JACC: CARDIOONCOLOGY VOL. 3, NO. 3, 2021

EDITORIAL COMMENT

Radiation-Associated Coronary Disease in Young Cancer Survivors

The Beat Goes On; We Must Preserve It*

James E. Bates, MD,[a] Ming Hui Chen, MD, MMSc,[b] Louis S. Constine, MD[c]

Radiotherapy (RT) is a critical component of breast cancer therapy, halving the risk of disease recurrence after lumpectomy. RT for breast cancer typically involves tangent fields: 2 opposed fields placed at a tangent to the chest wall on the site of the involved breast. For patients with left-sided breast cancer, this technique delivers a high radiation dose to a small anterior portion of the heart, and this often includes the left anterior descending coronary artery. For patients who require RT to the internal mammary chain nodes, heart RT dose is increased. Although modern techniques (deep inspiratory breath hold, lateral decubitus positioning, or proton therapy) may help reduce heart RT doses, they do not eliminate it.

RT-related cardiac disease is a significant concern in nearly all patients receiving thoracic-directed RT. Seminal papers by Darby et al (1) and van Nimwegen et al (2) established in breast cancer and Hodgkin lymphoma survivors that for each increase of 1 Gy in mean heart RT dose, there is a 7.4% excess relative risk of developing coronary artery disease (CAD). An analysis of the Childhood Cancer Survivor Study found that in pediatric survivors, mean heart doses in excess of 10 Gy were associated with increased risk for late cardiac disease, and this risk appears to continue to climb as survivors continue to age (3). Specifically, there is a suggestion that women may be more susceptible to these RT effects (4). Breast cancer survivors also receive systemic therapy as part of their treatment. Both anthracyclines and anti-HER2 therapies are frequently used in the treatment of breast cancer and may increase the risk of cardiotoxicity.

Multiple prior analyses have suggested that women receiving RT for left-sided breast cancer have an elevated risk of cardiac disease compared to those receiving RT for right-sided disease. However, these studies did not specifically focus on younger, premenopausal patients who have the longest remaining lifespan (and subsequently are at risk for cardiac late effects). In this issue of *JACC: CardioOncology*, Carlson et al (5) aim to address this question, evaluating CAD in the WECARE (Women's Environmental Cancer and Radiation Epidemiology) study among 972 women without pre-existing cardiovascular disease who received RT for breast cancer. Women treated with left-sided RT had a >2-fold risk (HR: 2.5) for development of CAD compared to women treated with right-sided RT. The 27.5-year incidence for CAD was over 10.5% for those receiving left-sided RT, with only 9% of those diagnoses occurring within the first 5 years of follow-up. The additive risk of left-sided RT appears particularly pronounced in the youngest patients: those ages 25 to 39 years receiving left-sided RT had a 27.5-year CAD risk of 5.9% versus 0% in those receiving right-sided RT. This critical analysis expands our understanding of RT-related CAD in breast cancer survivors and reaffirms the magnitude of risk in younger survivors regardless of systemic therapy received.

Several questions remain open in determining the best strategies to minimize the risk of RT-related cardiac disease in breast cancer survivors.

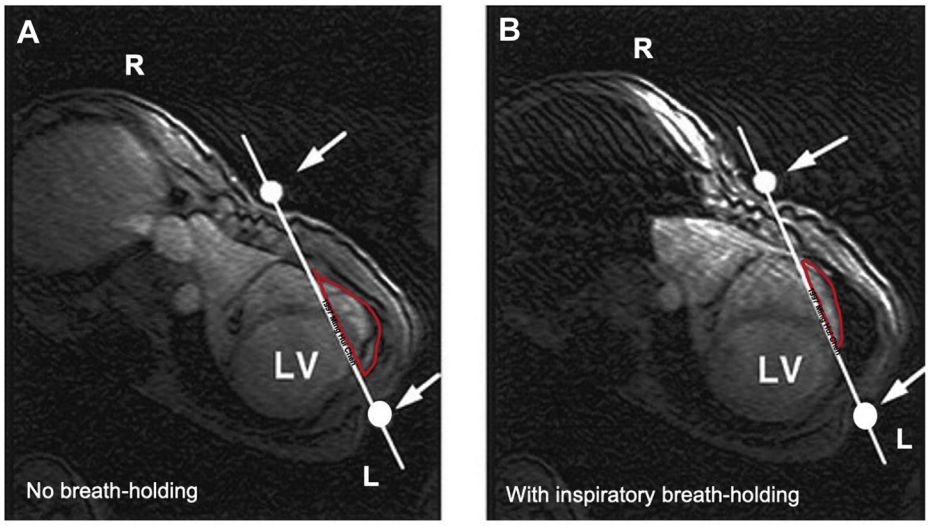
*Editorials published in *JACC: CardioOncology* reflect the views of the author and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From the [a]Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia, USA; [b]Departments of Cardiology and Pediatrics, Boston Children's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA; and the [c]Departments of Radiation Oncology and Pediatrics, Wilmot Cancer Institute, University of Rochester, Rochester, New York, USA.

