Adjuvant Whole Breast Radiotherapy Improve Survival in Women with Heart Failure with Reduced Ejection Fraction Receiving Breast-Conserving Surgery

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Research article

Keywords: breast cancer, radiotherapy-related cardiotoxicity, breast-conserving surgery, radiotherapy, survival

Posted Date: November 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-987933/v1

Version of Record: A version of this preprint was published at Journal of Personalized Medicine on December 13th, 2021. See the published version at https://doi.org/10.3390/jpm11121358.

Abstract

BACKGROUND: To date, no data on the effect of adjuvant whole breast radiotherapy (WBRT) on oncologic outcomes, such as all-cause death, locoregional recurrence (LRR), and distant metastasis (DM), are available in women with left-side breast intraductal carcinoma (IDC) and heart failure with reduced ejection fraction (HFrEF).

PATIENTS AND METHODS: We enrolled 294 women with left-breast IDC at clinical stages IA–IIIC and HFrEF receiving breast-conserving surgery (BCS) followed by adjuvant WBRT or non-adjuvant WBRT. We categorized them into two groups based on their adjuvant WBRT status and compared their overall survival (OS), LRR, and DM outcomes. We calculated the propensity score and applied inverse probability of treatment weighting (IPTW) to create a pseudo-study cohort. Furthermore, we performed a multivariate analysis of the propensity score–weighted population to obtain hazard ratios (HRs).

RESULTS: In the IPTW-adjusted model, adjuvant WBRT (adjusted HR [aHR]: 0.58; 95% confidence interval [CI]: 0.33–1.00) was a significant independent prognostic factor for all-cause death (P = 0.0494), and the aHR (95% CI) of LRR and DM for adjuvant WBRT was 0.25 (0.10–0.62; P = 0.0028) and 0.29 (0.14–0.60; P = 0.0007), respectively, compared with the nonadjuvant WBRT group.

CONCLUSION: Adjuvant WBRT was associated with a decrease in all-cause death, LRR, and DM in women with left IDC and HFrEF compared with nonadjuvant WBRT.

Introduction

Cardiovascular disease may be a complication of breast radiotherapy (RT) and the use of specific systemic agents in the treatment of breast cancer.[1] Incidental radiation to the heart as part of the initial treatment for breast cancer can result in a range of cardiotoxic effects, including coronary artery disease, cardiomyopathy, pericardial disease, valvular dysfunction, and conduction abnormalities.[2-4] At present, no recommended minimum radiation dose that is completely safe exists.[3] RT-related cardiotoxicity (RICT) is associated with a portion of the heart being placed in a radiation field.[1] For all patients with left-sided breast cancers, careful treatment planning is critical to minimize cardiac exposure to radiation.[1]

The association of RT with cardiotoxicity is not dependent on the presence or absence of a breast but on the volume of radiation to the heart.[3, 4] Thus, cardiotoxicities associated with RT differ between the postlumpectomy and postmastectomy settings; this is because in the postmastectomy setting, the RT field often includes the nodal tissues, and these nodes are not always targeted in the postlumpectomy setting.[5, 6] Thus, postmastectomy RT is more often associated with cardiac disease relative to postlumpectomy RT, but this is likely a result of the usually larger irradiated volumes of the heart in postmastectomy RT.[5, 6] Therefore, RICT in patients with breast cancer should be minimized by using different surgical techniques of breast-conserving surgery (BCS) and total mastectomy (TM).

Another crucial issue is whether adjuvant whole breast RT (WBRT) can be safely given to women with heart failure (HF) and left-side breast cancer who receive BCS. No data are available to address the value of adjuvant WBRT in women with breast cancer and HF receiving BCS. HF due to left ventricle (LV) dysfunction is categorized according to LV ejection fraction (LVEF) as HF with reduced ejection fraction (LVEF ≤ 40%, known as HFrEF).[7-9] Until now, no study has estimated the oncologic outcomes of adjuvant WBRT in women with breast intraductal carcinoma (IDC) and HFrEF receiving BCS.

Patients And Methods

Study population

In this cohort study, data were retrieved from the Taiwan Cancer Registry Database (TCRD). We enrolled women with HF with reduced ejection fraction (LVEF ≤ 40%; HFrEF)[7-9] who had received a diagnosis of left-side breast IDC between January 1, 2008, and December 31, 2018. The index date was the date of BCS, and the follow-up duration was from the index date to December 31, 2019. The TCRD of the Collaboration Center of Health Information Application contains detailed cancer-related

information of patients, including their clinical stage, pathologic stages, chemotherapy regimens, dose of chemotherapy, molecular status, drug use, hormone receptor status, radiation modalities and doses, and surgical procedures.[10-13] The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

The diagnoses of the enrolled patients with HFrEF were confirmed after their pathological data were reviewed, and the women with newly diagnosed left-side IDC were confirmed to have no other cancers or distant metastases. The women with HFrEF were included if they had received a left-side IDC diagnosis, were 20 years old or older, and had clinical stage IA–IIIC (American Joint Committee on Cancer [AJCC], 8th edition) without metastasis. Patients with HFrEF were excluded if they had a history of cancer before the IDC diagnosis date, unknown pathologic types, missing sex data, unclear staging, or non-IDC histology. In addition, patients undergoing neoadjuvant chemotherapy or with unclear differentiation of tumor grade, missing HR status, missing data on trastuzumab or anthracycline use, or unclear staging were excluded. Other adjuvant treatments such as adjuvant chemotherapy, hormone therapy, or the human epidermal growth factor receptor 2 inhibitors did not constitute exclusion criteria based on the National Comprehensive Cancer Network (NCCN) guidelines.[14] We also excluded patients with HFrEF with unclear data on surgical procedures such as BCS or TM, ill-defined nodal surgery, unclear Charlson comorbidity index (CCI), or unclear differentiation from our cohort. Hormone receptor positivity was defined as ≥1% of tumor cells demonstrating positive nuclear staining through immunohistochemistry.[15]

