Advances in Radiation Oncology (2021) 6, 100633

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

The Association Between Cardiac Mortality and Adjuvant Radiation Therapy Among Older Patients With Stage I Estrogen Positive Breast Cancer: A Surveillance, Epidemiology, and End Results (SEER)−Based Study on Cardiac Mortality and Radiation Therapy

Rachel B. Jimenez, MD,[a,*] Stephanie M. Wong, MD,[b] Andrew Johnson, BS,[a] Nafisha Lalani, MD, MPH,[c] and Kevin S. Hughes, MD[d]

[a]Department of Radiation Oncology, Massachusetts General Hospital, Boston, Masschusetts; [b]Department of Surgery, McGill University, JGH Segal Cancer Centre, Montreal, Canada; [c]Department of Radiation Oncology, University of British Columbia, Vancouver, Canada; and [d]Department of Surgery, Division of Surgical Oncology, Massachusetts General Hospital, Boston, Massachusetts

Received 11 September 2020; revised 2 November 2020; accepted 9 November 2020

Abstract

Purpose: We evaluated the risk of cardiac mortality in older patients who receive adjuvant radiation therapy (RT) for stage I breast cancer to determine whether this risk persists in the modern era.

Methods and Materials: Using the 2000 to 2015 Surveillance, Epidemiology, and End Results program data, we performed a population-based cohort study to evaluate the association between adjuvant breast RT, tumor laterality, and cardiac-specific survival (CSS) among patients 60 and older with stage I estrogen receptor positive breast cancer who received breast-conserving surgery and RT.

Results: At a median follow-up of 6 years (range, 0-15.9 years), patients receiving RT for left-sided breast cancer demonstrated no difference in 5- and 10-year CSS compared with those with right-sided breast cancer (5 year 98.3% vs 98.2%, 10 year 94.3% vs 93.9%; log-rank $P = .56$). Cox proportional hazards regression analysis confirmed the lack of association of tumor laterality on adjusted 5-year CSS (hazard ratio [HR] = 0.96; 95% confidence interval [CI] = 0.87-1.06), breast-cancer specific survival (HR = 0.96; 95% CI = 0.85-1.09), and overall survival (HR = 0.98; 95% CI = 0.94-1.03). There was also no association of inner versus outer quadrant location on adjusted 5-year CSS for right-sided (HR = 1.06; 95% CI = 0.89-1.12) and left-sided breast cancer (HR = 0.95; 95% CI = 0.79-1.15).

Sources of support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Disclosures: Dr Hughes receives Honoraria from Hologic (Surgical implant for radiation planning with breast conservation and wire free breast biopsy) and Myriad Genetics and has a financial interest in CRA Health (Formerly Hughes RiskApps). CRA Health develops risk assessment models/software with a particular focus on breast cancer and colorectal cancer. Dr Hughes is a founder and owns equity in the company. Dr Hughes is the cocreator of Ask2Me.Org, which is freely available for clinical use and is licensed for commercial use by the Dana Farber Cancer Institute and the MGH. Dr Hughes' interests in CRA Health and Ask2Me.Org were reviewed and are managed by Massachusetts General Hospital and Partners Health Care in accordance with their conflict of interest policies.

Research data are not available at this time.

* Corresponding author: Rachel B. Jimenez, MD; E-mail: rbjimenez@partners.org

https://doi.org/10.1016/j.adro.2020.100633

2452-1094/© 2020 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusions: With modern radiation therapy techniques, older patients who received left-sided RT for stage I estrogen-receptor positive breast cancer do not demonstrate an increased risk of cardiac mortality compared with patients with right-sided breast cancer. RT can be offered to older patients without concern for inducing cardiac-related death.
© 2020 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Whole breast irradiation is the standard of care for patients with early stage breast cancer after breast-conserving surgery.[1,2] The combination of breast-conserving surgery and radiation therapy has been recommended in consensus guidelines for more than 20 years.[3] Adjuvant radiation therapy provides significant clinical benefits; after breast-conserving surgery, whole breast irradiation reduces the risk of local recurrence by as much as two-thirds.[4,5]

Although radiation therapy provides significant benefit for cancer control, it also is associated with certain side effects, notably cardiac toxicity. It is well-documented that administration of radiation therapy in the adjuvant setting for early stage breast cancer results in long-term risk of cardiac-related disease and death.[6-9] This is of particular concern for patients with left-sided cancers who receive radiation in proximity to the cardiac silhouette. Multiple radiation therapy techniques to limit cardiac exposure including deep inspiration breath hold and prone positioning have subsequently been deployed to mitigate this risk.[10,11] However, clinicians must still estimate the risk-benefit ratio of radiation therapy for the individual patient by considering preexisting factors that increase the risk of cardiac toxicity associated with radiation therapy, such as smoking history, diabetes, hypertension, and prior history of heart disease.[7,8,12-14] The incidence of these comorbidities increases with age, making older patients an especially vulnerable population for developing radiation therapy—induced cardiac toxicity.

