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Authors

Tuzovic, Mirela
Finch, William
Yang, Eric H

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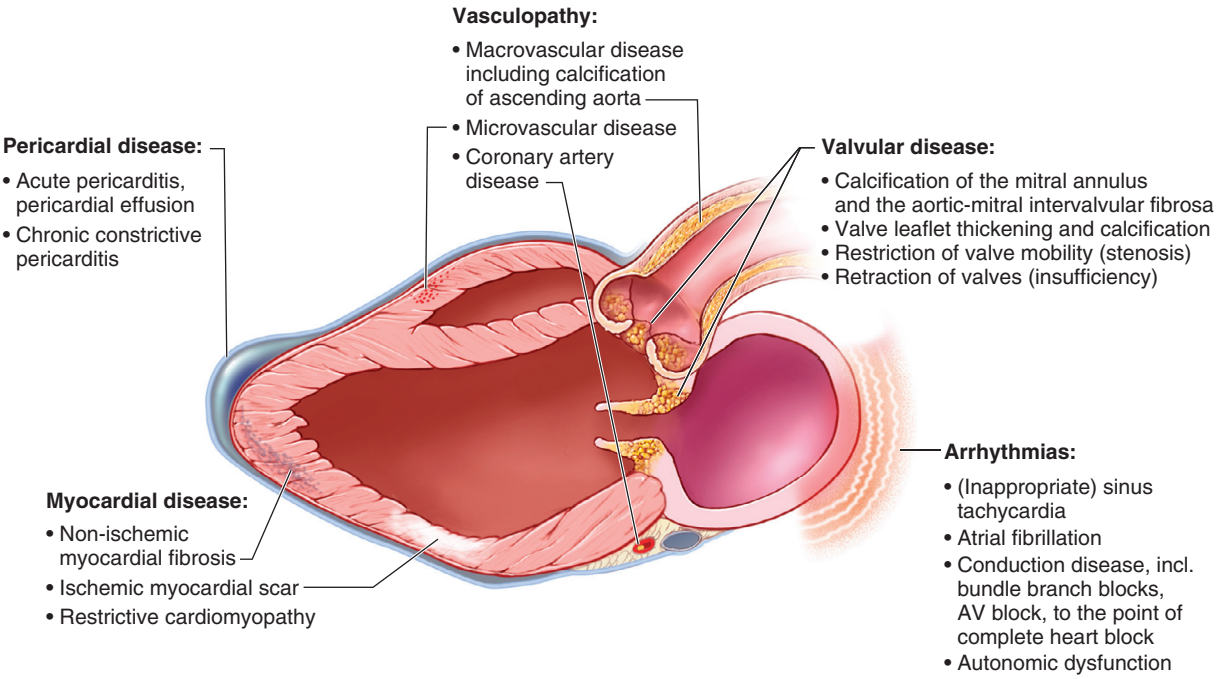
4 Radiation Therapy Cardiovascular Risks

MIRELA TUZOVIC, WILLIAM FINCH, AND ERIC H. YANG



CHAPTER OUTLINE

KEY POINTS

- Radiation therapy can lead to various forms of cardiovascular disease, including cardiomyopathy, heart failure, coronary artery disease, valvular heart disease, pericardial disease, and autonomic dysfunction.
- Dose sparing is the single most important preventive strategy, accomplished by shifting from a large field (e.g., mantle radiation) to an involved field, from photons to protons, and from none to standard use of ancillary techniques such as breath holding and prone positioning.
- Whereas advancements in the delivery of radiation therapy are expected to decrease the long-term risk

KEY POINTS—cont'd

of radiation-induced heart disease, no "safe" radiation dose threshold has been defined and the risk may be rather linear even in the low-dose range spectrum.

- Besides dose, risk factors for radiation-induced heart disease to consider include age at time of radiation exposure (<5 years and >65 years), additional cancer therapies (especially anthracyclines), and the presence of cardiac comorbid conditions (esp., ischemic heart disease and myocardial infarction).
- All risk factors should be considered to direct to the appropriate radiation techniques and patients should be appropriately counseled regarding risks and benefits mitigation strategies.
- Among cardiac surveillance parameters, strain imaging might be the most promising, indicating subclinical cardiac dysfunction during and early after radiation therapy; however, the long-term significance of those changes, including implications for treatment and long-term cardiotoxicity, are unknown.