After applying the inclusion and exclusion criteria, we enrolled 294 women with HFrEF and AJCC clinical stage IA–IIIC and left-side IDC who had received a BCS followed by sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) and divided them into two groups based on their adjuvant WBRT status to compare all-cause mortality: Group 1 (women with left-side IDC and HFrEF who received BCS followed by adjuvant WBRT) and Group 2 (women with left-side IDC and HFrEF who received BCS and no adjuvant WBRT). We also excluded women in Group 1 receiving nonstandard adjuvant WBRT (contrast with standard adjuvant radiotherapy consisting of irradiation to the whole breast with a minimum of 50 Gy). Contemporary RT techniques were included in our study and the conventional two-dimensional RT technique was excluded. The included contemporary RT techniques were three-dimensional RT and intensity-modulated radiation therapy. The incidence of comorbidities was scored using the CCI.[16, 17] Ischemic heart disease, heart valvular disease, cardiomyopathy, hypertension, diabetes, and arrhythmias and conduction disorders were excluded from the CCI scores to avoid repetitive adjustment in multivariate analysis. Only comorbidities observed within 6 months before the index date were included; they were coded and classified according to the *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes at the first admission or based on more than two repetitions of a code issued at outpatient department visits.

Study covariates and statistical analysis

Significant independent predictors, namely age, diagnosis year, CCI score, differentiation, pT, pN, hypertension, ischemic heart disease, heart valvular disease, cardiomyopathy, arrhythmias and conduction disorders, diabetes, adjuvant chemotherapy with anthracycline-based regimen, hormone receptor status, trastuzumab use, nodal surgery, hospital level (academic or nonacademic), and income, were analyzed using a multivariate analysis of the propensity score–weighted population to determine hazard ratios (HRs). We calculated the propensity score and applied inverse probability of treatment weighting (IPTW) to create a pseudo-study cohort; the weighted cohort avoids covariate bias and mimics randomized adjuvant WBRT or no adjuvant WBRT assignment: IPTW for patients with WBRT = 1/p(WBRT); IPTW for patients without WBRT = 1/(1 − p[WBRT]).[18, 19] The independent predictors were examined in multivariable analyses after IPTW adjustment. Moreover, they were controlled for and were stratified in the analysis. The endpoint was all-cause death in the women with left-side IDC and HFrEF who received BCS followed by adjuvant WBRT (Group 1, case group) and in the women with left IDC and HFrEF who received BCS and had no adjuvant WBRT (Group 2, control group).

The cumulative incidence of death was estimated using the Kaplan–Meier method, and differences in the overall survival (OS), locoregional recurrence (LRR)–free survival, and distant metastasis (DM)–free survival between women with left IDC and HFrEF

receiving BCS followed by adjuvant WBRT versus no adjuvant WBRT were determined using a log-rank test. After confounders were adjusted for, IPTW-adjusted models were used to determine the time from the index date to all-cause mortality in the women with left IDC and HFrEF who received BCS followed by adjuvant WBRT or no adjuvant WBRT. Subsequently, in a multivariate analysis, HRs were adjusted for age, diagnosis year, CCI scores, differentiation, pT, pN, hypertension, ischemic heart disease, heart valvular disease, cardiomyopathy, arrhythmias and conduction disorders, diabetes, adjuvant chemotherapy with anthracycline, hormone receptor status, trastuzumab use, nodal surgery, hospital levels, and incomes. All analyses were conducted using SAS (Version 9.3; SAS, Cary, NC, USA), and a two-tailed *P* value <0.05 was considered statistically significant.

Results

Study cohort

We enrolled 294 women with left-breast IDC at clinical stages IA–IIIC and HFrEF who received BCS followed by adjuvant WBRT or no adjuvant WBRT (Table 1). Among these women, 223 with left IDC and HFrEF received BCS followed by adjuvant WBRT (Group 1) and 71 with left IDC and HFrEF received BCS with no adjuvant WBRT (Group 2). After IPTW was executed using the propensity score, the covariates between Groups 1 and 2 were found to be homogenous. The median follow-up durations after the index date were 6.96 and 5.09 years for women with left IDC and HFrEF who received BCS followed by adjuvant WBRT or no adjuvant WBRT, respectively. All standardized differences in covariates were smaller than 0.1 (Table 1) and were homogenous between the two groups.

Effects of adjuvant WBRT on oncologic outcomes in women with left-side IDC and HFrEF receiving BCS

IPTW-adjusted models indicated that adjuvant WBRT was a significantly better independent prognostic factor for OS, LRR, and DM in the women with left IDC and HFrEF receiving BCS (Table 2). Adjuvant WBRT (adjusted HR [aHR]: 0.58; 95% confidence interval [CI]: 0.33–1.00) was a significant independent prognostic factor for all-cause death (*P* = 0.0494; Table 2). In the IPTW-adjusted model, the aHR (95% CI) for LRR in the adjuvant WBRT group was 0.25 (0.10–0.62; *P* = 0.0028; Table 2) compared with the no adjuvant WBRT group. Moreover, the aHR (95% CIs) for DM in the adjuvant WBRT group was 0.29 (0.14–0.60; *P* = 0.0007) compared with the no adjuvant WBRT group (Table 2).

