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EDITORIAL COMMENT

Early Tracking of Radiation-Induced Cardiotoxicity

Paradigm, Pragmatism, and Possibilities*

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"Nothing in life is to be feared; it is only to be understood. Now is the time to understand more, so that we may fear less."

—Marie Curie (1)

The cardiotoxicity of radiation therapy (RT) has been established for almost a century. Women with breast cancer who receive RT, despite all the technological advances in the delivery and dose of radiation, have 10× the odds of developing heart failure compared with age- and cancer-matched control subjects (2). Moreover, RT to the left chest increases the risk of cardiotoxicity even further (3). Radiated myocytes generate free radicals, which promote oxidative damage and microvascular dysfunction, eventually leading to myocardial fibrosis (4). Experimental studies have suggested that RT-related myocardial fibrosis and reduced microvascular density are associated with increased left ventricular (LV) diastolic stiffness, impaired LV relaxation, and elevated filling pressures despite a preserved ejection fraction (5). Therefore, current guidelines recommend an echocardiogram 5 years after exposure in high-risk subjects and at 10 years in all others, followed by 5-year subsequent interval screening (6). However, radiation-induced damage evolves gradually; therefore, identifying subclinical changes in cardiac structure and function with novel techniques could have important clinical implications and provide an early opportunity to intervene.

In this issue of *JACC: CardioOncology,* Tuohinen et al. (7) report post-radiation–induced diastolic changes in 60 patients with early-stage breast cancer who were treated with RT only. The investigators used strain rate as a marker to assess global or regional RT-induced early changes in diastolic function. All patients were screened for stable or subclinical cardiac conditions at baseline. They measured early diastolic strain rate (SRe) and other speckle-tracking and conventional echocardiographic variables before RT, immediately after RT, and at 3-year follow-up. Overall, there was an insignificant decline in the global SRe, but there was a significant decline in the regional SRe (apical) at a 3-year follow-up. A drop in global SRe was apparent in patients with a relative decrease of more than 15% in global longitudinal strain (GLS) over the study period. Changes in diastolic function and regional SRe appeared before changes in systolic strain, suggesting that diastolic parameters were sensitive markers of RT-induced cardiotoxicity.

How do the study findings enrich the existing cardio-oncology paradigm? Myocardial deformation and mechanics parameters have become key components of phenotyping in cancer-associated cardiovascular disease. In this context, Tuohinen et al. (7) should be congratulated for providing several pieces of new information. First, the average duration of clinical heart failure development is approximately 6 years after RT (2). However, the investigators showed that RT-induced cardiac damage could occur as early as 3 years, which suggested that patients should be screened as early as 3 years after RT. Second, the investigators showed that changes in SRe were more

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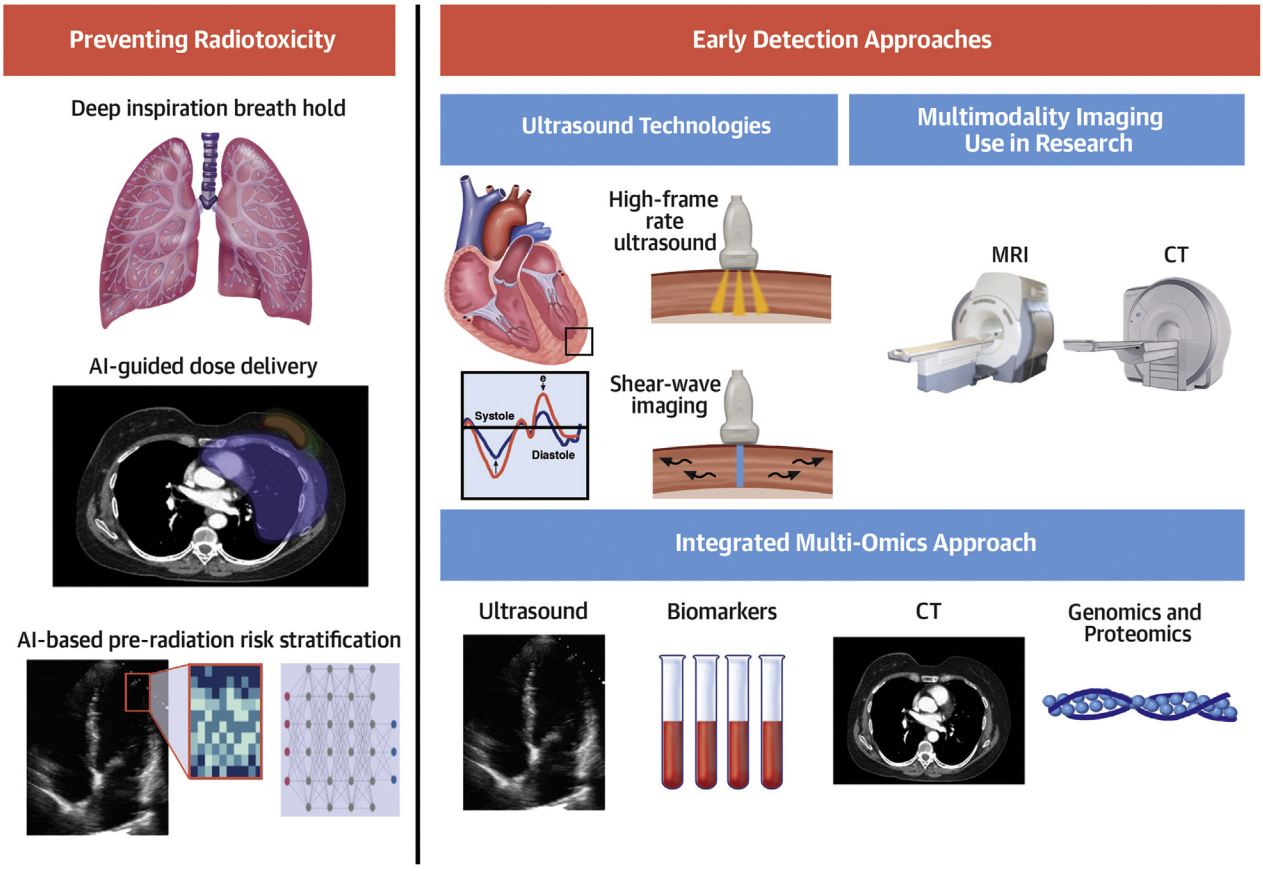
FIGURE 1 Current Knowledge and Future Directions of Early Detection of Radiation-Induced Cardiotoxicity



