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Original article

Cardiovascular outcome of breast cancer patients with concomitant radiotherapy and chemotherapy: A 10-year multicenter cohort study

Do Young Kim (MD)[a,b,1], Jong-Chan Youn (MD, PhD)[a,1,*], Myung-Soo Park (MD)[a], Sunki Lee (MD, PhD)[a], Suk-Won Choi (MD, PhD)[a], Kyu-Hyung Ryu (MD, PhD)[a], Lee Su Kim (MD, PhD)[c], Man-Shik Shim (MD)[d], Jae Jin Lee (MD, PhD)[d,**], Seongwoo Han (MD, PhD)[a,*]

[a] Division of Cardiology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea
[b] Division of Cardiology, Korea University Anam Hospital, Seoul, Republic of Korea
[c] Division of Breast and Endocrine Surgery, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea
[d] Department of Thoracic and Cardiovascular Surgery, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Republic of Korea

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ABSTRACT

Background: Cancer treatment increases the risk of cardiovascular (CV) events. However, the long-term CV outcome of breast cancer patients who undergo radiotherapy and chemotherapy concomitantly is unknown. This study aimed to determine the incidence and risk factors of CV events among these patients.
Methods: Six hundred sixty consecutive breast cancer patients older than 50 years from November 2005 to September 2015, were enrolled in four university hospitals. The primary endpoint was CV events including CV mortality, myocardial infarction, heart failure, and stroke. CV events occurred in 14 (2.1%) patients during the follow-up period (median, 47.1 months).
Results: Left-side irradiation was associated with increased risk of CV events in patients with doxorubicin dose $\geq$250 mg/m^2 but not in patients with doxorubicin dose $<$250 mg/m^2. On multivariable analysis, concomitant left-side irradiation with doxorubicin dose $\geq$250 mg/m^2 and hypertension were independent risk factors for CV events.
Conclusion: The risk of CV events was further increased with concomitant left-side irradiation and doxorubicin $\geq$250 mg/m^2 in breast cancer patients.

Introduction

Breast cancer is the most common malignancy in women worldwide, and its prevalence is increasing globally [1]. Advancements in breast cancer therapy have led to a significant improvement in breast cancer-specific survival [2]. However, there are some concerns regarding breast cancer therapy-related cardiac morbidity and mortality [3]. Previous studies have shown that radiation therapy (RT) increases the risk of cardiovascular (CV) diseases [4,5]. Although some studies reported that contemporary RT was not associated with a higher risk of CV disease [6,7], exposure of radiation to the heart is unavoidable, even with modern radiation techniques [8]. Furthermore, the additive or synergistic effect of chemotherapy on radiotherapy can induce cardiac injury. However, data on CV outcome of concomitant radiotherapy and chemotherapy are limited [3,9]. Hence, we evaluated the incidence and risk factors of CV events in breast cancer patients with concomitant radiotherapy and chemotherapy.

Materials and methods

Study population

We retrospectively investigated consecutive breast cancer patients treated at Hallym University Medical Center and four

* Corresponding authors at: Division of Cardiology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Keunjaebong-gil 7, Hwaseong-si, Gyeonggi-do 18450, Republic of Korea.
** Corresponding author at: Department of Thoracic and Cardiovascular Surgery, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Keunjaebong-gil 7, Hwaseong-si, Gyeonggi-do 18450, Republic of Korea.
E-mail addresses: jong.chan.youn@gmail.com (J.-C. Youn), jj58lee@hallym.or.kr (J.J. Lee), hansw29@hallym.or.kr (S. Han).
[1] Do Young Kim and Jong-Chan Youn contributed equally as first authors.

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affiliated hospitals (Hallym University Sacred Heart Hospital, Kangnam Sacred Heart Hospital, Chuncheon Sacred Heart Hospital, and Dongtan Sacred Heart Hospital) in Korea between November 2005 and September 2015. Female breast cancer patients (age ≥50 years) who underwent radiotherapy and with a follow-up duration of at least 240 days were included. Exclusion criteria were breast cancer in male patients and patients who had surgical treatment, radiotherapy, or chemotherapy in another hospital without accurate treatment information (Fig. 1). We examined stages and pathologic types of breast cancer, types of breast cancer surgery, cumulative anthracycline doses (converted into doxorubicin-equivalent dose) and radiation dose and field, co-morbidities including hypertension (HTN), diabetes mellitus (DM), chronic kidney disease, and atrial fibrillation, past history of myocardial infarction (MI), heart failure (HF), and stroke, and CV events after breast cancer treatment. The investigation conformed to the principles outlined in the Declaration of Helsinki and all data were anonymized. The study protocol was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB number 2017-101-I).