The Cancer and Leukemia Group B 9343 trial, a prospective trial evaluating the adjuvant treatment of patients aged 70 years and older with early stage, estrogen receptor (ER)+ breast cancer with or without radiation therapy was conducted to determine whether radiation therapy could be omitted to spare them the radiation toxicity, cost, and inconvenience without compromising cancer outcomes. After a median follow-up of 12.6 years, the study found a small improvement in locoregional recurrence with the addition of radiation therapy, but this did not translate to advantages in overall survival (OS), distant disease-free survival, or breast preservation.[15] Older patients with early stage, ER+ breast cancer are therefore considered eligible to forego adjuvant radiation therapy in favor of adjuvant hormone therapy alone. However, some patients are unable to tolerate hormone therapy or may wish to avoid additional long-term medication commitments due to polypharmacy.[16-18] An alternative approach evaluating adjuvant radiation therapy without hormone therapy in older patients with breast cancer is now being considered, but concerns remain for cardiac risks in this population.

Therefore, in this study, we evaluated the absolute risk of cardiac mortality in older women with early stage ER+ breast cancer who received adjuvant radiation therapy. We hypothesized that with modern radiation therapy techniques, adjuvant radiation therapy for patients receiving left-sided radiation would not be associated with an increased risk of cardiac mortality compared with patients receiving right-sided radiation.

Methods and Materials

Data source and study cohort

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) radiation and chemotherapy treatment database to ascertain our cohort. The SEER database is comprised of data from 18 geographic regions that together form a catchment area covering 28% of the United States population. The November 2017 submission was used in this study to identify women aged 60 years or older with a histologically confirmed, first diagnosis of unilateral stage I breast cancer diagnosed between January 1, 2000 and December 31, 2015 (n = 94,981, Supplementary Materials). The American Joint Committee on Cancer sixth edition staging system was used to classify the study cohort due to the period assessed in the analysis. Of note, all patients in the cohort were considered node negative using the extent of disease codes for number of cases with positive regional lymph nodes. No patients with micro metastases were included in the study. Our cohort included women with ER+ disease (n = 79,921) who underwent breast-conserving surgery (n = 60,740) and excluded patients who did not undergo adjuvant radiation or whose radiation status was unknown (n = 19,734). The final analytical cohort included 41,006 women with ER+, stage I breast cancer. Because the study used deidentified data, the protocol was considered exempt from the Massachusetts General Hospital institutional review board.

Table 1 Cohort characteristics (n = 41,006)

Characteristic	Total (n = 41,006)
Age, n (%)	
60-69 y	22,485 (54.8)
70-79 y	14,246 (34.7)
80 + y	4275 (10.4)
Race, n (%)	
Non-Hispanic White	32,155 (78.4)
Non-Hispanic Black	2426 (5.9)
Asian	2543 (6.2)
Hispanic	3555 (8.7)
Other	327 (0.8)
Laterality, n (%)	
Right-sided breast cancer	20,324 (49.6)
Left-sided breast cancer	20,682 (50.4)
Tumor location, n (%)	
Central/NAC	1768 (4.3)
Upper inner quadrant	6059 (14.8)
Lower inner quadrant	2921 (7.1)
Upper outer quadrant	15,271 (37.2)
Lower outer quadrant	3150 (7.7)
Overlapping quadrants/breast NOS	11,837 (28.9)
Tumor grade, n (%)	
Grade I	15,851 (38.7)
Grade II	19,043 (46.4)
Grade III	4734 (11.5)
Unknown	1378 (3.4)
Tumor size, n (%)	
0.1-0.5 cm	5825 (14.2)
0.6-1.0 cm	14,826 (36.2)
1.1-2.0 cm	20,355 (49.6)
Hormone receptor status, n (%)	
ER+/PR+	34,806 (84.9)
ER+/PR-	5580 (13.6)
ER+/PR unknown	620 (1.5)
HER2/neu receptor status, n (%)*	
HER2/neu amplified	1045 (6.2)
HER2/neu negative	15,921 (93.8)
Axillary management/no. lymph nodes removed, n (%)	
No nodes removed	2640 (6.4)
1-5 nodes removed (SLNB)	31,029 (75.7)
6 or more nodes removed (ALND)	7209 (17.6)
Unknown	128 (0.3)

Abbreviations: ALND = axillary lymph node dissection; ER = estrogen receptor; HERs = human-epidermal growth factor receptor 2; NAC = nipple areola complex; NOS = not otherwise specified; PR = progesterone receptor; SLNB = sentinel lymph node biopsy.

* HER2/neu receptor status only available for cases diagnosed from 2010 to 2015.

