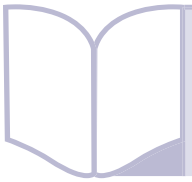
News and Views From the Literature



Thoracic Irradiation

Evaluation of Long-term Cardiovascular Effects

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Cardiac Complications of Thoracic Irradiation

Jaworski C, Mariani JA, Wheeler G, Kaye DM.
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Thoracic irradiation has been the mainstay for treatment of Hodgkin disease, localized breast cancer, and other malignancies such as lung cancer. As these patients remain long-term survivors, the cardiac and vascular complications of thoracic irradiation become evident. Cardiovascular disease is the most common nonmalignant cause of death in survivors of Hodgkin disease and breast cancer. Cardiovascular complications account for 25% of mortality in patients cured of Hodgkin disease.[1] Myocardial infarction is the most common cause of cardiac mortality. The manifestations of cardiovascular disease become evident approximately 20 years postexposure. Thoracic irradiation exposing the left side of the chest exposes the heart and great vessels, particularly the aorta. Survivors who have received radiation therapy are more likely to require coronary revascularization, implantable cardioverter defibrillators, pacemakers, valve surgery, and pericardial surgery. This increase in cardiovascular morbidity is associated with an increase in cardiovascular mortality (Table 1).

Radiation-sparing protocols that have recently been incorporated into treatment regimens still expose patients to significant doses. Patients with Hodgkin disease receive of 30 Gy, and breast cancer patients receive radiotherapy doses between 45 and 50 Gy. The decision whether to employ radiotherapy in treatment regimens needs to take into account the benefit in terms of cancer-free survival and the risk of late cardiac complications. The Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis during a time interval when older radiotherapy protocols were employed. They reported a reduction of annual breast cancer mortality of 13% with the use adjuvant radiotherapy; a concomitant increase in mortality from other causes was 21%.[2] The role of brachytherapy and its long-term risks and benefits, especially in localized breast cancer postlumpectomy, should be better explored.

Irradiation exposes the cardiovascular system to damage as it can affect the pericardium, myocardium, valves, coronary arteries, and conduction system. This damage occurs through a variety of mechanisms, including the increase in generation of reactive oxygen species, which

TABLE 1

Absolute Risk and Excess Risk of Cardiac Mortality in Hodgkin Disease Survivors

	Aleman et al[3]		Swerdlow et al[4]		Castellino et al[5]	
Years Posttreatment	RR	AR	RR	AR	RR	AR
0-5	7.7	6.1	1.7	4.6	—	—
5-10	7.0	10.6	2.3	10.9	5.1	—
10-15	4.5	10.7	1.9	8.5	12.3	—
15-20	6.8	28.7	4.1	28.9	12.3	—
> 20	8.3	63.9	3.1	22.2	26.0	—

AR, absolute risk; RR, relative risk.
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TABLE 2

Risk Factors for Radiation-induced Cardiotoxicity

Total dose > 30-35 Gy
Higher dose/fraction > 2 Gy/day
Field size (volume of heart irradiated)
Relative field weighting (anterior/posterior positioning)
Presence of tumor next to the heart
Younger age at exposure
Time since exposure
Type of radiation source (cobalt)
Cardiotoxic chemotherapy (eg, anthracycline)
Other cardiovascular risk factors (eg, diabetes, smoking)
Technique (reduced with CT plan)

CT, computed tomography.
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leads to an inflammatory response, increased capillary permeability, endothelial dysfunction, stimulation of growth factors, and fibrosis. Risk factors for radiation-induced cardiotoxicity are described in Table 2.

Coronary lesions in patients exposed to radiotherapy are longer as the disease is more diffuse, tubular, more likely to affect the left main artery, ostial right coronary artery, and left anterior descending artery with a greater fibrous content. Interstitial fibrosis within the myocardium is a common finding leading to systolic (but more likely to diastolic) dysfunction. The aortic and mitral valve seem most predisposed to radiation-induced injury with insufficiency—the most likely finding earlier after injury due to valve retraction. Aortic stenosis is observed ≥ 20 years following radiation exposure. Conduction abnormalities, including atrioventricular block, sick sinus syndrome, and QT prolongation, have been described. Right bundle branch block is observed more often than left bundle branch block. Acute radiation pericarditis weeks after exposure was observed more often before radiation reduction protocols were employed. Chronic pericarditis can be observed in 20% of patients who developed acute pericarditis.