Other independent predictors of all-cause death, LRR, and DM in the women with left IDC and HFrEF receiving BCS

Old age (>65 years), CCI ≥ 1, advanced pT stages (pT2–4), advanced pN stages (pN1–3), hormone receptor negative status, and differentiation Grade II and III were identified as crucial independent poor prognostic factors for OS (Tables 2). IPTW-adjusted models were adjusted for age, diagnosis year, CCI score, differentiation, pT, pN, hypertension, ischemic heart disease, heart valvular disease, cardiomyopathy, arrhythmias and conduction disorders, diabetes, adjuvant chemotherapy with anthracycline-based regimen, hormone receptor status, trastuzumab use, nodal surgery, hospital level, and income; the aHRs (95% CIs) of all-cause death for age > 65 years, CCI ≥ 1, pT2–4, pN1–3, differentiation Grades II and III, and hormone receptor positive status were 1.34 (1.18–3.26), 1.14 (1.08–1.72), 1.33 (1.05–2.34), 2.48 (1.37–4.47), 1.58 (1.15–2.17), 1.73 (1.26–2.36), and 0.68 (0.52–0.88) compared with age 20–65 years, CCI = 0, pT1, pN0, differentiation grade I, and hormone receptor negative status, respectively (Table 2). IPTW-adjusted models also revealed the aHRs (95% CIs) of LRR for pT2–4, pN1–3, differentiation grade II, differentiation grade III, and hormone receptor positive status to be 1.73 (1.01–1.71), 1.82 (1.43–4.53), 2.06 (1.71–3.27), 2.16 (1.89–3.46), and 0.66 (0.50–0.86) compared with pT1, pN0, differentiation grade I, and hormone receptor negative status, respectively. Moreover, the aHRs (95% CIs) of DM for pN1-3, differentiation grade II, differentiation grade III, and hormone receptor positive status were 1.75 (1.31–2.84), 2.02 (1.58–3.04), 2.94 (1.69–3.61), and 0.59 (0.32–0.75) compared with pN0, differentiation grade I, and hormone receptor negative status, respectively.

Survival curves of adjuvant WBRT or no adjuvant WBRT in women with left IDC and HFrEF receiving BCS

Figure 1 presents Kaplan–Meier curves that illustrate the OS of the women with left IDC and HFrEF receiving BCS with adjuvant WBRT or no adjuvant WBRT. The 5-year overall survival rates were 86.47% and 75.92% in the adjuvant WBRT and no adjuvant WBRT groups, respectively (Figure 1); the OS rate was associated with an increasing trend in the adjuvant WBRT group (log-rank test, $P = 0.0618$) compared with the non-WBRT group. Additionally, the 5-year LRR-free survival in women with left IDC and HFrEF receiving BCS was 95.78% and 86.11% in the adjuvant WBRT group and no adjuvant WBRT group, respectively (Figure 2; log-rank test, $P = 0.0083$). The 5-year DM-free survival in women with left IDC and HFrEF receiving BCS was 96.23% and 78.33% in the adjuvant WBRT group and no adjuvant WBRT group, respectively (Figure 3; log-rank test, $P = 0.0027$).

Discussion

The use of RT has contributed to significant improvements in disease-specific survival among patients with early stage breast cancer.[20] The success of RT, used either alone or in combination with other modalities, has resulted in large cohorts of breast cancer survivors who are vulnerable to late complications such as RICT from RT.[5, 21–27] Numerous treatment-related factors are responsible for cardiotoxicity in women with breast cancer.[28–38] Thus, we conducted the study to determine the survival benefits offered by adjuvant WBRT in women with left-side IDC and HFrEF receiving BCS.

Patients with breast cancer might experience adverse effects from many cardiotoxic treatments such as adjuvant RT, anthracycline-based chemotherapy, or trastuzumab.[6,][5, 21–38] Although cardiovascular diseases such as HF, heart attacks, and stroke remain the leading cause of death in women, many believe breast cancer to be more deadly.[39] In fact, the risk of RICT should be weighed against the potential benefits of adjuvant WBRT with respect to the patients' prognosis and likely clinical benefit.[5, 21–27] Until now, no data have been available for the evaluation of oncologic outcomes (OS, LRR, and DM) of adjuvant WBRT in women with left-side breast IDC and HFrEF receiving BCS. This is the first study to explore the value of adjuvant WBRT for women with left-side breast IDC and HFrEF receiving BCS. As shown in Table 2, adjuvant WBRT resulted in better OS, LRR-free status, and DM-free status compared with no adjuvant WBRT in women with left-side breast IDC and HFrEF receiving BCS. The potential reasons might be the recent decline in mortality in women with HF[40, 41] and the advances in contemporary RT techniques with reduced irradiation volumes to the heart.[2, 23, 24]

According to our literature review, this is the first study to estimate the oncologic outcomes of adjuvant WBRT among women with left-side breast IDC and HFrEF receiving BCS. No consensus or evidence for the use of adjuvant WBRT in women with left-side breast IDC and HFrEF receiving BCS is present. In the IPTW-adjusted models, adjuvant WBRT was associated with a decrease in the risk of all-cause death, LRR, and DM among women with left-side breast IDC and HFrEF receiving BCS (Table 2). The improvement in contemporary RT techniques with decreased irradiation doses and decreased volumes to the heart and the long-term improvement in mortality rates in patients with HFrEF over time might have caused the significant beneficial oncologic outcomes of adjuvant WBRT in women with left-side breast IDC and HFrEF receiving BCS.[2, 23, 24] Our study is the first to demonstrate that the potential benefits of adjuvant WBRT with contemporary RT techniques outweigh the risk of RICT given the patients' prognosis and likely long-term OS, LRR, and DM benefits (Table 2). According to our findings, we strongly suggested that women with left-side breast IDC and HFrEF receiving BCS should also receive adjuvant WBRT to decrease the risk of all-cause death, LRR, and DM.

