by Cox regression analysis. Statistical analysis was performed using IBM SPSS Statistics version 24.0 for Windows (IBM Corp., Armonk, NY). All tests were two-sided. *P*-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Clinicopathological features

A total of 1038 patients undergoing whole breast or chest with regional lymph node irradiation were eligible for inclusion in this study. Patients with recurrent or metastatic diseases (N = 32), those without comprehensive pathological or RT reports (N = 11), and those with bilateral BC who underwent irradiation for both breasts were excluded from the study to ensure a more representative cohort (N = 20). A total of 975 patients (478 irradiated on the right side and 497 irradiated on the left side) were included in the analysis. The flow chart of patient selection is illustrated in Supplementary Figure 2.

The characteristics of the groups who underwent right-sided or left-sided RT are presented in Table 1. The median age at diagnosis was 50 years (range, 25–88 years). In addition, the percentage of patients with a history of smoking and obesity (BMI higher than 27 kg/m^2) was 0.6 % and 17.6 %.

3.2. CVD risk factors and treatment characteristics

The percentage of patients with no, one, or two or more risk factors for CVD was 66.3 %, 19.0 %, and 14.8 %. There were no significant differences in age, obesity, smoking history, and CVD risk between the group who underwent right-sided or left-sided RT (Table 1). Similarly, there were no significant differences in pathological T and N stages between these two groups (Table 1). The majority of patients (72.7 %) had hormone receptor-positive disease (72.7 %), and almost all of them underwent anti-hormone therapy. Additionally, the percentage of patients who received chemotherapy and anthracycline-based chemotherapy was 97.8 % and 92.8 %. Approximately 27.5 % of the cohort received anti-human epidermal growth factor receptor 2 (HER2) targeted trastuzumab.

In this study, the most common chemotherapy regimens were CEF (cyclophosphamide, epirubicin, and 5-fluorouracil; 4 cycles) followed by Taxotere (docetaxel; 4 cycles) (129 patients), TEC (docetaxel, epirubicin, and cyclophosphamide; 6 cycles) (115 patients), CEF alone (6 cycles) (53 patients), CEF (4 cycles) with TH (docetaxel and trastuzumab; 4 cycles) (25 patients), and EC (epirubicin and cyclophosphamide; 4 cycles) followed by docetaxel (4 cycles) (23 patients). Hormone therapy (HT) predominantly included tamoxifen (177 patients), letrozole (106 patients), and tamoxifen shifted to letrozole (235 patients). The median HT duration was 8 years, and 149 patients completed 10 years of HT. Chemotherapy typically preceded RT, with HT generally initiated after chemotherapy, which is consistent with standard clinical practice during the study period. Overall, 9.8 % of patients underwent IMNI. There were no significant differences in systemic treatments between these two groups (Table 1).

Table 1
Patient characteristics.