There are no official protocols for following patients who have undergone radiation therapy that includes the chest in the therapeutic field. Troponin levels can be followed weeks following treatment to monitor for myocardial necrosis. B-type natriuretic peptide can be a biomarker for preclinical diastolic and systolic function. Stress echocardiography has been recommended 5 years following radiation therapy. Echocardiography can also be used to screen for the development of valvular calcification, insufficiency, and stenosis. Annual electrocardiograms can monitor the development of conduction abnormalities, and Holter monitoring may be helpful in some patients due to the increased incidence of atrial and ventricular arrhythmias. The value of coronary calcium screening has not been fully evaluated for determining the presence of early coronary artery disease. Cardiac and vascular magnetic resonance imaging are ideal technologies to assess the cardiac and vascular systems. Cardiac magnetic resonance is the gold standard for assessing left ventricular ejection fraction. It is also useful in evaluating diastolic function; with the employment of late gadolinium it can detect regional and diffuse fibrosis. ■

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Electrophysiology

Nonischemic Dilated Cardiomyopathy

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Association of Fibrosis With Mortality and Sudden Cardiac Death in Patients With Nonischemic Dilated Cardiomyopathy

Gulati A, Jabbour A, Ismail TF, et al.
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Identifying patients with nonischemic dilated cardiomyopathy (NIDC) who will benefit from internal cardioverter-defibrillators (ICDs) remains a major challenge in clinical electrophysiology. Being able to identify the patient at higher risk of sudden cardiac death (SCD) has major public health implications due to the relatively common prevalence of NIDC (1 in 2500 adults), the cost of ICD placement, inherent ICD implant risks, and the risk of inappropriate shocks.[1,2] Current American College of Cardiology/American Heart Association guidelines state that ICD therapy is indicated for primary prevention of SCD in patients with NIDC who have an ejection fraction $\leq$ 35% and who are in New York Heart Association functional class II or III.[3] However, the rate of appropriate discharge in patients with ICDs and left ventricular ejection fractions (LVEFs) $<$ 35% is only 5.1% per year, limiting the utility of this guideline-based approach.[4]

Gulati and coworkers evaluated the hypothesis that the presence of fibrosis within the left ventricular wall would add prognostic accuracy to LVEF in assessing the risk of SCD in patients with NIDC. They performed a prospective, longitudinal evaluation of 472 patients with NIDC referred to a single center in England between 2000 and 2008. Cardiovascular magnetic resonance imaging with late gadolinium enhancement (LGE-CMR) was used to determine the presence or absence of ventricular midwall fibrosis (MWF). The presence of LGE correlates histologically with the presence of fibrosis. In this study, the presence, location, and extent of fibrosis were assessed. The predefined endpoint was all-cause mortality with a predefined secondary endpoint being a composite of cardiovascular mortality, heart failure, stroke, or thromboembolic event. Two other prespecified endpoints included an arrhythmic composite of SCD or aborted SCD, and a heart failure endpoint of heart failure death, unplanned heart failure hospitalization, or cardiac transplantation.

Patients with MWF had an all-cause mortality of 26.8% compared with only 10.6% in those without MWF (hazard ratio = 2.96; $P < .01$). After a multivariate analysis, the presence of MWF remained a highly significant risk factor for total mortality and, to a lesser extent, the percentage extent of MWF. The secondary arrhythmic composite endpoint (sudden death, aborted sudden death, appropriate ICD shock, ventricular tachycardia, or sustained ventricular tachycardia) also was significantly higher in the patients with fibrosis (29.6% vs 7%; $P < .001$). Using the presence or absence of MWF in addition to LVEF, they found an additional 18.5% of patients who would have their SCD risk upgraded and undergo ICD implant and 10.6% of patients who would have their risk downgraded and avoid ICD implant.

The results of this single-center study show in dramatic fashion the potential utility of LGE-CMR for assisting with risk assessment of SCD and subsequent ICD implant. The results of this single-center study await confirmation by larger multicenter trials before generalized use can be recommended. ■

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