SA–CME Information

CARDIOTOXICITY AND RADIATION THERAPY: A REVIEW OF CLINICAL IMPACT IN BREAST AND THORACIC MALIGNANCIES

Description

Cardiotoxicity can be an unfortunate side effect from cancer therapies including chemotherapy, hormonal therapy, and radiation therapy (RT). Sub-acute cardiotoxicity can occur during systemic therapies but is often considered a late effect from RT. This manuscript reviews the current literature regarding the clinical impact of radiation-induced cardiotoxicity in the setting of breast cancers and thoracic malignancies including lung cancer, esophageal cancer and mediastinal lymphomas.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the clinical impact of radiotherapy-induced cardiotoxicity in breast cancers.
2. Understand the clinical impact of radiotherapy-induced cardiotoxicity in lung/esophageal cancers.
3. Understand the clinical impact of radiotherapy-induced cardiotoxicity in hemato-lymphoid malignancies.
4. Apply management approaches for radiotherapy-induced cardiotoxicity.

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Cardiotoxicity and Radiation Therapy: A Review of Clinical Impact in Breast and Thoracic Malignancies

Elizabeth M. Nichols, MD; Arezoo Modiri, PhD; Pranshu Mohindra, MD, MBBS

Cardiotoxicity can be an unfortunate side effect from cancer therapies including chemotherapy, hormonal therapy, and radiation therapy (RT). Subacute cardiotoxicity can occur during systemic therapies but is often considered a late effect from RT. Several different clinical conditions can result from radiation-induced cardiotoxicity (RIC): cardiomyopathy, myocarditis, pericarditis, acute coronary syndrome, congestive heart failure, and valvular disease. Cardiac injury remains multifactorial, however, with some patients receiving radiation dose to the heart and never experiencing a resultant clinical condition while others can be severely affected and even die. Data have shown that the existence of heart conditions (hypertension, diabetes, prior myocardial infarction, etc.) prior to therapy can result in a synergistic effect of cardiac injury.[1] In addition, receiving systemic therapy agents during or in close chronologic proximity to RT also can have a synergistic effect.[2-5] To date, no "protective" agent, except for decreased radiation dose, has been identified to minimize risk from RT.

A variety of imaging modalities are available to assess cardiac function, including multigated acquisition scans, single-photon emission computed tomography, echocardiography (and derivatives thereof), cardiac magnetic resonance imaging, and invasive procedures such as cardiac catheterization. Other cardiac imaging assessments can also be performed, such as CT angiography (CTA) and assessment of coronary calcifications; however, these do no assess cardiac function. To date the "best" modality has not been determined; each modality has strengths and weaknesses, and costs vary widely, as described in detail by several publications.[6,7] Table 4 in Lancellotti et al's review article gives a thorough and concise summary of imaging techniques for RIC diagnosis.[8] Additional work is needed to develop a standard method of assessing RIC. The pathophysiology of RIC is primarily associated with fibrosis and chronic inflammation. The mechanisms of action as currently understood have been described in previous publications. What remains lacking are models that can integrate the role of other medical comorbidities (hypertension, diabetes mellitus, hyperlipidemia, etc.) with cardiotoxic systemic effects.[9,10] **Table 1** describes several clinical conditions associated with RIC and the incidence as described in the literature.

The focus of this manuscript is to review the current literature regarding the clinical impact of RIC in the setting of breast cancers and thoracic malignancies including lung cancer, esophageal cancer and mediastinal lymphomas.

Impact by Disease Site

Breast Cancers

Three large cohort studies have shown a correlation between increased radiation dose to the heart and incidence of cardiac morbidity for women treated for breast cancer. The first study, by Darby et al, was published in 2013 and showed a linear 7.4% increased incidence of major coronary events per gray of radiation to the mean heart.[11] This study was a population-based, case-control study in which the incidence of major coronary events (including myocardial infarction, coronary revascularization, or death from ischemic heart disease) was counted in 2168 women who underwent breast radiation between 1958 and 2001. The average mean dose to the heart was 4.9 Gy. The study showed the risk of cardiovascular events to begin within the first 5 years following RT completion and continue to increase up to 30 years

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Table 1. RIC Endpoints and Their Reported Incidence, Severity and Time Course

