CARDIOVASCULAR TOXICITIES OF BREAST CANCER TREATMENT: EMERGING ISSUES IN CARDIO-ONCOLOGY

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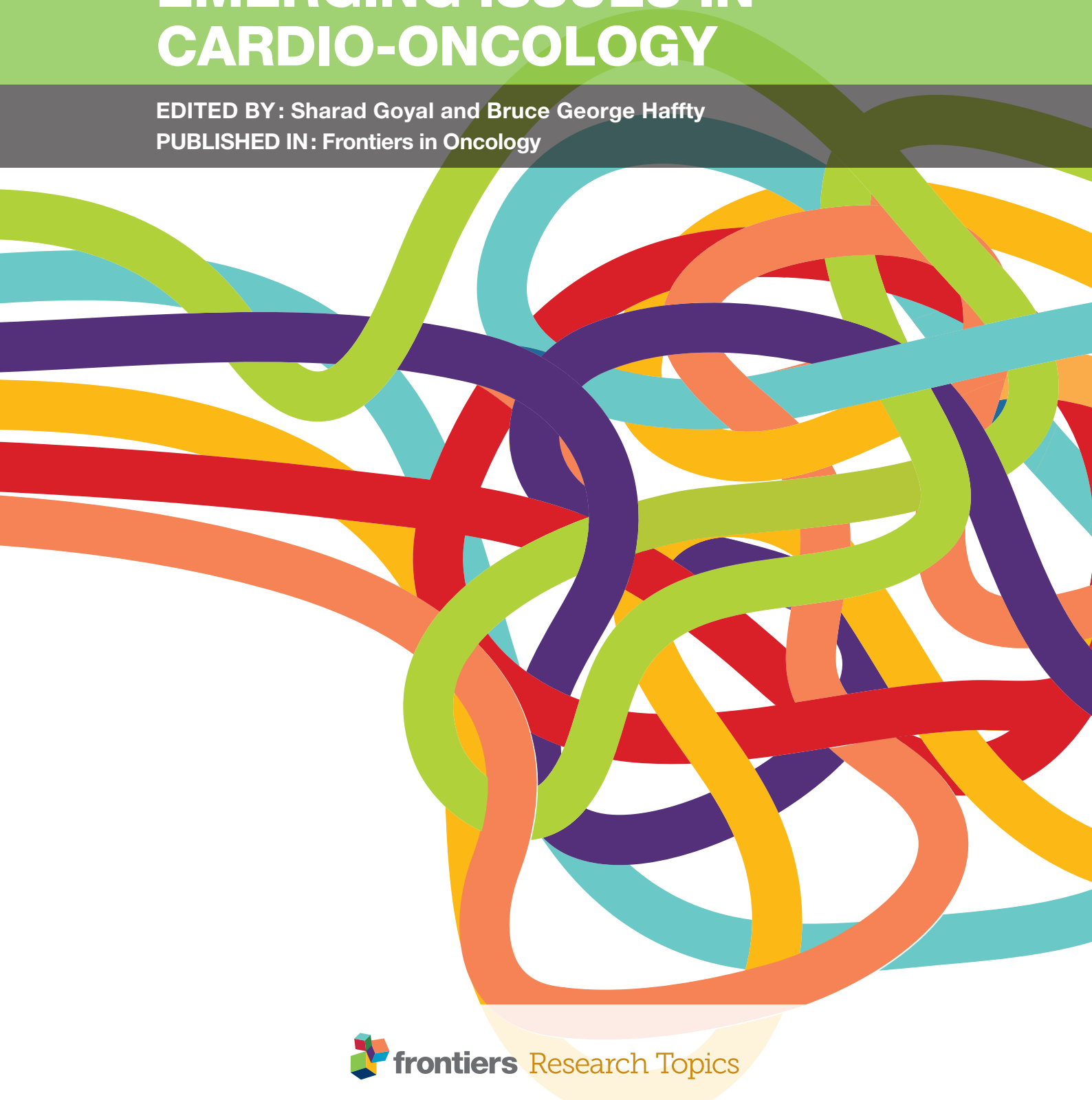

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CARDIOVASCULAR TOXICITIES OF BREAST CANCER TREATMENT: EMERGING ISSUES IN CARDIO-ONCOLOGY

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Cancer and cardiovascular disease (CVD) are the two most common causes of mortality and morbidity worldwide. The incidence of both cancer and cardiovascular disease increases with age. With increased life expectancy, the burden of both these diseases will increase substantially in coming years. Patients with CVD share multiple common risk factors and lifestyle behaviors in addition to frequently suffering from multiple comorbid conditions. Tobacco use, hypertension, high cholesterol, diabetes, physical inactivity, and poor nutrition are all established risk factors of heart disease. Patients with diseases such as breast cancer may develop CVD from treatment, such as use of chemotherapy and RT. Effects on the heart are a potentially significant and serious clinical problem in radiation therapy treatment of breast cancer. Over the course of the past 50 years, there have been great advances in the delivery of RT due to the development of new techniques, beam energy, improvement in imaging modalities, and development of image registration strategies. It is hypothesized that cardiac damage from RT is correlated to the dose absorbed by the heart and differs between left- and right-breast radiotherapy. The damage to cardiac micro- and macro-vasculature is the pathophysiological cause of RT-related heart disease.

Given the growing clinical relevance of cardio-oncology, this Frontiers in Oncology Research Topic provides a venue for disseminating focused reviews and cutting edge research in this quickly growing field. We encourage submission of original papers and reviews dealing with cardiac toxicity after breast cancer treatment, motion management to reduce cardiac exposure, imaging to evaluate potential cardiac toxicities and primary prevention of cardiac disease in the breast cancer patient.

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EDITORIAL
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Cardiovascular toxicities of breast cancer treatment: emerging issues in cardio-oncology

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In 2015, the American Cancer Society estimates that 234,000 new cases of breast cancer will be diagnosed along with an additional 60,000 cases of carcinoma *in situ*. Nearly 40,000 women will die due to breast cancer annually (1). Current management options for Stage 0, I, & II breast cancer include mastectomy, breast conserving surgery (BCS), or breast conserving surgery followed by whole breast radiation therapy (BCS + RT); the use of chemotherapy is independent of local therapy. Coronary artery disease (CAD) and cerebrovascular disease (CVD) are the first and third leading causes of death, respectively, among men and women in the United States (2). Patients with CVD share multiple common risk factors and lifestyle behaviors in addition to frequently suffering from multiple comorbid conditions. Tobacco use, hypertension, high cholesterol, diabetes, physical inactivity, and poor nutrition are all established risk factors of heart disease. The carcinogenic potential of antihypertensive medications has been widely debated and while a meta-analysis found no increase in cancer incidence or mortality, they could not rule this out with certain combinations of drugs (3). In addition, as antihypertensive medications for cardiovascular disease improve, patients are living longer and are at greater risk for developing cancer. Moreover, patients with diseases such as breast cancer may develop CVD from treatment, such as use of chemotherapy and radiation therapy (RT). Inherently within these competing risks of morbidity and mortality lays the intersection of the disciplines of cardiology and oncology.

Cardio-oncology is a relatively new field which offers an interdisciplinary and integrative management approach to cancer patients with cardiovascular risks specifically designed to mitigate risks of oncologic therapies and provide early detection and treatment of those at greatest risk of cardio-toxicity. Given the growing clinical relevance of cardio-oncology, this *Frontiers in Oncology Research Topic* is focused on providing information to practitioners in this quickly growing discipline. In this research topic, Mookadam et al. eloquently frames the current practice in cardio-oncology and provides future strategy and direction for this novice field.

Effects on the heart are a potentially significant and serious clinical problem in the treatment of breast cancer with RT. Over the course of the past 50 years, there have been great advances in the delivery of RT due to the development of new techniques, beam energy, improvement in imaging modalities, and development of image registration strategies. In this research topic, Yue et al. and Chen et al. present novel techniques to track cardiac motion during radiation treatments using fluoroscopy and cardiac MRI, respectively (4, 5). In addition, Beck et al. reviews the various radiotherapy treatment techniques used in breast cancer patients to reduce cardiac dose (6). The study reported by Merino Lara et al. attempts to translate the mean cardiac dose for various breast radiotherapy techniques to the risk of a major cardiovascular event (7). Finally, an editorial by Khan and colleagues expressively frames the debate of cardiac irradiation into perspective (8).

It is hypothesized that cardiac damage from RT is correlated to the dose absorbed by the heart and differs between left- and right-breast radiotherapy. The damage to cardiac micro- and macro-vasculature is the pathophysiological cause of RT-related heart disease. Taunk and colleagues summarize the literature regarding the underlying pathologic abnormalities and mechanisms of RT-related heart disease (9).

Other manuscripts in this issue reflect the eclectic nature of the field of cardio-oncology. Sharp and George review the potential benefit of stem cell therapy against cardio-toxicities from breast cancer treatments, while Tian et al. review the literature of serum biomarkers of cardiac toxicity after breast cancer treatments (10, 11). Finally, Guo and Wong discuss cardiovascular toxicities of chemotherapy and targeted therapies used in the systemic treatment of breast cancer (12).

It is our hope that through this research topic, we may continue the dialog of reducing collateral damage to the cardiovascular system by breast cancer therapies, both local and systemic. Guidelines regarding the prevention and treatment of cardiac toxicities are scant and collaborative efforts are needed to facilitate their development.

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Intersection of cardiology and oncology clinical practices

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INTRODUCTION

Globally, cancer is diagnosed in approximately 13 million people each year. Approximately 1.6 million cancer patients are seen by cancer clinics across the United States (US) at this time. Over the next two decades, cancer incidence is estimated to increase by approximately 45% to 2.3 million (1). In the US, the 5-year relative survival rate of patients diagnosed with cancer in 1975–1977 was 50%, improving to 68% in the period 1999–2005. Novel targeted chemotherapeutic agents and improved diagnostic techniques are responsible for this increased survival. However, with the improvement in life expectancy, the adverse effects of chemotherapeutic agents, especially cardiotoxicity, is an emerging health problem. Cardiovascular toxicity on its own has a detrimental effect on both the quantity and quality of life independent of the oncological prognosis.

Currently, more than two million women with breast cancer are at risk of anthracycline cardiotoxicity in the US (2). Human epidermal growth factor receptor II (HER2) positive disease comprises approximately 25% of all breast cancer patients and is associated with more aggressive disease activity and worse prognosis. Trastuzumab, a humanized monoclonal antibody used for patients with HER2 positive breast cancer in conjugation with chemotherapy, can provide longer survival and 20% reduction in risk of death (3). Cardiotoxicity becomes an important health issue because up to 27% of women with breast cancer receiving anthracyclines, cyclophosphamide, and trastuzumab showed cardiac dysfunction (3). Breast cancer mortality is reduced by approximately one-third, but the risk of heart toxicity is five times more likely for women receiving trastuzumab than women receiving standard therapy alone (4). Patients showing signs of cardiotoxicity often require a dose reduction, a change in the schedule dosing or even cessation of treatment with attendant consequences. Many patients with an asymptomatic decrease in left ventricular ejection fraction (LVEF) are receiving neither the American College of Cardiology/American Heart Association Class I-indicated treatments nor cardiovascular specialty consultation (5).

Concern for cardiotoxicity is not restricted to breast cancer survivors. Based on National Cancer Institute (NCI) data, the number of new renal cancer patients in 2013 is expected to be 65,000. In Europe, the incidence of renal cell carcinoma (RCC) has doubled in the last three decades (6). Improved treatment strategies have increased the 5-year survival of patients with RCC from 50% in 1975–1977 to 72% in 2002–2008. Within the last decade, the US Food and Drug Administration (FDA) has approved six drugs for the treatment of RCC including multitargeted tyrosine kinase inhibitors (TKIs); antibodies to vascular endothelial growth factor (VEGF); and mammalian target of rapamycin (mTOR) inhibitors. Sunitinib, a novel multitargeted TKI, has proven efficacy in advanced metastatic RCC demonstrating an increased median progression free survival of 8.3 months in these patients (7). In a study by Hall et al. (8), five of the approved targeted therapy drugs (sorafenib, pazopanib, bevacizumab, everolimus, and temsirolimus) have cardiotoxic side effects. In this 159-patient study, 73% of patients experienced some form of cardiotoxicity ranging from hypertension to severe heart failure (8). In a cohort of patients with renal and non-renal carcinoma, sunitinib was found to be associated with a 3.3-fold higher risk of heart failure (9). Other targeted agents such as imatinib mesylate, Dasatinib, Nilotinib, and Sorafenib are prescribed for treatment of various hematological malignancies, hepatocellular carcinoma (HCC), gastrointestinal stromal tumor (GIST), and myeloproliferative/myelodysplastic diseases and have been shown to be strongly associated to cardiotoxicity (10–13). Imatinib has been shown to be associated with decline in LVEF, especially in patients with other comorbidities including coronary artery disease, diabetes, and hypertension (10).

CURRENT PRACTICE FOR DETECTING CHEMOTHERAPY-INDUCED CARDIOTOXICITY

The overlap of symptoms between diagnosis of cancer, symptoms of cardiac dysfunction, and the wide spectrum of cardiac injury caused by chemotherapy makes the diagnosis of cardiotoxicity a challenge. These side effects can be categorized as: (a) direct cytotoxic effects of chemotherapy resulting in systolic dysfunction; (b) cardiac ischemia; (c) cardiac arrhythmia; (d) pericarditis; (e) or chemotherapy-induced repolarization abnormalities. Early diagnosis of these abnormalities requires routine baseline and post-chemotherapy monitoring of patients' cardiac status using symptoms, vital signs, and simple ancillary tests such as an electrocardiogram (ECG), echocardiogram, serum troponin levels, serum brain natriuretic peptide (BNP) where applicable and, less frequently, radionuclide angiocardiography.

The most common practice in the evaluation of cardiac function for patients on chemotherapy is ejection fraction assessment by echocardiography. Cardiotoxicity is most commonly defined as a reduction of the LVEF of >5% to that of a <55% with symptoms of heart failure or an asymptomatic reduction of the LVEF of >10 to <55% (14). Serial evaluation of LVEF multiple gated acquisition scan (MUGA) is currently used widely to monitor for cardiotoxicity secondary to chemotherapeutic drugs. In comparison to two-dimensional echocardiography, MUGA has lower inter- and intra-observer variability in measurement of LVEF. However, it carries risk of radiation exposure and, like the two-dimensional (2D) echocardiogram, provides limited information regarding cardiac structure and diastolic function, which limits its ability to detect subclinical myocardial damage (15, 16).

Three-dimensional (3D) echocardiography is reported to be more accurate than 2D echocardiogram in terms of intra- and inter-observer as well as test–retest variability (17) and cardiac magnetic resonance imaging for estimation of cardiac volumes and EF measurement (18). The myocardial motion during a systole is a complex phenomenon with shortening both longitudinally and circumferentially while thickening radially. Early cardiotoxic change in one of the myocardial motion can be compensated by another, giving a normal EF on testing. Chemotherapy-induced cardiotoxicity is regional, causing an ultrastructural damage that can precede the functional change of reduction in LVEF. Hence, assessing myocardial mechanics through deformation using strain analysis has emerged as a novel method to detect these early changes in myocardial function. Color tissue Doppler imaging uses the frequency shift between the original and tissue-reflected sonographic waves to calculate various cardiac functional parameters such as velocity, displacement, strain, and strain rate (SR). As the Doppler can only measure and detect changes in the direction of the sonographic beam, the Doppler-derived strain measurements have several restrictions such as angle dependency and inter-observer variability. Vector velocity imaging is another echocardiographic technique to quantitatively analyze myocardial mechanics, which is relatively angle independent. This technique is based on detecting frame-to-frame analysis of unique natural acoustic myocardial features referred to as "speckles." These "speckles" from the myocardium in conjunction with 2D or 3D echocardiography are analyzed for motion in longitudinal, radial, and circumferential directions simultaneously. This is a semi-automated technique where manual delineation of the myocardium, followed by automated tracking software using a complex algorithm for the measurement of instantaneous velocity vector for individual speckles measured by analyzing their frame-to-frame spatial variability. These speckles are then added to give global values for myocardial functional parameters. The ideal tracking requires good image quality, optimum frame rate and manual readjustment of tracking if necessary for proper wall motion analysis by the software (**Figure 1**). The 3D analysis of the speckle tracking has the theoretic advantage of tracking the speckle in all of the three dimensions simultaneously, which is not possible with 2D speckle tracking and Doppler tracking, and therefore, permits comprehensive analysis of cardiac function. Unlike LVEF measurement, speckle tracking allows complex analysis of all the physiological myocardial activity during a cardiac cycle including movement in longitudinal, circumferential, and radial direction and measurement of the twist and torsion of the heart. In a few studies, the peak systolic radial, longitudinal, and circumferential strain decreases with elevation in plasma troponin have been validated to be early predictors of cardiotoxicity by anthracyclines and trastuzumab (19). In general, a reduction of longitudinal strain >10% from baseline after 3 months may predict future cardiac injury with a sensitivity and

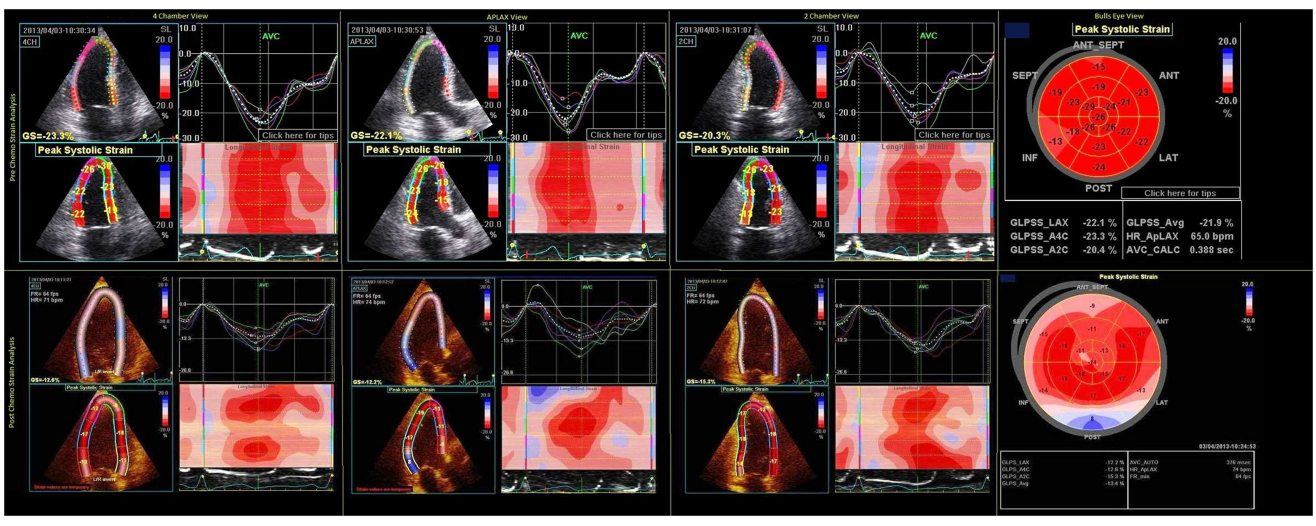

FIGURE 1 | Pre- and post-chemo strain imaging showing two chamber, three chamber, four chamber, and bull's eye view. The white and blue areas in ventricular strain imaging represent area of abnormal strain imaging. Global average longitudinal strain reduced from −21.9 to −13.4% after chemotherapy.

specificity of about 78 and 79%, respectively (19).

FUTURE PROSPECTS FOR PREVENTION OF CHEMOTHERAPY-INDUCED CARDIOTOXICITY

There is evidence of the use of angiotensin converting enzyme inhibitors (ACE-I) both for treatment and prophylaxis in chemotherapy-induced cardiotoxicity. Early treatment with these drugs seems to prevent and, to some extent, reverse the cardiotoxic effects of chemotherapeutic drugs (20). The US FDA has approved dexrazoxane, a derivative of ethylenediamine tetraacetic acid (EDTA), for use in adults if cumulative doses of doxorubicin exceed 300 mg/m^2 (4). It acts by preventing free radical formation at the cellular level but can also decrease the efficacy of some of chemotherapeutic agents by changing their pharmacokinetics. Other strategies are still under development and traditional approaches to reduce chemotherapy-induced cardiotoxicity including establishing stringent LVEF criteria for patient selection, monitoring cardiac function during therapy, and discontinuing potentially cardiotoxic therapy when cardiotoxicity arises still are the only ones available for clinicians currently.

INTEGRATION OF SPECIALTIES

Cardio-oncology and onco-cardiology are terms used to describe an integrated approach between cardiologists and oncologists. While chemotherapy is beneficial in destroying malignant cells, it can simultaneously cause injury or death to myocardial cells, which is described as cardiotoxicity. In the setting of neoadjuvant and adjuvant treatment and a laudable goal, a cancer survivor of today does not become the heart failure patient of tomorrow should be pursued.

Congestive heart failure contributes to the mortality and morbidity of cancer patients if not recognized early. In general, chemotherapeutic cardiac toxicity is classified as type 1 chemotherapy-related LV systolic dysfunction caused by agents such as doxorubicin, epirubicin, idarubicin, cyclophosphamide, and docetaxel. Type 2-mediated cardiotoxicity resulting from trastuzumab is generally not dose related and may be associated with reversible myocardial dysfunction. This class of agents also includes lapatinib, sunitinib, imatinib, and bevacizumab. This cardiac injury may occur early during the cancer treatment or may be delayed months to years after cancer has been successfully treated. Accurate cardiovascular monitoring at regular intervals during chemotherapy is particularly important with prolonged adjuvant therapy. With the use of vector velocity imaging or strain echocardiography, early detection of chemotherapy-induced cardiac injury is now within the realm of clinical practice. The aim of cardio-oncology collaboration is not to discontinue or reduce the dose of chemotherapy, which would reduce the efficacy of treatment, but to identify cardiotoxicity early and intervene so that congestive heart failure does not supervene.

The inter-disciplinary and integrative management of cancer patients with cardiovascular risks or patients who develop cardiovascular injury is: (a) early detection of patients at risk for cardiotoxicity; (b) early institution of cardioprotective agents; (c) preventing the mitigation of the chemotherapeutic agent as far as possible; (d) eliminating as much of the cancer as possible with the appropriate doses of chemotherapeutic agent while minimizing collateral damage, i.e., cardiotoxicity.

CONCLUSION

Virtually all anti-cancer drugs target tumor cell death that may result in collateral injury to healthy tissues. Bone marrow suppression and gastrointestinal toxicities associated with chemotherapy are well recognized. Much less recognized, however, are the cardiotoxic effects of the cancer treatment. These side effects can cause systolic dysfunction, cardiac ischemia, cardiac arrhythmia, pericarditis, or chemotherapy-induced repolarization abnormalities. Common factors that increase a patient's risk of developing cardiotoxic effects include cumulative dose, route of administration, age, prior irradiation, concomitant administration of other chemotherapeutics, and underlying heart disease. Radiation therapy (not discussed in this monograph) may result in coronary artery disease, valvular heart disease, pericardial injury, and myocardial disease from eventual fibrotic changes that occur post-radiation. Cardiovascular disease and cancer are the two leading causes of death in the USA; together they are responsible for nearly half of all deaths (21). As the survival population of the cancer patients increases, the acute and chronic cardiovascular effects of these drugs will become increasingly important. Therefore, the risk of cardiac toxicity should be balanced against the benefits of a particular chemotherapeutic agent based on individual case for optimal benefit to the patient. Much research is still needed to develop ideal guidelines to prevent or minimize cardiac injury in cancer patients undergoing chemotherapy. Early recognition using sensitive diagnostic techniques affords an opportunity for early treatment of these cardiotoxic effects. The Oncologist and cardiologist working in collaboration for patient care can ensure early diagnosis to improve quality of life and survival of the patients.

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Optimization of heart block in the left-sided whole breast radiation treatments

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Purpose: Blocks have been used to protect heart from potential radiation damage in left-sided breast treatments. Since cardiac motion pattern may not be fully captured on conventional 3DCT or 4DCT simulation scans, this study was intended to investigate the optimization of the heart block design taking the cardiac motion into consideration.

Materials and Methods: Whole breast treatment plans using two opposed tangential fields were designed based on 4DCT simulation images for 10 left-sided breast cancer patients. Using an OBI system equipped to a Varian Linac, beam-eye viewed fluoroscopy images were acquired for each of the treatment beams after patient treatment setup, and the MLC heart blocks were overlaid onto the fluoroscopy images with an in-house software package. A non-rigid image registration and tracking algorithm was utilized to track the cardiac motion on the fluoroscopy images with minimal manual delineation for initialization, and the tracked cardiac motion information was used to optimize the heart block design to minimize the radiation damage to heart while avoiding the over-shielding that may lead to underdosing certain breast tissues.

Results: Twenty-three sets of fluoroscopy images were acquired on 23 different days of treatment for the 10 patients. As expected, heart moved under the influences of both respiratory and cardiac motion. It was observed that for 16 out of the 23 treatments, heart moved beyond the planed heart block into treatment fields and MLC had to be adjusted to fully block heart. The adjustment was made for all but one patient. The number of the adjusted MLC leaves ranged from 1 to 16 (mean = 10), and the MLC leaf position adjustment ranged from 2 to 10 mm (mean = 6 mm). The added heart block areas ranged from 3 to 1230 mm^2 (mean = 331 mm^2).

Conclusion: In left-sided whole breast radiation treatments, simulation CT (and 4DCT) based heart block design may not provide adequate heart protection for all the treatments. A fluoroscopy-based method has been developed to adaptively optimize the heart MLC block to achieve optimal heart protection.

Keywords: heart block optimization, left breast radiotherapy, breast cancer, intra-fractional motion, image processing

INTRODUCTION

Radiotherapy is an effective treatment modality for early-stage breast cancer (1–7). However, during the treatments, especially in left-sided patients, the heart inevitably receives a non-negligible amount of radiation doses. Taylor et al. estimated the cardiac doses of 358 patients received from breast cancer radiotherapy in Sweden during the period of time from the 1950s to the 1990s (8). They found that in this group of patients treated with relatively outdated technologies the mean heart dose varied from 0.1 to 23.6 Gy while the mean left anterior descending coronary artery dose varied from 0.1 to 46.3 Gy. They also reported that heart doses were significantly higher among the patients treated for left-sided breast cancer than for right-sided breast cancer (respectively, 5.1 and 1.8 Gy in the 1950s, 10.5 and 4.7 Gy in the 1970s, and 3.0 and 1.9 Gy in the 1990s). It is interesting and unsurprising to notice that the heart doses changed with the time period that was associated with technology advancement, indicating the important roles of radiotherapy technologies in the management and reduction of the heart doses. Many studies have shown that the heart dose received during the breast treatments can lead to long-term side effects and toxicities (9–15). Darby et al. conducted a population-based case–control study of major coronary events in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark and concluded that exposure of the heart to ionizing radiation during breast cancer radiation treatment increases the subsequent rate of ischemic heart disease and the increase is proportional to the mean dose to the heart (9). A study by Nilsson et al. specifically investigated the distribution of

coronary artery stenosis after radiation for breast cancer (11). They found that stenosis in mid and distal left anterior descending artery and distal diagonal increased in irradiated left-sided breast cancer and an association between irradiated high risk areas and stenosis in hot spots of radiation, indicating a direct link between radiation and location of coronary stenosis in breast cancer radiotherapy treatments. These more recent results expanded or confirmed the findings by other investigators (10, 12–15).

To minimize the potential cardiac toxicities from breast cancer radiation treatments, various breath control techniques were investigated for their control of the heart doses received in the breast radiation treatments (16–19). The breath-hold and breathing gating techniques have been demonstrated and clinically implemented to reduce the heart doses and irradiated cardiac volumes for left-sided breast cancer treatments. Another commonly adopted method is direct block of heart in the radiation treatment fields of breast (**Figure 1**). This method can also be used along with the breath control techniques for some patients if those techniques are deemed inadequately protecting heart from radiation.

Heart blocks are usually designed based on the heart shapes outlined on the simulation CT images or directly on the beam's eye views of digitally reconstructed radiographs/regular radiographs of the radiation. However, since heart constantly moves, the heart outlines captured on the conventional CT images and radiographs may not reflect the full ranges of the motion. Although 4DCT may be used to analyze and incorporate the motion in the block design, it is often too slow to accurately estimate the heart motion. Furthermore, the heart block inevitably shields some breast tissues, which may require to be irradiated, from radiation, leading to potential target miss. The question remains on how to optimize a balance between minimal target miss and maximal heart block while incorporating heart beating motion. This study is to utilize an in-house developed fluoroscopy image rendering and registration algorithm to evaluate and optimize the heart block during left-sided whole breast irradiation treatments. The project was conducted under an IRB approved protocol.

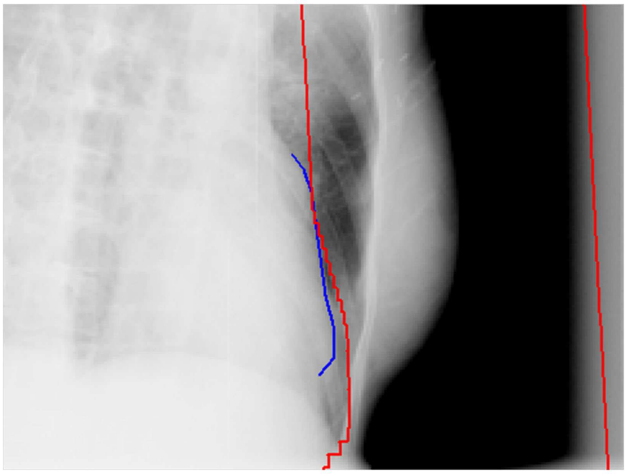

FIGURE 1 | An example of direct heart block in a tangential field of a whole breast radiation treatment. The red lines are the field edges and the blue line is the heart outline on the side of the field in the beam's eye view.

MATERIALS AND METHODS

For left-sided breast cancer radiation treatments that require heart blocks, due to the nature of potential heart movement, the fluoroscopy imaging modality of the On-Board-Imaging (OBI) system equipped to linear accelerators can be used to dynamically check the appropriateness of the heart block designs at treatment. Ten patients were randomly selected from a pool of left-sided breast cancer patients who would receive the whole breast irradiation and required heart blocks. The whole breast treatments, using two opposed tangential fields, were planned based on 4DCT simulation images. In the plans, the heart blocks were manually designed and shaped with MLCs (Millennium 120 MLC, Varian Medical Systems, Palo Alto, CA, USA). The heart block designs took the considerations of heart locations on the 4DCT and clinical evaluation of the blocked breast tissues. For the 10 patients included in this study, the heart blocks were all such designed so that the block edges covered the heart borders reflected on the 4DCT average image sets.

Using an OBI system equipped to a Varian Linac, beam-eye viewed fluoroscopy images (for a duration of 10–15 s) were acquired for each of the treatment beams after patient treatment setup, and the MLC heart blocks were overlaid onto the fluoroscopy images with an in-house software package. A non-rigid image registration and tracking algorithm was utilized to track the cardiac motion on the fluoroscopy images with minimal delineation for initialization, and the tracked cardiac motion information was used to optimize the heart block design to minimize the radiation damage to heart while avoiding the over-shielding that may lead to underdosing certain breast tissues. To be consistent with the principle of heart block design in plans, the fluoroscopy-based heart block optimization was achieved when the MLC edges were adjusted to cover the heart borders imaged on the fluoroscopy.

A brief description of the non-rigid image registration and tracking algorithm as well as the MLC shape optimization principle is presented as follows.

MOTION MODELING

Patient heart was initially delineated in fluoroscopy using the combination of CT to fluoroscopy image registration and was manually adjusted on the first frame of the fluoroscopy. The heart motion was then dynamically tracked in fluoroscopy using the registration propagation algorithm as briefly described below.

Given the initial heart delineation C, the registration between two fluoroscopy frames is based on an enhanced Demons algorithm, which uses the following equation of active force at point $i \in C$:

$$\vec{f}_i^{\,d} = (m_i - s_i) \times \left(\frac{\vec{\nabla} s_i}{\left\| \vec{\nabla} s_i \right\|^2 + a^2 (m_i - s_i)^2} + \frac{\vec{\nabla} m_i}{\left\| \vec{\nabla} m_i \right\|^2 + a^2 (m_i - s_i)^2} \right)$$

where m is the moving (target) frame, s is the static (source) frame, and a is a weighting parameter that controls the step size in the deformation. A constraint is defined as another force term $\vec{f}_i^c$ to maintain the smoothness of the contour (heart surface).

$$\vec{f}_i^c = \frac{1}{k}\sum_{j=1}^{k} f_j \exp(-\frac{d^2{}_{ij}}{\sigma^2})$$

where f_j is the image force at a neighboring point j on the heart contour, and σ is the size of the neighborhood in which the smoothness factor will be effective.

The accumulative force driving the deformation can be expressed as:

$$\vec{f}_i = \lambda_c \vec{f}_i^c + \lambda_d \vec{f}_i^d,$$

where λ_c and λ_d are weights for the image force and the object constraint, respectively. We use empirical values that $\lambda_c = 0.25$ and $\lambda_d = 0.75$ for the calculation of the overall deformation force in the registration since these two values performed the best.

