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Association of Breast Cancer Irradiation With Cardiac Toxic Effects
A Narrative Review

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IMPORTANCE To promptly recognize and manage cardiovascular (CV) risk factors before, during, and after cancer treatment, decreasing the risk of cancer therapy–related cardiac dysfunction is crucial. After recent advances in breast cancer treatment, mortality rates from cancer have decreased, and the prevalence of survivors with a potentially higher CV disease risk has increased. Cardiovascular risks might be associated with the multimodal approach, including systemic therapies and breast radiotherapy (RT).

OBSERVATIONS The heart disease risk seems to be higher in patients with tumors in the left breast, when other classic CV risk factors are present, and when adjunctive anthracycline-based chemotherapy is administered, suggesting a synergistic association. Respiratory control as well as modern RT techniques and their possible further refinement may decrease the prevalence and severity of radiation-induced heart disease. Several pharmacological cardioprevention strategies for decreasing cardiac toxic effects have been identified in several guidelines. However, further research is needed to ascertain the feasibility of these strategies in routine practice.

CONCLUSIONS AND RELEVANCE This review found that evidence-based recommendations are lacking on the modalities for and intensity of heart disease screening, surveillance of patients after RT, and treatment of these patients. A multidisciplinary and multimodal approach is crucial to guide optimal management.

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Supplemental content

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Identification of patients with cancer who have an increased risk of death from heart disease is especially important given the advent of improved cancer therapy and the increasing age of the surviving population.[1] Among patients with cancer in the US, the estimated heart disease–specific mortality rate is 10.61 per 10 000 person-years, which is 2.24 times higher than the standardized rate for fatal heart disease.[2] In 2017, coronary heart disease was the leading cause of deaths attributable to cardiovascular (CV) disease (42.6%) in the US, followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%), diseases of the arteries (2.9%), and other conditions (17.6%).[3]

Patients with prostate, colorectal, breast, or lung cancer constitute most of the patients with cancer dying of CV disease.[2] Much of the CV risk is associated with age, obesity, diet, and a sedentary lifestyle, all of which have a predisposition to both cancer and CV disease. Therefore, it is crucial for health care professionals to promptly recognize and manage CV risk factors before, during, and after cancer treatment to lower the risk of cancer therapy–related cardiac dysfunction. This necessity has led to the development of the field of cardio-oncology, which refers to the treatment of CV disease in patients with cancer that focuses on the adverse effects of cancer therapy.[4] After recent advances in breast cancer treatment, mortality rates from breast cancer have decreased. This decrease has led to a growing number of survivors with a potentially higher CV disease risk that might be associated with the multimodal approach, including anthracycline-based chemotherapy,[5] ERBB2 (formerly HER2) antagonists,[6] and breast irradiation.[7]

Radiotherapy (RT) for early-stage breast cancer decreases recurrence rates and improves breast cancer–specific survival for most patients.[8,9] Although radiation treatments for breast cancer have been optimized over time, long-term follow-up of some trials has shown that patients may have an increased risk of heart disease. This finding is most likely attributable to an incidental irradiation outside of the target volumes.[10] Women who underwent radiotherapy for cancer of the left breast had higher rates of major cardiac toxic effects than those who underwent radiotherapy for cancer of the right breast, with a relative increase in the rate of major coronary events of 7.4% per Gy of radiation received by the heart and with no apparent threshold.[11]