Characteristics	Total (N = 975)	Right-sided RT (N = 478)	Left-sided RT (N = 497)	*P*-value
Age (median)	50	50	50	0.543
≥50	528 (54.2 %)	261 (54.6 %)	267 (53.7 %)	0.783
<50	447 (45.8 %)	217 (45.4 %)	230 (46.3 %)	
Smoking	6 (0.6 %)	3 (0.6 %)	3 (0.6 %)	0.962
Obesity	172 (17.6 %)	75 (15.7 %)	97 (19.5 %)	0.117
CVD risk				0.586
No risk factor	646 (66.3 %)	312 (65.3 %)	334 (67.2 %)	
One risk factor	185 (19.0 %)	97 (20.3 %)	88 (17.7 %)	
Two or more risk factors	144 (14.8 %)	69 (14.4 %)	75 (15.1 %)	
Major Cardiovascular Events	32 (3.3 %)	15 (3.1 %)	17 (3.2 %)	0.911
IHD	7 (0.7 %)	2 (0.4 %)	5 (1.0 %)	0.242
Heart failure	16 (1.6 %)	10 (2.1 %)	6 (1.2 %)	0.277
Arrythmia	9 (0.9 %)	3 (0.6 %)	6 (1.2 %)	0.272
Pathological T stage				0.723
T1	211 (21.7 %)	102 (21.4 %)	109 (21.9 %)	
T2	451 (46.3 %)	226 (47.4 %)	225 (45.3 %)	
T3	179 (18.4 %)	80 (16.8 %)	99 (19.9 %)	
T4	24 (2.5 %)	12 (2.5 %)	12 (2.4 %)	
Tx	109 (11.2 %)	57 (11.9 %)	52 (10.5 %)	
Pathological N stage				0.592
N0	142 (14.6 %)	68 (14.3 %)	74 (14.9 %)	
N1	308 (31.7 %)	160 (33.6 %)	148 (29.8 %)	
N2	341 (35.1 %)	165 (34.7 %)	176 (35.5 %)	
N3	181 (18.6 %)	83 (17.4 %)	98 (19.8 %)	
Molecular subtypes				0.578
ER+/HER2-	567 (58.3 %)	273 (57.2 %)	294 (59.4 %)	
ER+/HER2+	150 (14.4 %)	71 (14.9 %)	79 (16.0 %)	
ER-/HER2+	123 (12.7 %)	61 (12.8 %)	62 (12.5 %)	
ER-/HER2-	132 (13.6 %)	72 (15.1 %)	60 (12.1 %)	
Hormone therapy	703 (72.1 %)	337 (70.5 %)	366 (73.6 %)	0.274
Anti-HER2 treatment	268 (27.5 %)	128 (26.8 %)	140 (28.2 %)	0.627
Chemotherapy	954 (97.8 %)	465 (97.3 %)	489 (98.4 %)	0.233
Anthracycline	905 (92.8 %)	440 (92.1 %)	465 (93.6 %)	0.361
Taxane	855 (87.7 %)	411 (86.0 %)	444 (89.3 %)	0.111
IMN irradiation	96 (9.8 %)	45 (9.4 %)	41 (10.3 %)	0.657

Abbreviations: N, number; CVD, cardiovascular disease; IHD, ischemic heart disease; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary nodes.
A chi-squared test was used for statistical significance analysis.

3.3. Risk factors for CV events

The median follow-up was 9.9 years. Among the 975 patients, 151 (15.5 %) died during follow-up, and 160 (16.4 %) were lost to follow-up at the end of follow-up on January 31, 2024. However, given the substantial median follow-up duration of 9.9 years, we believe that the

potential impact of the low number of patients lost to follow-up on the association between RT and CV events on our findings is limited. The 10-year cumulative incidence of major CV events was 3.7 % (Fig. 1) with no significant difference between patients undergoing right-sided (3.8 %) and left-sided RT (3.4 %; p = 0.892). None of the patients with major CV events died. The types of CV events are summarized in Supplementary Table 1. A total of 41.3 % of patients underwent partial mastectomy, while the remainder underwent mastectomy. There were no significant differences in the risk of CV events between these two types of surgery (hazard ratio [HR], 0.569, 95 % confidence interval [CI], 0.269–1.202, p = 0.139, Table 2).

The 10-year cumulative incidence of major CV events in the low-risk, intermediate-risk, and high-risk groups was 0.7 %, 2.5 %, and 13.7 % (Fig. 2A), with significant between-group differences (log-rank test, p < 0.001).

Univariate and multivariate analyses of risk factors for major CV events are detailed in Table 2. Smoking, obesity, RT site, IMNI, and the use of anthracycline, trastuzumab, or hormone therapy did not strongly affect the development of major CV events. Conversely, age >50 years, DM, HTN, dyslipidemia, CKD, and previous CVD were significantly associated with the development of such events. The multivariate analysis showed that HTN, CKD, and previous CVD were significantly associated with major CV events (p = 0.012, p = 0.013, and p < 0.001). However, DM was marginally associated with the development of these events (p = 0.097, Table 2).

3.4. Risk factors for developing CV events in patients who underwent left-sided RT

In the group without risk factors for CVD, the 10-year cumulative incidence of major CV events after left-sided RT and right-sided RT was 1.3 % and 0.0 % (p = 0.032) (Fig. 2B). The 10-year incidence of major CV events after left-sided and right-sided RT was 1.5 % and 3.4 % (p = 0.927) in the intermediate-risk subgroup, and 8.4 % and 13.7 % (p = 0.250) in the high-risk subgroup. The subgroup analysis of risk factors for CVD is presented in Fig. 3. In the group with risk factors for CVD, the incidence of major CV events was similar between left-sided and right-sided RT.