To improve the efficiency, the registration is conducted for cropped regions only. The size of the cropped region is automatically determined based on the delineation of the heart surface. Hierarchy strategy and frequency domain calculation are used to further speed up the registration process. After the registration, the motion vector $(d_x, d_y, d_z,)$ between corresponding pixels in different frames is calculated to generate a motion model so that the displacement at any point i in the heart contour on any two neighboring fluoroscopy frames can be expressed as:

$$(x, y, z)_j^i = (d_x^i, d_y^i, d_z^i)_{j,j+1} + (x, y, z)_{j+1}^i,$$

where $(x, y, z)_{j+1}^i$ and $(x, y, z)_j^i$ are the positions of the same point on the heart contour in different fluoroscopy frame $j+1$ and j, respectively. To retrieve the heart motion throughout the fluoroscopy, we propagate the registration to get the motion between any two arbitrary fluoroscopy frames j and k using:

$$\vec{d}_{jk} = (\vec{d}_{j,j+1} + \vec{d}_{j+1,k} + \vec{d}_{j,k-1} + \vec{d}_{k-1,k})/2.$$

The heart wall displacement with regard to the heart position in the first frame can be determined using the displacement map.

MLC ADJUSTMENT

The tracked cardiac motion was analyzed and taken into account for the adaptive optimization of the heart block design. The shape of the heart block was exported from the Eclipse (Varian) treatment planning system as the MLC file and loaded into our internally developed software. After the retrieval of heart motion, the maximal offset between the heart motion inside the treatment beam and the corresponding MLC leaf position is computed and used to adjust the MLC position in the original treatment plan to maintain full heart shielding.

In the heart block MLC position optimization process, if heart was adequately covered by the planned MLC positions, no MLC position adjustment was made; if it was found that heart was not adequately covered by the planned MLC, the MLC positions were adjusted so that the MLC edges covered the most infiltrating borders of heart into the corresponding field of radiation detected on the fluoroscopy images.

The optimized MLC heart blocks were checked for their appropriateness by an experienced radiation oncologist.

RESULTS

For the 10 patients, 23 sets of fluoroscopy images were acquired on 23 different days of treatment (**Table 1**). As expected, heart moved under the influences of both respiratory and cardiac motion. It was observed that for 16 out of the 23 treatments, heart moved beyond the planed heart block into treatment fields and MLC had to be adjusted to fully block heart. The adjustment was made for all but one patient, whose digital fluoroscopy was available for only one treatment. The number of the adjusted MLC leaves ranged from 1 to 16 (mean = 10), and the MLC leaf position adjustment ranged from 2 to 10 mm (mean = 6 mm). The added heart block areas ranged from 3 to 1230 mm^2 (mean = 331 mm^2). The results are summarized in **Table 1**.

In the cases investigated in this study, the dose distributions were recalculated using the updated MLC positions. The dose coverage of the whole breast was compared to that of the original

Table 1 | Summary of heart block adjustments for the investigated left-sided breast cancer patient whole breast radiation treatments.

Patient	No. of fluoro taken	Fluoro No.	Number of adjusted MLC leaves	Largest leaf adjustment (mm)	Total adjusted area (mm^2)
A	2	1	0	0.0	0.0
		2	7	2.3	45.4
B	2	1	0	0.0	0.0
		2	1	3.7	3.1
C	2	1	0	0.0	0.0
		2	16	5.6	285.4
D	4	1	10	5.0	171.5
		2	7	3.0	61.4
		3	12	8.8	347.8
		4	12	8.5	369.2
E	4	1	6	2.0	35.1
		2	0	0.0	0.0
		3	0	0.0	0.0
		4	0	0.0	0.0
F	2	1	15	6.3	349.3
		2	9	4.8	157.4
G	1	1	0	0.0	0.0
H	2	1	6	3.2	61.8
		2	13	9.2	481.9
I	2	1	8	10.3	307.8
		2	9	7.0	227.7
J	2	1	16	9.3	1162.0
		2	16	9.9	1230.4

corresponding plan. No significant dose distribution difference was observed.

DISCUSSIONS AND CONCLUSION

During whole breast radiation treatments, ideally the entire breast tissues should be irradiated and receive a therapeutic radiation dose. To minimize potential radiation damages to heart in the left-sided breast cancer treatments, heart blocks are added and their addition may compromise the irradiation of some breast tissues that fall under the blocks. This study only attempted to address the potential suboptimal heart protection, without trying to address the optimal balance between heart protection and breast tissue irradiation.

It is well known that patient organ motion (e.g., heart and respiration), in terms of motion frequency and magnitude, is very likely not exactly reproducible. The revised heart blocks, based on the fluoroscopy images acquired prior to the treatment, may not provide complete heart protection during the radiation beam-on time, if the organs do not exhibit the motion patterns as imaged on the fluoroscopy.

Dose distributions in the breast tissues, including both absolute and relative values, vary with beam field sizes. The changes of heart blocks at treatment will change the dose distributions and may introduce unexpected effects. As shown in **Table 1**, the observed mean area change was a little over 300 mm^2. Given that typical tangential breast field size is over 20,000 mm^2, it is reasonable to assume that for most cases, the heart block adjustment at treatment will have insignificant impact to the dose distributions with same machine outputs. However, in certain extreme cases, the block area change could be as large as over 1200 mm^2 (**Table 1**), the impact on the dose distribution may not be trivial and may have to be taken into account if the heart block is to be changed.

The algorithm to track the motion and optimize the heart block is very fast and takes only a few seconds to complete the entire process. However, the acquisition of the fluoroscopic images, which includes rotating machine gantry and image acquisition itself, can take up to a few minutes. Therefore, the clinical implementation of the technique may add a few more minutes to the treatment time.

In conclusion, simulation CT (and 4DCT) based heart block design may not provide adequate heart protection for all the fractions in left-sided whole breast radiation treatments. A fluoroscopy-based method has been developed to adaptively optimize the heart MLC block to achieve optimal heart protection. On the other hand, additional study needs to be conducted to seek an optimal balance between protection of heart and assurance of entire breast tissue irradiation.

AUTHOR NOTE

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OPINION ARTICLE
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Tagged MRI based cardiac motion modeling and toxicity evaluation in breast cancer radiotherapy

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INTRODUCTION

Recent research showed radiation for breast cancer can increase heart risks (1, 2). In Ref. (2), it has been noted that for every Gy of radiation a women's heart risk rises 7.4%. However, the correlation between radiation dose and heart tissue damage is still an open problem. A more accurate model of heart damage will significantly improve the heart safety for patients underwent radiotherapy.

Modern radiation treatment planning systems (TPS) use computed tomography (CT) images for dose calculation and evaluation. For evaluation of heart toxicity from radiotherapy, the dose-volume histogram (DVH), which is generated by overlying radiation dose distribution on heart delineations in CT images, is widely used. However, there are three major factors that deteriorate the accuracy of TPS-calculated heart dose distribution. First conventional CT is a fundamentally static imaging modality without the capability to capture and depict the cardiac motion. Instead, heart is usually blurred in CT images due to the motion artifacts. Second, without special contrast dye, CT provides limited contrast between blood in heart chambers and the surrounding myocardium. The heart region in TPS is actually a mixture of myocardium and blood, although only the radiation dose to the myocardium is accountable for heart risks. Finally, there is significant intra- and inter-fractional heart motion. As heart beats involuntarily during and between radiation treatments, myocardium deforms and moves non-rigidly against the fixed radiation beam so that the static dose distribution calculated in CT based TPS does not reflect the accurate radiation dose distribution in heart.

There is also concern on the choice of the heart function for the evaluation of radiation damage. Based on radiation beam geometry, only part of the heart will receive clinically significant level of radiation during breast cancer treatment. It is possible that the global heart function remains stable temporarily while cells in the irradiated part of the myocardium lose part or all of their functions. In this case, regional heart function, which can be derived from regional heart wall motion and strain analysis, is a better indication of heart damage corresponding to radiation dose.

Although cardiac MRI is widely used in radiology for the diagnosis of heart disease, its application in radiation treatment planning is limited. For multiple reasons, it is not practical to use MRI directly for radiation treatment planning of breast cancer patients. However, via multimodality deformable image registration (DIR) between MRI and CT, MRI images may play a more critical role in the evaluation of the heart damage from whole breast radiation.

Tagged MRI (tMRI) (3) is a relatively new imaging protocol that has been implemented in the detection and diagnosis of regional heart functional loss. tMRI methods record regional heart wall motion information as they create identifiable landmark bands (tags) in the myocardium to establish dense point to point correspondence between images. ECG-gated tMRI image sets can be acquired at different phases of the cardiac cycle using the corresponding pulse sequence. The 4D (3D plus time) cardiac motion model can be retrieved by image registration between tMRIs at different phases.

In the following sessions, we use tMRI as an example to explain how additional heart function information in MRI is retrieved. It is our objective to demonstrate the additional information retrieved from MRI can help the evaluation and protection of heart risks for breast cancer patients, and we want to discuss the possibility of using MRI to establish a more accurate correlation between regional heart functional loss and radiation dose.

METHOD

HEART MOTION UNCERTAINTY IN CT

First, we analyze the uncertainty in the CT based TPS-calculated radiation dose distribution of heart. The cardiac motion artifacts in CT acquisition has been previously studied (4) so we focus on the uncertainty related to the intra- and inter-fractional cardiac motion and location variation.

We used kV fluoroscopy imaging to monitor the intra-fractional cardiac motion during breast cancer treatment (experiment A). For a group of 10 left breast cancer patients without breath holding or external breath suppression, fluoroscopy was acquired weekly at the gantry angle of the treating beam for 15 s at 8 fps. The fluoroscopy radiation dose to the patient was clinical insignificant.

To estimate the inter-fractional heart location variation, we registered the weekly CBCT of two t-spine patients (experiment B). CBCT images were registered to match the left breast and the variation of the heart

location was evaluated by measuring the average distance of the heart surface in the registered image.

CARDIAC MOTION RETRIEVAL FROM MRI

For preliminary research purpose, we retrospectively studied two sets of anonymous tMRI data acquired using the Spatial Modulated Magnetization (SPAMM) pulse sequence. Both tMRI sets were ECG-gated and acquired at 24 phases during the cardiac cycle. Each tMRI sets included three long axis (LA) image sets (corresponding to the two chamber, three chamber, and four chamber view), a short axis (SA) image set, and an ECG-gated non-tMRI image set acquired at the end of diastole. The slice thickness of SA tMRI was 5 mm. The spacing between tags was 8 mm. There were both horizontal and vertical tags in the image.

Given tMRI and the corresponding CT images of the breast cancer patient, the work flow to estimate the correlation between radiation dose and regional heart functional loss is illustrated in **Figure 1**.

The tMRI images went through preprocessing first to remove the intensity non-uniformity introduced by the surface coils used in the MRI process, and to reduce the impact of the decay of image intensity between different phases of the cardiac cycle.

The epi- and endo-myocardial contours were generated from tMRI using frequency domain analysis. The modulated tags corresponded to high frequency components in the frequency domain and can be effectively removed from the image using frequency filtering. We segmented the myocardium automatically in the SA image using the method in Ref. (5). The myocardium contours could be automatically or manually generated in the LA images.

There were multiple means to track the movement of the tags during the cardiac cycle, such as active contours (6), B-Spline (7), physics deformable models (8), and meshless deformable model (9).

The reconstructed cardiac motion model had two uses. First, the myocardial strain distribution was derived from the myocardium motion, and the abnormality in the distribution was used as the indication of local heart tissue damage. Second, the cardiac model was integrated with the CT-MRI image registration to calculate the accumulative radiation dose distribution in the myocardium during cardiac cycle. The radiation dose to the blood was ignored, as it would not directly cause heart risks.

Given the motion distribution, the myocardial strain was computed as the derivative of the displacement vectors at image pixels. Strain depicted the variation in motion between different parts of the heart. Abnormalities (either high or low value) in strain distribution reflected local myocardial motion abnormalities, which was a direct indication of regional heart functional loss.

The CT-MRI image registration was conducted to build a connection between the TPS and the tMRI image domain. First, we register CT to the end-of-diastole non-tMRI using mutual information based multimodality image fusion. The 4D heart model (including both the cardiac motion and the volumetric myocardium model) in the MRI with regard to the beam geometry in the CT images was determined after the registration. In the next step, we accumulated the myocardial dose distribution

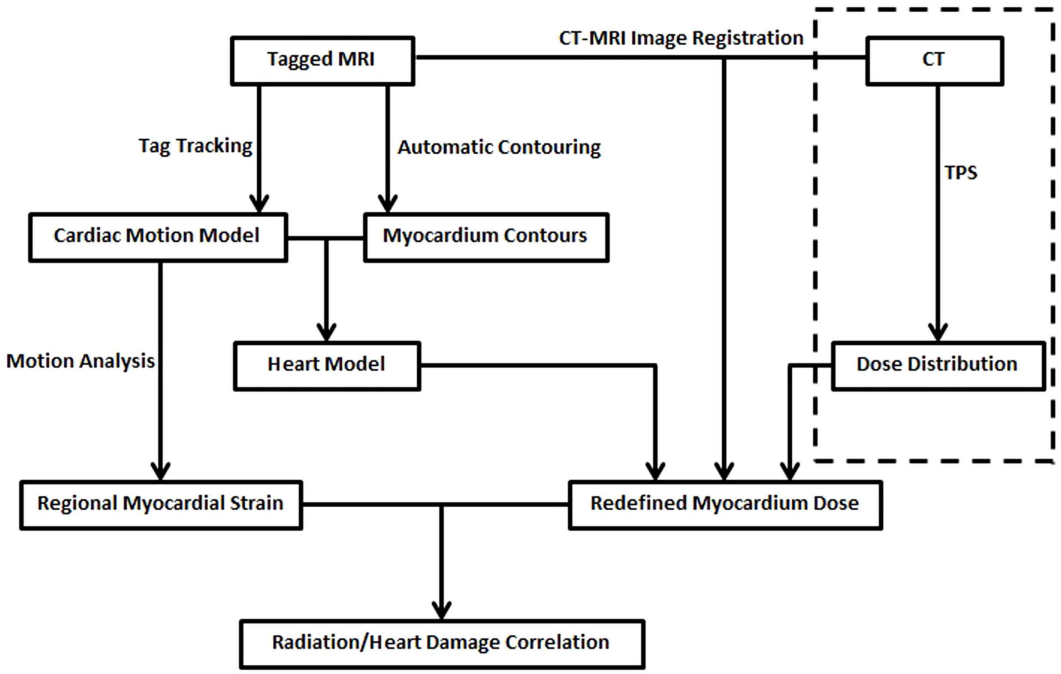

FIGURE 1 | The work flow of the cardiac motion tracking and myocardium dose evaluation method. The part encircled by the dashed line is the current CT based heart dose calculation and evaluation in the treatment planning system.

at different cardiac phases to reconstruct the cardiac-motion-adjusted accumulative myocardium dose distribution. The final step was to align the strain distribution to the motion adjusted dose distribution. The correlation between the strain and radiation dose was calculated to enable us to establish the radiation-dose-to-heart-risk model in future research.

DISCUSSION

The uncertainty in the TPS dose distribution caused by CT imaging was not considered explicitly in previous studies. The cardiac motion artifacts in CT imaging can be reduced after using modern technology such as the multi-detector computed tomography (MDCT), however currently the high cost limited wide use of such techniques at radiation oncology clinics. The low blood-to-tissue contrast in CT can be increased by injecting contrast dye during patient simulation, although this requires longer preparation time and the improvement is limited if the imaging motion artifact was not well addressed. Based on experiment A, the average infra-fractional motion of the heart wall, as projected to the beam eye view in kV fluoroscopy, was 1.3 ± 0.3 cm. Average inter-fractional heart location variation can be as much as 1.5 cm as measured in the CBCT images acquired in experiment B.

To address the uncertainties in heart location and the corresponding dose distribution, we proposed to use MRI in the evaluation of heart risks for breast cancer patients. As demonstrated by the tMRI-based cardiac analysis framework, MRI had less motion artifacts, higher blood-to-tissue contrast (by using appropriate pulse sequence), and provided infra-fractional cardiac motion information.

The accuracy of the MRI-based cardiac analysis was determined by the accuracy of fundamental image processing modules such as registration, segmentation, and motion tracking. Multimodality image registration between CT and MRI was a well-studied problem and commercial software is now available to generate satisfactory registration results. However, it should be noted that the couch top used in radiation oncology CT simulator, and diagnosis MRI, were different. A DIR should be conducted to correct for the variation of anatomy caused by different couch tops. It was also critical that the registration should align the surface markers in the CT and MRI images since they determined the radiation beam geometry in breast cancer radiation treatment. Effective approaches to automatically delineate the myocardium and to derive the strain from MRI images have been proposed in previous studies. The image registration and motion tracking uncertainties have been discussed in previous research efforts (9, 10). The overall uncertainty in the proposed methodology also depended on the interpolation and extrapolation error during the projection process to transfer the displacement and the radiation dose distribution between different image domains. Interpolation and extrapolation errors were hard to quantify or validate directly. We can use the inverse minimization procedure to reduce the error, at the cost of extra processing time.

The major technical challenge in MRI-based heart risk analysis was the reconstruction of the cardiac-motion-adjusted accumulative radiation dose distribution. To get the accumulative dose, one needed to deform the original CT image to regenerate CT images at different cardiac phases using the cardiac motion derived from the tMRI images. The difficulty increased as the CT and the tMRI imaging planes were not the same and intersected each other at oblique angles. The accuracy of the regenerated CT images needed further validation before using for dose recalculation.

Given adequate information, a polynomial fit can be generated to describe the correlation between regional heart function loss and the radiation dose. The fitted model can be used to quantitatively estimate the heart risk based on accumulative radiation dose.

Finally, it should be noted that although the motion adjusted radiation dose distribution is more accurate and specific than the currently used heart DVH in treatment planning CT, it was still an approximation to the actual dose distribution. The method we proposed did not consider inter-fractional heart location variation and the impact of respiration on heart location. Moreover, the patient heart beat pattern may change during the course of radiation treatment. All these factors caused extra uncertainties in the calculated accumulative myocardium dose.

CONCLUSION

We discussed the uncertainties of using CT calculated dose to evaluate the radiation damage to the heart. To improve the quality of heart risk analysis for breast cancer patients, we proposed a tMRI-based framework to derive the cardiac motion, the myocardium strain, and eventually the regional heart function loss. The proposed framework demonstrated the possibility and technical challenge of establishing a correlation between myocardium damage and radiation dose for breast cancer patients using MRI. By using MRI, regional heart function loss could be detected and the radiation dose can be adjusted by generating the accumulative dose during cardiac cycle. We plan to collect tMRI data from more patients to improve the accuracy, efficiency, and statistical robustness of the proposed framework in future studies.

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Treatment techniques to reduce cardiac irradiation for breast cancer patients treated with breast-conserving surgery and radiation therapy: a review

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Thousands of women diagnosed with breast cancer each year receive breast-conserving surgery followed by adjuvant radiation therapy. For women with left-sided breast cancer, there is risk of potential cardiotoxicity from the radiation therapy. As data have become available to quantify the risk of cardiotoxicity from radiation, strategies have also developed to reduce the dose of radiation to the heart without compromising radiation dose to the breast. Several broad categories of techniques to reduce cardiac radiation doses include breath hold techniques, prone positioning, intensity-modulated radiation therapy, and accelerated partial breast irradiation, as well as many small techniques to improve traditional three-dimensional conformal radiation therapy. This review summarizes the published scientific literature on the various techniques to decrease cardiac irradiation in women treated to the left breast for breast cancer after breast-conserving surgery.

Keywords: breast cancer, radiation, heart, dosimetry, cardiotoxicity

INTRODUCTION

The American Cancer Society estimates that in 2014 about 232,000 new cases of invasive breast cancer will be diagnosed, as well as 62,500 cases of breast carcinoma *in situ* (1). The majority of these women will receive breast-conserving surgery followed by radiation. Breast irradiation has been shown to decrease the risk of local recurrence after breast-conserving surgery with few adverse effects (2). One of the most concerning complications of breast radiotherapy is cardiotoxicity from radiation to the heart.

Early studies showed decreased left ventricular function in breast cancer patients treated with radiation (3). Excess risk of cardiac mortality due to radiation, from two European randomized trials involving five different techniques, has been estimated to be 1.8% (4), though this data also suggested that only heart doses greater than 30 Gray (Gy) were important to calculate risk of cardiac toxicity. Cardiotoxicity is most frequently reported as decreased myocardial function or coronary artery disease (also reported as ischemic heart disease or decreased cardiac perfusion). However, less common toxicities can include myocardial infarction, congestive heart failure, pericarditis, arrhythmias, angina, or valve dysfunction (5, 6). While generalized decreased cardiac function has been generally reported, some studies in this review have specifically shown decreased left ventricular or left anterior descending coronary artery (LAD) function or perfusion after radiation.

A review of over 1600 patients with 16 years of follow-up found that left-sided breast cancer patients treated with radiation had a 38% increase in cardiovascular disease compared to right-sided cancer patients, though the rates of cardiovascular disease did not correlate with volume of heart irradiated (7). Recently, another review of 2168 women who underwent radiotherapy for breast cancer in Sweden and Denmark found that the average mean heart dose was 4.9 Gy and that there was a significant linear correlation between mean heart dose and rate of major coronary events, with an increase of 7.4% per Gy (8). Another study estimated the risk of cardiotoxicity to increase 4% per Gy mean heart dose (9).

It should be remembered that for patients with long follow-up, the treatment techniques used may be relatively outdated compared to those used today, and therefore, their reported cardiac doses may not represent typical doses today. In addition, for such patients, 3D dose and image data, which are routinely available today, were generally not available in many older studies, requiring more uncertain methods of estimating cardiac dose. While rates of cardiotoxicity are improving, and methods of delivering and quantifying dose of radiation to the heart have become more sophisticated, reducing potential for any cardiotoxicity remains one of the primary aims of improving adjuvant radiation techniques for patients with left-sided cancers.

This paper will focus on treatment of patients treated with radiation after breast-conserving surgery. Treatment fields, angles, and other radiotherapy techniques may be different for post-mastectomy patients compared to patients with intact breasts. It is beyond the scope of this paper to attempt to discuss all aspects of plan evaluation for the studies discussed, such as planning target volume coverage, dose homogeneity, and dose to other organs. This review will focus solely on techniques to decrease radiation to the heart for women receiving radiation to the left breast.

MATERIALS AND METHODS

A Pubmed literature search was performed on March 5, 2014 to review any papers discussing breast cancer heart dosimetry. Articles were excluded if they reviewed non-breast cancer data, post-mastectomy radiation, exclusively evaluated patients with pectus excavatum, bilateral breast irradiation, or did not have heart

dosimetric data. Articles were reviewed specifically for data from patients treated to the left breast. For this review, all studies are assumed to deliver whole breast irradiation unless partial breast treatment is stated.

RESULTS

SUPINE 3D

Traditionally, breast cancer has been treated in the supine position with arms above the head with two opposed tangent photon fields. The earliest data on cardiac toxicity originated from the Stockholm Breast Cancer trial, which treated patients to 45 Gy at 1.8 Gy per fraction, and found a 15-year excess cardiac mortality of 6.8% attributed to the radiation (10). A review of patients treated in that trial estimated the mean volume of heart treated to the 50% isodose (22.5 Gy) to be 25% (11). One of the first trials to show an alternative approach to reduce heart dose was a review of the plans of 100 women with left-sided T1N0MO breast cancer status post-lumpectomy treated with three-dimensional conformal radiation therapy (3DCRT) planning to 50 Gy at 2 Gy per fraction, which reviewed the dose to the heart for these patients and found the volume treated to 50% isodose to be 5.7% (approximately 33 cc) (12). This significant reduction of heart dose led to the widespread adoption of 3D conformal planning for breast cancer. Some have shown that simply using 3DCRT to account for individual organ location, by putting a limit of 1 cm of heart in the tangent field, would cause at most a 1 per thousand patient risk of cardiac mortality (13). Several other studies have also shown reductions in planned heart dose with 3D conformal compared to two-dimensional planning (14, 15). However, one study showed no difference in mean heart dose, V20, or V5 heart dose comparing 2D, standard 3DCRT, and field-in-field (FiF) techniques (16).

Since the adoption of 3DCRT, many techniques have been attempted to further reduce cardiac radiation dose. A large study involving 217 left-sided breast cancer patients evaluated 3DCRT vs multi-segmented conformal radiation therapy and found no difference in mean heart dose (17). Another study confirmed this finding (18). A study evaluating tangential single wedge, double wedge, and FiF techniques found no significant differences in cardiac dose (19). A single study evaluating treating women with large breasts in the left lateral decubitus position was able to achieve a mean heart dose of 1.35 Gy for left-sided cancers (20). Using FiF planning can produce lower heart mean dose, V10, and V20 compared to standard 3DCRT plans (21). One study found that treating patients with their bra on decreased V5 to the heart from 9.8 to 2.7% (22). Hypofractionated whole breast regimens are becoming more common and have been shown to have equal slightly improved 2 Gy dose equivalent doses to the heart (23, 24).

PRONE

The largest and most current experience with prone breast treatment includes 200 women with left-sided breast cancer and has shown a significant decrease in in-field heart volumes compared to supine tangent plans with a mean reduction of 7.5 cm^3, which corresponded to a 85.7% reduction in in-field heart volume (25). However, there was no benefit for women with smaller breasts (less than 750 cm^3), and 15% of women overall had decrease in in-field heart volume when planned in the supine position. The second largest study comparing supine and prone planning, comparing whole breast and partial breast plans, found that prone positioning decreased cardiac doses for large breasted women but increased cardiac doses for women with smaller breast volume (26), a finding that has also been concluded in other studies (27, 28). One study found improvement in heart doses with prone positioning, but at the cost of a 50% reduction in coverage of the axillary nodes (29). Some smaller series have found no difference between supine and prone heart doses (29–31). **Figure 2** provides examples of prone breast and an external beam accelerated partial breast irradiation (APBI) plans with corresponding isodose lines.

INTENSITY-MODULATED RADIATION THERAPY

As has been shown in many sites treated with intensity-modulated radiation therapy (IMRT), left-sided breast cancer patients treated with IMRT limits high dose to the heart without limiting low doses (32–35). Different techniques, including forward-planned IMRT, inverse-planned IMRT, and modulated arc therapies have been studied. A study of multiple partial arc volume-modulated arc therapy had a mean V25 to the heart of 2.52% of the heart volume, while having a mean total dose of 7.61 Gy (36). IMRT incorporating a simultaneous boost, even with respiratory gating, showed a mean heart dose of 22.98 Gy but reduced treatment duration by 6 fractions (37). Whether standard sequential boost or IMRT concomitant boost was used did not significantly affect heart dose (38). Forward-planned IMRT has been shown in one study to significantly reduce mean heart dose compared to inverse IMRT and arc radiotherapy (5.46 vs 15.48 vs 12.73 Gy) (39).

Many studies comparing IMRT to 3DCRT have shown decreased heart mean, V25, and V30 with IMRT compared to standard tangent fields (40–47), however, with no improvement over tangents with FiF (48). Other studies have failed to show a significant difference in most heart constraints for IMRT over 3DCRT (49). The largest study comparing 3DCRT vs IMRT, comparing 201 forward-planned IMRT cases to 131 3DCRT plans, stratified by breast size and use of supraclavicular nodal irradiation, found a non-significant trend toward reduced heart constraints with IMRT (50).

TECHNOLOGICAL SOLUTIONS

Breath hold, accomplished by having the patient take and hold a deep inspiration during CT simulation and during treatment each day, has been shown to significantly reduce heart dose. Several studies have shown that deep inspiration breath hold (DIBH) compared to free breathing (FB) reduced mean heart dose and several other dose constraints to the heart by 50%, with mean heart doses around 2–3 Gy (51–55). A comparison of thoracic anatomy and radiation isodose lines with FB and DIBH can be seen in **Figure 1**, which demonstrates how the breath hold can change thoracic anatomy to potentially reduce cardiac dose received of radiation. A selective approach to using DIBH was used in one study, which evaluated 53 left breast patients and evaluated all patients with standard tangent field plans. Any patients with greater than 10 cm^3 of heart receiving 50% of the prescription dose were selected for DIBH IMRT, and these DIBH IMRT cases had significantly reduced whole heart and LAD doses (56). One study combined DIBH with IMRT and significantly reduced heart

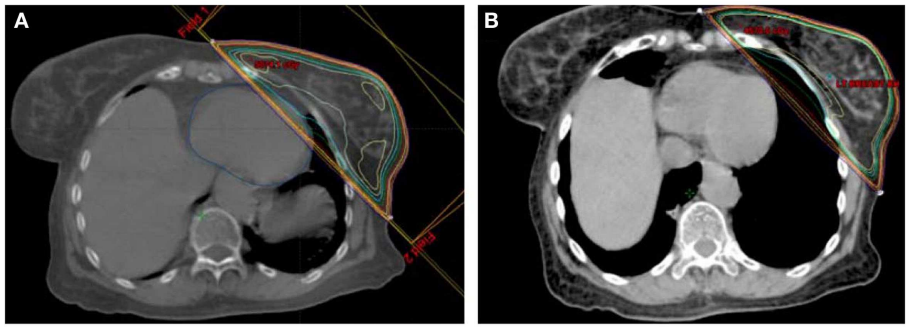

FIGURE 1 | Example of (A) free breathing and (B) deep inspiration breath hold plans for a single patient.

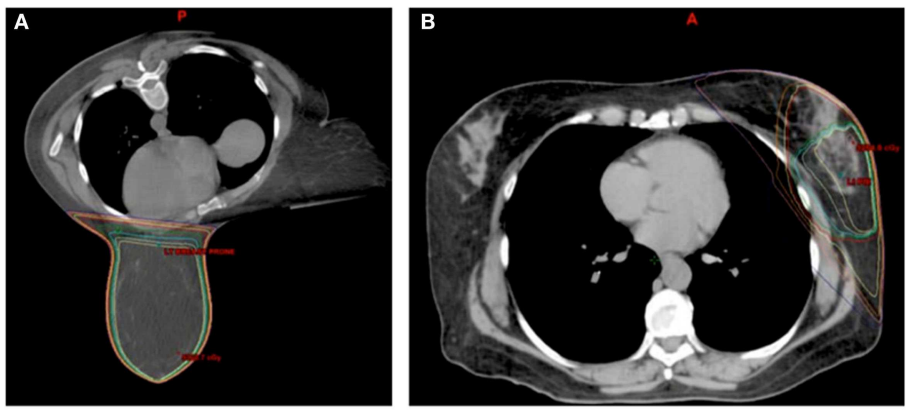

FIGURE 2 | Examples of (A) prone breast and (B) external beam APBI plans.

V30 in two-thirds of the patients and was able to avoid any heart irradiation in 22% of cases (57). Another study, using cardiac MRI, similarly found that breath hold could displace the heart entirely out of the radiation field in 21% of patients (58).

One consideration of breath hold techniques is inter-fraction reproducibility of patient geometry and anatomy. When the breath hold is voluntary, respiratory coaching is required to ensure consistency. Two studies have shown good inter-fraction reproducibility with DIBH (53, 59). Monitoring technology such as magnetic sensors or real-time surface imaging can be used to verify and improve voluntary breath hold reproducibility (59, 60). Several studies rely on technology sometimes referred to as active breathing control, in which a patient breathes through a device that monitors breathing air volumes and automatically holds the patient's breath at prespecified volumes for a defined period of time (55, 57, 61–64). Some studies have explored the use of gating rather than breath hold to address intra-fraction respiratory motion (60, 65). Even with respiratory motion management such as breath hold, cardiac motion may still be an issue. Under breath hold conditions, one study showed that the LAD can show substantial displacement due to cardiac contraction (66). Another study used fluoroscopy to show potentially significant cardiac motion that was not evident using 4DCT techniques (67).

Changing the radiation particle from photons to protons and using MRI-linacs for photon treatment delivery are two newer approaches to improving treatment delivery. Proton radiotherapy is not commonly used for the breast; however, one study projected that a reduced risk of cardiac mortality might be achieved, based on planned cardiac doses, for proton and IMRT plans compared to 3DCRT (68). A study of breast radiotherapy using integrated MRI-linacs found no difference in heart D2cc or V25 for whole breast tangential and 7-field IMRT APBI plans (69). One potential application for future MRI-linacs is the appropriate application of a reversible transverse magnetic field, which in simulation resulted in a 26.0% mean heart dose reduction (70).

APBI

Accelerated partial breast irradiation is a newer technique in women with low risk of recurrence for breast cancer to treat only the lumpectomy cavity with a small margin, rather than the whole breast and regional lymph nodes. Only women at least 60 years old with T1, node negative, estrogen receptor positive, unifocal or unicentric breast cancers with no lymphovascular invasion and negative margins are fully "suitable" for APBI, with a select group also considered "cautionary," per the American Society for Radiation Oncology (71). More recently, APBI guidelines were also

created by the American Brachytherapy Society with slightly different criteria for "suitable" patients, such as slightly older age and no DCIS allowed (72). However, these guidelines are created by consensus panels for patients off protocol, rather than by randomized trials with set selection criteria. While APBI is only available for a select group of breast cancer patients, it is often able to significantly reduce dose to nearby structures including the heart.