Radiation therapy (RT) is commonly used to cure, halt, or palliate the manifestations and/or symptoms of many types of cancers (e.g., Hodgkin lymphoma [HL], breast, lung, and esophageal cancer), often in combination with surgical resection and/or chemotherapy. Although RT can provide significant benefit for the treatment of cancer, it is important to recognize that RT carries significant risks to healthy tissue that may inadvertently be exposed. RT causes tissue injury primarily through the generation of oxidative stress; inflammation is seen acutely and fibrosis over time.[1]

Radiation-induced heart disease (RIHD) is typically noted in patients who receive high doses of radiation for thoracic malignancies where the cardiac silhouette overlaps with the radiation field. RIHD can manifest in a variety of disease states, including cardiomyopathy, coronary artery disease, valvular dysfunction, and pericardial disease (see Central Illustration). The risk of RIHD is influenced by multiple factors, including the radiation dose and technique, concomitant administration of cardiotoxic chemotherapy such as with anthracycline agents, age at the time of exposure, time interval since exposure, and patient-specific cardiovascular risk factors (Table 4.1). It is critical for providers to consider the risk, appropriately counsel patients, and to participate in discussions with care team providers regarding the best modes of therapies and risk mitigation strategies before radiation therapy is applied. The specific disease elements of RIHD, including screening and management, will be discussed in Chapter 26.

RADIATION DOSE AND TECHNIQUE

Modern RT for the treatment of HL, breast, lung, and esophageal cancer is performed using medical linear accelerators to produce megavoltage x-ray beams, with the beam being tailored to the tumor using collimators and blocks.[2] Radiation dose is commonly described in terms of gray (Gy), the International System (SI) unit for absorbed radiation dose (Table 4.2). Therapeutic doses of radiation for common malignancies range from 30 to 60 Gy delivered to the tumor. They are fractionated into multiple doses separated temporally (Table 4.3). Dose-sparing is the single most important preventive strategy; a list of techniques used to reduce radiation exposure to the heart is provided in Table 4.4.

Historically, large areas (e.g., mantle field radiation) and high doses of radiation (40 to 45 Gy) were

TABLE 4.1 Types of Radiation-Induced Heart Disease and Relevant Risk Factors

RADIATION-INDUCED HEART DISEASE	RISK FACTORS
Pericarditis	Radiation dose
Ischemic heart disease	History of coronary artery disease, cardiovacular risk factors, younger age at time of exposure
Cardiomyopathy/congestive heart failure	Anthracycline use, cardiovacular risk factors
Valve disease	Radiation dose, anthracycline use

TABLE 4.2 Units of Radiation Exposure

UNIT	TYPE OF UNIT	CONVERSION FACTOR
Rad[a]	Absorbed radiation dose	1 rad = 0.01 Gy
Gray (Gy)[a]	Absorbed radiation dose; SI unit	1J/kg = 1 Gy = 100 rad
Rem[b]	Dose equivalent	1 rem = 0.01 Sv; 1 rem = 1 rad[c]
Sievert (Sv)[b]	Dose equivalent; SI unit	1 Sv = 100 rem; 1 Sv = 1 Gy[c]

[a]Rad and grays are units of energy per mass.
[b]Rem and sieverts are units of energy per mass adjusted by a dimensionless factor to account for a potential for biological damage.
[c]Rem and rad are equivalent and sieverts and grays are equivalent for radiograph and gamma radiation.

TABLE 4.3 Malignancies Whose Treatment May Include Radiation Therapy at the Outlined Doses and Generation of a Radiation Risk to the Heart

MALIGNANCY	DOSE (Gy)
Hodgkin lymphoma	30–36
Breast cancer	45–50
Gastric carcinoma	45–50
Esophageal carcinoma	45–50
Lung cancer	50–60
Thymoma	60

Adapted from Finch W, Lee MS, Yang EH. Radiation-induced heart disease: long-term manifestations, diagnosis, and management. In: Herrmann J, ed. *Clinical Cardio-oncology*. 1st ed. Philadelphia: Elsevier, 2016.