Variable selection for predicting CV events

We used irradiation laterality as a surrogate risk factor of radiation, because left-sided-irradiated patients receive a higher dose of radiation to the heart than those with right-sided-irradiation [10,11]. The doxorubicin-equivalent dose was categorized as <250 mg/m^2 (including patients without anthracycline therapy) and ≥250 mg/m^2. To set up the cut-off value of doxorubicin equivalent dose as 250 mg/m^2, we considered that doxorubicin cumulative dose of usual adjuvant chemotherapy regimen is 240 mg/m^2 (6 cycles of 40 mg/m^2 of doxorubicin) [12] and expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy recommended additional evaluation of left ventricle function at each cycle of chemotherapy for patients who are planned to have doxorubicin-containing chemotherapy exceeding 240 mg/m^2 of doxorubicin cumulative dose [13]. Secondly, the earliest step up in CV events is observed between 250 and 350 mg/m^2 and cancer survivors exposed to doxorubicin of doses of 250 mg/m^2 or more have a significantly higher risk of anthracycline-induced cardiomyopathy [14,15]. Thirdly, expert consensus suggested that doxorubicin dose ≥250 mg/m^2 is considered as a high-dose therapy with high risk of developing cardiac dysfunction [16]. Therefore, we suggested that ≥250 mg/m^2 would be an appropriate cut-off value of doxorubicin equivalent cumulative dose.

Definition of CV events

The primary endpoint was CV events, including CV mortality, MI, HF, and stroke. MI was defined as (i) typical ischemic chest pain lasting for more than 30 min, (ii) significant ST-segment elevation or depression in two contiguous leads in a standard 12-lead electrocardiogram, (iii) either elevation of the creatine kinase-MB isoform to more than twice the normal upper limit or a rise in troponin T exceeding 0.1 ng/ml. Patients who displayed rapid onset of signs or symptoms of HF with elevated N-terminal fragment of B-type natriuretic peptide (NT-pro BNP) or B-type natriuretic peptide (BNP) level and one of the following criteria were considered to have had an HF event: (i) lung congestion or (ii) objective findings of left ventricular systolic dysfunction or structural heart disease. Cut-off points of NT-pro BNP and BNP for diagnosis HF were ≥125 pg/ml and ≥35 pg/ml, respectively [17]. Lung congestion was defined as “congestion” on chest radiography or as rales on physical examination. Stroke was defined as an episode of relevant focal deficits with acute onset, documented by neurological examination and lasting >24 h. All medical records of patients with CV events were reviewed and validated by an independent adjudication committee.

Formula of the doxorubicin-equivalent dose

We used the following formulas from a previous report [18] to convert to the doxorubicin isotoxic equivalent dose before calculating the total cumulative anthracycline dose: for doxorubicin, we used the total dose; for daunorubicin, we multiplied the total dose by 0.5; for epirubicin, we multiplied the total dose by 0.5; and for idarubicin, we multiplied the total dose by 2.

Statistical analysis

Normally distributed continuous variables were expressed as mean and standard deviation, and categorical data were expressed as numbers and percentages. Non-parametrically distributed data were reported as median values with interquartile ranges. For comparison across groups, continuous variables were compared using the Student's *t*-test or analysis of variance, as appropriate, and categorical variables were analyzed using the chi-square test

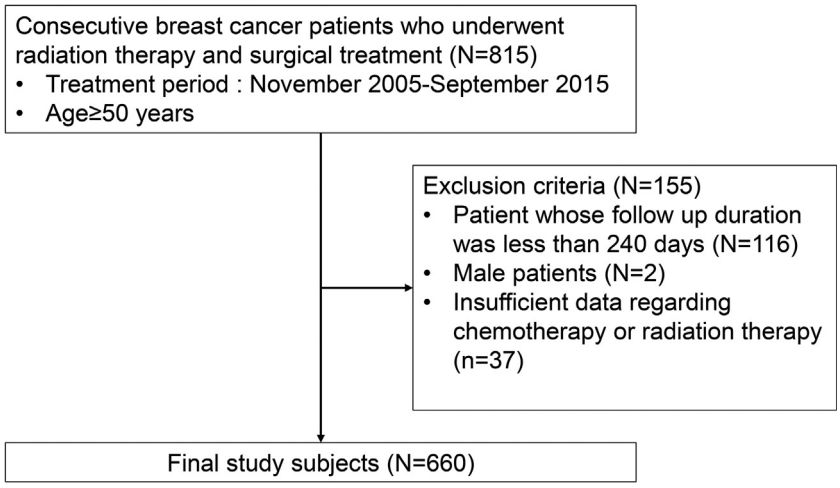

Fig. 1. Flow diagram of the study.