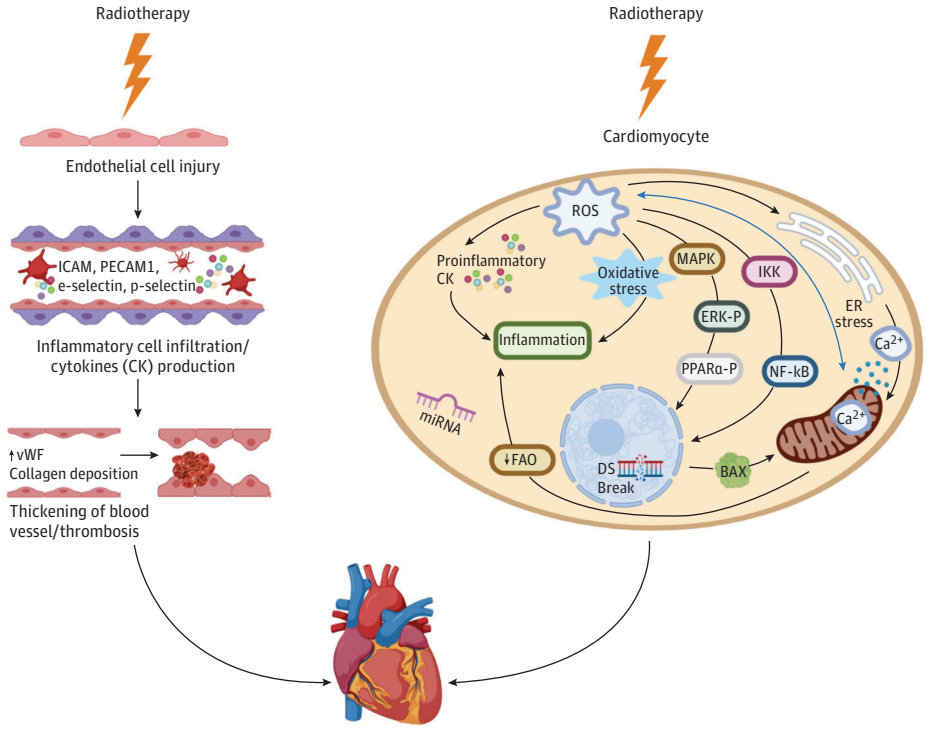
This narrative review focuses on the pathophysiological mechanisms, clinical presentation, assessment and diagnosis, and toxic effect predictive models of radiation-induced heart disease (RIHD) as well as the strategies for treatment and prevention of morbidity and mortality in long-term heart disease.

Observations

Pathophysiological Mechanisms

Radiation-induced heart disease can occur as acute radiation myocarditis, although it mostly develops as a long-term consequence

Figure 1. Overview of Putative Pathogenesis of Radiation-Induced Heart Disease



BAX indicates BCL2-associated X protein; Ca, calcium; CK, cytokines; DS, double-stranded; ER, endothelial reticulum; ERK-P, extracellular signal-regulated kinase; FAO, fatty acid oxidation; ICAM, intercellular adhesion molecule; IKK, inhibitor of nuclear factor κ B kinase; MAPK, mitogen-activated protein kinase; miRNA, micro RNA; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PECAM1, platelet endothelial cell adhesion molecule; PPARα-P, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; and vWF, Von Willebrand factor. This image was created using BioRender software (http://www.biorender.com).

of fibrosis leading to ventricular dysfunction or restrictive cardiomyopathy.[7] Even though the pathophysiological mechanisms of RIHD are not completely understood, it is known that multiple factors are involved in cardiac toxic effects. Early damage from RT is mostly associated with acute and chronic inflammatory changes, and late toxic effects are partly associated with both oxidative stress and inflammation.[12] Macrovascular and microvascular injury, which develops in a multifactorial manner by endothelial cell damage, leads to activation of inflammatory and atherosclerotic responses.[13] Several signaling pathways within the cardiomyocytes, including apoptosis and mitochondrial dysfunction, have been correlated with RIHD.[14] Specifically, a vicious cycle of reactive oxygen species produced by mitochondria and Ca^{2+} release caused by the endoplasmic reticulum may be a factor in long-term toxic effects, which eventually leads to cell cycle arrest.[15] MicroRNAs have also been found to be involved in the regulation of radiation-induced DNA damage and premature aging.[16] An overview of the putative pathogenesis of RIHD is shown in **Figure 1**.