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 Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2021.08.002

FIGURE 1 Axial Magnetic Resonance Imaging



This magnetic resonance image shows the cardiac volume included in the left breast radiation field **(A)** without and **(B)** with deep inspiratory breath holding. Note the smaller cardiac volume **(red contour)** that would be exposed to radiotherapy with breath holding **(B)**. Modified with permission from Figure 1, Chen MH, Chuang ML, Bornstein BA, Gelman R, Harris JR, Manning WJ. Impact of respiratory maneuvers on cardiac volume within left breast radiation portals. *Circulation*. 1997;96:3269-3272. L = left; LV = left ventricle; R = right.

DO MODERN RT TECHNIQUES SIGNIFICANTLY ALTER THE RISK OF CARDIAC DISEASE?

The WECARE study included young breast cancer survivors diagnosed between 1985 and 2008, with the majority (60%) being diagnosed from 1990 to 1999. RT for breast cancer has changed dramatically in the intervening decades. Dose-fractionation has shifted from the conventional 50 Gy in 25 fractions with or without a boost to hypofractionated regimens of either 42.5 Gy in 16 fractions or 40 Gy in 15 fractions in patients not receiving comprehensive nodal RT. Whether this changes CAD risk remains an open question, although early evidence suggests that it does not.

Evolving and elegant RT techniques may reduce the dose to the heart using several strategies. Partial-breast RT has similar in-breast tumor control as whole-breast RT. By irradiating only a portion of the breast, cardiac sparing can be enhanced. Techniques such as deep inspiratory breath hold and intensity-modulated RT can also reduce the cardiac RT dose in patients receiving RT for left-sided breast cancer. This breath-holding technique, first piloted by cardiologist Chen et al (6) in breast cancer survivors in 1997, is now widely implemented. Chen et al found that the addition of breath-holding maneuvers during RT was able to displace the left heart caudally and out of the RT field in most women (Figure 1). Proton therapy can also reduce heart RT doses. The ongoing RADCOMP (Radiotherapy Comparative Effectiveness) study includes all patients 21 years and older requiring nodal RT for breast cancer and randomizes them to receive either proton or photon RT with a primary outcome of major cardiac events. This study will be critical in determining whether further heart RT dose reductions afforded by proton therapy have a clinically meaningful benefit on CAD. While awaiting the results from RADCOMP, we urge further analyses of late cardiac disease in survivors of breast cancer treated with modern treatment techniques.

WHICH RT DOSE METRIC IS MOST PREDICTIVE OF CARDIAC DISEASE?

Foundational studies describing the risk of RT-related cardiac disease considered mean heart dose (1,2). This likely significantly oversimplifies RT exposure to the heart because it is a heterogeneous organ with many substructures, likely with varying sensitivities to RT. This is particularly critical in patients with breast

cancer; those treated with tangent RT typically have only a very small portion of their anterior heart exposed to a relatively high dose of RT. This portion of the heart often includes the left anterior descending artery and left ventricle in patients receiving RT for left-sided breast cancer (**Figure 1**). It is well established that mean heart dose does not adequately describe the dose to the ventricles and coronary arteries (7) and is not an optimal metric to assess cardiotoxicity in patients with breast cancer.

Burgeoning evidence across disease sites suggests that the specific RT dose to substructures, specifically the left anterior descending artery and left ventricle, may be more predictive of cardiac disease than RT dose to the whole heart (8,9). Better understanding these relationships is critical to developing actionable dose constraints that can be used in RT planning to minimize the long-term cardiac risk in these patients.

WHICH APPROACH TO SURVEILLANCE FOR CARDIOTOXICITY WILL AFFECT CLINICAL OUTCOME AND BE COST EFFECTIVE?

