

MINI-FOCUS ISSUE: RADIATION AND CARDIOVASCULAR DISEASE

STATE-OF-THE-ART REVIEW

Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification



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ABSTRACT

Radiation therapy is an important component of cancer therapy for many malignancies. With improvements in cardiac-sparing techniques, radiation-induced cardiac dysfunction has decreased but remains a continued concern. In this review, we provide an overview of the evolution of radiotherapy techniques in thoracic cancers and associated reductions in cardiac risk. We also highlight data demonstrating that in some cases radiation doses to specific cardiac substructures correlate with cardiac toxicities and/or survival beyond mean heart dose alone. Advanced cardiac imaging, cardiovascular risk assessment, and potentially even biomarkers can help guide post-radiotherapy patient care. In addition, treatment of ventricular arrhythmias with the use of ablative radiotherapy may inform knowledge of radiation-induced cardiac dysfunction. Future efforts should explore further personalization of radiotherapy to minimize cardiac dysfunction by coupling knowledge derived from enhanced dosimetry to cardiac substructures, post-radiation regional dysfunction seen on advanced cardiac imaging, and more complete cardiac toxicity data. (J Am Coll Cardiol CardioOnc 2021;3:343-359) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Radiation therapy (RT) is a critical component of treatment for more than one-half of adult patients with cancer (1). Thoracic malignancies, including lung, esophageal, gastric, and breast cancers, as well as childhood cancers and lymphomas, often include RT in definitive curative treatment regimens. However, cardiac radiation exposure can lead to long-term adverse outcomes, including

cardiac death. Although the heart was originally considered a relatively radiation resistant organ, data examining the association of cardiac radiation dose and adverse outcomes indicate that there can be a ~4%-16% relative risk of heart disease and major cardiac events per Gray (Gy) of mean heart dose (MHD) of radiation (2-4), with no safe dose identified. Thus, even though advances in RT techniques have

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received January 27, 2021; revised manuscript received June 7, 2021, accepted June 9, 2021.

ABBREVIATIONS AND ACRONYMS

CAC	= coronary artery calcium
CAD	= coronary artery disease
CMRI	= cardiac magnetic resonance imaging
CT	= computed tomography
HL	= Hodgkin lymphoma
LAD	= left anterior descending artery
LV	= left ventricular
MHD	= mean heart dose
NSCLC	= non-small cell lung cancer
RICD	= radiation-induced cardiovascular disease
RT	= radiation therapy
SBRT	= stereotactic body radiation therapy

decreased incidental cardiac doses, late cardiac toxicity can still develop. Many studies in patients with breast cancer or lymphoma have demonstrated that radiation-induced cardiac disease (RICD) most often occurs a number of years after RT. However, data showing correlations between higher heart radiation exposure and cardiac events and survival in patients with lung or esophageal cancer have led to a reexamination of the severe cardiac effects that can occur within the first 2 years after RT (5-8). In addition, an increasing number of studies have examined correlations between radiation doses to specific cardiac regions and cardiac morbidity and mortality (Central Illustration) (3,5,9-29). Although uniform standardized cardiovascular surveillance recommendations for cancer survivors with cardiac radiation exposure are lacking, modern cardiac imaging allows more sensitive determination of subclinical cardiac dysfunction in the heart, including individual cardiac regions. Together with data on cardiac substructure sensitivities, the knowledge gained from modern cardiac imaging techniques has the potential to ultimately guide RT treatments and post-RT surveillance. Distinct from RT for malignancies, over the past few years there have been increasing cohorts of noncancer patients receiving high-dose RT to the heart for treatment of refractory ventricular tachycardia (30). Data from the effects of such high-dose RT on the heart may also inform mechanisms and biomarkers of RICD in patients with cancer. Although RT exposure to areas outside of the thorax can also cause cardiovascular dysfunction (31), potentially through inflammation or other mechanisms, here we focus solely on thoracic RT-induced cardiotoxicity. In this review, we summarize clinical data on RICD in thoracic malignancies, correlations between doses in different cardiac regions and cardiac outcomes, and the utility of biomarkers and cardiac imaging in post-RT surveillance. We also discuss future directions toward more refined and personalized RT for patients, which can result in reduced RICD.

RICD IN THORACIC MALIGNANCIES

HODGKIN LYMPHOMA RT DOSE AND FIELD EVOLUTION OVER TIME. In the 1960s, pioneering work by Kaplan et al from Stanford University further advanced radiation oncology through the development of the linear accelerator, definition of RT fields and doses for curative treatment for early Hodgkin lymphoma (HL), and promotion of early randomized

HIGHLIGHTS

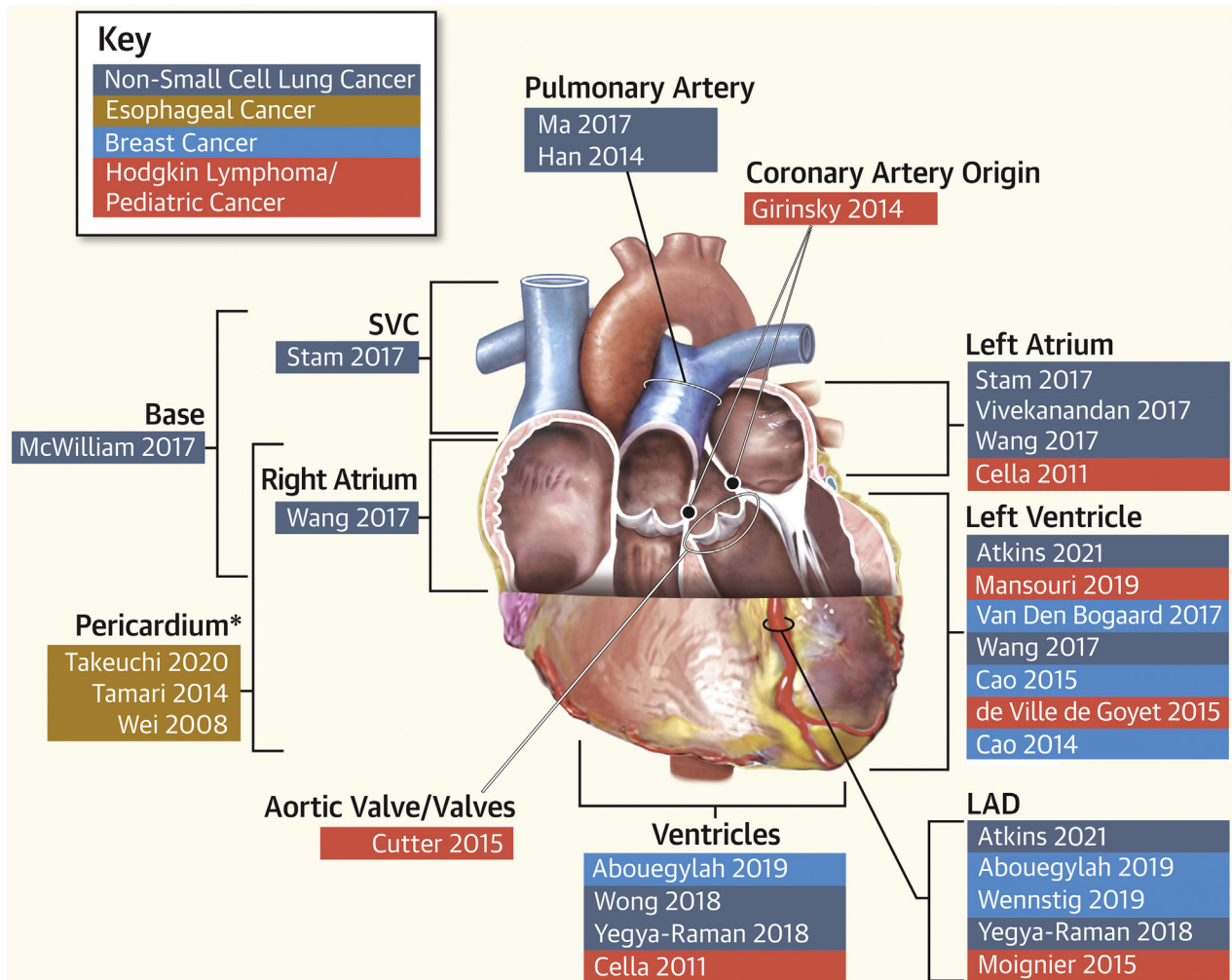
- Despite improvements in radiation techniques, radiation-induced cardiac dysfunction can occur in those with thoracic cancers.
- Newer studies have examined associations between cardiac substructure doses and cardiac outcomes and/or survival.
- Advanced cardiac imaging allows assessment of regional dysfunction after cardiac radiation exposure.
- Enhanced dose tracking, imaging, and comprehensive clinical data hold promise for personalized approaches to minimize cardiotoxicity.

