

No association between tumor laterality and cardiac-related mortality in breast cancer patients after radiotherapy: a population-based study

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Introduction: To assess the effect of tumor laterality to cardiac-related deaths of breast cancer in the current radiation practices using a large modern population-based study.

Methods: Women diagnosed with breast cancer from 2000 to 2008 were included using the current Surveillance, Epidemiology, and End Results database. The primary outcome of this study was the cardiac-related mortality. Multivariate analysis was performed using the Cox proportional hazards model to analyze the cardiac-related mortality including demographic, clinicopathologic, and treatment factors.

Results: We identified 168,761 breast cancer patients, including 85,006 (50.4%) patients with left-sided tumors and 83,755 (49.6%) patients with right-sided tumors. The median follow-up period was 8.8 years. The 10-year cardiac-related mortality was 2.3% and 2.3% in left- and right-sided tumors, respectively ($P=0.685$). The results indicated that patients with older age, non-Hispanic Black, receipt of mastectomy, and married status were the independent adverse factors for cardiac-related mortality. However, left-sided tumors were not associated to a higher risk of cardiac-related mortality than right-sided tumors following postoperative radiotherapy (right vs left, hazard ratios 1.025, 95% CI 0.856–1.099, $P=0.484$). The risk of cardiac-related mortality in the entire cohort was increased with the extension of follow-up time. However, there was still not significantly different between left- and right-sided tumors. Subgroup analysis also found no association between tumor laterality and cardiac-related mortality after postoperative radiotherapy based on various demographics and treatment factors.

Conclusion: With a median follow-up of 8.8 years, no significant differences were found in cardiac-related mortality between left- and right-sided tumors under current radiation practices of breast cancer patients.

Keywords: breast cancer, radiotherapy, tumor laterality, cardiac mortality

Introduction

Postoperative radiotherapy (PORT) is an important component of the comprehensive treatment of breast cancer. Long-term studies indicate that PORT following breast-conserving surgery (BCS) in eligible patients results in similar efficacy, including local tumor control and overall survival, compared to mastectomies.¹ In addition, the locoregional recurrence rates and survival outcomes in locally advanced breast cancers with tumors larger than 5 cm and four or more axillary lymph node metastases are improved with postoperative mastectomy radiotherapy.^{2,3} However, the administration of PORT for breast cancer may expose the heart and blood vessels to late radiotherapy-induced complications, and several recent population-based studies have indicated that PORT

used in breast cancer has an increased risk of ischemic heart disease, valvular disease, and pericarditis.⁴⁻⁶ The dose to the heart has decreased with the development of radiotherapy techniques.⁷ However, much uncertainty remains on the long-term cardiac toxicity effects of PORT.

In breast cancer patients with left-sided tumors, the heart is exposed to a significantly higher dose than in right-sided tumors.⁷ Furthermore, the long-term cardiac toxicity due to PORT between the two tumor lateralities remains controversial. Several studies using large cohorts have found that the risk of cardiac-related mortality in left-sided tumors was significantly higher than right-sided tumors after PORT.⁵⁻¹¹ However, there were also studies which showed similar cardiac-related mortality between the two groups.¹²⁻¹⁵ In addition, specific patients, including patients who have had previous cardiac disease or older survivors (aged 65+ years), might also be at an increased risk of cardiac-related mortality in left-sided tumors compared with right-sided tumors.^{16,17} Differences in the enrolled population, therapy duration, radiotherapy techniques, target volume, chemotherapy regimen, and follow-up time may be the main explanation for conflicting results of cardiac-related mortality in the above-mentioned studies. In the present study, we assessed the effect of tumor laterality on cardiac-related mortality in the current radiation practices using a large modern population-based database.

Materials and methods

Surveillance, Epidemiology, and End Results (SEER) database

The SEER database is maintained at the National Cancer Institute,¹⁸ and contains de-identified information on approximately 28% of cancer patients in the USA. The demographics, clinicopathological features, therapeutic factors (including surgery, radiotherapy and chemotherapy), and patient-specific survival are recorded in the current SEER database. SEER database is a worldwide public database, and we have permission to access the SEER database (authorization code 10702-Nov2017). This study was approved by the Institutional Review Board of the First Affiliated Hospital of Xiamen University and performed in accordance with their guidelines.

