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EDITORIAL COMMENT

CMR-Derived Regional Strain and Radiation-Induced Cardiotoxicity

The Importance of Myocardial Inflammation*

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Radiation therapy (RT) is used in more than 50% of all cancer patients and it is a critical component of treatment regimens for Hodgkin's lymphomas, and lung and breast cancers. Even though contemporary techniques use strategies to improve RT delivery, and methods to minimize ionizing radiation exposure to tumor-adjacent tissues without jeopardizing treatment efficacy, cardiac tissue damage is frequently unavoidable (1). Consequently, RT has been consistently associated with cardiovascular morbidity and mortality due to coronary artery disease, valvular heart disease, pericarditis, and cardiomyopathy associated with diffuse fibrosis and arrhythmias (2). Although left ventricular (LV) dysfunction and cardiotoxicity are uncommon findings early after RT, preclinical studies have shown that myocardial tissue damage does occur and, if left untreated, may progress to heart failure (3). There is growing interest in the assessment of LV function by echocardiography-derived global longitudinal strain as a strategy to detect early cardiotoxicity due to its high sensitivity and reproducibility. Strain may also be important in defining cancer therapy-related cardiac dysfunction (CTRCD) prognosis and the role of cardioprotective therapy (4,5). However, cardiovascular magnetic resonance (CMR)-derived strain is also highly accurate and has the additional benefit of a unique ability to identify subclinical pathological changes of the myocardial tissue through novel mapping techniques. T1 and T2 mapping relaxation times become prolonged in the presence of myocardial tissue injury and edema, respectively (6).

In this issue of *JACC: CardioOncology*, Ibrahim et al. (7) present a novel preclinical study in which they explore the utility of CMR imaging to assess LV function and use tissue characterization techniques to establish early imaging markers of RT injury and their association with myocardial histopathological as well as cellular changes. These investigators used an inbred salt-sensitive rat strain that has been previously shown by the authors to be a reproducible model of cardiac tissue injury induced by a high single dose of RT (24 Gy) (8,9). CMR-derived LV volumes, and circumferential, radial, and longitudinal strains as well as T1/T2 maps were acquired 8 and 10 weeks after RT and compared to nonirradiated animals. Subsequently, cardiac tissue was examined to assess interstitial fibrosis, cardiomyocyte vacuolation and necrosis, and inflammatory cell infiltration (mast cells). The authors make several important observations. First, the mean LV ejection fraction increased by 11 and 12 percentage points at 8 and 10 weeks post-RT, respectively, when compared to nonirradiated animals. This was accompanied by an increase in LV mass. Interestingly and despite a preserved LV ejection fraction and a compensatory increase in LV wall thickness, global circumferential strain worsened at these time points and lateral segments of the myocardium were more severely affected. These subacute abnormalities in strain corresponded with a ~27% increase in T2 relaxation times at 8 weeks which slightly decreased by

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10 weeks post-RT, but remained elevated compared to nonirradiated rats. Both global circumferential strain and T2 were associated with post-necropsy qualitative assessment of myocardial necrosis and vacuolation, denoting myocardial edema (10), particularly in the lateral wall where strain was more compromised. Interestingly, the investigators observed a decrease in capillary density along with an increase of mast cell infiltration; prior studies suggest that mast cells are protective against RT myocardial injury (11). However, strong experimental evidence in other models of heart failure suggests that mast cells play a critical role in the fibrotic remodeling of the cardiac extracellular matrix by the production and release of cytokines and growth factors that enhance excess matrix deposition (12). In this study, interstitial fibrosis measured by T1 mapping and histopathology (diffuse and perivascular fibrosis) were unchanged after RT. It is possible that inflammatory cell recruitment precedes the initiation of cardiac fibrotic remodeling. Importantly, these observations raise the provoking question of whether modulation of inflammation may thwart the progression of adverse LV remodeling induced by RT. These findings underscore the complexity of the pathophysiology of myocardial remodeling induced by cancer therapies.

Although it seems clear by the findings reported here that segmental strain deterioration and T2 prolongation are early imaging biomarkers, it remains to be determined if these early changes forecast the development of CRTCD. Furthermore, the complexity of RT in clinical practice limits the interpretation and translation of the results. First, it is important to recognize that the rats in this study received 1 relatively large dose of whole heart radiation that does not resemble the typical fractionated scheme of RT used in humans. Second, the study used healthy adult rats that fail to account for pre-existing cardiovascular risk factors (e.g., coronary artery disease, hypertension, and obesity) or more vulnerable populations such as pediatric and elderly cancer patients. Similarly, an important factor that significantly increases the risk of CTRCD after RT is the use of concomitant cardiotoxic cancer therapies such as chemotherapy and targeted therapies. Third, because CMRs were performed on a 9.4-T scanner, it remains uncertain whether the changes in imaging biomarkers in small animals, especially regional differences, can be detected using clinical 1.5-T and 3-T field strengths, in addition to the lack of standardized analysis protocols, and variability across different vendors.

In summary, efforts such as those reported here conducted by a team of clinicians and scientists continue to be essential and should be encouraged. Ibrahim et al. (7) have shown that CMR-derived segmental strain incorporating tissue characterization techniques are useful to identify subclinical myocardial injury. Most importantly, the implications of this report suggest that future investigations should be directed toward successfully translating the finding into clinical practice to improve the surveillance and prevention of cardiotoxicity in cancer patients undergoing RT.

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