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EDITORIAL COMMENT

Assessing Silent Cardiotoxicity in Long-Term Lymphoma Survivors Treated With Radiotherapy*

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Mediastinal radiotherapy (RT) and anthracycline-containing chemotherapy (ACT) for the treatment of lymphomas, particularly Hodgkin lymphoma (HL), have long been associated with future cardiotoxicity in long-term survivors of this malignancy.[1-3] Multiple studies have reported on the excess risk for cardiac morbidity and mortality in HL survivors.[1-3] In a recent analysis by van Nimwegen et al[3] consisting of 2,524 patients with HL, the 40-year cumulative incidence of cardiovascular disease was 50%, with increased risks for valvular disease and heart failure in those receiving RT or ACT and an additional increased risk for coronary disease in patients receiving RT. Furthermore, a number of studies have characterized, in detail, cardiovascular diseases associated with mediastinal RT and ACT.[4] What has been underreported, however, is evidence of subclinical cardiovascular disease in survivors previously treated with these regimens. Detection of this "silent" (subclinical) disease was previously limited because of a lack of appropriate testing techniques. Cardiac magnetic resonance (CMR) imaging, though, has shown enormous potential in assessment of cardiotoxicity following oncological therapy and may also help identify subclinical disease.

In this issue of *JACC: CardioOncology*, van der Velde et al[5] identify markers of subclinical cardiovascular disease with CMR imaging in survivors of primarily HL. The study included 80 predominantly HL survivors who were treated with mediastinal RT (median RT dose 36 Gy; interquartile range: 36-40 Gy) with or without ACT (88% received ACT) and were disease free for at least 5 years without known histories of coronary artery disease. All patients were age- and sex-matched to healthy control subjects and underwent 12-lead electrocardiography, transthoracic echocardiography, and CMR, with a mean time between diagnosis and CMR of 20 ± 8 years. The investigators report a number of interesting findings. First, when analyzing left ventricular (LV) and right ventricular (RV) function, significantly lower LV ejection fraction (53% ± 5% vs 60% ± 5%; $P < 0.001$) and LV mass (47 ± 10 g/m^2 vs 56 ± 8 g/m^2; $P < 0.001$) and higher LV end-systolic volume (37 ± 8 mL/m^2 vs 33 ± 7 mL/m^2; $P = 0.013$) were found in lymphoma survivors. Although RV ejection fraction was similar between the groups, lymphoma survivors had significantly lower RV volumes compared with healthy control subjects ($P < 0.001$). Both global longitudinal strain ($P = 0.013$) and global circumferential strain ($P < 0.001$) of the left ventricle were reduced in lymphoma survivors. Second, regarding tissue characterization, native myocardial T1 (980 ± 33 ms vs 964 ± 25 ms; $P = 0.007$) and extracellular volume fraction (31 ± 7 mL/m^2 vs 39 ± 6 mL/m^2; $P < 0.001$) were significantly higher in lymphoma survivors with late gadolinium enhancement detected at sites other than hinge point location, in 11% of the survivors. Finally, univariable and multivariable analysis showed that RT dose and diabetes were

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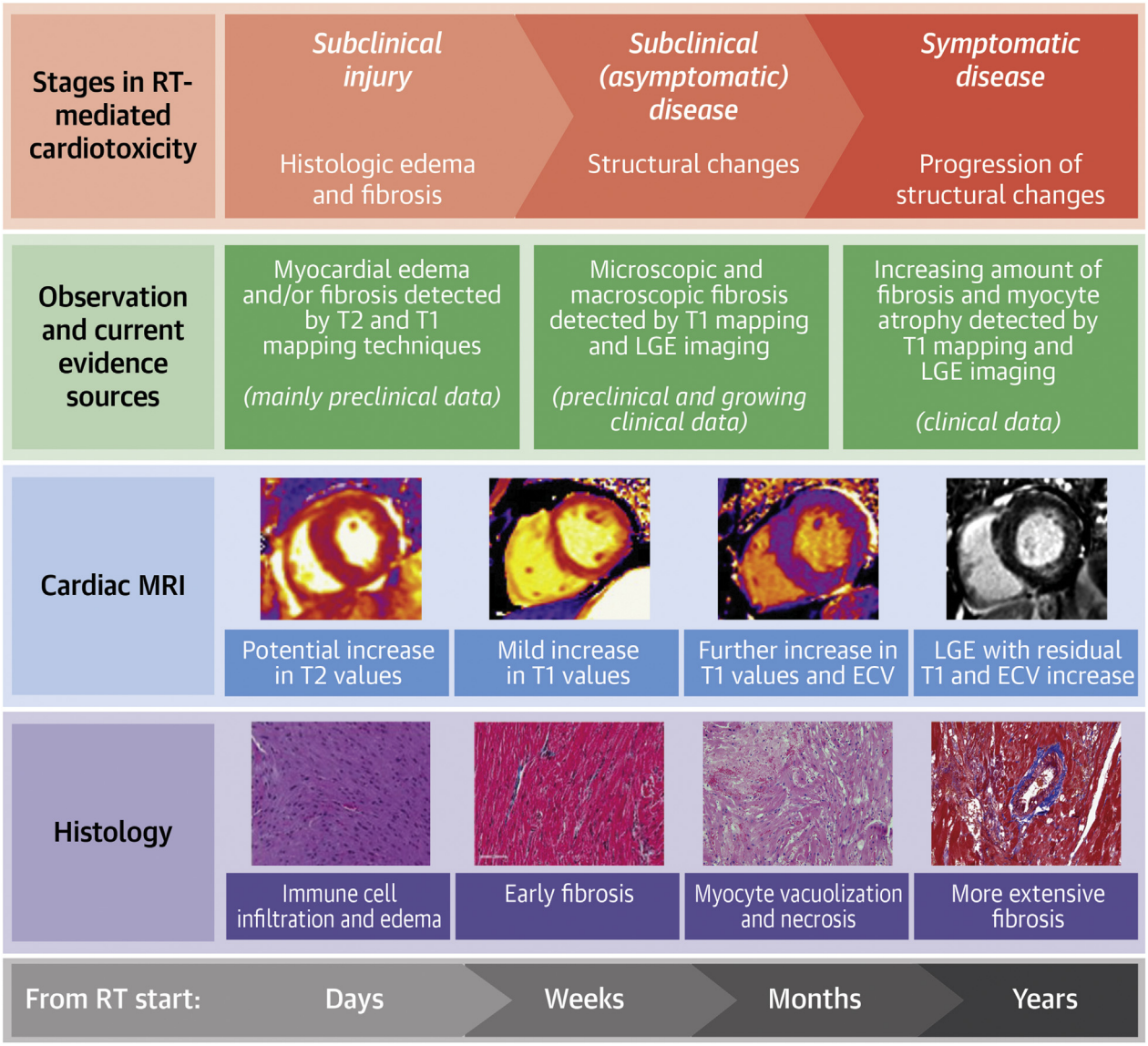
FIGURE 1 **Detectable Stages of RT-Induced Cardiac Injury (Remodeling) Over Time**