TABLE 4.4 Cardiac-Sparing Mechanisms

TECHNIQUE	CARDIAC-SPARING MECHANISM
Breath hold	With inspiration, distance from chest wall to the heart increases
Prone position	Breast falls away from chest wall Increases distance from the heart to radiation therapy (RT) beam
Intensity modulated RT	Computerized leaves and dose planning algorithms allow for shaping of radiation field to limit cardiac dose
Proton beam irradiation	Utilizes difference in properties of protons compared with photons to allow for reduced dose fall off
Accelerated partial breast irradiation	Smaller target volume allows for possible decreased dose to the heart
Intraoperative RT	Smaller target volume and, in some cases. lower energy reduced dose to the heart

Adapted from Shah C, Badiyan S, Berry S, et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. *Radiother Oncol*. 2014;112(1):9–16.

used for the treatment of HL. Of note, doses of 30 Gy or higher have been associated with the greatest proportion of morbidity and mortality caused by RIHD.[3] With the aforementioned dose-sparing techniques, such as radiation blocks (shielding), smaller dose fractions, and involved-node radiation therapy (in which only the involved nodes are irradiated),[4,5] the relative cardiovascular mortality risk could be reduced from 5.3 to 1.4.[5] Acute manifestations, such as pericarditis, are nearly eliminated nowadays.[6]

The cardioprotective benefit of dose fractionation is supported by experimental studies.[4,7,8] For patients, the ideal fractionation regimen to reduce RIHD is not known, but hypofractionated whole breast irradiation (42.56 Gy/16 fractions) resulted in a lower rate of acute toxicity compared with conventional radiation (50 Gy/25 fractions).[9] Otherwise there are no indications of inferior outcomes at 10 years when hypofractionated RT is compared with conventional RT.[9–11] Evidence of obstructive coronary artery disease and abnormalities on myocardial perfusion scans correlate with the left ventricular volume included in the radiation therapy field.[12] Newer radiation techniques with smaller radiation fields help to minimize the radiation volume. Intensity-modulated radiation therapy (IMRT), for example, can improve dose distribution with the ultimate goal of delivering homogeneous radiation to target tissue and minimizing doses absorbed by critical structures[13] (Fig. 4.1A). IMRT may be particularly beneficial in patients undergoing repeat RT for relapsed disease or for patients with very large tumor burden.[14]

In addition to fractionation and minimizing the delivered dose, RT planning and custom radiation blocks can reduce the dose absorbed by the heart. In the case of breast cancer, RIHD is primarily a concern with RT of the left breast, which results in at least twice the radiation dose to the heart compared with that to the right breast, and a higher risk for accelerated atherosclerosis.[15,16] No safe threshold of cardiac radiation dose exists: for every gray of absorbed dose there is an approximate 7% increased risk of coronary artery disease (CAD), with a higher risk observed in patients with conventional CAD risk factors.[17] The lowest dose that has been found to be associated with CAD is 2.8 Gy.[18] This being said, no "safe" radiation dose threshold has been defined and the risk may be rather linear even in the low-dose range spectrum (Fig. 4.2).