RIC Endpoints	Incidence/Severity/Time Course as Reported in Relevant Studies
Hearth failure and death from any RT-induced cardiotoxicity[3,11,13,15,18,23,3133,38,39,41,42,44,51-55]	The risk of a fatal cardiac event in patients with any cancer type is 1.5-3 times higher in those treated with TMRT compared to those not treated with RT. Age at first treatment is inversely correlated with standardized mortality ratio of myocardial infarction but directly correlated with absolute excess risk of death from myocardial infarction. The statistically significant increase in the risk of myocardial infarction mortality stays for 25 years post-RT. Supradiaphragmatic RT and cardiotoxic chemotherapy (anthracyclines or vincristine) independently increase this risk. A 25-year cumulative risk of heart failure is associated with dose to LV.
Symptomatic myocardial infarction[3,11,12,43]	The median interval between treatment and myocardial infarction (or angina pectoris requiring intervention) is 19.0 years. There is a 2.5-fold increased risk for patients receiving a mean TMRT dose of 20 Gy to the heart, compared with patients not treated with TMRT. The excess incidence risk seems to decrease with each tertial of age at treatment. Having an existing cardiac risk factor directly impacts incidence risk; a high level of physical activity inversely impacts this risk.
Vessel/artery damage and conduction disorder[11,39,40,44,56-58]	Coronary artery atherosclerosis and fibrotic build-up in the tunica media may develop 5-20 years post-TMRT and initially tend to be asymptomatic but can lead to myocardial infarction. The left internal mammary artery, preferred for coronary artery bypass grafting, can be damaged due to TMRT-induced stenosis. The right bundle branch is likely to be damaged by RT as well.
Ischemia[11,12,23,32,44,46,59]	Ischemia incidence is seen as early as 6 months post-RT with an increased rate at 24 months post-RT. Heart mean dose, dose homogeneity, male sex, and age are significant predictors.
Pericarditis and effusion[32,39,40,42,60-63]	Acute pericarditis is caused after > 40 Gy TMRT. Patients may present with chest pain, possibly a fever, electrocardiogram abnormalities, and mild elevations in cardiac markers within days to weeks of therapy. Many patients with pericarditis have effusion or constrictive diseases that, on average, present about 3-5 years post-RT. Some patients may be asymptomatic or develop progressive shortness of breath before a pericardial effusion that is detectable by imaging months post-RT. Constrictive pericarditis is usually the most severe form of pericarditis and commonly presents 10 years post-RT as congestive heart failure.
Valvular damage[15,39,40,42,44,47,48,64-70]	A large percentage of patients receiving TMRT experience valvular damage. A few such patients require valve surgery for symptomatic valvular disease, while the majority have mild valvular diseases. RT progressively degenerates the valvular tissue for many years. Valvular damages include isolated aortic valve disease, isolated mitral disease and combined aortic and mitral valve diseases.
Cardiomyopathy[23,40,58,71,72]	Cardiomyopathy (LV ejection fraction < 50%) is more common in survivors treated with RT than those without. Five-year survival after cardiac transplantation due to radiation-induced restrictive cardiomyopathy is found less than in those not exposed to RT.
Autonomic dysfunction and arrhythmia[44,73-75]	The incidence of abnormal heart rate recovery times is 3.5 times more in patients who received TMRT compared to those who did not. This becomes more important when considering the increase in 3-year all-cause mortality in patients with abnormal heart rate recovery. In children treated with TMRT, persistent sinus tachycardia is common.

Also see Table 2 in Bhattacharya et al[76] and Table 3 in Lancellotti et al[8] review articles.
Key: RT = radiation therapy, TMRT = thoracic/mediastinal RT, LV = left ventricular.

after treatment. They found no difference in proportional increase in the rate of major coronary events per radiation dose unit in women with or without known cardiac risk factors at the time of RT. Criticisms of this study include changes across the eras of RT delivery as well as changing diagnosis and treatment of cardiac disease/events. Patients in this study did not undergo CT-based planning, and mean heart doses were estimated from 2-dimensional techniques. Concern was thus raised about the accuracy of the prediction model. The strength of this study, however, was the long-term data provided.

