Seminars in RADIATION ONCOLOGY

Contemporary Breast Radiotherapy and Cardiac Toxicity

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Long-term cardiac effects are an important component of survivorship after breast radiotherapy. The pathophysiology of cardiotoxicity, history of breast radiotherapy, current methods of cardiac avoidance, modern outcomes, context of historical outcomes, quantifying cardiac effects, and future directions are reviewed in this article. Radiation-induced oxidative stress induces proinflammatory cytokines and is a process that potentiates late effects of fibrosis and intimal proliferation in endothelial vasculature. Breast radiation therapy has changed substantially in recent decades. Several modern technologies exist to improve cardiac avoidance such as deep inspiration breath hold, gating, accelerated partial breast irradiation, and use of modern 3-dimensional planning. Modern outcomes may vary notably from historical long-term cardiac outcomes given the differences in cardiac dose with modern techniques. Methods of quantifying radiation-related cardiotoxicity that correlate with future cardiac risks are needed with current data exploring techniques such as measuring computed tomography coronary artery calcium score, single-photon emission computed tomography imaging, and biomarkers. Placing historical data, dosimetric correlations, and *relative* cardiac risk in context are key when weighing the benefits of radiotherapy in breast cancer control and survival. Estimating present day cardiac risk in the modern treatment era includes challenges in length of follow-up and the use of confounding cardiotoxic agents such as evolving systemic chemotherapy and targeted therapies. Future directions in both multidisciplinary management and advancing technology in radiation oncology may provide further improvements in patient risk reduction and breast cancer survivorship.
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Introduction

Survivorship care is critical to the care of the modern day woman with breast cancer. As part of this, the magnitude of cardiac risk conferred by breast radiation with modern techniques must be understood. Radiation therapy for breast cancer has changed substantially over recent decades. Challenges from prior decades included 2-dimensional (2D) fluoroscopic treatment planning, low-energy radiation, and the lack of clinical data regarding the effect of incidental cardiac irradiation. Significant leaps in technology and clinical technique define the current era, as computed tomography (CT) simulation, computerized planning, and radiobiological knowledge exponentially increased. Darby et al[1] provided valuable data that the dose does matter, and care taken to limit the dose to the heart can translate into real decreases in clinically observed cardiac toxicity. The role of active breathing modalities, patient positioning, careful planning, or accelerated partial breast irradiation (APBI) in cardiac avoidance are discussed. Additionally, the effect of hypofractionation in incidental cardiac radiation is explored. The radiographic, biological, and dosimetric correlates for clinically significant cardiovascular outcomes are reviewed in detail.

Given the multifactorial effects of oncologic treatment, interdisciplinary survivorship care is valuable for patients with risk factors for coronary artery disease (CAD) or cardiomyopathies. This article reviews the cardiac toxicity of breast radiotherapy and covers historical context, evolution of modern treatment, quantifying current outcomes, and future directions for breast cancer management.

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Pathophysiology of Radiation-Induced Cardiac Disease

Late effects of radiation on blood vasculature is because of endothelial, smooth muscle cell, and myofibroblast intimal proliferation as well as lipid-containing macrophages forming plaque buildup along the lining of arterial walls. Initial endothelial cell radiation and oxidative injury leads to proinflammatory cytokines as well as profibrotic cytokines such as fibroblast growth factor, platelet derived growth factor, and TGF-beta, among others.[2-4] Changes are characterized by collagen deposition and endothelial cell proliferation, similar pathologically to atherosclerosis, in medium and large size vessels. In small to medium size vessels, additional accumulation of foam cells and lipid-laden macrophages are noted in the intima, along with subendothelial fibrosis.[5] These potentiate the age-related progression of CAD. Additionally, microvascular damage to myocardium leads to inflammatory and prothrombotic changes that can cause cell death. This results in the replacement of myocardial tissue with progressive fibrosis. Hence, these pathologic changes influence cardiac perfusion, wall motion, and ventricular filling. Pericardial disease is secondary to acute and late pericardial injury from radiation causing fibrin deposition and pericardial fat replacement by collagen. Valvular disease and cardiac arrhythmias are associated with microvascular damage causing fibrotic changes to valves or microvascular damage causing cardiac myocyte conduction abnormalities.[5] Breast radiation therapy effects to vessels and myocardium primarily potentiate CAD or perfusion defect cardiomyopathy, whereas pericarditis, valvular disease, and arrhythmias are less commonly seen.

