Cardiovascular Toxicities of Radiation Therapy

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ABSTRACT: As cancer survival outcomes improve, there is a growing focus on survivorship and long-term morbidity after cancer treatment. In particular, there has been concern about the long-term effects of radiotherapy on cardiac function. In this review, we discuss the cardiac effects of radiotherapy in the context of potential confounding factors, examine the potential parameters of interest when studying and modeling cardiac injury, highlight current treatment techniques to minimize radiation to the heart, and consider future areas of improvement and study.

INTRODUCTION

As cancer survival outcomes continue to improve, there is increasing concern about the long-term side effects from cancer treatment. All modalities of cancer treatment (surgery, systemic therapy, and radiotherapy) are associated with long-term morbidities that are magnified the longer a patient lives. For radiotherapy (RT), there has been significant concern about the long-term cardiac effects. However, determining the absolute risks of cardiac dysfunction has been difficult. Long-term studies were conducted when older techniques were used. Since then, substantial improvements have made newer RT techniques and technologies ubiquitous.

This review discusses historical data on the cardiac effects of RT as well as more contemporary literature from the modern RT era, with the acknowledgement of potential confounding factors. In addition, we explore the potential parameters of interest when studying/modeling cardiac injury. Finally, we review current treatment techniques to minimize RT exposure to the heart and examine potential future directions for improvement.

PHYSIOLOGY OF RADIATION-INDUCED HEART DISEASE

Radiotherapy exerts its cardiac effects through different mechanisms, depending on the specific cardiac structure affected. Pathologically, its effect on the coronary vessels appears similar to atherosclerosis.[1] Radiation injury to the coronary endothelial cells causes oxidative injury and release of proinflammatory/profibrotic cytokines, which in turn leads to collagen deposition and proliferation of endothelial cells, smooth muscle cells, and myofibroblasts.[2–4] Radiotherapy can also affect the myocardium, inducing microvascular damage that results in proinflammatory changes and eventual myocardial cell death.[1,5] Consequently, myocardial tissue is eventually replaced with fibrotic tissue consisting of proliferating collagen bands.[1,5] These changes can ultimately result in cardiac ischemia, congestive heart failure, and cardiac wall motion abnormalities visible on echocardiogram.[6] Electrical conduction abnormalities may also be seen, including arrhythmias, conduction blocks, and dysfunction in the autonomic nervous system.[7]

The pericardium is another cardiac structure susceptible to RT damage. Pericarditis is a known complication of RT that can present in the acute or chronic setting. Acute pericarditis is characterized by a pericardial exudative effusion in the pericardial sac. This can manifest clinically as pleuritic chest pain, tachycardia, and even cardiac tamponade. Chronic pericarditis is characterized by fibrin deposition in the pericardial space, leading to collagen deposition and pericardial fibrosis.[1,5] The most severe form of chronic pericarditis is constrictive pericarditis, which typically presents 10 or more years after radiotherapy.[8] The definitive treatment is pericardial stripping or pericardiectomy, although it is associated with poor outcomes.[9]

Valvular disease characterized by fibrosis and calcification is another possible consequence.[10] The exact incidence of radiation-induced valvular disease is unclear, but one report indicated that clinically significant disease was especially likely at doses above 30 Gy.[11] It can lead to either stenosis or regurgitation and is commonly seen in the aortic valve more than in the mitral or right heart valves.[1] For patients with clinically significant aortic valve disease, surgical replacement has been associated with improved survival regardless of cancer status.[12] Minimally invasive techniques, such as transcatheter aortic valve replacement and MitraClip procedures, may provide relief for patients who are poor surgical candidates.