In 2017, van den Bogaard et al published a study looking at 910 women treated at a single institution with RT following breast-conserving therapy.[12] The primary endpoint of the study was to evaluate the incidence of acute coronary events (ACE). The investigators evaluated mean heart doses as well as

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dose to cardiac substructures, including the right and left atria and ventricles, to determine whether dose to a particular cardiac substructure correlated with more risk. All patients underwent CT-based planning. The mean heart dose was 2.37 Gy, with a median follow-up of 7.6 years. Three percent of patients experienced an ACE. This study showed a risk of 16.5% increased incidence of ACE per gray of RT to the mean heart within the first 9 years after RT, with a c-statistic of 0.79 that ultimately validated Darby's model. When evaluation by cardiac substructure was performed, the volume of the left ventricle receiving 5 Gy was the most important predictor of acute coronary events, with increasing doses predicting increased risk. Based on their statistical analysis, a threshold of mean value of 16.85% was associated with no ACE while a mean value of 29.4% was associated with an ACE. Of note, however, increasing doses of RT to the left ventricle were associated with increasing risks of an ACE. The authors also evaluated risk by decade of life at diagnosis (40s, 50s, 60s, 70s, 80s) and showed the highest risks for women in their eighth decade compared to the fourth decade. They also evaluated incidence by cardiac risk factor and found patients with a prior history of ischemic heart disease to have an exponentially worse risk of ACE compared to those with prior histories of hypertension or diabetes. The strengths of this analysis include the CT-based planning nature of their study with exact heart dosimetry and dosimetry to cardiac substructures, modern methods of diagnosis and treatment of ACEs, and moderately long follow-up. Weaknesses include the shorter nature of follow-up (compared to Darby et al). The incidences would likely continue to increase, with a slight modification of the risk ratio over time.

Taylor et al performed a systematic review of individual patient data published from 2010 to 2015.[13] Their analysis included more than 40 000 patients, with a median follow-up of 10 years. Estimates of heart doses were used in this study rather than individual dosimetric data. They found an increased risk of cardiac mortality with an increased risk ratio of 1.3 (95% confidence interval [CI], 1.15 to 1.46) and a 0.04 excess rate ratio of cardiac mortality per gray of whole-heart dose. Their study found a history of ischemic heart disease and smoking to be confounding factors for risk of cardiac death. The fact that this study focused on cardiac death as opposed to cardiac events likely resulted in the lower correlation of mean whole-heart dose per gray.

Some feel the risk ratios presented by the Darby and van den Boggard analyses may be overestimated.[14] For example, a study of > 70 000 Dutch stage I to III breast cancer patients showed that only death due to valvular heart disease was more frequent in these patients compared to the general Dutch population.[15] Further work is needed to clarify the best dosimetric parameters to use regarding heart and/or cardiac substructures and subsequent treatment planning goals, although a general consensus targets achieving the lowest dose possible to the mean heart and left ventricle. The ongoing multicenter, prospective MEDIRAD EARLY HEART study seeks to identify and validate new cardiac imaging and circulating biomarkers of RIC focusing on changes arising within first 2 years of breast cancer RT.[16] Patients receiving chemotherapy will be excluded. With plans to accrue 250 patients in the age group of 40-75 years, the data generated will also allow an opportunity to explore risk models correlating dose metrics of cardiac structures with the studied biomarkers while incorporating patient-specific risk factors. In a preliminary retrospective study, RT planning based on risk models that included patient age, smoking status, and existing cardiac risk factors at the time of RT was assessed.[17] The risk models were developed using published multi-institutional data. In 39 patients with left-sided breast cancer treated with comprehensive postlumpectomy locoregional conformal RT planning, median total decrease achieved in mortality or recurrence was 0.4% (range = 0.06 to 2.0%) and 0.5% (range = 0.11 to 2.2%) without and with existing cardiac risk factors, respectively.