Clinical Presentation and Assessment and Diagnosis

Clinical presentations of RIHD (although cardiac injury may also have a subclinical presentation) include a spectrum of syndromes: pericardial disease (acute and delayed pericarditis, pericardial effusion, and constrictive pericarditis), coronary artery disease, myocardial infarction, valvular heart disease, and rhythm disturbances.[17] Clinical signs are often indistinguishable from those of any other cause, representing a challenge for the clinician. These signs may include chest pain, shortness of breath, peripheral edema, fatigue, and arrhythmias (**Table 1**).[11,17-21] The risk of RIHD development has been associated with the amount of substructures exposed to RT; age; the interval since RT; combination with drugs, including chemotherapy; and the presence of coexisting CV risk factors, such as hypertension, smoking status, high body mass index, dyslipidemia, and diabetes.[3] Although the relative risk is substantial, the absolute risk for RT-related cardiac morbidity remains low compared with the general population. Moreover, modern technologies may have lower toxic effects given that patients with breast cancer are currently treated with lower radiation doses and advanced RT techniques, allowing doses to organs at risk to be kept far below the recommended constraints.

Different strategies have been implemented to detect RIHD. Early diagnosis can decrease long-term damage and thus the incidence of fatal events. Because RIHD is a lifelong risk, assessment requires long-term follow-up.[18] However, clear recommendations are lacking on the modalities and intensity of heart disease screening and surveillance after RT. Three-dimensional echocardiography currently represents the criterion standard for detecting early signs of cardiac toxic effects. Early detection allows for analysis of both morphological characteristics and functional aspects,[22] including left ventricular ejection fraction, global longitudinal strain, left ventricular diastolic function, left ventricular filling pressure, pulmonary pressure, and right ventricular function.[23] Cardiac computed tomography is not routinely used, although it is more accurate than other techniques in detecting coronary artery calcification.[24] Non–ionizing radiation modalities may be most appropriate because of concerns regarding cumulative radiation dose in patients with cancer; that is, cardiac computed tomography can expose patients to substantial radiation with each examination. Echocardiography provides additional information on car-

Table 1. Timing, Symptoms, and Differential Diagnosis in Patients With Heart Disease After Radiation Treatment for Breast Cancer[a]

Timing	Heart disease	Symptom/sign	Differential diagnosis between RIHD and other causes
5 to 20 y	CAD	Angina; myocardial infarction Nonanginal chest pain (common occurrence within 3 y)	Morphological structure of RT-related CAD same as CAD Assessment of time to symptoms onset and coexistent cardiac risk factors
10 y (symptomatic)	Myocardial injury	Restrictive cardiomyopathy leading to diastolic dysfunction, partially accompanied by a slight reduction of LV systolic function	Predictive parameters of RT-related CAD: Dose to the mediastinum >30 Gy Dose 35% >38 Gy (heart volume) Mean dose to 5% >12 Gy (heart volume within the beam) Mean dose >2.5 Gy (whole-heart volume) RT to internal mammary nodes
4.5 to 11.5 y (asymptomatic) >16.5 y (symptomatic)	Valvular disease	Angina, syncope, dyspnea, and/or heart failure	For patients with breast cancer, data are conflicting on the association of RT with valvular dysfunction Incidence associated with mediastinal RT doses of >30 Gy Increased risk with younger age at irradiation Interruptions of elastic fibers without rheumatic endocarditis changes (pathology)
6 mo to 20 y (peak at 5 y)	Conduction system disease	All degrees of AV block, sick sinus syndrome, bundle branch block, prolongation of the QTc interval	Presentation analogue to other causes Rarely clinically relevant after-RT exposure for breast cancer
During treatment (wk) or after treatment up to 10 y	Pericardial disease	Pleuritic chest pain, dyspnea, fever, friction rub, and decreased QRS voltage	Predictive parameters of RT-related pericardial disease: Mean dose >26 Gy Maximum dose >47 Gy Protein-rich exudates in the pericardial sac and fibrin in the mesothelial lining pericardial cavity (pathology)

Abbreviations: AV, atrioventricular; CAD, coronary artery disease; LV, left ventricular; RIHD, radiation-induced heart disease; RT, radiotherapy.