LARGE-SCALE EVIDENCE OF RADIOTHERAPY EFFECTS

Breast Cancer

Much of the literature on RT's cardiac effects is based on the experience of treating patients with breast cancer, the most common noncutaneous malignancy in women. The fact that

RT is a primary therapy for breast cancer allows for analysis of a large patient population.[13] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has published several meta-analyses of clinical trials examining the benefits and risks of RT for breast cancer. A 2000 EBCTCG report of trials prior to 1990 showed that RT after either breast-conserving surgery or mastectomy reduced local recurrences and breast cancer mortality compared to no RT. However, all-cause mortality was not improved because of an increase in vascular mortality with RT.

A 2005 EBCTCG update found that the irradiated group had a 27% increase in mortality from heart disease compared to the nonirradiated group.[14] However, the effect of this increased cardiac mortality had to be weighed against the benefits. After mastectomy, there was a difference in RT effects for node-positive versus node-negative patients.[14] For node-positive mastectomy patients, RT decreased rates of local recurrence at 5 years and of breast cancer and overall mortality at 15 years. However, for node-negative mastectomy patients, RT decreased local recurrence rates at 5 years but did not improve breast cancer mortality or overall mortality at 15 years.[14] This lack of survival benefit was attributed to the increase in cardiac mortality.

Comparing the effects of breast tumor laterality further suggests the impact of RT on cardiac mortality. Because the heart is on the left side of the thorax, RT fields for cancer in the left breast may include a portion of the heart (depending on an individual patient's anatomy). A Surveillance, Epidemiology, and End Results (SEER) database study found that cardiac mortality after breast RT was higher for patients with left-sided breast tumors compared to right-sided tumors.[15] Since there was no difference in cardiac mortality for left versus right breast tumors in patients who did not receive RT, the increase in cardiac mortality for left-sided tumors was attributed to RT.

Further efforts were made to quantify the effect of RT on cardiac mortality. An EBCTCG analysis found that the risk of death from heart disease increased by 3% per Gy of the mean heart dose.[16] A population-based study of more than 2,000 women in Denmark and Sweden by Darby et al. found that major coronary events increased by 7.4% per Gy of the mean heart dose, regardless of the presence of cardiac risk factors.[16] The increase started within the first 5 years after RT and continued into the third decade. However, this study was limited by use of older treatment techniques and lack of individual patient data. Prototypical patient anatomy was used to generate estimates and is a major criticism of this study. Using the Darby et al. model and incorporating individual patient anatomy data, Crijns et al. found that cardiac risk increased by 16.5% per Gy of mean heart dose in the first 9 years after RT.[17]

Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is another malignancy with a well-documented connection between RT and cardiac effects. HL is a relatively common malignancy in young adults and has an excellent prognosis.[18] As a result, survivors are likely to exhibit the long-term morbidities associated with treatment. Traditionally, HL was treated with RT alone via expansive mantle fields that included the cervical, supraclavicular, axillary, mediastinal, and pulmonary hilar lymph nodes and resulted in significant doses to the heart. Studies following patients treated with this technique found a relative risk of 3.1 for cardiac death and 55.2 for acute myocardial infarction.[19,20] Younger age (< 20 years) and higher doses (> 30 Gy) were associated with higher risk.[19] A case-control study of more than 2,600 HL survivors treated between 1965 and 1995 found that the risk of coronary heart disease increased linearly by 7.4% per Gy mean heart dose (similar to what was seen in breast cancer).[21] Pre-existing risk factors for coronary heart disease independently increased this risk.

As systemic therapy improved, the treatment paradigm shifted to combined treatment with both chemotherapy and RT. This allowed for lower RT doses and smaller RT fields that dramatically reduced mean heart dose. It should be noted, however, that the systemic therapy for HL is anthracycline, which may carry additional cardiac toxicity. Despite this, longitudinal studies found substantially lower rates of cardiac death and dysfunction.[22,23] A cohort of 1,100+ patients were followed across different dose regimens.[23] Patients treated with doses as high as 36 Gy had a 10% cumulative incidence of cardiac disease at 25 years, whereas doses of 20 Gy and 30 Gy had risks of 5% and 6%, respectively. Early follow-up of a trial of 1,500+ patients using more contemporary techniques (doses of 20-30 Gy and smaller RT fields) found that the risk of cardiac death ranged from 0.6% to 1.4%.[22]

Even more restrictive RT field techniques have since been adopted, with promising results.[24] Additional longitudinal data is needed to confirm that these techniques further reduce the risk of heart disease while maintaining strong disease control.