As shown in Table 2, adjuvant WBRT was a significant prognostic factor for OS, LRR, and DM compared with no adjuvant WBRT in women with left-side IDC and HFrEF receiving BCS; moreover, old age (>65 years), CCI ≥ 1, advanced pT stages (pT2–4), advanced pN stages (pN1–3), hormone receptor negative status, and differentiation Grade II–III were significant prognostic factors for OS, compatible with findings of previous studies.[10, 11, 42–49] Moreover, advanced pN stages (pN1–3), hormone receptor negative status, and differentiation Grade II–III were significant poor prognostic factors for LRR and DM in women with left-side breast IDC and HFrEF receiving BCS, which is also compatible with findings of previous studies.[10, 11, 42–49] Our findings of prognostic factors for OS, LRR, and DM in women with IDC and HFrEF receiving BCS are similar with those of

previous studies,[10, 11, 42–49] and no additional prognostic factor has been identified in previous studies other than the ones determined in the current study irrespective of whether underlying HFrEF was present.

A strength of our study was that it was the first cohort study to estimate the survival outcomes of adjuvant WBRT or no adjuvant WBRT among women with left-side IDC and HFrEF receiving BCS. The covariates between the adjuvant WBRT and no adjuvant WBRT groups were homogenous for women with left-side IDC and HFrEF receiving BCS, with no selection bias (Table 1). No study has estimated the effect of adjuvant WBRT on women with left-side IDC and HFrEF receiving BCS. In our study, the poor prognostic factors for OS in women with left-side IDC and HFrEF receiving BCS were old age, CCI ≥ 1, advanced pT stages (pT2–4), advanced pN stages (pN1–3), hormone receptor negative status, and differentiation Grade II–III of (Table 2), which are consistent with factors in women with breast cancer without HFrEF reported in previous studies.[45–49] Furthermore, our study is the first to demonstrate the benefits of adjuvant WBRT with contemporary RT techniques for OS, LRR, and DM in women with left-side IDC and HFrEF receiving BCS. Our findings should be considered in future clinical practice and prospective clinical trials. We suggest that adjuvant WBRT is valuable to achieving better outcomes of OS, LRR, and DM in women with left-side IDC and HFrEF receiving BCS.

This study has some limitations. First, because all women with left-side breast IDC and HFrEF were enrolled from an Asian population, the corresponding ethnic susceptibility compared with the non-Asian population remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. However, no evidence exists as to the differences in oncologic outcomes in Asian versus non-Asian patients with breast IDC and HFrEF receiving BCS. Second, the diagnoses of all comorbid conditions were based on ICD-10-CM codes. However, the combination of Taiwanese TCRD and National Health Insurance Research Database (NHIRD) data appears to be a valid resource for population research on cardiovascular diseases, stroke, or chronic comobidities.[50–52] Moreover, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of the diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently be heavily penalized if any malpractice or discrepancy is detected. Accordingly, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Finally, the TCRD does not contain information regarding dietary habits or body mass index, which may be risk factors for mortality. Nevertheless, considering the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to affect the conclusions.

Conclusions

Adjuvant WBRT was associated with a decrease in all-cause death, LRR, and DM among women with left-side breast IDC and HFrEF compared with no adjuvant WBRT. We suggest adjuvant WBRT for women with left-side IDC receiving BCS, even if they have HFrEF.

Abbreviations

WBRT, whole breast radiotherapy; LRR, locoregional recurrence; DM, distant metastasis; IDC, intraductal carcinoma; HFrEF, heart failure with reduced ejection fraction; BCS, breast-conserving surgery; OS, overall survival; aHR, adjusted hazard ratio; HR, hazard ratio; IPTW, inverse probability of treatment weighting; CI, confidence interval; AJCC, American Joint Committee on Cancer; TCRD, Taiwan Cancer Registry Database; SD, standard deviation; Her-2, human epidermal growth factor receptor-2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CKD, chronic kidney disease; CCI, Charlson comorbidity index; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; RICT, radiotherapy-related cardiotoxicity; TM, total mastectomy; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; T, tumor; N, nodal; pT, pathologic tumor stage; pN, pathologic nodal stage; NHIRD, National Health Insurance Research Database

Declarations

Ethics approval and consent:

The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Consent for publication:

Not applicable

Availability of data and material:

The data sets supporting the study conclusions are included in this manuscript and its supplementary files.

For software:

Project name: Not applicable

Project homepage: Not applicable

Archived version: Not applicable

Operating system(s): Not applicable

Programming language: Not applicable

Other requirements: Not applicable

License: Not applicable

Any restrictions for use by nonacademicians: Not applicable

Competing interests:

The authors have no potential conflicts of interest to declare. The data sets supporting the study conclusions are included in the manuscript.

Research Funding:

Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013). Taipei Medical University-Wan Fang Hospital (Funding Number: 107TMU-WFH-08) supports Tsai-Mu Cheng's work.