[a] Data from Darby et al,[11] 2013; Gagliardi et al,[17] 2010; Darby et al,[18] 2010; Larsen et al,[19] 1992; and Carlson et al,[20] 1991.

diac structure, valve function, hemodynamics, and physiological features that are not typically found with computed tomography scanning. The need to improve early detection has increased the use of cardiac magnetic resonance imaging. Although cardiac magnetic resonance imaging is not cost effective (because of limitations in availability and cost), it is capable of providing myocardial tissue characterization, including the detection of myocardial edema and fibrosis.[25] Moreover, with the incorporation of global longitudinal strain, echocardiography is more sensitive to subtle damage of the myocardial ultrastructure that would otherwise be undetectable. The increase of both troponin T and N-terminal pro–brain natriuretic peptide levels in the blood has been reported to be a highly sensitive and specific biomarker correlated with myocardial damage.[26,27] In a more recent study, an increase in ST2 level, a marker of fibrosis, during postoperative RT was associated with worsening cardiac systolic function over time.[28]

Toxic Effect Predictive Models

Cardiac toxic effect rates from breast cancer randomized clinical trials are summarized in **Table 2**.[7,8,29-38] Based on these studies, several predictive models have been proposed for estimating the risk of RIHD.[39] Combining dosimetric data with toxic effect outcomes is fundamental to estimating the risk of cardiac toxic effects.[11] Although no clear threshold (or safe) radiation dose exists for cardiac exposure,[11] the mean heart dose (MHD) has been a pragmatic and relevant parameter for RIHD prediction for decades.[11] A 7.4% increase in the relative risk of a major cardiac event has been estimated for each additional Gy of MHD.[11,39] The Early Breast Cancer Trialists' Collaborative Group performed a systematic review of lung and heart doses in breast cancer regimens and individual data meta-analyses of 40 781 women randomized to RT or no RT in 75 trials.[40] The cause-specific mortality and excess rate ratios per Gy of MHD for cardiac mortality was 1.30 (95% CI, 1.15-1.46; $P < .001$) on the basis of 1253 cardiac deaths. Detailed analyses indicated 0.04 (95% CI, 0.02-0.06) excess rate ratios per Gy whole-heart dose. Other research groups found that the relative risk of coronary artery disease increased by 16.5% per Gy of MHD during the first 9 years after irradiation.[41] However, MHD might be considered an obsolete way to estimate the risk of heart damage; the newest research looks at the dose to individual substructures such as vessels. Replacing MHD with the proportion of the volume of the left ventricle receiving a dose of 5 Gy or more was found to be another reliable parameter that could improve the estimation of acute cardiac events.[41] Because different doses at each cardiac substructure have distinct pathophysiological outcomes, different normal tissue complication probability models based on the anatomical dose distribution to estimate CV radiation risks also could be used.[42]

Table 2. Cardiac End Point Outcomes From Main Randomized Clinical Trials on Breast Cancer