Lung Cancer

The cardiac effects of RT when treating lung cancer have not been well studied. Patients with lung cancer often present with locally advanced unresectable disease; as a result, survival outcomes have remained dismal.[25] It has been suggested that the long-term cardiac manifestations of RT are not well

documented due to the comparatively poor prognosis in these patients. However, with continued improvements in survival outcomes, there is growing concern about late cardiotoxicity in patients with lung cancer.[26]

The relevance of long-term cardiac toxicity in lung cancer came into focus in the Radiation Therapy Oncology Group (RTOG) 0617 trial,[27] a phase III randomized trial examining the benefit of dose-escalated RT for non-small cell lung cancer (NSCLC). Previous phase II trials suggested an improvement in tumor control with dose escalation, and the RTOG 0617 trial aimed to confirm these findings.[28] Unexpectedly, the dose-escalated arm actually demonstrated worse overall survival.[27] On multivariable analysis, increased dose to the heart also was found to be associated with worse survival, leading to the belief that cardiotoxicity was at least partially responsible for the worse outcomes seen in the dose-escalated arm.[27]

These results stimulated further investigation of RT-induced cardiac effects in lung cancer. An analysis of patients with locally advanced NSCLC who were treated on four prospective RT therapy trials found that the 24-month cumulative incidence of grade ≥ 3 cardiac events exceeded 10%.[29] On multivariable analysis, pre-existing cardiac disease and higher mean heart dose were associated with higher rates of cardiac events. In a subset of patients without pre-existing cardiac disease, increased mean heart dose remained significantly associated with grade ≥ 3 cardiac events.

Heart-Directed Radiotherapy

Radiation may be directed to the heart to treat specific cardiac conditions. Intravascular brachytherapy (IVB) is an established technique that uses intracoronary gamma/beta radiation (directed via an endovascular catheter) to reduce endothelial proliferation after percutaneous stent placement. It was first introduced due to significant rates of in-stent restenosis after successful intracoronary stent implantation. Clinical studies using this technique demonstrated decreases in the rates of angiographic and clinical in-stent restenosis.[30] Furthermore, acute toxicity was minimal, with a decreased rate of cardiac events in the RT groups. There was a trend in late thrombosis seen in the RT groups,[30] possibly due to the lack of prolonged antiplatelet therapy that has now become standard of care for stent placement.[31]

Over time, however, IVB was used less frequently in lieu of drug-eluting stents (DES), which significantly lowered the rates of in-stent restenosis compared to bare metal stents.[32] However, IVB may still be an option for patients who fail treatment with multiple overlapping DES. In a matched cohort, IVB led to significantly lower rates of major cardiac events in patients with multilayered DES restenosis when compared with other percutaneous options.[33] There was no increase in death, myocardial infarction, or stent thrombosis seen with IVB in these patients. As a result, IVB may serve as an effective option for patients with multilayered DES restenosis, especially since few good treatment options exist.

Radiotherapy in the form of external stereotactic body radiation therapy (SBRT) is being explored in the treatment of cardiac arrhythmias. SBRT delivers high-dose ablative RT precisely to targets in the body with minimal damage to nearby normal tissues.[34] Combined with noninvasive cardiac imaging methods, such as cardiac magnetic resonance imaging and computed tomography,[35] SBRT (delivered as 25 Gy in a single fraction) may allow for noninvasive ablation of abnormal electrical substrates in the heart. Animal studies showed effective results without evidence of acute/subacute injury.[35] Initial case reports demonstrated efficacy with no evidence of acute or late toxicity. In a case series of five patients, SBRT reduced episodes of ventricular tachycardia by 99.9%.[35] No complications occurred during the treatment or hospital stay, and treated patients were discharged home 1 to 3 days after treatment. No late effects were seen with treatment, although there were inflammatory changes seen in nearby lung tissue that resolved by 12 months. SBRT may serve as a noninvasive means of treating cardiac arrhythmias, making it an attractive option for patients at high risk of complication from invasive interventions. There does not appear to be significant toxicity with this technique, but further study is needed to determine the long-term clinical effects, and it should only be attempted in the setting of a clinical trial.