A few studies have compared whole breast irradiation to ABPI. A study evaluating APBI using IMRT compared to whole breast using FiF planning (using radiobiologically adjusted results to account for the different fractionations) found that the APBI plan reduced the heart mean from 3.17 to 0.80 Gy ($p = 0.002$) using APBI and reduced V5 from 8.75 to 4.94% ($p = 0.041$) (73). Another review of patients being treated on NSABP-B39 for external beam APBI compared to plans for whole breast irradiation has significantly improved V2.5, V5, and V10 for lateral lumpectomy cavities but not for medial cavities, though V20 was improved with APBI regardless of lumpectomy location (74). Mammosite brachytherapy APBI compared to whole breast irradiation has been shown to significantly reduce maximum heart dose and V5, but not mean heart dose or V10 in one study (75), but single-source APBI brachytherapy did show an improvement in mean heart dose over whole breast from 2.52 to 1.65 Gy in another study (76).

Accelerated partial breast irradiation can be delivered via external beam radiation or via brachytherapy catheter(s) placed in the lumpectomy cavity. Studies of brachytherapy APBI have shown mean heart dose between 1.65 and 2.45 Gy and mean V5 between 1 and 59.2% (77–80). One study achieved a mean maximum heart doses around 2.2 Gy in both Mammosite and Clearpath brachytherapy catheters, though patients in this study have lesions closer to skin than chest wall (81). External beam studies have shown mean heart doses of 1.2 Gy and V5 of 1% (82, 83). RTOG 0413 showed external partial breast irradiation with a mean V5 value at 1.1% for left-sided patients (84).

Accelerated partial breast irradiation with protons has been shown to be very effective at limiting heart dose with one study showing no dose greater than 3 Gy to the heart (85). One study evaluating volumetric-modulated arc radiotherapy (VMAT) was able to achieve an APBI plan with a mean heart dose of 0.72 Gy, which was further reduced to 0.34 Gy (a 53% reduction) when VMAT was combined with dynamic couch rotation to account for respiratory motion (86). When evaluating IMRT, VMAT, and continuous arc rotation of the couch APBI plans separately, compared to a 3DCRT APBI plan, the IMRT and continuous arc plans were able to significantly reduce the mean heart V5 from 3 to 1.1% and 1.7%, respectively (87). Another study found that for pendulous breasts treated prone with IMRT APBI combined with dynamic couch motion could produce a plan that would deliver less than 0.1% of the prescribed dose to the heart (88).

INTERNAL MAMMARY NODE AND BOOST CARDIAC CONTRIBUTION

Slight variations in dose exist though most studies are close to a biologic equivalent dose (at 2 Gy per fraction) of 50 Gy, though a significant variation in the implementation and dose of a boost to the surgical bed exist between studies. Another difficulty in evaluating cardiac dose is variability in treatment volume. Variability in coverage of internal mammary nodes (IMN), axillary, or supraclavicular nodes exists between studies. Adding axillary nodal or IMN coverage to tangent fields has been shown to increase the Dmax of the heart by 7–10% (89). Adding IMN coverage to whole breast irradiation increases the volume of heart irradiated by 13.8% for left breast cancers (90). When comparing plans with IMN in the treatment field, one study found no difference between wide-field, oblique photon-electron, and perpendicular photon-electron techniques (91), while another found decreased mean heart dose, V10, and V20 with wide tangents compared to plans using a separate IMN field (92).

The use and dose of a boost to the lumpectomy cavity is not standardized between studies, nor among practitioners, which contributes to the difficulty in comparing studies. The added mean heart dose of a 10 Gy boost in four fractions is 0.33 Gy for electron boost and 0.73 Gy for a photon boost via VMAT (93). Other studies have found decreased cardiac doses for proton and photon compared to electron boosts (94), and comparable V20 for Mammosite brachytherapy boost compared to electron boost (95).

DISCUSSION

One of the difficulties in comparing studies in radiation cardiac toxicity is the variable reported parameters to evaluate potential toxicity. For example, as mentioned previously, early studies evaluated the volume receiving 50% of the prescription dose (10–12). Another study reviewed SPECT perfusion scans in 20 women 6 months after breast radiation and found minimal decrease in perfusion if RT dose was kept less than 10 Gy and a 20% perfusion reduction if greater than 40 Gy (96), suggesting V10 and V40 as potential targets for plan evaluation. Strain rate imaging has also been used to evaluate cardiac damage from radiation and has shown that radiation of left breast patients led to a significant 2% reduction in left ventricle strain after radiation, particularly observed in regions of the heart exposed to 3 Gy or more (97), which was observed immediately after radiation and persistent when evaluated 14 months after radiation (98). Cardiac biomarkers have also been evaluated following breast irradiation, and while there was a significant increase in mean values of troponin I and Brain Natriuretic Peptide (from 0.007 to 0.014 ng/mL and 123 to 159 pg/mL, respectively), the increase was not above normal reference values (99). A study of 681 breast cancer patients treated in Denmark who did not develop ischemic heart disease found that left-sided breast cancer patients had a mean heart dose of 6 Gy, despite receiving coverage of IMN and supraclavicular fields (100). Mean heart dose is also used as a common reference dose constraint given reports of clinical outcomes in studies using this parameter (8). **Table 1** provides a comparison of many studies that included mean heart dose data; however, caution should be used in comparing studies, as many studies included low numbers of patients, and extent of breast and nodal tissue covered differs from one study to another. Studies have failed to consistently show that LAD dose is independently predictive of cardiotoxicity more than whole heart measures and more reproducible from one physician to another. Therefore, whole heart dose remains a standard measure at present. However, further data are needed to more rigorously establish standards for dosimetric cardiac constraints.

Another challenge is defining the volume used to calculate these dose constraints. Slight variations in heart contours can exist from

Table 1 | Summary of studies evaluating mean heart dose.

Reference	*n*	Treatment technique	Mean heart dose (Gy)
(19)	15	3DCRT (with 16 Gy boost). Tangential single wedge vs double wedge vs FiF	3.31 vs 3.31 vs 3.07
(16)	15	2D vs 3D vs FiF	4.42 vs 5.33 vs 5.17
(101, 102)	358	3DCRT	5.1 if treated in 1950s and 3.0 Gy if treated in 1990s
(17)	217	3DCRT vs multi-segmented conformal radiation therapy	4.8 vs 4.8
(103)	50	3DCRT	2.3
(92)	32	3DCRT including IMNs: 2 plans with separate IMN fields vs wide tangents	6.4 vs 8.1 vs 3.8
(21)	10	Bilateral wedge tangents vs FiF	2.2 vs 1.89
(20)	26	3DCRT in left lateral decubitus position	1.35
(55)	87	3DCRT vs moderate DIBH using active breathing control	4.23 vs. 2.54
(56, 66)	53	3DCRT, if V50 > 10 cm^3, then DIBH IMRT	3.17 vs 1.32
(51)	30	IMRT with simultaneous integrated boost in free breathing and DIBH	6.9 vs 3.9
(52)	12	FB vs DIBH	6.2 vs 3.1
(28)	12	Prone vs supine: wedged tangents, FiF, and multibeam IMRT	Wedged tangents: 1.9 vs 3.9. FiF: 1.6 vs 3.3. IMRT: 1.6 vs 2.5
(104)	5	Prone tomotherapy IMRT	8.7
(36)	10	Multiple partial volumetric-modulated arc therapy technique	7.61
(37)	24	Respiratory gated simultaneous integrated boost IMRT	22.98
(39)	10	Forward-IMRT vs inverse-IMRT vs intensity-modulated arc radiotherapy	5.46 vs 15.48 vs 12.73
(33)	20	Small breasted women treated with wedged tangents vs FIF vs T-IMRT vs M-IMRT vs VMAT	3.7 vs 3.2 vs 2.2 vs 4.4 vs 4.6
(48)	10	3DCRT vs tomotherapy IMRT vs FiF	4.0 vs 3.0 vs 3.0
(38)	11	Hypofractionated concomitant boost radiotherapy using IMRT vs standard sequential boost technique	2.2 vs 3.2
(42)	13	Tomotherapy vs 3DCRT	1.35 vs 2.22
(44)	14	3D vs IMRT for unfavorable thoracic geometry patients	6.85 vs 8.52
(73)	12	APBI IMRT vs 3DCRT with FiF	0.80 vs 3.17
(75)	6	Mammosite HDR brachytherapy APBI vs 3DCRT	3.5 vs 3.8
(76)	26	Single-source HDR brachytherapy APBI vs 3DCRT	2.52 vs 1.65
(80)	60	Brachytherapy ABPI	2.45
(82)	25	External beam APBI (2 minitangent beams and en face electron beam)	1.2
(93)	14	Dose contribution from 10 Gy/4 fraction boost using few leaf electron collimator-based modulated electron radiotherapy vs conventional direct electron vs VMAT	0.34 vs 0.33 vs 0.73

n: number of left-breast women in study (total number if left breast not specified); 3DCRT: three-dimensional conformal radiation therapy; FiF: field-in-field; IMN: internal mammary nodes; DIBH: deep inspiration breath hold; IMRT: intensity-modulated radiation therapy; FB: free breathing; APBI: accelerated partial breast irradiation; FB: free breathing; HDR: high dose rate; VMAT: volumetric-modulated arc therapy.

one radiation oncologist to another. Also, some have questioned whether it may be valuable to contour the LAD or other coronary vessels individually and whether to include the pericardium. For this reason, a heart atlas for CT contouring, developed jointly by cardiology, cardiac radiology, and radiation oncology, to delineate whole heart and separate coronary vessels, has been shown to improve accuracy of cardiac contours, and more consistent mean heart dose reporting, in a tested group of radiation oncologists (105). While this atlas was verified in a group, it is not used by all radiation oncologists and has not been used for contouring in other studies evaluating heart data, because such atlases are still relatively new. User contour variations, therefore, exist between studies. Some studies have suggested that the maximum heart distance in a treatment field, measured anterior to posterior, is relatively simple and correlates well with mean heart dose and other cardiac dose measurements (101, 106). However, another study showed that maximum heart distance only correlated with dose to the LAD when accounting for respiratory motion (107). A study of left-sided breast cancer patients where all plans had LAD, right, and circumflex coronary arteries contoured separately

found that the mean whole heart dose was 2.3 Gy, and 7.6 Gy to the LAD, and 2 Gy to the right and circumflex arteries (103). A recent study of supine standard tangential field plans found that for every 100 cGy increase in mean heart dose the mean LAD dose increased by 4.82 Gy, with direct correlations also seen with several other constraints, suggesting that LAD dose correlates very closely with whole heart parameters and LAD does not need to be contoured separately (108). However, another study using 3 field mono-isocentric partial wide tangents found that 11 of 24 patients had significant variability between mean heart dose and LAD dose (109). A study of 32 women on a randomized trial, treated with breast radiotherapy, evaluated the cardiac perfusion before and 1 year after radiation, and found no significant change in cardiac perfusion after radiation, even when assessing various cardiac subvolumes (110).

Variability in dose planned to dose received can exist. It can be difficult to determine the actual dose received. However, some studies provide insight into means of limiting the variability between these doses. It has been shown that patient setup errors of greater than 3 mm in the posterior direction result in significant increased dose to the heart (111, 112). The maximum anterior/posterior distance of heart in the treatment field has shown a strong linear correlation with mean heart dose (100). Even with image guidance, planning margins may be advisable as variability can exist between bone and/or surface anatomy and cardiac (25, 60, 111).

The implementation of improving techniques for breast cancer radiotherapy can significantly reduce the heart radiation dose that breast cancer patients receive. A review of 358 women treated over several decades in Sweden found that even though a number of different treatment techniques were used, the overall mean heart dose to left-sided breast cancer patients was 5.1 Gy in the 1950s compared to 3.0 Gy for women treated in the 1990s (102). However, it should be remembered that even clear dosimetric advantages in the treatment planning stage may not translate to improvements in clinical outcomes (63).

Radiation is not the only factor contributing to cardiac toxicity in breast cancer patients, as other aspects of their treatment can influence cardiac toxicity. For example, a large study involving doxorubicin and cyclophosphamide chemotherapy with radiation to either the right or left breast (with or without IMN coverage) found that the number of cycles of doxorubicin was a more significant factor in cardiac toxicity than the amount of heart in the radiation field (113). Therefore, all aspects of patient care must be accounted for to reduce cardiac toxicity.

The decision of which treatment planning technique for delivery of radiotherapy following breast-conserving surgery includes consideration of many factors about the patient. One important factor in that decision is radiation doses received to the heart, as decreasing radiation doses to the heart can potentially prevent unnecessary cardiotoxicity. Many different techniques are available, as discussed in this review, to significantly reduce radiation doses to the heart, thereby providing means to decrease cardiac toxicity risk for women undergoing such treatment.

Several techniques have been shown to improve cardiac doses over standard supine 3DCRT tangents. Prone positioning has been shown to improve cardiac doses for patients with large pendulous breaths, though not for smaller breasted patients. Breath hold can also significantly reduce heart dose by displacing the heart away from the chest wall. APBI can be effective in reducing cardiac radiation doses though this is dependent on the location of the tumor/lumpectomy cavity and is only suitable for a select portion of breast cancer patients. Use of seroma boost and IMN irradiation has been shown to increase cardiac dose, though the cardiac risk needs to be weighed against the risk of recurrence.

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Measurement of mean cardiac dose for various breast irradiation techniques and corresponding risk of major cardiovascular event

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After breast conserving surgery, early stage breast cancer patients are currently treated with a wide range of radiation techniques including whole breast irradiation (WBI), accelerated partial breast irradiation (APBI) using high-dose rate (HDR) brachytherapy, or 3D-conformal radiotherapy (3D-CRT). This study compares the mean heart's doses for a left breast irradiated with different breast techniques. An anthropomorphic Rando phantom was modified with gelatin-based breast of different sizes and tumors located medially or laterally. The breasts were treated with WBI, 3D-CRT, or HDR APBI. The heart's mean doses were measured with Gafchromic films and controlled with optically stimulated luminescent dosimeters. Following the model reported by Darby (1), major cardiac were estimated assuming a linear risk increase with the mean dose to the heart of 7.4% per gray. WBI lead to the highest mean heart dose (2.99 Gy) compared to 3D-CRT APBI (0.51 Gy), multicatheter (1.58 Gy), and balloon HDR (2.17 Gy) for a medially located tumor. This translated into long-term coronary event increases of 22, 3.8, 11.7, and 16% respectively. The sensitivity analysis showed that the tumor location had almost no effect on the mean heart dose for 3D-CRT APBI and a minimal impact for HDR APBI. In case of WBI large breast size and set-up errors lead to sharp increases of the mean heart dose. Its value reached 10.79 Gy for women with large breast and a set-up error of 1.5 cm. Such a high value could increase the risk of having long-term coronary events by 80%. Comparison among different irradiation techniques demonstrates that 3D-CRT APBI appears to be the safest one with less probability of having cardiovascular events in the future. A sensitivity analysis showed that WBI is the most challenging technique for patients with large breasts or when significant set-up errors are anticipated. In those cases, additional heart shielding techniques are required.

Keywords: breast neoplasms, radiotherapy, heart diseases, brachytherapy, radiation dosage

INTRODUCTION

In developed countries, breast cancer is the most common type of cancer in women (2, 3). With implementation of mammographic screening, the majority of the cases are diagnosed at an early stage. The standard treatment for early stage breast cancer includes removing the tumor and sampling the axillary lymph nodes using limited surgery (4). This is followed by whole breast radiotherapy and possibly regional radiation if nodes are positive. Currently, there is a general trend toward treatment de-escalation. Radiation oncology studies demonstrate that the duration of whole breast irradiation (WBI) can be shortened from 6 to 3 weeks (5–7), and other showing that for selected cases the amount of irradiated breast tissue could be limited to a small portion surrounding the surgical cavity (8, 9). This leads to a technique called accelerated partial breast irradiation (APBI). It combines a reduction of the irradiated breast volume and delivery of higher dose per fraction. Multiple APBI techniques have been proposed including external beam 3D-conformal radiotherapy (3D-CRT), high-dose rate (HDR) interstitial brachytherapy using multicatheter or balloon, and permanent breast seeds implants (10, 11). As a result, patients with early stage breast cancers are treated with a variety of radiation techniques that appears comparable in terms of effectiveness (12, 13).

Along with the changes in radiation oncology practice mentioned above, the increased early detection of breast cancer due to screening programs has also resulted into improvement of the breast cancer treatment outcomes, with specific survival rates of 98.6% at 5 years (14). With improved survival, the reduction of treatment induced morbidity and mortality has gained importance as they may eliminate the need for adjuvant radiotherapy. Several studies with long-term follow-up have shown that standard external beam radiotherapy can increase the risk of ischemic heart

disease and a recent large case control study suggests that a dose–response relationship between the mean dose to the heart and the long-term risk of major cardiovascular events including mortality (1, 15–18). It is unknown if all the radiation techniques used in early stage breast cancer have similar cardiac risks since there are no long-term prospective data comparing them on this specific outcome. There is a limited number of studies reporting or comparing the heart dose (19–25) for one or two techniques but there has not been thorough comparison of the mean dose to the heart for all breast techniques, for various breast sizes and/or seroma locations. In most of cases, commercial treatment planning systems (TPS) are used for estimation of the heart's dose. Since this dose is calculated outside the field where photon scattering dominates, some concern about the accuracy of those calculations exists (26, 27).

Given the inaccuracies in calculating out of field dose with the current clinical TPS, the purpose of this study was to measure and compare the mean heart dose for different breast irradiation techniques delivered to the left breast of an anthropomorphic phantom. In addition, the robustness of our findings was tested using a sensitivity analysis looking at the added influence of breast size, seroma location, and organ motion.

MATERIALS AND METHODS

PREPARATION OF PHANTOMS

An anthropomorphic Rando phantom (The Phantom Laboratory, Salem, NY, USA) was modified using molded pieces of a tissue equivalent gel for mimicking various breast sizes. In order to prepare the necessary phantom, three CT scans of patients with left sided breast cancer having typically small (300 cc), medium (800 cc), and large breast (1200 cc) volumes were selected from our institution's dosimetry database. Each CT slice was spaced by 1 cm and was printed on a scale 1:1 and used to create a realistic 3D breast shape assembling several styrofoam sheets of 1 cm thickness. The printout of the patient contour was pasted on individual styrofoam sheets and cut following the chest wall and breast contours (**Figure 1**). A negative breast mold was then made using a thermoplastic sheet. This negative mold was then filled with a tissue equivalent powdered ballistics gelatin (Vyse, Schiller Park, IL, USA) dissolved in water. The breast phantom was refrigerated overnight. The resulting gelatin phantom has an average CT number of 24 Hounsfield units (HU), which is similar to fibroglandular breast tissue. The phantom was kept at 5°C to limit melting and water evaporation. It was tightly fixed on the Rando phantom chest wall for planning and treatment.

TREATMENT SIMULATION AND VOLUME DEFINITION

Treatment simulation for small, medium, and large breasts was done following standard institution protocol (28). The Rando phantom with various breast volumes placed on the torso was positioned on a breast board. Five radio-opaque beads and/or pen marks were placed on the skin in the lateral, medial, inferior, and superior aspects of the chest to ensure treatment reproducibility. CT slices of 5 mm spacing and 5 mm thickness were acquired with a Philips CT scanner (Philips Healthcare, Andover, MA, USA) and transferred to either the Pinnacle 3 (RaySearch Americas Inc., Garden City, NY) or the Oncentra Brachytherapy planning systems (Nucletron Elekta, Stockholm, Sweden).

For WBI the clinical target volume (CTV) was defined as whole breast gel phantom limited by the Rando chest wall and a 5 mm layer below the phantom surface. For APBI, the CTV were defined either on the medial or the lateral quadrants of the breast. To ensure comparison of similar target volumes, CTVs of 60 cc were delineated. For brachytherapy, the planning target volume (PTV) included a 1.5 cm expansion from the CTV but limited to the Rando chest wall and 5 mm below the breast surface, while for 3D-CRT APBI the PTV included an expansion of 2.5 cm, similarly to the NSABP-B39 protocol (29).

TREATMENT PROTOCOLS

External beam radiotherapy

Whole breast irradiation was planned following standard breast IMRT protocol (30) using a prescription dose of 50 Gy in

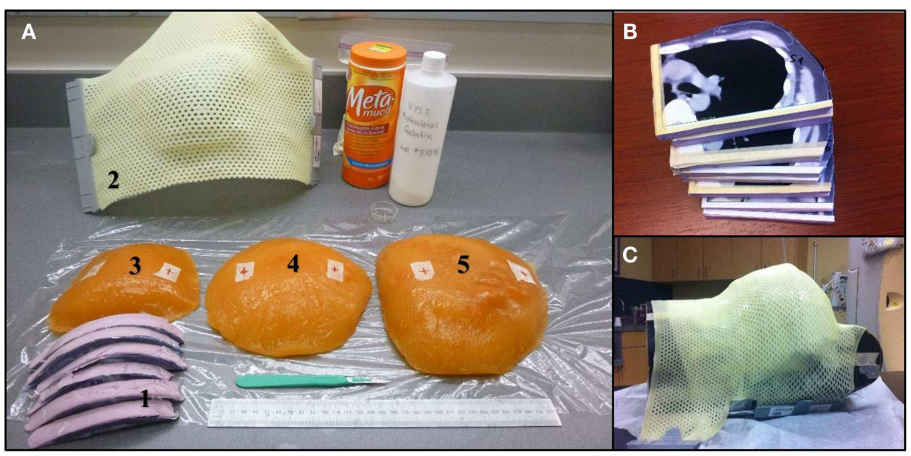

FIGURE 1 | (A) Materials used during the breast phantom manufacture. (1) Styrofoam slices cut to fit CT contours. (2) Thermoplastic 3D breast contour obtained from the Styrofoam mold. (3–5) Small, medium, and large size of gelatin-based breast phantoms. **(B)** Styrofoam slices cut to the patient profile using CT images. **(C)** Thermoplastic mold over the Rando phantom modified with the large breast to ensure good contact.

FIGURE 2 | Fields arrangement and various breast treatments dosimetry. **(A.1)** Medium size WBI treatment dosimetry and **(A.2)** tangential fields 3D representation. **(B.1)** 3D-CRT APBI dosimetry and **(B.2)** five fields no coplanar 3D representation. **(C)** Multicatheter HDR APBI dosimetry.

25 fractions. For the small and the medium-sized breast phantoms, the beam energy was 6 MV, while a mix of 6 and 18 MV beams was used for the large breast volume. In this protocol, a multileaf collimator (MLC) is used to shape several field-in-field beams to compensate for missing tissue and to improve the dose distribution homogeneity. Plans were normalized to a prescription point set at mid-separation, 2/3 of the distance between skin and a base of the tangential fields. Heart shielding involved ensuring the anterior heart volume was away from the posterior beam edge. Standard treatment set-up procedures were followed including verification of each field using portal imaging.

For 3D-CRT APBI, three to five non-coplanar beams were aimed (**Figure 2**) at the PTV (29, 31) and a dose of 38.5 Gy in 10 BID fractions was prescribed. The distribution was normalized on the PTV centroid.

Treatments were delivered using a 6/18 MV Elekta Synergy linac equipped with a multileave collimator (Elekta Inc., Crawley, UK). Treatment was delivered after verification of the correctness of the set-up using portal imaging.

Brachytherapy

Using a free-hand technique, 13 catheters were inserted (**Figure 3**) in a triangular pattern and evenly spaced by 1.5 cm in the horizontal plane and 1 cm in the vertical plane (32). The implanted Rando phantom was CT simulated and the images were transferred to the planning system for target segmentation and dose optimization. A dose of 34 Gy in 10 fractions was prescribed on the minimal peripheral dose (MPD) and dwell times were optimized using the IPSA optimization module (33) to ensure that at least 90% of the target volume (D_{90}) will receive at least 90% of the prescribed dose, and that the volume receiving more that 200% of the prescribed dose (V_{200}) would be <20 cc. HDR brachytherapy was delivered using a ^{192}Ir HDR remote afterloader (Flexitron, Elekta, Stockholm, Sweden). To replicate a balloon catheter HDR treatment, a 3 cm diameter surgical cavity was made in the breast gel phantom and a Foley catheter was positioned inside before being filled with saline. A single catheter was inserted into the Foley catheter and used to deliver a dose of 34 Gy in 10 fractions at the point located 1 cm from the balloon surface.

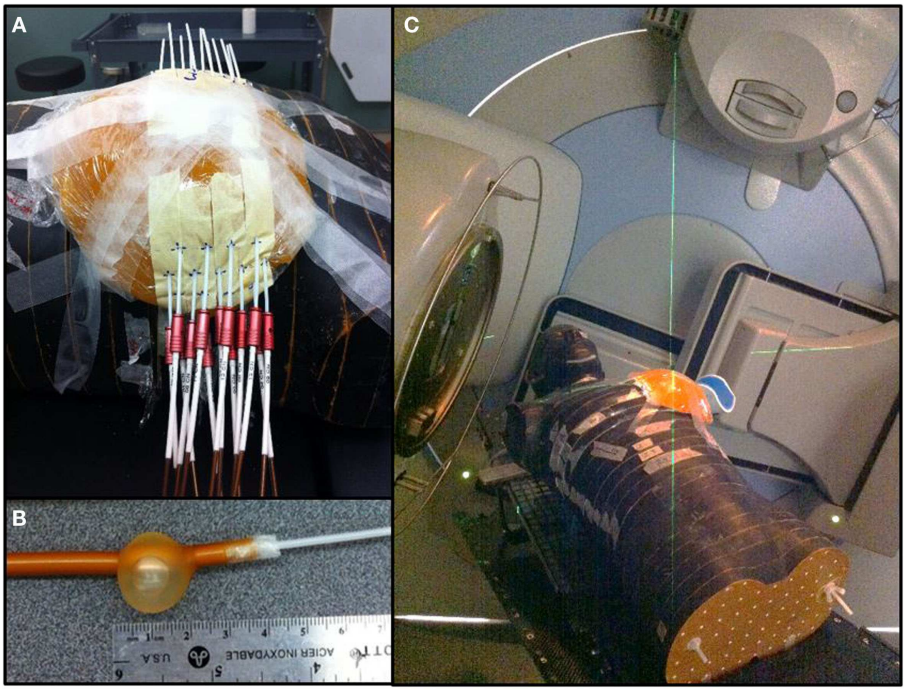

FIGURE 3 | Breast treatments. **(A)** Multicatheter HDR APBI. **(B)** Foley catheter used for balloon HDR APBI. **(C)** 3D-CRT APBI.

PLACEMENT OF DOSIMETERS

Two types of dosimeters were used for dose measurements, optically stimulated luminescent dosimeter (OSLD) high-accuracy Nanodot dosimeters (Landauer Inc., Glenwood, IL, USA) and Gafchromic EBT3 films (Ashland Inc., Covington, KY, USA). OSLD dosimeters were placed in areas corresponding to a left descending artery, and the center of left and right ventricles. The detectors were placed inside a bolus material between the three consecutive Rando phantom slices where the heart was identified (**Figure 4**).

Three Gafchromic films were used to evaluate the heart's dose distribution in 3D. They were positioned at different location evenly spaced by 1.5 cm. In total, 24 films were irradiated at the three films positions (Apex, medium heart, and base of the heart). For the each technique, films were placed between slices inside the anthropomorphic phantom and fixed in clearly established positions for every experiment. To indicate the exact position of the contour of the heart, the heart contour was drawn on the film with a permanent marker.

In accordance with recommendations of AAPM TG55, the Gafchromic films were kept in a dry and dark area at room temperature for at least 24 h before reading. The heart contours identified on the films were segmented and the optical density was found using the Epson Expression 10000XL scanner (EPSON Deutschland GmbH, Meerbusch, Germany). Optical densities were converted into dose using a calibration curve. All measured dose were expressed as a percentage of the prescribed dose. The doses measured with the 2D film were assumed to represent the average dose absorbed in the adjacent heart's volume and cumulative DVH were built.

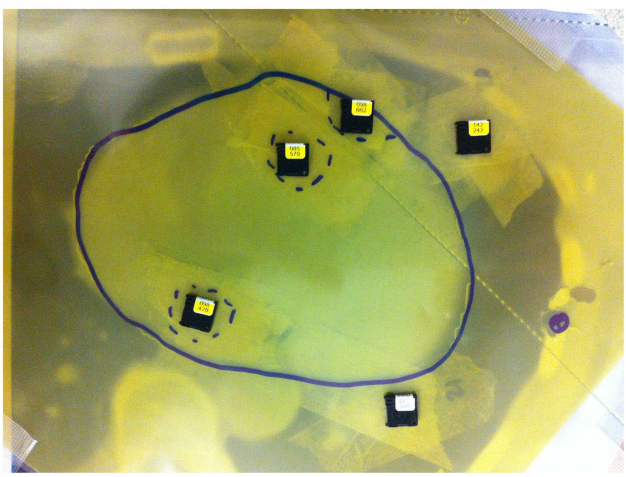

FIGURE 4 | Optically stimulated luminescent dosimeters and Gafchromic film placement between Rando slices with a 5 mm bolus.

SENSITIVITY ANALYSIS

Except the used radiation techniques, other changing factors such as the breast size, shape, and location of the seroma, and distance between a heart and a field's border or a HDR source could also impact on the mean heart dose (34). A meaningful evaluation of the mean heart dose should also account for potential patient set-up error, also called inter-fraction error, for anatomical factors such as heart volume variations between the systolic and diastolic phases or due to patient's phenotype. To evaluate the impact of

those variations for various radiation techniques, the Gafchromic films were reanalyzed shifting the heart position by 1.5 cm. This value is the average of the distance between the field border and the tip of the heart measured on portal imaging for the worse case scenario group in Goody's study (35). In this report, 11% of the 128 patients had the heart protruding in the irradiation field from 10 to 20 mm.

ESTIMATION OF MAJOR CARDIAC EVENTS

Following the model reported by Darby (1), major cardiac were estimated assuming a linear risk increase with the mean dose to the heart of 7.4% per gray (95% confidence interval, 2.9–14.5; $p < 0.001$). Those major cardiac events include myocardial infarction, coronary revascularization, and death from ischemic heart disease, but angina episodes are not included.

RESULTS

QUALITY ASSURANCE

The OSLD dose measurements performed inside breast of various sizes were in very good agreement with those calculated with Pinnacle TPS. The dose measured using three to five detectors placed inside the breast was 95% (SD = 2.5%) of the calculated one for the small breast, and 101% (SD = 0.8%) of the calculated one for the medium size breast.

A very good agreement between OSLD measurements and the Gafchromic film measurements were received (**Figure 5**). A correlation coefficient R^2 of 0.98 ($p < 0.001$) is calculated.

MEAN DOSE TO THE HEART

The measured mean heart's doses received with different irradiation technique for medium size breast are shown in **Table 1**. WBI yielded the highest mean heart dose, 2.9 Gy, leading to an estimated increased risk of major coronary events of 22%, while the lowest mean heart dose was measured for the 3D-CRT APBI, 0.5 Gy, leading to a negligible 4% increased risk of cardiac events. The summarized cumulative DVHs for different radiation techniques and different anatomical structures are shown on **Figures 6–9**.

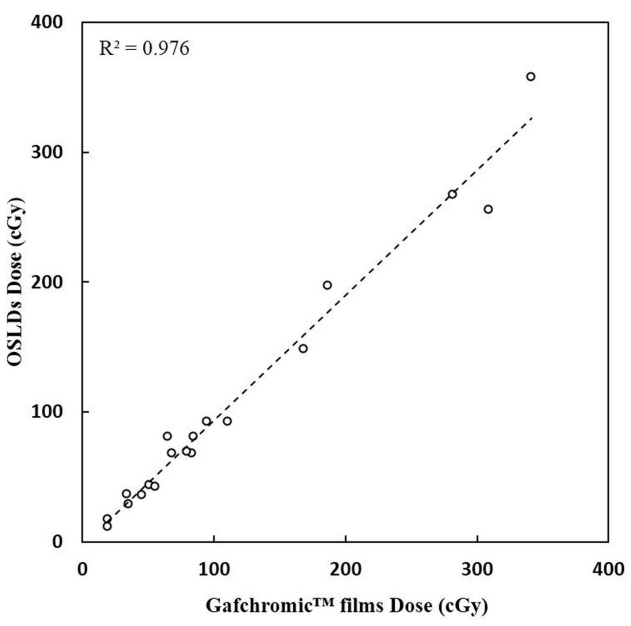

FIGURE 5 | Correlation between OSLDs and Gafchromic films measurements.