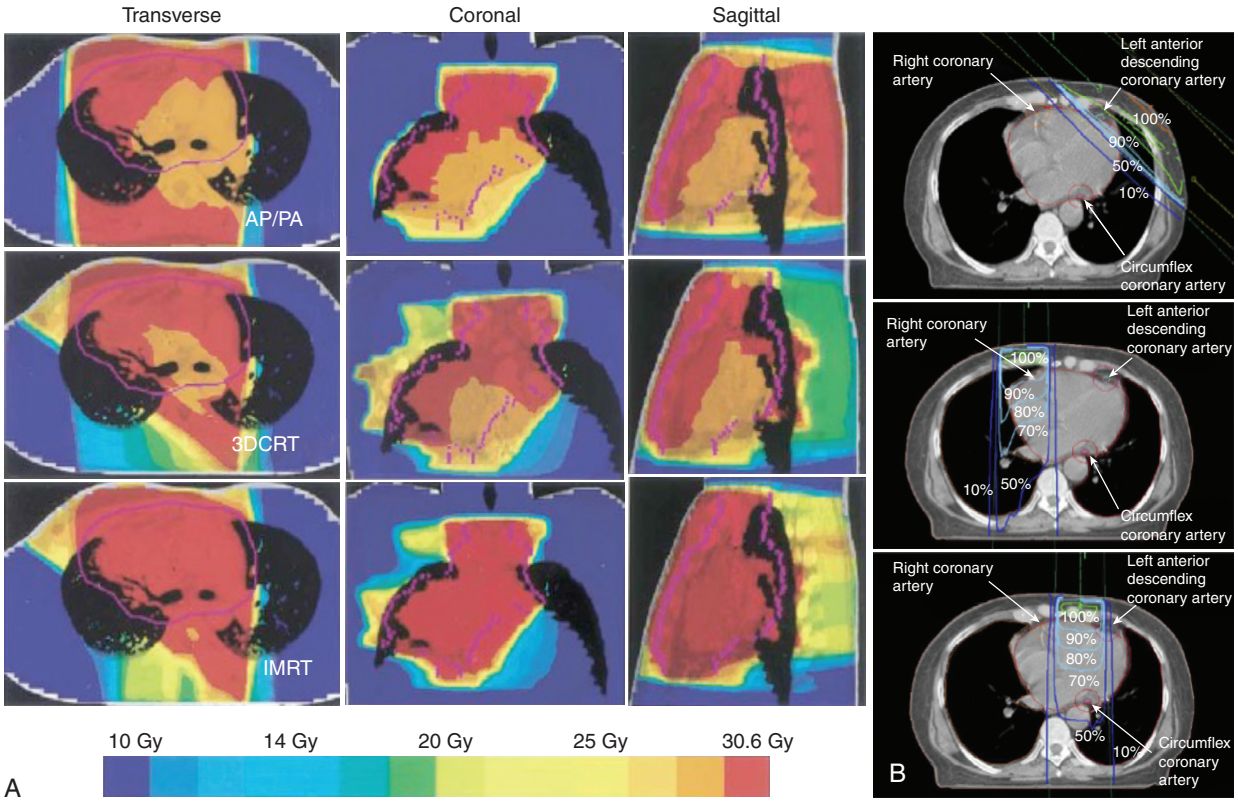


FIG. 4.1 **A,** Comparison of dose distribution of conventional parallel opposed (*AP/PA*) versus three-dimensional conformal radiation therapy (3-*DCRT*) versus intensity-modulated radiation therapy (*IMRT*) plans. (a) Example 1: large volume. (b) Example 2: repeat radiation therapy (RT). **B.** Axial computed tomography sections showing dose distributions from right and left 6-MV direct anterior internal mammary fields and left ^{60}Co pair radiotherapy. *Isodose lines* correspond to percentages of given dose. Three main coronary arteries are outlined, with 1-cm margin added to each. (**A,** From Goodman KA, Toner S, Hunt M, Wu EJ, Yahalom J. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. *Int J Radiol Oncology Biol Phys.* 2005;62:198–206. **B,** From Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 1950–1990s. *Int J Radiation Oncology Biol Phys.* 2007;69(5):1484–1495.)

Strategies to reduce cardiac dose during left breast RT include computed tomography planning to ensure the heart is not within the radiation field (see Fig. 4.1B), tangential (as opposed to anterior) radiation beams, and cardiac radiation protection blocks.[19–21] Historically the myocardium involving the left anterior descending coronary artery would receive higher doses, but with contemporary RT CAD is no longer lateralized, depending on which breast is treated.[22,23] Furthermore, the recent Danish Breast Cancer Cooperative Group trials, which randomized patients to RT and surgery or surgery alone, found no increase in atherosclerotic cardiovascular disease with RT.[21,22] These more recent studies suggest that modern cardiac dose reduction strategies are proving effective at minimizing RIHD. RT of the internal mammary chain of lymph nodes is also utilized. Internal mammary node RT, which is often delivered using anterior fields, increases the absorbed dose of the heart and techniques between 1979 and 1986 continued to be associated with an elevated risk of heart failure.[24] With modern techniques the overall cardiac toxicity of internal mammary RT appears to be low at least on short-term follow up.[25] Internal mammary RT has not been found to result in increased RIHD-related mortality at 10-year follow up and it reduces the risk of breast cancer recurrence.[26,27]