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Financial Support: Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013). Taipei Medical University-Wan Fang Hospital (Funding Number: 107TMU-WFH-08) supports Tsai-Mu Cheng's work.

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Final Approval of Manuscript: All authors

Key points:

Question: Is adjuvant whole breast radiotherapy (WBRT) worthy for women with left-side breast intraductal carcinoma (IDC) and heart failure with reduced ejection fraction (HFrEF) receiving breast-conserving surgery (BCS)?

Findings: In the IPTW-adjusted models, adjuvant WBRT was associated with a decrease in all-cause death, LRR, and DM in women with left IDC and HFrEF compared with no adjuvant WBRT.

Meaning: We suggest adjuvant WBRT for women with left-side IDC receiving BCS, even when they have HFrEF.

Acknowledgement

Access to Data statement: We used data from the National Health Insurance Research Database (NHIRD) and Taiwan Cancer Registry database (TCRD). The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. The data utilized in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to the “Personal Information Protection Act” executed by Taiwan’s government, starting from 2012. Requests for data can be sent as a formal proposal to obtain approval from the ethics review committee of the appropriate governmental department in Taiwan. Specifically, links regarding contact info for which data requests may be sent to are as follows: http://nhird.nhri.org.tw/en/Data_Subsets.html#S3 and http://nhis.nhri.org.tw/point.html. Szu-Yuan Wu, MD, PhD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Role of funder statement: Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu’s work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013) for design and conduct of the study.

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Tables

Table 1

Demographics of patients with breast cancer and heart failure with reduced ejection fraction who received breast conservative surgery in the propensity score–weighted population through inverse probability of treatment weighting (IPTW)

		Propensity score–weighted population				
		Adjuvant WBRT N = 223		No adjuvant WBRT N = 71		
Variable		n	(%)	n	(%)	Standardized difference
Age	Mean (SD)	62.3	(11.4)	63.5	(11.6)	0.0311
	Median (IQR, Q1–Q3)	63	(54-70)	63	(54-71)	
	20–65	167	(73.6)	52	(73.2)	0.0224
	>65	60	(26.4)	19	(26.8)	
Diagnosis year	2008–2012	89	(39.2)	28	(39.4)	0.0000
	2013–2017	138	(60.8)	43	(60.6)	
CCI score	0	73	(32.7)	22	(31.0)	0.0231
	≥1	150	(67.3)	49	(69.0)	
Differentiation	I	44	(19.7)	16	(22.5)	-
	II	112	(50.2)	34	(47.9)	0.0566
	III	67	(30.0)	21	(29.6)	0.0452
AJCC clinical stage	I	112	(50.2)	33	(46.5)	0.0831
	II–III	111	(49.8)	38	(53.5)	
AJCC pathologic stage	I	109	(48.9)	34	(47.9)	-
	II	97	(43.5)	32	(45.1)	0.0242
	III	18	(8.1)	6	(8.5)	0.0170
pT	pT1	137	(61.4)	41	(57.7)	0.0737
	pT2–4	86	(38.6)	30	(42.3)	
pN	pN0	164	(73.5)	49	(69.0)	0.0705
	pN1–3	59	(26.5)	22	(31.0)	
Hypertension		161	(72.2)	50	(70.4)	0.0584
Ischemic heart disease		88	(39.5)	27	(38.0)	0.0352
Valvular disease		17	(7.6)	6	(8.5)	0.0276
Cardiomyopathy		71	(31.8)	23	(32.4)	0.0381
Arrhythmias and conduction disorders		6	(2.7)	2	(2.8)	0.0114
Diabetes mellitus		76	(34.1)	27	(38.0)	0.0779
Chemotherapy with anthracycline		103	(46.2)	34	(47.9)	0.0072
Hormone receptor positive		109	(48.9)	35	(49.3)	0.0089
Trastuzumab use		21	(9.3)	7	(9.9)	0.0131
Nodal surgery	ALND	139	(61.2)	40	(56.3)	0.0618

		Propensity score–weighted population				
		Adjuvant WBRT N = 223		No adjuvant WBRT N = 71		
Variable		n	(%)	n	(%)	Standardized difference
	SLNB	84	(38.8)	31	(43.7)	
Hospital level	Academic center	110	(49.3)	35	(49.3)	0.0000
	Nonacademic center	113	(50.7)	36	(50.7)	
Income	<NTD 18,000	65	(29.1)	20	(28.2)	-
	NTD 18,000–24,000	74	(33.2)	23	(32.4)	0.0231
	NTD 24,000–36,000	40	(17.9)	12	(16.9)	0.0143
	>NTD 36,000	44	(19.7)	16	(22.5)	0.0712

IQR, interquartile range; SD, standard deviation; AJCC, American Joint Committee on Cancer; Her-2, Human Epidermal Growth Factor Receptor-2; WBRT, whole-breast radiotherapy; CCI, Charlson comorbidity index; T, tumor; N, nodal; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy; NTD, New Taiwan dollar

Table 2

Multivariate analysis of propensity score–weighted population with breast cancer and heart failure with reduced ejection fraction receiving breast conservative surgery

