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Radiation-Associated Cardiac Disease

A Practical Approach to Diagnosis and Management

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ABSTRACT

Radiation-associated cardiac disease (RACD) results in complex clinical presentations, unique management issues, and increased morbidity and mortality. Patients typically present years or even decades after radiation exposure, with delayed-onset cardiac damage sustained from high cumulative doses. Multimodality imaging is crucial to determine the manifestations and severity of disease because symptoms are often nonspecific. Comprehensive screening using a coordinated approach may enable early detection. However, timing of intervention should be carefully considered in these patients because surgery is often complex and high-risk second surgeries should be minimized in the long-term. This review aims to provide treating physicians with a comprehensive and clinically focused overview of RACD, including clinical/imaging manifestations, multi-modality screening recommendations, and management options.
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Several radiation-sensitive thoracic malignancies have obvious spatial orientation to cardiovascular structures including the following: breast cancer (particularly left-sided), Hodgkin lymphoma, lung cancer, esophageal cancer, and various other mediastinal tumors. Although survival and recurrence data support radiation therapy, it can result in sustained dose to cardiovascular structures, leading to radiation-associated cardiac disease (RACD) (1-3). Acute radiation damage to the heart has been recognized since the 1920s, when high-dose, wide-field radiation therapy thoracic portals were the norm and minimization of cardiovascular irradiation was not necessarily prioritized (4). The delayed cardiovascular effects of such therapies have been recognized more recently, largely due to the latency of presentation and particularly in those treated for Hodgkin's disease 20 to 40 years ago (5). Contemporary radiation regimens incorporate provisions to optimize radiation delivery to the tumor, while minimizing repeated irradiation of surrounding normal structures, including the heart (6). These include the following: shielding measures, advanced respiratory gating techniques with deep inspiratory breath-holds and activated breathing control, using smaller repeated fractions, and using advanced treatment algorithms with narrow tangential beams at different angles (**Figures 1 and 2, Table 1**). Radiation alternatives, such as proton therapy, are also proving to be efficacious and less cardiotoxic options (7). Although these measures will likely reduce the risk of RACD, current outcomes in RACD still remain considerably influenced by historical practices (8,9).

This review aims to provide a clinically focused overview of RACD, including clinical/imaging manifestations, screening recommendations, and management options. Data for this review were identified using MEDLINE, Current Contents, and PubMed and using the screening terms "radiation" and "heart disease." Historical articles published in English from the 1950s onward provide information about remote treatment practices, whereas current management recommendations are based upon articles published during the last 20 years and our own cumulative institutional experience.

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INCIDENCE AND MANIFESTATIONS OF RACD

RACD is a spectrum of deleterious effects, ranging from preclinical findings to symptomatic clinical disease (Table 2). Acute cardiac inflammation can occur at the time of treatment, resulting in myocarditis or pericarditis. If apparent, this may potentially suggest that an individual has sustained increased cardiac dose, or is more susceptible to longer-term RACD. Late cardiovascular effects manifest decades after treatment and result from diffuse interstitial fibrosis and collagen deposition, along with luminal narrowing of both arteries and arterioles due to accumulation of myofibroblasts and resultant intimal proliferation. This can result in a variety of cardiovascular complications grouped under the umbrella of RACD including the following: myocardial fibrosis, valvular heart disease (regurgitation and/or stenosis), vasculopathy including coronary artery disease (CAD), pericardial disease, and conduction system dysfunction (Central Illustration). Clinically, there is often overlap of pathologies manifesting within individuals. This can contribute to significant management challenges, especially because many patients have additional radiation damage to their lung parenchyma and present with nonspecific symptoms, such as dyspnea or fatigue, which can be difficult to differentiate from cardiac disease and may affect cardiac surgical risk. Multimodality imaging is, therefore, crucial to diagnose and differentiate the concurrent pathologies, as well as to guide subsequent treatment.

MYOCARDIAL DISEASE. Myocardial damage appears related to total radiation dose, fraction size, and volume of heart in the radiotherapy field. Radiation-related cell damage can result in activation of acute inflammatory cascades and development of a pro-fibrotic milieu, translating into myocardial fibrosis, with reduced micro-vascular proliferation and density. This radiation-induced myocardial fibrosis can result in myocardial dysfunction spanning progressive stages of diastolic dysfunction to overt systolic heart failure. The prevalence of radiation-associated cardiomyopathy is ~10%. The anterior position of the right ventricle makes it susceptible to damage, although this is often under-recognized due to relative wall thinness and suboptimal visualization.

Biventricular radiation-associated fibrosis is diffuse and typically follows a nonischemic pattern.

ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CT = computed tomography

ECG = electrocardiogram

LVEF = left ventricular ejection fraction

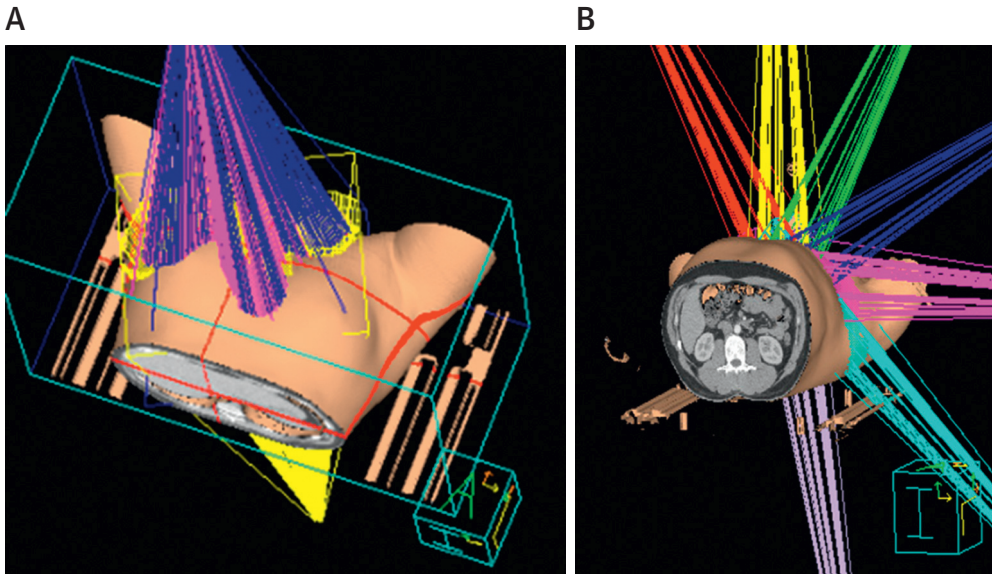
PCI = percutaneous coronary intervention

RACD = radiation-associated cardiac disease

RAPD = radiation-associated pulmonary disease

TAVR = transcatheter aortic valve replacement

FIGURE 1 Radiotherapy Arrangements for Chest Radiation in Lymphoma



(A) Traditional anterior-posterior approach, **(B)** intensity-modulated radiation therapy, where overlapping beams minimize cardiac dose.