Editorial Commentary

Radiation and cardiovascular disease

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Cardiovascular disease and cancer are the two leading causes of death in the US (1). By year 2030, it is estimated that there will be more than 22.1 million cancer survivors in US (2). With increasing cancer survivorship, further emphasis has been placed on reducing cancer treatment related cardiotoxicity. Radiotherapy is a common cancer therapeutic strategy and is especially important in treating breast cancer, lung cancer, and lymphomas. Autopsy studies have shown that patients treated with radiation therapy develop various cardiac abnormalities including coronary artery disease, pericardial disease, valvular disease, and myocardial fibrosis that may lead to heart failure both with preserved and reduced ejection fraction (3). The Swedish Council of Technology Assessment in Health Care performed a systematic review of radiation therapy for breast cancer which included 41,204 patients and it showed strong evidence of cancer disease free survival but the benefits were abrogated by strong evidence of an increased non-cancer mortality in those receiving radiotherapy (4). There was moderate evidence that cardiovascular disease was the cause of increased non-cancer mortality (4). Patients with lymphoma treated with radiotherapy showed a 21% incidence of cardiac complications which were observed late after radiotherapy (5). Patients with lung cancer receiving radiotherapy are often inoperable and have high cancer mortality but cardiac toxicity is still seen and is independently associated with mean heart dose (6).

The recognition of radiation-induced heart disease has led to several changes in how radiotherapy is administered with a focus on limiting cardiac doses. In addition, radiation techniques, such as breath holds and computerized tomography (CT) based treatment planning, have helped to minimize cardiac radiation. For patients with breast cancer treated with older techniques higher mortality rates due to myocardial infarction were observed for those with left sided breast cancer when compared to those with right-sided disease (7). Using modern radiotherapy techniques, the risk of cardiac mortality did not increase for patients who received left-sided irradiation for breast cancer, compared with right sided irradiation, for the 10–12 years of follow up after treatment (8,9). The cardiac toxicity is dependent on several factors, which include total dose, mean heart dose, fractionation schedules, and percentage of the heart receiving radiation (10,11).

Radiation induced heart disease is an all-encompassing phrase for the cardiac side effects from radiotherapy. While this term is inclusive it lacks specificity. This creates difficulty for identifying mechanisms and predictors of a multi-faceted and ill-defined outcome. In addition, heart disease and cancer have several shared risk factors. While cardiovascular events are independently associated with mean heart dose, they are also independently associated with the patient's baseline cardiovascular comorbidities and risk factors (6). Furthermore, patients with cancer receive chemotherapy in addition to radiotherapy. Anthracyclines, which have well-established cardiotoxicity, are commonly used in treating breast cancer and lymphomas. Patients with breast cancer over-expressing HER2 also receive trastuzumab, which has known cardiotoxicity. Patients exposed to radiation therapy are likely more predisposed to develop cardiomyopathy (12).

In a retrospective cohort study involving 14,358 cancer survivors, it was found that survivors of cancer were significantly more likely than siblings to report congestive heart failure [hazard ratio (HR) 5.9; 95% confidence interval (CI), 3.4 to 9.6; P<0.001]. Exposure to 250 mg/m^2 or more of anthracyclines and radiation dose of more than 1,200 cGy to the heart increased the relative hazard of congestive heart failure by 2- to 6-fold as compared to nonirradiated survivors (12).

The interaction among the different cardiac side effects of radiation complicates the picture. For example, radiation induced aortic stenosis can lead to heart failure but it is unclear how much and what role concomitant radiation related cardiac fibrosis plays in such cases. The task of investigators and cardiologists is to tease out the role of each of these factors, some radiation-related, some due underlying risk factors and some a combination of both.

The study by Demissei *et al.* (13) represents one of the few prospective studies to look at cardiac biomarker changes early after radiotherapy. The study is novel in that it examines both traditional cardiac biomarkers such as high sensitivity troponin T (hs-cTnT) and N-terminal B-type natriuretic peptide (NT-proBNP) in addition to a vascular biomarker in placental growth factor (PIGF) and an inflammatory biomarker in growth differentiation factor 15 (GDF-15). The hope is that by identifying early cardiac damage by changes in biomarkers we will be able to predict those patients who may develop clinical radiation induced heart disease. Earlier identification may allow for better prognostication and more aggressive monitoring or intervention for this group of selected patients.