U.S. clinical trials (32). Subsequent studies reported on the relationship between mediastinal RT and the risk of fatal cardiovascular complications manifesting 5-10 years after treatment (33,34). Additional manifestations of RICD in HL survivors can include coronary artery disease (CAD), pericarditis, valvular dysfunction, arrhythmia, and heart failure, with risks persisting for up to 40 years (35,36). However, much of the data on RICD following RT for HL are based on patients treated decades ago with full-mantle fields to the standard curative RT dose of ≥ 40 -44 Gy, resulting in high radiation exposure to the heart (Figure 1).

The relationship between radiation dose and the risk of heart disease was first demonstrated by Hancock et al, who found significantly increased cardiac mortality after HL in patients who received mediastinal RT doses >30 Gy (34). Other studies also have observed an association between mediastinal RT dose and risk of cardiac disease among childhood HL survivors (37-39). In those studies, the prescribed RT dose was used to estimate cardiac doses. More modern analyses use volume-based analysis of cardiac radiation doses to calculate RICD risks. A significant linear relationship was found between the estimated MHD and the risk of cardiovascular disease, with a 1.5%-7% increase in risk per 1 Gy MHD (40,41). A number of studies have found significant relationships between mean doses to the heart/cardiac substructures and the long-term cumulative incidence of cardiac events, including coronary heart disease, heart failure, and valvular disease (Central Illustration) (14,15,19,42).

As data on the late cardiac effects of HL accumulated, simultaneous efforts have improved cancer outcomes. More effective chemotherapy, advances in

CENTRAL ILLUSTRATION Heart Regions Associated With Radiation-Induced Cardiovascular Disease and/or Survival



Bergom, C. et al. *J Am Coll Cardiol CardioOnc.* 2021;3(3):343-359.

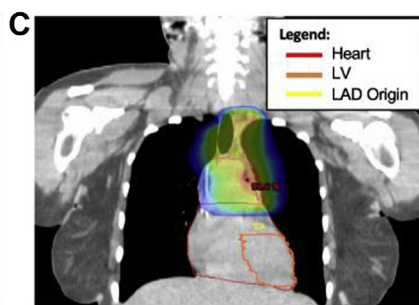
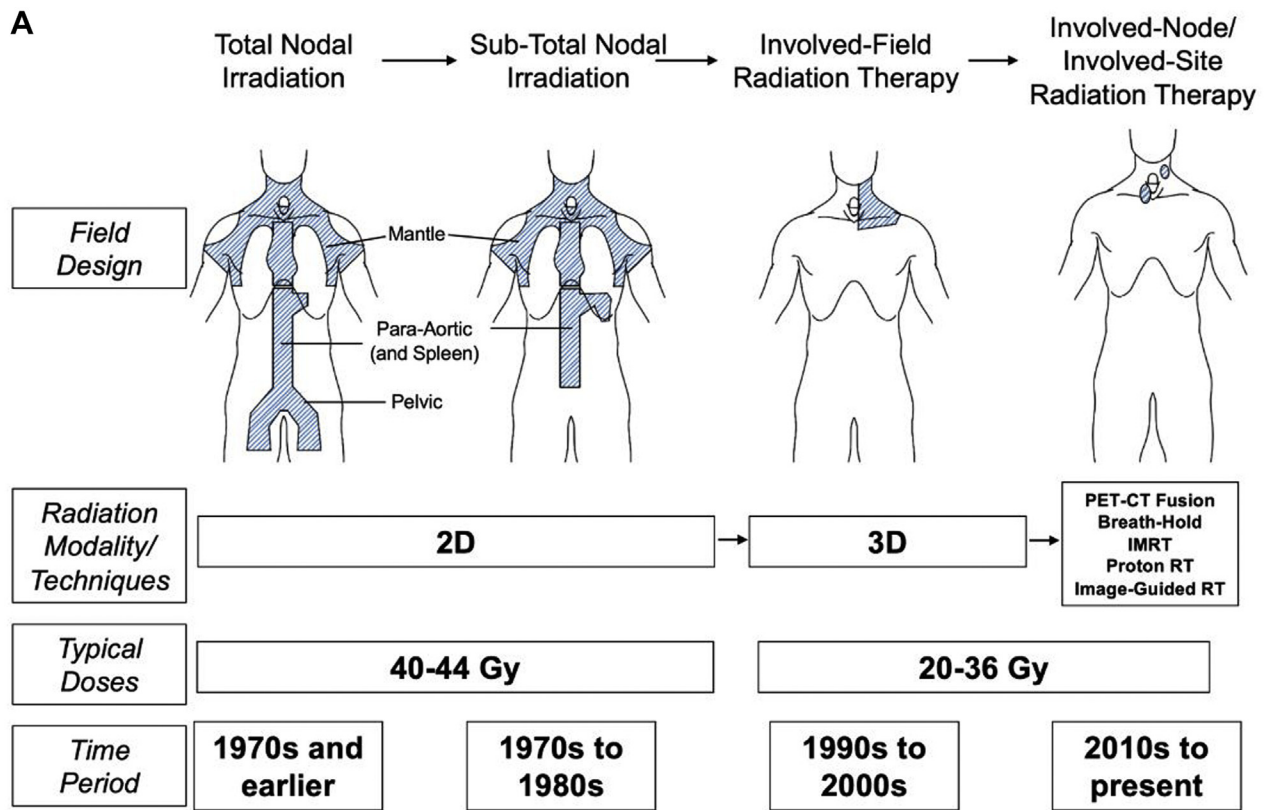
First author and year of publication are listed. Highlighted colors indicate cancer type (see Key). Studies demonstrating associations between total heart doses and outcomes are not included. *Pericardium, not including the heart. LAD = left anterior descending artery; SVC = superior vena cava.

imaging, improved staging and response assessment, and patterns of relapse analyses have allowed the use of more limited RT fields and volumes, with resulting lower incidental cardiac radiation exposure. RT treatment fields for HL have evolved from extended-field to involved-field and then to involved-node/involved-site RT (Figure 1) (43,44). In conjunction with chemotherapy, RT doses have decreased from 40-44 Gy to as low as 20 Gy in selected patients (Figure 1). In addition, there have been significant technologic advancements in RT treatment planning and delivery. The prior 2-dimensional-based RT has been replaced by much more conformal approaches,

such as 3-dimensional (3D) conformal RT, intensity-modulated RT, and proton beam therapy (45). The adoption of daily image guidance and respiratory motion management further improves conformal target coverage and normal-tissue sparing (45) (Table 1). A typical MHD from a mantle field is estimated to be 25-30 Gy, but with modern fields, doses, and techniques, an MHD of <10 Gy can often be achieved when targeting mediastinal disease (46) (Figure 1).