AGE AT TIME OF EXPOSURE

Children are more vulnerable to serious radiation-related complications compared with adults, both

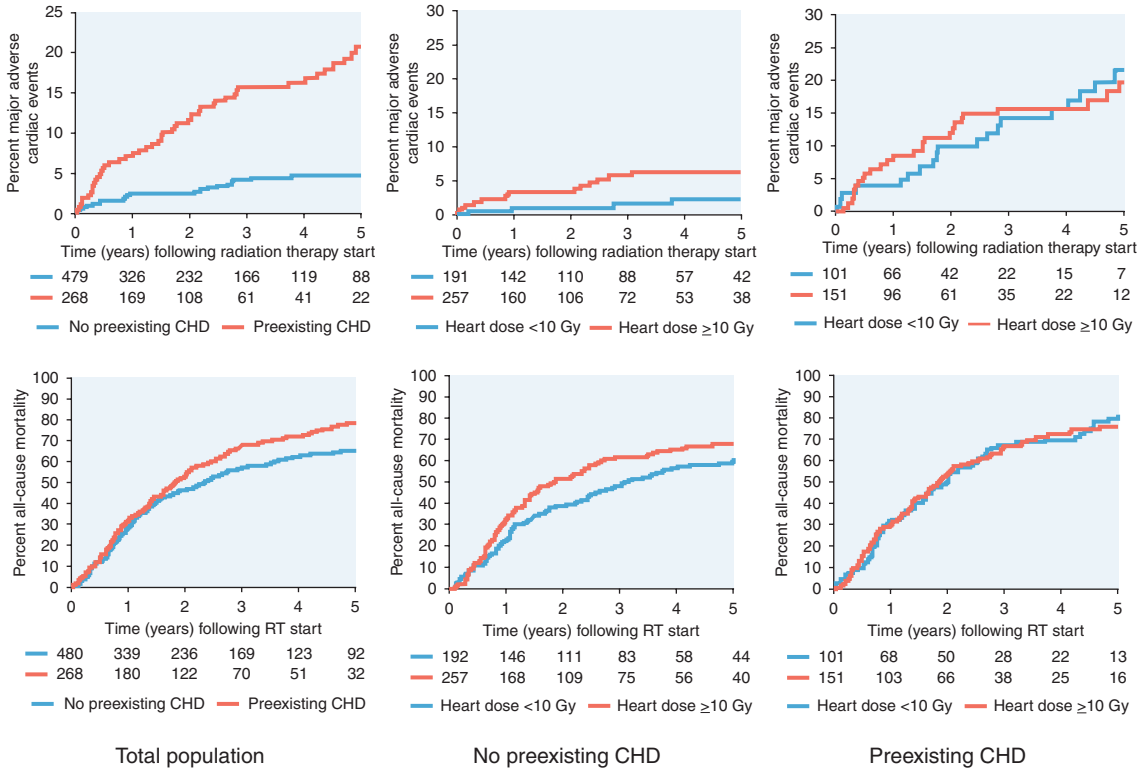


FIG. 4.2. Cardiac radiation dose, cardiac disease, and mortality in patients with lung cancer. *Upper panels*: Cumulative incidence of major adverse cardiac events (MACE) stratified by preexisting coronary heart disease (*CHD*) (Gray's $P < .001$) or MHD in patients without preexisting CHD (Gray's $P = .025$) and patients with preexisting CHD (Gray's $P = .98$). *Lower panels:* All-cause mortality estimates stratified by preexisting CHD (log-rank $P = .003$) or mean heart dose (MHD) in patients without preexisting CHD (log-rank $P = .014$), and patients with preexisting CHD (log-rank $P = .66$). (From Atkins KM, Rawal B, Chaunzwa TL, et al. Cardiac Radiation Dose, Cardiac Dose, and Mortality in Patients with Lung Cancer. *J Am Coll Cardiol*. 2019:73:2976–987.)