Outcomes of interest

Our primary outcomes of interest were all-cause mortality and cardiac-specific survival (CSS) by laterality of the primary breast cancer. Dates and cause of death for all patients were obtained from the SEER Cause of Death recode, which is derived from the International Classification of Diseases 9th and 10th revisions (ICD-9, ICD-10). Patients whose noncancer causes of death included "diseases of the heart" (ICD-10 I00-I09, I11, I13, I20-I51), "atherosclerosis" (ICD-10 I70), "aortic aneurysm and dissection" (I71), and "other diseases of arteries, arterioles, capillaries" (ICD-10 I72-I78) were considered to have had cardiac-related mortality. Survival time was calculated from the date of diagnosis of the stage I breast cancer to the date for which the last complete vital status was available, with all living patients censored on December 31, 2016. In addition to CSS and OS, breast cancer-specific survival (BCSS) was calculated.

Control variables

Demographic variables included age at diagnosis, which were grouped as 60 to 69 years, 70 to 79 years, and 80+ years, and race/ethnicity, classified as non-Hispanic white, non-Hispanic black, Hispanic, Asian/pacific islander, and other/unknown. Tumor location within the breast (central/nipple areola complex, upper inner quadrant, lower inner quadrant, upper outer quadrant, lower outer quadrant, and overlapping quadrants/breast not otherwise specified), tumor grade (grade I, II, III, or unknown), and tumor size (T1a, 0.1-0.5 cm; T1b, 0.6-1.0 cm; and T1c, 1.1-2.0 cm) were also obtained. Because all patients were ER+, hormone receptor status was determined by progesterone receptor (PR) status, yielding 3 subgroups: ER+/PR+, ER+/PR-, and ER+/PR unknown. Human-epidermal growth factor receptor 2 (HER2/neu) status was only available for cases diagnosed between 2010 and 2015. With regards to surgical management, women were considered to have undergone breast-conserving surgery if they received 1 of the following surgical procedures: partial mastectomy, partial mastectomy with nipple resection, lumpectomy, excisional biopsy, reexcision of the biopsy site, or segmental mastectomy. Because SEER had not reported details on the extent of axillary nodal evaluation until 2013, axillary lymph node management was determined using extent of disease codes to quantify the number of regional lymph nodes examined and the number of regional lymph nodes positive. Using this information, 1 to 5 lymph nodes removed were considered a surrogate for sentinel lymph node biopsy (SLNB), whereas patients with 6 or more lymph nodes removed were considered to have undergone axillary lymph node dissection. Receipt of chemotherapy was dichotomized as "yes" or "no/unknown if received chemotherapy."

Statistical analysis

Demographic and clinicopathologic data between right- and left-sided breast cancer cases were compared using Wilcoxon rank sum test for continuous variables,

Table 2 Comparison of clinical and pathologic characteristics according to laterality in women with stage I, ER+ breast cancer treated with breast conserving surgery and adjuvant radiation (n = 41,006)

Characteristic	Right sided breast cancer (n = 20,324)		Left sided breast cancer (n = 20,682)		*P* value
Age, n (%)					
60-69 y	11,135	(54.8)	11,350	(54.9)	.89
70-79 y	7055	(34.7)	7191	(34.8)	
80+ y	2134	(10.5)	2141	(10.4)	
Race, n (%)					
Non-Hispanic white	15,917	(78.3)	16,238	(78.5)	.67
Non-Hispanic black	1230	(6.1)	1196	(5.8)	
Asian	1260	(6.2)	1283	(6.2)	
Hispanic	1747	(8.6)	1808	(8.7)	
Other	170	(0.8)	157	(0.8)	
Tumor location, n (%)					
Central/NAC	865	(4.3)	903	(4.4)	<.001
Upper inner quadrant	2821	(13.9)	3238	(15.7)	
Lower inner quadrant	1379	(6.8)	1542	(7.5)	
Upper outer quadrant	7717	(38.0)	7554	(36.5)	
Lower outer quadrant	1571	(7.7)	1579	(7.6)	
Overlapping quadrants/breast NOS	5971	(29.4)	5866	(28.4)	
Tumor grade, n (%)					
Grade I	7996	(39.3)	7855	(38.0)	.01
Grade II	9363	(46.1)	9680	(46.8)	
Grade III	2325	(11.4)	2409	(11.7)	
Unknown	640	(3.2)	738	(3.6)	
Tumor size, n (%)					
0.1-0.5 cm	2833	(13.9)	2992	(14.5)	.13
0.6-1.0 cm	7311	(36.0)	7515	(36.3)	
1.1-2.0 cm	10,180	(50.1)	10,175	(49.2)	
Hormone receptor status, n (%)					
ER+/PR+	17,232	(84.8)	17,574	(85.0)	.60
ER+/PR-	2793	(13.7)	2787	(13.5)	
PR unknown	299	(1.5)	321	(1.6)	
HER2/neu receptor status, n (%)*					
HER2/neu amplified	511	(6.1)	534	(6.2)	.70
HER2/neu negative	7904	(93.9)	8017	(93.8)	
Axillary management, n (%)					
No nodes removed	1360	(6.7)	1280	(6.2)	<.001
1-5 nodes removed (SLNB)	15,184	(74.7)	15,845	(76.6)	
6 or more nodes removed (ALND)	3708	(18.2)	3501	(16.9)	
Unknown	72	(0.4)	56	(0.3)	
Adjuvant chemotherapy, n (%)					
Yes	1607	(7.9)	1637	(7.9)	.98
No/unknown	18,717	(92.1)	19,045	(92.1)	

Abbreviations: ALND = axillary lymph node dissection; ER = estrogen receptor; HERs = human-epidermal growth factor receptor 2; NAC = nipple areola complex; NOS = not otherwise specified; PR = progesterone receptor; SLNB = sentinel lymph node biopsy.