A number of dosimetric studies demonstrate significant reduction in cardiac RT doses with the use of involved-node/involved-site RT compared with

FIGURE 1 Evolution of RT in HL



D

	Mantle	Involved-Site RT
Organ at Risk	Mean Dose	
Heart	29.8 Gy	2.1 Gy
LAD	32.1 Gy	0.6 Gy
LV	21.0 Gy	0.3 Gy
Lungs	22.1 Gy	4.2 Gy

(A) Schematic representation of field design, radiation therapy (RT) doses, and radiation techniques for adult Hodgkin lymphoma (HL) as they have evolved over time. **(B, C)** RT plan comparison of an HL patient treated with involved-site RT to the mediastinum including colorwash dose distribution. Recreated historical mantle field **(B)**, anterior-posterior technique, treated to a dose of 40 Gy, versus involved-site RT using IMRT **(C)**, with deep-inspiration breath hold (note expansion of lungs and elongation of mediastinal structures, displacing lungs and heart away from target volume) with arms down on inclined board (further displacement of heart inferiorly), treated to 30 Gy with a 6-Gy boost to a level 5 node. **(D)** Dosimetric comparison of plans in **B** and **C**. IMRT = intensity-modulated radiation therapy; LAD = left anterior descending artery; LV = left ventricle; PET-CT = positron emission tomography-computed tomography.

historical treatment fields such as mantle or involved-field RT (Figure 1) (46,47). In a study evaluating HL treated with involved-node RT to 30-36 Gy, the authors constructed simulated mantle fields to a dose of 36 Gy in the same patients. Comparing the mantle RT and involved-node RT, mean doses to the heart were 27.5 Gy versus 7.7 Gy, respectively, and mean doses to

the left anterior descending artery (LAD) were 23.1 Gy versus 8.9 Gy (48). Using estimates, the 25-year absolute excess risk of cardiovascular disease based on the estimated MHD demonstrated a significant risk reduction with the use of involved-node versus mantle RT (1.4% vs 9.1%; $P < 0.001$) (48). Deep-inspiration breath hold can further reduce heart

TABLE 1 Cardiac-Sparing Radiation Therapy Techniques and Modalities

Cardiac-Sparing Technology/Technique	Description	Cancers Where These Techniques May Be Used				
		Lymphoma	Breast Cancer	Esophageal Cancer	Lung Cancer	Pediatric Cancer
Modality						
3-dimensional conformal radiation therapy	Photon beams designed using forward planning; minimize low dose bath; less conformality of high dose; can use a "heart block" to eliminate heart from the field using beam edge	✓	✓	✓	✓	✓
Intensity-modulated radiation therapy/volumetric-modulated arc therapy	Inverse planning using multiple photon beams or arcs to achieve conformality of high dose at the cost of increased low-dose exposure	✓	✓	✓	✓	✓
Proton therapy	Particle beam with Bragg peak phenomenon resulting in elimination of exit dose; enables both minimization of low dose and conformality of high dose	✓	✓	✓	✓	✓
Cardiac Displacement and motion management techniques						
Deep-inspiration breath hold	Using a device to measure depth of inspiration, patient is guided to hold breath for 10-20 seconds to displace thoracic anatomy from the heart	✓	✓			
Gating	Using an external abdominal device to gauge respiration, the beam is delivered during a set phase of the respiratory cycle when the heart is farthest from the target, and the beam shuts off when the patient exits this portion of the respiratory cycle	✓	✓	✓	✓	
Prone positioning	Displaces the target anatomy from the heart in many patients		✓			
Image-guided radiation therapy						
Cone-beam computed tomography (CT)	Low-dose CT obtained in treatment vault permits alignment based on visualization of internal anatomy	✓	✓	✓	✓	✓
Surface alignment	Uses surface anatomy for patient positioning; cannot visualize internal anatomy; no radiation exposure for this alignment technique		✓			

dose by elongation of mediastinal structures and displacement of the heart outside of the RT beams (Figure 1, Table 1).

Most of the studies assessing the relationship between radiation dose and risk of RICD used reconstructed MHD owing to the challenges of retrospectively estimating doses to individual cardiac substructures. However, in the context of involved-site RT, the shape and distribution of the clinical target volume and its proximity to critical cardiac substructures can vary significantly from case to case. With the use of highly conformal techniques with a steep dose gradient, it is important to track doses to critical cardiac substructures including the coronary arteries, cardiac chambers, and valves to allow better individual risk assessment, as well as to further establish dose-volume effects of cardiac substructures on subsequent RICD to guide future treatment planning (49), as discussed below.

PEDIATRIC MALIGNANCIES AND RICD. Many patients with HL are children or young adults. However, treatment of other pediatric malignancies can also result in significant cardiac radiation exposure, often concurrently administered with potentially cardiotoxic systemic treatment. In fact, cardiovascular events are the leading cause of noncancer death in childhood cancer survivors. Mulrooney et al (38) evaluated >14,000 children treated from 1970 to 1986 in the Childhood Cancer Survivor Study with the use of a questionnaire to assess for cardiac disease, with

comparison to a sibling cohort. At 30 years after diagnosis, the incidence of heart failure, valvular abnormalities, and pericardial disease was 3%-4% each, with the cumulative incidence increasing over time and reaching 5-6 times that of the sibling cohort. Heart failure was associated with a cardiac dose of >15 Gy, and myocardial infarction was associated with a cardiac dose of >35 Gy (38). Updated data on >23,000 children diagnosed through 1999 demonstrated patients treated in the 1980s-90s had a lower risk of CAD than patients treated in the 1970s, likely owing to modifications in therapy intended to decrease cardiac toxicity, including decreased RT use and improved techniques. However, cardiac disease still occurred in the majority of patients, with 80% affected by a single cardiac condition and 19% by two or more conditions (50). Reconstructing the estimated cardiac radiation doses of children in the Childhood Cancer Survivor Study allowed evaluation of cardiac dose-volume relationships with outcomes. At 30 years after diagnosis, the cumulative incidence of cardiac disease was 4.8% (51). Both cardiac volume and radiation dose are important considerations in estimating the risk of cardiac toxicity. Doses of 5-19.9 Gy to ≥50% of the heart and doses ≥20 Gy to <30% of the heart were associated with an increased risk of cardiac disease (relative risks: 1.6 and 2.4, respectively). This dose-response relationship was amplified in those ≤13 years of age who received anthracyclines (51).

A French study also identified a dose-response relationship for left ventricle (LV) dose ≥ 30 Gy and heart failure in pediatric cancer survivors diagnosed from 1945 to 2000 (24). The cumulative incidence of heart failure was 2.5% at 30 years after diagnosis and 5.7% at 50 years, with 10% of those affected by cardiac disease requiring heart transplantation. The risk ratio increased from 3.6 to 24.6 as the volume of the LV receiving 30 Gy increased from $<10\%$ to $\geq 50\%$, with risk further increased with anthracycline use (24). In a study of 1,362 pediatric patients with cancer, the 30-year marginal cumulative incidences of a grade ≥ 3 cardiac event were 17%, 8% and 4.5% for those receiving anthracycline and cardiac RT, anthracycline without cardiac RT, and cardiac RT alone, respectively (52). In a study of $\geq 36,000$ patients across Europe, patients who received both RT and chemotherapy compared with receipt of either or none had the highest rates and earliest onset of ischemic heart disease, with 1 in 18 survivors developing severe or fatal ischemia (53).

The American Heart Association has published an extensive scientific statement on the pathophysiology, surveillance, treatment, and prevention of cardiovascular toxicity for people treated for malignancy at a young age (54). Other groups also have published guidelines for surveillance of childhood cancer survivors for late cardiotoxicity, specifically after receipt of anthracycline chemotherapy, mediastinal RT, and neck RT (55,56).