SENSITIVITY ANALYSIS

We performed a sensitivity analysis. There was no significant difference in the value of the mean heart's dose when the small and medium breast size phantoms were used. At the same time, its value doubled from 2.99 Gy to 6.39 Gy when the largest breast size phantom was used (**Table 2**). This was due to the posterior shift of the beam edge needed to fully cover the breast volume. The seroma location had little impact when using whole breast radiotherapy or 3D-CRT APBI. It increased the mean heart's dose by 17% for a medially compared to laterally located seroma using multicatheter brachytherapy, and by 32% using balloon brachytherapy. This was essentially due to the closer proximity to the radioactive source. The most dramatic increase of mean heart's dose was seen when we were testing set-up or organ motion errors for external beam radiotherapy. An anterior shift of the heart's edge by 1.5 cm resulted in a 150% increase. For a large breast volume, the mean heart dose could reach 10.8 Gy, which corresponds to almost a twofolds increased risk of major coronary events. The set-up errors and organ motion effects were much less pronounced for brachytherapy techniques and this was the consequence of the smoother isodose gradient on the Gafchromic films anteriorly to the heart compared to external beam with heart shielding.

Table 1 | Mean heart dose measured with Gafchromic films for the medium (800 cc) and large breast (1200 cc) phantom using different radiation techniques.

Technique	Mean dose (Gy)	Relative to prescribed dose (%)	Increased risk of coronary events in % (95% CI)[b]
WBI			
Medium (800 cc)	2.99	5.99	22.0 (8.7–43.4)
Large (1200 cc)[a]	6.39	12.79	47.2 (18.5–92.6)
3D-CRT-APBI			
Lateral	0.57	1.48	4.2 (1.7–8.3)
Medial	0.51	1.34	3.8 (1.5–7.4)
HDR MULTICATHETER			
Lateral	1.44	4.28	10.6 (4.2–20.9)
Medial	1.58	4.67	11.7 (4.6–22.9)
HDR BALLOON			
Lateral	1.27	3.73	9.4 (3.7–18.4)
Medial	2.17	6.38	16.0 (6.3–31.5)

[a] *Large pendular breast treated wide tangents.*

[b] *Increased risk in major coronary events (myocardial infarction, coronary revascularization, and death from ischemic heart disease) is 7.4% (95% confidence interval 2.9–14.5%) per Gray (16).*

WBI, whole breast irradiation; 3D-CRT APBI, 3D-conformal radiation therapy accelerated partial breast irradiation.

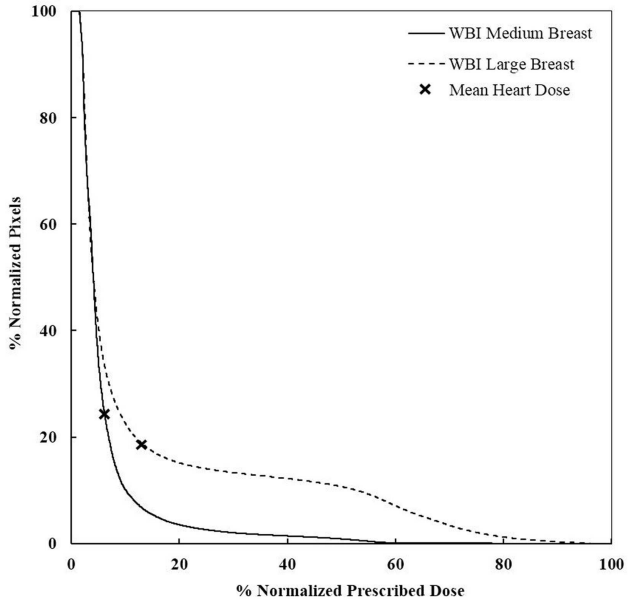

FIGURE 6 | DVHs for WBI of medium and large breasts. More heart is receiving a higher dose for large breasts. WBI, whole breast irradiation.

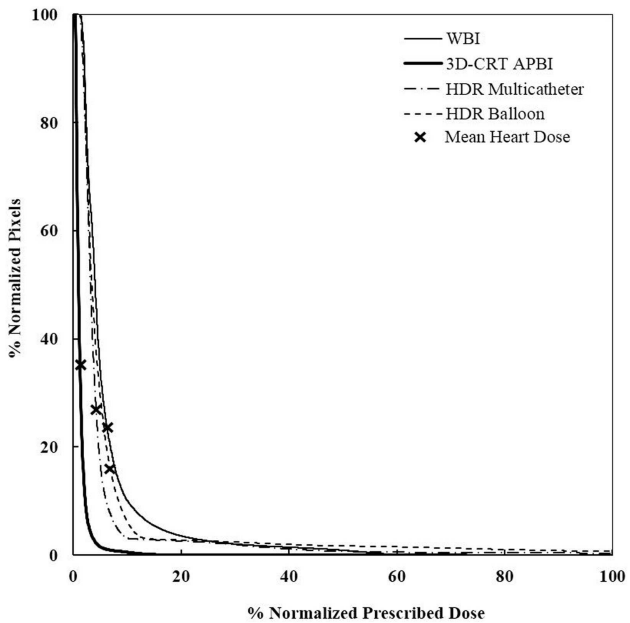

FIGURE 7 | Cumulative DVHs for various adjuvant breast irradiation techniques for a medially located tumor and a medium breast. The 3D-CRT APBI appears to be the safest by far. WBI, whole breast irradiation; 3D-CRT APBI, beam 3D-conformal radio therapy accelerated partial breast irradiation; HDR, high-dose rate.

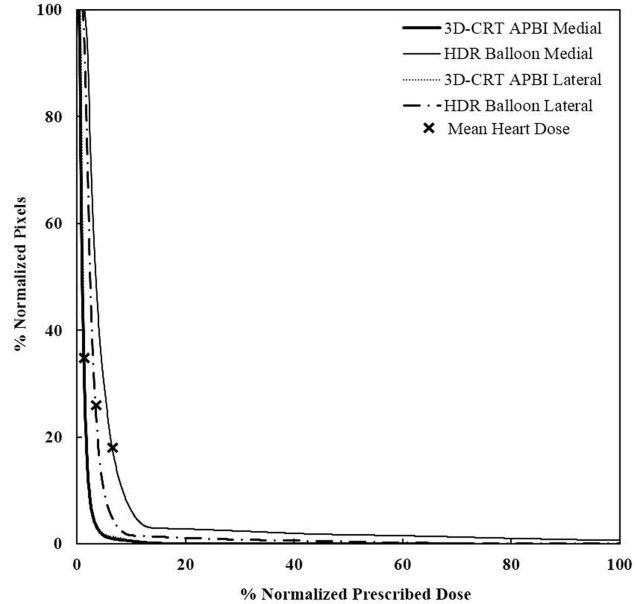

FIGURE 8 | Cumulative DVHs for various tumor locations and APBI techniques. There is no impact of location for 3D-CRT as opposed to HDR techniques. 3D-CRT APBI, beam 3D-conformal radio therapy accelerated partial breast irradiation; HDR, high-dose rate.

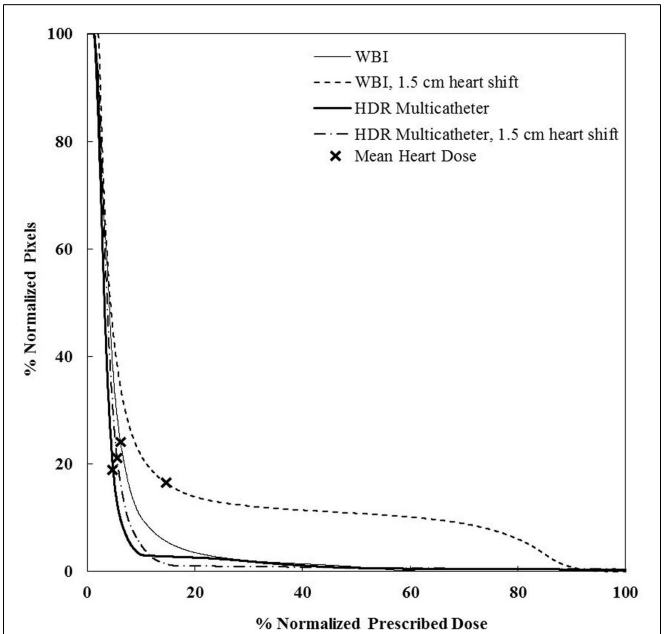

FIGURE 9 | Cumulative DVHs for the sensitivity analysis on set-up error and motion effect for a medium sze breast and a medially located seroma. There is little impact of those factors for HDR, but a dramatic effect for WBI. WBI, whole breast irradiation; HDR, high-dose rate.

DISCUSSION

This work reports the mean cardiac doses measured in an anthropometric phantom mimicking, a patient receiving breast radiotherapy with various techniques currently used for early stage breast cancer treatment. This study provides experimental data that could be considered more reliable compared to those calculated in commercial TPS. According to other publications,

Table 2 | Set-up error and organ motion sensitivity analysis of the mean heart dose for the medium (800 cc) and large breast phantom (1200 cc) using a 1.5 cm anterior heart shift.

Technique	Mean dose (Gy)	Relative to prescribed dose (%)	Increased risk of coronary events in % (95% CI)
WBI			
Medium (800 cc)	7.11	14.22	52.6 (20.6–100)
Large (1200 cc)[a]	10.79	21.59	79.8 (31.3–100)
3D-CRT-APBI			
Lateral	0.69	1.81	5.1 (2.0–10.0)
Medial	1.20	3.14	8.9 (3.5–17.4)
HDR MULTICATHETER			
Lateral	1.68	4.97	12.4 (4.9–24.4)
Medial	1.70	5.00	12.6 (4.9–24.7)
HDR BALLOON			
Lateral	1.34	3.96	9.9 (3.9–19.4)
Medial	2.44	7.19	18.1 (7.1–35.4)

[a] *Large pendulous breast treated wide tangents.*

WBI, Whole breast irradiation; 3D-CRT APBI, 3D-conformal radiation therapy accelerated partial breast irradiation.

commercial TPS significantly underestimate the scatter dose outside the irradiation field (27, 35). Howell previously reported that the Eclipse's analytic anisotropic algorithm gave a dose at the point 11.25 cm away from the treatment field border less by 55% than that of measured directly with thermoluminescent dosimeters (TLD) (35). To address this issue, our group used Monte Carlo simulation to estimate the dose delivered to the left anterior descending artery in an anthropometric phantom. Because secondary photons rarely crossed the volume of interest (VOI) the transport of a very large number of photons and multiple variance reduction strategies were necessary. Major simplifications have been made to the description of the phantom including large tally volumes (36).

Yet, since very low values are expected, the measurement of scattered dose remains challenging. The following quality assurance measures were undertaken to control the validity of our measurement. First, the doses at several points were checked using two independent methods, namely, the OSLDs and the Gafchromic films. Both are energy independent and the second one enables capturing a 3D spatial dose distribution stacking films. Second, we compared doses measured inside the high-dose treated volume and those calculated by the TPS. Those checks were considered satisfactory if they show differences in dose lower than 5%. Third, we repeated the experiments two times to ensure no major set-up error was made.

The most noteworthy finding of our study is that the mean heart dose was almost halved when using HDR APBI compared to WBI, even for the worst case scenario of a medially located left breast tumor. In this instance, the balloon brachytherapy technique does slightly worse, but still better than whole breast radiotherapy. The use of 3D-CRT APBI reduced the mean heart dose to one-third of what is received with use of HDR and to a sixth compared to WBI. This was essentially due to the limited extension of the posterior field border compared to WBI. It turns out the 3D-CRT APBI is the safest radiation technique and its use has the lowest risk of having major cardiovascular events. Those findings are consistent with previously reported ones. In a dose modeling study, Hiatt reported a sixfolds dose reduction when 3D-CRT was used instead of whole breast using IMRT (37). Also, Valach (25) reported a mean heart's dose of 2.45 ± 0.94 Gy when balloon brachytherapy was used and the seroma was located in the inner quadrant of the left breast. Our measured value for a similar case was equal to 2.17 Gy.

One limitation of the present study is linked to the use of the Rando phantom that imposes estimating the 3D mean heart's dose using only three Gafchromic films. Since the dose gradients are very smooth for the APBI technique, any impact would mainly concern the WBI technique where steep gradients are seen in the portion of the heart close to the beam edge. However, the films were placed perpendicular to the beam direction, such that a fine dose resolution was obtained in 2D. It is hence unlikely that any cold or hot spot may have been missed and that additional resolution would significantly change our findings. In addition, the main goal of the present study is not to provide exact value of mean heart's dose since they could vary depending on many factors. The purpose of this study was mainly to compare different breast techniques, so using the same methodology enable a fair comparison among them. Another limitation of our work relates to the conversion of mean heart's dose to major cardiovascular event risks for each radiation technique (18). The isodose fall-off in the heart is very different between WBI, HDR, and 3D-CRT APBI. It is much steeper for the first one and gradual for the other ones. This leads to very different DVH profiles and it is eventually unclear if comparing the mean instead of, for example, the median heart's dose is the right approach. Identifying the critical structures involved in the radiation damage to the heart remains challenging. Coronary arteries including the left anterior descending artery or ventricles have been suggested (38). There is, however, no data correlating the doses received on those volumes to a prospectively evaluated clinical endpoint. We used the model proposed by Darby, as it remains the only one showing a statistically significant correlation between a risk of major cardiac events and a dosimetry parameter. But, we acknowledge that the risk we calculated for the various breast techniques maybe over or underestimated.

Using the predictive model proposed by Darby (18), a large variation in the values of the major coronary event risk is obtained. It ranges from a negligible 4–5% increase, in case of 3D-CRT and a medially or laterally located tumor, to a concerning 80% increase in case of a patient with a large breast having a systematic set-up error and/or motion exceeding 1.5 cm. This emphasizes the need of individual evaluation of risks accounting for potential intra-fraction errors and for patients with a large size breast with risk of set-up error measures to reduce the dose delivered to the heart must be taken. Those measures include gating the radiation delivery to the breathing cycle, using a prone position, 3D-CRT APBI technique, or proton therapy (39–41). Techniques like moderate deep inspiration breath hold have now been widely introduced into clinic. Although there is no long-term data to confirm its benefit in term of major cardiac event reduction, long-term experience shows that the mean heart's dose is reduced by 40% (40).

It must be noted that although the finding of a better cardiac shielding using APBI is clearly appealing for a cancer population with excellent survival rates, the long-term outcomes of APBI remains unknown. If the early outcomes from large trials and multiple cohort studies appear promising (12, 13, 42, 43), a large population-based study shows contrariwise a marginal increased rate of mastectomy likely linked to local recurrence (44). It is eventually difficult to evaluate the final impact on the overall survival when balancing those opposite effects.

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Cardiac avoidance in breast radiotherapy: many choices for a worthwhile objective

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In this Research Topic, Goyal and Haffty have collected a series of papers on the emerging field of cardio-oncology. Indeed, Darby et al.'s paper demonstrating an incremental 7% increase in risk of ischemic events per gray increase in mean heart dose has been a watershed moment in our efforts to improve the therapeutic ratio of adjuvant breast radiotherapy (1). While a 0.07 increase over baseline risk per Sievert may seem high, it is important to understand this relative increase in risk in the context of the absolute baseline risk. Darby and colleagues do not provide a denominator for eligible patients in the two population registries from which they drew their cases and controls. Instead, they estimate the baseline risk using data from 15 Western European nations, and in Table S12 of the Supplementary Material, go on to estimate the absolute risk increase by age 80 years in women exposed to RT at various ages and with various co-morbid risk profiles. The excess absolute risks appear to be modest at first glance. For example, for a young 40-year-old woman receiving a high mean heart dose of 10 Gy, the estimated absolute excess risk of *dying* from cardiac disease is about 1.4%. Should the same woman have at least one co-morbid risk factor, her excess risk is 2.3%. These numbers may seem small, but are certainly relevant at the population level, especially given that the mortality benefit of adjuvant radiotherapy is also modest (2). Current efforts at reducing the risks of incidental cardiac irradiation have included advanced radiotherapy techniques for cardiac avoidance such as breath hold (3), gating treatments (4), proton therapy (5), prone positioning (6), and combinations thereof such as respiratory gating in the prone position (7).

Cardiac avoidance techniques are illustrative of the general potential that technological innovations can have on human health. Going back to the very development of megavoltage machines, improvements in radiation delivery have consistently improved the therapeutic ratio in any number of settings. Recent reports have demonstrated fewer late second malignancies in children treated with proton therapy (8), lower rates of desquamation in breast cancer patients treated with IMRT (9), higher rates of local control in lung cancer patients treated with SBRT (10), and improved biochemical control in patients treated with highly conformal, high-dose radiotherapy for prostate cancer (11). Similar improvements in image-guided gynecological brachytherapy (12), IMRT in head/neck (13), GI (14), and gynecological malignancies (15), as well as intracranial SRS (16) have all demonstrated better outcomes compared with control data. Even as the calls for controlling costs become ever more constant, it is important to remember that the current excitement for a genomically driven model of cancer care has become possible only because of technological improvements in sequencing technologies. As such, continued funding, both federal and private, for technology innovations is critical and should not be relegated to lower tiers of priority.

Coming back to breast cancer patients and the cardiac risks they face from radiotherapy, one additional (seemingly obvious) point needs to be made. While we can invoke continually advancing technologies for the purposes of cardiac avoidance (17), sometimes a return to simpler solutions may be all that is needed. Many women with early-stage breast cancer are eligible for off-protocol accelerated partial breast irradiation as a standard of care option (18). As one would expect, irradiating a smaller volume of breast tissue leads to lower incidental heart doses (19). Current studies and protocols examining, for example, breath hold parameters or prone positioning often include a large contingent of women who are candidates for partial breast irradiation. One rather elegant way to avoid treating the heart is to simply not treat it.

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Radiation-induced heart disease: pathologic abnormalities and putative mechanisms

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Breast cancer is a common diagnosis in women. Breast radiation has become critical in managing patients who receive breast conserving surgery, or have certain high-risk features after mastectomy. Most patients have an excellent prognosis, therefore understanding the late effects of radiation to the chest is important. Radiation-induced heart disease (RIHD) comprises a spectrum of cardiac pathology including myocardial fibrosis and cardiomyopathy, coronary artery disease, valvular disease, pericardial disease, and arrhythmias. Tissue fibrosis is a common mediator in RIHD. Multiple pathways converge with both acute and chronic cellular, molecular, and genetic changes to result in fibrosis. In this article, we review the pathophysiology of cardiac disease related to radiation therapy to the chest. Our understanding of these mechanisms has improved substantially, but much work remains to further refine radiation delivery techniques and develop therapeutics to battle late effects of radiation.

Keywords: breast cancer, radiation side effects, radiation therapy, radiation fibrosis

INTRODUCTION

Breast cancer is a common diagnosis in women with an estimated diagnosis of 235,000 new cases made in 2014. Annually approximately 40,000 women are expected to die from breast cancer (1). Adjuvant radiation therapy (RT) following either breast conserving surgery (BCS) or mastectomy has been shown in comprehensive meta analyses to reduce the risk of local recurrence by approximately 75%. Unfortunately, RT to the breast and chest has been associated with radiation-related morbidity and mortality that may offset some of the benefit of breast radiation. The spectrum of radiation-induced heart disease (RIHD) includes pericarditis, cardiomyopathy and myocardial fibrosis, coronary artery disease, pericardial effusions or constriction, valvular disease, and arrhythmias (2, 3). The spectrum of RIHD in patients undergoing other thoracic and mediastinal RT has been described since 1960s. Today, breast cancer patients likely constitute the largest population of patients exposed to chest radiation (4, 5). Recently published studies indicating that breast RT may pose an increased risk of heart disease have re-emphasized the importance of minimizing the heart dose (6). Modern techniques including three-dimensional planning, conformal blocking, deep-inspiration breath hold, and prone positioning, among others, have allowed the radiation oncologist to reduce the heart dose during breast RT, potentially reducing or eliminating RIHD. In this article, we review the pathophysiology of RIHD from several common pathways, and mechanisms for the specific cardiac pathologies. It is important to know that RIHD is a heterogenous group of pathologic abnormalities. Substantial work has been performed in histologic description, but further characterization of the biochemical pathways is required.

NORMAL HEART TISSUE ANATOMY

The heart comprised three layers of tissue: endocardium, myocardium, and epicardium. The epicardium is superficial outer layer of the heart composed of a sheet of mesothelial cells. It is also considered the visceral layer of the serous pericardium. The epicardium is responsible for producing pericardial fluid that provides lubrication between the inner serous and outer fibrous pericardium and protection of the heart from external contusion. Pericardial disease includes pericarditis (inflammation of the pericardium), pericardial effusion (fluid accumulation in the pericardial sac), cardiac tamponade (pericardial effusion leading to hemodynamic compromise), constrictive pericarditis, and other less common pathologies (4, 7–11). The endocardium most closely resembles endothelial tissue and lines the inner surface of the heart. Endothelial cells modulate the function of the cardiac myocytes in the underlying myocardium. Ventricular endocardium also contains fibers of the cardiac conduction system. The myocardium is a highly vascular tissue with a capillary density approaching 2800 capillaries per mm^2; capillary density of skeletal muscle is approximately 350 capillaries per mm^2. Capillaries surround individual myocytes completely and normally are always open to perfusion. Prior to initiation of an action potential, cardiac myocytes are in a resting, well-perfused state. The action potential causes a series of processes resulting in actin-myosin crossbridging and contraction. Normally, spontaneous phase 4 depolarization in cells of the sinoatrial node, the most rapid site of rhythmic discharge, initiates atrial depolarization that propagates via the atrioventricular nodes, to the His–Purkinje fibers, and to the ventricular myocytes. The myocardial blood supply is critical and relies on a developed arteriolar capillary system as there are no major vessels that course through this tissue. Any radiation-induced damage to the vascular

endothelial cells that line the myocardial capillaries can result in decreased myocardial perfusion and poor contractility (12–14).

The major blood supply to the heart is from the coronary arteries. The right and left coronary arteries originate at the root of the aorta. The left coronary artery divides into the left anterior descending artery (LAD) and the left circumflex artery. The LAD is more often implicated in RT-related morbidity as it courses on the anterior surface of the heart and is most often contacted by external beam radiation (15, 16). Any disruption to arterial flow, whether by progressive occlusive disease or acute thrombotic event causing complete obstruction, can result in ischemia and potential infarct.

PATHOPHYSIOLOGY OF RADIATION-INDUCED HEART DAMAGE

A major common endpoint for RIHD is tissue fibrosis. Tissue irradiation is a major model to study fibrosis (17). In a simple characterization, radiation exposure leads to endothelial cell damage and subsequent microvascular dysfunction due to fibrosis.

Radiation damage is characterized by both acute and chronic changes in cardiac tissue. Within minutes of ionizing radiation, cellular injury causes vasodilation and increased vascular permeability. Damaged endothelial cells secrete adhesion molecules and growth factors prompting activation of the acute inflammatory response. Recruited inflammatory cells secrete profibrotic cytokines (17, 18). Inflammatory cytokines include monocyte chemotactic factor, tumor necrosis factor (TNF), and interleukins (IL) including IL-1, IL-6, and IL-8. The predominant cells in the acute phase are neutrophils, which become present in all layers of the heart in RT exposed regions. Within hours of RT, profibrotic cytokines such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), and connective tissue growth factor (CTGF), among others, are released (19). While some factors promote recruitment of inflammatory cells and profibrotic cells, others such as IL-1, act as a tissue radioprotector (20). Matrix metalloproteinases degrade the endothelial basement membrane, allowing efficient recruitment of pro-inflammatory cells to sites of tissue injury to consume injured tissue and initiate healing. Initial microvascular damage also triggers the coagulation cascade, resulting in immediate fibrin deposition. The acute phase courses for several days after RT administration. Following this acute infiltration, there exists a quiescent period where there are no obvious microscopic changes in the tissue (21).

The acute pro-inflammatory environment is a powerful initiator of fibrosis (19). Fibroblasts are recruited from a number of different sources: derived from mesenchymal cells, recruited from bone marrow, or sourced from epithelial–mesenchymal cell transition. These changes are characterized by collagen deposition and endothelial cell proliferation. Extracellular matrix deposition by fibroblasts results in late pathologic dysfunction of myocytes, vascular endothelial cells, and the pericardium (**Figure 1**). Aside from the acute inflammatory response, there is an immediate expression of proto-oncogenes including c-myc and c-jun, which may prompt late fibrotic changes (22, 23). Multiple mediators ultimately result in long-term recruitment of matrix metalloproteinases, inflammatory mediators such as IL-4, IL-13, and TGF-β, and smooth muscle cell proliferation. IL-13 is a known potent fibrotic mediator produced by inflammatory T cells and in certain mouse models, IL-13 knockouts do not experience fibrosis (17). TGF-β is known as a fibroblast mediator and can induce fibroblast differentiation. TGF-β can alter the balance of extracellular matrix remodeling to induce collagen synthesis, decrease production of collagenase and other proteases, and increase the production of protease inhibitors. TGF-β has a multitude of effects and its expression is continues in irradiated tissues (24). After myofibroblasts have been activated, collagen deposition and fibroblast differentiation can continue independent of TGF-β signaling by autocrine induction (19, 22). Chronic oxidative stress with free radical production and this persistent pro-inflammatory facilitate the development of late atherosclerotic disease.

It is already well-known that tissue irradiation ultimately leads to fibrosis; however, radiation changes the biology of pro-fibrotic cells. Ionizing radiation induces premature differentiation of fibroblasts. In normal fibroblast differentiation, 25–35 cell division cycles are required. After ionizing radiation, progenitor fibroblasts differentiate into post-mitotic fibroblasts within 2–3 weeks, representing only 3–4 cell cycles. The lifespan of these terminally differentiated radiation-induced fibrocytes is nearly 40–45% shorter than naturally differentiated cells. These post-mitotic cells are shown to be five to eight times more active in the production of interstitial collagens I, III, and IV compared to progenitor fibroblasts. Ionizing radiation, on its own, can induce premature terminal differentiation of progenitor fibroblasts to post-mitotic fibrocytes that are more active in collagen deposition (25, 26). Myofibroblasts are permanently activated in these tissues even after repair of initial damage, unlike in normal wound repair (27). Chronic deposition of collagen and other components of other extracellular matrix components can produce a fibrotic scar reducing functionality of the affected tissue. Pathologic examination of these lesions show elevated inflammatory cells, fibroblasts, and excessive extracellular matrix, such as collagens, proteoglycans, and fibronectin.

The inflammatory pathway is likely the predominant profibrotic mediator, but other pathways contribute significantly. Another mediator is chronic oxidative stress, the result of chronic free radical production. The oxidative stress simultaneously increases inflammatory mediators, proteases, and adhesion molecules, and decreases nitric oxide, a vascular protectant that blocks platelet aggregation and vascular smooth muscle proliferation. Nuclear factor-kappa B (NF-κB), a protein complex that regulates DNA transcription and is involved in cellular response to various stresses, may serve as a key link between oxidative stress and inflammatory pathways (**Figure 2**). In a study of irradiated human neck arteries, NF-κB is chronically upregulated locally in irradiated human arterial vascular cells anywhere from 4 to 500 weeks after treatment (28, 29).

In addition to NF-κB, other changes in gene expression mediate a pro-fibrotic environment. Chronic hypoxia from microvessel damage leads to upregulation of hypoxia inducible factor α (HIF1-α), which is another stimulator of TGF-β (19). This provides further evidence how local radiation can result in chronic gene expression changes leading to long term and late pathology (28, 29).

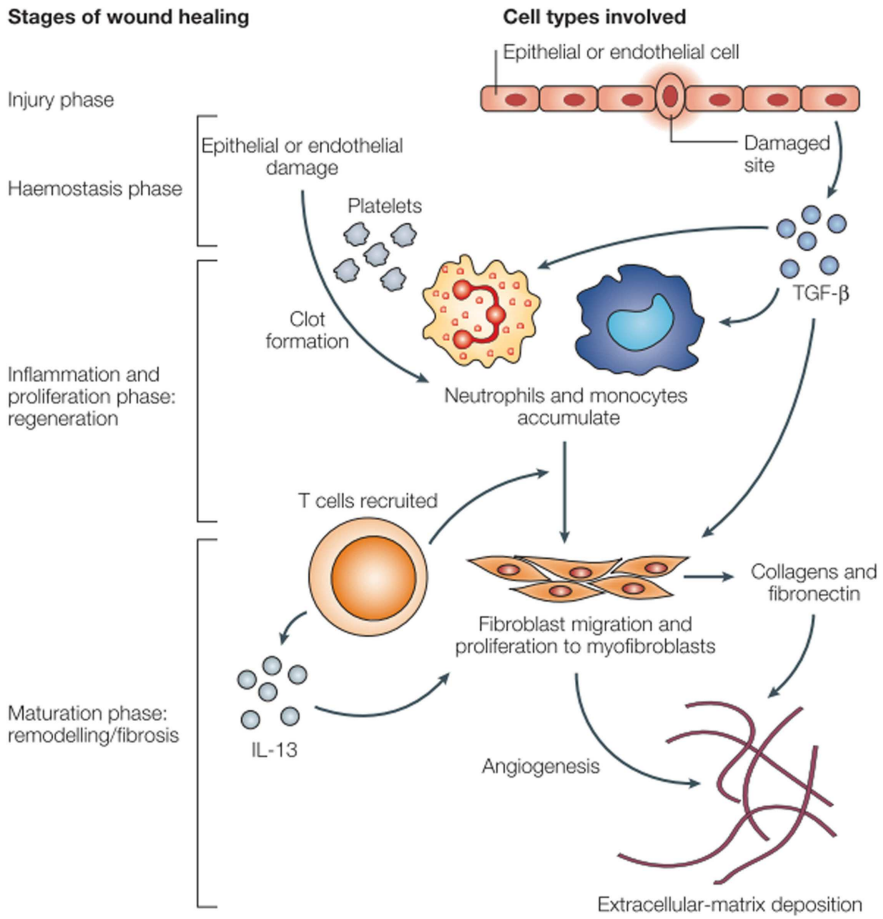

FIGURE 1 | Wound healing and fibrosis in tissue (17).

Fibrosis is both acute and late effect of tissue irradiation. It is the result of multiple converging pathways including inflammation, oxidative stress, and chronic changes in gene expression (**Figure 3**). There is broad involvement of the DNA damage response, TGF-β signaling, and the chronic inflammatory pathways. Acute changes largely result from direct radiation damage and the immediate inflammatory response. Long-term changes in the tissue and characterization of characterization of epigenetic changes, altered cell signaling, and stem cell loss are critical to understanding late and persistent fibrosis (27). The incredibly complex interplay between multiple converging pathways may lead to a variety of clinical targets to combat fibrosis. However, many of these targets have pleiotropic effects leading to other toxicity, and knocking down a single pro-fibrotic pathway may not be sufficient to show clinical benefit.

CORONARY ARTERY DISEASE

The initiation of RIHD in the coronary arteries is similar to that of most other tissues as radiation leads to microvascular damage, inflammation, and subsequent fibrosis. In general, the pathologic changes observed in RIHD are morphologically similar to atherosclerotic disease in medium and large vessels (100–500 and >500 μm, respectively) (30). In small-sized arteries, there is often subendothelial fibrosis, accumulation of acellular collagenous material in the media, and accumulation of lipid-laden macrophages (foam cells) in the intima (31). In medium-sized arteries, foam cells, fibroblasts, and collagen accumulate in the intima. Occasionally, there is acute vasculitis with a predominantly lymphocytic rich infiltrate in the media and adventitia. It is presumed this pathology is self-limited based on animal models. In one swine study with coronary and iliac arteries subjected to P^{32} endovascular brachytherapy, 51% of arterioles sampled near exposed coronary arteries and 100% of arterioles near iliac arteries had evidence of vasculitis in doses from 6 to 40 Gy at 28 days post-exposure. This was noted to be morphologically dissimilar than other systemic vasculitides (32). The smooth muscle layer in the arteries is noted to be replaced instead by fibrous tissue (33). Large arteries are not as often affected as smaller vessels, given that a large luminal diameter allows for larger plaque accumulation before clinical evidence of disease, and thick walled vessels may have more radioresistant cells. However, large radiation-associated plaques with concomitant underlying atherosclerotic disease can lead to plaque rupture and thrombosis (**Figure 4**).

The endothelial cells respond with inflammatory markers and adhesion molecules to recruit peripheral leukocytes with doses as little as ≥2 Gy. Once monocytes enter the subendothelial space, they may transform into activated macrophages. Activated macrophages can ingest lipids, forming fatty streak in the intima leading to early atherosclerotic lesions. Late proliferation of myofibroblasts can further the growth of these luminal-narrowing lesions. Dose of RT ≥8 Gy are associated with increased size and number of these lesions in the major arteries. In addition, the plaques that result may be more unstable and macrophage-laden (34). Unlike stable collagenous plaques, radiation-related plaques tend to grow, rupture, and lead to a myocardial infarction or cerebrovascular accident more often (35). It is important to note that these dose–response data include series from *in vitro* models and limited autopsy assessment. Although the data appear to confirm clinical suspicion, further assessment would be

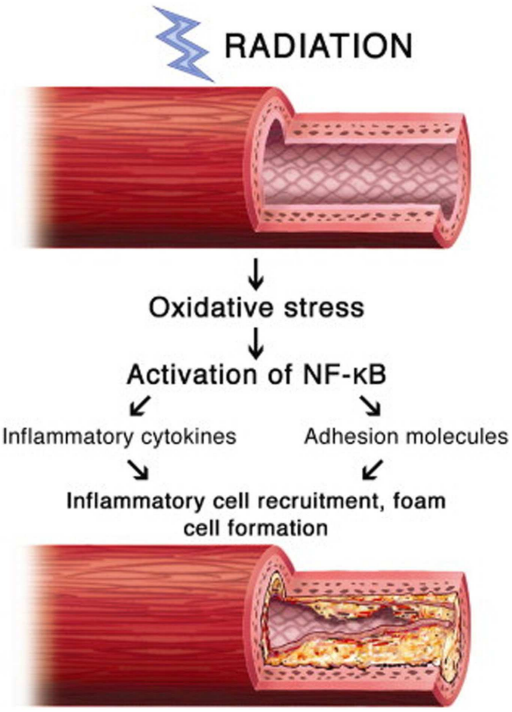

FIGURE 2 | Proposed mechanism of involvement of NF-κB in radiation-induced vascular disease (28).

