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Original article

Late cardiac morbidity of adjuvant radiotherapy for early breast cancer – A population-based study

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ABSTRACT

Purpose: The purpose of this study was to assess the long-term cardiac morbidity and mortality after breast irradiation using contemporary irradiation techniques.
Methods: We used the Catastrophic Illness dataset from the National Health Insurance Research Database to explore the possible association between late cardiotoxicity and women with early breast cancer treated with breast conservation therapy from 2000 to 2010. The Cox proportional-hazards model was used to compare breast cancer patients who received adjuvant radiotherapy versus without adjuvant radiotherapy for the end points with the following primary diagnoses (International Classification of Diseases, 9th Revision codes): ischemic heart disease (410–414, 36.0, 36.1), valvular heart disease (394–397, 424, 35), congestive heart failure (428, 402.01, 402.11, 402.91), and conduction abnormalities (426, 37.7–37.8, 37.94–37.99).
Results: Three hundred and thirty patients received adjuvant radiotherapy and 4802 patients did not receive radiotherapy. Median follow-up was 3.5 years. There was no difference in overall morbidity and mortality from any cardiac cause ($p = 0.13$) in breast cancer patients who received adjuvant radiotherapy versus without radiotherapy by using modern radiotherapy techniques.
Conclusion: There were no significant differences in cardiac morbidity and mortality after radiotherapy for breast cancer with a 9-year follow-up period in our population.
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Introduction

The risk of long-term cardiac injury from whole breast radiation therapy for breast cancer after breast-conserving surgery remains a controversial issue. Many studies demonstrated that adjuvant radiation after breast-conserving surgery decreases the risk of local recurrence by two-thirds, with a high level of patient satisfaction on cosmetic outcome [1–7]. However, radiotherapy is not without toxicities. Most studies published before 2000 reported that adjuvant radiotherapy may increase the risk of cardiovascular mortality, particularly among those who received treatment to the left side [8–13]. Over the last decades, the number of patients developing cardiotoxicity induced by radiotherapy has decreased with the development of improved treatment-planning tools and modern techniques, which decreased both the volume of cardiac tissue exposed to radiation and the dose of radiation delivered to the heart. Many studies reported no significant differences in cardiac morbidity after either adjuvant hypofractionated or conventional radiotherapy for left- versus right-sided breast cancer [14–16]. A review article published in 2014 added evidence to the present hypothesis that using modern radiotherapy techniques does not suggest a higher incidence of cardiac mortality [17]. This study was conducted to determine the long-term cardiac mortality and morbidity after breast irradiation using modern radiotherapy techniques from a large population-based database in Taiwan.

Methods

Data source

This population-based retrospective cohort study used the Catastrophic Illness Patient Databases (CIPD) to identify newly diagnosed early breast cancer patients. The CIPD was the subset of the National Health Insurance Research Database (NHIRD). The

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database includes information on patient demographics (with encrypted patient identification numbers, birthdates, and sex), inpatient or outpatient claim data, pharmacy records, laboratory and diagnostic test data, dates of visits, lengths of hospitalization, and diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The database represents over 99% of the 23 million inhabitants of Taiwan who are registered with the National Health Insurance program (NHI). We identified patients based on the inclusion criteria by using the CIPD dataset from January 1, 2000 to December 30, 2010, which is the specific data subsets of the NHI Research Database constructed for research purposes. We confirm that all data were de-identified and analyzed anonymously.

Identification of cases and controls

The study women were identified with a diagnosis of early breast cancer (ICD-9-CM 174.0–174.9) and received adjuvant radiotherapy between 2000 and 2010. We excluded patients according to the exclusion criteria.

Exclusions

Cases were excluded if they had a diagnosis of other cancer history, cardiac disease within 1 year before/after the date of breast cancer diagnosis, did not receive breast conserving surgery and treated with the following drugs: anthracyclines, mitoxantrone, cyclophosphamide, trastuzumab, sunitinib, imatinib, capecitabine, bevacizumab, and 5-fluorouracil during the period of January 1, 2000 to December 30, 2010. Patients who received adjuvant radiotherapy less than radiation treatment course (treatment code = 36012B less than 50 times) were also excluded. For avoiding potential bias due to the existence of disease, patients with at least over 1 year of follow-up and the index date was defined the date after 1 year of radiotherapy treatment.