CONFOUNDING FACTORS

Older Radiotherapy Techniques

Substantial improvements in RT techniques have occurred over the last half century. Radiotherapy equipment has improved from older orthovoltage and cobalt machines to higher energy megavoltage linear accelerators, which allow for a lower integral dose to normal structures. Other improvements in RT delivery, including the use of multileaf collimators and field-in-field techniques, have allowed for enhanced control of radiation delivery.

Improvements in imaging, dose calculations, and disease knowledge have also resulted in reduced doses. Imaging improvements ushered in the transition from 2-dimensional (2D) imaging with plain film x-rays to 3D imaging with computed tomography. Three-dimensional imaging at the time of treatment planning enhanced visualization of the entire heart. Combined with improved dose/therapy calculations using computerized modeling software, the improvements in imaging allowed

physicians to measure the actual dose being received by the heart.

The increase in clinical knowledge has resulted in decreased doses to the heart. For example, older field designs for breast cancer included coverage of the internal mammary and supraclavicular nodal regions, even for patients at low risk of nodal involvement. For lymphoma, treatment shifted from RT alone (with larger fields and higher doses) to combined modality treatment with chemotherapy and RT (smaller fields and lower doses). Better understanding of which patients benefit from additional RT doses/coverage yielded risk-adapted treatment options; only patients at risk for recurrence and cancer mortality are treated with more aggressive RT.

With these improvements, radiation oncologists are now able to customize a treatment plan based on an individual patient's anatomy and minimize dose to the heart. There is evidence that these improvements have resulted in reductions in cardiotoxicity. A SEER-Medicare analysis of breast cancer patients from 1973 to 1989 found that the absolute risk of left breast cardiac mortality decreased with each period, from 13% (1973-1979) to 9.5% (1980-1984) to 5.8% (1985-1989).[36]

Systemic Therapy

Systemic chemotherapy also has cardiotoxic effects that may confound the effects of RT. Anthracycline chemotherapy has a prominent role in the treatment of breast cancer and is a mainstay of treatment in HL, but it has well-documented cardiotoxic effects.[37] In an insurance database study of 16,000+ breast cancer patients, 4.6% of patients receiving anthracyclines developed heart failure at a median of 8 months compared to 4% for those not receiving anthracyclines ($P = .048$).[38] The hazard ratio was 1.53 for anthracyclines; other risk factors included increased Charlson/Deyo comorbidity scores, hypertension, and valvular disease.

Almost all patients with HL receive an anthracycline-based regimen. In an analysis of nine randomized trials of more than 6,000 patients treated with anthracyclines and RT, both mean heart radiation dose and cumulative dose of anthracyclines were significant predictors of cardiovascular disease.[39]

Breast cancer patients include patients that express HER2. HER2-targeted therapy (eg, trastuzumab) can result in cardiac dysfunction. However, unlike with anthracyclines, cardiotoxicity for trastuzumab is not dose dependent and is often reversible with treatment discontinuation because it causes dysfunction rather than necrosis.[40] In an insurance database study of roughly 16,000 breast cancer patients, the rate of heart failure among those treated with trastuzumab was 8.3% compared with 2.7% for those who were not treated with trastuzumab (HR 2.01, $P < .001$). The introduction of trastuzumab after anthracyclines has been found to further increase these risks.[41] Since HER2-targeted therapy is a relatively new treatment option, it is unclear how the combination of trastuzumab, anthracyclines, and RT would affect the risks of heart disease.