History of Breast Radiotherapy: The Scope of the Problem

Although megavoltage (MV) linear accelerators were developed in the 1950s, more widespread adoption began in the 1960s and 1970s.[6] The era of the 1970s and 1980s included the transition from orthovoltage and cobalt machines to higher energy MV linear accelerators. Although therapeutic radiology advanced, equally significant advances were made in diagnostic imaging. After the first clinical use of the CT scan in the 1971 for a head CT, adoption of body cross-sectional imaging became progressively more common in the 1980s and 1990s.[7] With the use of imaging technology, radiotherapy transitioned from 2D planning with x-rays and standardized chest measurement for fields, to customized planning made possible by visualization of individual patient anatomy with CT scans. Computer-based software emerged, allowing for advanced treatment planning. Dose and therapy calculations done by hand, assuming standardized geometry, gave way to computerized dose calculations, inhomogeneity corrections, and customized treatment based on individual anatomy.[6] CT scans were used for better target delineation, and on-board imagers including initially MV and later kilovoltage imaging have improved accuracy of treatment delivery.[8]

Independent of technological advancements, increased clinical knowledge allowed for omission of fields or nodal coverage in appropriate patients to decrease toxicity. Treatment of node-negative patients with comprehensive nodal radiotherapy was standard for the Danish premenopausal and postmenopausal trials enrolling from 1982-1989 and 1982-1990, respectively.[9,10] Additional data on outcomes from low-risk patients ushered the eventual omission of internal mammary (IM) and supraclavicular coverage by radiation oncologists.[11,12] Field designs previously used in the 1980s and 1990s, such as the reverse hockey stick field (also used in postmastectomy radiation therapy trials), increased cardiac exposure with the heart directly in beam.[13,14] With improvements in clinical knowledge, such techniques were abandoned with improved visualization of the underlying anatomy and greater recognition of the effect of long-term cardiac toxicity.[12]

The use of breast radiation therapy increased as clinical data established radiation as an integral component to breast cancer treatment. For instance, use of radiation as primary initial treatment increased from 18% in 1973 to over half of all patients with breast cancer receiving treatment by 2011.[15] With a greater proportion of the population receiving radiation therapy, the importance of long-term toxicity—particularly cardiac toxicity—increased. Meta-analyses noting the overall survival benefit from radiation therapy also noted an increase in noncancer mortality, owing primarily to cardiovascular causes from women treated in the 1960s through the 1980s.[16] Thus, improvements in technology and the clinical awareness of late long-term cardiac toxicity ushered in a new era of cardiac avoidance.

Modern Advances in Treatment: A New Era

As data accumulated on the cardiac effects of breast radiation, radiation oncologists and physicists rose to the challenge and developed new ways of treating the breast without excessive cardiac radiation. Advances in cardiac avoidance are numerous and include heart blocking, enhanced patient positioning and verification, active breathing modalities, accelerated partial breast treatment, altered fractionation, 3D or fixed gantry intensity modulated radiation therapy (IMRT) treatment planning, and protons.

Heart Blocks

Customization of the treatment field with a heart block may be appropriate, particularly in patients with well-visualized surgical beds. Using this technique, the average percentage of breast tissue that may be underdosed is 2.8%.[17] Overall, local recurrence rates were not significantly different between patients with field heart blocks vs those without blocks.[17] In the appropriate patient, heart blocks offer an alternative to more advanced techniques to decrease cardiac volume while maintaining local control.