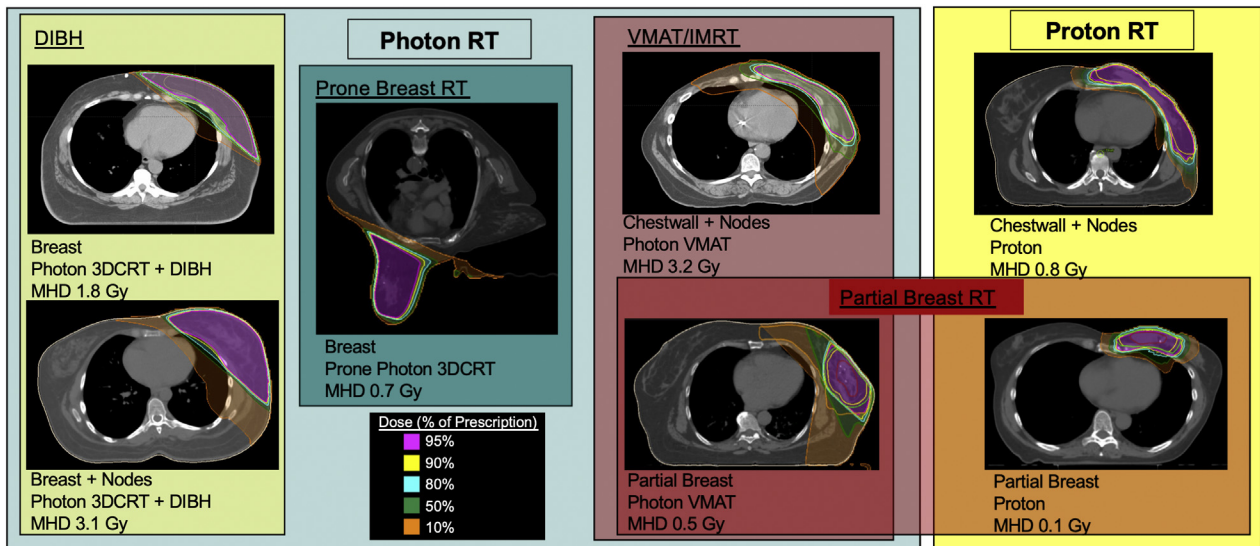
RICD IN BREAST CANCER. In the early decades of RT, field design was based on bony anatomic borders identified on X-rays. Measurements of target coverage and doses to adjacent organs were not possible in that 2-dimensional RT era. Data from those earlier radiation treatments in patients with breast cancer demonstrate significant efficacy of RT in disease control, but at a cost of heart and lung injury (57). The laterality of the breast cancer is also important, because the heart sits in closer proximity to the left breast. Thus, the risk of RICD is higher in patients with left-side breast cancer (58). For breast cancer RT, there was a slow adoption of 3D-contour-based planning. The earliest uses of contouring with the use of 3D-conformal RT in phase 3 cooperative group trials were the NSABP-B39/RTOG 0413 study partial breast irradiation arm (59) and RTOG 1005 (60), which opened to accrual in 2005 and 2011, respectively. A number of breast cancer contouring atlases have been published, with more recent atlases delineating cardiac substructures as well (61), allowing determination of associations between substructure doses and cardiac outcomes. Cardiac radiation

exposure has decreased over time owing to improved techniques, although a number of factors influence the cardiac-sparing techniques used for patients with breast cancer (Figure 2, Table 1) (62).

MHD is the typical metric used to evaluate cardiac exposure in present-day clinical practice. Current cooperative group trials use a threshold of 3-5 Gy MHD to consider a plan acceptable (eg, NSABP-B51, Alliance-A221505). Data in breast cancer demonstrate a linear no-threshold model for cardiac radiation, with a relative risk of ischemic heart disease increased by 4%-16% per Gy of MHD (2-4). Jacobse et al (2) also demonstrated a linear relationship between MHD and subsequent myocardial infarction (63). However, the absolute increase in risk of major cardiac events from an MHD of 5 Gy is $\sim 1\%$, although this varies by age and cardiac risk factors. In most 3D-conformal RT plans for breast cancer, only the anterior aspect of the heart is exposed to radiation, and a large portion of the heart does not receive radiation (Figure 2). This uneven distribution of radiation dose to the heart begets the question of the relevance of the MHD metric for breast cancer. Duane et al, using 10 randomly selected computed tomography (CT) planning scans, evaluated doses to cardiac substructures in Scandinavian women with breast cancer treated from 1958 to 2001. Standard breast RT techniques were used to recreate dose on the CT scans, and the heart and cardiac substructures were contoured. A wide range of doses to segments within the LV and coronary arteries was seen, as well as a high correlation between doses to different substructures, such as the LV and the LAD, and dose to the whole heart (64). Emerging data have found associations between LAD and LV doses and cardiac outcomes in breast cancer (Central Illustration) (see discussion below) (3,20,21,25,29). These data have led to suggestions for dose-volume limits for the LV and LAD in breast cancer RT (65).

In modern radiotherapy, a range of options exist in addition to 3D-conformal RT to decrease heart dose for breast and other cancers (49,62,66,67) (Figure 2). These include prone positioning, respiratory management including deep-inspiration breath hold and gating, intensity-modulated RT (IMRT)/volumetric-modulated arc therapy (VMAT), and proton therapy (described in Table 1). Beam arrangements and beam energies are optimized for individual anatomy. In many cases, 3D techniques are optimal, but in others, IMRT/VMAT or proton therapy permits increased conformality of high doses (Figure 2). Current limitations to proton therapy include higher cost and accessibility. For selected women with early-stage breast cancer, the target volume can be decreased

FIGURE 2 Example Breast Plans Using Different RT Techniques and Modalities



Example plans using cardiac-sparing techniques and different target volumes are shown. The selection of techniques and modalities is complex, involving availability of the technology, patient anatomy, and target volumes. All plans shown prescribed 50 Gy in 2-Gy fractions, except partial breast RT was prescribed 30 Gy in 5 fractions. 3DCRT = 3-dimensional conformal radiation therapy; DIBH = deep-inspiration breath hold; IMRT = intensity-modulated radiation therapy; MHD = mean heart dose; RT = radiation therapy; VMAT = volumetric-modulated arc therapy.

from the whole breast to partial breast, targeting the lumpectomy cavity with a margin of surrounding tissue to limit the exposure of intrathoracic organs. Partial breast irradiation can be delivered in several ways, including brachytherapy and external beam photon or proton therapy (59) (Figure 2). Ultimately, the choice of RT technique, treatment volumes, and modalities used must be personalized for each patient based on availability of technology, a patient's anatomy, and cancer-specific variables.

LUNG AND ESOPHAGEAL CANCER: RICD IN THE SETTING OF HIGHER CARDIAC RADIATION DOSES.

Over the decades, data regarding the incidence of RICD after RT for intrathoracic malignancies have steadily increased following improvements in overall survival with novel therapeutics and treatment approaches. For esophageal cancer, some of the earliest RICD data came from Japan (68,69), where the incidence of esophageal cancer is among the highest worldwide. In more than 70 patients with esophageal squamous cell carcinoma treated with definitive chemoradiation therapy from 2002 to 2005, age ≥ 75 years was significantly associated with a higher 2-year cumulative incidence of grade ≥ 3 cardiopulmonary toxicities (~30% for age ≥ 75 years vs 3% for age <75 years) (68). Because squamous cell esophageal

cancers are predominately in the upper and/or middle esophagus, treatment fields would have included large mostly anterior-posterior mediastinal fields for lymph node coverage for the first 40 Gy, followed by a 20 Gy boost to the primary tumor with the use of oblique fields (68). Chemotherapy typically consisted of concurrent cisplatin and 5-fluorouracil, which on meta-analysis has a 1%-4% incidence of symptomatic cardiotoxicity (70). More recently, a systematic review examining the relationship between esophageal cancer treatment and RICD found the crude incidence of symptomatic cardiac toxicity, including pericardial effusions, ischemic heart disease, and heart failure, to be 10% (7). The majority of these events occurred within 2 years, and the most common finding was pericardial effusions. Although this timeline to symptomatic cardiac events appears shorter than that in many breast cancer or HL patients, esophageal and lung cancers often occur in patients with other confounding variables, including concurrent chemotherapy and significant smoking histories, and patients typically receive higher overall cardiac radiation exposure, which can influence the rates of cardiac events (6).