* HER2/neu receptor status only available for cases diagnosed from 2010 to 2015.

and Pearson's χ^2 test for categorical data. Unadjusted 5- and 10-year CSS were calculated using the Kaplan-Meier method, with survival differences between right- and left-sided groups assessed using the log-rank test. After visual inspection of the Kaplan-Meier curves revealed no evidence of violation of the proportional hazards assumption, Cox proportional hazards regression was used to calculate the hazard ratio (HR) for CSS with adjustment for age, race, tumor location (quadrant), and chemotherapy receipt. Further subgroup analyses were

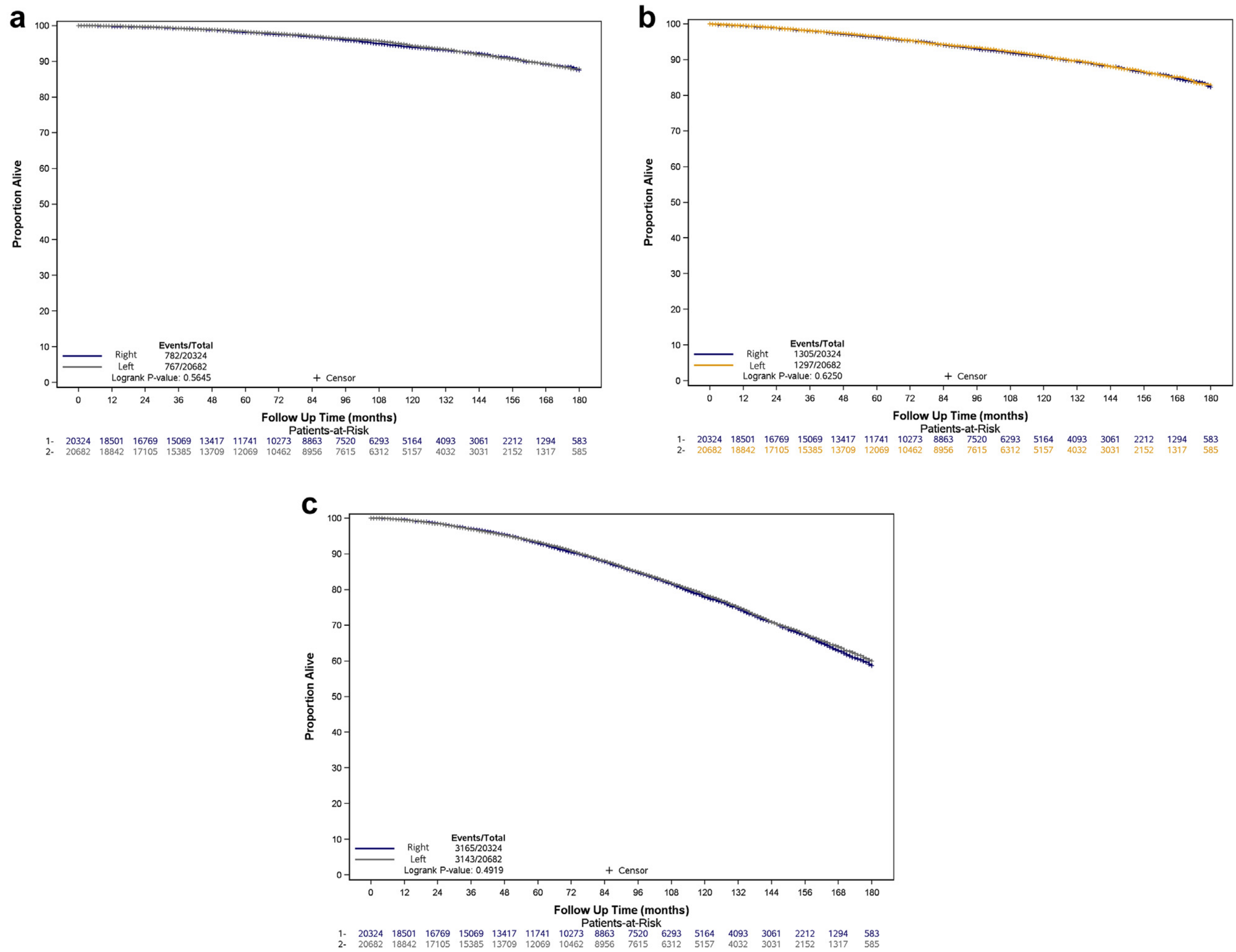

Figure 1 (a) Kaplan-Meier curves demonstrating cardiac-specific survival (CSS), (b) breast cancer-specific survival (BCSS), and (c) overall survival (OS) according to tumor laterality.