		All-cause death			Local recurrence			Distant metastasis		
		aHR*	(95% CI)	p value	aHR*	(95% CI)	p value	aHR*	(95% CI)	p value
Adjuvant WBRT	No	Ref		0.0494	Ref		0.0028	Ref		0.0007
	Yes	0.58	(0.33–1.00)		0.25	(0.10–0.62)		0.29	(0.14–0.60)	
Age	20–65	Ref		0.0002	Ref		0.5433	Ref		0.4948
	>65	1.34	(1.18–3.26)		1.18	(0.63–1.95)		1.70	(0.65–1.95)	
Diagnosis year	2009–2012	Ref		0.4611.	Ref		0.1881	Ref		0.8695
	2013–2017	0.81	(0.73–1.42)		0.74	(0.48–1.16)		0.94	(0.58–1.86)	
CCI score	0	Ref		0.0401	Ref		0.5281	Ref		0.8993
	≥1	1.14	(1.08–1.72)		1.05	(0.73–1.74)		1.06	(0.44–1.58)	
Hypertension	Yes	1.17	(0.69–1.96)	0.5656	0.95	(0.60–1.50)	0.8313	0.98	(0.68–1.42)	0.9253
Ischemic heart diseases	Yes	1.32	(0.81–2.15)	0.2725	0.75	(0.48–1.21)	0.7022	0.95	(0.76–1.55)	0.2315
Valvular disease	Yes	1.15	(0.75–2.11)	0.2144	1.00	(0.69–1.45)	0.9866	0.96	(0.49–1.90)	0.9081
Cardiomyopathy	Yes	1.13	(0.88–1.65)	0.1312	0.77	(0.45–1.82)	0.3404	0.92	(0.63–2.57)	0.5322
Arrhythmias and conduction disorders	Yes	1.08	(0.88–1.46)	0.1786	0.89	(0.53–2.67)	0.2762	0.76	(0.41–1.39)	0.3174
Diabetes	Yes	1.06	(0.84–1.14)	0.3127	0.91	(0.67–1.20)	0.4714	0.68	(0.52–1.28)	0.8784
pT	pT1	Ref		0.0329	Ref		0.0468	Ref		0.2525
	pT2–4	1.33	(1.05–2.34)		1.73	(1.01–1.71)		1.56	(0.73–3.32)	
pN	pN0	Ref		0.0026	Ref		0.0198	Ref		0.0299
	pN1–3	2.48	(1.37–4.47)		1.82	(1.43–4.53)		1.75	(1.31–2.84)	
Differentiation	I	Ref		0.0005	Ref		0.0001	Ref		0.0001
	II	1.58	(1.15–2.17)		2.06	(1.71–3.27)		2.02	(1.58–3.04)	
	III	1.73	(1.26–2.36)		2.16	(1.89–3.46)		2.94	(1.69–3.61)	
Chemotherapy with anthracycline	Yes	0.98	(0.30–182)	0.1411	0.78	(0.31–1.96)	0.1422	0.72	(0.59–1.87)	0.3855
Hormone receptor positive	Yes	0.68	(0.52–0.88)	0.0042	0.66	(0.50–0.86)	0.0024	0.59	(0.32–0.75)	0.0013
Trastuzumab	Yes	1.03	(0.42–	0.9547	1.65	(0.73–	0.9085	1.16	(0.73–	0.5321

use			2.51)			3.74)			1.83)	
Nodal surgery	ALND	Ref		0.8831	Ref		0.3162	Ref		0.3488
	SLNB	1.17	(0.96–1.25)		1.29	(0.84–2.21)		1.39	(0.70–2.74)	
Hospital level	Medical centers	Ref		0.1667	Ref		0.4441.	Ref		0.7028
	Nonmedical centers	1.08	(0.81–1.24)		0.92	(0.61–2.57)		0.92	(0.71–1.49)	
Income	<NTD 18,000	Ref		0.4221	Ref		0.8651	Ref		0.7629
	NTD 18,000–24,000	1.34	(0.61–2.93)		1.22	(0.69–2.14)		1.17	(0.69–1.96)	
	NTD 24,000–36,000	1.53	(0.88–2.65)		1.37	(0.73–2.45)		1.53	(0.78–2.18)	
	>NTD 36,000	1.68	(0.92–3.09)		1.73	(0.94–2.96)		2.14	(0.83–3.25)	

aHR, adjusted hazard ratios; CIs, confidence intervals; HR, hormone receptor; Her-2, human epidermal growth factor receptor-2; WBRT, whole-breast radiotherapy; CCI, Charlson comorbidity index; T, tumor; N, nodal; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy; ref, reference group; NTD, New Taiwan dollar

*All covariates mentioned in Table 2 were adjusted.