A number of esophageal cancer studies have found associations between whole-heart radiation doses and cardiac events and/or survival (69). In addition,

studies have found associations between doses to the pericardial rim surrounding the heart predicted the risk of pericardial effusions, the most common manifestation of RICD in those patients (**Central Illustration**) (11-13). Similarly to anatomic concerns in esophageal cancer, RT fields for locally advanced non-small cell lung cancer (NSCLC) can span a large proportion of the mediastinum when covering NSCLC with ipsilateral mediastinal involvement and can lead to high-dose gradients in the heart. Correlations between cardiac doses in NSCLC and overall survival have been found in a number of studies (69).

For both esophageal and lung cancers, it can be difficult to balance limiting of both lung and cardiac doses. Typically, lung doses are prioritized because of the risk of severe radiation pneumonitis. For example, in the RTOG 0617 NSCLC study, the heart was the last-priority organ at risk, behind the spinal cord, lungs, esophagus, and brachial plexus, with acceptable criteria including 40 Gy to <100% of the heart (71). RTOG 0617 was a phase III randomized trial to evaluate the potential role of dose escalation for locally advanced NSCLC (60 Gy vs 74 Gy) (71). No benefit with RT dose escalation was found, and decreased survival occurred in the high-dose RT arm. On dosimetric analysis, the volume of heart receiving ≥ 40 Gy (V40) was significantly associated with worse overall survival (67). A recent combined analysis of prospective multicenter NSCLC trials showed a 2-year cumulative incidence of grade ≥ 3 cardiac events of 11%, with MHD independently associated with cardiac events and grade ≥ 3 cardiac events associated with decreased survival (6). Another pooled analysis of patients enrolled in locally advanced NSCLC trials demonstrated that 23% experienced a symptomatic cardiac event, with the rate of symptomatic cardiac events increasing with increasing MHD (72). However, MHD does not always correlate with outcomes and survival in NSCLC studies (69).

For early-stage lung cancer, stereotactic body RT (SBRT) has emerged as the gold standard for inoperable lung cancer. SBRT is characterized by high-dose per fraction treatments with very steep dose fall-off. While the treatment volumes are significantly smaller than locally advanced NSCLC (and without concurrent chemotherapy), the point doses to the heart and its substructures can be significantly higher than those seen with conventionally fractionated RT. When tumor targets are near cardiac substructures for SBRT, serious toxicities have been described, although there is not always a correlation between total heart doses and outcomes (73). However, others have reported an association between overall survival

and maximum dose to the bilateral ventricles (27) or doses to the left atrium (10) or superior vena cava (10). Understanding the association between cardiac dose, cardiac toxicity, and overall survival has proven to be relatively more challenging than in locally advanced NSCLC, because patients receiving SBRT are often nonoperative candidates owing to cardiopulmonary comorbidities.

DATA ON THE IMPORTANCE OF LOCATION OF RADIATION DEPOSITION IN THE HEART. Linear relationships between MHD and cardiac outcomes have been identified in patients treated with RT for breast cancer (2-4), HL (40,41), and childhood cancers (38,51,74). However, for patients with lung cancers, the association between MHD and outcomes has not been as robust (69). This could be due, in part, to the variability in dose distributions across the heart for lung cancers, which are in contrast to the relatively uniform areas of the heart that receive radiation in tangential breast cancer RT or in mediastinal nodal treatments previously given for many lymphomas. Thus, correlations between heart doses and outcomes may be more evident when regions of the heart receiving RT are examined versus whole-heart doses. In addition, with decreasing cardiac doses in breast cancer over time, doses to certain cardiac structures may become more critical to predict the risk of cardiac outcomes.

Correlations between cardiac substructure doses and outcomes have been examined in a number of recent studies, with many associations identified (**Central Illustration**) (3,5,9-29). Studies have demonstrated associations between LAD radiation doses and cardiac and/or survival outcomes (20-22,28). LAD doses correlated with >10% decreases in LV ejection fraction (20) and coronary artery stenosis in patients with breast cancer (21) and coronary artery segment dose correlated with coronary artery stenosis in patients with HL (23). In patients with lung cancer, LAD doses correlated with acute coronary syndrome and heart failure (22) as well as major acute coronary events, especially in patients without CAD (28). Wang et al also reported that LV doses, as well as whole-heart doses, correlated with symptomatic cardiac events in patients with NSCLC (72). In addition, breast cancer studies have found that LV doses correlated with coronary toxicity (3,25). In studies of patients with childhood cancers, LV doses correlated with heart failure (24) and increased left atrial volumes on cardiac magnetic resonance imaging (CMRI) (26). Other studies have found that doses to the ventricles correlate with outcomes such as decreased LV ejection fraction, valvular defects, acute coronary

syndrome, and/or survival (19,20,22,27). In lung cancer, doses to the base of heart and its structures (atria and proximal great vessels) have repeatedly been found to correlate with cardiac outcomes and survival. McWilliam et al used an unbiased approach to identify the base of heart as a region correlating with worse survival in >1,100 patients with lung cancer (9). Other studies have identified associations between cardiac toxicity/survival in patients with lung cancer and doses to the proximal pulmonary artery (16,17), proximal superior vena cava (10), and left atrium (5,10,18,19). In patients with HL, the coronary artery origin (14) and valvular doses (15) correlated with development of coronary stenosis and valvular heart disease. Taken together, studies such as those shown in the **Central Illustration** (3,5,9-29) are beginning to unveil specific areas of the heart for which radiation injury correlates directly with cardiac dysfunction and/or survival. Additional research and prospective studies will further refine our knowledge and ultimately allow better personalization of RT planning to minimize doses to the most critical cardiac structures.

CARDIAC RISK STRATIFICATION, SCREENING, AND SURVEILLANCE

IMPACT OF CARDIOVASCULAR RISK FACTORS. In addition to the risk caused by the radiation itself, a patient's cumulative hazard of RICD is also directly related to underlying cardiovascular risk factors. Consistent with studies in the general population, both traditional risk factors (smoking, hypertension, diabetes mellitus) and imaging risk factors (coronary artery calcifications) have been linked to future cardiovascular events in survivors receiving cardiac radiation across multiple cancer types. In patients with breast cancer undergoing RT, the presence of cardiovascular risk factors doubles the risk of a major coronary event, and baseline ischemic heart disease carries >6-fold higher risk of a future event (2). Similarly, at a median follow-up of 18 years in 4,414 patients with breast cancer treated with and without RT, the combination of smoking and RT tripled the risk of myocardial infarction during follow-up (hazard ratio: 3.04; 95% confidence interval [CI]: 2.0-4.6; $P = 0.039$ for more than an additive effect) compared with nonsmokers who did not receive RT (75). Cholesterol levels also have been linked to development of coronary atherosclerosis in 43 irradiated Hodgkin lymphoma survivors ($\beta = 308$; 95% CI: 213-403) (76). In a cohort of 701 patients undergoing RT for locally advanced NSCLC, baseline coronary heart disease or the equivalent (peripheral vascular disease, stroke, or significant coronary calcifications)

had a 25-fold increase in the hazard ratio of major adverse cardiovascular events, with hypertension carrying a nearly 3-fold increase on multivariable analysis (28). Even risk factors that develop during follow-up after RT, especially hypertension, have been found to add a synergistic and multiplicative increase in the risk for major adverse cardiovascular events in pediatric survivors of cancer (77).