owing to growing and developing organs and to a longer life expectancy with more time to develop complications.[28,29] Adult childhood cancer survivors from the Childhood Cardiac Registry in the Netherlands had a 27% prevalence of cardiac dysfunction based on screening with echocardiography. Multivariate regression analysis showed that younger age at diagnosis (age 0 to 5 had an odds ratio [OR] of 2.94 compared with age >15 years), time since diagnosis (>25 years following diagnosis had an OR of 0.11 compared with 5 to 10 years following treatment), anthracycline dose (cumulative doses of 151 to 300 mg/m^2 had an OR of 3.98, whereas cumulative doses of >450 mg/m^2 had an OR of 10.58 when compared with 1 to 150 mg/m^2), and thoracic radiotherapy were all predictive of left ventricular dysfunction. It is worth noting that two-thirds of the patients had also received chemotherapy with anthracyclines, which are known to cause cardiomyopathy.[30] Children and adolescents with HL treated with radiation and/or chemotherapy at Stanford Hospital between 1961 and 1991 had high risks of death from heart disease (relative risk [RR], 29.6), death from acute myocardial infarction (MI; RR, 41.5), and death from other cardiac disease (RR, 21.2).[31] Patients who died had received between 42 and 45 Gy of radiation to the mediastinum between the ages of 9 and 20 years.[32] A second analysis on a broader spectrum of 2232 patients with HL treated with radiation therapy (72% mantle field) at Stanford Hospital between 1960 and 1990 confirmed a 45 times higher risk of death owing to acute MI with radiation exposure before age 19.[5]

TIME INTERVAL AFTER RADIATION THERAPY

As alluded to above, the risk of RIHD and cardiac mortality increases with a longer duration after radiation therapy. In the Stanford study noted above, the risk of cardiac death increased substantially with increasing duration of follow up: the relative risk of death caused by an acute MI was 2 for patients within 5 years of treatment compared with a relative risk of 5.6 at 20 years following radiation.[5] A retrospective cohort study of the medical records of 2524 Dutch patients with HL treated between 1965 and 1995 evaluated more types of cardiac disease, which showed a significant increase in the risk of ischemic heart disease, as well as cardiomyopathy/congestive heart failure (HF) and valvular heart disease even 35 years or more after treatment. The highest risk of cardiac disease was noted in patients treated before age 25 and in those who were 20 to 47 years posttreatment (when compared with those patients treated 5 to 10 years ago).[30] Similar results have been shown for patients with breast cancer where the excess risk of cardiac death may not be apparent until up to 20 years following treatment in patients with left-sided disease compared with right-sided disease.[33] In a large, long-term follow-up study of 7425 patients with breast cancer, longer follow-up time was associated with increasing risk of cardiovascular death: HR 1.0 at ≤10 years, HR 1.5 at 10 to 20 years, and HR 2.9 >20 years.[34] A review of 19 published reports on patients with breast cancer is likewise in agreement with the conclusion that extended follow-up duration is associated with excess risk of cardiac mortality.[35]

ANTHRACYCLINE EXPOSURE

Anthracyclines, which are commonly used to treat various hematologic and solid cancers, represent the classic cardiotoxin.[36] Although there is likely no "safe" dose of anthracyclines, the risk of cardiotoxicity seems to be significantly increased with cumulative doses >240 mg/m^2. Although anthracyclines and RT independently increase the risk for cardiotoxicity, they may also have a synergistic effect on cardiac toxicity. In a study of 1474 patients with HL, RT and anthracycline treatment was found to increase the risk of congestive HF (HR, 7.37 and 2.44, respectively). Combination treatment with RT and anthracyclines further increased this risk for congestive HF and valve disease (HR, 2.81 for congestive HF and 2.10 for valve disorders compared with RT alone), but not for MI or angina.[37] A prospective study of 299 patients with breast cancer undergoing either 5 or 10 cycles of chemotherapy with cyclophosphamide and doxorubicin showed that patients treated with 10 cycles have an increased risk of cardiac events compared with those in the Framingham population, whereas those treated with 5 cycles do not. Treatment with RT in addition to chemotherapy, which accounted for 41% of patients, was associated with an increased risk of events, particularly in those patients receiving moderate to high doses of radiation.[38]