Patients, covariates, and treatment information

Women diagnosed with breast cancer between 2000 and 2008 who met the following criteria were included: non-metastatic disease, left- or right-sided tumors, underwent BCS or

mastectomy, received adjuvant beam radiotherapy following primary surgery, and followed-up more than 60 months. Patients without defined tumor laterality, who underwent preoperative radiotherapy or PORT with implants/isotopes alone, and did not undergo PORT were excluded.

We gathered demographic and clinicopathologic characteristics data including age, race/ethnicity, histological subtype, tumor stage, nodal stage, hormone receptor status, marital status, and tumor laterality. Patient staging was extrapolated to the 7th Union for International Cancer Control/American Joint Committee on Cancer Tumor-Node-Metastasis staging system. Primary and adjuvant treatments include surgical procedures, chemotherapy, and completion of the first course of PORT. The primary end-point measured in this study was the probability of cardiac-related mortality. Data on risk factors for cardiac-related mortality were collected 5 years post breast cancer diagnosis.

Statistical analyses

Differences in demographics, clinicopathology, and treatment characteristics by tumor laterality were examined by chi-squared test. In addition, we evaluated the probability of cardiac-related mortality by tumor laterality using the Kaplan–Meier method, with *P*-values based on log-rank tests. Multivariate analysis was performed using the Cox proportional hazards model to analyze the risk factors for cardiac-related mortality including age, race/ethnicity, marital status, surgical procedures, chemotherapy, and tumor laterality by assessment of the hazard ratios (HRs) and their corresponding 95% confidence interval (95% CI). Subgroup analysis was performed to assess the effect of different demographics and treatment factors on the risk of cardiac-related mortality in patients with left- and right-side tumors using univariate analysis. Analyses resulting in *P*-values of <0.05 were considered statistically significant. All analyses were performed using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, USA).

Results

We identified 168,761 patients who met the criteria described above, including 85,006 (50.4%) patients with left-sided tumors and 83,755 (49.6%) patients with right-sided tumors. The median age of the entire cohort was 58 years (range, 13–100 years). A comparison of demographic, clinicopathologic, and treatment factors by tumor laterality is shown in Table 1. The distribution of lymph nodes status (*P*<0.001), estrogen receptors status (*P*<0.001), and progesterone receptors status (*P*=0.016) by tumor laterality reached statistical

Table 1 The demographic, clinicopathologic, and treatment factors by tumor laterality

Variables	n	Left-sided, n (%)	Right-sided, n (%)	P-value
Age (years)				
<65	112,946	56,748 (66.8)	56,198 (67.1)	0.137
≥65	55,815	28,258 (33.2)	27,557 (32.9)	
Race/ethnicity				
Non-Hispanic White	129,187	64,864 (76.3)	64,323 (76.8)	0.062
Non-Hispanic Black	13,556	6,888 (8.1)	6,668 (8.0)	
Hispanic (all races)	13,466	6,910 (8.1)	6,556 (7.8)	
Other	12,552	6,344 (7.5)	6,208 (7.4)	
Histologic subtype				
Ductal	122,359	61,654 (72.5)	60,705 (72.5)	0.581
Lobular	12,896	6,539 (7.7)	6,357 (7.6)	
Other	33,506	16,813 (19.8)	16,693 (19.9)	
Tumor stage				
T1	118,039	59,548 (70.1)	58,491 (69.8)	0.681
T2	40,206	20,149 (23.7)	20,057 (23.9)	
T3	7,214	3,634 (4.3)	3,580 (4.3)	
T4	3,302	1,675 (2.0)	1,627 (19.4)	
Nodal stage				
N0	116,566	58,447 (68.8)	58,119 (69.4)	<0.001
N1	35,448	18,064 (21.3)	17,384 (20.8)	
N2	11,624	5,991 (7.0)	5,633 (6.7)	
N3	5,123	2,504 (2.9)	2,619 (3.1)	
Surgical procedure				
BCS	140,722	70,949 (83.5)	69,773 (83.3)	0.385
Mastectomy	28,039	14,057 (16.5)	13,982 (16.7)	
Chemotherapy				
No/unknown	89,198	44,781 (52.7)	44,417 (53.0)	0.147
Yes	79,563	40,225 (47.3)	39,338 (47.0)	
ER status				
Negative and borderline	28,985	14,889 (17.5)	14,096 (16.8)	<0.001
Positive	129,286	64,706 (76.1)	64,580 (77.1)	
Unknown	10,490	5,411 (6.4)	5,079 (6.1)	
PR status				
Negative and borderline	46,535	23,625 (27.8)	22,910 (27.4)	0.016
Positive	109,726	54,995 (64.7)	54,731 (65.3)	
Unknown	12,500	6,386 (7.5)	6,114 (7.3)	
Marital status				
Unmarried	60,246	30,515 (35.9)	29,731 (35.5)	0.150
Married	104,114	52,251 (61.5)	51,863 (61.9)	
Unknown	4,401	2,240 (2.6)	2,161 (2.6)	

Abbreviations: BCS, breast-conserving surgery; ER, estrogen receptor; N, node; PR, progesterone receptor; T, tumor.

significance. In addition, the distribution of age, race/ethnicity, histological subtypes, tumor stage, surgical procedure, chemotherapy, and marital status did not differ by tumor laterality.