or Fisher's exact test, as appropriate. Survival data were analyzed by the Kaplan–Meier method using the log-rank test. Univariate Cox proportional hazards regression analysis was performed to identify the variables that were statistically significant for predicting CV events. A multivariate Cox proportional hazards regression analysis model was used to investigate the independent risk factors of CV events. Variables which showed p-value 0.05 or less than 0.05 from the univariate Cox proportional hazards regression analysis model were included in the multivariate Cox regression models. Anthracycline is inheritably continuous variable. However, categorical value might have more clinical implications when clinicians do risk-stratification of breast cancer patients. Consequently, anthracycline was categorized by doxorubicin equivalent dose of <250 mg/m^2 or ≥ 250 mg/m^2. Common covariates which were included in the Cox regression model were HTN, DM, and prior MI. Age was not included in the models because it did not have enough power to be included in the multivariate models with current inclusion criteria (age ≥ 50 years). For the competing risk analysis, cumulative incidence of CV events and non-cardiac deaths were estimated using Gray's method in the competing risk setting and non-CV deaths were treated as competing risks of CV events. Time-dependent receiver-operating characteristic (ROC) curves and the c-index at 5 years for censored survival data were used to quantify the discriminative abilities of each risk factor in the prediction of CV events [19]. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed by R version 3.2.1 (Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. The mean age was 59.2 ± 8.1 years, and the median follow-up duration was 47.1 (interquartile range, 24.4–67.3) months. The overall prevalence of HTN and DM was 25.9% and 13.5%, respectively.

All subjects underwent surgical treatment and RT. The most frequent type of surgery was breast-conserving surgery (78.8%), followed by radical mastectomy (20.4%). Palliative surgery was performed in 0.8% of the study subjects. The median total radiation dose was 61.0 (interquartile range, 50.0–61.0) Gy. Seventy-seven percent of the study population had chemotherapy and 66.4% of patients underwent chemotherapy with anthracycline. Among patients with anthracycline treatment, those who had chemotherapy with doxorubicin or epirubicin were 67.6% and 32.4%, respectively. The median cumulative doxorubicin-equivalent dose was 240.0 mg/m^2, and 0.6% of subjects had anthracycline at a cumulative doxorubicin-equivalent dose >400 mg/m^2.

Causes of deaths in breast cancer patients

All-cause deaths occurred in 21 patients (3.2%) during the follow-up period. Of the subjects, 2 CV deaths and 10 non-CV deaths occurred within 4 years after RT. Nine non-CV deaths occurred 5 or more years after RT. Cancer ($n = 14$, 2.1%), was the most common cause of death, followed by infection ($n = 3$, 0.5%) and CV disease ($n = 2$, 0.3%).

Risk factors for CV events in breast cancer patients

In this study, 14 CV events (2.1%) occurred during the median follow-up duration of 47.1 months. Among 14 subjects with CV events, 11 CV events occurred within 4 years.

Table 1
Baseline characteristics of the study population.

	Value ($n = 660$)
Age (years)	59.2 ± 8.1
HTN, n (%)	171 (25.9)
DM, n (%)	89 (13.5)
CKD, n (%)	11 (1.7)
Atrial fibrillation, n (%)	3 (0.5)
Prior MI, n (%)	7 (1.1)
Prior HF, n (%)	5 (0.8)
Prior stroke, n (%)	22 (3.3)
Follow-up duration (months)	47.1 [24.4–67.3]
Cancer stage, n (%)	
0	10 (1.5)
I	278 (42.1)
II	245 (37.1)
III	121 (18.3)
IV	6 (0.9)
Stage 0 or I, n (%)	288 (43.6)
Total radiation dose (Gy)	61.0 [50.0–61.0]
Left or both side irradiation, n (%)	305(46.2)
Type of surgical treatment, n (%)	
BCS	520 (78.8)
Radical mastectomy	135 (20.4)
Others	5 (0.8)
Chemotherapy, n (%)	513 (77.7)
Use of anthracycline, n (%)	438 (66.4)
Doxorubicin equivalent dose (mg/m^2)	240.0 [0.0–250.0]
Doxorubicin equivalent dose ≥ 400 mg/m^2	4 (0.6)
Use of trastuzumab, n (%)	130 (19.7)
Patients with CV event, n (%)[a]	14 (2.1)
HF, n (%)	6 (0.9)
MI, n (%)	2 (0.3)
Stroke, n (%)	6 (0.9)
Cardiac death, n (%)	2 (0.3)