Dosimetry data were available for only 35 patients treated after January 2014. The mean breast volume was 394.1 ± 172.7 mL. Among the 21 patients receiving left-sided RT, the median mean heart dose was 192.8 cGy (range, 99.9–281.8 cGy), and the median mean left ventricle (LV) dose was 310.2 cGy (range, 153.1–548.2 cGy). The median LV volume receiving ≥25 Gy (LV V25Gy) was 2.65 % (range, 0–7.3 %). Three patients had LV V25Gy >4 %, a threshold previously associated with elevated CV risk [14]; however, none of them experienced clinically significant CV events. In contrast, patients with right-sided RT (N = 14) had substantially lower cardiac exposure (median mean heart dose, 39.60 cGy [range, 20.7–79.3 cGy]; median LV mean dose, 5.70 cGy [range, 1.7–21.7 cGy]), with LV V25Gy at 0 % [range, 0.0–0.0 %]) (Supplementary Table 2). Notably, none of the 35 patients in this subgroup experienced major CV events during follow-up.

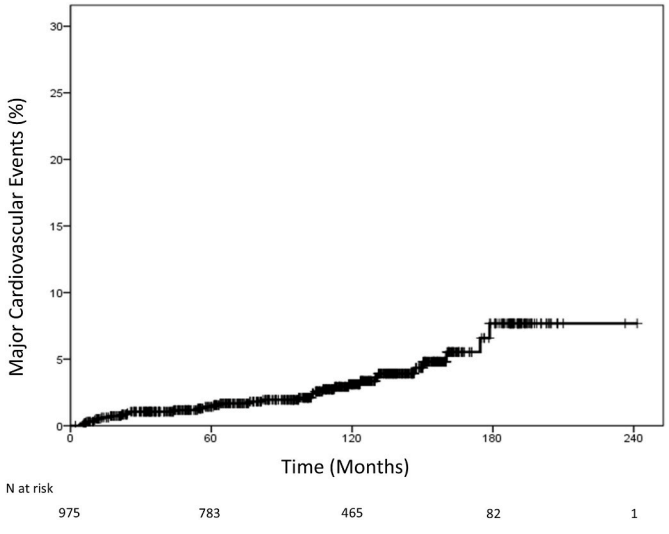

Fig. 1. Major cardiovascular events in the study population.
Cumulative incidence of major cardiovascular events.

4. Discussion

The 10-year incidence of major CV events in Asian BC patients undergoing RT was 3.7 %, and none of our patients died of cardiovascular causes during follow-up. Approximately two-thirds of our cohort had no identifiable risk factors for CVD. The number of CVD risk factors was positively correlated with the risk of major CV events. Multivariate analysis showed that HTN, CKD, and previous CVD strongly affected the risk of developing CV events. In the subgroup without CVD risk factors, the 10-year cumulative incidence of major CV events was significantly higher in patients who underwent left-sided RT than in those undergoing right-sided RT (1.3 % vs. 0.0 %, p = 0.032). In turn, in patients with identifiable CVD risk factors, there was no significant difference in this parameter between these two subgroups.

While the correlation between cardiotoxicity and breast RT has been extensively studied [3,4,6,7,9], the manifestations of cardiotoxicity may take more than 10 years, and many studies are based on RT treatments from an earlier era. Technological advancements in RT, the transitioning from Cobalt 60 to linear accelerators and from 2D to 3D and IMRT techniques, have reduced the incidence of CV events without using cardiac-sparing approaches [15]. The analysis of the Surveillance, Epidemiology, and End Results database has shown that left-sided breast RT does not increase long-term cardiac-related mortality [8,16]. A study evaluated cardiac morbidity for BC patients undergoing adjuvant RT from 1986 to 1993 and found no significant differences in the incidence of IHD, valvular heart disease, conduction abnormalities, and heart failure at 15 years post-radiation between patients with right-sided and those with left-sided BC [8]. Moreover, the incidence of myocardial infarction was higher in BC patients receiving left-sided RT treated before 1980 than in those treated after 1980 [9]. This result suggests that the adverse impact of RT on CV events decreases as RT techniques, CVD care, and risk reduction strategies improve. In our cohort, all patients were treated after 2004. The incidence of major CV events was modest, and none of our patients died from CV events. Evaluating the impact of RT on the incidence of CV events is challenging because the incidence is low. Among patients with underlying CVD risk factors, the risk of CV event was similar between patients undergoing left-sided or right-sided RT. This finding indicates that improvements in clinical care and treatment efficacy have decreased the incidence of CV events and the effect of RT on this incidence in this low-risk population.