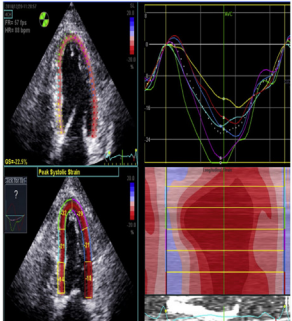
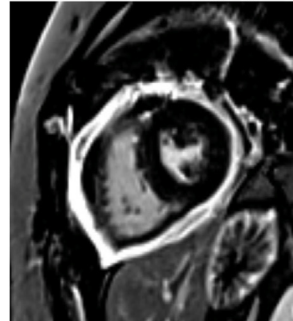
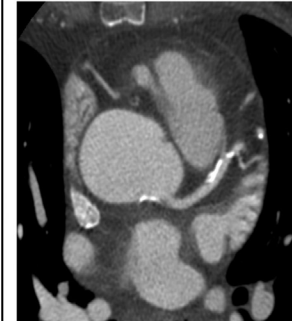
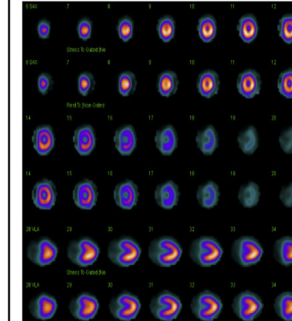
Assessing for coronary artery calcifications can help to further refine a patient's risk for future cardiovascular events after RT. Coronary artery calcium (CAC) on noncontrast CT is a direct measure of a patient's atherosclerotic burden and has been shown to be the best predictor of future cardiovascular events in the general population (78). Significant coronary calcifications before RT have been independently associated with cardiac events after breast RT as well, even after adjustment for the MHD (79). CAC noted on a patient's radiation planning CT or cancer surveillance or staging examinations correlate with more formal CAC assessments, although false negatives can exist owing to slice thickness and lack of gating (80).

IMAGING MODALITIES FOR SCREENING FOR AND DIAGNOSIS OF CARDIOVASCULAR TOXICITY.

In survivors of mediastinal RT, several imaging tools have been used to screen for and diagnose cardiovascular toxicity. Echocardiography, cardiac magnetic resonance imaging, cardiovascular CT, and functional stress testing all have strengths and weaknesses in their sensitivity, specificity, and overall ability to detect and quantify cardiac damage (Figure 3) (81). Although clinical trials are lacking to guide screening intervals and recommendations for particular imaging modalities, a strong understanding of the relative benefits of each modality and research findings to date can help guide clinicians and future research in this area. In addition, expert consensus guidelines exist to help guide the clinician in screening intervals (56,81-85) (Table 2). The goal of screening is to detect heart injury before clinical symptoms develop, especially if preventive medicine can be used.

Optimal employment of each imaging tool will depend on the individual patient's comorbidities, RT exposure, and any previous treatment with anthracyclines or other cardiotoxic therapy. Patients at high risk of cardiotoxicity have been defined as those receiving >30 Gy with the heart in the treatment field, those who received both RT and anthracyclines, younger patients (<50 years of age), high-dose RT fractions (>2 Gy/day), presence and extent of tumor in or next to the heart, and cardiovascular risk factors (81,82). Significant radiation to specific structures in

FIGURE 3 Comparison of Cardiovascular Imaging Modalities for Assessment of Radiation-Induced Cardiovascular Disease

Echocardiography	Cardiovascular Magnetic Resonance Imaging	Cardiovascular Computed Tomography	Stress SPECT
			
<p>Strengths</p> <ul style="list-style-type: none"> • 3D echo and contrast 2D echo have good LVEF reproducibility • No additional radiation • Stress echo is highly specific for ischemia assessment • Readily available • Best for valve assessment <p>Limitations</p> <ul style="list-style-type: none"> • Less accuracy of 2D LVEF without contrast • Prone to artifacts • Limited in coronary disease assessment • May not detect non-obstructive CAD 	<p>Strengths</p> <ul style="list-style-type: none"> • Best in LVEF assessment • No additional radiation • Stress CMR is highly sensitive and specific for ischemia assessment • Best for myocardial fibrosis and pericardial assessment <p>Limitations</p> <ul style="list-style-type: none"> • May not detect non-obstructive CAD • Limited expertise available • Longer time for acquisition 	<p>Strengths</p> <ul style="list-style-type: none"> • Best in coronary disease assessment • Multiple modes of acquisition to decrease radiation exposure • Good for pericardial assessment and for structural procedures <p>Limitations</p> <ul style="list-style-type: none"> • Limited expertise available • Additional, but minimal, radiation exposure 	<p>Strengths</p> <ul style="list-style-type: none"> • Sensitive technique to assess for ischemia • Readily available <p>Limitations</p> <ul style="list-style-type: none"> • May not detect non-obstructive CAD • Not as specific as stress echo • Additional, but minimal, radiation exposure

Major strengths and limitations of 4 major cardiovascular imaging modalities are shown. CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; echo = echocardiography; LVEF = left ventricular ejection fraction; SPECT = single-photon emission computed tomography.

the heart, such as the LAD, should also be considered to confer higher risk (**Central Illustration**) (3,5,9-29), and special consideration should be given to patients who need to undergo surgery, especially cardiac surgery, after cardiac radiation exposure (84,86-88).

Based on the incidence of heart failure and other cardiac abnormalities after RT, current expert consensus guidelines generally recommend echocardiography to screen for cardiac abnormalities 5-10 years after RT and every 5 years thereafter (81,83,84). Patients at high risk for RICD (such as those receiving >30 Gy with the heart in the RT field or combination treatment with RT and anthracyclines), may benefit from echocardiography as early as 6-24 months after receiving RT (56,82). Functional stress testing to evaluate for ischemia and to detect CAD also has been recommended every 5 years beginning 5-10 years after RT (81,83). The recent International Cardio-Oncology Society (ICOS) recommendations place a higher value on detecting nonobstructive CAD with the use of CT imaging in order to start early preventive therapy (84). In patients who are ultimately diagnosed with obstructive CAD, severe valvular disease, or other RICD requiring intervention, additional consideration

needs to be given to risks for radiation-induced fibrosis and scarring in the mediastinum that can affect surgical outcomes and may favor percutaneous intervention (84,87,88). As a particular example, in patients with breast cancer receiving regional nodal irradiation, the ipsilateral internal mammary artery is often in the target volume owing to treatment of the internal mammary lymph nodes (89), making evaluation of left internal mammary artery patency very important in candidates for coronary artery bypass grafting (84).

Echocardiography. Echocardiography is generally the initial imaging test to screen for RICD owing to its wide availability and accessibility, low risk profile, and ability to assess diastolic and systolic function, valvular pathophysiology, and pericardial disease. A comprehensive diastolic assessment is essential in RT survivors, because they are at particular risk of diastolic dysfunction due to RT-induced fibrosis and endothelial dysfunction (90). Resting wall-motion abnormalities can occur secondary to radiation damage directly to the myocardium, but their presence should also alert the treating physician to a high probability of underlying CAD (91).

