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COMMENTARY

Cardiac Toxicity: The More We Learn, the Less We Know

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Albert Einstein once pointed out "The more I learn, the more I realize I don't know." This quote resonates with us regarding the complex issue of radiation-induced heart disease (RIHD). Over the past few decades, numerous publications have informed our understanding of RIHD. However, despite the growing body of literature, many questions remain unanswered. What dose of radiation to what part of the heart actually causes toxicity? Are there doses that are safe for the heart? What is the mechanism of RIHD? What is the most meaningful cardiac parameter for treatment planning? Should we automatically adopt any technique that lowers cardiac dose? There is vast disagreement in the radiation oncology community on many of these issues; and although progress is being made, we must concede our limited understanding of these seemingly fundamental questions.

In this edition of the *International Journal of Radiation Oncology, Biology, Physics* (the Red Journal), 3 important articles shed light on this highly debated and sometimes emotional topic of cardiac dose and toxicity. These 3 reports (1-3) try to address 3 relevant questions: (*1*) Does treating the internal mammary nodes (IMN) in the radiation field increase the cardiac exposure? (*2*) Does treating the IMN chain increase the chance of having cardiac morbidity? and (*3*) Does using a multifield technique have a positive or negative impact on cardiac dose? The authors of all 3 articles should be commended on completing and reporting well-designed, large-scale studies.

We agree with the sentiment that recent publications (4-6) have led to an increasing trend toward covering the IMN chain in more patients with stage 2/3 disease, making cardiac exposure, optimal treatment planning guidelines, and risks of RIHD more topical than ever. The issue of whether the IMN chain should be irradiated, and for which subsets of patients, is not addressed directly in these articles, and we will therefore not address it directly here.

First, we would like to review our current understanding of RIHD. With thousands of patients and long-term follow-up, investigators at the Early Breast Cancer Trialists' Collaborative Group identified a 1.27 increase in cardiac events in irradiated patients and a 1.12 increase in cardiac death (7). When evaluated by treatment era, it was encouraging to see that patients treated from 1993 to 2001 were not found to have higher rates of heart disease for the first time. This reduction in cardiac morbidity has also been reported from other data sets (8) and has coincided with the advent of computed tomography–based planning and reduced cardiac doses (9, 10). In the following years several other large trials failed to demonstrate a significant difference in cardiac morbidity, suggesting that perhaps radiation-induced cardiac morbidity was no longer a concern in the computed tomography–based modern era (11).

A resurgence of interest in this topic followed the high profile publication from Darby et al (12) in the *New England Journal of Medicine*. This study is often cited for 2 novel findings. First, there is no threshold (or "safe") dose of radiation to the heart. Second, there is a 7.4% increase in relative risk of a major cardiac event for each additional 1 Gy of mean heart dose. Two other important findings from this landmark study that have gained less

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attention are: (*1*) RIHD begins in the first few years after treatment, with more than two-thirds of the risk coming in the first 10 years; and (*2*) the absolute incremental risk of cardiac events is low, though the relative risk is high (based on the data presented in that article's supplemental tables 12 and 13 [12]). For example, for an average 50-year-old women pretreated with modern chemotherapy (typically including cardiotoxic drugs), these tables predict an increase in the risk of experiencing a major cardiovascular event of 10.8% from a baseline of 8%. Thus the attributable absolute increase in risk from radiation therapy (RT) is 2.8%, even though the relative increase in risk is 35%.

In this edition of the Red Journal, Pierce et al (1) provide valuable information from a large, robust data set from a high-quality consortium in Michigan, the Michigan Radiation Oncology Quality Consortium. This study describes the real-world practice across 20 academic and community practices in Michigan. Their data set of nearly 5000 patients demonstrates the value of peer review and quality monitoring. The mean heart doses achieved across these providers in Michigan was very low (<2 Gy) and much lower than historical controls. Not surprisingly, they identified that treatment of the IMN was the largest driver of cardiac dose. This large database should continue to give us insightful information in future publications as the group pursues analysis of more detailed treatment plans in subsets of patients.

