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EDITORIAL COMMENT

Progress Toward Improving Recommended Screening Practices in Survivors of Childhood Cancer at Risk for Cardiomyopathy*

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Improved survival for childhood cancer has led to recognition of late-occurring health complications (1,2), including cardiomyopathy associated with prior anthracycline chemotherapy and/or chest-directed radiation (3-6). Survivors are 15 times more likely than their siblings to develop heart failure (1) and are 7 times more likely than the general population to die of cardiac causes (7). Given that as many as 60% have received anthracyclines and/or chest-directed radiation (8,9), it is critical to appropriately identify those who are at highest risk and/or amenable to early intervention to effectively allocate available medical resources.

To meet this need, many survivorship guidelines have recommended risk-based cardiomyopathy surveillance, in some cases lifelong, beginning after completion of cancer-directed therapy, allowing for early detection and treatment of asymptomatic cardiomyopathy (10,11). Echocardiography has been the preferred screening modality due to its relatively low cost, acceptable sensitivity and specificity, and widespread availability (11). The establishment of large cohort studies has facilitated identification of important demographic and treatment-related risk factors associated with cardiomyopathy (12). However, there has been a paucity of longitudinal studies to inform optimal surveillance strategies, including data regarding the prognostic value of baseline post-treatment and subsequent echocardiograms. With the maturation of these cohorts and accumulation of decades of risk-based assessments, there is now an opportunity to inform optimal screening strategies in a growing population of cancer survivors.

In this issue of *JACC: CardioOncology*, Leerink et al. (13) present findings from a retrospective analysis of surveillance echocardiograms obtained in childhood cancer survivors at risk for cardiomyopathy. They evaluated the risk of left ventricular dysfunction (ejection fraction [EF] <40%), including predictive associations of an EF of 40% to 49% and ≥50% at initial follow-up assessment (~17 years from cancer diagnosis), and validated their findings in an independent cohort. Lower EF at baseline (first echocardiogram ≥5 years after cancer diagnosis) was associated with an increased risk for a subsequent EF <40% (hazard ratio: 9.6 per 10-point EF decrease). Inclusion of the initial EF to cumulative anthracycline and chest-directed radiotherapy doses improved the ability to predict a later EF <40% (integrated area under the receiver-operating characteristic curve 0.74 vs. 0.87).

Compared with a baseline EF ≥50%, a midrange EF (40% to 49%) conferred an 8-fold (hazard ratio: 7.8; 95% confidence interval: 2.1 to 29.5) risk of developing an EF <40%. This is consistent with the rate of progression from subclinical cardiomyopathy to heart failure in the general population (14), affirming risk estimates used to inform the natural history of cardiomyopathy in previous screening cost-effectiveness models (15-17). Additionally, the authors investigated

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the impact of integrating the baseline echocardiogram results on risk-stratification endorsed by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (11). Survivors considered to be at moderate risk by IGHG, who had a baseline EF ≥50%, had a ≤3% risk of developing an EF <40% in the subsequent 10 years: the negative predictive value of which was on the order of 99% (95% confidence interval: 98% to 100%). The results suggested that for at least 75% of survivors, the 10-year probability of developing an EF <40% was ≤3%, potentially resulting in the reclassification of as many as one-half of survivors into a lower-risk IGHG stratum for at least 10 years.

These results add to emerging evidence suggesting that screening for low-risk survivors can potentially be reduced or eliminated (15–18); however, inconsistent definitions of risk have challenged interpretation of results. The IGHG (11) offers a harmonized definition for more recent studies (15) to evaluate, which is a strength of the accompanying paper (13). To date, echocardiogram results have not been included in survivor cardiomyopathy prediction models (19). The inclusion of real-time surveillance data into decision algorithms would mirror strategies utilized in other practices (e.g., colorectal screening), in which subsequent intervals are dependent upon the most recent surveillance findings (20). A conditional approach has not been widely utilized to screen survivors for cardiomyopathy, likely due to a lack of longitudinal data to inform such decision-making. Notably, the strength of this approach would be in the negative predictive value of normal echocardiograms, as in many practices, a midrange EF would prompt referral to and continued management by a cardiologist, thereby removing individuals from screening algorithms.

The authors appropriately acknowledge key study limitations. Notably, the relatively small overall population size and low frequency of events (n = 11), resulting in wide confidence intervals for risk estimates in the derivation cohort, gives pause when interpreting the results. Perhaps the most significant implication of this was an inability to adjust for comorbid conditions such as hypertension. Prior studies have demonstrated that comorbidities potentiate risk associated with cancer treatments (21), and in turn, increase the risk of EF decline over time. Thus, the effects that hypertension and other cardiovascular risk factors may have on the predictive impact of a baseline survivorship echocardiogram remain unknown. Confirmation of the findings of Leerink et al. (13) in large cohorts may assuage these concerns and is essential prior to integration into future guidelines.

Ongoing efforts to reduce low-value care across medical disciplines, such as the Choosing Wisely campaign (22), have focused on practices affecting large populations. While the number of childhood cancer survivors is increasing, achieving a critical mass necessary to fall within this scope is unlikely. Consequently, the responsibility to do so rests on the survivorship research community. The importance is further heightened by poor adherence to survivorship guidelines and that successful strategies to improve adherence have not been widely scalable (23), highlighting a need for more effective resource allocation. Despite these practicalities, a move toward reductions, omissions, or even deviations from fixed-interval surveillance practices may be met with trepidation by providers concerned that less frequent assessments may increase loss to follow-up, delay recognition of potentially mitigatable cardiomyopathy, or overlook high-risk individuals concealed within broad, population-level risk-stratifications. Indeed, patient-level variances (e.g., genetic variants) can substantially increase cardiomyopathy risk in those otherwise classified as “low-risk” by guidelines. Although such variables have not yet been included in routine surveillance practices, future risk prediction efforts may need to integrate clinical, treatment-related, echocardiographic, and potentially genomic variables in determining long-term risk, setting the stage for a precision-survivorship approach to improve resource allocation and clinical care. Despite the aforementioned limitations, this study is believed to be the first to utilize baseline screening echocardiograms to predict subsequent risk for cardiomyopathy. Leerink et al. (13) should be commended for taking a much needed step toward identifying subsets of childhood cancer survivors for whom cardiomyopathy screening can potentially be safely reduced, ultimately lessening the burden on survivors and health care systems.

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