Study end point

We determined the risks of cardiac morbidity associated with radiotherapy by the presence of ICD-9 codes of ischemic heart disease (410–414, ICD-9-CM code 36.0–36.1), valvular heart disease (339–397, 424 and ICD-9-CM code 35), congestive heart failure (402.01, 402.91, 425 and 428), pericarditis (420 and 423), and conduction abnormalities (426, 427, and IC-9-CM code 37.7–37.8, 37.94 and 37.99). Each study patient was followed from the date after 1 year of radiotherapy treatment until the patients were censored for loss to follow-up or last withdrawal from NHI or until December 31, 2010, the end of the follow-up (whichever came first).

Potential covariates

Potential covariates that have been previously established as cancer risk factors were used to adjust multivariate analyses. We adjusted for co-morbidities presented prior to the index date (the date of radiotherapy treatment), such as hypertension (ICD-9-CM 401–405), hypercholesterolemia (ICD-9-CM 272), and diabetes. The Charlson comorbidity index (CCI) score was used to predict 10-year mortality and cardiac morbidity for a patient who may have a range of comorbid conditions [18].

Statistical analysis

The demographic characteristics including age group, location of tumor, CCI score level, and co-morbidities were compared between patients with and without radiotherapy using chi-square tests. For the differences of mean age and CCI score between two cohorts we used *t*-test. The incidence of cardiac morbidities (per 1000 person-years) was calculated in both groups. The survival rate (per 1000 person-years) for the radiotherapy and non-radiotherapy groups was compared to examine whether the two groups differed with respect to cardiotoxicity. A multivariate Cox regression analysis was used to determine the effects of cardiac morbidity and mortality on the breast cancer risk with radiotherapy treatment compared to non-radiotherapy treatment by calculation of the hazard ratios (HRs) and 95% confidence interval (95% CI). Rate of overall survival in patients with cardiotoxicity in two groups was evaluated by the Kaplan–Meier method and compared by log-rank test [10,11]. All analyses were performed by SAS statistical software (version 9.1 for Window; SAS Institute, Inc., Cary, NC, USA). A value of $p < 0.05$ was considered significant.

Results

Patient characteristics

We identified 330 women with breast cancer from the CIPD between January 1, 2000 and December 30, 2010 according to the inclusion criteria as cases and 4802 patients without radiotherapy as controls. The median follow-up time was 3.5 years. The mean age was 51.3 years in the case cohort and 50.6 years in the control group. No significant differences in age ($p = 0.64$), comorbidities ($p = 0.28$), hypertension ($p = 0.81$), hyperlipidemia ($p = 0.051$), and CCI score were found between the two groups (Table 1).

Cardiac morbidity

When we adjusted for baseline risk factors, including age, CCI score, hypertension, and hyperlipidemia, the results showed that the overall risk of developing congestive heart disease, valvular heart disease, ischemic heart disease, conduction abnormalities, and pericarditis between breast cancer patients who received radiotherapy and no radiotherapy was not significant (HR = 0.81, 95% CI 0.57–1.15) (Table 2).

The incidence of overall cardiac diseases development after breast surgery adjuvant with radiotherapy was lower than those

Table 1
Demographics between patients received radiotherapy and no radiotherapy.

Variable	Radiotherapy N = 330		No radiotherapy N = 4802		*p* value
	n	%	*n*	%	
Age, years					0.64
20–59	262	79.4	3864	80.5	
60+	68	20.6	938	19.5	
Mean (SD)[a]	51.3	(10.9)	50.6	(11.3)	0.27
CCI[b] score					0.01
0	303	91.8	4525	94.2	
1–2	21	6.36	250	5.21	
3+	6	1.82	27	0.56	
Mean (SD)[a]	0.16	(0.70)	0.09	(0.41)	0.051
Location of primary					
Outer quadrants	104	31.5	1403	29.2	
Central quadrants	19	5.7	252	5.2	
Inner quadrants	32	9.6	684	14.2	
Sites of breast					
Nipple and areola	21	6.3	236		
Axillary tail	2	0.6	8		
Other specified sites	49	14.8	694		
Unspecified	103	31.2	3561	74.2	
Hypertension	81	24.6	1055	22.0	0.28
Hyperlipidemia	48	14.6	722	15.0	0.81

Chi-square test.
[a] *t*-test.
[b] Charlson comorbidity index.

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