TABLE 2 Imaging Screening Guidelines and Consensus Recommendations by Major Societies Following Chest Radiation Therapy

Organization(s) (Ref. #)	Year	Significant Risk Factors	Cardiac Structure and Function Screening	Coronary Ischemia Screening
European Association of Cardiovascular Imaging and American Society of Echocardiography (81)	2013	Anterior or left chest RT with ≥ 1 risk factor: <ul style="list-style-type: none"> • High cumulative dose (>30 Gy) • Younger patients (<50 y) • Higher doses of radiation fractions (>2 Gy/d) • Presence and extent of tumor in or next to the heart • Lack of shielding • Concomitant chemotherapy (eg, anthracyclines) • Cardiovascular risk factors • Pre-existing cardiovascular disease 	TTE 5 y after RT in patients at high risk, TTE 10 y after RT in patients not at high risk, TTE every 5 y thereafter	Stress testing 5 y after RT in patients at high risk, and every 5 y thereafter in patients without previous inducible ischemia
International Late Effects of Childhood Cancer Guideline Harmonization Group (56)	2015	Surveillance recommended in those with: <ul style="list-style-type: none"> • Chest radiation dose ≥ 35 Gy • Moderate to high doses of anthracyclines (≥ 100 mg/m²) combined with moderate-to high-dose chest radiation (≥ 15 Gy) • May be reasonable in those with moderate doses of radiation (≥ 15 to <35 Gy) 	TTE no later than 2 y after completion of therapy in high-risk survivors, again at 5 y, and every 5 y thereafter	N/A
American Society of Clinical Oncology (82)	2017	High-dose RT (>30 Gy) where the heart is in the treatment field Lower-dose anthracycline (eg, 250 mg/m ² doxorubicin or 600 mg/m ² epirubicin) in combination with lower-dose RT (<30 Gy) where the heart is in the treatment field	TTE 6-12 months after completion of therapy in patients at increased risk, no specific screening interval recommended thereafter	N/A
Children's Oncology Group (85)	2018	Increased risk: <ul style="list-style-type: none"> • Any anthracycline exposure <i>or</i> • ≥ 15 Gy radiation Highest risk: <ul style="list-style-type: none"> • ≥ 35 Gy <i>or</i> • ≥ 15 Gy in combination with <250 mg/m² doxorubicin (or equivalent) <i>or</i> • Any radiation in combination with ≥ 250 mg/m² doxorubicin (or equivalent) Additional risk factors to consider: <ul style="list-style-type: none"> • <5 y old at treatment, anteriorly weighted radiation field, lack of subcarinal shielding, longer time since treatment 	Annual physical and electrocardiography in patients with ≥ 15 Gy Echocardiography every 5 y: <ul style="list-style-type: none"> • 15-35 Gy <i>or</i> • <250 mg/m² doxorubicin and 0-15 Gy. Echocardiography every 2 y: <ul style="list-style-type: none"> • ≥ 35 Gy <i>or</i> • ≥ 15 Gy and any anthracyclines <i>or</i> • ≥ 250 mg/m² doxorubicin 	Cardiology consultation 5-10 y after radiation in patients at highest risk
European Society of Medical Oncology (83)	2020	Mediastinal RT \pm cardiotoxic chemotherapy, not further specified	Cardiac biomarkers and potentially cardiac imaging 6-12 months after therapy, 2 y after treatment, and possibly periodically thereafter	Evaluation for CAD and ischemia starting at 5 y after RT and every 3-5 y thereafter
International Cardio-Oncology Society (84)	2021	Reasserted previously defined high-risk groups: <ul style="list-style-type: none"> • Mediastinal RT ≥ 30 Gy with the heart in the treatment field • Lower dose RT (<30 Gy) with anthracycline exposure • Patients aged <50 years and longer time since RT • Higher doses of RT fractions (>2 Gy/d) • Presence and extent of tumor in or next to the heart • Presence of cardiovascular risk factors. • Pre-existing cardiovascular disease. 	Guided by individual patient risk: TTE as early as 6-12 months after RT in patients at high risk, and all patients should have TTE by 5 y after RT. Additional TTE and/or NT-proBNP every 5 y can be useful	Focus on diagnosing early CAD rather than ischemia for initiation of preventive therapy Review available CT scans for coronary calcifications In patients without known CAD, screening with stress testing, CAC, or CT angiography every 5 y

CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RT = radiation therapy; TTE = transthoracic echocardiography.

Early post-RT subclinical changes on echocardiography can be seen 1 day after completing RT and include increased echodensity of the anterior cardiac segments (right ventricle wall and ventricular septum), as well as evidence of reduced right ventricular systolic function (92,93). However, these changes have not yet been correlated with future cardiovascular events. Global longitudinal strain

measure via echocardiography may also identify subclinical cardiotoxicity in patients with breast cancer undergoing RT (94), and worse global longitudinal strain has been associated with increased mortality in patients undergoing cardiac surgery (95). LV dosimetry has been shown to be predictive of subclinical dysfunction-related changes in global longitudinal strain following RT (96). The aorto-

mitral curtain thickness on transthoracic echocardiogram may also be used to prognosticate patients with RICD undergoing cardiac surgery, with a value of ≥ 0.6 cm predicting increased mortality (97).

Cardiac magnetic resonance imaging. CMRI is especially useful in patients with poor acoustic windows on echocardiography and for evaluation of myocardial fibrosis and/or pericardial constriction. CMRI is considered to be the reference standard in LV ejection fraction assessment (98), and it can identify myocardial edema and fibrotic changes in the myocardium (99,100). In addition, if transthoracic echocardiography is unable to assess aortic stenosis related to RICD because of technical limitations, CMRI can assess aortic valve area by means of planimetry and aortic valve velocities by means of phase-contrast velocity mapping (101). However, CMRI performs better in identifying regurgitant valvular lesions than in identifying stenotic lesions, and phase contrast may underestimate peak velocities owing to limitations in temporal resolution (101). Real-time cine and myocardial tagging can help in the diagnosis of constrictive pericarditis (102), which can occur as a late complication from RT (86). Myocardial fibrosis can develop secondary to RT (103), and techniques such as late gadolinium enhancement (100), T1 mapping, and extracellular volume fraction (100) allow for its identification. CMRI appears to be more sensitive than echocardiography in detecting LV systolic dysfunction in childhood survivors of cancer with and without previous RT (98). Earlier detection of cardiac dysfunction could allow for earlier intervention, although this approach still needs validation.

Functional stress testing. Patients are at risk for underlying CAD even with normal resting cardiac function. Stress echocardiography, stress single-photon emission CT (SPECT)/positron emission tomography (PET), and stress CMRI are appropriate functional tests to detect evidence of ischemia in survivors of RT. Exercise testing is preferred over pharmacologic studies when possible, given the additional prognostic information derived from a patient's functional status. In deciding between two modalities with similar risk/benefit ratios, non-radiating techniques or techniques with lower additional radiation exposure may be advantageous. Stress PET has the unique ability of assessing coronary physiology noninvasively (104). However, its role in patients with history of RT has not yet been determined. Both stress echocardiography and radionuclide perfusion imaging have been specifically shown to identify post-RT patients with obstructive CAD (91). In a cohort of 294 patients with HL and

>35 Gy to the mediastinum, abnormal stress echocardiography had higher specificity for obstructive CAD than nuclear scintigraphy (89% vs 11%) with similar sensitivity (59% vs 65%) (91).

Perfusion abnormalities are relatively common in RT survivors. In a study by Hardenberg et al, 60% of patients with left breast cancer had resting perfusion defects at 6 months after RT (105). A larger follow-up study from the same group showed persistently high SPECT-perfusion defects, with 57%-71% incidence at 3-6 years after RT (106). In patients with distal esophageal cancer, 42% had LV inferior ischemia after RT according to stress SPECT (107). However, findings in stress SPECT in patients with lung or esophageal cancers receiving RT have not been predictive of future cardiac complications (108).