Source	Cardiac end point	Study design	Cases, No.	Cardiac events	Cardiac events, No. (%)		RT planning
					RT cohort	No RT cohort	
Rutqvist et al,[29] 1992	Cardiac mortality[a]	RT vs no RT	639 (RT); 321 (no RT)	All events	41 (6.4)	18 (5.6)	3D
				Death from myocardial infarction	24 (3.8)	8 (2.3)	
				Other cardiovascular disease	17 (2.7)	10 (2.8)	
Valagussa et al,[30] 1994	Cardiac events[a]	RT vs no RT	360 (RT); 465 (no RT)	All events	63 (17.5)	25 (5.4)	2-D
				ECG ST-segment and T-wave transient abnormalities	23 (6.4)	2 (0.4)	
				ECG signs suggestive of ischemic heart disease	11 (3.1)	6 (1.3)	
				Disturbances of heart rate and rhythm and/or conduction	10 (2.8)	NR	
				Pericarditis	2 (0.6)	NR	
				Death form congestive heart failure	2 (0.6)	NR	
				Other cardiovascular diseases	15 (4.2)	NR	
Cuzick et al,[7] 1994	Cardiac mortality[b]	RT vs no RT	3935 (RT); 4006 (no RT)	All events	151 (3.8)	108 (2.6)	2-D
				Death from cardiac disease	151 (3.8)	108 (2.6)	
Houghton et al,[31] 1994	Cardiac mortality[b]	RT vs no RT	1400 (RT); 1424 (no RT)	All events	55 (3.9)	38 (2.7)	2-D
				Death from cardiac disease	55 (3.9)	38 (2.7)	
Højris et al,[32] 1999	Cardiac events[a]	RT vs no RT	1525 (RT); 1521 (no RT)	All events	89 (5.8)	93 (6.1)	2-D
				Ischemic heart disease	46 (3.0)	49 (3.2)	
				Acute myocardial infarction	26 (1.7)	22 (1.4)	
				Death from ischemic heart disease	12 (0.8)	13 (0.9)	
				Death from myocardial infarction	5 (0.3)	9 (0.6)	
Woodward et al,[33] 2003	Cardiac events[b]	RT vs no RT	470 (RT); 1031 (no RT)	All events	12 (2.6)	5 (0.5)	2-D
				Death from myocardial infarction	8 (1.7)	5 (0.5)	
Clarke et al,[8] 2005	Cardiac mortality[b]	RT vs no RT	32 800	All events	2961 (9.0)	NR	NR
				Death from circulatory disease	1510 (4.6)		
				Death from heart disease	1106 (3.4)		
				Death from stroke	345 (1.0)		
Halyard et al,[34] 2009	Cardiac events[a]	RT vs no RT	1418 (RT); 520 (no RT)	All events	23 (1.6)	16 (3.0)	3D
				Congestive heart failure	22 (1.5)	14 (2.7)	
				Death from cardiac disease	1 (0.1)	2 (0.4)	
Killander et al,[35] 2014	Cardiac mortality[a]	RT vs no RT	682 (RT); 358 (no RT)	All events	90 (13.2)	26 (7.2)	2D
				Death from cardiac disease	90 (13.2)	26 (7.2)	
Hennequin et al,[36] 2013	Cardiac events[b]	IM-MS RT vs no IM-MS RT	1334	All events	26 (1.9)	NA	2D
				Cardiac disease, IM-MS RT	15 (1.1)		
				Cardiac disease, no IM-MS RT	11 (0.8)		
Poortmans et al,[37] 2015	Cardiac events[b]	IM-MS RT vs no IM-MS RT	3866	All events	234 (6.0)	NA	2D to 3D
				Cardiac disease, IM-MS RT	125 (3.2)		
				Cardiac disease, no IM-MS RT	109 (2.8)		
Whelan et al,[38] 2015	Cardiac events[b]	Regional RT vs no regional RT	1820	All events	12 (0.6)	NA	2D to 3D
				Cardiac disease, regional RT	8 (0.4)		
				Cardiac disease, no regional RT	4 (0.2)		

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; ECG, electrocardiogram; IM-MS, internal mammary and medial supraclavicular nodes; NA, not applicable; NR, not reported; RT, radiotherapy.

[a] Primary end point of the study.

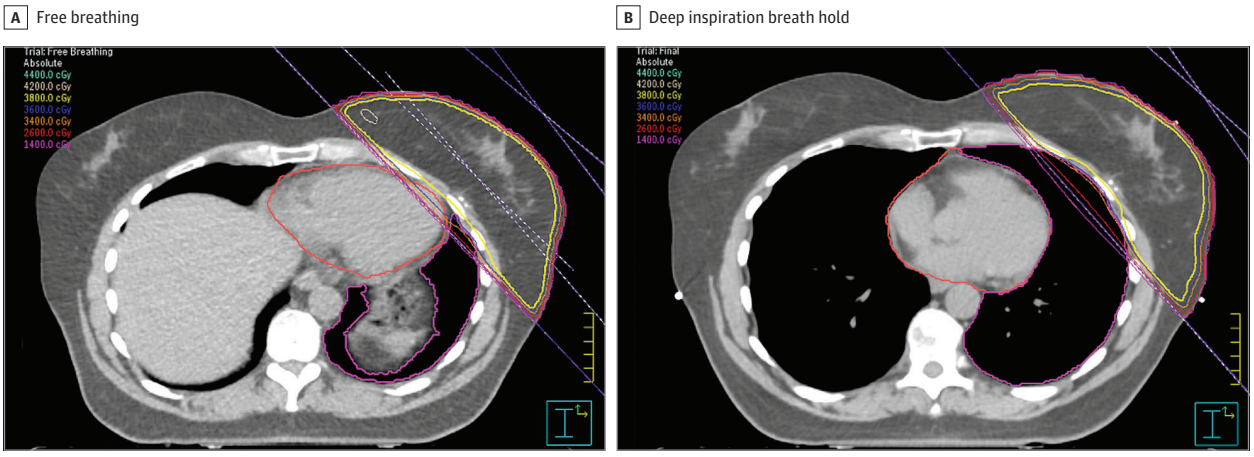
[b] Secondary end point of the study.