Based on available data, a clear relationship exists between whole-heart dose and risk of cardiac events following RT for breast cancer with a significant increase in risk for left-sided breast cancer patients.[15,18] The clinical reality is that, as radiation oncologists, we are often unaware of the cardiac events our patients may experience. In addition, great heterogeneity in the length and frequency of patient follow-up for breast cancer contributes to this underappreciation. Patients, with a particular focus on those with left-sided disease, should be evaluated for cardiac-sparing techniques, including but not limited to deep-inspiration breath hold (DIBH), gating, prone positioning, and/or proton therapy, to achieve the lowest dose possible. Partial-breast irradiation can also be considered for suitable patients to decrease heart exposure. In addition to dose–volumetric parameters, radiation oncologists also must engage in smoking cessation counseling as well as education and discussion of the synergistic risks of other cardiac risk factors. As a result of the available data showing the confounding nature of cardiac risk factors, additional care should be taken when delivering RT for women with a history of ischemic cardiac disease.

Thoracic Malignancies (Lung and Esophageal Cancers)

Because of the overall higher mortality, evaluation of RIC in lung and esophageal cancers has proven more problematic than in breast cancer. Most patients do not live long enough to develop a cardiotoxicity. Nevertheless, recent recommendations for early screening of high-risk populations (ie,

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Table 2. RIC Endpoints with Known Dosimetric Correlates by Site

Primary Malignancy	Patient Population	Study Institution /Type	Dosimetric Parameter	Outcome
Breast cancer	Stage I-III (receiving RT)	Multi-institutional, retrospective[11]	Mean heart dose, left ventricle V5	Acute coronary/cardiac events: 7.4% increased risk per Gy of mean heart dose
Lung cancers	Stage I-II NSCLC	Multi-institutional, retrospective[31]	Maximum dose on the left atrium and dose to 90% of the superior vena cava	Noncancer death: Median 6.5 Gy EQD2, range = 0.009-197, HR = 1.005, $p = 0.035$ and median 0.59 Gy EQD2, range = 0.003-70, HR = 1.025, $p = 0.008$, respectively
	Stage III NSCLC	RTOG 0617, prospective[27]	Heart V5 and V30 Gy	Overall survival
	Stage III NSCLC	Tianjin Medical University Cancer Institute, retrospective[22]	Mean Heart Dose < 10 Gy, ≥ 10-20 Gy, and > 20 Gy	2-year competing-risk adjusted RIC rates 4%, 7% and 21%, respectively
	Locally Advanced NSCLC	Washington University, retrospective[26]	Heart V50 Gy < 25% vs ≥ 25%	2-year overall survival 45.9% vs 25%, $p < 0.0001$
Lymphoma	HL and NHL survivors	French-British cohort analysis[41]	Cardiac dose 5-14.9 Gy vs > 15 Gy	Relative risk of death: 12.5 vs 25.1, a linear relationship between the average cardiac radiation dose and the risk of cardiac mortality (estimated excess RR at 1 Gy = 60%)
	Multiple childhood cancers	Childhood Cancer Survivor Study, retrospective[42]	Cardiac dose > 15 Gy	2- to 6-fold increased risk of cardiac events
	HL	Princess Margaret Hospital, retrospective[46]	V5 of left anterior descending artery, and V20 of left circumflex artery	Ischemic Cardiac Events: HR = 0.98, $p = 0.003$ and HR = 1.03, $p < 0.001$
	HL	National Research Council of Italy, retrospective[47]	V25 Gy of left atrium, V30 Gy of left ventricle and V30 Gy of right ventricle	Mtral, aortic and tricuspid valvular disease
	HL	Analysis of prospective EORTC-LYSA trials[44]	Mean heart dose	Increased cardiovascular disease risk with each 1 Gy increase in dose, HR 1.015 [95% CI = 1.006-1.024], $p = 0.0014$

Key: Vx = the percentage volume receiving ≥ x Gy, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, CI = confidence interval, HR = hazard ratio.