Figures

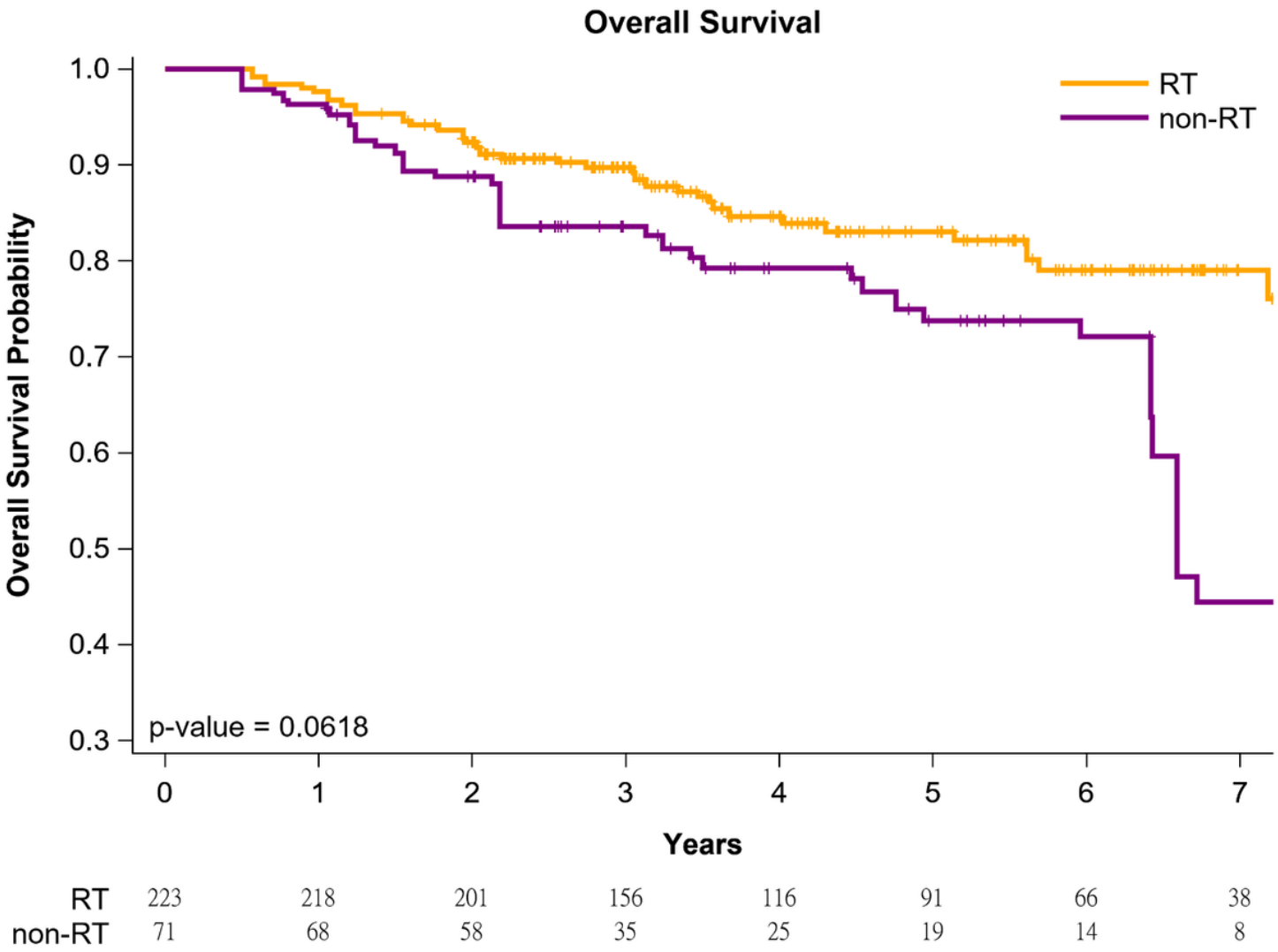

Figure 1

Kaplan–Meier overall survival curves of propensity score–weighted population with breast cancer and heart failure with reduced ejection fraction receiving breast conservative surgery