We also assessed the interplay between underlying CVD risk factors and RT. In this aspect, a study evaluated the long-term cardiac risks associated with RT using randomized trial data and found that each Gy of radiation exposure to the heart increased the relative risk of heart disease mortality by 0.041 [17]. Further, this effect was more pronounced among smokers, such that the risk of IHD-associated death in those treated or not with left-sided breast RT with an average mean heart dose of 400 cGy was 9.2 % and 8 %. In non-smokers, the risk in these two subgroups was 2.1 % and 1.8 %. A Dutch registry study evaluated the association of underlying CVD risk factors (smoking, HTN, DM, history of IHD, and hypercholesterolemia) with RT and observed that smoking enhanced the effect of RT on the risk of myocardial infarction (HR of 3.04 vs. 1.34 for patients with or without RT, p = 0.039) [9]. These results indicated that only smoking was strongly associated with an increased risk of IHD obtained from RT [9,17], consistent with our findings since the risk of radiation-induced

Table 2
Cox regression analyses for the risk factors of major cardiovascular events.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
Age (≥ 50 vs. <50)	2.765 (1.241–6.158)	0.013[a]	1.185 (0.488–2.877)	0.708
Radiotherapy site (Left vs. Right)	0.953 (0.477–1.907)	0.892		
IMN irradiation (Yes vs. No)	1.144 (0.399–3.280)	0.803		
Mastectomy (Partial vs. Total)	0.569 (0.269–1.202)	0.139		
Smoking (Yes vs. No)	0.049 (0.000->9143)	0.782		
Obesity (Yes vs. No)	1.231 (0.532–2.846)	0.628		
DM (Yes vs. No)	3.823 (1.842–7.935)	<0.001[a]	1.971 (0.884–4.391)	0.097
Hypertension (Yes vs. No)	6.800 (3.273–14.129)	<0.001[a]	3.152 (1.284–7.735)	0.012[a]
Dyslipidemia (Yes vs. No)	2.328 (1.133–4.785)	0.021[a]	1.082 (0.505–2.317)	0.839
CKD (Yes vs. No)	11.602 (5.005–26.899)	<0.001[a]	3.229 (1.283–8.131)	0.013[a]
Previous CVD (Yes vs. No)	18.818 (8.027–44.114)	<0.001[a]	7.560 (2.876–19.872)	<0.001[a]
Anthracycline (Yes vs. No)	0.357 (0.137–1.928)	0.535		
Trastuzumab (Yes vs. No)	0.966 (0.433–2.151)	0.932		
Hormone therapy (Yes vs. No)	0.577 (0.278–1.198)	0.140		

Abbreviations: IMN, internal mammary nodes; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval.
[a] Statistically significant.

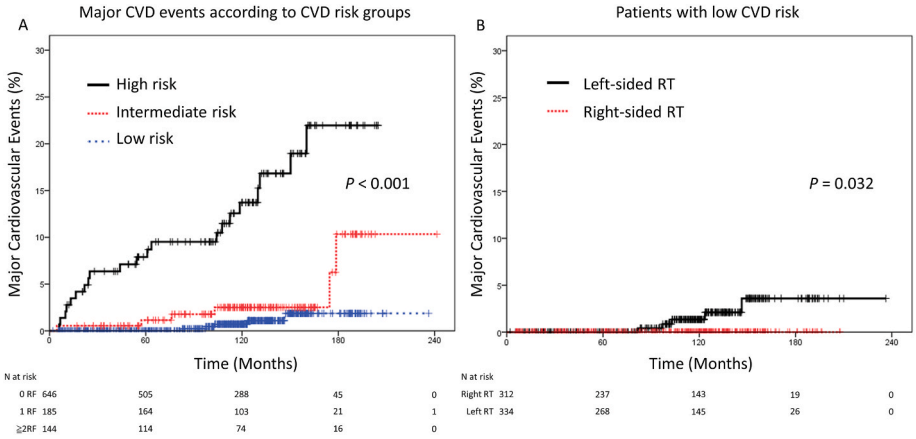

Fig. 2. Major cardiovascular events according to cardiovascular disease (CVD) risk groups.
(A) Cumulative incidence of major cardiovascular events based on the number of baseline risk factors for CVD: low risk (no identifiable risk factors), intermediate risk (one risk factor), and high risk (two or more risk factors).
(B) Cumulative incidence of major cardiovascular events in patients with a low risk of CVD who underwent left-sided or right-sided radiotherapy.

cardiotoxicity was similar between right-sided and left-sided RT groups among patients with DM, HTN, CKD, or a history of CVD events (smoking: only 0.6 % population in our cohort).