Prevention and Treatment Strategies

Heart Dose and RT Techniques

Because of the increased awareness of the risk of RT-related CV disease, the breast cancer RT community has strived to decrease heart dose. Modern RT presents considerably fewer risks than the techniques from 20 years ago,[40] and evidence shows that heart doses are decreasing.[43] Traditionally, the most used technique for whole-breast irradiation is 3-dimensional conformal RT (3D-CRT) with 2 opposing tangential photon beams. However, more advanced techniques, including intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), are increasingly used. These advanced techniques use multiple beams

Figure 2. Changes in Internal Anatomy Between Free Breathing and Deep Inspiration Breath Hold (DIBH)



Both images represent the same anatomical level within the breast tissue, but the inflation of the lungs causes the heart (outlined in red) to rotate away from the chest wall. Notice that the tangential radiation beams (purple) intersect the heart (hence deposit dose) in free breathing but not in DIBH. Image reproduced with permission from Katherine Jones, MSc, The Christie NHS Foundation Trust, Manchester, England.

and computer-driven optimization to achieve highly conformal dose distributions around often complex target volumes, frequently leading to a larger volume of nontarget tissue receiving a low-dose bath.[44] Hybrid techniques (combination of 3D-CRT and IMRT or VMAT) have been proposed as a possible compromise.[45] The simplest and most common implementation of hybrid RT is often called *field-in-field technique* or *tangential IMRT* and can improve dose homogeneity (important for cosmesis) without increasing the number of beam angles.[46,47] Multifield (multiangle) IMRT and VMAT techniques may further improve homogeneity in complex cases, but they are not always associated with a reduction in heart dose compared with tangential techniques (3D-CRT or field-in-field technique).[46,48-50]

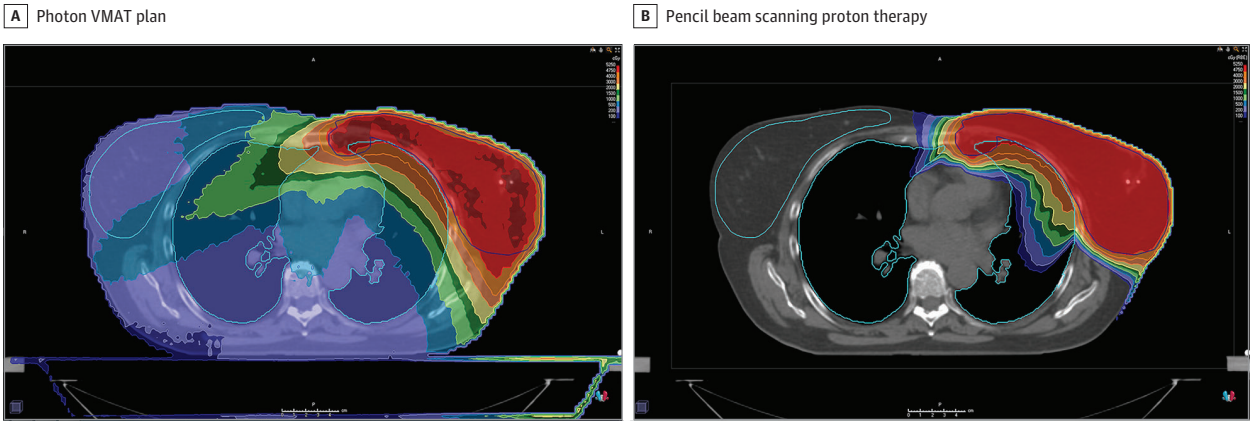
Heart dose varies with patient anatomy, cancer laterality, and the inclusion of nodal regions as target volume.[51] A systematic review of published breast RT studies showed that including the internal mammary chain increases MHD by about 4 Gy, but does so with large variations even within apparently similar techniques.[52]