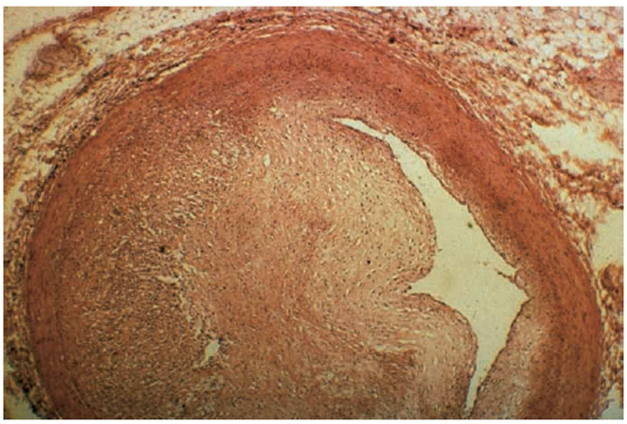

FIGURE 4 | Significant fibrosis of the left anterior descending (LAD) artery after chest radiation (58).

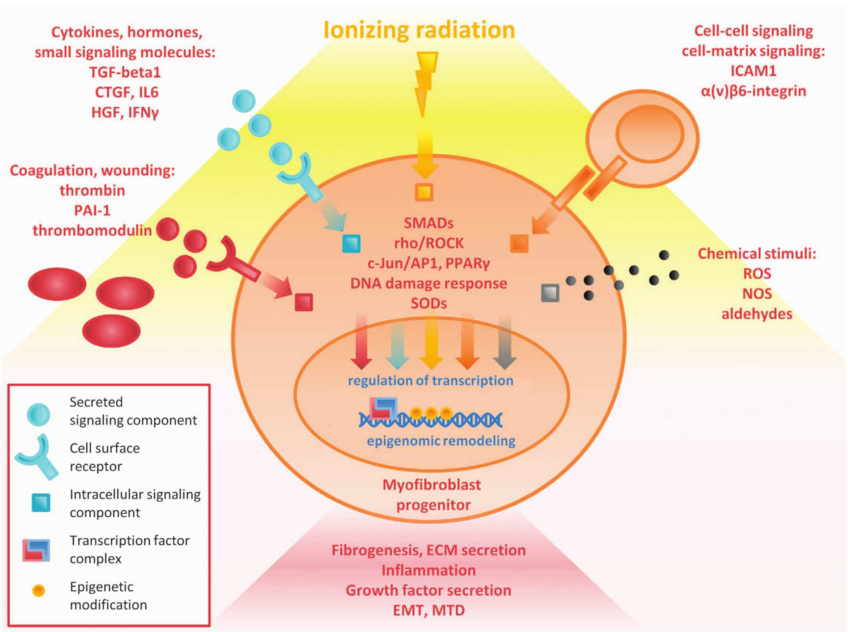

FIGURE 3 | Overview of complex pathways in tissue fibrosis (27).

required particularly in the era of modern radiation techniques with different dose constraints and refined treatment planning.

The arteries affected and plaque location differs from usual atherosclerotic disease. Compared to usual atherosclerotic disease, the LAD artery tends to be often involved in RIHD. This may be due to RT biased toward involvement of the anterior chest. Lesions in RIHD tend to involve a longer length of artery than usual atherosclerotic plaques. Maximum luminal narrowing tends to be at the distal ends of the lesions, and often at arterial bifurcations (16).

Arterial fibrosis is a well-studied phenomenon in RIHD and radiation exposure is an independent risk factor for long-term cardiovascular disease. This is apparent in early stage breast cancer, Hodgkin's disease, and other childhood cancer. There is epidemiologic evidence associating high-dose exposure with cardiac morbidity, including coronary artery disease (2, 36, 37). The dose–response relationship leading to clinically meaningful morbidity is still poorly understood, particularly with low-dose radiation exposure. Preclinical data report that dose of 2 Gy does not alter vessel phenotype in moderate-term followup and ultra-low-dose exposure of <0.5 Gy can even have anti-atherosclerotic effect (38). However, new clinical data in breast cancer survivors suggest that there is no low-dose threshold that increases the risk of RIHD (6). Conventional and three-dimensional RT (3DCRT) has given way to newer technologies such as intensity-modulated radiation therapy (IMRT) that offers increasing dose homogeneity in the target volume with potential for normal tissue sparing. It remains an open question what effect spreading of low-dose radiation with IMRT from multiple beam angles will have on atherosclerotic disease.

MYOCARDIAL FIBROSIS AND CARDIOMYOPATHY

The myocardial subunit is composed of cardiac myocytes, capillaries, and stromal tissue. Each myocardial subunit has a network of capillaries and relies on diffusion for nutrient metabolism, as there are no arterioles in the tissue. Damage to the myocardium occurs after capillary loss from radiation-induced microvasculature damage. Decrease in capillary density results in islands of hypoxia in the myocardial tissue (18). In a study by Fajardo and Stewart, it was noted that 100 days after RT exposure, there was a significant reduction in the ratio of capillaries to cardiac myocytes. There was also endothelial cell membrane alteration with subsequent microthrombus formation (34). There may be some compensatory transient capillary proliferation; however, this largely appears to be inadequate to compensate for progressive and chronic microvascular damage.

Microvascular damage also leads to inflammatory and prothrombotic changes. After cell damage and death, pathologic changes are indicative of progressive fibrosis replacing myocardial tissue. Chello et al. conducted an autopsy study of normal heart tissue compared to left ventricular tissue of patients with post-radiation pericarditis. In the ventricular tissue of irradiated hearts, there was a significant increase in total tissue collagen concentration compared to non-irradiated hearts, consistent with long-term fibrosis. Both Type I and Type III collagen were increased; however, there was a disproportionate increase in the amount of Type I collagen. Type I is more often found in repair tissue whereas Type III collagen is more often found acutely in granulation tissue. This may lead to decreased distension of the ventricles during filling (39).

Progressive fibrosis of the myocardium ultimately leads to decrease in tissue elasticity and distensibility, particularly after replacement with Type I collagen. This leads to reduction in ejection fraction and increase in left ventricular end-diastolic volume and reduced ejection fraction. Marks et al. conducted a study of 114 patients with left sided breast cancer designed to study changes in regional and global cardiac function using technetium-99_m sestamibi or tetrofosmin scans before and after breast radiation. At 6, 12, 18, and 24 months, 27, 29, 38, and 42% of patients, respectively, had new perfusion defects. These patients with perfusion defects were also more likely to have regional wall motion abnormalities (40). This suggests that microvascular damage leads to tissue fibrosis with clinically detectable cardiac function. The final outcome is that irradiation ultimately results in loss of tissue elasticity. This pertains primarily to the ventricles rather than the coronary arteries.

The cardiovascular system responds differently to RT-related myocardial damage compared with ischemia-related heart failure. In RT-unrelated myocardial damage, the body activates the sympathetic nervous system continuously, while simultaneously down-regulating β-adrenergic receptors. In contrast, RT-related myocardial damage results in no augmentation of the sympathetic nervous system in the adrenal glands, but β-receptors initially are upregulated in the heart. This upregulation of the receptors may allow the heart to stabilize cardiac output despite damage. Eventually, as damage progresses, further reductions in cardiac output occur near the onset of congestive heart failure (41–43).

Fibrosis dominates both atherosclerotic disease and myocardial damage. There is similar debate regarding the relative contribution of low-dose radiation to clinical apparent cardiac morbidity. High-dose radiation exposure to the left ventricle can be obviated by a variety of heart sparing radiation techniques such as multileaf collimator (MLC) or cerrobend blocking, deep inspiration breath hold, or prone positioning. However, some low-dose exposure is unavoidable. Cardiac perfusion imaging studies have yet to show perfusion defects in areas with low exposure (heart $D_{mean} < 5$ Gy or doses of 0–10 Gy) (44, 45). This remains a very active area of study, but it is advisable to keep heart dose as low as reasonably possible particularly in the era of cardiotoxic systemic therapy.

VALVULAR DISEASE

Valvular disease is less well characterized compared to changes in the myocardium and coronary arteries. Fibrotic damage in the valves is unlikely related to microvascular damage as the heart valves are avascular. The damage is likely related to other myocardial disease. In one example, RT-related dilated cardiomyopathy may induce regurgitation, although the exact mechanism is poorly understood. Although valvular disease has a high incidence of pathologic changes, the majority of patients do not appear to have more than moderate clinical symptoms (33, 46). One post-mortem series of patients who received at least 35 Gy to heart indicated up to 81% (13 of 16) of patients showed evidence of valvular dysfunction and fibrosis, without or without dystrophic calcification. Specimens showed focal thickening of the valvular endocardium by elastic fibers (33). Veinot conducted a study of

27 patients with multiple cardiac tissue specimens. These patients represented breast cancer, as well as lymphomas and other thoracic cancers. A clear majority of patients experienced RT-related valvular disease with a mean dose of 46 Gy. There was a significant latent period before the development of valvular symptoms with mean time at 98 months. All the valves showed diffuse cusp or leaflet fibrosis. There were no changes indicative of chronic inflammation or neovascularization, suggesting that another RT-related mechanism drives valvular pathology. There was a spectrum of mild to severe stenosis or incompetency (46). Although available series indicate a significant percentage affected with valvular disease, the incidence may likely be lower in often used tangent breast radiation given a significantly lower dose to the heart compared to thoracic or mediastinal radiation.

PERICARDIAL DISEASE

Up to 70–90% of patients with significant mediastinal radiation exposure may have evidence of pericardial disease (33, 46). In pathologic cardiac specimens after >35 Gy to the heart in young patients aged 15–33, 15/16 had thickened pericardia. Of these, five patients had pericardial tamponade (33). Initial series of Hodgkin's disease patients indicated up to 40% of patients experienced clinical pericarditis. Use of reduced total and daily doses, as well as conformal techniques has reduced this risk nearly to 2% (21, 47). The incidence in breast radiation is likely even lower given the limited dose to the heart compared to mediastinal radiation.

There is both acute and late pericardial injury present, driven by inflammation and immediate fibrin deposition. Initial injury to the pericardium is due to microvascular damage that leads to episodic ischemia. Tortuous and permeable neovascularization occurs in irradiated pericardium, leading to additional ischemia and late fibrosis. Additional fibrosis of venous and lymphatic channels in the heart decreases the ability to drain extracellular fluid, leading to accumulation of a fibrin-rich exudate (21). Early clinical pericardial disease is generally represented by effusions (46).

Nearly 20% of patients who experienced late significant fibrosis of the pericardium may have initially had effusions (21). Fibrinous exudates on the visceral pericardium are later replaced by fibroblasts laying down collagen, leading to long-term fibrosis of the pericardium. Normal pericardial adipose tissue is replaced by collagen and fibrin. An increase in Type I collagen deposited in the pericardium decreases diastolic compliance of the ventricles, and the pericardium can be thickened from 1 to 7 mm in severe disease after radiation (39, 46). These changes can lead to a spectrum of pericardial pathologies including acute and delayed pericarditis, pancarditis, and possible severe constrictive pericarditis, resulting in tamponade (48). In Veinot's series, patients who were found to have significant constriction became symptomatic after 18 months, suggesting a long latent period after exposure (46).

CARDIAC ARRHYTHMIAS

Conduction system abnormalities are not as well-documented or reported as the other cardiac pathologies. Arrythmias are likely due to microvascular damage, leading to cardiac myocyte conduction abnormalities or direct damage to critical structures such as the sinoatrial or atrio-ventricular nodes. This may result in AV-nodal bradycardia or all types of heart block, including complete heart block. Right bundle branch block has been observed, due to either direct damage to the conducting myocytes or adjacent microvascular damage resulting in ischemia. In a series of three Hodgkin's lymphoma patients treated nearly 10 years prior with mantle radiation, two of the three had partial or complete right bundle branch block before the age of 35 (49). Fibrosis of the left ventricular wall is associated with increased ventricular ectopy. Nearly 12 years after thoracic irradiation, a report of six patients all showed complete atrio-ventricular node block requiring permanent pacemaker implantation. Of the six patients, five had right bundle branch block or alternating right bundle branch block. The mean RT dose was 52 Gy (50). As expected, all of these patients had multiple other pathologies, including myocardial fibrosis, pericardial disease, and coronary artery disease. In a series of nearly 200 breast cancer survivors, a significant percentage had conduction abnormalities at both 6 months and 10 years after treatment. Nineteen percent of patients had pre-treatment conduction abnormalities, which increased to 45% at both 6 months and 10 years after therapy. The predominant changes at 6 months were T wave abnormalities in left sided breast cancer patients. At 10 months, there were fewer T wave changes, but increased ST depression. Although present in a large percentage of breast cancer patients, these changes were largely reversible and clinically insignificant (51).

Ventricular ectopic beats (VEB) are commonly seen in outpatient medicine and are often benign. These include often asymptomatic premature ventricular contractions (PVC) to more dangerous ventricular tachycardia and ventricular fibrillation. The incidence is nearly 1% in clinically normal people using electrocardiogram (ECG) detection, and up to 75% in clinically well patients using Holter monitoring (52, 53). Although chest radiation may increase the incidence of VEB, a comprehensive assessment must first be performed to rule out other exacerbating factors such as ischemic heart disease, structural heart disease, substance ingestion, or smoking.

To suggest that AV abnormalities may be related to prior RT, one series suggests the following criteria be met (1) total RT dose to the heart >40 Gy (2) latency of >10 years since RT (3) an abnormal interval ECG (4) prior pericardial involvement (5) associated cardiac or mediastinal disease (54). However, these criteria would not often be met in breast cancer survivors. In long-term survivors, vigilance will be required in patients who have experienced other RIHD pathologies or who have underlying atherosclerotic disease. There must be great care in attributing arrhythmias to RT versus competing causes.

FUTURE DIRECTIONS

There exist clear mechanisms by which RT leads to acute and long-term changes in cardiac tissue. Pathologic changes after radiation exposure with clinical implication have been well-documented. However, there are a tremendous number of unanswered questions that will be critical in understanding, prevention, and treatment of RIHD. The bulk of damage appears to be from acute and chronic inflammatory changes, but persistent oxidative stress and genetic changes also significantly contribute. It will be important to characterize the relative contribution of each pathway to evaluate, which will be the most meaningful target of therapeutics.

High-dose radiation exposure is clearly associated with cardiac toxicity; however, the contribution of low-dose radiation is not completely characterized. In addition, it is even unclear if there is a low-dose threshold before which clinically meaningful morbidity appears. The relative contribution of high-dose and low-dose radiation exposure may be augmented further by cardiotoxic systemic therapy such as anthracycline chemotherapy, or underlying patient comorbidities such as diabetes, pre-existing heart disease, and smoking.

Given the multiple pathways leading to RIHD, there are a number of potential therapeutic targets. These include anti-inflammatory mediators, anti-fibrotics, genetic modulators, and even stem cell treatment (55–57). Studies have largely been preclinical, to date, and therapeutics are either in clinical trials or under development. However, establishment of an excellent therapeutic would likely require large numbers of patients with extensive long-term follow-up.

CONCLUSION

Radiation-induced heart disease represents a collection of cardiac pathology including coronary artery disease, myocardial fibrosis, pericardial disease, arrhythmias, and valvular abnormalities. There are several common pathways involved in the development of RIHD including microvascular damage, inflammation, and fibrosis, although other pathways contribute. The interaction of multiple biochemical markers and cytokines such as TGF-β and interleukins, drive a significant portion of chronic inflammation and late fibrosis. Although there exist substantial evidence RIHD has a significant incidence and can lead to substantial morbidity, the exact mechanisms of the various RIHD pathologies are not entirely understood. The development of therapeutic targets to prevent microvascular damage, inflammation, and late fibrosis will hinge on our increased understanding of RIHD.

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Stem cell therapy and breast cancer treatment: review of stem cell research and potential therapeutic impact against cardiotoxicities due to breast cancer treatment

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A new problem has emerged with the ever-increasing number of breast cancer survivors. While early screening and advances in treatment have allowed these patients to overcome their cancer, these treatments often have adverse cardiovascular side effects that can produce abnormal cardiovascular function. Chemotherapeutic and radiation therapy have both been linked to cardiotoxicity; these therapeutics can cause a loss of cardiac muscle and deterioration of vascular structure that can eventually lead to heart failure (HF). This cardiomyocyte toxicity can leave the breast cancer survivor with a probable diagnosis of dilated or restrictive cardiomyopathy (DCM or RCM). While current HF standard of care can alleviate symptoms, other than heart transplantation, there is no therapy that replaces cardiac myocytes that are killed during cancer therapies. There is a need to develop novel therapeutics that can either prevent or reverse the cardiac injury caused by cancer therapeutics. These new therapeutics should promote the regeneration of lost or deteriorating myocardium. Over the last several decades, the therapeutic potential of cell-based therapy has been investigated for HF patients. In this review, we discuss the progress of pre-clinical and clinical stem cell research for the diseased heart and discuss the possibility of utilizing these novel therapies to combat cardiotoxicity observed in breast cancer survivors.

Keywords: chemotherapy–cardiotoxicity, stem cells, cardiac regeneration, differentiation, paracrine factors

INTRODUCTION

Advances in cancer treatments have led to a significant reduction in the incidence of mortality amongst breast cancer patients; a major accomplishment of today's cancer therapies. The 5-year survival rate for females in the United States is 89%, and 78% at 15 years (1). Associated with increased breast cancer survival is an increase in cardiovascular co-morbidities (2). The scope of this issue has not been adequately studied and is not readily ascertained from clinical trial data on emerging chemotherapeutic agents. Clinical trials often consist of small cohorts of patients with under representation of specific patient populations and exclude those with co-morbidities. In addition, the incidence of adverse cardiac events has usually not been evaluated. It is not surprising that novel cancer therapeutics can cause adverse cardiac events given the fact that cancer drugs influence cell survival (3–5). In concert with these novel reagents, some cancer treatment plans incorporate classical chemotherapeutics (anthracyclines) that are known to be more toxic to the cardiovascular system (6–8). Whether the pathways (survival and growth) by which these agents inhibit tumor progression overlap with those which preserve cardiovascular cell physiology, remains largely unknown. In our view, there is a need to investigate different therapeutics strategies to combat any adverse cardiovascular event observed in cancer patients.

Cancer therapeutics cause cardiomyopathy in large part by causing the death of cardiac myocytes and supportive tissue (4, 5, 9–14). Therefore, cell therapies that repair existing myocardium or regenerate new myocardium to replace lost tissue could improve cardiac function in cancer survivors. Researchers and physician-scientist have been investigating cell-based therapy since the early 1980s (15). In striving to understand the basic biology of adult stem cells, tremendous progress has been made in comprehending their therapeutic potential against disease states like acute myocardial infarction (AMI) and ischemic heart disease, culminating with numerous clinical trials since early 2002 (16). While still somewhat controversial, the scientific community is beginning to define the mechanism(s) responsible for the beneficial effects of those stem cell therapies tested to date. Regardless of the treatment strategy used to prevent or reverse adverse cardiovascular events in breast cancer patients, it will become increasingly important to screen patients, optimize treatment strategies, and monitor cardiac function prior to-, during-, and after cancer treatment.

BREAST CANCER AND THE ETIOLOGY OF CARDIOTOXICITY

In 2013, the projected number of new *in situ* and invasive breast cancer cases was just shy of 300,000 (1). Breast cancer death rates have been dropping since the early 1990s (1), due to better awareness by women to have annual mammograms, which has led to earlier detection and better success of treatment strategies. With over 2.9 million women living in the United States with a medical history indicating breast cancer (17), there has become a greater need for an understanding of the therapeutics utilized to combat breast cancer and their potential effects on other organ systems.

Physicians have a variety of treatment options and strategies to slow, inhibit, and/or eliminate breast cancer. Newer generation chemotherapeutics have the capability of targeting specific pathways; usually interrupting cell survival (3, 8, 11, 18–20), growth (21), and proliferation (3, 8, 11, 18, 22, 23). Selective targeting therapeutics are a true testament to the amount a basic and clinical research that has gone into comprehending cancer biology over the last several decades. Ideal cancer therapeutics should affect cancer cells without effects on normal tissues. Unfortunately even target specific agents have "off target" effects on normal cells in the heart and other tissues. Radiation therapy has also been improved as a therapeutic against breast cancer. With advances in technology, clinicians have the ability to more accurately direct the radiation treatment while minimizing the dose need; but still there are major side effects observed with both treatment options, and the incidence of cardiotoxicity is on the rise (24).

While treatment may lead directly to cardiovascular dysfunction in some patients, in others it may hinder their ability to cope with preexisting or newly acquired cardiovascular diseases such as ischemic heart disease and hypertension. It is important to point out that only a fraction of patients in chemotherapeutic clinical trials have reported adverse cardiac events (25, 26); 4–7% of patients in initial trials suffered from cardiotoxicity when treated with monoclonal antibody chemotherapeutics, which manifested itself as a decrease in left ventricular ejection fraction (LVEF) (27). This percentage was drastically increased (27%) when patients were treated concurrently with adjuvant chemotherapeutics, like anthracyclines (14).

There are several hypotheses as to mechanism by which chemotherapeutic treatment initiates and/or exacerbates cardiotoxicity observed in breast cancer patients (4, 11, 12). The more classical drugs, like anthracyclines, most notably Doxorubicin, have been linked to greater increase in reactive oxygen species (ROS) causing more stress at the cellular level (10, 28, 29). In cardiomyocytes, there is an abundance of mitochondria, which produce free radicals from anthracyclines, which are taken-up by the cell (30). This predisposes cardiac tissue to create high levels of ROS. This suggests high levels of newly formed ROS limits the amount of antioxidants that are found endogenously. With depletion of these much needed antioxidants, homeostasis is not maintained leading to an unfavorable cellular environment. A single basic research study, by De Angelis et al., looked directly at mechanisms by which chemotherapeutics are cardiotoxic and their effects on endogenous cardiac stem cells (CSC's) (31), which are thought to be involved in endogenous cardiac repair. It was shown that classic chemotherapeutics (anthracyclines) increased ROS formation, caused DNA damage, induced p53 expression and cell cycle arrest in the G2/M phase, while decreasing CSC growth (31).

Cardiotoxicity due to radiation therapy predominantly leads to pericardial and coronary vasculature damage. While early radiological practices lead to constrictive pericarditis; new technology and techniques to minimize the exposure of the heart to radiation and the incidence of pericarditis is still largely unknown due to limiting number of years post-technology development (32). Cell types, which are part of the coronary vascular framework have been shown to induce inflammation and lead to cardiovascular events, which can cause ischemic heart disease (33). In a study which compared the effects of left- or right-sided radiation demonstrated an increase in coronary stenosis in patients who received left-side treatment; specifically the left anterior descending coronary artery (9). Again, with new techniques and better technology being utilized, this adverse event can be minimized.

More reviews have come forth over the last several years discussing chemotherapeutic cardiotoxicity (3, 4, 8, 19, 20, 34–38) and there has been the formation of guidelines with clinical interdisciplinary cross talk between oncologists and cardiologists (11, 39–41) to more effectively treat the toxicity to organs such as the heart. Again, whether the primary treatment strategy is pharmacological or radiological, physicians have come to a consensus that adjuvant therapy increases the probability of initiating or exacerbating cardiotoxicity in breast cancer patients (4, 11, 12, 14). New basic, translational, and clinical studies will be essential to define the mechanisms of cardiotoxicity of chemotherapeutics and radiation therapy. It will also be important to carefully follow the increasing number of breast cancer survivors, to define their long-term cardiovascular risk.

STEM CELL THERAPY

In this review, we suggest that stem cell therapy should be considered for cancer survivors who develop cardiomyopathy. Currently, one of the most impressive aspects of stem cell therapy for the heart is the wide variety of cell types that could be considered as potential candidates through pre-clinical (**Table 1**) and clinical research (**Table 2**). This reflects the true unmet need for a therapeutic avenue to be developed in order to treat and prevent the progression and manifestation of heart failure (HF) in patients who suffer cardiac injuries, like myocardial infarction or breast cancer therapy-induced cardiomyopathy. Here, we discuss endogenous cardiac regeneration and some of the more popular cell types that are being looked at as potential candidates for cell-based therapy.

CARDIAC REGENERATION

The heart has a limited capacity for repair after injury. This limited repair capacity is the bases for cardiac dysfunction after ischemic insult or damage from cancer chemotherapeutics. Why the heart has such a limited ability to repair itself and how cell therapy might enhance repair is an important topic in need of further study. Most questions about cardiac regeneration are still not resolved. Interestingly, fish and other less developed species have an ability to regenerate lost portions of their hearts, primarily via proliferation of surviving myocytes that reenter the cell cycle (66, 67) post insult. This characteristic is also present in the fetal and early neonatal mammalian heart, but is generally absent in adult mammalian human heart tissue. Regardless of the robustness of endogenous cardiac repair it is clear that the adult human heart cannot repair itself after multiple forms of injury which can lead to HF.

Adult cardiac myocytes are largely withdrawn from the cell cycle. Therefore the loss of myocytes with disease requires new myocyte formation to prevent cardiac functional decline. New myocytes could be derived from old myocytes that reenter the cell cycle or from a stem cell population with cardiogenic capacity. Some laboratories have demonstrated there is a small rate

Table 1 | Overview of animal studies with stem cell therapy.

Study	Host	Etiology of dysfunction	Route of administration	Outcomes
BONE-MARROW MONONUCLEAR CELLS (BMMNCs)				
Orlic et al. (42)	Mice	Ligation of LAD	IM	↑ LV function Trans-differentiation
Mathieu et al. (43)	Dog	Ligation of LAD	IM	↑ LV function, ↓ Scar ↓ Brain natriuretic protein Neovascularization
Bel et al. (44)	Sheep	Ligation of CX	IM	No Δ LVEF or remodeling
Waksman et al. (45)	Pig	Permanent occlusion	IM	↓ Scar Trans-differentiation Angiogenesis
BONE-MARROW-DERIVED HEMATOPOIETIC STEM CELLS (HSCs)				
Balsam et al. (46)	Mice	Ligation of LAD	IM	No trans-differentiation
Kajstura et al. (47)	Mice	Ligation of LAD	IM	↑ LV function, ↓ Scar Trans-differentiation
MESENCHYMAL STEM CELLS (MSCs)				
Hatzistergos et al. (48)	Pig	I/R	IM	↑ LV function, ↓ Scar Trans-differentiation Homing of endogenous SCs
Cai et al. (49)	Rat	Ligation LAD	IM	↑ LV function ↓ Remodeling
Quevedo et al. (50)	Pig	I/R	IM	↑ LV function, ↓ Scar Trans-differentiation Angiogenesis
Schuleri et al. (51)	Pig	I/R	IM	↑ LV function, ↓ Scar Angiogenesis
CARDIAC STEM CELLS (CSCs)				
Linke et al. (52)	Dog	Occlusion of LAD	IM	↑ LV function Trans-differentiation Angiogenesis
Beltrami et al. (53)	Rat	Ligation of LAD	IM	↑ LV function ↓ Remodeling Trans-differentiation
Fischer et al. (54)	Mice	Ligation of LAD	IM	↑ LV function ↓ Scar Trans-differentiation Angiogenesis
Li et al. (55)	Mice	I/R	IC	↑ LV Function ↓ Remodeling Trans-differentiation

↑, Increase; ↓, decrease; No Δ indicates change; CX, circumflex coronary artery; LAD, left anterior descending coronary artery; I/R, ischemia-reperfusion; LV, left ventricle; IM, intramyocardial; IC, intracoronary.

of turnover in myocytes in the adult heart (68–70) but not at a sufficient rate to repair the heart back to basal functional levels post injury. Other than cardiac transplantation, there is no therapy, which ultimately addresses the issues caused by myocardial injury and the progression of cardiac remodeling. With chemotherapeutic agents and radiation therapy affecting survival, growth, and proliferation pathways, while increasing oxidative stress and DNA damage, frank loss of heart muscle, and deterioration of myocardial support structure mimics other types of cardiac injury such as myocardial infarction. Whether this cardiotoxicity

Table 2 | Overview of clinical trials with stem cell therapy.

Study	No. patients	Route of administration	Primary end-point	Outcomes
BONE-MARROW MONONUCLEAR CELLS (BMMNCs)				
Perin et al. (56)	Cell = 14 Control = 7	IM	Echocardiography	↑ LV function ↓ Remodeling ↓NYHA Class
Perin et al. (57)	Cell = 11 Control = 9	IM	Echocardiography	No Δ LV function ↑ Exercise capacity ↑ Perfusion
Galinanes et al. (58)	Cell = 14 No Control	IM (during CABG)	Dobutamine stress Echocardiography	↑ LV function ↑ Wall motion
Hendrikx et al. (59)	Cell = 10 Control = 10	IM (during CABG)	MRI	No Δ LV function ↓ Remodeling ↓ NYHA class
Fischer-Rasokat et al. (42) (TOPCARE-DCM)	Cell = 33 No Control	IC	MRI LV angiography	↑ LV function ↑ Wall Motion
BONE-MARROW-DERIVED HEMATOPOIETIC STEM CELLS (HSCs)				
Vrtovec et al. (60)	Cell = 28 Control = 27	IC	Echocardiography	↑ LV function
Vrtovec et al. (56)	Cell = 55 Control = 55	IC	Echocardiography	↑ LV function
Patel et al. (61)	Cell = 10 Control = 10	IM (during CABG)	Echocardiography	↑ LV function
MESENCHYMAL STEM CELLS (MSCs)				
Hare et al. (62) (POSEIDON)	Cell = 31 No Control	IM	Computed tomography	No Δ LV function ↓LVEDV ↑ Physical performance
Karantalis et al. (63)	Cell = 6 No control	IM (during CABG)	MRI	↑ LV function, ↓ Scar
CARDIAC STEM CELLS (CSCs)				
Bolli et al. (64) (SCIPIO)	Cell = 16 Control = 7	IC	Echocardiography MRI	↑ LV function, ↓Scar
Makkar et al. (65) (CADUCEUS)	Cell = 17 Control = 8	IC	MRI	No Δ LV function, ↓Scar

↑, increase; ↓, decrease; No Δ, no change; Cell, Cell-treated patients; CABG, coronary artery bypass graft surgery; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Failure Association; LV, left ventricle; IM, intramyocardial; IC, intracoronary.

occurs acutely or chronically in breast cancer patients is unclear but the end result is most notably DCM or RCM (20, 31, 71–73).

The fundamental principle that the human heart does not have an adequate endogenous repair mechanism has led to the discovery of isolating adult stem cells for use as a therapeutic for treating and preventing HF, which has exploded in the scientific research community and has given a new sense of hope to the idea of cell-mediated repair of the heart.

BONE-MARROW-DERIVED STEM CELLS

The bone-marrow is a diverse tissue that houses many cell types, including a variety of stem cells (56, 60, 74–76). Due to the ease of acquisition, with already approved clinical methods and their relatively high abundance, bone-marrow-derived stem cells have been and continue to be investigated as a possible source of cells that can be applied toward cardiac regeneration. This cell source is one of the most widely examined in pre-clinical experimentation and clinical trials to date. Here, we outline the major populations and their potential as cell therapy.

Unfractionated bone-marrow mononuclear cells

Bone-marrow mononuclear cells are a heterogeneous mixture of multiple cell types [hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitors, and other more committed cell population] (57–59, 74). Through a density gradient centrifugation, bone-marrow mononuclear cells (BMMNCs)

are isolated easily from whole bone-marrow fraction. With the easy of isolation and low maintenance *in vitro*, these cells have been utilized as a source of cell therapy in many animal models. In the acute MI setting, BMMNCs have shown much promise (42, 43). In contrast under chronic conditions of HF, the jury is still out; conflicting results in large animal models (43–45) and smaller scale preliminary clinical trials (77–79) still leave many questions as to the true mechanism(s) of action and the efficacy of this cell population. In a pig (45) model of HF, transplantation of BMMNCs provided no therapeutic benefit in terms of left ventricular (LV) function, but the study described an increase in angiogenesis and reduced infarct size. In another large animal study post infarct (43), BMMNC therapy showed an improvement in LV function, and reduced probrain natriuretic peptides (BNP) levels in the plasma, will also sparking angiogenesis.