The baseline risk of CVD is lower in populations from East Asia (Japan, China, and Taiwan) than in populations from Western countries [13,18]. A distinctive feature of the Taiwanese population is the extremely low prevalence of smoking. A study from Taiwan showed that a high dose of RT to cardiac structures correlated with a higher risk of IHD [14]. The overall 10-year cumulative incidence of major ischemic events was 4.5 % (95 % CI, 3.5–5.6 %) [14]. The percentage of smokers was higher in their cohort than in ours (4.7 % vs. 0.6 %). The overall 10-year cumulative incidence of major CV events and IHD in our cohort was 3.7 % and 0.7 %, lower than in a previous study [14].

The generally low baseline CVD risk in Asian populations may have contributed to the negative findings when assessing RT-related cardiac toxicity. A Korean cohort with low rates of obesity (3.7 % with BMI >30 kg/m^2) and smoking (3.4 %) showed no clinically significant differences in the rates of acute coronary events between patients with breast cancer receiving left-sided RT and those receiving right-sided RT [19]. Similarly, a Singapore population-based study reported no differences in IHD-related mortality or overall mortality between left- and right-sided RT in patients with breast cancer [20]. Both studies mentioned above used acute coronary events and IHD-related mortality as primary endpoints. Given that modern RT techniques may further reduce RT-induced cardiac risks, we included symptomatic CV events such as arrhythmia and heart failure in our analysis, potentially enhancing the sensitivity to detect even subtle differences in CV events within this low-risk population.

In our cohort, the number of CVD risk factors was positively correlated with the risk of developing major CV events (Fig. 2A), which is consistent with the findings of two recent Korean cohort studies [21,22], in which a history of HTN, DM, or an underlying cerebrovascular accident was a risk factor for developing CV events. Conversely, the 10-year cumulative incidence of major CV events in the group without CVD risk factors was significantly higher in our patients who received left-sided RT than in those who received right-sided RT (1.3 % vs. 0.0 %, p = 0.032; Fig. 2B). These results suggest that the impact of RT sites on CVD risk is higher in patients without a smoking history or other baseline CVD risk factors, and that the effect of RT was higher in this low-risk group.

Several studies have discussed how radiation impacts different risk groups [23–25]. In BC, radiation in the absence of the DIBH technique increases the 10-year risk of CV events by 0.55 % [26], according to PROCAM 10-year CVD risk scores [23]. The baseline 10-year risk of CV event risk was 11.76 % and 3.11 % in patients with and without DM and 5.6 % and 3.2 % in patients with and without a smoking history [26].