Advancement in artificial intelligence (AI), integration of multimodality data including clinical biomarkers, and other echocardiographic techniques can improve early detection of cardiotoxicity. CT = computed tomography; MRI = magnetic resonance imaging.

sensitive than changes in GLS. Although this was consistent with previous data that emphasized that diastolic dysfunction preceded changes in systolic dysfunction (5), the incremental value of SRe over GLS was an important observation. Moreover, the investigators showed that regional SRe (apical and anteroseptal segments) might serve as a fingerprint for RT-induced cardiotoxicity. These findings were consistent with the BACCARAT (Breast Cancer and Cardiotoxicity Induced by Radiotherapy) study. Regional differences in the systolic longitudinal strain at baseline and 6 months following RT were also localized to the LV apical region (8). The susceptibility of the LV apex might most likely be related to anatomical proximity of the LV apex to the irradiated region and the cumulative burden of RT dose (9). The findings of Tuohinen et al. (7) of apical involvement signified the previous finding of radiation-induced perfusion defects in the apex on functional nuclear imaging, emphasizing the importance of even early detection of radiation-induced cardiotoxicity. Finally, the investigators observed that the reduction in the SRe was related to the overall burden of associated comorbidities. Striking a balance between effectively treating cancer and avoiding exposure to the cardiac tissue, as well as managing comorbidities, should be an important step in minimizing RT-induced cardiotoxicity.

Despite the novel observations, the study of Tuohinen et al. (7) had limitations. First, the applicability of strain rates were not clinically standardized for their reproducibility and were without thresholds of normality across age and sex. This is important before routine adoption in clinical practice. Second, there is a need for an age-matched control group, which is important because strain rate reduces with advancing

age (10,11). Patients with baseline cardiac conditions subsequently developed the greatest changes in SRe; therefore, the progression of underlying comorbidities could have influenced subsequent changes in SRe.

Where does the field go from here? First, future validation of the observations reported by Tuohinen et al. (7) across larger multicenter studies is needed. Second, the work also suggests a need for focusing on steps that can mitigate the risks of RT. In a small single-center study, the use of contemporary radiation techniques that limited the mean heart dose was associated with no evidence of subclinical myocardial dysfunction or injury as measured using conventional echocardiography and cardiac strain imaging up to 1 year post-RT (12). Perhaps more sensitive imaging methods will be further needed to ensure the safety of contemporary radiation techniques. In this regard, the evolution of newer ultrasound techniques may have relevance—for example, methods for assessing myocardial mechanics using high frame-rate, plane-wave imaging and 3-dimensional tissue Doppler imaging or the assessment of myocardial stiffness using ultrasonic shear wave imaging. This is a technique that measures cardiac stiffness by quantifying the speed of transient tissue distortions that are created and travel perpendicularly to the direction to an ultrasonic beam (13,14). The diagnostic and increment value of these novel techniques over other cardiac imaging modalities (eg, cardiac magnetic resonance) derived direct assessments of myocardial fibrosis using T1 mapping. Extracellular volume fraction assessments will need to be assessed with a direct comparison.

Finally, the addition of bioinformatics and an omics approach that use machine learning techniques to integrate relevant clinical and imaging biomarkers may help predict patterns of individual susceptibility (15) (**Figure 1**). Patients with metastatic cancers often undergo surveillance computer tomography (CT) imaging. The potential development of a pipeline that tracks tissue texture changes over time on CTs may be particularly advantageous to detect early cardiotoxicity. Cardiac structures and chambers can be auto-segmented for region-specific analysis, enabling CT-based analysis (16,17). As we learned in the current study, apical segments are at high risk, and auto-segmentation techniques can focus on this region for early surveillance. This study reinforces the need for developing innovative strategies for predicting and mitigating radiation-induced cardiotoxicity. These techniques offer tremendous opportunities for the cardio-oncologists in designing the blueprint of future therapies by "understanding [RT-induced myocardial disease] more so that we may fear less."

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