The median follow-up was 8.8 years (106 months, range, 61–167 months). A total of 3,169 patients died of heart-related disease. During the follow-up period, the 8-year, 10-year, and 13-year cardiac-related mortality rates were 1.2%, 2.2%, and 3.9%, respectively. In the entire cohort, the risk of cardiac-related mortality steadily declined over the

study period (Figure 1A). There were also similar trends in left- and right-sided tumors (Figure 1B, C). A total of 1,588 and 1,581 patients died of heart-related disease in left- and right-sided tumors, respectively, and the 10-year heart-related disease rates were 2.3% and 2.3%, respectively ($P=0.685$) (Figure 2). The rates of cardiac-related mortality by tumor laterality by the years of diagnosis are listed in Figure 3, indicating that the risk of cardiac-related mortality was increased with the extension of follow-up time. However, there was still no significant difference between left- and right-sided tumors.

The multivariate Cox proportional hazards model including demographic, clinicopathologic, treatment factors, and tumor laterality was used to assess the risk of cardiac-related mortality (Table 2). The results indicated that patients with older age, non-Hispanic Black, receipt of mastectomy, and married status were the independent adverse factors for cardiac-related mortality. However, no association was found between left- and right-sided tumors and cardiac-related mortality (right vs left, HR 1.025, 95% CI 0.856–1.099, $P=0.484$).

We further analyzed the effect of different demographics and treatment factors on the risk of cardiac-related mortality in patients with left- and right-sided tumors. The results demonstrate that left-sided tumors were not associated with a significantly higher risk of cardiac-related mortality than right-sided tumors by various demographics and treatment factors (Table 3).

Discussion

In our study, we performed a large modern population-based study to assess the effect of tumor laterality on cardiac-related mortality with current radiation practices of breast cancer. Our study found that the risk of cardiac-related mortality in patients with left-sided tumors between 2000 and 2008 was not significantly higher than that of patients with right-sided tumors.

The effect of tumor laterality on cardiac-related mortality following PORT remains controversial. A meta-analysis including 289,109 patients found that heart-related mortality in left-sided tumors following PORT was significantly higher than in right-sided tumors and was more apparent after ≥15 years of follow-up.⁸ A long-term study by Bouillon et al also found that among women who had received PORT between 1954 and 1984, left-sided tumors had a 1.56-fold (95% CI 1.27–1.90) higher risk of cardiac-related mortality than right-sided tumors, even after 20 years.¹¹ In addition, the population-based case-control study also indicated a significant increase in long term cardiac-related mortality in women with left-sided tumors treated with PORT.⁶ However,