performed to assess CSS between inner and outer quadrant tumors after stratification by laterality. A similar regression was performed to evaluate BCSS and OS by laterality, with adjustment for age, race, tumor location, histologic grade, size, PR status, lymph node surgery, and adjuvant chemotherapy receipt. Sensitivity analysis was then performed in those with confirmed ER+/HER2- disease diagnosed between 2010 and 2011, to ensure stability of 5-year survival estimates. All *P* values were 2-sided, with a threshold of .05 used to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

Results

Patient characteristics

After applying exclusion criteria, the final patient cohort consisted of 41,006 patients with stage I ER+ breast cancer. Half (54.8%) of the patients were 60 to 69 years old at time of diagnosis, followed by 34.7% for 70 to 79 years old, and 10.4% at 80+ years old. The majority (78.4%) of patients identified as non-Hispanic white. Cancer laterality was balanced with 49.6% right-sided cancers and 50.4% left-sided breast cancer. Upper outer quadrant was the most common (37.2%) tumor location, followed by overlapping quadrants/breast not otherwise specified (28.9%) and upper inner quadrant (14.8%). The other quadrants fell below 10% occurrence in the cohort. Most tumors consisted of grade I or II disease (38.7% and 46.4%, respectively) and were either 0.6 to 1.0 cm or 1.1 to 2.0 cm in size (36.2% and 49.6%, respectively). The vast majority (84.9%) of tumors had ER+/PR+ hormone receptor status and only 13.6% had ER+/PR- hormone receptor status. In addition to breast conserving surgery, 75.7% of patients underwent SLNB alone and 17.6% received axillary lymph node dissection, with or without sentinel lymph node biopsy, as defined earlier (Table 1).

The clinical and pathologic characteristics of the cohort were well balanced between left- and right-sided breast cancer groups with respect to age, race, tumor size,

Table 3 Unadjusted survival rates in patients with stage I, estrogen-receptor positive breast cancer undergoing breast conservation and adjuvant radiation, 2000-2015, according to laterality (n = 41,006)

Characteristic	Right sided breast cancer (1)		Left sided breast cancer (2)		Log-rank *P* value
	%	95% CI		95% CI	
CSS					.56
5-y CSS	98.2	(98.0-98.4)	98.3	(98.1-98.5)	
10-y CSS	93.9	(93.4-94.4)	94.3	(93.8-94.7)	
BCSS					.62
5-y BCSS	96.2	(95.9-96.5)	96.4	(96.1-96.7)	
10-y BCSS	90.8	(90.2-91.3)	90.9	(90.4-91.5)	
OS					.49
5-y OS	93.0	(92.6-93.4)	93.2	(92.8-93.6)	
10-y OS	77.9	(77.1-78.7)	78.4	(77.6-79.2)	

Abbreviations: BCSS = breast cancer specific survival; CI = confidence interval; CSS = cardiac-specific survival; OS = overall survival.

Table 4 Cox proportional hazards regression, comparing CSS, BCSS, and OS in patients with stage I, estrogen-receptor positive breast cancer undergoing breast conservation and adjuvant radiation, 2000-2015, according to laterality (n = 41,006)

Characteristic	Cardiac-specific survival		Breast cancer-specific survival		OS	
	HR*	95% CI	HR†	95% CI	HR*	95% CI
Laterality						
Right-sided breast cancer	Ref		Ref		Ref	
Left-sided breast cancer	0.96	(0.87-1.06)	0.96	(0.85-1.09)	0.98	(0.94-1.03)

Abbreviations: BCSS = breast cancer specific survival; CI = confidence interval; CSS = cardiac-specific survival; HR = hazard ratio; OS = overall survival.

* With adjustment for age, race, tumor location, histologic grade, size, progesterone receptor status, lymph node surgery, adjuvant chemotherapy receipt.

† With adjustment for age, race, tumor location (quadrant), chemotherapy receipt.

hormone receptor status, HER2/neu status, and receipt of adjuvant chemotherapy. Tumor location, grade, and axillary management showed some association according to breast cancer laterality; upper inner quadrant tumors were more common for left-sided breast cancer (15.7% vs 13.9%, $P < .001$), and patients with right-sided breast cancer were more likely to have grade I tumors (39.3% vs 38.0%, $P = .01$) (Table 2). In terms of axillary management, patients with left-sided breast cancer underwent SLNB more frequently than those with right-sided breast cancer, though the absolute difference was minimal (76.6% vs 74.7%, $P < .001$).