smokers) have increased the probability of diagnosing lung cancer at an earlier stage with longer life expectancy and less comorbidity.[19] A 2019 statistical analysis of 11 3945 stage III non-small cell lung cancer (NSCLC) patients treated in 2004 to 2013 showed that 28% of the patients were younger than 60 years.[20] Similarly, another 2019 study of 44 498 stage IV NSCLC patients treated in 2013 to 2014 showed that 31% of the patients were younger than 60 years.[21] These findings highlight the importance of detecting and avoiding survival-compromising secondary complications in lung cancer RT as well as other types of thoracic RT. One study estimated the risks of RIC in lung cancer survivors to be as high as 33%.[22,23] Another analysis of 127 stage III NSCLC patients treated between 1996 and 2009 showed that 2-year competing risk-adjusted RIC rates for patients with a heart mean dose of < 10 Gy, ≥ 10 to 20 Gy, and > 20 Gy were 4%, 7%, and 21%, respectively.[22,24] Stam et al performed a study in 469 locally advanced NSCLC patients that showed a significant inverse correlation between increasing heart dose and survival.[25] A retrospective single-institutional multivariate analysis of 251 patients with locally advanced NSCLC from Washington University, St. Louis, Missouri, for which cardiac structures were recontoured, increasing heart V50 (Vx: the percentage volume receiving ≥ x Gy), was independently associated with survival (2-year overall survival increased from < 25% for V50 ≥ 25%, to 45.9% for V50 < 25%, $p < 0.0001$).[26]

In the more recently published RTOG 0617 study, RT dose to the heart was found to be prognostic for likelihood of death. On both univariate and multivariate analysis, V5 and V30 of

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heart were associated with increased risk of death.[27] In a secondary analysis reported subsequently, the incidence of grade 3+ cardiovascular events were lower with intensity-modulated RT (IMRT) vs 3-dimensional conformal RT (3D-CRT) (11% vs 21%, $p = 0.131$).[28] It was postulated that heart dose might best explain inferior outcomes in the 74 Gy arm. While there were recommended constraints for heart, this was not a compliance criterion. Expectedly, to limit lung doses, an incidental increase in cardiac dose may have been seen in both groups.[29] An important realization from the RTOG 0617 study was the significance of heart doses in a patient population with a median follow-up of < 24 months. This may become even more relevant in the modern era of consolidation immunotherapy, which is associated with a small risk of cardiac-related deaths.[30] Dose to heart (sub) structures has also been linked with noncancer death in early stage NSCLC patients treated with stereotactic body RT (SBRT).[31] In an analysis of 803 patients, at a median follow-up of 34.8 months, multivariate analysis identified maximum dose on the left atrium (median 6.5 Gy EQD2 [equivalent dose in 2 Gy fractions], range = 0.009 to 197, hazard ratio [HR] = 1.005, $p = 0.035$), and the dose to 90% of the superior vena cava (median 0.59 Gy EQD2, range = 0.003-70, HR = 1.025, $p = 0.008$) were significantly associated with noncancer death.

As in lung cancer, the risks of esophageal cancer RIC have previously been underreported because of poor overall prognosis. Beukema et al conducted a retrospective analysis of patients receiving definitive concurrent chemoradiation.[32] Grade 3 or higher cardiac events such as ischemia, effusions and heart failure were noted with a median follow-up of 26.1 to 57 months with an incidence ranging from 5.8 to 11.1%. Molenaar et al performed a Surveillance Epidemiology and End Results (SEER) analysis of patients receiving RT for esophageal cancer from 1973 to 2013.[33] They analyzed 6514 patients, of whom 53% received RT and 44% did not. Nine percent of 5-year survivors experienced cardiac death: 336 who received RT compared to 254 who did not, with mean times to death of 25.3 and 32.2 years, respectively. On multivariate analysis, risks were highest in patients diagnosed prior to 1995 and in those with squamous cell carcinoma. Increased cardiac death in 1995 was likely partially the result of older RT techniques.

In both lung and esophageal cancers, RT techniques have progressed so that the majority of these patients are now treated with IMRT rather than 3D-CRT.[34-36] IMRT has the ability to spare high doses of RT to smaller heart volumes at the cost of spreading lower doses over larger volumes. It remains unclear which is most important in avoiding RIC with data to support negative impact of both dosimetric parameters (**Table 2**). Not having data to guide the decision, both lowering mean dose to whole heart and limiting high dose values to small volumes should be emphasized during treatment planning. The risk of RIC in both lung and esophageal cancers is heavily confounded by age as well as risk factors. The risk factors inherent in disease development are also risk factors for cardiac disease; as such, these patient populations are at even higher risk for RIC. In addition, many patients have been diagnosed with cardiac disease prior to their cancer diagnosis, highlighting an even greater need for heart avoidance. Because of the anatomic proximity of these cancers to the heart, however, radiomodulatory techniques such as DIBH or gating may not be as helpful in reducing heart dose; thus, other techniques, such as proton therapy, may be needed.