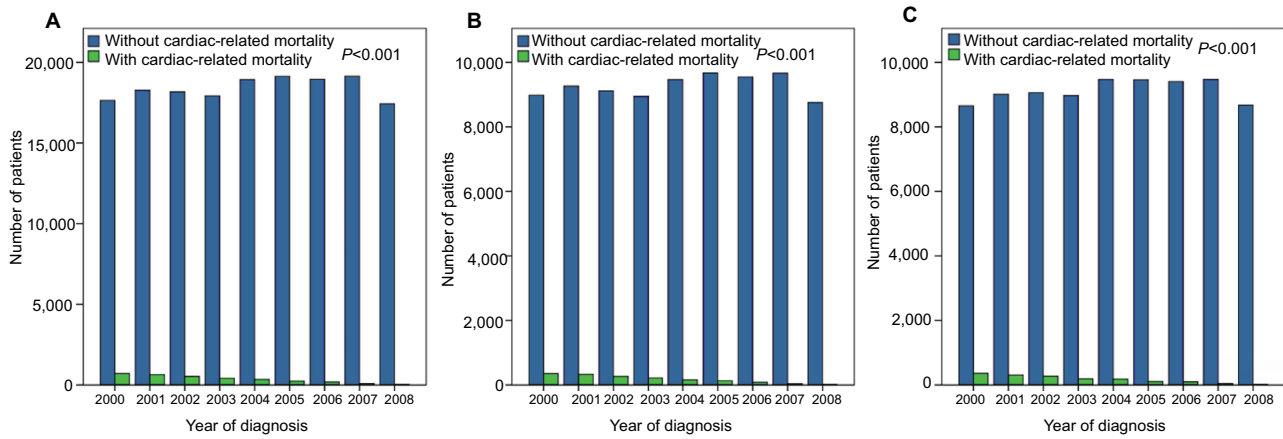


Figure 1 The cardiac-related mortality by tumor laterality during the study period.
Notes: (A) Entire cohort; (B) left-sided tumors; (C) right-sided tumors.

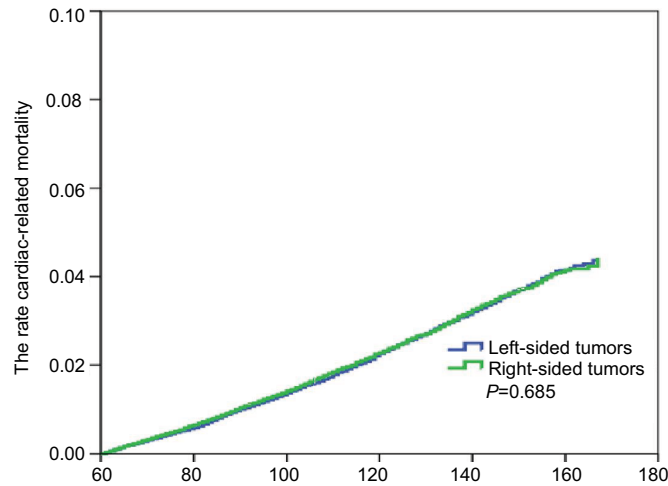


Figure 2 Kaplan–Meier analysis of cardiac-related mortality by tumor laterality.

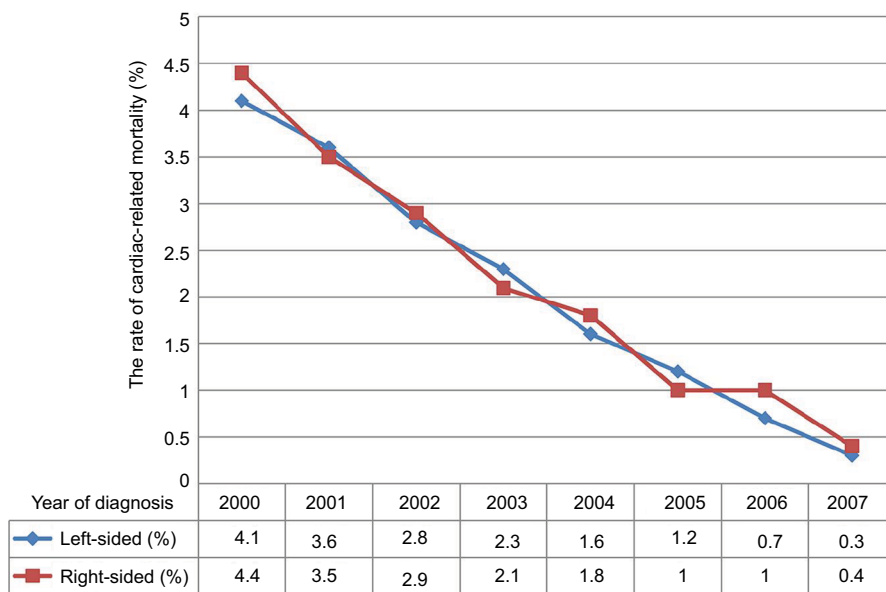


Figure 3 The rates of cardiac-related mortality by tumor laterality by the year of diagnosis.

Table 2 Multivariate analysis of cardiac-related mortality by tumor laterality

Variables	HR	95% CI	P
Age (years) (continuous variable)	1.131	1.127–1.136	<0.001
Race/ethnicity			
Non-Hispanic White	1		
Non-Hispanic Black	1.517	1.337–1.722	<0.001
Hispanic (all races)	1.082	0.930–1.260	0.307
Other	0.759	0.633–0.909	<0.001
Surgical procedure			
BCS	1		
Mastectomy	1.505	1.364–1.661	<0.001
Chemotherapy			
No/unknown	1		
Yes	0.986	0.893–1.089	0.781
Marital status			
Unmarried	1		
Married	0.684	0.635–0.737	<0.001
Unknown	0.954	0.771–1.181	0.667
Tumor laterality			
Left	1		
Right	1.025	0.856–1.099	0.481

Abbreviation: BCS, breast-conserving surgery.