Investigators from the University of Michigan also reported clinical cardiac outcomes on more than 2200 patients treated at their institution over the course of more than 20 years (2). They reported that there was no statistically significant increase in ischemic cardiac events in women receiving left IMN RT versus no IMN RT (4.0% vs 5.1%), despite an increase of approximately 2 Gy (from 1 Gy to 3 Gy) when delivering IMN RT on the left side.

A few important points are notable. First, the mean heart doses are much lower than has been described historically with IMN RT (13). The authors stated that they tried to achieve at least 80% the prescription dose of 45 to 50 Gy to the IMN volume, but the actual IMN coverage was not reported.

Second, there was no description of how the IMN clinical target volume (CTV) was contoured. Although we might assume that the IMN contour was similar to that described in the Radiation Therapy Oncology Group atlas, this was not discussed. Moreover, for photon techniques, planning target volume margins are usually used to account for setup uncertainty and motion. For example, in the current national breast protocol (National Surgical Adjuvant Breast and Bowel Project B51), 5-mm margins are added to the CTV contour in the medial and lateral dimensions (14).

Third, the authors acknowledge that they were willing to compromise coverage to reduce heart dose when needed. A recent patterns of failure study from the Mayo Clinic showed that only 53% of IMN recurrences would be included if only the vessel pair is contoured as CTV, suggesting that a larger contour may be needed to cover the IMN areas at risk (15). Studies have also shown that, at baseline, classic 3-dimensional conformal fields often result in poor IMN coverage (16). Other national breast trials, such as Radiotherapy Comparative Effectiveness (RADCOMP)/Radiation Therapy Oncology Group 3510, recommend more stringent IMN coverage of >90% of prescription dose to 90% of the volume of the CTV. In addition, the RADCOMP-recommended IMN CTV extends laterally to include any visible fat (17). Using this IMN coverage requirement, the mean heart dose in RADCOMP participants treated to the left IMN chain with photon therapy is approximately 4.5 Gy with a CTV IMN D90% of approximately 48 Gy (personal communication, Justin E. Bekelman).

It would be helpful to know more about the IMN coverage in the Michigan study to understand how they achieved such low heart doses. It is possible that the mean heart dose achieved in the University of Michigan study is based on more limited IMN coverage and is not representative of the mean heart dose that would result if more-robust IMN coverage was mandated. Because IMN irradiation has been shown to reduce metastatic disease and improve breast cancer survival, there is uncertainty over whether target coverage or heart dose should be prioritized. There are few precedents in our field in which 80% target coverage is acceptable. Thus, given the variation in practice patterns, we call for consensus guidelines on appropriate IMN contouring and coverage.

Despite the issues related to IMN coverage, it is interesting to note that the increase in ischemic cardiac events identified by Dess et al (2) is proportional to the increase that would be predicted by the Darby data. The increase in cardiac exposure from 1 Gy to 3 Gy between treating the IMN nodes and not treating the nodes would be expected to increase the cardiac event rate by 15% per the Darby data, which is quite close to the 18% identified by the investigators in this study. The authors from the University of Michigan correctly acknowledge this limitation, stating that an 18% relative increase might become statistically significant with more patients and longer follow-up.

So can we conclude that IMN RT does not increase cardiac toxicity? Not on the basis of the data presented here, but it is probably fair to conclude that the absolute toxicity is low as long as the cardiac dose is kept low. It is also satisfying that these data seem to corroborate the Darby estimates of additional attributable risk based on mean heart dose.

The third article in this edition of the Red Journal focuses on the how to optimize treatment delivery to limit cardiac toxicity (3). Investigators from Yale analyzed a community data set from 21st Century Oncology and found that multi-beam IMRT resulted in significantly higher heart dose (4.7 Gy vs 2.0 Gy) than standard tangent fields. In this study most of the patients had early-stage disease and were