Several national and international groups have strived to provide recommendations on dose constraints to the whole heart (eTable 1 in the Supplement), but a general consensus is lacking. In addition, the constraints that referred to 25-fraction and 15- to 16-fraction regimens need to be revised for recently introduced extreme hypofractionation regimens (ie, 5.2 Gy × 5 fractions).[53] For accelerated partial breast irradiation treatments, the dose constraints reflect the low doses delivered to the heart because of the decreased target volume. Recent reports include dose constraints at cardiac substructures, such as the left anterior descending artery or left ventricle. More substructures may be included as the understanding evolves and as advanced tools (eg, automatic delineation using artificial intelligence) become more widely available.[54] Those constraints serve as guidelines; therefore, a balance between target coverage and organs-at-risk doses that are as low as reasonably achievable must be reached in each patient according to the patient's anatomy and risk factors.

Respiratory control, often referred to as (moderately) *deep inspiration breath hold*, is arguably the most common approach used to decrease the dose to the heart (**Figure 2**). At deep inspiration, the inflation of the lungs increases the distance between the heart and the chest wall, decreasing the dose to the heart[52] and the lungs[55] while facilitating tumor coverage.[56] Positioning the patient prone or on the side can also be beneficial for patients with large, pendulous breasts, requiring no regional irradiation[52]; however, this positioning requires dedicated equipment and poses additional challenges in patient setup.[57] Deep inspiration breath hold is compatible with several RT techniques, such as IMRT or VMAT and proton beam therapy (PBT). Proton beam therapy can also decrease the dose to the heart, which can be useful in select patients such as those with pectus excavatum.[58] However, increased skin toxic effects and suboptimal cosmetic results have been reported with the use of PBT[59,60] and were mostly associated with the use of older PBT techniques. Similar to photon-based RT, PBT technology has evolved dramatically in the past decade: newer PBT facilities include advanced intensity modulation (eg, pencil beam scanning) and on-board image guidance. Future clinical research is needed to provide evidence of the role of this complex and expensive treatment modality in breast cancer (**Figure 3**).

The change of fractionation regimens (eg, from 50 Gy/25 regimen to 40 Gy/15 regimen) will lead to decreases in physical and radiobiologically equivalent heart doses. Appelt et al[61] compared heart dose distributions for different hypofractionation schedules (START [UK Standardisation of Breast Radiotherapy] A and B trials[62] and the Canadian trial [Hypofractionated Radiotherapy Post-Lumpectomy in Women With Node Negative Breast Cancer][63]) with the conventional 50 Gy per 25 regimen. Appelt et al[61] found that the dose to the heart, which was adjusted for fraction size using the linear quadratic model, was generally lower after hypofractionated compared with conventionally fractionated schedules, even for low values of α or β. However, whether this decrease will lead to a reduction in cardiac toxic effects remains unknown.

Figure 3. An Example of Dose Distribution From Photon Volumetric Modulated Arc Therapy (VMAT) Compared With Pencil Beam Scanning Proton Therapy for a Patient Treated for Breast and Internal Mammary Nodes in Free Breathing



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Precision Medicine and De-escalation of Treatments

Several de-escalation approaches have been evaluated over time as strategies to decrease the burden of treatments while maintaining equivalent efficacy outcomes. Both tumor stage and biological qualities are factors in survival outcomes for breast cancer and should be the cornerstone of precision medicine.[64] Omission of postoperative RT for patients aged 65 years or older (or for frail patients with considerable comorbidities) with early-stage hormone receptor–positive, node-negative, low-risk breast cancer can be considered, providing that adjuvant endocrine therapy is prescribed.[65]

In several countries, moderate hypofractionation represents the standard of care for whole breast irradiation after breast-conserving surgery.[63] Currently, further reduction of treatment times might be expected given that delivering 26 Gy of whole breast irradiation in 5 fractions has been demonstrated to be equivalent at 5 years with 40 Gy in 15 fractions for whole-breast and chest wall irradiation.[53] Conversely, given some of the long-term outcomes observed in the FAST trial (FAST Phase III Trial of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer) and the established track record of 40 to 42.5 Gy in 15 to 16 fractions,[66] further research and a wide consensus are needed before a 5-fraction regimen can be adopted in our clinical practice. Partial-breast irradiation has been introduced as an alternative treatment approach to whole-breast irradiation for selected low-risk patients. Several large phase 3 trials have demonstrated the noninferiority of partial breast vs whole-breast irradiation in terms of local recurrence and similar or decreased toxic effect using different available techniques.[67-70] Physical RT properties are different for each partial-breast irradiation technique, substantially altering dose distribution, irradiated volumes, dose homogeneity, and skin doses, all of which may have different clinical outcomes.[71] Specific studies focusing on technical concerns, safety profile, and new relevant end points for patients at low risk of recurrence, such as quality of life, will further help the decision-making process.