Values are presented as mean $\pm$ standard deviation, n (%), or median [interquartile ranges].
HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; MI, myocardial infarction; HF, heart failure; Gy, Gray; BCS, breast-conserving surgery; CV, cardiovascular.
[a] One patient experienced MI and HF developed following MI and one other patient was diagnosed with HF and died of HF.

Left-side or bilateral irradiation with a cumulative doxorubicin-equivalent dose ≥ 250 mg/m^2 [hazard ratio (HR), 5.17; 95% confidence interval (CI), 1.97–16.53; $p = 0.001$], HTN (HR, 3.87; 95% CI, 1.34–11.17; $p = 0.01$), and DM (HR, 3.73; 95% CI, 1.25–11.14; $p = 0.02$) were significantly associated with the development of CV events in the univariate Cox regression analysis. Age, irradiation side, total radiation dose, anthracycline at a cumulative doxorubicin-equivalent dose ≥ 250 mg/m^2 or trastuzumab use did not show significant association with CV event development in the univariate Cox regression model (Table 2). The result of the multivariate Cox regression model for CV events is listed in Table 2. Left-side or bilateral irradiation with anthracycline treatment at a cumulative doxorubicin-equivalent dose ≥ 250 mg/m^2 (HR, 6.99; 95% CI, 2.34–20.85; $p < 0.001$) and HTN (HR, 4.25; 95% CI, 1.47–12.29; $p = 0.01$) were selected as independent predictors of future CV events. Figure 2A shows the unadjusted survival curves comparing the right-side RT group with the left-side RT group among patients with doxorubicin ≥ 250 mg/m^2. In the subgroup analysis of patients with doxorubicin ≥ 250 mg/m^2, left- or both-side irradiation was significantly associated with CV events in the multivariate Cox regression model adjusted with HTN, prior MI, DM, and doxorubicin dose (HR, 8.54; 95% CI, 1.02–71.63; $p = 0.048$). By contrast, unadjusted survival curves of patients with doxorubicin <250 mg/m^2 did not show significant effect of left-side irradiation on CV event-free survival rate (Fig. 2B).

Table 2
Univariate and multivariate Cox proportional hazard analysis for CV events in breast cancer patients with radiotherapy.

	Univariate analysis		Multivariate analysis model	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.01 (0.95–1.08)	0.68		
HTN	3.87 (1.34–11.17)	0.01	4.25 (1.47–12.29)	0.01
DM	3.73 (1.25–11.14)	0.02	2.09 (0.60–7.34)	0.25
CKD	5.44 (0.71–41.68)	0.10		
Prior MI	7.39 (0.97–56.57)	0.05	4.21 (0.46–38.73)	0.20
Prior stroke	2.17 (0.28–16.59)	0.46		
Stage 0 or I	0.52 (0.16–1.60)	0.27		
Total radiation dose (Gy)	0.94 (0.87–1.00)	0.14		
Dox $\geq$250 mg/m^2	2.04 (0.71–5.88)	0.19		
Use of Trastuzumab	1.82 (0.570–5.83)	0.31		
Left RT[a]	2.26 (0.76–6.75)	0.14		
Left RT[a] + Dox $\geq$250 mg/m^2	5.17 (1.97–16.53)	0.001	6.99 (2.34–20.85)	<0.001

CV, cardiovascular; HR, hazards ratio; CI, confidence interval; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; MI, myocardial infarction; Gy, Gray; Dox, cumulative doxorubicin equivalent dose; RT, radiation therapy.
[a] Left RT included left-sided and bilaterally irradiated subjects.