Survival outcomes

Median follow-up for the cohort was 6 years (range, 0-15.9 years). According to the Kaplan-Meier curves presented in Figure 1, left-sided breast cancers receiving adjuvant radiation therapy had similar unadjusted 5- and 10-year CSS to those with right-sided breast cancer treated with adjuvant radiation therapy (5-year 98.3% vs 98.2%,10-year 94.3% vs 93.9%; log-rank $P = .56$). The 5- and 10-year rate of BCSS also showed no significant differences between the 2 groups (Table 3). Furthermore, Cox proportional hazards regression analysis confirmed the lack of association of tumor laterality on adjusted 5-year CSS (HR = 0.96; 95% confidence interval [CI] = 0.87-1.06), BCSS (HR = 0.96; 95% CI = 0.85-1.09), and OS (HR = 0.98; 95% CI = 0.94-1.03) (Table 4). Further stratified according to tumor laterality and quadrant location, Cox proportional hazards regression analysis showed no association of inner versus outer quadrant on adjusted 5-year CSS for right-sided (HR = 1.06; 95% CI = 0.89-1.12) and left-sided breast cancer (HR = 0.95; 95% CI = 0.79-1.15) and no association with BCSS for right-sided (HR = 0.93; 95% CI = 0.74-1.16) and left-sided breast cancer (HR = 1.15; 95% CI = 0.93-1.43).

Discussion

Among patients with early stage, ER+ breast cancer treated with breast conserving surgery and adjuvant radiation therapy, we found no increased risk in CSS or OS associated with left-sided tumor laterality. Past studies have suggested an association between cancer laterality, as well as receipt of radiation therapy in general, and

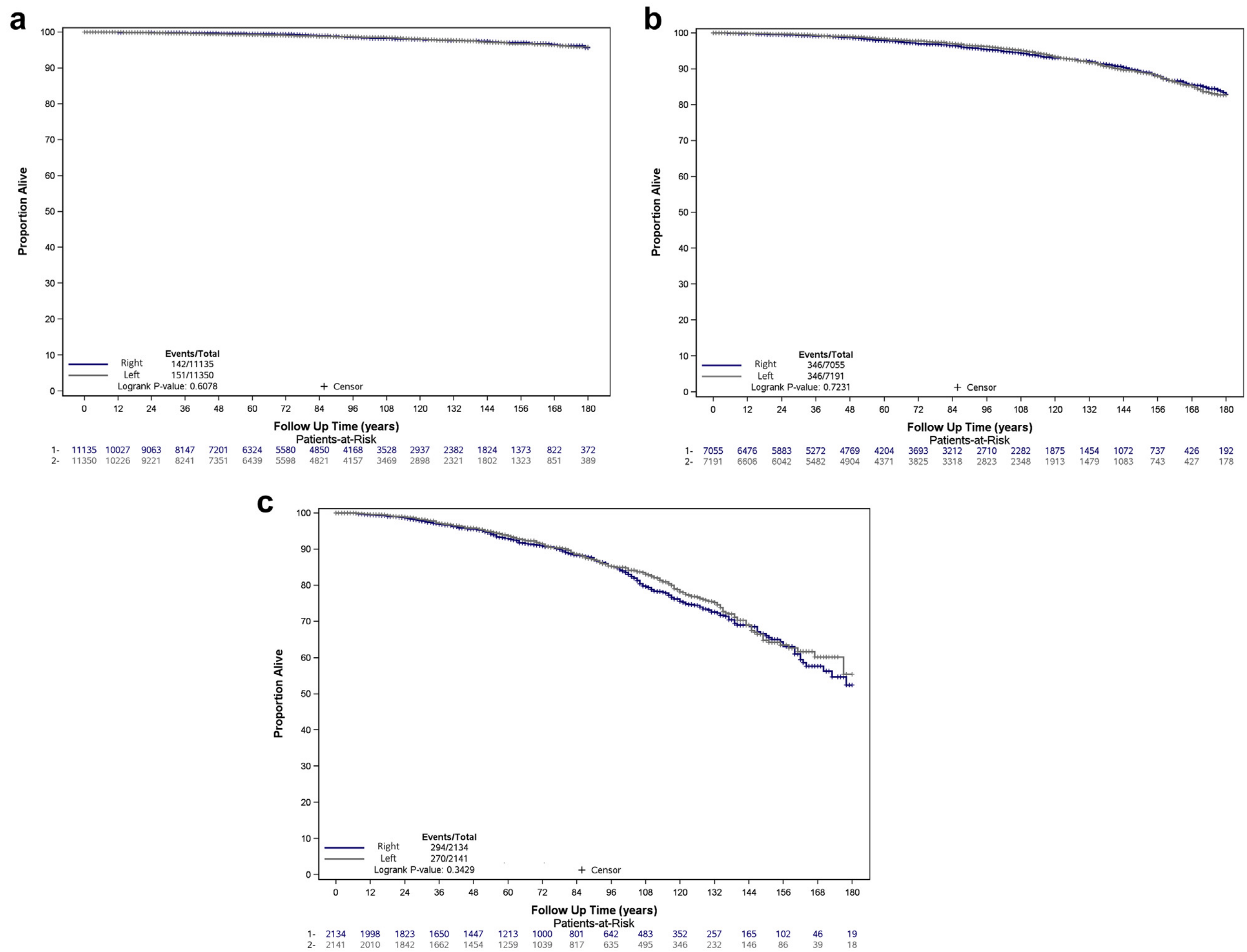

Figure 2 Cardiac-specific survival (CSS) according to tumor laterality in (a) women 60 to 69 years of age at diagnosis, (b) women 70 to 79 years of age at diagnosis, and (c) women 80 years or older at diagnosis.