Table 3 Multivariate univariate analysis of cardiac-related mortality by tumor laterality based on various demographics and treatment factors

Variables	Tumor laterality	HR	95% CI	P
Age (years)				
<65	Left	1		
	Right	0.939	0.791–1.114	0.471
≥65	Left	1		
	Right	1.034	0.958–1.116	0.386
Race/ethnicity				
Non-Hispanic White	Left	1		
	Right	1.002	0.928–1.082	0.955
Non-Hispanic Black	Left	1		
	Right	1.060	0.834–1.346	0.634
Hispanic (all races)	Left	1		
	Right	1.175	0.876–1.576	0.281
Other	Left	1		
	Right	0.933	0.655–1.330	0.702
Surgical procedure				
BCS	Left	1		
	Right	1.028	0.953–1.109	0.471
Mastectomy	Left	1		
	Right	0.938	0.783–1.125	0.491
Chemotherapy				
No/unknown	Left	1		
	Right	1.045	0.966–1.130	0.270
Yes	Left	1		
	Right	0.894	0.769–1.041	0.149
Marital status				
Unmarried	Left	1		
	Right	0.979	0.893–1.073	0.646
Married	Left	1		
	Right	1.067	0.956–1.192	0.247

Abbreviation: BCS, breast-conserving surgery.

the abovementioned studies had notable flaws. The cohorts were treated within a wide timespan, from 1954 to 2002, which comes with large differences in planning and delivering radiotherapy, including therapy duration, radiotherapy techniques, fraction size, and target volume. A previous SEER study demonstrated higher cardiac-related mortality in left-sided tumors compared to right-sided tumors following PORT between 1973 and 1982. However, no evidence of heart-related mortality was found between the two groups since 1983.⁹ Our study includes patients from 2000–2008, well within the era of modern radiotherapy, and our results suggest comparable trends of cardiac-related mortality in tumor laterality.

With the advancement of radiotherapy techniques, the risk of cardiac-related mortality in breast cancer patients may be comparable between tumor laterality. Several studies include patients in the era of modern radiotherapy, and the results demonstrate that the risk of cardiac-related mortality does not increase in patients receiving left-sided PORT compared to right-sided PORT, with the exception of women with a history of cardiac disease.^{12,15,16,19} A population-based study also confirmed that the 10-year cardiac-related mortality rate in left- and right-sided tumors following PORT was only 2.4% and 1.9%, respectively,¹⁹ which was similar to our study. However, our study also found that the risk of cardiac-related mortality steadily declined over the study period. Furthermore, heart related deaths are independent of tumor laterality, due to the significant improvements in radiotherapy techniques and accuracy of radiation delivery. Indeed, these produce significantly less scatter and thereby decrease excessive exposure to the heart.²⁰ Moreover, the computed tomography-based target volume delineation and treatment planning could also significantly reduce the dose to heart. Therefore, modern radiotherapy techniques might further reduce the cardiac-related mortality compared to previous studies, and the survival benefits of the radiotherapy may far outweigh the risks for women being considered for breast cancer radiotherapy.

Although the modern radiotherapy techniques have advantage in dosimetry, data of cardiac dose sparing techniques regarding late cardiac events are limited due to the difficulties of long-term follow-up. There are several cardiac biomarkers to evaluate early cardiac injury including brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide, which could be useful minimally invasive markers to detect early cardiac injury.^{21,22}

The dose to the heart is exposed to differs between left- and right-sided tumors. A systematic review of publications between 2003 and 2013 found that the average dose of heart

is exposed to in left- and right-sided tumors was 5.4 Gy (range, <0.1–28.6 Gy) and 3.3 Gy, respectively.²³ A practice pattern survey from 82 radiation oncology departments demonstrated that 5 Gy was a “safe” dose to the heart.²⁴ However, a recent study by Darby et al indicated a linear correlation between the risk of major coronary events and the mean dose to the heart (7.4% per Gy), with no clear threshold.⁶ In addition, the volume of the left ventricle receiving 5 Gy may be a better predictor for acute coronary event than mean heart dose in breast cancer.²⁵ Therefore, reducing radiation exposure of the heart might further decrease the risk of acute coronary event or cardiac-related mortality after PORT of breast cancer.