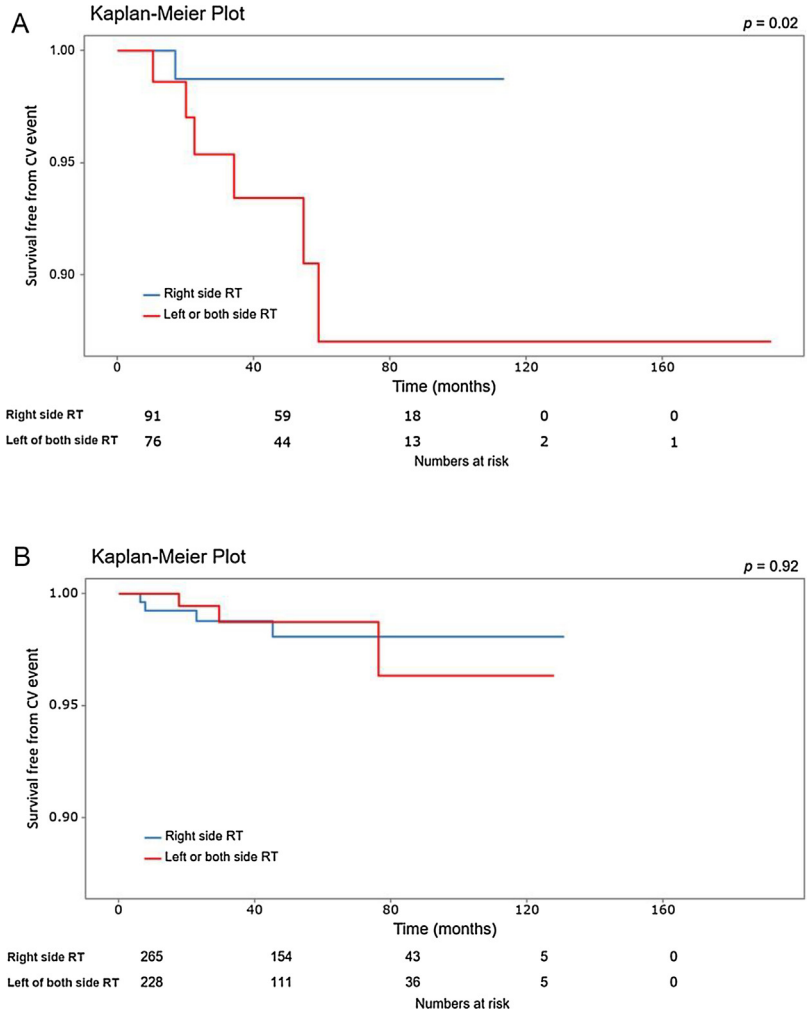

Fig. 2. Kaplan–Meier estimates of CV event-free survival rate in patients with accumulative doxorubicin dose $\geq$250 mg/m^2 (A) and accumulative doxorubicin dose <250 mg/m^2 (B) according to irradiation laterality. CV, cardiovascular; RT, radiation therapy.

Incidence rates and HR of CV events according to irradiation side and doxorubicin dose are shown in Table 3. Left-sided irradiation with cumulative doxorubicin-equivalent dose $\geq$250 mg/m^2 showed a higher incidence rate of CV events and was associated with a higher risk of CV events as compared with right-sided irradiation plus cumulative doxorubicin-equivalent dose <250 mg/m^2 (HR, 5.22; 95% CI 1.67–21.15; $p = 0.006$).

Further multivariate analyses showed that concomitant use of left or bilateral irradiation with doxorubicin equivalent dose $\geq$250 mg/m^2 was a significant predictor of HF (HR, 30.79; 95% CI

Table 3
Multivariate Cox regression analysis for CV events according to doxorubicin equivalent dose and laterality of irradiation.

	Incidence rate[a]	HR (95% CI)[b]	p
Doxorubicin dose			
Dox <250 mg/m^2	0.36	Reference	
Dox ≥250 mg/m^2	0.97	2.43(0.81–7.29)	0.11
RT side			
Right RT	0.33	Reference	
Left RT	0.76	2.38(0.80–7.11)	0.12
Doxorubicin dose with RT side			
Right RT + Dox <250 mg/m^2	0.37	Reference	
Left RT[c] + Dox <250 mg/m^2	0.34	1.00(0.22–4.47)	0.99
Right RT + Dox ≥250 mg/m^2	0.24	0.83(0.09–7.62)	0.87
Left RT[c] + Dox ≥250 mg/m^2	1.95	6.57(1.77–24.33)	0.005

CV, cardiovascular; HR, hazards ratio; CI, confidence interval; Dox, cumulative doxorubicin equivalent dose; RT, radiation therapy; HTN, hypertension; MI, myocardial infarction.
[a] CV events per 100 person-years.
[b] Adjusted for HTN and prior MI.
[c] Left RT included left-sided and bilaterally irradiated subjects.