COMORBID CONDITIONS

Most data suggest that the presence of cardiovascular comorbidities, especially preexisting coronary artery disease increases the risk of RIHD (Figs. 4.2 and 4.3). A history of cardiac problems, including MI, arrhythmias, valvular dysfunction, right atrial hypertrophy, and ventricular septum defects, indicated they were important modifiers of ischemic heart disease risk following radiation.[39] Likewise, the incidence of fatal and nonfatal ischemic cardiac disease was higher than expected (based on age, gender, and calendar period) for patients treated with mediastinal radiation for HL (between 30 and 45 Gy) who had cardiovascular risk factors such as hypertension, smoking, obesity, hypercholesterolemia, diabetes mellitus, or a history of ischemic cardiac disease (RR, 2.36).[40] Although it is clear that patients treated with radiation during childhood are particularly vulnerable to RIHD, as patients approach middle age, the relative rate of ischemic cardiac events decreases when compared with the rate of expected events, even though the absolute rate increases.[5]

How much optimal risk factor control reduces the risk remains to be determined.[24,33]

RISKS DURING OR EARLY AFTER RT

Whereas RIHD typically manifests years to decades following treatment, acute pericarditis can develop during treatment. Acute pericarditis usually occurs

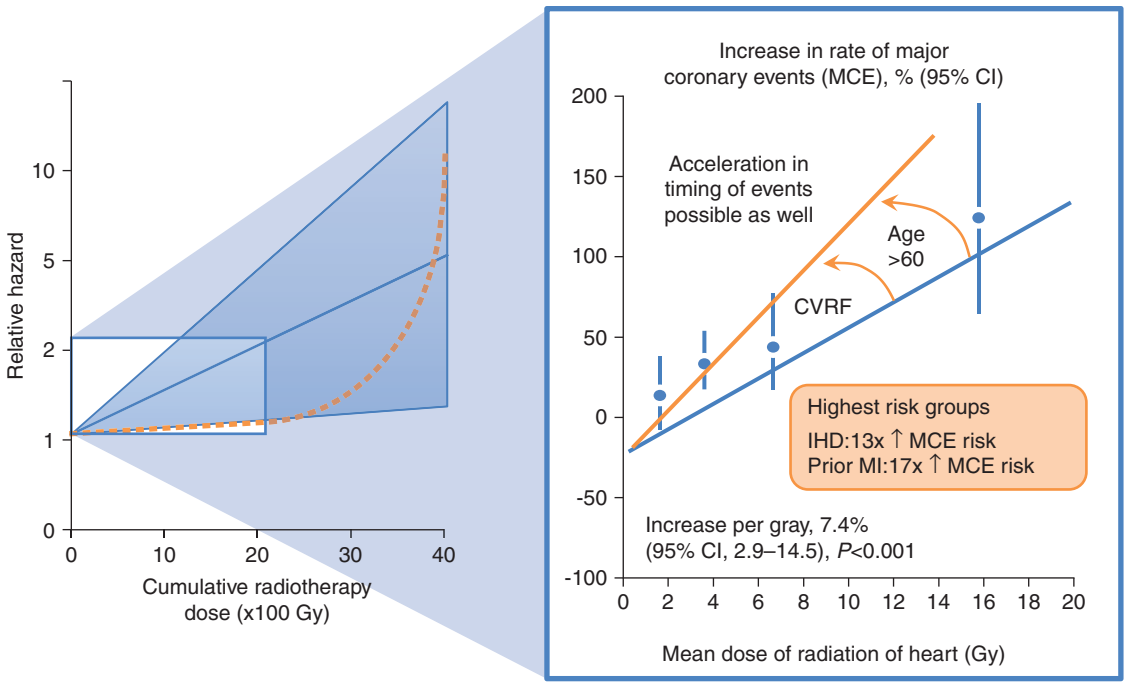


FIG. 4.3. *Left panel:* Rate of major coronary events according to mean radiation dose to the heart in a conceptual exponential (cut-off) or linear model based on dose estimates in patients (major coronary events includes myocardial infarction, coronary revascularization, and death from ischemic heart disease). *Right panel:* The values for the *solid line* were calculated with the use of dose estimates for individual women. The *circles* show values for groups of women, classified according to dose categories; the associated *vertical lines* represent 95% confidence intervals. All estimates were calculated after stratification for country and for age at breast-cancer diagnosis, year of breast-cancer diagnosis, interval between breast-cancer diagnosis and first major coronary event for case patients or index date for controls (all in 5-year categories), and presence or absence of a cardiac risk factor. The radiation categories were less than 2, 2 to 4, 5 to 9, and 10 Gy or more, and the overall averages of the mean doses to the heart of women in these categories were 1.4, 3.4, 6.5, and 15.8 Gy, respectively). *CVRF*, Cardiovascular risk factors. (Modified from Darby SC, Ewertz M, McGale P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med.* 2013;368(11):987–998.)

in patients with large mediastinal tumors.[41] It is thought to develop owing to inflammation from tumor necrosis as opposed to direct radiation injury to the pericardium.[41] Acute pericarditis, which is less common than chronic pericarditis, typically presents with chest pain, fever, tachycardia, and a pericardial rub. Typical electrocardiographic (ECG) features include diffuse ST elevations with PR depressions. An effusion may or may not be present; however, if present, development of a pericardial effusion may be a risk factor for chronic pericarditis.[42]