In the clinical arena, the results have been similar to the observations in the basic research community. The first clinical evaluation of BMMNCs as a therapeutic was performed by Perin et al. (77); 21 patients were enrolled (14 cell-treated and 7 control). Functional improvements were observed at 2–4 months; in patients receiving cell therapy there was a 9% increase in LVEF as compared to baseline and a reduction in the end-systolic volume (77). Subsequent other trials confirmed these observations of improved cardiac function with intramyocardial injection of BMMNCs (78). In contrast, when cell were injected directly in the core of the damage region in 20 patients all beneficial effects were negated, there was no significant difference in LVEF or wall thickness by MRI (80). These vastly different outcomes have many factors, which may be playing a role in the results obtained, particularly the location of the injected cells. The microenvironment plays a pivotal role in the efficacy and any potential benefit cell therapy may have, as observed in these contrasting clinical trials (one with injection into the border zone of the infarct and the other into the core). In studies, which investigated the role of BMMNC therapy for non-ischemic cardiomyopathies there were promising results (81). BMMNCs therapy increase the regional LV function and improved microvascular function in Transplantation of Progenitor Cells and Recovery of LV Function In Patients With Non-ischemic Dilative Cardiomyopathy (TOPCARE-DCM), which enrolled 33 patients to receive intracoronary administration of BMMNCs (81).

Studies of BMMNCs as a viable option for cell therapy have yielded inconsistent results both at the bench and in small scaled clinical trials, this is largely due to the heterogeneity of the cell population and the yield of actual progenitors in each isolation for therapeutic use. Larger scale trial's must be run in order truly understand what effect(s) this cell type may be having as an option for cardiac regenerative therapy.

Hematopoietic stem cells

Hematopoietic stem cells reside within the bone-marrow and commit to two different cell lineages, myeloid and lymphoid. The major cell surface marker which is used to distinguish this sub-population of cells from other progenitors which reside is in the bone-marrow is cluster differentiation 34 (CD34) (82–84); a transmembrane cell adhesion protein that has implicated in the literature to denote stem cells, which has a hematopoietic or vascular lineage. HSCs are mobilized from the bone-marrow into the peripheral blood during ischemic events to begin the process, which leads to revascularization (75). Researchers and clinicians felt that by isolating this population of cells and reintroducing them in more concentrated numbers would promote greater revascularization than observed by endogenous mechanisms post cardiac injury (46, 47, 75).

Numerous clinical trials have been performed evaluating CD34+ cells in patients with both ischemic (61) and non-ischemic (56, 60) cardiomyopathy. Vrtovec et al. (56) looked to understand the beneficial effects of this cell population against non-ischemic cardiomyopathy by delivering the cells intracoronary to 55 of the 110 patients enrolled; this led to a ~5% increase in LVEF, improvement in the 6-min walk test and decreased probrain natriuretic peptide plasma levels. A 5-year follow-up study was able to demonstrate that the transplantation of these cells had an effect over a sustained period much longer than most trials (60). The true mechanism by which this population of cells is having an effect is still not understood, but the major consensus amongst those in the field would be an increase in perfusion via revascularization. Preliminary clinical work with CD34+ hematopoietic cells is promising for both ischemic and non-ischemic cardiomyopathy, as with most of the cell types discussed here, a major limitation is the small sample sizes in these trials and lack of understanding as to the mechanism of action, which is due to an inability to apply standard methods utilized in basic research, toward human patients (i.e., immunohistochemistry, fluorescent microscopy, and molecular analysis).

An important issue concerning this cell population is the fact that only autologous transplantations have been performed. For the average patient who has been enrolled in such Clinical trials to date, this resident population of cells can be easily harvested and utilized for cell-based therapy. In terms of the subset of patients discussed here, this may not be the case. For individuals who have received or continue to undergo chemotherapy and radiation treatment, the CD34+ HSC population may be exhausted or non-existent all together (85, 86). This would subsequently eliminate this population of progenitors as a viable option for cell-based therapy to treat any cardiomyopathy induced by chemotherapeutic treatment of breast cancer. If this population of stem cells were to be beneficial against cardiotoxicity, it may be necessary for patients to undergo isolation prior to cancer treatment, so that cells could be isolated and expanded for future autologous cell-based therapy if needed. Other populations within the bone-marrow do exist and do not have to be autologous in nature for transplantation.

Mesenchymal stem cells

Bone-marrow-derived MSCs are a sub-population of cells characterized by their adherence in culture (87). They also have begun to characterize a host of cell surface marker, which identifies this population within isolated bone-marrow. The majority of MSCs express CD29, CD73, CD90, and CD105 while being negative for hematopoietic lineage markers CD34 and CD45 (87, 88). Others have demonstrated sub-populations within the MSCs, which express these markers and a plethora of others (89, 90). The multipotentiality of these cells to differentiate into osteoblast, chondrocytes, adipocytes *in vitro* (91–94) is well documented and cardiomyocytes *in vivo* (95–97), which is still controversial (98).

Paracrine signaling is one of the major mechanisms thought to elicit improvement by MSC therapy (48, 99) in the heart. This is due to release of numerous growth- (48), anti-apoptotic- (100, 101), and/or angiogenic- (49, 102) factors helping protect the myocardium and augment some of the adverse remodeling. Furthermore, MSCs demonstrate a capacity to engraft in a large animal model of MI (50, 51, 103) and have shown an ability to evade immune rejection (52, 104–106). In recent studies, results indicate MSC contributed directly to inhibition of inflammatory responses (107, 108), which may be the mechanism behind the observed reduction in scar size in both animal models and clinical trials (51, 62, 63). While there is still skepticism, this characteristic could allow MSCs to be used as an allogeneic source of cells, overcoming the need for isolation and expansion of autologous cell sources.

With many clinical trials looking to understand the beneficial effect of numerous different cell types in patient suffering from cardiac related dysfunction, MSCs in recent years has become more popular for translational applications in patients (62, 63). Hare et al. (62) investigated MSC's and their effect(s) on 15 of the 30 patient enrolled in the clinical trial Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON). This trial look to see if there was any dose dependent effect of MSC's in patients who were suffering from ischemic cardiomyopathy (ICM). The data demonstrated, at all three doses, that MSC administration was favorable when measuring end-points of quality of life, functional capacity and ventricular remodeling (62). Krantalis et al. (63), in the Prospective Randomized Study of Mesenchymal Stem Cells Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial, investigated the injection of MSC's in six patients receiving coronary artery bypass graft surgery (CABG). Those regions of the myocardium, which received cell therapy demonstrated a decrease in scar mass compared with baseline at 18 months follow-up (63). An overwhelming number of clinical trials that are "recruiting" encompass MSC's therapy exclusively or as part of their treatment strategy (109). At this point, MSC's are becoming more promising for clinical applications and widely investigated for the utility of cardiac regeneration in the clinical setting.

CARDIAC STEM CELLS

Cardiac-derived stem cells have also been in the spot light of animal investigations and recently, clinical trials (53, 54, 65, 110–113). The discovery that the heart is in fact an organ, which has the ability to have cellular turnover and renewal (both of myocytes and non-myocytes) refutes the long withstanding dogma that the heart is a post-mitotic organ. This renewal is thought to be derived from a population of stem cells, which reside as niches within the myocardium (110). New methodology has been developed over the last decade to isolate (53) and characterize these cells *in vitro* (53, 111) and investigate their therapeutic potential. The isolation of CSCs has given hope that these cells will be predisposed to an increased probability of neomyogenesis as compared to other cell types discussed previously.

C-kit (+)/hematopoietic lineage (−) CSCs

This cell population was first described in 2003 by Beltrami et al., cells were isolated from a rodent heart (53). The manuscript describes a cell population isolated from cardiac tissue that expressed a tyrosine kinase receptor c-kit, now a known marker of stemness (53). This population not only fit the classical definition of a "stem cell" (self-renewing, clonogenic, and multipotent) but also differentiated into cardiomyocytes, smooth muscle cells, and endothelial cells *in vitro* and *in vivo* (53, 110, 111). Human cardiac c-kit+ positive cells were isolated some 4 years later (111). Since then, injection of isolated c-kit+ CSCs and studying the beneficial effects has been overwhelming; multiple laboratories and basic research studies have demonstrated that post injection an alleviation of LV dysfunction and adverse remodeling, while showing the elicit response of regeneration due to injection (54, 55, 114). With such positive outcomes in rodent models (54, 55, 115), this cell type was soon moved to a pre-clinical large animal model. Bolli et al. (64) investigate the role on intracoronary infusion of CSCs 3 months post-MI and found a significant difference in LVEF as compared to vehicle treated animals, while demonstrating increased wall thickness and beneficial changes in the maximal developed pressure, as well as, a lower diastolic pressure. With that, this work in the large animal model laid the ground work for a human clinical trial investigating the efficacy and safety of CSC's in patients. The Stem Cell Infusion in Patients with CardiOmyopathy (SCIPIO) clinical trial update discussed the infusion into the coronary circulation, 1 million c-kit+/lineage – CSC's into 16 patients with LV dysfunction (113). The authors concluded that these cells produced better LV systolic function through reduction of scare size in patients with MI, and further clinical trials should be performed (113). With promising results in the phase I trial, CSCs are bidding to become the superior choice in choosing a cell type for cardiac cell therapy. While clinical trials are ongoing, there has only been one small animal study investigating the therapeutic potential of CSC therapy post chemotherapeutic cardiotoxicity, this study as discussed above (cardiotoxicity section) looked to solidify the mechanism by which the cardiotoxicity occurs and utilized c-kit+ CSCs as a therapeutic intervention to combat the adverse effects observed (31). De Angelis et al. (31) concluded that cell-based therapy promoted regenerative capacity of the myocardium, improved cardiac pump function, and decreased mortality.

Collectively, with all the successes of pre-clinical and clinical trials to date, there is much more work that is needed to fully understand the therapeutic potential of cell-based therapy for all types of cardiac disease states regardless of the etiology.

CELL THERAPY POTENTIAL FOR CHEMOTHERAPEUTIC/RADIATION-INDUCED CARDIOTOXICITY IN BREAST CANCER PATIENTS

With the plethora of basic science and clinical research performed on isolating and characterizing a number of adult stem cells to be utilized for cardiac cell therapy in the past two decades, we as a field still do not know which cell type, and/or combination of cells will be most beneficial. The work has yielded some rewards despite most questions still not having answers; we now understand that multiple tissues have population of stem cells that have the capacity to be beneficial toward heart function post injury and inhibit adverse remodeling, while improving quality of life in patients suffering from many different cardiac disease states

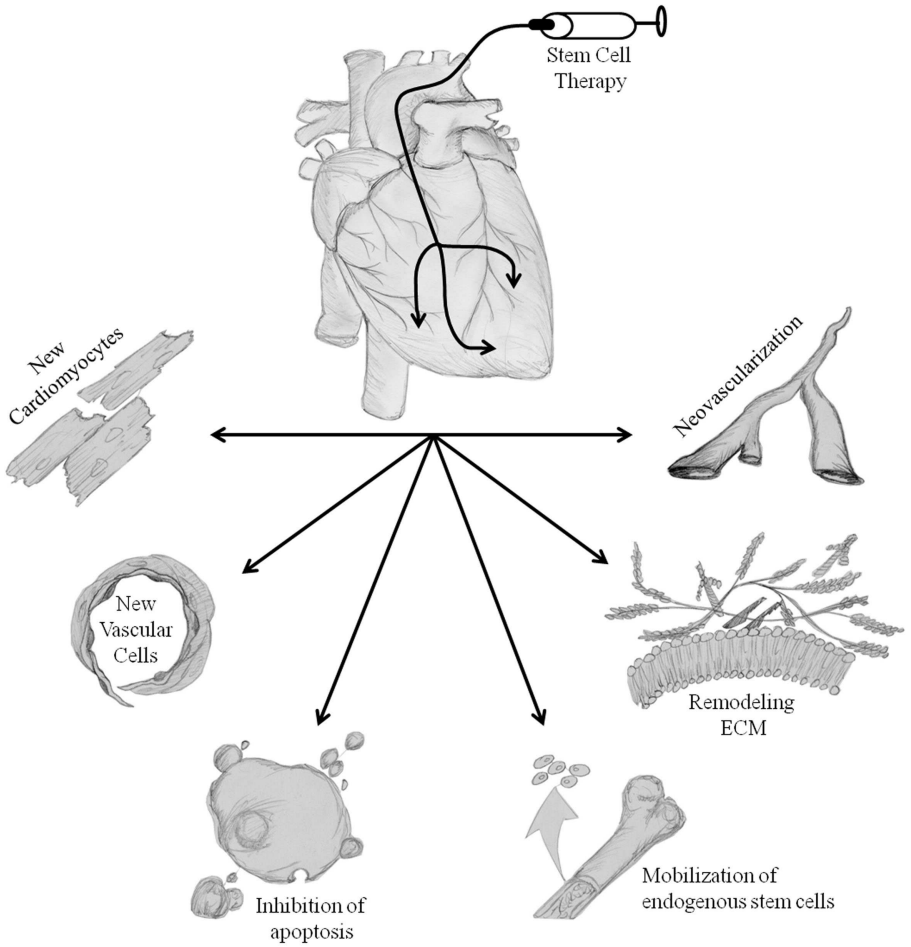

FIGURE 1 | Proposed mechanisms of stem cell-mediated repair. Transplantation of stem cells into the heart initiates repair of damaged tissue. The hypothesized repair mechanisms are both direct and indirect, trans-differentiation of stem cells into new cardiomyocytes and vascular cells, inhibition of apoptosis, mobilization of endogenous cell populations, alterations in ECM remodeling, and neovascularization. Collectively, these processes reduce adverse cardiac remodeling, increase the possibility of perfusion, repair/regenerate damaged tissues, and ultimately improve left ventricular cardiac pump function & patients clinical end-points. Illustration credit: Thomas E. Sharp III.

(15, 16, 42, 50, 51, 56, 62, 64, 69, 83, 100, 102, 113). Despite not fully understanding the mechanism of action, the field has a general consensus on ways in which stem cell therapy is working to improve cardiac function (**Figure 1**); animal studies have shown beneficial effects of stem cell therapy through paracrine factor secretion (48, 99, 100), trans-differentiation into multiple cell types, which help to improve cardiac function (92, 116) and through homing of endogenous stem cells to the site of injury (48, 76). The cell types discussed above do not all work with the same mechanism of action; it has been demonstrated that MSCs most likely work through paracrine factor production and secretion (48, 51, 74, 117–119), while BMMNCs and CSCs have the ability to form new blood vessels for better perfusion (46, 47, 53–55, 59, 75–77, 79, 85, 86, 89, 96, 110, 120, 121) and create new myocyte from transplanted cells (53, 55, 64, 111–115, 122, 123). Below, we discuss the major mechanisms and how they may be beneficial toward patients suffering from cancer treatment-related cardiotoxicity.

TRANS-DIFFERENTIATION OF TRANSPLANTED CELLS

The logical explanation for using stem cell therapy to repair the heart is the idea in which transplanted cells will form new myocardium replacing lost or damage tissue. As obvious as this may seem, data acquired thus far in the field of cardiac regeneration would suggest that little trans-differentiation is actually occurring, and that this is probably the least likely mechanism of action for the observed improvements post therapy. Much of the debate still goes on as to the amount or proportion of beneficial effects that should be attributed toward trans-differentiation. Still highly controversial is the notion that cell populations derived from the bone-marrow (HSC's, MSC's, and CD34+ SC's) form new cardiac myocytes; numerous laboratories have evidence supporting such notions (124, 125), while others contest these conclusions (46, 126). Alternatively, some suggest that the mechanism of action is fusion of the injected cells with endogenous surviving myocytes (127, 128). Discussed in more detail below, most would agree that the major mechanism of action may be

paracrine factor production and secretion (100, 101). While in the acute MI disease model, there is strong evidence for trans-differentiation (53, 110, 129–131); in the post-MI HF large animal model the data would suggest that the amount of trans-differentiation observed is insufficient to explain the significant increase in cardiac function post injury and after therapeutic intervention (64). In recent years, the debate has turned more toward understanding the proportion of new myocyte formation in the different cell types (discussed above) and how the quantification of this trans-differentiation is proportionate or disproportionate to the improved cardiac function. In patients suffering cancer therapy cardiotoxicity, trans-differentiation of transplanted stem cells may allow for the replacement of cells that may otherwise have died from necrosis (132) or other proposed mechanisms (3, 6, 14, 18–20, 31, 36, 38, 133) due to chemotherapeutic treatment and in turn limit the amount of fibrosis which develops. In limiting the fibrosis, in patients suffering from chemotherapeutic/radiation cardiotoxicity, we would anticipate less adverse remodeling and subsequently better outcomes over time. As discussed above, this mechanism is likely unable to account for any or all the benefit which may occur in these patients post-stem cell treatment.

NEOVASCULARIZATION

The creation of new blood vessels *de novo* may be of great benefit to patients who suffer from chronic or persistent coronary occlusion, which develops into ICM. This may occur in cancer patients due to the anti-angiogenic nature of classical chemotherapeutics (3, 5, 40) and frank loss of vascular structure from radiation therapy. On the contrary, those who suffer from non-ischemic cardiomyopathy, it is difficult to see the beneficial aspects of utilizing cells which have demonstrated in experimental models to create new vasculature. What may be the most important mechanism or alternative action, which has allowed for the most benefit, is paracrine factor production/secretion and signaling.

PARACRINE SIGNALING

In reality, the inability (up to now) to solidify the mechanism of action by which stem cells act on the heart has led to great emphasis on the paracrine hypothesis (100). This concept hypothesizes that transplanted cells modulate the myocardial milieu in the injury site by secreting factor that signal to the surrounding cells and tissue(s). Paracrine signal may in fact promote a multitude of reparative and regenerative processes, like: promoting cell survival, the inhibition of cell apoptosis, promoting a new blood vessel formation, favorable changes to the extracellular matrix (ECM), modulation of the inflammatory response which occurs upon injury, and activation/homing of endogenous stem cell populations to the site of injury. This signaling can also play a key role in the ability for transplanted stem cells to thrive in a harsh environment by autocrine signaling and positive feedback loops. In concert, these actions promote better LV function and slower progression of remodeling and development of HF.

Cell survival and inhibition of apoptosis

Numerous basic research studies have suggested the production and secretion of paracrine factors [like, insulin like growth factor-1 (IGF1) and secreted frizzled-related protein-2 (SFRP2)] inhibit cardiomyocyte apoptosis (101, 134). Another parameter, which may assist in the pro-survival hypothesis is the modulatory affect of the stem cells toward the immune response (101, 108, 135). In augmenting the immune response one could hypostulate less activation of the positive feedback loop within the innate and adaptive immune responses to cardiac injury. This in turn, would limit cell death and deposition of ECM proteins, which could potential preserve the myocardium and LV function.

Angiogenesis

In a recent study of a rodent model of MI, Duran et al. (136) was able to demonstrate the production of specific paracrine factors by stem cells, which promote angiogenesis and incorporation of stem cells into newly formed vasculature *in vivo*. Multiple cell populations have been described as producing angiogenic factor such as: fibroblast growth factor-2 and -7 (FGF) (137), platelet-derived growth factor (PDGF) (138), and vascular endothelial growth factor (VEGF) (100, 137). With chemotherapeutics being highly toxic and anti-angiogenic (3, 5, 40), utilizing stem cell therapy to maintain/repair vasculature and promote the neovascularization of areas, which may be lacking blood supply is an important idea. While some may caution the notion of promoting neovascularization and angiogenesis in patient suffering from cancer in fear of potentially promoting vascularization of present tumors and causing metastasis, one should withhold their reservations, as techniques, which are used to deliver the stem cells are usually performed locally within the organ [intracoronary delivery (55, 64, 65, 102, 121, 139, 140) and intramyocardial injection (77, 119, 141–143)]. Aside from this minor concern, this therapeutic benefit from stem cell administration is one of the more promising for patients who have been administered chemotherapeutics or undergone radiation treatment, which are hailed for the ability to inhibit vasculature formation.

ECM remodeling

Under the paracrine hypothesis, stem cells have been ascribed the ability to augment deleterious alterations in the ECM (138, 144–146). Post stem cell therapy has shown in rodent models of MI to reduction in scar size, reduced fibrosis, and subsequently inhibition of LV remodeling (74, 118, 137, 140, 146–148). While there is no significant scar formation in patients who suffer direct cardiotoxicity from chemotherapy, the reduction in fibrosis may play an important role in these patients. In having the capacity to change the cell niche with which myocardial cells reside is an important factor, as most chemotherapeutic cardiotoxicity is not due to ischemia, rather a change in the abundance of fibrosis in the cellular milieu (3, 5, 13, 20, 40) and cell death.

Homing of endogenous progenitor populations

With a wide variety of paracrine factors being produced by stem cells, specific factors have been implicated in mobilizing and homing endogenous stem cells pools to the site of injury or sites of transplantation of exogenous cells (48, 140). Such factor include: stem cell-derived factor (SDF) (138), hepatocyte growth factor (HGF), and IGF (100, 101). These factor collectively permit endogenous stem cell homing, proliferation, and differentiation into myocardial cell types (myocytes and vascular cells), concurrently with some of the other beneficial effects observed with such

factors as IGF [which has demonstrated to be pro-survival (101)]. In patients who have undergone chemotherapy, this mechanism of mobilizing native stem cells is probably not likely, as with most of the basic research studies performed thus far have concluded that chemotherapeutics are deleterious to endogenous stem cell population (23, 31, 132, 149).

Autocrine signaling

While the paracrine signaling hypothesis discusses the therapeutic nature of growth factor signaling on endogenous tissue(s), the hypothesis has also given rise to scientific investigation of this signaling on the cells, which produces them. Many laboratories have demonstrated that autocrine signaling of growth factors and factors of stemness are necessary for self-renewal, maintenance, survival, and growth. FGF (150–152) has been shown to drive self-renewal, inhibit cellular senescences, and inhibit apoptosis. While others have demonstrated that SDF plays a critical role in survival and maintenance of the stem cell(s) (153). This paracrine/autocrine signaling may help enhance the other effects that transplanted cells may have on endogenous tissue by allowing the transplanted cells to be retained and produce more of these factors, while also enhancing the possibility of trans-differentiation, due to longer retention.

While these major mechanisms of action are being vetted in animal models, one thing has become certain; the therapeutic benefit of stem cells is not exclusively made up of a single mechanism but more likely multi-factorial and in different proportions depending on the stem cell population chosen for therapeutic intervention. While most studies have not looked at stem cells therapy for chemotherapeutic/radiation cardiotoxicity, some basic research publications have indicated improvement with stem cell administration (31).

CHALLENGES FACING CELL-BASED THERAPY

With any novel therapeutic in the R & D phase there are many unknowns and obstacles, which must be investigated. Clinical trials of stem cells therapy for patients suffering from cardiac pathologies similar to those observed in patients with chemotherapeutic/radiation cardiotoxicity have shown promise (56, 62, 65, 77, 78, 113, 121, 154, 155), but there is more work needed to be done in order to truly understand the mechanisms behind the improved cardiac function. Once recognizing and establishing more concrete comprehension of the therapeutic benefit of such an intervention, the medical community will be able to make a more informed decision as to whether or not stem cells are a viable option for treatment of chemotherapeutic cardiotoxicity. There are many questions, which are still unresolved, for example: (1) understanding what stem cell populations are optimal for regeneration, (2) is there a dose dependent effect, and (3) what time points should cell therapy be administered and how frequent. These issues can only be answered with more careful planned pre-clinical and clinical trials, not only for more broad cardiac disease states (like acute MI and congestive HF), but also in concentrating on understanding the negative effects of chemotherapeutic/radiation cardiotoxicity and the potential of cell-based therapy in this context. With this, we believe that stem cell-based therapy is one of the frontiers still left in medicine today. There is an enormous amount of potential for regenerative medicine in context of the heart and will probably be a viable option for the treatment of chemotherapeutic/radiation-induced cardiotoxicity.

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Serum biomarkers for the detection of cardiac toxicity after chemotherapy and radiation therapy in breast cancer patients

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Multi-modality cancer treatments that include chemotherapy, radiation therapy, and targeted agents are highly effective therapies. Their use, especially in combination, is limited by the risk of significant cardiac toxicity. The current paradigm for minimizing cardiac morbidity, based on serial cardiac function monitoring, is suboptimal. An alternative approach based on biomarker testing, has emerged as a promising adjunct and a potential substitute to routine echocardiography. Biomarkers, most prominently cardiac troponins and natriuretic peptides, have been evaluated for their ability to describe the risk of potential cardiac dysfunction in clinically asymptomatic patients. Early rises in cardiac troponin concentrations have consistently predicted the risk and severity of significant cardiac events in patients treated with anthracycline-based chemotherapy. Biomarkers represent a novel, efficient, and robust clinical decision tool for the management of cancer therapy-induced cardiotoxicity. This article aims to review the clinical evidence that supports the use of established biomarkers such as cardiac troponins and natriuretic peptides, as well as emerging data on proposed biomarkers.

Keywords: breast cancer, cardiac biomarkers, chemotherapy, radiation therapy, cardiotoxicity

INTRODUCTION

Due to earlier detection and highly effective multi-modality treatments, cancer has become a largely curable disease and a chronic illness. There were an estimated 11.7 million cancer survivors in 2007, a number that has grown from 3.0 million in 1970, to 9.8 million in 2001 (1). The Centers for Disease Control estimated in 2007 that 64.8% of cancer survivors had lived at least 5 years past their initial diagnosis, and approximately 60% of survivors were at least 65 years old. Because of the now-chronic nature of malignant diseases, and the age composition of the survivors, the cardiac side effects of cancer treatments must be heeded. Cytotoxic chemotherapies such as doxorubicin, targeted therapies including trastuzumab, and radiotherapy have all been implicated as risk factors for subsequent cardiac disease. The timing of cardiac toxicity can vary from acutely during treatment, to chronically months after treatment completion. The most clinically significant endpoint is impaired left ventricular ejection fraction (LVEF) and ensuing symptomatic heart failure. The current standard of detection is by serial echocardiography, a resource-intensive test whose accuracy is operator-dependent. Biomarkers on the other hand, can be tested at closer intervals given its low-cost approach; and its accuracy is independent of operator skill. Most importantly, biomarkers have demonstrated the ability to predict cardiotoxicity before it becomes clinically apparent. The use of cardiac biomarker in specific settings have been reviewed several times, and most recently in 2011 (2–6). However, the role of biomarkers is continually redefined by ongoing investigations. The purpose of this review is to provide a comprehensive assessment of the evidence on cardiac troponins and natriuretic peptides as biomarkers of cardiac toxicity. Results for other proposed biomarkers, including heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase isoenzyme BB (GPBB), C-reactive protein (CRP), myeloperoxidase (MPO), and nitric oxide (NO) will also be examined.

CARDIAC TOXICITY AFTER CANCER TREATMENT

Anthracyclines (AC), either used alone, or in combination with other chemotherapy agents, are widely used agents for the treatment of breast cancer (7). However, their use has been limited by significant cardiotoxicity (8). AC-induced injury has been described as "type I" cardiotoxicity, a dose-dependent, progressive, and generally irreversible type of toxicity (9). Its mechanism is based on oxidative damage, mediated by reactive oxygen species, and leads to necrosis and apoptosis (10). Risk of developing AC-induced cardiotoxicity varies between individuals, and even low doses have led to clinical cardiac dysfunction for certain patient subsets (11). Risk factors for developing AC-induced cardiotoxicity include cumulative dose, age, female gender, exposure to cardiotoxic agents, prior AC chemotherapy, and mediastinal radiation. The clinical manifestations of AC-associated cardiotoxicity range from left ventricular dysfunction to progressive cardiomyopathy. Doxorubicin administration is generally limited to a cumulative dose of 600 mg/m^2 in patients without underlying cardiac morbidity (12).

The pediatric population is particularly susceptible to AC-induced cardiomyopathy; and there is likely no safe dose in children (13). The incidence of cardiotoxicity after AC treatment in childhood is similarly dose-dependent: 11, 23, 47, and 100% suffered from cardiac complications after being treated with <400, 400–599, 600–799, and >800 mg/m^2 of AC-based chemotherapy (14, 15). Treatment with ACs has long-term implications. Survivors of pediatric cancers are 8.2 times more likely to die from cardiac causes than the general population, and 15 times more likely to experience heart failure, with some eventually requiring heart transplants (16–18).

About 25–30% of breast cancers overexpress the cell surface receptor HER2. These malignancies are typically more aggressive, with enhanced proliferation and metastatic potential, and are associated with poor prognosis (19). Trastuzumab (Herceptin) is a monoclonal antibody that binds to the extracellular domain of the HER2 protein. Its efficacy in the adjuvant setting has been investigated in numerous clinical trials. A meta-analysis demonstrated reduction in mortality, recurrence and metastases rates, and improved disease-free survival with trastuzumab (20). Trastuzumab, though generally well tolerated, is associated with an infrequent but clinically significant risk of long-term cardiotoxicity. Unlike AC-induced cardiac injury, trastuzumab is described as "type II" cardiotoxicity. The risk of damage is dose-independent, generally reversible with discontinuation, and causes minimal ultrastructural changes (21–23). The risk of developing trastuzumab-induced heart failure has been reported as 2–4% when given alone, but as high as 27% when administered in conjunction with ACs (24, 25). With the advent of newer HER2-directed therapies, additional consideration will need to be given to long-term cardiac side effects associated with their use. Clinical trials have reported fewer grade three or four cardiac toxicity with lapatinib, pertuzumab, trastuzumab emtansine (T-DM1), or neratinib in comparison to trastuzumab (26–34). As other HER2-targeted agents are under development or evaluation for combinatorial therapy, cardiotoxicity will remain a topic of interest.

Radiation therapy (RT) is major component cancer treatment; and adjuvant radiotherapy for breast cancer reduces the risk of local recurrences and mortality (35). However, mediastinal irradiation has been linked to increased cardiotoxicity, via micro- and macrovascular damage (36, 37). A surveillance, epidemiology, and end results (SEER) analysis of 15,165 breast cancer patients found that of those who died more than 10 years after radiotherapy, 42% died from recurrent breast cancer, while 22% died from heart disease (38). The severity of cardiac injury is related to the radiation dose absorbed by the heart, and mean heart dose is typically higher when RT is to employed to treat left-sided breast cancer. The SEER study found patients with left-sided cancers had a 44% increased risk of cardiac mortality. Based on several randomized studies, the relative risk for significant cardiac events ranges 1.2–3.5 after RT (39). As RT is often combined with chemotherapy, cardiac irradiation has been described repeatedly as an additional risk factor for AC-induced cardiotoxicity (40, 41). Though data are still maturing on the cardiac risks of radiotherapy delivered concurrently with trastuzumab, an analysis of the NCCTG N9831 trial showed no additional cardiotoxicity with RT (42). Advances in radiation delivery technology, such as conformal radiation, which limit the amount of radiation absorbed by the myocardium, have proven useful in reducing the burden of radiation-induced cardiac morbidity (38, 43, 44). Regardless, prior mediastinal irradiation remains a significant cause of excessive mortality.

DETECTION OF CARDIAC DYSFUNCTION

Clinically detectable cardiotoxicity is generally preceded by an interval of subclinical cardiac dysfunction. The ability to assess the risk of potential cardiac impairment has three major implications. Risk stratification provides an opportunity to modify ongoing treatment, alter the frequency of subsequent surveillance, and to provide direct interventions to reduce the risk of cardiotoxicity. For these reasons, techniques for early and reliable detection of clinically silent cardiotoxicity have been widely studied. Though several methods been explored, the optimal approach and timing of monitoring cardiac function remains an area of active investigation.

Serial endomyocardial biopsies, though considered the gold standard are invasive and impractical for routine screening purposes (45). The most prevalent screening method is based on measuring LVEF before, during, and after chemotherapy with conventional 2-D transthoracic echocardiography (TTE) (46). Monitoring with multiple-gated acquisition (MUGA) radionuclide angiography has also been recommended on the basis of improved accuracy (47). Because 2-D TTEs can be often limited by operator skill, and inherently less reproducible, efforts have been directed toward increasing its precision with refinements such as 3-D echocardiography, strain and strain rate measurements, and cardiac magnetic resonance (48–51). LVEF measurements based on cardiac imaging lack the sensitivity to detect early subclinical cardiotoxicity, and as a corollary, the ability to predict future declines in cardiac function (52, 53). Detectable changes in LVEF usually coexist with significant functional impairment, at which point the ability to regain normal cardiac function becomes limited. Thus, the traditional approach for detecting subclinical signs of cardiotoxicity is suboptimal and there remains a need to effectively identifying patients who are at risk of developing serious cardiac complications after chemotherapy or RT.

Over the past 15 years, serum molecules, such as cardiac troponins and natriuretic peptides, have been evaluated for their role as biomarkers of cardiac toxicity in the oncology setting. The ability of these biomarkers to identify patients with potential cardiac morbidity has been investigated in adult and pediatric populations, after chemotherapy, radiation, and targeted therapies. Biomarkers represent a non-invasive, resource-efficient, and robust approach to risk-stratify patients who have undergone cardiotoxic treatments.