3.43–276.24; $p = 0.002$) and a composite of MI and stroke events (HR, 5.09; 95% 1.21–21.4; $p = 0.03$) with adjustment of HTN, MI, and DM.

To account for the competing risk of non-CV deaths, the competing risk analysis was performed. Online Figs. 1 and 2 show the cumulative incidence of CV events and non-CV deaths, respectively among left-side irradiated patients with doxorubicin-equivalent dose ≥250 mg/m^2 versus rest of the population. The cumulative incidence of CV events was significantly higher among the left-side irradiated patients with doxorubicin-equivalent dose ≥250 mg/m^2 group ($p < 0.001$) and the cumulative incidence of competing risk (non-CV deaths) was not significantly different ($p = 0.189$) between two groups.

Performance of combination risk factor with irradiation laterality and doxorubicin dose in discriminating breast cancer patient with high risk of CV events

Finally, we examined the c-indexes of irradiation laterality, doxorubicin, and combination risk factors with irradiation laterality and doxorubicin dose to assess the performance of each risk factor in discriminating breast cancer survival with high CV risk. The time dependent c-index of left- or both-sided irradiation plus doxorubicin dose of 250 mg/m^2 or greater than 250 mg/m^2 was 71.0 (95% CI 57.26–86.0; $p < 0.001$). The c-indexes of doxorubicin dose of ≥250 mg/m^2 or left-sided irradiation alone were 62.03 (95% CI 47.47–80.34; $p < 0.001$) and 61.94 (95% CI 48.65–75.23; $p < 0.001$), respectively. The c-index of the left-sided irradiation plus doxorubicin dose ≥250 mg/m^2 was significantly superior to those of the left-sided irradiation or doxorubicin dose ≥250 mg/m^2 (both $p < 0.001$).

Discussion

We evaluated the prevalence and risk factors of CV events in consecutive cohort of breast cancer patients with concomitant radiotherapy and chemotherapy. In this retrospective cohort study, left-side irradiation, itself showed limited effect on the incidence of CV events. However, the effect of left-side irradiation on the incidence of CV events was significant in patients with a cumulative doxorubicin dose ≥250 mg/m^2. Left-side irradiation with a cumulative doxorubicin equivalent dose ≥250 mg/m^2 was a significant risk factor for CV events and was an independent predictor of both HF and a composite of MI and stroke events which could be assumed as an atherosclerotic event during mean follow up duration of 47.1 months.

Breast cancer patients who had left-side irradiation generally receive a higher dose of radiation to the heart than those with right-side irradiation [10,11]. Previous studies used irradiation laterality as a surrogate for cardiac exposure to radiation [20] and demonstrated that increased CV risk is associated with left-side irradiation compared with right-side irradiation [21–24]. However, recent studies demonstrated that RT laterality may have no influence on CV risk in breast cancer patients and the risk has decreased since the 1980s or later [21,25]. Studies that showed the hazard of left-side irradiation included patients treated in the 1970s or earlier, when older RT techniques were used, which exposed a higher volume of the heart and lungs to larger doses of irradiation than current standard tangential beams [25]. Therefore, these inconsistent results could be explained by advancements in RT techniques, which led to a significant decrease in radiation dose to the heart since the 1980s [21,25]. Although the cardiac hazard of RT has generally decreased, the risk of RT-related CV events cannot be avoided completely [10] and the risk can be increased by concomitant use of chemotherapy [26]. In a study by Shapiro et al., the investigators showed that the cardiac risk with high-dose anthracycline (cumulative doxorubicin dose, 450 mg/m^2) was further increased in patients who had left-side irradiation, as compared with those who had right-side irradiation [26]. The result of our study also suggests that the CV risk of radiation can be further increased by concomitant use of anthracycline. Historically, there have been concerns for the lifetime cumulative doxorubicin dose exceeding 400 mg/m^2 because the incidence of HF increases steeply and reaches 3–5% at a cumulative dose of 400 mg/m^2 [25,27]. Recent reports, however, showed that CV events or cardiomyopathy could be increased at doxorubicin of doses of 250 mg/m^2 [14,15] and an expert consensus considered doxorubicin dose ≥250 mg/m^2 as a risk factor of cardiac dysfunction in survivors of cancer [16]. Our study appears to be meaningful in showing that left-side irradiation may increase CV risk even in breast cancer patients with anthracycline therapy exceeding the cumulative doxorubicin-equivalent dose of 250 mg/m^2.