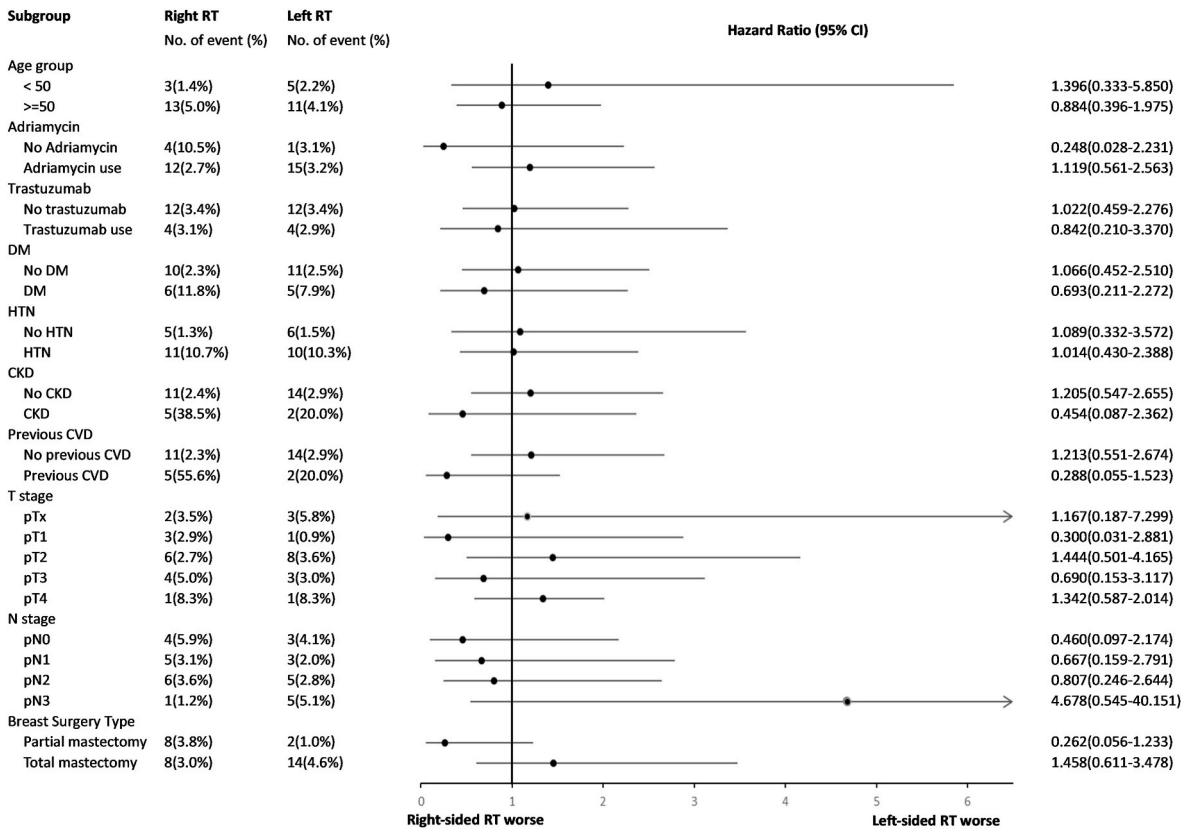

Fig. 3. Subgroup analysis of the effect of radiation on the risk of major cardiovascular events.
Forest plots showing hazard ratios and 95 % confidence intervals in a Cox proportional hazard model for major cardiovascular events in patient subgroups receiving left-sided or right-sided radiotherapy (RT).

However, in the presence of the DIBH technique, the additional risk from radiation decreased by 40 % (from 0.55 % to 0.35 %) [26]. Nonetheless, the effect of pre-existing CVD on 10-year CVD risk was stronger than that of radiation exposure [26]. In our cohort, only 9.8 % of patients underwent IMNI, and this irradiation did not significantly influence cardiotoxicity. The reduced use of IMNI, combined with a low overall incidence of CV events, can explain why the additional radiation dose to the heart was not associated with major CV events. According to the results of the Danish Breast Cancer Cooperative Group study [24], the mean heart dose during tangential breast irradiation was 240 cGy, lower than the dose of 540 cGy administered to patients receiving left-sided RT with regional nodal irradiation [24]. Our cohort also received tangential breast or chest wall irradiation using the forward FiF IMRT technique. Such variations in heart dose across studies could account for the differences in therapeutic outcomes.

Although this cohort received breast regional nodal irradiation, less than 10 % received IMNI, and most patients underwent tangential breast or chest wall irradiation. Our dosimetry analysis of a subgroup treated after 2014 revealed that the median mean heart dose was relatively low (median 192.8 cGy [range, 99.9–281.8 cGy]) for left-sided breast irradiation. Therefore, the heart dose in our cohort may be more comparable to that in patients with early-stage BC than to that in patients with locally advanced disease. This relatively low heart dose may partly explain the modest incidence of major CV events observed in our study. To analyze the impact of different treatment techniques, fields, and heart doses on CV outcomes in similar Asian cohorts, we compared our results with those of Lai et al. [14] and Chung et al. [21]. In Lai et al.'s cohort, 96.1 % of the patients received 3D conformal RT, and only 0.9 % received IMNI. The routine use of DIBH in left-sided RT resulted in a relatively low median mean heart dose (267 cGy) compared with that in Chung et al.'s cohort, in which DIBH was not applied, and a higher proportion of IMNI was administered, resulting in a higher median mean heart dose of 629 cGy. However, both studies showed a relatively low incidence of CV events (10-year breast cancer-related heart disease incidence of 5.7 % in the Chung study vs. a 10-year major ischemic heart disease incidence of 4.5 % in the Lai study). Our limited dosimetric data revealed results (left-sided RT, median mean heart dose of 192.8 cGy [range, 99.9–281.8 cGy]) similar to those reported by Lai et al., in which the 10-year CV event rate was 3.7 %. Taken together, these findings suggest that although the heart dose of RT influences CV event risk, the absolute risk remains comparatively low in Asian populations, especially when compared to Western cohorts [24].