Pre-Existing Comorbidities

Across all malignant diagnoses, pre-existing comorbidities and cardiac risk factors have been found to independently increase the risk of heart disease. In a study of breast cancer patients from Denmark and Sweden, women with other previous circulatory diseases, diabetes, chronic obstructive pulmonary disease, tobacco use, or high body mass index had a higher rate ratio of radiation-induced heart disease (1.92).[42] In a systematic literature review of roughly 40,000 breast cancer patients, continued smoking increased the risk of RT-related cardiac mortality compared to nonsmokers or former smokers (8% vs 1.8%, respectively).[43]

In a cohort of HL survivors in the Netherlands, smoking, hypertension, diabetes, and hypercholesterolemia all increased the risk of cardiovascular disease in addition to the effects of RT and anthracyclines.[44] A different case-control study of HL survivors found that the risk of coronary heart disease after chemoradiation was independently increased when patients had risk factors for coronary heart disease (diabetes, hypertension, hypercholesterolemia).[21]

In NSCLC, both pre-existing cardiac disease and mean heart dose were associated with higher rates of cardiac events on multivariable analysis of multiple clinical trials.[29] However, even when removing patients with pre-existing cardiac disease, increased mean heart dose remained significantly associated with grade ≥ 3 cardiac events. In a separate analysis of radiation dose-escalation trials for NSCLC, coronary artery disease was associated with increased risk of cardiac events on univariable analysis.[45] Unfortunately, this was not examined independently on multivariable analysis.

RADIATION DOSE PARAMETERS

Typically, mean heart dose has been the parameter of interest when discussing RT dose to the heart. However, mean heart dose may be acting as a surrogate for radiation dose with regard to specific cardiac substructures. If the dose to specific substructures is elevated, the mean heart dose will generally also be elevated. On the other hand, it is possible that the mean dose to the entire heart may be low, but specific structures (such as the coronary vasculature) may be receiving

high doses that may predispose a given patient to cardiotoxicity. For example, in a dosimetric study of 50 patients with left-sided breast cancer, there was excellent correlation between mean heart dose and left anterior descending (LAD) artery dose.[46] However, for every 1 Gy increase in mean heart dose, the mean LAD dose increased by 4.82 Gy, indicating that mean heart dose may potentially be serving as a surrogate for LAD dose.

Conversely, the review by Darby et al. found that coronary artery doses were not significantly associated with the rate of ischemic heart disease events after the mean whole heart dose was taken into account.[16] Again, this model used prototypical patient anatomy and did not account for individual patient data. It is clear that the dose to the LAD and coronary vasculature can vary from patient to patient (due to individual anatomic variation)[47] or even from treatment to treatment for one patient (due to setup/positioning errors caused by breathing and heartbeats).[48]

It is also possible that the dose delivered to different cardiac substructures may predict different types of cardiotoxicity. In a review of 125 HL patients, a whole heart model of dose outperformed a coronary artery model when all types of cardiotoxicity (including pericardial disease, conduction disorders, valvular disease, and ventricular function abnormalities) were evaluated.[49] However, when looking at events due to ischemic cardiotoxicity, the coronary artery-based model was superior to the whole heart model.

Clearly, further research is needed to fully elucidate the parameters most predictive of cardiac dysfunction. In the meantime, it appears reasonable to record both the dose to the whole heart as well as to specific cardiac substructures to allow for comprehensive data collection and subsequent analysis.

