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RESEARCH LETTER

Assessment of Cardiac Function in Chemotherapy Naive Women With Breast Cancer Undergoing Contemporary Radiation Therapy

Radiation therapy (RT) is an established treatment for breast cancer and is associated with a reduction in disease recurrence and death. Thoracic RT is associated with incidental cardiac exposure, which can lead to a spectrum of radiation-induced heart disease (RIHD) (1). The mechanisms underlying RIHD are multifactorial, including direct cellular damage, endothelial dysfunction, inflammation, and fibrosis (1). Identification of surrogate endpoints that predict the development of latent cardiac RIHD could help to guide primary prevention (2). Previous research has included heterogeneous populations with variability in RT dose and use of combination chemoradiation (2,3), resulting in difficulty in differentiating the adverse effects of each treatment modality. Accordingly, we sought to isolate a population of breast cancer patients undergoing RT without adjuvant chemotherapy.

Chemotherapy-naive women with left-sided breast cancer were consecutively enrolled. The protocol was approved by the institution's Human Research Ethics Committee (HREC/17/Austin/533). Whole-breast radiation without regional nodal radiation was delivered with tangential, 3-dimensional conformal methods. Prescription dose was 50 Gy in 25 fractions or 42.4 Gy in 16 fractions administered over 6 weeks. Treatment planning included deep inspiration breath-hold scans. Mean heart dose (MHD) was calculated.

Patients underwent serial echocardiography with global longitudinal strain (GLS) at 3 time points: baseline, at completion of RT, and 12 months. Left ventricular ejection fraction (LVEF) and GLS were calculated according to the American Society of Echocardiography guidelines. A significant decline in left ventricular function was defined as a decrease in LVEF of more than 10% to below the lower limit of normal (ejection fraction 53%) or a decrease of >15% in GLS compared with baseline, independent of symptoms. The reproducibility of echocardiographic parameters including GLS in our laboratory has previously been reported (4).

High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) were measured daily during the first week of RT, and weekly thereafter. hs-cTnT assays have a limit of detection of 5 ng/l and a coefficient of variation of <10% at the 99th percentile upper reference limit of 14 ng/l. The reference range for NT-proBNP was <125 pg/ml for patients age 0 to 74 years and <450 pg/ml for patients age 75 to 99 years.

Continuous variables are expressed as mean ± SD or median with 25th and 75th percentiles (Q1 to Q3) and compared using the Student's paired *t*-test; change in biomarker concentrations was evaluated by 1-way repeated analysis of variance with Bonferroni correction. Tests of normality were performed using the Shapiro-Wilk test. The data analysis was carried out using Stata 13.0 (StataCorp LP, College Station, Texas). A p value <0.05 was considered statistically significant.

In total, 20 patients were recruited and underwent baseline assessment. One patient was lost to follow-up. Of the 19 patients included in the final analysis, the mean age was 64 ± 12 years. Patient and echocardiographic characteristics are presented in **Table 1**. The mean heart dose was 1.3 ± 0.7 Gy and the maximum heart dose was 3.9 Gy. Baseline LVEF was 62.8 ± 3.9% and GLS was −20.1 ± 2.5%. No significant change was recorded at 6 weeks post-RT in LVEF (63.1 ± 4.7%; p = 0.77) or GLS (−20.2 ± 2.8%; p = 0.95), or at 12 months post-RT (LVEF 64.1 ± 4.2%; p = 0.36 and GLS −20.0 ± 2.8; p = 0.91). Serum hs-cTnT and NT-proBNP were unchanged throughout RT (median [Q1 to Q3] NT-proBNP 59 pg/ml [39 to 115 pg/ml] at baseline vs. 69 pg/ml [48 to 120 pg/ml] at conclusion of the study; p = 0.99; hs-cTnT 5 ng/l [5 to 7 ng/l] at baseline vs. 6 ng/l [5 to 7 ng/l] at the conclusion of the study; p = 0.42).

Although contemporary RT techniques limit the MHD, it is not yet known whether this translates to reduced cardiotoxicity. There is growing enthusiasm in the detection of surrogate endpoints for latent RIHD that could identify patients at risk and guide preventative therapies. Although the use of biomarkers and GLS has shown potential for detecting early signs of chemotherapy-induced cardiotoxicity, we did not determine significant changes in these markers with RT. Unlike previous studies, our patient

TABLE 1 Patient and Echocardiographic Characteristics (n = 19)

Age at diagnosis, yrs	63.6 ± 11.5
Body mass index, kg/m^2	29.4 ± 6.0
Cardiovascular risk factors	
Hypertension	10 (53)
Dyslipidemia	5 (26)
Diabetes mellitus	1 (5)
Current smoker	2 (11)
Hormone receptor status	
Positive	16 (84)
Surgery type	
Breast conserving	18 (95)
Mastectomy	1 (5)
Radiation treatment	
3DCRT	18 (95)
IMRT	1 (5)
Mean heart dose, Gy	1.3 ± 0.7
Baseline echocardiographic parameters	
E/E′	8.4 ± 2.3
Left ventricular end-diastolic dimension, mm	4.5 ± 0.4
Left ventricular end-systolic dimension, mm	2.8 ± 0.4
Interventricular septum, mm	1.0 ± 0.2
Posterior wall thickness, mm	0.9 ± 0.2
Left atrial volume index, ml/m^2	35.3 ± 8.6
Estimated right ventricular systolic pressure, mm Hg	20.0 ± 2.1
Left ventricular ejection fraction, %	
Pre-radiation therapy	62.8 ± 3.9
6 weeks post-radiation therapy	63.1 ± 4.7
12 months post-radiation therapy	64.1 ± 4.2
Global longitudinal strain, %	
Pre-radiation therapy	−20.1 ± 2.5
6 weeks post-radiation therapy	−20.2 ± 2.8
12 months post-radiation therapy	−20.0 ± 2.8

Values are mean ± SD or n (%).

3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulation radiation therapy; RT = radiation therapy.

population had no prior exposure to cardiotoxic therapy such as anthracycline chemotherapy or trastuzumab, which have been independently associated with cardiac dysfunction (5). Additionally, the MHD in our study of 1.3 Gy was low compared with the majority of historical studies examining RIHD (1).

Research using cardiac biomarkers in the detection of RIHD have largely examined cardiac troponins and natriuretic peptides. Although widely available and commonly used, we did not detect any significant changes with RT. The reason for this admittedly is unclear; these markers may be less relevant to RT cardiotoxicity, or it may also be that there is no detectable injury or stress with RT in the acute setting that can be quantified by these circulating markers. Demissei et al. (3) have studied alternative markers indicative of vascular dysfunction and inflammation with promising results.

Given the difference in the magnitude of radiation exposure and chemotherapy use across different disease types and sites, isolating a chemotherapy-naive breast cancer population is a strength of this study. However, the interpretation of our results is limited by the small sample size, observational design, and intermediate duration of follow-up.

In this single-center study, we found no evidence of subclinical myocardial dysfunction or injury during and up to 12 months post-RT. This suggests that RT delivered with contemporary techniques is not associated with early cardiac sequelae. Larger studies are needed to further verify this hypothesis and establish the long-term risks of RIHD.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

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