All our patients were treated with 3D conformal or forward FiF IMRT planning, and none received VMAT. VMAT is being increasingly used in BC treatment as it provides better regional nodal coverage and reduces the radiation dose to the heart and coronary arteries, but increases low-dose exposure of RT to the lung [25,27]. During our study period (between 2004 and 2014), modern heart-sparing techniques such as DIBH and VMAT were not standard practices and thus were not used in our cohort. The routine application of these techniques in the future could further reduce cardiac exposure to radiation doses, particularly in patients without baseline CVD risk factors who appear more sensitive to left-sided RT. Further longitudinal studies are required to confirm the effectiveness of DIBH and VMAT in reducing long-term CV events in patients with BC undergoing left-sided RT.

In patients with a higher baseline CVD risk, traditional factors, such as HTN, diabetes, dyslipidemia, or previous CVD incidents, may overshadow the relative contributions of RT. In contrast to patients with a higher baseline CVD risk, patients with a lower risk might receive less frequent cardiovascular monitoring and follow-up, and have delayed the detection of symptomatic CV events. Considering the relatively fewer effects of CV events contributed by underlying CVD risk factors, the

increased number of CV events observed in patients with low-risk factors undergoing left-sided RT than in those receiving right-sided RT reflects the impact of RT. These findings highlight the need for personalized RT planning and careful long-term cardiac surveillance, even among patients initially classified as having a low CVD risk.

This study has limitations. First, the study's single-center retrospective design may lead to patient selection bias, suggesting that the selection bias may potentially influence the results. Second, the percentage of smokers was low in our cohort and may not accurately reflect the general Asian population with BC. Furthermore, despite the long follow-up, some patients were lost to follow-up because of the study's retrospective nature, potentially underestimating the rates of survival and CV events and limiting the power of the study. The baseline characteristics of the patients lost to follow-up were comparable to those of the patients who remained in the study (Supplementary Table 3), suggesting a limited impact on the overall findings. Despite the use of multivariate analysis to identify risk factors for RT-induced CV events in our patients, residual confounding factors from unmeasured or inadequately assessed variables could not be completely ruled out.

Additionally, CV events were retrospectively identified from medical records, and asymptomatic or mildly symptomatic cases may have been underreported because routine follow-ups by cardiovascular specialists were not performed unless clinically indicated. Because echocardiography and EKG were performed only when the patients became symptomatic, our follow-up strategy was inherently reactive rather than proactive. Although this reflects real-world practice in many centers, it almost certainly leads to the under-recognition of asymptomatic or subclinical cardiotoxicity, such as early left ventricular dysfunction, silent ischemia, or subclinical arrhythmias, which may be detected by scheduled cardiac imaging or biomarker surveillance. Our results may have been skewed toward an underestimation of CV events because outcome ascertainment depended on patient-reported information at follow-up and institutional EMRs, which may have overlooked the cardiac procedures performed outside our hospital network unless patients disclosed CV-related symptoms. Although our network's outpatient interactions were recorded, this symptom-driven surveillance probably failed to identify subclinical or externally managed incidents, which could explain the low number of CV events in our study.

Another anatomical factor that may have contributed to the relatively low CV event rate in our cohort was the breast volume. The mean breast volume in our patients was 394.1 ± 172.7 mL, which is lower than those typically reported in Western populations. For example, a recent MRI-based study of Western women demonstrated a mean unilateral breast volume of approximately 764–771 mL, which clearly exceeds our cohort average [28]. Similarly, a large normative dataset of 356 women measured using 3D scanning revealed a broad distribution ranging from 48 to 3100 mL, with breast size substantially increasing with BMI [29]. Importantly, breast size has been shown to influence the cardiac dose. Regardless of other treatment parameters, the mean cardiac dose increased by 1.5–1.7 % for every centimeter of breast separation beyond 22 cm, as reported in a multicenter registry of 4688 patients [30]. These findings support the hypothesis that smaller breast volumes in Asian patients may allow for a more advantageous dosimetry distribution, including sparing the heart, which, in turn, may help explain our cohort's lower observed risk of radiation-associated CV events.