Troponin

Cardiac biomarkers including troponins and natriuretic peptides are well-established tools for detecting ischemia and cardiac damage due to clinical conditions such as heart failure and left ventricular hypertrophy (14). They have been increasingly studied for utility as measurement tools to detect subclinical radiotherapy-induced cardiac damage. The findings of Troponin T decrease in both breast cancer and lymphoma/lung cancer patients presented by the authors is an interesting finding that the authors suspect was from prior anthracycline administration resulting in elevated levels at the beginning of radiotherapy (13). Early studies found that troponin T levels did not change acutely during radiotherapy for breast cancer, suggesting that should not be used as a marker of radiotherapy damage (15). Similarly, in a prospective study of patients with thoracic malignancy, only 2 out of 25 patients (of which one had a history of hypertension and diabetes mellitus) had transient detectable Troponin I level at the end of radiation therapy (16). Studies have shown an increase in troponin T level early after radiotherapy but still it is not clear if these portend to the development of clinical cardiovascular events or not (17,18). These and other studies of biomarkers and their association with chemotherapeutic agents, have resulted in the inclusion of troponin assay in American Society of Echocardiography guidelines for monitoring of chemotherapy related cardiac dysfunction (19). The authors defined an elevation in troponin T as an increase above 14 ng/L or a 30% rise (13). It is worth noting that all patients had values less than 100 ng/L both pre and post radiotherapy with most having values less than 50 ng/L (13). It is debatable what constitutes a clinically significant cut-off of troponin T with recommendations for 52 or 100 ng/L for acute myocardial infarction (20). Regardless, the role of troponin T or I in monitoring or diagnosis of radiation-induced heart disease is still not clear.

BNP

B-type natriuretic peptide (BNP) and the cleavage fragment, NT-proBNP are useful biomarkers to detect myocardial strain as it is released by ventricles in response to myocyte stretch and has been implicated in the regulation of cardiac remodeling (21). The authors found no significant change in NT-proBNP levels pre and post radiotherapy as defined by a 30% elevation. Unfortunately, as with troponin T, this is another readily available cardiac biomarker that has not clearly shown to be a predictive marker of radiation induced heart disease. One study found that even at 5 years post radiation in breast cancer patients, the BNP was still normal. Although this study did correlate the change in BNP with the mean heart and ventricular dose received (22). This same correlation between BNP and heart dose received has been observed in additional studies although later than at 1 year (23). Further long-term studies are needed to assess whether these small early incremental changes in BNP or NT-proBNP correlate with long-term clinical outcomes.

PIGF, GDF-15

PIGF and GDF-15 have been studied in the context of predicting the development and progression of

cardiovascular disease in the general population (24,25). The proposed mechanism of radiation-induced cardiotoxicity is early acute inflammation of small and medium-sized vessels, with hypoxia-induced cardiomyocyte necrosis as a result of microvascular damage and interstitial fibrosis (26). PIGF contributes to angiogenesis and atherogenesis through vascular inflammation and plaque destabilization. GDF-15, as a cytokine member of the transforming growth factor β family is expressed and secreted in response to tissue injury, inflammation, oxidative stress, hypoxia, and oncogene activation. Demissei *et al.* observed that only patients with lymphoma/lung cancer who had received a higher mean cardiac radiation doses as opposed to breast cancer patients developed significant increases in PIGF and GDF (13). This provides valuable insight to understanding the pathophysiology of radiation-related cardiac injury and that at least early effects are more related to the vascular biomarkers than the traditional troponin and BNP biomarkers.

LVEF and strain

Echocardiographic imaging has demonstrated detection in early changes in left ventricular ejection fraction (LVEF) and global longitudinal left ventricular strain, which may be a promising method of identifying subclinical early regional myocardial dysfunction. LVEF decrease and strain increase were found to be related to cardiac doses (27). While it has not been delineated which cardiac chambers are affected most by radiation, some studies have found a significant association with the dose to the left ventricle (28). Factors that have been considered include how much total muscle volume compared to vascularization contributes to making the cardiac tissue more sensitive to the effects of radiation. With ventricles comprising the bulk of cardiac muscle, it has been suggested that dose escalation in the ventricles is one of the critical factors leading to radiotherapy-induced cardiac damage.

The authors did not find an association between early biomarker changes and changes in LVEF, longitudinal strain, or circumferential strain (13). Very few studies have assessed the early changes in strain after radiotherapy and most are confounded by recent cardiotoxic chemotherapeutic administration. Despite this, some small studies have seen early changes in strain and strain rate after radiotherapy. In particular Erven *et al.* showed left-sided breast cancer patients had reduced strain and strain rate immediately following radiotherapy that persisted at 2 months (29). Similarly, left-sided breast cancer patients receiving radiotherapy showed a worsened strain at 2 months post radiotherapy as described by Lo *et al.* (30). Limited evidence for early changes in strain imaging after radiotherapy exists but may have a role in predicting eventual cardiovascular events.

Conclusions

With improvement in cancer therapy, survival rates continue to improve and a greater focus is needed on the toxicities of radiotherapy. Understanding whether known biomarkers of cardiac damage, inflammation or angiogenesis can identify patients at risk of cardiotoxicity may allow for insight into radioprotective drugs, tailored early intervention, monitoring and appropriate cardiac follow-up, or modification of mediastinal radiation therapies to prevent further toxicity. The role of early changes in biomarkers and advanced imaging modalities such as strain imaging need further study for their ability to predict long-term sequelae. Possibly a combined approach of biomarkers and imaging will allow us to identify those at greatest risk.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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