Cardiovascular computed tomography. Anatomic imaging has the advantage of detecting non-obstructive CAD early in the disease process before ischemia develops, thus allowing for potentially earlier use of preventive medications. Coronary computed tomographic angiography (CCTA) can noninvasively detect and quantify the burden of noncalcified plaque and coronary stenosis in symptomatic and asymptomatic patients, and it has been used to identify asymptomatic CAD in patients with a history of RT to the chest, even with normal stress imaging (109). CCTA notably also has a powerful negative predictive value in ruling out CAD, and the radiation exposure (1-4 mSv) is lower than nuclear perfusion or coronary angiography (109). CAC scans (noncontrast CTs) are able to evaluate for calcified, but not noncalcified plaque, and they have an advantage of even lower radiation exposure (1-1.5 mSv). CAC scans can identify the presence of coronary atherosclerosis secondary to RT (110,111), in addition to helping to risk-stratify asymptomatic CAD in patients with cancer before their RT treatment.

In patients with breast cancer, CAC on RT planning CTs correlated with future cardiac events (79), and CAC on surveillance CTs after RT were more predictive of cardiac events than Framingham risk scores (112). Without requiring further testing, reviewing available CT images may allow for identification of patients at higher risk of CAD and help to direct preventive therapy (113). In patients with NSCLC, coronary calcifications are often present at the time of cancer diagnosis, although unfortunately, an incidental finding of coronary calcifications on CT rarely results in prescription of preventive therapy (114). Small single-center studies suggest that baseline CAC might help to identify subclinical CAD and predict cardiovascular outcomes in those patients (115-117). There may also be a role for CAC surveillance in RT patients to assess RT-

related CAD progression (110,111). Reviewing prior chest imaging may be important in establishing CV risk and can affect management. CCTA is also useful in planning transcatheter valve replacement in patients with RICD-related valve disease (109).

Biomarkers. Natriuretic peptides and troponin levels drawn early after RT have not shown any consistent ability to detect subclinical cardiotoxicity or future cardiomyopathy among several small, generally underpowered, studies across different cancer types. One of the more recent and larger studies examined N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T, placental growth factor (PIGF), and growth differentiation factor (GDF)-15 before and a median of 20 days after RT in 87 patients with cancer (60 breast cancers, 14 lymphomas, and 13 lung cancers) (118). There was no significant increase in troponin or NT-proBNP levels after RT. There was a significant increase in PIGF ($P = 0.005$) and GDF-15 ($P = 0.006$) in patients with lymphomas or lung cancer and a modest increase of borderline statistical significance ($P = 0.054$) in GDF-15 in patients with breast cancer. The study was not able to evaluate whether these biomarker changes correlated with subsequent LV dysfunction. In a small prospective cohort of 51 patients with breast cancer undergoing RT and 78 control subjects, Chalubinska-Fendler et al (119) found no difference in NT pro-BNP or troponin T between the patients with cancer or control subjects before or after RT. Levels of lipopolysaccharide-binding protein, however, drawn 24 hours and 1 month after RT, correlated with heart- and lung-associated dose volume. Higher levels were also associated with diastolic dysfunction (assessed by E/E') measured by means of echocardiography 3 years later (24-hour level: $\beta = 0.41$; $P = 0.032$; 1 month level: $\beta = 0.43$; $P = 0.028$). Future research is warranted to further evaluate this novel biomarker. In survivors of childhood cancer more than 10 years after treatment, NT-proBNP was a useful tool to predict future occurrence of cardiomyopathy (120). Incorporating NT-proBNP into future screening algorithms for long-term survivors of RT is reasonable.

THE THERAPEUTIC APPLICATIONS OF RT TO THE HEART IN THE TREATMENT OF VENTRICULAR ARRHYTHMIAS

Although radiation dose to healthy cardiac tissue can be associated with the development of RICD, as discussed in this review, there are now applications of RT to physiologically and structurally abnormal arrhythmogenic heart tissue that leverage RT-induced changes for clinical benefit. It had been

previously theorized that an ablative RT dose to the electrophysiologic pathways of the heart could intentionally create a heart block. Preclinical work using SBRT on the normal cardiac conduction systems of animal models laid the groundwork in understanding the dose-response relationship and histologic changes of the target and nontarget heart tissue. Pulmonary vein and atrioventricular node radioablation in preclinical models was previously demonstrated with the use of 25 Gy SBRT (121). Lehmann et al also showed a median time to complete atrioventricular block of 11 weeks with no evidence of short-term toxicity in a large animal model (122).

With the demonstration of feasibility of electrical conduction blockade in nonhuman animal models with the use of a dose and fractionation that could be delivered with current RT approaches, the phase I/II ENCORE-VT (Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia) trial was developed to assess the safety and efficacy of this therapy for patients with refractory ventricular tachycardia. The primary end point of reduction in ventricular tachycardia events was achieved in 94% of trial patients. The treatment was well tolerated with a low rate of grade ≥ 3 toxicities (123).

A surprising finding from the ENCORE-VT trial was that the decrease in events emerged in the days following treatment, rather than on the orders of months seen in the preclinical models with normal cardiac substrate (123). These changes also occurred much sooner than subacute cardiac toxicities described in prospective NSCLC trials, where even the earliest cases of atrial fibrillation, heart block, or pericardial effusion occurred no sooner than 1 month after treatment (72). Because the antiarrhythmic effect of RT on the scar target tissue of ENCORE-VT participants occurred within the first 6 weeks, this suggested that the efficacy of RT is likely by a mechanism different from previously proposed myocyte cell death and creation of homogenous replacement fibrosis (turning a functional scar into a nonfunctional scar). In addition, while electrocardiographic (ECG) changes occurred in almost 90% of ENCORE-VT patients with complete ECG data, more than one-half of the changes occurred within the first 3 days. For RT patients who subsequently underwent heart transplantation or died from other causes, their donated heart specimens showed no significant difference in fibrosis levels between the targeted and nontargeted heart tissue (123).

As follow-up from ENCORE-VT continues, secondary analyses are underway to evaluate for long-term changes in cardiac conductivity and function. Although ECG changes were seen in the majority of

patients, there were no clinically significant conduction changes apparent (such as atrioventricular block or dysrhythmias). In patients undergoing trans-thoracic echocardiography before treatment and >12 months after treatment, no LV ejection fraction changes were seen (124). A number of centers have now also treated ventricular tachycardia with SBRT, with similar efficacy in reducing ventricular tachycardia episodes and relatively rapid efficacy (30). Continued surveillance of patients who have received noninvasive cardiac radioablation will better define longer-term cardiac changes, and these findings may inform knowledge of cardiotoxicity following other thoracic RT approaches.

SUMMARY AND CONCLUSIONS

Increasingly advanced and complex RT techniques have significantly improved sparing of cardiac tissue during RT delivery. However, RICD remains a potentially significant toxicity for many patients with thoracic cancers. Improved knowledge of how the location of radiation deposition within the heart affects the risk of RICD will allow better personalization of RT in the future, including creation of dose constraints to specific cardiac substructures in appropriate patients. Long-term data from patients receiving focal high-dose RT for refractory VT may also enhance our knowledge of factors important in

the development of RICD. Enhanced understanding of the pathophysiology of RICD can contribute to improvement in screening protocols to identify pre-clinical RICD and allow for earlier interventions. Together with aggressive cardiovascular risk modification, such efforts should further reduce development of symptomatic cardiac disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the National Institutes of Health (R01HL147884) and National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR002345). Dr Bergom has received research funding from the National Institutes of Health, Susan G. Komen Foundation, and Innovation Pathways. Dr Bradley has received an Ion Beam Application travel grant (April 2018) and funding from the Bankhead Coley Foundation and Ocala Royal Dames Foundation. Dr Ng has received funding from ViewRay. Dr Robinson has received research funding from the National Institutes of Health and the American Heart Association. Dr Mitchell has received research funding from Pfizer, Longer Life Foundation, and Children's Discovery Institute and consultancy for Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS breast cancer, cancer survivorship, childhood cancer, esophageal cancer, imaging, lung cancer, lymphoma, radiation physics