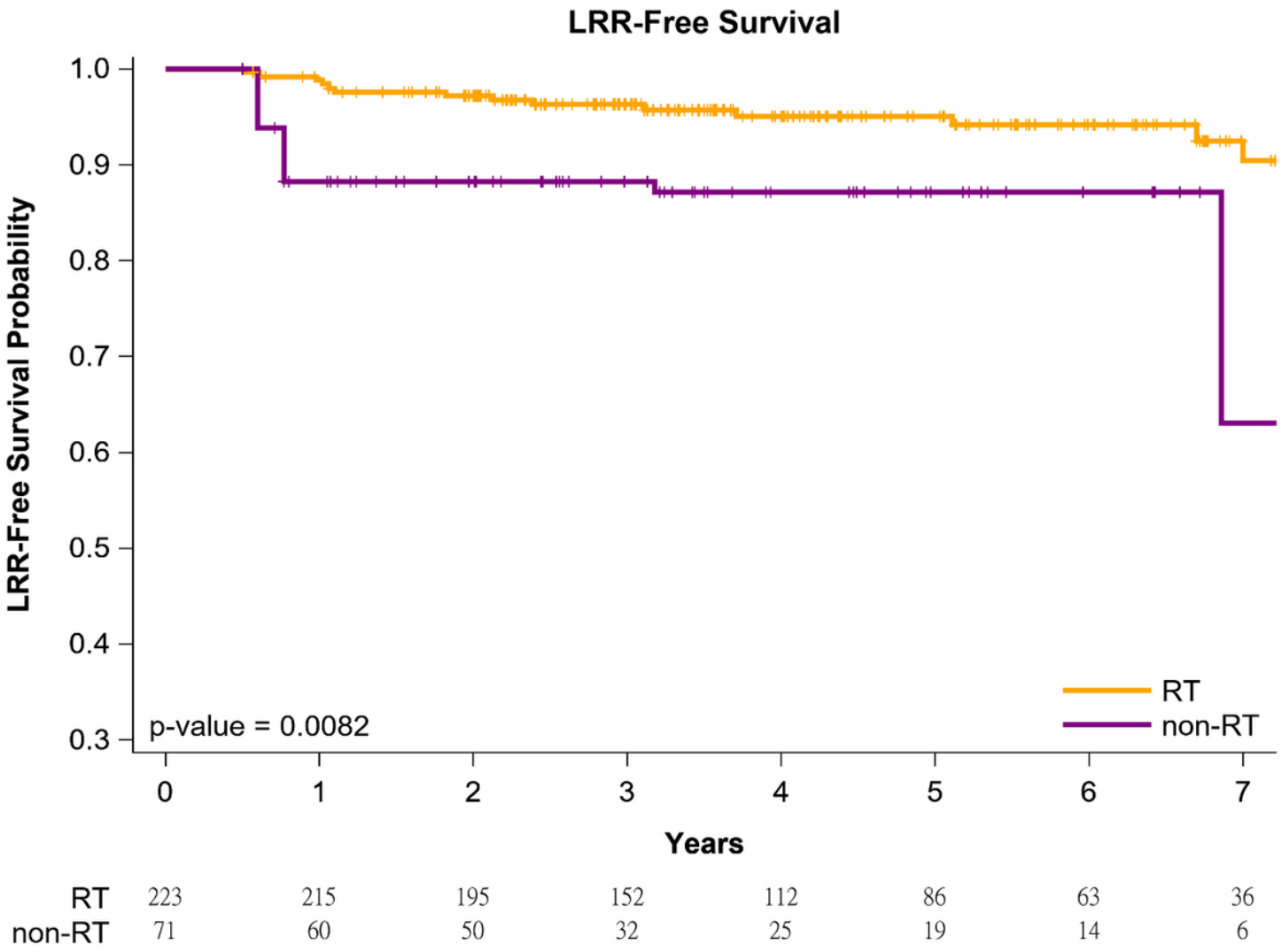

Figure 2

Kaplan–Meier locoregional recurrence-free survival curves of propensity score–weighted population with breast cancer and heart failure with reduced ejection fraction receiving breast conservative surgery

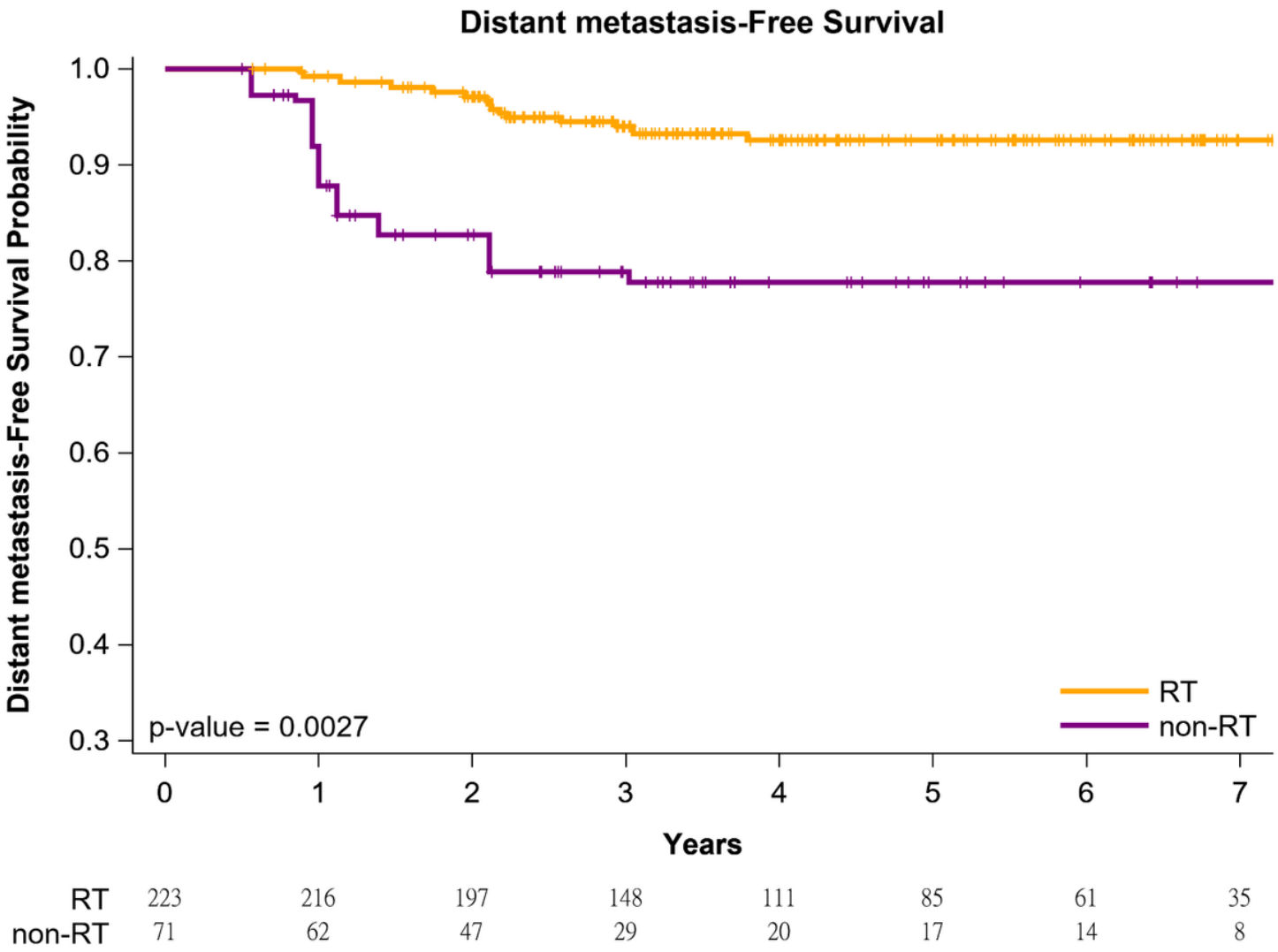

Figure 3

Kaplan–Meier distant metastasis–free survival curves of propensity score–weighted population with breast cancer and heart failure with reduced ejection fraction receiving breast conservative surgery