Lymphoma

RT continues to play an integral role in the management of Hodgkin lymphoma (HL) and is still used in select cases of non-Hodgkin lymphoma (NHL). Both diagnoses involve treatment with cardiotoxic systemic agents that further enhance cardiac risks of RT.[37] Cardiac-related death is the third most common cause of death among lymphoma survivors, who have a 5.3 to 7.3 times increased risk of cardiac mortality compared to the general population.[38] Among HL survivors, the risk of fatal myocardial infarction has been found to be 2.5 times higher than in the general population.[3] Most of the cardiotoxicity data is derived from childhood survivors of HL, a highly curable disease, with toxicities including valvular heart disease (21% to 41%), coronary heart disease (17% to 23%), heart failure (8% to 17%), conduction disorders (12%) and pericardial abnormalities (10%).[39]

Data regarding relative contribution of doxorubicin-based chemotherapy and RT in causing RIC are heterogeneous. In a single-institutional analysis of 615 HL patients from Princess Margaret Hospital, Toronto, Canada, it was shown that while the rate of cardiac morbidity was highest among patients treated with both doxorubicin and mediastinal RT (HR = 2.77, $p < 0.0001$), mediastinal RT without chemotherapy also significantly increased this risk (HR = 1.82, $p < 0.038$).[5] In a report from the German-Austrian Pediatric Hodgkin's Disease Study Group, a longitudinal follow-up analysis of 1132 HL survivors who received treatment before 18 years of age in consecutive trials between 1978 and 1995, cumulative incidence of RIC after 25 years dropped with reduced radiation dose (21% with 36 Gy RT vs 3% with no RT, $p < 0.001$).[40] Valvular defects were diagnosed most frequently, followed by coronary artery diseases, cardiomyopathies, conduction disorders, and pericardial abnormalities. A similar linear dose-response relationship was noted in another French-British cohort analysis of 4122 children, including HL and NHL survivors treated in 8 cancer treatment centers in France and the United Kingdom.[41] Cumulative anthracycline dose

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and average radiation dose to the heart increased the risk of death from cardiac diseases (anthracycline RR [relative risk] = 4.4, cardiac dose 5 to 14.9 Gy RR = 12.5, cardiac dose > 15 Gy RR = 25.1) with a linear relationship between the average cardiac radiation dose and the risk of cardiac mortality (estimated excess RR at 1 Gy = 60%). A Childhood Cancer Survivor Study from 26 institutions evaluated 14358 5-year survivors of cancer diagnosed under age 21 and noted a 2 to 5 times increased risk of congestive heart failure, pericardial disease, and valvular abnormalities compared with untreated sibling survivors.[42] Cardiac radiation exposure > 15 Gy also resulted in a 2- to 6-fold increased risk of the above cardiac events. A Dutch case-control study of HL patients diagnosed before age 51 years who had a 5-year follow-up showed a higher mean left ventricular dose (MLVD) (16.7 Gy vs 13.8 Gy, $p = 0.003$).[43] The risk of heart failure was also correlated with MLVD (MLVD 1 to 15 Gy, 16 to 20 Gy, 21 to 25 Gy, and ≥ 26 Gy: RR of heart failure 1.27, 1.65, 3.84, and 4.39, respectively, $P_{trend} < 0.001$). Further, this risk was increased with anthracycline use (MLVD 0 to 15 Gy, 16 to 20 Gy, and ≥ 21 Gy: Cumulative risk of heart failure was 4.4%, 6.2%, and 13.3%, respectively, without anthracycline and 11.2%, 15.9%, and 32.9%, respectively, with anthracycline). The largest analysis of prospective data comes from EORTC-LYSA trials for patients with HL.[44] Dose to the heart and carotids was reconstructed to a demonstrated increased risk of cardiovascular disease with an increased mean heart dose (per 1 Gy increase in dose, HR = 1·015 [95% CI, 1·006-1·024], $p = 0·0014$). Dose to carotid arteries did not correlate with a similar risk.