Pharmacological Interventions

There has been an ongoing interest in biomedical substances that may counteract the adverse effects of ionizing radiation. Studies suggest that RIHD can be prevented by using some drugs, including statins, angiotensin-converting enzyme inhibitors, and antioxidants (eTable 2 in the Supplement).[72,73] In the acute response period after radiation exposure to normal tissues, statins can inhibit the activation of transcription factor NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells).[72] Angiotensin-converting enzyme inhibitors impede the production of reactive oxygen species to decrease myocardial injury and increase the production of nitric oxide to protect vascular cells by reducing the adverse effects on the bradykinin system.[73] Moreover, several antioxidants have shown decreased adverse cardiac effects when administered before irradiation in preclinical settings. Several therapeutic targets are being explored, including anti-inflammatory, antifibrotic, and antiapoptotic mediators (eTable 2 in the Supplement). Given its antioxidant and antifibrotic properties, metformin hydrochloride has been shown to reduce radiation-induced cardiac toxic effects, possibly minimizing radiation damage to the heart or coronary artery.[74] Overall, the benefits of several compounds have been demonstrated in preclinical studies, but data on these drugs in patients with RIHD are limited.

Discussion

Although radiation treatments for breast cancer have been optimized over time, long-term follow-up has shown that patients with breast cancer may have an increased risk of CV disease. Many of the reported studies are old, however, and do not apply to the modern RT era, in which the cardiac doses have decreased dramatically with new techniques (ie, IMRT, VMAT, and deep inspiration breath hold), and the current risk of cardiac events has become substantially low. Stroke and heart disease have similar pathophysiological functions in patients with cancer, and the incidence of both conditions increases with RT.[2,21] However, clear recommendations are lacking on the modalities and intensity of CV disease screening and surveillance in patients with breast cancer after exposure to ionizing radiation.

Patients with breast cancer are often treated with cardiotoxic agents, in addition to RT (ie, anthracycline-based chemotherapy and

anti-ERBB2 therapies). The risk of cardiac toxic effects is higher in these patients, suggesting a synergistic association with cardiac risk. Preclinical evidence showed that RIHD might be modulated by the programmed cell death 1 axis and that programmed cell death 1 blockade should be administered with careful RT planning.[75]

Respiratory control is arguably the most practical and successful approach to minimizing the radiation dose to the heart. De-escalation approaches decrease the burden of treatments, including the radiation dose to the organs at risk, thereby lowering late CV complications. Treatment prescription, including target volume selection and dose coverage, should be individually balanced on the basis of estimated risks of both tumor and CV risk factors. This balance may result in accepting underdosing and/or omitting parts of the target volumes, such as internal mammary nodes, in patients in whom CV risk factors prevail, whereas in others increased heart doses might be accepted in case of high-risk tumor factors.

Although several pharmacological cardioprevention strategies have been identified for patient candidates to receive an anticancer therapy with cardiotoxic agents,[4] no feasible treatment for RIHD is currently available in routine clinical practice. Strategies to decrease CV risk factors (ie, blood lipids, arterial tension, obesity, and diabetes) should be handled with even more precision in patients who are being treated for cancer, depending on their CV risk factors and oncological prognosis.

Conclusions

Adopting strategies aimed at decreasing the cardiac RT dose, combined with advances in pharmacological cardiological interventions, should lead to both a decrease in the absolute risk of toxic effects and a relative increase in cardiac toxic effects for patients who undergo irradiation. Patient awareness of the cardiac risks associated with RT for breast cancer and multidisciplinary counseling are crucial in the management of patients with breast cancer.

ARTICLE INFORMATION

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