Consequently, the incidences reported here likely represent a conservative estimate of the true cardiotoxic burden. Prospective studies incorporating routine protocol-driven cardiac assessments (e.g., serial echocardiography with global longitudinal strain, cardiac biomarkers, or stress testing) are required to fully characterize the spectrum of radiation-associated cardiac injury in this population. However, all identified CV events were centrally reviewed by a cardiologist to ensure consistency in the diagnostic criteria and reporting of CV events. This review enhanced the consistency and reliability of our retrospective identification of RT-induced CV events.

Owing to the replacement of our treatment planning system in January 2014, comprehensive dosimetry for cardiac structures was only retrievable for a subset of 35 patients treated thereafter. This limited dataset restricted our ability to robustly evaluate the dose-response relationships between cardiac radiation exposure and CV events in our patients. The median mean heart dose was 192.8 cGy for 21 patients receiving left-sided RT (Supplementary Table 2). The absence of observed CV events within this subset further constrained meaningful correlation analyses. Notably, all three patients whose LV V25Gy exceeded the previously suggested 4 % threshold remained event-free; however, the absence of events in such a small sample should be interpreted cautiously, as it precludes any definitive conclusions regarding the validity of this cut-off in our population. To substantiate, or refine, dose constraints such as LV V25Gy >4 %, future studies must include a substantially larger cohort with complete dosimetric data and a sufficient number of observed cardiovascular events. Future prospective studies with complete dosimetric assessments of the mean dose of the heart and LV and percentage of LV V25Gy of patients receiving left-sided whole breast or chest wall RT using the forward FiF IMRT technique are necessary to better define the relationship between cardiac substructure dose and IHD in Asian patients. Despite a substantial median follow-up of 9.9 years, cardiotoxicity may manifest beyond this timeframe (>10 years), potentially underestimating long-term risks. Future analyses with longer follow-up periods are warranted to fully capture late-onset CV events.

In summary, our results indicate that the 10-year cumulative incidence of major CV events was lower in an Asian population with a low baseline risk of CVD. Left-sided RT had a stronger effect on the incidence of CV events in patients without underlying CVD risk factors than in those with pre-existing risk factors. A summary of the study design and main findings is presented in the **graphical abstract.** This result highlights the need to perform personalized risk assessments in RT planning to decrease heart irradiation in patients with BC who need adjuvant RT. The study advocates for individualized dosage adjustments during RT, particularly in patients more susceptible to the effects of RT, such as those with a low risk of CVD. These modifications can enhance the efficacy and specificity of treatment interventions by catering to patients' needs. Importantly, these conclusions were drawn in a real-world setting, one in which cardiac assessments were performed reactively rather than on a fixed protocol and where retrospective retrieval of complete dosimetric data was not possible for a portion of the cohort. Such pragmatic constraints mirror routine clinical practice and lend external validity to our findings; however, they also suggest that the reported cardiotoxicity rates are likely conservative estimates, reinforcing the need for prospective, systematically monitored studies to refine risk thresholds and heart-sparing strategies. In the future, truly personalized RT planning should integrate each patient's baseline cardiovascular profile with tailored heart-dose constraints and individualized post-treatment cardiac surveillance to ensure that therapeutic choices maximize tumor control while minimizing long-term cardiac risk.

CRediT authorship contribution statement

Wen-Chi Yang: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yu-Hsuan Chen:** Resources, Investigation. **Chia-Chun Wang:** Resources, Formal analysis. **Shih-Fan Lai:** Resources, Formal analysis. **Szu-Huai Lu:** Methodology, Investigation, Formal analysis. **Li-Ting Ho:** Methodology, Investigation, Formal analysis. **Chiun-Sheng Huang:** Supervision, Resources. **Sung-Hsin Kuo:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Conceptualization.

Declaration of competing interests statement

Wen-Chi Yang had no potential conflict of interest to disclose.

Yu-Hsuan Chen had no potential conflict of interest to disclose.
Chia-Chun Wang had no potential conflict of interest to disclose.
Shih-Fan Lai had no potential conflict of interest to disclose.
Szu-Huai Lu had no potential conflict of interest to disclose.
Li-Ting Ho had no potential conflict of interest to disclose.
Chiun-Sheng Huang had no potential conflict of interest to disclose.
Sung-Hsin Kuo had no potential conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104581.

Data availability

The data presented in this article are represented in the main text. Additional information can be shared after reasonable request to the corresponding author.

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