CARDIAC TROPONINS

Cardiac troponin I (TnI) and cardiac troponin T (TnT) are two highly sensitive and specific biomarkers of cardiac damage. They are two tissue-specific isoforms of proteins that constitute the contractile apparatus in cardiac muscle. Since 2000, the European Society of Cardiology and the American Cardiac College of Cardiology have recognized cardiac troponins for their role in the diagnosis of acute myocardial infarctions (54, 55). Cardiac

troponins have been useful in quantifying the extent of acute cardiomyocyte injury in many other clinic settings, including heart failure, pulmonary embolism, stroke, sepsis, and drug-induced cardiotoxicity (56–58). Notably, because cardiac troponin concentrations have been linked to the severity of myocyte injury and subsequent clinical outcomes, troponins have become a tool for risk stratification.

The validity of using cardiac troponins in detecting chemotherapy-induced cardiotoxicity was demonstrated in an early animal study that linked TnT elevations to histologic evidence of cardiac damage (59). Using spontaneously hypertensive rats treated with increased higher doses of doxorubicin, TnT and Billingham cardiomyopathy scores (based on number of myocytes showing myofibrillar loss and cytoplasmic vacuolization) were both related to the cumulative dose of doxorubicin. Cardiac troponins have consistently demonstrated clinical value in predicting subsequent cardiotoxicity after high-dose chemotherapy (HDC), irrespective of cancer type. This result is based on four major experiences that enrolled approximately 200–700 patients each (**Table 1**) (60–63). Cardiac troponins are sensitive and specific markers in predicting the development, and severity of, subsequent ventricular dysfunction. The largest study, involving 703 patients (46% breast cancer) with advanced cancers treated with HDC (62). TnI was assayed immediately and 1 month after chemotherapy, while cardiac function was measured by LVEF at baseline, and 1, 2, 6, and 12 months after completing chemotherapy. Thirty percent (208) of patients demonstrated immediate TnI elevations, and 30% of that subset showed elevated TnI on repeat testing at 1 month. Maximal LVEF reduction was predicted by both persistent ($r = 0.92$, $p < 0.001$), and early ($r = 0.78$, $p < 0.001$) troponin elevations. Most importantly, TnI proved to be a biomarker with clinical implications, and not simply a proxy for imaging-based measures. Forty-four percent of patients with persistent TnI elevations developed symptomatic heart failure, compared to 12% in the early positive group, and 0.2% in the TnI negative population. Troponin positivity over 0.08 ng/m^2 predicted future cardiac events with a positive predictive value (PPV) of 84% and negative predictive value (NPV) of 99%. TnI's high NPV has been a recurrent theme seen in many studies.

Left ventricular ejection fraction compromises with high-dose chemo can be evident as early as the first month, and was typically followed by progressive deterioration over the next year (61). In addition, smaller studies have found substantial relationships between troponin velocity during early follow-up and decreased LVEF (83). Elevated troponins have been implicated in predicting diastolic dysfunction via parameters such as E/A ratio in particular patient subsets treated with AC (69). Conversely, the role for troponin in low and moderate chemotherapy doses in unclear, as evaluated in a study with 100 patients treated with AC (median cumulative dose 226.1 mg/m^2) (71). Even with TnT being assayed at five intervals from the first dose of chemotherapy to 12 months after its completion, no patient had recorded TnT values above the 0.1-ng/ml threshold. Of those who showed TnT rises after treatment, the majority reported normal LVEF and E/A ratio values just 1 year after completing chemotherapy.

Notably, cardiac troponins have been key in facilitating the evaluation of cardioprotective agents in two prospective randomized trials (68, 84). Both randomized children diagnosed with acute lymphoblastic leukemia (ALL) to doxorubicin with or without dexrazoxane, a free radical scavenger. In both studies, dexrazoxane drastically reduced the incidence of above-threshold values TnT during treatment. In the more recent experience, TnI levels during the first 90 days of treatment predicted lower LV mass and LV end-diastolic posterior wall thickness 4 years later (84).

Reports of troponin as a prognostic tool in asymptomatic survivors of childhood cancers have been largely disappointing. An early study of children treated with doxorubicin found the magnitude of TnT elevation after the first dose of chemotherapy predicted for the risk of subsequent echocardiographic abnormalities, including LV dilation ($r = 0.8$, $p = 0.003$), and LV wall thinning ($r = 0.61$, $p = 0.04$) 9 months later (65). The timing of injury markers supported the hypothesis that AC-induced injury can begin as early as the first dose, and is driven by continuous oxidative stress rather than acute necrosis. However, numerous studies discovered either no above-threshold troponin values, or lacked substantial relation with late-onset cardiac toxicity in survivors of childhood malignancies (67, 74, 87, 90).

In parallel with the growing usage of adjuvant trastuzumab in patients with HER2 overexpressing or amplified breast cancer, several large-scale studies have found a well-defined relationship between either troponin value or its interval change and tratuzumab-induced cardiac dysfunction. Cardinale et al. provided the earliest evidence cardiac troponin values can stratify patients on risk of developing trastuzumab-induced cardiotoxicity, based on 251 breast cancer patients who were followed for a median of 14 months after completion of trastuzumab treatment (75). Thereafter, systolic function (LVEF) was evaluated via echocardiography at baseline, every 3 months during trastuzumab treatment and the first year of follow-up, and then every 6 months. Forty-two (17%) patients developed cardiac review and evaluation committee (CREC)-defined cardiac dysfunction; however, those with above-threshold TnI concentrations were at significantly higher risk for cardiotoxicity (62 vs. 5%, $p < 0.001$). Moreover, TnI positivity was the strongest independent predictor of cardiotoxicity (HR = 17.6, $p < 0.001$) and persistent LVEF impairment (HR 2.33, $p < 0.001$). Troponin positivity predicted LVEF recovery with a PPV of 65% and NPV of 100%. This suggested that negative TnI measurements during treatment can be used to assign a lower risk status to select patients who are less likely to benefit from cardiac screening at routine intervals.

With regard to the timing of troponin rises with trastuzumab treatment, Morris et al. found peak TnI elevations peaked occurred approximately 2 months and four after dose-dense AC-based chemotherapy (79). Importantly, it preceded maximum LVEF decline by 4 months. Two studies by Sawaya et al. supported these results. Both examined TnI in patients who were treated with AC and trastuzumab sequentially. They first found that elevated high-sensitivity (hs)TnT measurements 3 months after chemotherapy was an independent predictor of cardiac toxicity at 6 months (81). The follow-up study combined circulating biomarkers with echocardiographic measures to refine their predictive model. Using an ultrasensitive troponin assay that established 30 pg/ml

Table 1 | Role of cardiac troponins in the evaluation of chemotherapy and radiation-induced cardiotoxicity.

Reference	Population	N	Treatment	Tn type	Cutoff	Troponin evaluations	Results and conclusions
Hugh-Davies et al. (64)	Breast cancer	50	ACs and RT	T	0.1 ng/ml	Pre- and post-treatment	No change in TnT after 45–46 Gy delivered to the whole breast
Lipshultz et al. (65)	ALL	15	ACs	T	0.03 ng/ml	Baseline, and 1–3 days after each cycle	Correlation between TnT and LV end-diastolic dimension and wall thickness
Herman et al. (59)	Animal study	37	ACs	T		Before, and 1 week after chemotherapy	TnT and histological myocardial changes in both related to cumulative doxorubicin dose
Cardinale et al. (60)	Various	204	HDC	I	0.5 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	Elevated TnI during treatment predicted for LVEF decline
Cardinale et al. (61)	Breast cancer	211	HDC and RT	I	0.5 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	Correlation between max TnI, number of TnI positive assays, and max LVEF reduction
Auner et al. (66)	Hematologic malignancies	78	ACs	T	0.03 ng/ml	Within 48 h of treatment start, then every 48 h during treatment	Correlation between TnT increase and median LVEF decline
Sandri et al. (63)	Various	179	HDC	I	0.08 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	TnI increase predicted subsequent LVEF decline
Cardinale et al. (62)	Various	703	HDC	I	0.08 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle, and 1 month after treatment	Persistent TnI positivity predicted for subsequent LVEF decline
Kismet et al. (67)	Pediatric solid cancers	24	ACs	T	0.01 ng/ml	With imaging, >1 month after chemo	No relationship between TnT and echocardiographic abnormalities
Lipshultz et al. (68)	ALL	76	ACs	T	0.01 ng/ml	Throughout chemotherapy	TnT persistently increased during treatment, and predicted for cardioprotective response
Kilickap et al. (69)	Various	41	ACs	T	0.01 ng/ml	Baseline, after first and last cycle	Correlation between TnT increase and diastolic dysfunction (E/A ratio)
Perik et al. (70)	Breast cancer	17	ACs and T	I	0.1 g/l	Before, and throughout T therapy	No TnI elevations in 15/16 patients
Dodos et al. (71)	Various	100	ACs	T	0.1 ng/ml	After first dose, last dose, and 1, 6, 12 months after last dose	No TnT elevations detected
Kozak et al. (72)	Lung and esophageal CA	30	ChemoRT	T		Baseline, 2 weeks after start of treatment and after	TnT undetectable in 29/30 patients
Cil et al. (73)	Breast cancer	33	ACs	I		Before and after chemotherapy	No correlation between TnI and LVEF decline
Mavinkurve-Groothuis et al. (74)	Various pediatric	122	ACs	T	0.01 ng/ml	Once, with imaging	No patients with elevated TnT levels

(Continued)

Table 1 | Continued

Reference	Population	N	Treatment	Tn type	Cutoff	Troponin evaluations	Results and conclusions
Cardinale et al. (75)	Breast cancer	251	ACs and T	I	0.08 ng/ml	Before T, every 3 months during treatment, 1 year after start, every 6 months	Elevated TnI values are an independent predictor of cardiotoxicity, and LVEF recovery
Nellessen et al. (76)	Lung and breast CA	23	RT	I	0.03 ng/ml	Before RT, every week during RT for 4–6 weeks	Log-transformed TnI increased during treatment
Fallah-Rad et al. (51)	Breast cancer	42	ACs and T	T		Before chemotherapy, before T, and 3, 6, 9, and 12 months after start of T	No change in TnT values over time
Feola et al. (77)	Breast cancer	53	ACs	I	0.03 ng/ml	Baseline, after 1 month, 1, and 2 years	TnI concentrations elevated at 1 month, then returned to normal
Goel et al. (78)	Breast cancer	36	ACs and T	I	0.20 ng/ml	Baseline, before and 24 h after T	No elevated TnI values throughout
Morris et al. (79)	Breast cancer	95	ACs and T	I	0.04–0.06 ng/ml	Every 2 weeks during treatment, then at 6, 9, and 18 months	Elevated TnI values preceded maximal LVEF decline, but no relationship with max LVEF decline
Romano et al. (80)	Breast cancer	92	ACs	I	5 or 0.08 ng/ml (age $\leq$50 or $>$50)	Every 2 weeks during treatment, then at 3, 6, and 12 months	No correlation between TnI change and subsequent LV impairment
Sawaya et al. (81)	Breast cancer	43	ACs and T	I	0.015 ng/ml	Baseline, 3 and 6 months after chemotherapy	Elevated TnI at 3 months predicted for cardiotoxicity within 6 months
D'Errico et al. (82)	Breast cancer	60	ChemoRT	I	0.07 ng/ml	Before, and after RT	No elevated TnI concentrations
Garrone et al. (83)	Breast cancer	50	ACs	I	0.03 ng/ml	Baseline, 5, 16, and 28 months after	TnI kinetics correlated with LVEF decline
Lipshultz et al. (84)	ALL	156	ACs	T	0.01 ng/ml	Before, and daily during induction, and after treatment	Lower incidence of detectable TnT during treatment with dexrazoxane
Onitilo et al. (85)	Breast cancer	54	Taxanes and T	I	0.1 ng/ml	Baseline, and every 3 weeks during treatment	TnI undetectable throughout
Sawaya et al. (86)	Breast cancer	81	ACs and T	I	30 pg/ml	Before, every 3 months during, and after T treatment	Elevated TnI values at end of treatment predictive of subsequent cardiotoxicity
Sherief et al. (87)	Acute leukemias	50	ACs	T	0.01 ng/ml	Once, with imaging	No elevated TnT values
Erven et al. (88)	Breast cancer	72	RT	I	0.13 ng/ml	Before and after RT	Higher TnI values in L-sided breast patients
Ky et al. (89)	Breast cancer	78	ACs and T	I	121.8 ng/ml	Baseline, 3 and 6 months after start of chemotherapy	Interval change in TnI predicted cardiotoxicity

Tn, troponin; AC, anthracycline; RT, radiation therapy; HDC, high-dose chemotherapy; T, trastuzumab; LVEF, left ventricular ejection fraction; ALL, acute lymphoblastic leukemia.

as the cutoff concentration, they found TnI alone predicted subsequent cardiotoxicity with PPV of 44% and NPV of 77% (86). Adding peak systolic longitudinal strain of <19% improved the specificity of the model, yielding a PPV of 67% and NPV of 77%. Interestingly, baseline LVEF at the time of AC completion did not predict for future cardiotoxicity. Though the majority of studies evaluating troponins in trastuzumab-induced cardiac damage have demonstrated its usefulness, several experiences have been negative (51, 77–79).

Despite abundant literature on radiation-induced cardiac injury, troponins have yet to demonstrate any clinical utility. Studies in which considerable numbers of patients were treated with RT as a single modality are relatively scarce. Of those that try to isolate the effect of radiotherapy, none have been able draw clinically valuable conclusions regarding the value of troponin in predicting radiation-induced cardiotoxicity (64, 72, 82). In fact, of four studies that included patients with breast, lung, and esophageal cancer, only one saw significantly elevated TnI concentrations after RT (88).

NATRIURETIC PEPTIDES

Natriuretic peptides, such atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and its amino-terminal component (NT-proBNP) have been widely investigated and used in acute and chronic heart failure for diagnosis and prognosis. In response to increased wall stress, BNP is synthesized by ventricular cardiomyocytes as a 134-amino acid (aa) pre-pro peptide, which is then cleaved into a 108-aa precursor molecule (proBNP). Upon release, proBNP is cleaved into an inactive N-terminal component (NT-proBNP) and the 32-residue active hormone BNP. To counteract volume overload, biological actions of BNP include natriuresis, vasodilation, and suppression of sympathetic activity (91). Chronic elevations in BNP reflect increased LV wall stress diastolic pressure, and volume overload (92, 93). Moreover, NT-proBNP concentrations have been related to LVEF values and the severity of hearth failure (94). Thus, using natriuretic peptides to risk-stratify patients with potential cardiotoxicity would intuitively be an attractive strategy, as they represent hemodynamic aberrancy and ventricular remodeling, and can appear prior to symptomatic heart failure and LVEF decline (95).

A large number of studies have described significant BNP and NT-proBNP elevations with doxorubicin, epirubicin, trastuzumab, and thoracic irradiation, either alone in combination therapy, though substantially fewer have found clinical relevant relationships (**Table 2**). One early study that established the predictive value of NT-proBNP examined its role in patients with various advanced malignancies treated with high-dose AC-based chemotherapy (63). Sandri et al. measured NT-proBNP at baseline, and then at five time points within 72 h of completing each treatment cycle. Persistent NT-proBNP measurements predicted for the development of cardiac dysfunction at 12 months when quantified by three LV diastolic indices. The predictive value of early NT-proBNP rises was also seen with a cohort of breast cancer patients with doxorubicin to a cumulative dose of 300 mg/m^2 (80). Post-chemotherapy NT-proBNP increases were related to subsequent LVEF decline ($r = 0.7$, $p \leq 0.001$). An ROC analysis using a cutoff of >36% NT-proBNP increase from baseline to peak predicted LV impairment at 12 months after therapy with 79.2% sensitivity and specificity. Similar correlations between NT-proBNP elevations and LVEF values in the setting of breast cancer treated with moderate dose epirubicin and non-Hodgkin lymphoma patients after six cycles of CHOP chemotherapy (96, 97).

Though early BNP increases have been the focus of many studies for its predictive capabilities, BNP levels can remain elevated up to 2 years after AC-based treatment. This suggests that persistent neurohormonal activation, independent of acute tissue toxicity, is one underlying mechanism of late-onset AC-induced cardiotoxicity (77). BNP monitoring during chemotherapy has also been linked to significant diastolic dysfunction with CHOP. A study by Nousiainen et al. revealed associations between BNP, fractional shortening (FS) ($p = 0.04$), E/A ratio ($p = 0.006$), and trend to significance with LA diameter ($p = 0.062$) (99). Studies involving AC in the adult population have also seen substantial increases in NT-proBNP with no significant interactions with echocardiographic or clinical outcomes (71, 73, 98, 100).

While there has been great interest in validating natriuretic peptides as predictors of cardiotoxicity in the pediatric population, studies in this setting have seen mixed results. NT-proBNP has been shown to be an effect indicator of cardioprotective interventions (84). Specifically, children with ALL were randomized to receive doxorubicin with or without dexrazoxane, an effective free radical scavenger. Lipshultz et al. discovered drastically reduced NT-proBNP concentrations after dexrazoxane treatment (47 vs. 20%, $p = 0.07$). Increased NT-proBNP in the first 90 days of treatment also predicted abnormal LV thickness-to-dimension ratios, suggestive of late-onset LV remodeling. Germanakis et al. evaluated BNP nearly 4 years after AC treatment to find an association between NT-proBNP with LV mass reductions ($p = 0.003$) in asymptomatic survivors (103). Lastly, NT-proBNP concentrations have been consistently identified as a proxy for cumulative AC dose in survivors of childhood cancers (74, 105, 108).

The experience with natriuretic peptides corroborates large-scale studies that have shown the clinic onset of RT-induced cardiotoxicity can occur years after therapy. Significant NT-proBNP elevations have been detected as early as 9 months, and as late as 6.7 years after radiation to the thorax for breast and esophageal cancer (82, 101, 106). In 64 patients with esophageal cancer treated to median dose of 60 Gy, increased NT-proBNP concentrations were found beginning at 9 months (when compared to baseline), and persisted at 24 months after radiotherapy. Additionally, NT-proBNP may be an early indicator of radiation-induced myocardial damage. Substantially, higher natriuretic peptide concentrations were found in subjects with high F-fluorodeoxyglucose (FDG) accumulation on positron emission tomography (PET) corresponding to the irradiated fields (106). Similarly, NT-proBNP has also been linked to cardiac doses in left-sided breast cancer. D'Errico et al. found significant associations between NT-proBNP and V_{3Gy} (volume receiving at least 3 Gy), and two ratios for the heart: D_{15cm3}/D_{mean} and $D_{15cm3}/D_{50\%}$ (where D_{mean} is the mean dose, $D_{50\%}$ is the median dose, and D_{15cm^3} is the minimum isodose received by 15 cm^3) (82).

Table 2 | Role of natriuretic peptides in the evaluation of chemotherapy and radiation-induced cardiotoxicity.

Reference	Population	N	Treatment	BNP type	Cutoff	BNP evaluations	Results and conclusions
Meinardi et al. (98)	Breast cancer	39	ACs and RT	BNP	10 pmol/l	Baseline, 1 month, and 1 year after chemotherapy	BNP increased as early as 1 month after chemo; no correlation with LVEF decline
Nousiainen et al. (99)	Non-Hodgkin lymphoma	28	CHOP	BNP	227 pmol/l	Baseline, after every cycle, and 4 weeks after last cycle	Correlation between BNP increases and parameters of diastolic function (FS and PFR)
Daugaard et al. (100)	Various	107	ACs	BNP		Before, and at various points during treatment	BNP correlation with decreased LVEF, but baseline and BNP change could not predict LVEF decline
Perik et al. (101)	Breast cancer	54	ACs and RT	NT-proBNP	10 pmol/l	Median 2.7 and 6.5 years after chemotherapy	BNP increased with time and was related to dose; cardiotoxic effects develop over years
Sandri et al. (102)	Various	52	HDC	NT-proBNP	153 ng/l (M $\leq$50), 227 ng/l (M $>$50), 88 ng/l (F $\leq$50), 334 ng/l (F $>$50)	Baseline, and 0, 12, 24, 36, and 72 h after each cycle	Persistent NT-proBNP elevation at 72 h predicts later systolic and diastolic dysfunction
Germanakis et al. (103)	Pediatric cancers	19	ACs	NT-proBNP	0.2 pmol/ml	Mean 3.9 years after chemotherapy	Correlation between NT-proBNP and LV mass decrease
Perik et al. (70)	Breast cancer	17	ACs and T	NT-proBNP	125 ng/l	Baseline and throughout T treatment	Higher pre-treatment NT-proBNP values in those who developed HF during treatment
Aggarwal et al. (104)	Pediatric cancers	63	ACs	BNP		Once, $>$1 year after treatment completion	Higher BNP in patients with late cardiac dysfunction by ECHO
Ekstein et al. (105)	Pediatric cancers	23	ACs	NT-proBNP	350 pg/ml	Before and after each AC dose	Dose-related increase in BNP from baseline seen after first AC dose
Jingu et al. (106)	Esophageal cancer	197	RT	BNP		Before, $<$1 month, 1–2, 3–8, 9–24, and $>$24 months after RT	Increased BNP over time and in those with abnormal FDG accumulation
Kouloubinis et al. (97)	Breast cancer	40	ACs	NT-proBNP		Before and after chemotherapy	Correlation between NT-proBNP increase and LVEF decline
Dodos et al. (71)	Various	100	ACs	NT-proBNP	153 or 227 ng/l for M $\leq$50 or $>$50; 88 or 334 ng/l for F $\leq$50 or $>$50	After first dose, last dose, and 1, 6, and 12 months after last dose	No significant increase in NT-proBNP with treatment; cannot replace serial ECHO for monitoring of AC-induced cardiotoxicity
Kozak et al. (72)	Lung and esophageal CA	30	ChemoRT	NT-proBNP		Baseline, after 2 weeks of RT, and after RT end	No change in NT-proBNP during treatment
Cil et al. (73)	Breast cancer	33	ACs	NT-proBNP	110 pg/ml	Before and after chemotherapy	Despite association, pre-chemo NT-proBNP did not predict for later LVEF
ElGhandour et al. (96)	Non-Hodgkin lymphoma	40	CHOP	BNP		Before first cycle and after sixth cycle of chemotherapy	Correlation between BNP values after chemotherapy and LVEF

(Continued)

Table 2 | Continued

Reference	Population	N	Treatment	BNP type	Cutoff	BNP evaluations	Results and conclusions
Mavinkurve-Groothuis et al. (74)	Pediatric cancers	122	ACs	NT-proBNP	10 pmol/l (M), 18 pmol/l (F), age-adjusted in children (107)	Once, with imaging	NT-proBNP levels related to cumulative AC dose
Nellessen et al. (76)	Lung and breast CA	23	RT	NT-proBNP	100 pg/ml	Before RT, every week during RT for 4–6 weeks	Log-transformed NT-proBNP increased during treatment
Fallah-Rad et al. (51)	Breast cancer	42	ACs and T	NT-proBNP		Before chemotherapy, before T, and 3, 6, 9, and 12 months after start of T	No change in NT-proBNP values over time
Feola et al. (77)	Breast cancer	53	ACs	NT-proBNP	5 pg/ml	Baseline, after 1 month, 1, and 2 years	NT-proBNP increased acutely with treatment, and in patients with systolic dysfunction
Goel et al. (78)	Breast cancer	36	ACs and T	NT-proBNP	110 pg/ml (age <75), 589 pg/ml (age >75)	Baseline, before and 24 h after T	No change in NT-proBNP with trastuzumab
Romano et al. (80)	Breast cancer	92	ACs	NT-proBNP	153 pg/ml (age ≤ 50), 222 pg/ml (age >50)	Every 2 weeks during treatment, then at 3, 6, and 12 months	Interval change in NT-proBNP predicated for LV impairment at 3, 6, and 12 months
Sawaya et al. (81)	Breast cancer	43	ACs and T	NT-proBNP	125 pg/ml	Baseline, 3 and 6 months after chemotherapy	No relation between NT-proBNP levels before and after treatment and LVEF change
D'Errico et al. (82)	Breast cancer	60	ChemoRT	NT-proBNP	125 pg/ml	Before, and after RT	Correlation between NT-proBNP, V_{3Gy} for the heart, D_{15cm^2}/D_{mean} and $D_{15cm^3}/D_{50\%}$
Lipshultz et al. (84)	ALL	156	ACs	NT-proBNP	150 pg/ml (age <1), 100 pg/ml (age ≥ 1)	Before, and daily during induction, and after treatment	Correlation between NT-proBNP and change in LV thickness-to-dimension ratio 4 years later
Mladosievicova et al. (108)	Childhood leukemias	69	ACs	NT-proBNP	105 pg/ml (F), 75 pg/ml (M)	Median 11 years after treatment	Increased NT-proBNP with exposure to ACs
Onitilo et al. (85)	Breast cancer	54	Taxanes and T	BNP	200 pg/ml	Baseline, and every 3 weeks during treatment	No correlation between elevated BNP values and cardiotoxicity
Pongprot et al. (90)	Pediatric cancers	30	ACs	NT-proBNP	Age-adjusted (109)	Once, with imaging	Correlation between NT-pro BNP values and FS and LVEF
Sawaya et al. (86)	Breast cancer	81	ACs and T	NT-proBNP	125 pg/ml	Before, every 3 months during, and after T treatment	NT-proBNP did not change with treatment
Sherief et al. (87)	Acute leukemias	50	ACs	NT-proBNP	Age-adjusted (107)	Once, with imaging	NT-proBNP linked to AC dose and abnormal tissue Doppler imaging parameters

(Continued)

Table 2 | Continued

Reference	Population	N	Treatment	BNP type	Cutoff	BNP evaluations	Results and conclusions
Kittiwarawut et al. (110)	Breast cancer	52	ACs	NT-proBNP	45 pg/ml	Baseline, and end of fourth cycle	Correlation between NT-proBNP and FS
Ky et al. (89)	Breast cancer	78	ACs and T	NT-proBNP		Baseline, 3 and 6 months after start of chemotherapy	No relationship between NT-proBNP values and cardiotoxicity

BNP, brain natriuretic peptide; NT, N-terminal; AC, anthracycline; RT, radiation therapy; HDC, high-dose chemotherapy; T, trastuzumab; LVEF, left ventricular ejection fraction; HF, heart failure; ALL, acute lymphoblastic leukemia; FS, fractional shortening; PFR, peak filling rate.

The role of NT-proBNP in predicting trastuzumab-induced cardiac dysfunction has been evaluated in five recent studies. Higher pre-treatment (immediately post-chemotherapy) NT-proBNP concentrations were found in patients with metastatic breast cancer who developed symptomatic heart failure during treatment ($p = 0.009$) (70). The other four failed to find any meaningful relationship between BNP or its interval changes with measures of cardiac function; often no significant changes were found between pre- and post-treatment NT-proBNP concentrations (51, 78, 81, 89). Concerns regarding sufficient follow-up and superimposed AC-induce cardiotoxicity make it unclear whether NT-proBNP has any clinical usefulness in predicting trastuzumab-induced cardiac dysfunction.

OTHER PROPOSED MARKERS

Heart-type fatty acid-binding protein and glycogen phosphorylase isoenzyme BB have been evaluated jointly as potential biomarkers of cardiac toxicity in several studies. Both GPBB and H-FABP are considered markers of early cardiac injury. GPBB is a cardiac-specific enzyme of glycogenolysis, which provides glucose to cardiac muscle. Because GPBB is released into circulation 2–4 h after myocardial injury, it may be a sensitive, and early marker of acute coronary syndromes. Moreover, GPBB has been found useful for the risk stratification in acute coronary syndromes, as it is an independent predictor of mortality (111). Similarly, H-FABP is a low molecular weight protein normally found in the cytoplasm, but can be detected within 2–3 h after significant myocardial injury (112, 113). In three studies that evaluated GPBB in patients with leukemias and lymphomas, Horacek et al. found approximately 17–21.7% of patients with elevated GPBB concentrations after either AC-based chemotherapy or a preparative regimen for hematopoietic stem cell transplantation (114–116). Based on threshold values of 7.30 μg/l for GPBB and 4.50 μg/l for H-FABP, no study reported significant elevations in H-FABP, and only one found a correlation between GPBB elevation and LV diastolic dysfunction via impaired relaxation (114). However, in a cohort of non-Hodgkin lymphoma subjects treated with doxorubicin-based chemotherapy, H-FABP measured 23 h after the first cycle of CHOP was correlated with LVEF assessed after six cycles ($r = -0.836$, $p < 0.001$) (96). Though numerous studies have found elevated GPBB after chemotherapy, and one has related H-FABP with subsequent systolic dysfunction, none have yet linked biomarker elevations with clinical outcomes in larger populations, which leaves the clinical relevance of these two ischemic markers unclear.

C-reactive protein is an acute phase protein that is synthesized during an inflammatory response. Its expression is regulated by cytokines such interleukin (IL)-1, IL-6, and tissue necrosis factor-α (TNF-α). In the context of stable coronary artery disease, myocardial infarction, and congestive heart failure, elevated CRP is predictive of decreased LVEF and diastolic dysfunction (117–119). Using a high-sensitivity (hs) assay in breast cancer patients, hsCRP concentrations ≥3 mg/l predicted impaired LVEF with 92.9% sensitivity and 45.7% specificity (PPV, 40.6%; NPV, 94.1%). As maximum hsCRP elevations were seen on average 78 days before echocardiographic detection, hsCRP may prove to be effective in identifying patients who are less likely to benefit from more stringent follow-up. While Lipshultz et al. found higher CRP values in survivors of various childhood cancers, regardless of exposure to cardiotoxic treatment with modest correlation with LV mass, wall thickness, and dimension (120), multiple studies have found no clinical value in CRP measurements (79, 84, 89).

Myeloperoxidase is a proinflammatory enzyme that expressed by polymorphonuclear neutrophils that is indicative of oxidative stress, and involved in lipid peroxidation. It has also been identified for its prognostic value in predicting future cardiovascular events in acute coronary syndromes and adverse outcomes in heart failure (121, 122). MPO was identified as one of two predictors of cardiotoxicity in breast cancer patients treated with ACs and Herceptin, from a panel of potential biomarkers including CRP, NT-proBNP, growth differentiation factor (GDF)-15, placenta growth factor (PlGF), soluble fms-like tyrosine kinase receptor (sFlt)-1, and galectin (gal)-3 (89). Ky et al. found that for patients with 90th percentile MPO interval change from baseline (422.6 pmol/l increase), the probability of CREC cardiotoxicity at 15 months was 34.2%, and the risk of future cardiac toxicity was amplified with each standard deviation increase in MPO concentration (HR 1.34, $p = 0.048$). When considered jointly with 90th percentile interval TnI elevations, the risk of cardiotoxicity by 15 months was 46.5%.

Nitric oxide is a small molecule generated by NO synthase from L-arginine in numerous cell types, including endothelial cells, platelets, neutrophils, and macrophage (123). NO is a key regulator of cardiomyocyte contractility, and inducible NO synthase has been implicated in the pathophysiology of heart failure and cardiomyopathy (124, 125). Dysregulated NO synthesis has been found to be one mechanism involved in doxorubicin-induced cardiotoxicity, as studies in bovine endothelial cells have linked

redox activation of doxorubicin with endothelial NO synthesis in doxorubicin-induced apoptosis (126, 127). NO has been described as a potential marker of subclinical cardiac dysfunction in the pediatric setting. Guler et al. found significantly higher nitrite values in children treated with doxorubicin compared to healthy controls, and in those with abnormal/borderline LVEF and FS values (92.35 vs. 59.26 μmol/l, $p = 0.038$) (128).

CONCLUSION AND FUTURE DIRECTIONS

Cardiac toxicity associated with cancer treatment is a growing source of significant morbidity and mortality. Current screening practices are suboptimal as they provided limited opportunity to intervene and change the course of disease progression. Serum biomarkers, and especially cardiac troponins in patients treated with HDC, represent an effective method for monitoring cardiac status, and identifying patients who may benefit from early medical intervention. There is also growing evidence for a combined approach in which biomarkers and echocardiograms are co-interpreted.

A discussion of any screening test's validity would be incomplete without considering Wilson and Junger's classic screening criteria (129). Of the 10 criteria, some are evident, such as "the condition sought should be an important health problem." And of the 10, the two that deserve additional mention here are "there should be an accepted treatment for patients with recognized disease," and "there should be an agreed policy on whom to treat as patients." Both of these questions were addressed by a large randomized study that evaluated the cardioprotective effects of enalapril, an angiotensin-converting-enzyme inhibitor routinely used for congestive heart failure (130). Of 413 patients treated with high-dose ACs in the study, 114 patients developed early increases in TnI and were randomized to receive either enalapril ($n = 56$) or placebo ($n = 58$). In the intervention arm, enalapril was given for 1 year, starting 1 month after chemotherapy. The placebo arm suffered from a significant and progressive decline in LVEF (62.4 vs. 48.3% at 12 months, $p < 0.001$), as well as increases in end-diastolic and end-systolic volume. Moreover, the treatment group benefited from a lower incidence of adverse cardiac events (2 vs. 52%, $p < 0.001$). Other investigators have evaluated the beta-blockers nebivolol and carvedilol in the randomized setting, finding treatment during AC chemotherapy offered significant protection of LVEF in both interventions (131, 132). Though investigations are still ongoing, the results accumulated so far suggests cardiotoxicity, if detected early enough, and treated appropriately, is a potentially treatable condition. Additionally, the study populations and criteria used for treatment have provided a foundation for management decisions that can further refined.