Possible explanation for the additive or synergistic effect of the RT and the anthracycline on CV risk is not well known [3]. One possible explanation could be that both RT and anthracycline-induced cardiac injuries are mediated by reactive oxygen species at a cellular level [3,28] and concomitant RT and anthracycline may have an additive impact on a cellular injury. Another explanation is the RT-induced myocardial fibrosis. The RT accelerates atherosclerosis of coronary artery which leads to ischemic heart disease. On a microvascular level, RT leads to a decrease in capillary density which can lead to myocardial fibrosis [3,29]. HF involves pathological myocardial remodeling characterized by excessive deposition of myocardial fibrosis which decreases tissue compliance and contractile dysfunction [30]. Therefore, the RT-induced myocardial fibrosis can contribute to the development of anthracycline-induced HF. Our study also showed that HTN is an independent risk factor of CV events in breast cancer patients who underwent modern RT. In a previous study, HTN was associated with a higher risk of CV events in left-side-irradiated patients [9]. Therefore, early diagnosis and proper management of blood pressure may reduce the risk of CV events in breast cancer patients [3].

In our study, CV events increased significantly among the left-side irradiated patients with anthracycline therapy exceeding the cumulative doxorubicin-equivalent dose of 250 mg/m^2 during the median follow-up duration of 47.1 months. Previous reports suggested that the risk of CV diseases would increase significantly at least 10 years after radiation exposure [3,31]. However, more recent data suggest that the onset of CV events after concomitant chemotherapy and irradiation is sooner than the onset of earlier reports and lasts over 20 years [10,32]. This observed discrepancy

may reflect improvement in breast cancer-specific mortality, which put more breast cancer survivors at risk for cancer treatment-related CV diseases [3]. Besides, early-onset anthracycline-induced cardiomyopathy can develop within 1 year of treatment [3,16]. Recent studies showed that earlier detection and treatment of anthracycline-induced cardiotoxicity using beta-blockers and renin–angiotensin–aldosterone inhibitors were associated with an improvement in left ventricular systolic function [33,34]. Strict management of blood pressure, glucose, and hypercholesterolemia and therapeutic life style modification can be helpful for primary prevention of CV events in those breast cancer patients with high risk of CV disease [16]. Therefore, close monitoring of breast cancer patients who have high CV risk factors such as HTN or concomitant RT and anthracycline therapy might be considered immediately after the cancer treatment.

The present study has several potential limitations. First, the small number of the CV events prohibited the use of all significant variables in our multivariate analysis. Second, the CV events could have been underestimated because the primary endpoint of our study is symptomatic CV events. Lastly, since our study excluded patients who were younger than 50 years, the results may not be applicable to patients younger than 50 years.

However, our study represents the real-world evidence of CV risk in breast cancer patients. Unselected breast cancer patients were consecutively enrolled in this study, and more than half of the subjects had concomitant RT and relatively safe dose of anthracycline therapy. Because the long-term survival benefits of anthracycline-based chemotherapy began to be reported in the mid-1990s [35,36], other studies on the cardiac risk of contemporary RT enrolled a limited number of patients with anthracycline [10,20–22,25,37]. Another strength of this study is the investigation of the CV risk of Asian breast cancer patients, who have limited data on cancer therapy-related CV risk. Our data can also be interpreted to mean that with careful monitoring of radiation and anthracycline dosing, the incidence of CV complications is relatively small; thus, the modern care of patients with breast cancer has made great strides.

Conclusion

Left-side irradiation with anthracycline treatment at a cumulative doxorubicin-equivalent dose $\geq$250 mg/m^2 and HTN independently predict CV outcome in breast cancer patients with radiotherapy. Individualized CV disease screening and preventive measures in high-risk breast cancer patients might be important in the improvement of the CV outcome in these patients.

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Conflicts of interest

The authors have declared that no competing interests exist.

Authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.02.001.

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