A major limitation of such survivorship studies is lack of details on true 3D cardiac dose and treatment with conventional large-field treatments including mantle/mini-mantle, total body radiation or use of cobalt-60 machines. With the evolution of more modern treatment planning principles of reduced treatment dose targeting smaller involved-site and involved-nodal regions combined with increasing use of modern treatment technologies such as IMRT and proton therapy, dose to cardiac substructures may become more relevant than whole cardiac dose.[45] In a random sample of 125 HL patients treated with mediastinal RT, 44 cardiac events were documented, of which 70% were ischemic.[46] In a subanalysis of ischemic cardiac events, V5 of the left anterior descending artery (HR = 0.98, $p = .003$), and V20 of the left circumflex artery (HR = 1.03, $p < .001$) were found to be significant predictors. In a modern cohort analysis, 56 patients undergoing cytotoxic chemotherapy and involved-field 3D-CRT for HL were retrospectively analyzed.[47] V25 Gy of left atrium, V30 Gy of left ventricle and V30 Gy of right ventricle correlated with mitral, aortic and tricuspid valvular disease, respectively, yielding 32.1% of patients developing valvular regurgitation and/or stenosis after a median follow-up of 70.5 months. In a more recent prospective analysis, 179 consecutive asymptomatic patients with HL were evaluated with coronary CTA.[48] With a median follow-up of 11.6 years, 26% survivors demonstrated CTA abnormalities, with 15% of patients demonstrating changes within 5 years and 6.7% demonstrating severe stenoses requiring surgical procedures. Radiation dose to the coronary artery origins was noted to be prognostic.

Ongoing efforts will require continued monitoring of 3D dose-distribution to cardiac substructures in the era of modern radiation planning and delivery principles to refine the dosimetric constraints. Equally important will be efforts toward cardiac rehabilitation.

Treatment and Management of Radiation-Induced Cardiotoxicity

To date, no treatment is available to reverse or treat the effects of RIC. The focus of treatment paradigms has been on optimizing medical management of other cardiac risk factors, such as hypertension and diabetes, and preventing disease through education toward a smoke-free and heart-healthy lifestyle. Smoking cessation and counseling have played critical roles in reducing risk.

Over the last several years, the field of cardio-oncology has emerged as a multidisciplinary field of cardiologists, medical oncologists, and sometimes radiation oncologists specializing in both temporary and long-term effects of oncology-related cardiotoxicity with a goal of improving the quality of life of cancer survivors.[49] A pilot project in lymphoma patients undergoing stem cell transplant demonstrated improved exercise levels and physical functioning with guided cardiac-rehabilitation exercises.[50] Similar efforts should be initiated for patients receiving cardiac exposure from RT. The indications for patient referral for this field vary by institution/locale. In some cases, any patient at potential risk for cardiotoxicity may be referred for consultation and subsequent follow-up. In others, patients may be referred only when they begin to show signs of cardiotoxicity (eg, a patient who develops a decreased ejection fraction while on trastuzumab). As the number of cancer survivors continues to increase, the role of cardio-oncology becomes more important, with a call for a greater number of providers.

Conclusion

RIC is a known late effect of breast and thoracic RT in childhood cancer survivors. Population-based and institutional analyses in recent years have provided some dosimetric correlates to better predict the risk of RIC in relationship to cardiac radiation exposure. However, assessments are limited by lack of 3D anatomical data, use of conventional treatment planning and delivery technology, and relative lack of dosimetric significance of dose to various cardiac substructures. Furthermore, true assessment of RIC is limited

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by lack of follow-up, cancer-related mortality, pre-existing conditions and age-related changes. In the absence of an approved treatment for RIC, reducing the clinical impact of RIC focuses on minimizing dose to the heart through advanced RT delivery techniques, smaller RT volumes and/or decreased doses of RT. Treatment paradigms also focus on preventing cardiac risk factors. With the evolution of more modern treatment planning principles of reduced treatment dose targeting smaller involved-site and involved-nodal regions combined with increasing use of modern treatment technologies such as IMRT and proton therapy, dose to cardiac substructures may become more relevant than whole cardiac dose. All radiation oncologists should be aware of RIC, with a call to action to support advanced delivery techniques. Although these techniques may sometimes come at an increased short-term cost, reducing RIC will lead to long-term gains for patients, for the scientific understanding of cardiac toxicity, and for the medical establishment.

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