As data on the treatment of chemotherapy-induced cardiotoxicity continue to accumulate, the objective of validating and refining biomarker-based screening strategies becomes more and more clear. Because, clinically apparent signs of cardiac injury often occur years after initial therapy, there are few studies that have been able to link early rises in biomarker concentrations with clinical endpoints. Thus, there is a need longer for long-term data to either confirm or refute any meaningful relationship between early biomarker status and long-term cardiac morbidity. Additionally, because the optimal schedule of biomarker assessments remains unclear, the integration of biomarker evaluations into large prospective clinical trials is critical. As the burden of antineoplastic therapy-induced cardiac morbidity increases, so does the need to find effective strategies for risk stratification and management of therapy-induced cardiotoxicity.

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Cardiovascular toxicities from systemic breast cancer therapy

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Cardiovascular toxicity is unfortunately a potential short- or long-term sequela of breast cancer therapy. Both conventional chemotherapeutic agents such as anthracyclines and newer targeted agents such as trastuzumab can cause varying degrees of cardiac dysfunction. Type I cardiac toxicity is dose-dependent and irreversible, whereas Type II is not dose-dependent and is generally reversible with cessation of the drug. In this review, we discuss what is currently known about the cardiovascular effects of systemic breast cancer treatments, with a focus on the putative mechanisms of toxicity, the role of biomarkers, and potential methods of preventing and minimizing cardiovascular complications.

Keywords: cardiotoxicity, heart failure, chemotherapy, breast cancer, anthracycline, trastuzumab

INTRODUCTION

Breast cancer remains the most common cancer among women. It is estimated that more than 3.1 million women with a history of invasive breast cancer are alive in the United States. By 2024, that number is estimated to increase to 3.9 million (1). Advances in breast cancer treatments have fortunately led to improvements in survival. However, with more women living longer, delayed toxicities of therapy have become more significant. Cardiovascular complications from therapy can occur to varying degrees and, in severe cases, can have devastating consequences.

Cardiotoxicity from breast cancer therapy is seen most commonly after treatment with anthracyclines and trastuzumab, at times necessitating discontinuation of otherwise effective treatment. Yet despite the large number of studies that have addressed the cardiotoxic effects from breast cancer therapy, few guidelines exist for the detection, monitoring, and management of patients with treatment-related cardiotoxicity.

Cardio-oncology has emerged as a new field that focuses on preserving cardiovascular health in cancer patients. Key areas of research include understanding the mechanisms of cardiac dysfunction, developing biomarkers for early detection, and instituting appropriate therapy for both the prevention and treatment of cardiac toxicity.

ANTHRACYCLINE-INDUCED CARDIOTOXICITY

The role of anthracyclines in the treatment of breast cancer is well-established (2, 3). However, the benefit of this class of drugs is often limited by the risk of myocardial damage which, in severe cases, can progress to symptomatic congestive heart failure (CHF). Anthracycline-induced cardiotoxicity can take on a variety of forms. Acute cardiotoxicity is relatively uncommon and is usually not life threatening. It can manifest as electrocardiogram changes, arrhythmias, and transient depression of myocardial contractility. These changes generally occur during intravenous administration and normally resolve on their own with discontinuation of the drug (4–6). Chronic anthracycline-induced cardiotoxicity, on the other hand, is more common and of much greater clinical concern. This type of cardiotoxicity is classified as Type I and is dose-related, progressive and irreversible.

Chronic cardiotoxicity typically presents within 1 year of treatment but late manifestations can occur up to 10 or more years following anthracycline therapy (7). Asymptomatic diastolic dysfunction may be an early finding in patients exposed to anthracycline therapy; this may progress to heart failure with preserved left ventricular ejection fraction (LVEF) and eventually to heart failure with reduced EF. Endomyocardial biopsies performed on patients exposed to anthracyclines have demonstrated ultrastructural changes such as vacuolization, myofibrillar disorganization, and myocyte necrosis, even in the absence of overt clinical symptoms (8, 9).

The dose-dependent relationship of anthracyclines and cardiotoxicity has been well-characterized since the late 1970s. In a retrospective analysis of 4018 patients with a variety of tumors who received doxorubicin, the number of patients who developed CHF was 3% at a cumulative doxorubicin dose of 400 mg/m^2, 7% at a cumulative dose of 550 mg/m^2, and 18% at a dose of 700 mg/m^2 (4). However, another analysis of doxorubicin-associated cardiotoxicity revealed an even higher incidence of CHF at 26% with a cumulative dose of 550 mg/m^2 (10). These authors also found that CHF occurred at total cumulative doses of <300 mg/m^2, although

this was relatively infrequent. Based on these observations, it is generally recommended that the cumulative dose of doxorubicin be limited to 400–450 mg/m^2 in adults (see **Table 1**).

While cumulative dose remains the most significant risk factor for the development of cardiotoxicity, other risk factors include older age, radiation therapy, concomitant chemotherapy, and factors that may predispose to cardiovascular disease such as hypertension and diabetes (4, 10–13). However, there is great variability in patient susceptibility to cardiotoxicity. In the analysis by Von Hoff, five patients received over 1000 mg/m^2 of doxorubicin and did not develop clinical cardiotoxicity, while others developed CHF at much lower cumulative doses (4). Genetic polymorphisms may account at least in part for some of the differences in susceptibility, although studies performed in the pediatric population have yielded conflicting results (14, 15).

Table 1 | Incidence of doxorubicin-induced CHF in the metastatic setting.

Study	Number of patients in analysis	Malignancy	Overall incidence of CHF (%)	Incidence of CHF based on cumulative dose of doxorubicin
Von Hoff et al. (4)	4018	Variety of tumors	2.2[a]	3% at 400 mg/m^2 7% at 550 mg/m^2 18% at 700 mg/m^2
Swain et al. (10)	630	Metastatic breast cancer and small cell lung cancer	5.1[b]	5% at 400 mg/m^2 16% at 500 mg/m^2 26% at 550 mg/m^2 48% at 700 mg/m^2

[a] *Based on clinical signs and symptoms of CHF.*

[b] *Protocol definition of CHF included two or more of the following: cardiomegaly on chest X-ray; basilar rales; S3 gallop; or paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion.*

MECHANISM OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Cardiac myocytes have limited regenerative capabilities and thus are especially susceptible to irreversible damage. The mechanism by which anthracyclines induce cardiotoxicity has been a topic of great debate and multiple hypotheses have been proposed. Until recently the most widely accepted explanation has been the oxidative stress model whereby generation of reactive oxygen species (ROS) by redox cycling and iron–anthracycline complexes leads to myocyte damage. However, this hypothesis has been called into question given the failure of antioxidants such as vitamin E, coenzyme Q10, and *N*-acetylcysteine and iron chelators such a deferasirox to confer a cardioprotective effect in the clinical setting (16–19).

More recently, investigators from MD Anderson Center proposed an alternate explanation for anthracycline-induced cardiotoxicity via the topoisomerase (Top) 2b enzyme (20). Anthracycline binding to Top2 is a well-established mechanism of cellular damage and antitumor activity. Top2a is overexpressed in cancer cells but is absent in normal cells, whereas Top2b is expressed only in normal cells, including cardiac myocytes. Using a mouse knockout model, the researchers demonstrated that cardiomyocyte-specific deletion of Top2b conferred protection against doxorubicin-induced DNA damage, mitochondrial dysfunction and generation of ROS. In addition, mice lacking the Top2b gene in cardiac muscle did not develop progressive heart failure, whereas those with intact Top2 showed a decrease in EF after doxorubicin exposure. Based on these findings, the investigators are now evaluating the utility of a Top2 blood test in predicting sensitivity to doxorubicin-induced cardiac toxicity. If the Top2 hypothesis is confirmed, one potential alternative to avoid doxorubicin-induced cardiotoxicity could be to develop Top2a-specific anthracyclines that would have maximum antitumor activity without causing cardiotoxicity.

CARDIOPROTECTANTS

Several strategies have been used in an attempt to minimize anthracycline-induced cardiotoxicity. Dexrazoxane is a cardioprotective agent that is currently indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in patients with metastatic breast cancer, who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control. Multiple studies have demonstrated a cardioprotective effect when this agent is used during anthracycline treatment for advanced breast cancer (21–25). In all of these studies, patients who received dexrazoxane had a decreased incidence of CHF compared to those who did not receive the drug. Yet despite these consistent positive findings, the use of dexrazoxane has not been widely adopted. This is due in part to the suggestion from a single study that dexrazoxane may lower response rates, although there was no impact on time to progression (TTP) or overall survival (OS) seen in that trial (23). This finding has not been seen in other studies, and a meta-analysis of five randomized trials ($n = 818$) showed that there was no difference in response rates between control patients and patients receiving dexrazoxane (26).

The mechanism by which dexrazoxane is thought to confer cardioprotection has not been fully elucidated. By binding to the anthracycline–iron complex and removing iron, dexrazoxane may prevent free radical-induced lipid peroxidation of mitochondrial membranes and endoplasmic reticulum (27, 28). However, this theory of iron chelation does not fully explain the cardioprotective mechanism of the drug given the observation that deferasirox, an efficient iron-chelating agent that has been shown to enter myocytes and displace iron from the anthracycline-iron complex, is unable to protect myocytes from doxorubicin damage (19, 28). An alternate hypothesis involves the ability of dexrazoxane to prevent anthracycline binding to Top2. As discussed above, when doxorubicin binds to Top2b in cardiac myocytes, it leads to DNA damage, activation of the apoptotic pathway, and induction of transcriptome change that leads to generation of ROS. Dexrazoxane binds to both Top2a and Top2b, thereby preventing anthracycline binding of Top2 and consequent doxorubicin-induced cell death (29). This hypothesis is supported by the observation that ICRF 161, an analog of dexrazoxane with iron-chelating

properties but lacking activity against Top2, is unable to confer cardioprotection in rat models (30).

REDUCING THE RISK OF TOXICITY

Other strategies to reduce cardiotoxicity have also been evaluated. Continuous infusion of doxorubicin is associated with less cardiac toxicity than bolus infusion (31, 32). However, this schedule is less convenient and hence is not a widely used strategy.

4′-Epidoxorubicin, or epirubicin, is an analog of doxorubicin with equivalent efficacy and less cardiotoxicity on a milligram to milligram comparison (33–36). In a prospective randomized comparison of doxorubicin and epirubicin in patients with breast cancer, epirubicin was associated with a longer median duration of response at 11.9 months compared to 7.1 months with doxorubicin. The cumulative doses at which CHF occurred was 1134 mg/m^2 with epirubicin compared to 492 mg/m^2 with doxorubicin (15). In a meta-analysis of 13 studies comparing doxorubicin with epirubicin, the majority of which included women with advanced or metastatic breast cancer, epirubicin was associated with a significantly decreased risk of clinical cardiotoxicity, subclinical cardiotoxicity, and any cardiac event compared to doxorubicin (32). Epirubicin-induced cardiotoxicity is also dose-dependent (37), and the United States Food and Drug Administration (FDA) recommends a maximum cumulative dose of 900 mg/m^2. However, in an analysis of 1097 patients, the safe maximum cumulative dosage was found to be lower when risk factors such as age, radiation, and underlying cardiac risk factors were taken into consideration (38).

Altering the pharmacokinetic and pharmacodynamic profile of doxorubicin via liposome encapsulation has been an extremely effective strategy to minimize cardiotoxicity and maximize efficacy (39). One formulation of liposomal doxorubicin (Myocet) has polyethylene glycol embedded in the lipid layers, allowing the drug to stay in the liposome until it reaches the target tumor site (40). It is thought that the small size of the liposomes enables the drug to penetrate the compromised vasculature of tumors, allowing preferential delivery of the drug to the target tumor. Pegylation protects the liposome from uptake by the reticular-endothelial system, thereby increasing blood circulation time. Pegylated liposomal doxorubicin (PLD [Doxil/Caelyx]) has a half-life of 73.9 h; this prolonged circulation time enables greater uptake of the drug by tumor. A phase III trial was conducted in 509 women with metastatic breast cancer to compare the efficacy and safety of PLD and conventional doxorubicin in the first-line setting. Response rates, progression-free survival (PFS), and OS were similar in both arms; however, overall risk of cardiotoxicity was significantly higher with conventional doxorubicin than with PLD ($P < 0.001$, HR = 3.16) (41). In a meta-analysis of four studies comparing liposomal doxorubicin with conventional doxorubicin for the treatment of breast cancer or multiple myeloma, liposomal doxorubicin appeared to have similar efficacy to doxorubicin but was associated with significantly less risk of clinical or subclinical cardiotoxicity or any cardiotoxic event (32).

TRASTUZUMAB-INDUCED CARDIOTOXICITY

Approximately 20–25% of breast cancers overexpress the human epidermal growth factor receptor-2 (HER2 or ErbB2) (42, 43). Such overexpression has been associated with more aggressive tumor biology, altered responsiveness to therapy, and poor clinical outcome including shortened survival (44). The development of trastuzumab, a humanized monoclonal antibody that targets the HER2 receptor, has been a major advance in the treatment of HER2-positive breast cancer.

The pivotal trial that led to the FDA approval of trastuzumab in 1998 enrolled 469 patients with previously untreated HER2-positive metastatic breast cancer who were randomized to receive chemotherapy alone (consisting of an anthracycline plus cyclophosphamide in anthracycline-naïve patients or paclitaxel in patients previously treated with an anthracycline) or chemotherapy plus trastuzumab (45). The combination of chemotherapy plus trastuzumab resulted in an improved response rate (50 versus 32%; $P < 0.001$), TTP (median 7.4 versus 4.6 months; $P < 0.001$), and OS (median 25.1 versus 20.3 months; $P = 0.046$) when compared with chemotherapy alone.

An unanticipated serious adverse event that emerged from the study was cardiac dysfunction. The rates of cardiac toxicity in patients randomized to doxorubicin and cyclophosphamide (AC) with trastuzumab versus AC alone were 27 and 8%, respectively, and the rates of cardiac dysfunction in patients who received paclitaxel and trastuzumab versus paclitaxel alone were 13 and 1%, respectively. The incidence of New York Heart Association (NYHA) class III or IV heart failure was highest among patients receiving AC plus trastuzumab: 16%, compared with 3% for patients receiving AC alone, 2% for paclitaxel plus trastuzumab, and 1% for paclitaxel alone. Because the combination of trastuzumab plus doxorubicin resulted in unacceptably high rates of cardiac toxicity, these agents are generally not administered concurrently unless within the context of a clinical trial.

As a result of the above findings, the major adjuvant trials allowed only sequential administration of anthracyclines and trastuzumab (46–54). In addition, patients with abnormal cardiac function were excluded, the cumulative doxorubicin dose was limited to 300 mg/m^2, and strict cardiac monitoring was mandated. The incidence of severe cardiotoxicity (NYHA class III or IV) in the adjuvant trials was modest: 0–4.1% in trastuzumab-treated patients versus 0–1.3% in the non-trastuzumab population (see **Table 2**). A meta-analysis of the five major adjuvant trials reported a 2.5-fold higher risk of cardiotoxicity with trastuzumab (54). Not surprisingly, a higher incidence of cardiotoxicity has been noted in patients also treated with anthracyclines and in patients who received a longer duration of trastuzumab in the adjuvant setting (55, 56).

Risk factors for the development of trastuzumab-related cardiotoxicity include prior or concurrent anthracycline use, age >50 years, pre-existing cardiac dysfunction, use of antihypertensive medication, and higher body mass index (56–59). The risk appears to be highest when trastuzumab is administered concurrently with anthracyclines, mostly when the cumulative dose of doxorubicin exceeds 300 mg/m^2 (60). Cumulative doses up to 180 mg/m^2 may in fact be safe to administer concurrently with trastuzumab (61), although there are no data demonstrating that such an approach would be more effective than sequential administration.

Table 2 | Incidence of trastuzumab-associated cardiac events in adjuvant breast cancer trials.

Trial	Number of patients in analysis	Treatment arm	Incidence of cardiac events (%)	Definition of cardiac event
NSABP B-31 (46, 51)	814	AC → P	0.8	NYHA class III/IV CHF or
	850	AC → PH	4.1	possible/probable cardiac death
NCCTG N9831 (52)	664	AC → P	0.3	Symptomatic CHF or
	710	AC → P → H	2.8	probably/definite cardiac death
	570	AC → PH	3.3	
HERA (53)	1744	Chemotherapy	0.1	NYHA class III/IV CHF with decrease
	1682	Chemotherapy + 1 year of Trastuzumab	0.8	in LVEF ≥10% from baseline to LVEF
	1673	Chemotherapy + 2 years of Trastuzumab	1.0	<50%; or cardiac death
BCIRG 006 (48)	1073	AC → T	0.7	NYHA class III/IV CHF
	1074	AC → TH	2	
	1075	TCH	0.4	
FinHer (95)	116	Chemotherapy	1.7	Symptomatic heart failure
	115	Chemotherapy + Trastuzumab	0.9	

AC, doxorubicin + cyclophosphamide; P, paclitaxel; H, trastuzumab; T, docetaxel; C, carboplatin.

MECHANISM OF TRASTUZUMAB-INDUCED CARDIOTOXICITY

Unlike anthracycline-induced cardiotoxicity, trastuzumab-related cardiotoxicity is classified as Type II and is clinically and mechanistically distinct (62). Type II cardiotoxicity is not dose-dependent, is highly reversible, and is not associated with ultrastructural changes. This was demonstrated in a study of 38 patients with suspected trastuzumab-related cardiotoxicity, all of whom had received prior doxorubicin (63). Mean LVEF prior to initiation of trastuzumab was 61%, decreased to 43% after trastuzumab, and increased to 56% after withdrawal of trastuzumab. Increases of LVEF were seen in 37 out of the 38 patients and mean time to recovery was 1.5 months. Six of the patients recovered without medical treatment. Nine patients underwent endomyocardial biopsy and the ultrastructural changes typical of anthracycline damage were not seen. The absence of such changes on biopsy demonstrates that the mechanism by which trastuzumab induces cardiac dysfunction is different from anthracyclines and is likely due to myocardial stunning or hibernation.

The pathogenesis of trastuzumab cardiotoxicity is not completely understood. The HER2 signaling pathway is essential for cardiac development and function (64), and mouse models lacking HER2 exhibit multiple characteristics of dilated cardiomyopathy, including chamber dilation, wall thinning, and decreased contractility (65). HER2 signaling is upregulated in animal models when the myocardium is under stress (66) Binding of trastuzumab to HER2 is thought to disrupt HER2-HER4 heterodimerization, thus disabling the protective mechanisms in the cardiac myocyte that are essential during exposure to adverse conditions or cardiac toxins (67). This hypothesis is consistent with the observation that increased cardiac toxicity is seen when trastuzumab is used in association with anthracyclines. Indeed, HER2-deficient cardiac myocytes are more susceptible to anthracycline-induced damage (65, 68). Activation of HER2 signaling by neuregulin-1 has been shown to improve cardiac myocyte function and survival, and upregulation of this pathway in the heart may be a potential therapeutic approach (69).

CLINICAL USE OF TRASTUZUMAB

The risk of cardiac toxicity with trastuzumab needs to be considered within the clinical context. In the metastatic setting, the benefits conferred by the addition of trastuzumab often outweigh the potential cardiac risks. On the other hand, in the early-stage setting, a significant number of patients will be cured with local therapy alone and may not in fact require adjuvant systemic therapy. However, since it is not currently possible to identify these patients, adjuvant therapy is offered to many who may not in fact derive benefit. One must therefore be especially judicious when selecting an adjuvant regimen, which may expose a patient to unnecessary toxicities, including CHF.

Because of the increased risks of cardiac toxicity seen with both the anthracyclines and trastuzumab, there has been much interest in the development of non-anthracycline-containing trastuzumab regimens. Of the pivotal adjuvant trastuzumab trials, Breast Cancer International Research Group (BCIRG) 006 was the only one to include a non-anthracycline-containing arm (48). In this study, 3222 patients with HER2+ breast cancer were randomized to receive AC followed by docetaxel (AC-T), AC-T plus trastuzumab initiated concurrently with docetaxel (AC-TH), or docetaxel + carboplatin + trastuzumab (TCH). No significant differences in DFS and OS were found between the two trastuzumab regimens. However, there were significant differences in the incidence of CHF: 0.4% in the AC-T arm, 2.0% in the AC-TH arm, and 0.7% in the TCH arm. In addition, AC-TH was associated with a significantly increased risk of persistent decline in EF at 4 years compared to TCH.

A recent retrospective population-based cohort study evaluated the long-term risk of heart failure (in this case defined as hospitalization or two ambulatory visits within 12 months)

associated with adjuvant trastuzumab and chemotherapy (70). Women included in this study were diagnosed with early-stage breast cancer between 2003 and 2009. Those with metastatic breast cancer or a pre-existing diagnosis of heart failure were excluded. 19,074 women treated with chemotherapy were identified, of whom 18% also received adjuvant trastuzumab. After a median follow-up of 5.9 years, investigators found that adjuvant trastuzumab was associated with an increased risk of heart failure (5.3 versus 2.6%, $P < 0.0001$). However, the increased risk was seen only within the first 1.5 years of treatment (HR = 5.77, 95% CI 4.38–7.62, $p = 0.0004$); thereafter, there was no difference in the risk of developing CHF between women treated with trastuzumab plus chemotherapy and those treated with chemotherapy alone (HR = 0.87, 95% CI 0.57–1.33, $p = 0.53$). These data are reassuring in that the risk of trastuzumab-associated cardiotoxicity appears to be limited to the period of active treatment.

No evidence-based guidelines exist for cardiac monitoring while on trastuzumab therapy. The FDA-approved manufacturer's package insert recommends that a baseline assessment of cardiac function be performed prior to the initiation of therapy and LVEF measurements should be repeated every 3 months during and upon completion of therapy (71). If trastuzumab is withheld for significant cardiac dysfunction, LVEF measurement should be repeated at 4-week intervals. In the adjuvant setting it is recommended that LVEF be assessed every 6 months for at least 2 years following completion of therapy. In the metastatic setting, however, symptom-triggered evaluation of LVEF may be more appropriate given the risk-benefit ratio.

Trastuzumab should be held for 4 weeks if LVEF declines ≥16% from baseline or if there is a ≥10% decrease in LVEF from baseline to below the lower limit of normal. Treatment may be restarted if LVEF returns to normal within 4–8 weeks. Trastuzumab should be discontinued in the presence of symptomatic heart failure.

CARDIOVASCULAR RISK WITH OTHER HER2-DIRECTED THERAPIES

Lapatinib is a reversible small tyrosine kinase inhibitor that targets both the epidermal growth factor receptor (EGFR or HER1) and HER2. It is indicated for use in combination with capecitabine for the treatment of metastatic HER2+ breast cancer after progression on an anthracycline, taxane and trastuzumab. In the phase III trial that led to its approval, asymptomatic declines in EF occurred in 4 of 164 (2.4%) of patients receiving lapatinib plus capecitabine versus 1 of 152 (0.7%) of patients receiving capecitabine alone. All four patients who experienced a cardiac event on lapatinib recovered and there were no symptomatic events (72) (see **Table 3**). It is important to note that the patients in this trial were highly selected as all had previously received trastuzumab and cardiac dysfunction was an exclusion criterion.

In a retrospective analysis of 3689 patients with various solid tumor types treated with lapatinib, only 1.6% of patients developed a cardiac event (73). Similar rates of cardiotoxicity were noted in patients who were pretreated with anthracyclines or trastuzumab compared to those who were not pretreated. Most of the cardiac events were usually asymptomatic and reversible, indicating a Type II cardiac toxicity. More recently, data were presented from the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial in which patients with early-stage HER2+ breast cancer were randomized to receive adjuvant chemotherapy with trastuzumab, chemotherapy with concurrent trastuzumab and lapatinib, or chemotherapy with sequential trastuzumab and lapatinib (74). The incidence of NYHA Class III/IV heart failure was <1% in all arms, with 97% of all patients having received an anthracycline.

Pertuzumab is a humanized monoclonal antibody that binds to HER at its dimerization subdomain. When combined with trastuzumab and docetaxel in the first-line setting for metastatic HER2+ breast cancer, there was an improvement in PFS and OS compared to trastuzumab and docetaxel (75). Interestingly, in a cardiac analysis of the trial, left ventricular dysfunction was numerically higher in the control arm (8.3 versus 4.4% for all grades). Declines in EF of at least 10% from baseline to <50% occurred in 6.6 versus 3.8% of patients in the placebo and pertuzumab arms, respectively (76). Thus the combination of both antibodies did not increase the risk of cardiac adverse events.

Table 3 | Incidence of cardiac events with other HER2-directed therapies.

Trial	Number of patients in analysis	HER2-directed therapy	Incidence of cardiac events (%)	Definition of cardiac event
Geyer et al. (72)	161	Capecitabine	0.7	Symptomatic decline in LVEF or decrease ≥20% from baseline to below institution's lower limit of normal
	163	Lapatinib plus Capecitabine	2.4	
ALTTO (74)	2097	Trastuzumab alone	0.86	NYHA Class III/IV CHF or cardiac death
	2091	Trastuzumab followed by Lapatinib	0.25	
	2093	Trastuzumab concurrent with Lapatinib	0.97	
CLEOPATRA (76)	397	Trastuzumab + docetaxel plus placebo	6.6	LVEF decline to <50% with decrease ≥10% from baseline
	407	Trastuzumab + docetaxel plus Pertuzumab	3.8	
EMILIA (77)	445	Lapatinib + capecitabine	1.6	LVEF decline to <50% with decrease ≥15% from baseline
	481	T-DM1	1.7	

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate which combines trastuzumab with the cytoxic agent emtansine. The EMILIA trial randomized 991 patients with advanced breast cancer previously treated with trastuzumab and a taxane to TDM-1 versus lapatinib plus capecitabine. Results demonstrated an improvement in PFS and OS with T-DM1 compared to lapatinib plus capecitabine. Cardiotoxicity was 1.7% with T-DM1 versus 1.6% in the other arm (77).

CARDIOVASCULAR RISK WITH BEVACIZUMAB

In recent years, there has been considerable interest in the use of antiangiogenic agents for the treatment of various cancers. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), was initially granted accelerated approval in 2008 for metastatic breast cancer based on impressive results in the first-line setting when combined with paclitaxel (78). However, while subsequent trials in the first-line metastatic setting confirmed a benefit in PFS, the magnitude of benefit was small, and no OS benefit was shown in any of the studies (79, 80). Three subsequent large adjuvant studies also failed to demonstrate a benefit in DFS or OS and consequently the FDA withdrew approval for bevacizumab in 2011. Nevertheless, as this agent is still used widely in other types of solid tumors, familiarly with its potential cardiac toxicities is important.

A meta-analysis of 5 randomized trials in metastatic breast cancer showed a statistically significant increased risk in grade 3 or higher hypertension (9.71 versus 0.64%, OR = 12.76) and left ventricular dysfunction (1.73 versus 0.78%, OR = 2.25) in patients treated with bevacizumab compared to those who did not receive the drug (81). Similar increased risks were also seen in other studies, including the three adjuvant trials (82–84). The mechanism of bevacizumab-induced hypertension is not known but may be related to nitric oxide: VEGF is thought to increase production of nitric oxide, resulting in vasodilation (85). Inhibition of nitric oxide by bevacizumab therefore leads to vasoconstriction and consequent hypertension. The mechanism of CHF is also unclear, but the development of secondary hypertension itself could be a contributing factor.

BIOMARKERS

Current methods for detecting cardiotoxicity rely on evaluation of LVEF by either echocardiography or Multiple Gated Acquisition (MUGA) scan. However, by the time a decrease in EF is detected there has already been considerable myocardial damage. There is therefore a need to develop biomarkers that enable the early identification of cardiac deterioration. Such a strategy would allow for the implementation of preventive measures prior to the development of functional impairment.

Cardiac troponins I (cTnI) and T (cTnT) are sensitive and specific biomarkers of myocardial damage, whereas B-type natriuretic peptide (BNP) is a marker of volume overload. These markers have been studied as potential indicators of treatment-related cardiotoxicity.

In a study of 204 patients with a variety of malignancies receiving high-dose chemotherapy, investigators measured levels of cTnI in the plasma after every cycle. Patients were divided into troponin positive (cTnI+) and troponin negative (cTnI−) groups. In the cTnI− group, LVEF decreased transiently after chemotherapy, with a nadir after 3 months, but later recovered. On the other hand, patients in the cTnI+ group sustained greater reductions in LVEF, and the declines persisted even at the end of 7 months' follow-up (86). The same group of investigators also evaluated the significance of persistent elevations in cTnI+ and found that patients treated with high-dose chemotherapy who had persistent increases in cTn1 had a higher incidence of cardiac toxicity (85%) compared to patients with transient increases (37%) or who had no elevation in cTn1 (1%) (87). Similarly, persistent proBNP elevation following chemotherapy has been associated with significantly lower LVEF (88). Given the heterogeneity of the study populations, however, definitive conclusions cannot be drawn at this time and more research is needed to determine whether these findings can be replicated.

TREATMENT AND PREVENTION OF LV DYSFUNCTION

Beta-blockers and angiotensin converting enzyme (ACE) inhibitors are standard treatments that have been shown to improve outcomes in patients with heart failure from a variety of etiologies. Treatment of cardiac dysfunction resulting from antineoplastic therapy follows the general cardiology guidelines for heart failure, although this practice seems to be based primarily on extrapolation rather than on evidence specifically addressing heart failure in the cancer population.

In a study of 201 consecutive patients with anthracycline-induced CHF with LVEF ≤45%, enalapril and, when tolerated, carvedilol were initiated as soon as LVEF impairment was detected (89). The investigators found that time elapsed from the end of chemotherapy to the start of heart failure therapy was a crucial variable for recovery of cardiac function. Among patients treated within 2 months after the end of chemotherapy, 64% had a complete recovery of LVEF. After 2 months, however, the percentage of patients decreased, with no complete recovery seen after 6 months.

There has been significant interest evaluating the role of beta-blockers and ACE inhibitors as prophylactic agents in patients who are at risk of developing treatment-related cardiotoxicity. In a study that enrolled 50 patients receiving anthracycline therapy for a variety of cancers, patients were randomized to receive prophylactic carvedilol or placebo (90). Baseline LVEF was similar in both groups prior to initiation of chemotherapy. At 6 months of follow-up, one patient in the carvedilol group had EF < 50% compared to five patients in the control group. The mean EF in the carvedilol group remained unchanged at the end of follow-up (70.5 versus 69.7%) but was significantly lower in the control group (68.9 versus 52.3%). However, there were some discrepancies in the reported anthracycline doses used in the study and caution should therefore be exercised when interpreting these data.

In a trial by Cardinale et al., 114 patients receiving high-dose chemotherapy and deemed at high risk for cardiotoxicity based on troponin I elevation were randomized to receive the ACE inhibitor enalapril or not (91). Enalapril was started 1 month after chemotherapy and continued for 1 year. The primary endpoint was an absolute decrease of >10% in LVEF, with a decline below the lower limit of normal. Forty-three percent of patients in

the control arm met the primary endpoint, compared to none in the treatment group ($P < 0.001$). These results suggest that in patients with evidence of early cardiac damage as measured by elevated troponin I values, early institution of ACE inhibitor therapy may prevent the progression of cardiac toxicity. The prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA) trial is an ongoing randomized, placebo-controlled study evaluating the role of beta-blockers and ACE inhibitors in preventing cardiac dysfunction during adjuvant breast cancer therapy (92).

LACK OF CLINICAL GUIDELINES

Unfortunately, the American College of Cardiology and the American Heart Association have not provided any guidelines for the detection, prevention, monitoring, or treatment of cardiotoxicity from antineoplastic therapy. All patients receiving potentially cardiotoxic anticancer drugs are considered candidates for Stage A heart failure, meaning they are at increased risk of developing cardiac dysfunction (93). The European Society of Medical Oncology has published a comprehensive set of clinical practice guidelines for the management of patients with cardiotoxicity from chemotherapy, targeted agents, and radiation (94). A similar consensus statement from the major American cardiology societies would be extremely helpful to practicing clinicians to ensure maximal anticancer benefits from therapy with minimal cardiac complications.

CONCLUSION

While much progress has been made in the treatment of breast cancer, cardiac complications resulting from therapy remain a significant concern. Both anthracyclines and novel targeted agents can inflict cardiac damage, although the mechanisms by which they do so and their clinical manifestations appear to be distinct. The challenge for the future will be to develop methods for early detection of cardiac dysfunction, identify strategies for prevention and treatment of cardiotoxicity, and establish clinical guidelines for practicing physicians. Many questions remain unanswered, and ongoing research and collaboration between oncologists and cardiologists are needed to ensure optimal efficacy and safety of current and future anticancer agents.

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