Stages of cancer radiation therapy (RT)–mediated cardiotoxicity and the evolution over time of myocardial changes on histopathology and corresponding abnormalities detected by cardiac magnetic resonance imaging (MRI).[6-9] ECV = extracellular volume; LGE = late gadolinium enhancement.

significant predictors for LV ejection fraction, while male sex, time between diagnosis and CMR, and diabetes were predictors of impaired global longitudinal strain.

These data add to a growing body of evidence suggesting that myocardial fibrosis, as measured by CMR, is a prevalent sequela of RT exposure. In preclinical models, RT exposure induces cellular remodeling, hallmarked by early injury with edema, immune cell response, vacuolization, and atrophy and latter histologic fibrosis and cellular apoptosis (**Figure 1**).[6,7] Dating back to the 1960s, serial autopsy studies have well documented the presence of myocardial fibrosis and atrophy to distinguish those with cardiac toxicity following RT treatments.[8,9] However, until recently these changes were almost imperceptible in living patients. CMR, including parametric mapping, provides a novel avenue to understand and identify RT's effects on the myocardium, even during normal living state.[10,11] The

investigators characterize long-term effects of RT on fibrosis development, as well as other imaging measures such as strain, mass, and LV ejection fraction, even in the absence of symptoms.[5] Because of the historically higher doses of RT many lymphomas were exposed to, these data define prevalent change many years after therapy and provide important hints to the changes likely underlying the elevated CVD risk commonly seen in survivors.

The results presented in this study have far-reaching implications beyond HL. RT is used as a primary therapy in a number of other thoracic malignancies in which potentially much higher doses of radiation are delivered to the heart because of the relative radioresistance of these neoplasms in comparison with HL. Although patients diagnosed with HL generally have a more favorable prognosis than those with non-small-cell lung cancer (NSCLC) or esophageal cancer, development of novel targeted therapy and immunotherapy has improved survival rates in this patient population, emphasizing the need to further reduce late complications from therapy.[12,13] Furthermore, even with the competing risk for cancer-related mortality, increased RT dose to the heart was associated with major adverse cardiac events and all-cause mortality in patients without pre-existing coronary heart disease in a large retrospective study of 748 patients with locally advanced NSCLC.[14] Similarly, in esophageal cancer, higher heart doses have been associated with an increased risk for cardiac events, with a recent study reporting clinically significant cardiac events occurring in 18% of patients after completing RT for esophageal cancer.[15] In addition, cardiac events seem to happen much earlier in patients with NSCLC or esophageal cancer than HL, with multiple studies reporting that the majority of events occur within 2 to 4 years after completion of RT.[15]

Putting other malignancies in the context of the study by van der Velde et al[5] raises a number of questions. 1) Is there a role for CMR in screening those at highest risk for cardiotoxicity following thoracic RT? 2) Do the findings of subclinical disease predict future cardiac events? 3) Should CMR, inclusive of T1 and T2 mapping, be performed routinely in the future to rule out early, asymptomatic cardiotoxicity? and 4) How would subclinical disease respond to cardioprotective therapy? The present study provides a startling glimpse of what we might be missing in RT-treated cancer survivors, while lighting a path forward.

Despite remaining questions, this timely study provides a solid foundation for future investigations focused on the role of CMR in predicting incident cardiovascular disease after RT exposure for lymphoma control. If CMR detects subclinical disease earlier in the post-RT period, it may allow a new opportunity to reshape the course of RT-induced cardiotoxic disease, hopefully leading to improvement in patient outcomes.

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