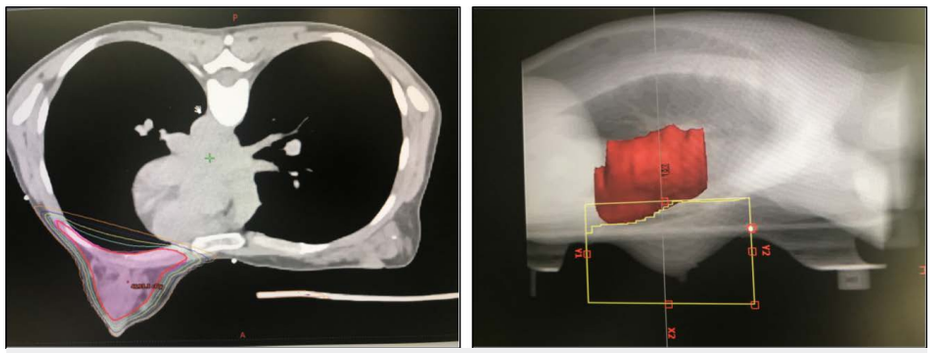

Figure 1.
Prone breast positioning increases separation of the breast from the chest wall to allow for decreased dose to the heart and lung in a majority of patients with left-sided breast tumors. Custom cardiac blocks further reduce heart dose.

TECHNIQUES TO REDUCE RADIATION DOSE TO THE HEART

There are multiple techniques to minimize RT dose to the heart. The use of a breast board for patients with breast cancer improves the angle of treatment along the chest wall to minimize the dose to the heart anteriorly, reducing the mean heart dose by as much as 60%.[50] Patients may also be placed in the prone position to reduce dose to the heart, particularly for large-breasted patients (Figure 1). A study by Formenti et al. found that prone positioning decreased heart volume in the treatment field in 85% of patients.[51] In addition, gating and breath hold techniques allow for RT delivery only when the most minimal heart volume is present in the field. A dosimetric study found that gating may reduce cardiac volumes by approximately 80%.[52]

Advanced RT technologies have also led to decreased heart doses. Intensity-modulated radiotherapy uses multiple beam angles and intensities to maximize dose coverage of the tumor and minimize dose to normal structures. Proton therapy is a more advanced technology that uses proton particles to treat the tumor target without the exit dose seen with traditional x-ray photons, decreasing the dose to the heart and other normal structures.[53] However, proton therapy is not yet widely available due to high capital and operational expense. Further study is needed to determine if the reduced RT doses to the heart achieved with these advanced technologies actually result in clinically meaningful benefits.

FUTURE DIRECTIONS

There are multiple avenues for more robust study and improvement. Further collection of survivorship data using modern RT techniques will allow for improved patient counseling regarding the risks and benefits of RT. Continued advancements in RT technology may produce additional decreases in dose to the heart and its substructures. Advances in imaging technology may allow for better targeting of RT or earlier detection of RT-induced heart disease. Analysis of current imaging datasets using machine learning algorithms may help detect patterns unseen by individual researchers. In addition, early involvement of cardio-oncology specialists in the care of patients receiving thoracic RT may accelerate the early detection, intervention, and optimization of pre-existing cardiac risk.

On the biological side, improvements in genomics analysis may help identify

patients at higher risk for radiation-induced heart disease. Likewise, further research into biomarkers of cardiotoxicity may lead to earlier detection and treatment. For patients already with significant cardiac dysfunction, development of advanced treatment and recovery options may hasten the recovery and healing of damaged heart tissue.

CONCLUSIONS

Radiation therapy has known deleterious effects on the heart, but the risks of RT have diminished with time. Advances in RT technology, imaging technology, and clinical knowledge have helped spare the heart and its substructures from excessive dosing, with resultant decreases in the rates of cardiotoxicity. Current treatment techniques have minimized cardiac risks, and future advances will continue to improve the therapeutic window of RT for cancer patients.

KEY POINTS

- Radiation therapy has known long-term effects on the heart; however, the risks of radiotherapy have diminished over time.
- Advances in radiotherapy techniques have allowed for increased sparing of the heart and its substructures, with resultant decreases in the rates of cardiotoxicity.
- Future advances in radiotherapy (and medicine as a whole) will continue to improve the therapeutic ratio of radiotherapy for cancer patients.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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