incidence of death due to cardiac disease. The 2005 Early Breast Cancer Trialists' Collaborative Group update by Clarke et al[9] found that the irradiated group had a 27% increase in mortality from heart disease compared with the nonirradiated group. In a large retrospective series of 4456 women treated with adjuvant radiation therapy at Institut Goustave Roussy, Bouillon et al[6] also found a significantly higher risk of dying of cardiac disease for left-sided breast cancer compared with right-sided breast cancer (HR = 1.56; 95% CI = 1.27-1.90). Both studies collectively assessed a patient cohort treated with radiation therapy between 1954 and 2000, before the widespread utilization of cardiac sparing radiation therapy techniques. The lack of association between adjuvant radiation therapy and the laterality of the breast cancer on CSS in this study, with a cohort ranging from 2000 to 2015, supports the safety of modern radiation therapy techniques for patients who require whole breast radiation therapy.

Additionally, no significant difference in CSS was observed across each age group when associated with tumor quadrant location, which supports the safety of modern radiation therapy techniques for patients of any age, including an older population (Fig 2). Historically, the data have suggested an increase in the rate of coronary events associated with adjuvant radiation therapy in older populations. Darby et al[8] found the highest increase in rate of major coronary events (9.7% increase/Gy; 95% CI = −2.9 to 11.6) for the 70- to 74-year-old cohort at time of diagnosis. They also found the highest increase in rate of major coronary events in the first 5 years after radiation therapy (16.3% increase/Gy; 95% CI = 3.0-64.3). Furthermore, a follow-up study by van den Bogaard et al[19] to validate the predictive model generated by Darby et al confirmed the dose effect relationship for cardiac events within 5 years of radiation as well as a similar cumulative incidence increase of cardiac events in the first 9 years after treatment (16.5% increase/Gy; 95% CI = 0.6-35.0). This study also found that the cumulative incidence of cardiac events increased by 9% with increasing age within the first 9 years after radiation therapy treatment (95% CI = 1.049-1.133; *P*

< .001).[19] Although our study was not able to examine nonfatal cardiac outcomes by tumor laterality, and therefore cannot definitively confirm the safety of radiation therapy in this population, our data suggest no increased risk of CSS in the setting of modern radiation therapy techniques after a 5- and 10-year follow-up period for all age groups.

The safety of adjuvant radiation therapy after breast conserving surgery in the elderly population lends support to prospective studies evaluating the use of lumpectomy and adjuvant radiation with omission of hormone therapy for this patient cohort. Hypofractionated and accelerated partial breast irradiation techniques also provide a similar safety and efficacy profile for low-risk breast cancer treated after breast conserving surgery compared with standard radiation therapy, providing an even more convenient option for adjuvant treatment.[20-22] Ultimately, the current findings support further research to prevent the undertreatment of this vulnerable population.

There are several limitations to the current study. First, although the population-based nature of this study reflects the "real world" administration of radiation therapy, this data set lacks detailed radiation therapy information, including the dose, fractionation, and radiation techniques, that could have provided more nuanced information about cardiac exposure across the population. Without this specific information included in the analysis, the current study cannot assess the safety of radiation therapy in this population in a more definitive manner. Specifically, the aforementioned studies assessing the relationship between cardiac dose and excess risk of cardiac events suggest the importance of further work, including detailed radiation therapy information, to bolster the results of the present study. In addition, it is possible that a minority of ER+ patients in the overall cohort were also HER2/neu+, which could influence survival outcomes and receipt of cardiotoxic anti-HER2 therapy, and this was not controlled for in adjusted analyses. However, when examined in patients diagnosed after 2010, this subgroup represented a very small proportion (6%) of the overall cohort, and in sensitivity analysis, 5-year survival estimates showed no significant difference among left- and right-sided cancers when excluding this group of HER2/neu+ patients diagnosed between 2010 to 2015 (Appendix E1).