In breast cancer, the internal mammary node radiation remains one of the major determinants of cardiac toxicity regardless of tumor laterality. The rate of radiation administration to internal mammary node has decreased since the 1980s;⁹ this might be one explanation for the reductions of radiation-related cardiac mortality in left-side tumors. However, there might be more patients who received internal mammary node radiation based on the results of EORTC 22922/10925 and MA.20.^{26,27} The guidelines of the National Comprehensive Cancer Network recommend the irradiation dose to internal mammary nodes since 2016.²⁸ Although the argument against internal mammary node radiation is cardiac toxicity,⁶ studies have indicated that the cardiac toxicity is a multifactorial process with only a small portion directly related to radiotherapy.²⁹ In addition, with advances of radiotherapy techniques in internal mammary radiation, the average dose the heart is exposed to has decreased to 1.0 Gy, which is significantly lower than 6.4 Gy for tomotherapy, 4.5 Gy for volume modulated arc therapy, and 5.3 for wide tangential irradiation.³⁰

In this study, the probability of cardiac-related mortality was significantly higher in patients undergoing PORT after mastectomy than in patients receiving BCS followed by PORT. The mean dose to the heart in BCS has declined in recent years to 2–7 and 1.5 Gy for left- and right-sided tumors, respectively.^{31,32} However, in patients with left-sided tumors who received mastectomy, the mean dose was 8.1–8.8 Gy using three-dimensional conformal radiotherapy, and 7.0–7.3 Gy using intensity modulated radiation therapy.^{33,34} Moreover, most patients undergoing PORT after mastectomy were locally advanced stages, and the probability of receiving chemotherapy for patients undergoing mastectomy in our study was significantly higher than in patients receiving BCS (84.5% vs 39.7%, $P < 0.001$). A study from the Danish Breast Cancer Cooperative Group reported that PORT in left-sided tumors was associated with a significantly higher

risk of cardiac disease compared to right-sided tumors, with the largest increases observed among women who also received anthracycline-based chemotherapy.¹⁰ In addition, patients who received PORT following a mastectomy may have received additional regional nodal radiotherapy resulting in excessive exposure to the heart and increasing the risk of cardiac-related mortality. A large cohort including 70,230 stage I to III breast cancer patients between 1989 and 2005 indicated that the risk of any cardiovascular event did not change with longer follow-ups after left-sided PORT after BCS, whereas the risk of left-sided PORT following mastectomy increased with longer follow-up duration.⁵ Therefore, the dose to the heart is exposed to should be reduced for patients who received mastectomy to decrease the risk of cardiac-related death.

Our study confirms a previous study which reveals that patients of older age, unmarried status, or African American descent are both associated with higher rates of cardiac-related mortality.¹² This may be explained by the baseline risks of these subgroups rather than any relation to radiotherapy.^{35–38} However, our subgroup analysis found no association between long-term cardiac-related mortality by tumor laterality and various demographics and treatment factors.

Several limitations should be acknowledged when interpreting our results. First, there is an inherent weakness of selection bias in a population-based observational study. The main advantage of our study is that it includes a large cohort of population-based patients with sufficient power to detect relatively small increases in cardiac risk. Additionally, our study includes patients from 2000, which are more reflective of the current radiation practices compared to previous studies. Second, the follow-up in our study was relatively short, with a median of 8.8 years in the total cohort. The study by Darby et al³⁹ indicated that the cardiac-related mortality in left-sided tumors following PORT did not become significantly higher compared to right-sided tumors until 10–15 years after their PORT. Therefore, the median follow-up of 8.8 years in our study may not be long enough. We plan to repeat our analysis in the next 5–10 years to investigate the long term cardiac-related mortality by tumor laterality. Third, we could only include cardiac-related mortality in our study due to the lack of information in the SEER database. Indeed, time of the diagnosis and treatment results of specific cardiovascular diseases were not included in the current SEER database. In addition, there was a lack of data for the chemotherapy, endocrine, and targeted therapy regimens given, and the details of PORT in specific patients, which may be potentially confounding factors in assessing the effect of tumor laterality on cardiac morbidity of patients.

Conclusion

In conclusion, with a median follow-up of 8.8 years, no significant differences were found in cardiac-related mortality between left- and right-sided tumors in the current radiation practices of breast cancer. Longer follow-up studies with modern adjuvant radiotherapy are needed to assess the effects of tumor laterality on cardiac-related mortality in breast cancer patients.

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Disclosure

The authors report no conflicts of interest in this work.

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