Optimal screening of at-risk patients offers the potential to intervene and mitigate morbid outcomes. Will preclinical detection of toxicity and therapeutic intervention derail a sequence of events that would result in morbidity? What screening modality is clinically and economically efficient? How often should this be performed? As suggested by Carlson et al (5), risk stratification is possible to titrate approaches to higher- versus lower-risk patients. Preexisting cardiovascular risk factors (hypertension, diabetes, smoking history) should also enhance risk stratification. This is clearly a complicated set of questions and would require either prospective trials or elegant modeling with evidence-based assumptions and sensitivity analyses. A recent example of such an effort was performed in survivors of childhood cancer (10).

This study also reaffirms the role of prolonged surveillance for CAD in younger survivors. Given the latency between radiation exposure and the development of cardiovascular events, it is important that young women who have received left breast RT be considered at higher risk over their lifetime. Additive to the increased risk of RT-associated CAD is the age-related risk of CAD. Although Carlson et al (5) examined body mass index and smoking in the WECARE study, other reversible risk factors were not included. Reversible or modifiable cardiac risk factors such as hyperlipidemia and hypertension affect the cardiovascular late effects of RT and should be promptly and aggressively addressed in this population (11,12). Patient education and follow-up with primary care hopefully will help establish lifelong cardiac prevention for breast cancer survivors. Involvement of a cardio-oncologist may increase the likelihood of consistent management of cardiac risk factors and serve as a resource for young women who have survived breast cancer in minimizing the long-term risk of CVD from RT.

Carlson et al (5) reaffirm the enhanced risk for late cardiac disease conferred by RT to left-sided breast cancer in younger adult patients. This adds to our depth of knowledge in this area and underscores the need for continued surveillance in this population. Just as maximizing displacement of the heart outside of the RT field was developed as result of collaboration between cardiologists and radiation oncologists, integration of preplanning RT protocols with teams experienced in cardiac physiology, imaging, and radiation simulation will continue to benefit future breast cancer survivors. Further knowledge of the impact of modern RT techniques and updated RT dose constraints considering cardiac substructure dosimetry will enhance our ability to understand and reduce the burden of late RT-associated cardiotoxicity.

ACKNOWLEDGMENT The authors thank Laura Finger for editorial assistance.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Louis S. Constine, University of Rochester Medical Center, 601 Elmwood Avenue, Box 647, Rochester, New York 14642, USA. E-mail: louis_constine@urmc.rochester.edu.

REFERENCES

1. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998.

2. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol*. 2016;34:235–243.

3. Bates JE, Howell RM, Liu Q, et al. Therapy-related cardiac risk in childhood cancer survivors: an analysis of the Childhood Cancer Survivor Study. *J Clin Oncol*. 2019;37:1090–1101.

4. Rizwan R, Gauvreau K, Vinograd C, et al. Vo_2 peak in adult survivors of Hodgkin lymphoma: rate of decline, sex differences and cardiovascular events. *J Am Coll Cardiol CardioOnc*. 2021;3:263–273.

5. Carlson LE, Watt GP, Tonorezos ES, et al. Coronary artery disease in young women after

radiation therapy for breast cancer: the WECARE Study. *J Am Coll Cardiol CardioOnc*. 2021;3(3):381–392.

6. Chen MH, Chuang ML, Bornstein BA, Gelman R, Harris JR, Manning WJ. Impact of respiratory maneuvers on cardiac volume within left breast radiation portals. *Circulation*. 1997;96:3269–3272.

7. Hoppe BS, Bates JE, Mendenhall NP, et al. The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern radiation therapy era. *Pract Radiat Oncol*. 2020;10:e147–e154.

8. van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood*. 2017;129:2257–2265.

9. Wennstig A-K, Garmo H, Isacsson U, et al. The relationship between radiation doses to coronary arteries and location of coronary stenosis requiring intervention in breast cancer survivors. *Radiat Oncol*. 2019;14:40.

10. Ehrhardt MJ, Ward ZJ, Liu Q, et al. Cost-effectiveness of the International Late Effects of Childhood Cancer Guideline Harmonization Group Screening Guidelines to prevent heart failure in survivors of childhood cancer. *J Clin Oncol*. 2021;38(33):3851–3862.

11. Chen MH, Blackington LH, Zhou J, et al. Blood pressure is associated with occult cardiovascular disease in prospectively studied Hodgkin lymphoma survivors after chest radiation. *Leuk Lymphoma*. 2014;55:2477–2483.

12. He X, Ji J, Dai X, et al. Association of cardiovascular disease risk factors with late cardiotoxicity and survival in HER2-positive breast cancer survivors. *Clin Cancer Res*. Published online June 11, 2021. https://doi.org/10.1158/1078-0432.CCR

KEY WORDS breast cancer, cancer survivorship, coronary artery disease, radiotherapy