In addition, although the data suggest a clear lack of increased risk in 5- and 10-year BCSS and CSS according to tumor laterality, tumor location, and patient age, first cardiac events typically precede cardiac death by several years, and this study could not account for any potential differences in nonfatal cardiac events that could have occurred in this population. However, our study focused specifically on older patients, and this population demonstrates a shorter interval to cardiac morbidity and mortality based on the greater likelihood of preexisting cardiac risk factors in this cohort. The predictive model presented by Darby et al and validated by van den Bogaard et al confirms the increase of cumulative incidence of cardiac events within a 10-year period, including in an elderly population as presented in the current study. These data account for 5 age groups from 40 to 80 years old, stratified into 4 groups: no comorbidities, diabetes, ischemic cardiac event, and hypertension. Therefore, this shorter latency to events paired with an overall more modest life expectancy in the elderly would support a 10-year BCSS endpoint as clinically relevant for this population.[13,23,24] However, as Darby et al note, the increased risk of a cardiac event due to radiation exposure continues for at least 2 years. While the elderly population in this study demonstrates a likelihood of an interval to a cardiac event within 10 years, and a life expectancy of 20 years or greater is less likely in an elderly population of 60+ years old, further study with a median follow-up greater than 10 years would prove valuable in assessing the safety of radiation therapy in this population.

Additionally, this study strictly compared patients receiving left breast radiation, in proximity to the cardiac silhouette, to those receiving right breast radiation, and not to patients who received no radiation therapy. This study design does limit the conclusions that can be rendered from the data; however, other influential series, including Harris et al,[13] have analyzed cardiac morbidity and mortality with this study design to reduce selection bias. Patients captured in the SEER database that did not receive radiation may have had other baseline cardiac risk factors that could not be ascertained from the database and that led them to forgo radiation therapy. Therefore, we used a comparison of left- to right-sided patients in an attempt to reduce any introduction of selection bias to the study sample.

Finally, because the results of the current study apply to breast-only radiation therapy, it cannot lend support to cohorts receiving regional nodal irradiation due to the increased risk of cardiac exposure associated with treatment of the internal mammary lymph nodes. Ongoing trials evaluating the safety of such radiation therapy techniques remain appropriate to examine any association with radiation-induced cardiac toxicity.

Conclusions

In conclusion, in the era of modern radiation therapy techniques, for older women with right- or left-sided early stage ER+ breast cancer, the use of adjuvant radiation therapy is not associated with increased risk of cardiac mortality within 10 years after treatment. Radiation therapy can be offered to older patients with early stage breast cancer as appropriate to ensure cancer control without concern for inducing cardiac-related death in the short term. Further research with a longer follow-up interval and more detailed radiation therapy information, including the cardiac dose, would reinforce these findings. Future prospective research should evaluate the potential utility of adjuvant radiation without hormone therapy in an elderly population.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.100633.

References

1. Tailby E, Boyages AMJ. Conservation surgery and radiation therapy in early breast cancer- An update. *Austral Fam Phys*. 2017;46:214-219.
2. Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: Assessment and management. *Breast Cancer: Targ Ther*. 2015;7:21-25.
3. Gradishar W, Anderson B, Balassanian R. *NCCN clinical practice guidelines in oncology: Breast cancer. Version 2, 2015*. Fort Washington, PA: NCCN; 2015. Available at www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed July 18, 2020.
4. Housri N, Haffty B. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Breast Dis: Year Book Quart*. 2012;23:266-267.
5. Buchholz TA. Radiotherapy and survival in breast cancer. *Lancet*. 2011;378:1680-1682.
6. Bouillon K, Haddy N, Delaloge S, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer. *J Am Coll Cardiol*. 2011;57:445-452.
7. Hooning MJ, Botma A, Aleman BMP, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007;99:365-375.
8. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New EnglJ Med*. 2013;368:987-998.
9. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;366:2087-2106.
10. Beck RE, Kim L, Yue NJ, Haffty BG, Khan AJ, Goyal S. Treatment techniques to reduce cardiac irradiation for breast cancer patients treated with breast-conserving surgery and radiation therapy: a review. *Front Oncol*. 2014;4:327.
11. Shah C, Badiyan S, Berry S, et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. *Radiother Oncol*. 2014;112:9-16.
12. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol*. 2007;50:1435-1441.
13. Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncology*. 2006;24:4100-4106.
14. Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol*. 2017;35:1641-1649.
15. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31:2382-2387.
16. Lash TL, Fox MP, Westrup JL, et al. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat*. 2006;99:215-220.
17. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *J Clin Oncol*. 2011;29:2534-2542.
18. Puts MT, Tu HA, Tourangeau A, et al. Factors influencing adherence to cancer treatment in older adults with cancer: A systematic review. *Annal Oncol*. 2014;25:564-577.
19. van den Bogaard VA, Ta BD, van der Schaaf A, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol*. 2017;35:1171-1178.
20. Kinj R, Chand ME, Gal J, Gautier M, Lam Cham Kee D, Hannoun-Lévi JM. Five-year oncological outcome after a single fraction of accelerated partial breast irradiation in the elderly. *Radiat Oncol*. 2019;14:234.
21. Hannoun-Levi JM, Lam Cham Kee D, Gal J, et al. Accelerated partial breast irradiation in the elderly: 5-Year results of the single fraction elderly breast irradiation (SiFEBI) phase I/II trial. *Brachytherapy*. 2020;19:90-96.
22. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:259-268.
23. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011;100:167-175.
24. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol*. 2016;23:7475-7482.