Radiation therapy on its own does not appear to cause any significant changes on ECG acutely.[40,43] In one study of 16 patients aged 15 to 33 years who received >3500 rads to the heart, ECG abnormalities included nonspecific ST segment or T-wave changes, low voltage, or complete right bundle branch block.[44] However, the exact timing of the electrocardiogram with respect to completion of radiation therapy was not specified; therefore, some of the ECG changes may be owing to progressive RIHD as opposed to acute radiation injury.

CARDIAC BIOMARKERS

Radiation therapy alone does not commonly increase the levels of typical cardiac biomarkers, and in general, abnormal biomarkers warrant further evaluation for the etiology and should not be routinely attributed to radiation-induced injury. In patients with breast cancer undergoing ~45 Gy of whole-breast radiation treatment, no changes in troponin levels were seen before and after treatment.[45] Similarly, in patients with thoracic malignancies,

biomarkers including troponin, NT-proBNP, and CK-MB were not significantly elevated during or after completion of radiation treatment.[46] Only one study showed troponins did increase following radiation in patients with left-sided breast cancer compared with those with right-sided disease; however, the increased values were still within the normal range.[47] NT-proBNP levels may be more affected by RT compared with troponin levels. NT-proBNP was elevated in patients with breast cancer after RT compared with the control group that consisted of patients with breast cancer who were radiation naïve.[14] Increase in NT-proBNP correlated with receiving high doses in a small volume of the heart and ventricles.[14] Consistent with the other studies, troponin levels remained normal in both groups.[14]

STRAIN IMAGING

Deformation imaging with strain is a sensitive way to detect myocardial dysfunction and is widely used in the assessment of oncology patients, particularly those undergoing treatment with anthracyclines.[48] Evidence indicates that strain is abnormal in patients with cancer exposed to radiation and regional changes in strain correspond to the RT fields used during therapy.[49] Regional strain changes can present immediately and up to 14 months following RT in patients with left-sided breast cancer, but are not seen in patients with right-sided breast cancer.[47,50] The long-term significance of these early changes in strain imaging after RT are unclear.

FUTURE AVENUES

Cardiovascular risk assessment remains a challenging task owing to the heterogeneous modalities of RT, accompanying chemotherapy and targeted therapy regimens, preexisting cardiovascular risk factors, and other multifactorial variables. An individualized assessment for each cancer case is essential, which includes a risk-to-benefit discussion of potential short- and long-term consequences of RT in the absence of large-scale evidence. Aggressive management of cardiovascular comorbidities should be pursued to the degree that is tolerated during and after cancer treatments, particularly with malignancies that confer favorable, long-term prognosis.

In regard to society guidelines reflective of cardiovascular risk assessment with RT, the American Society of Clinical Oncology Clinical Practice Guidelines in 2017 stated that patients with cancer who experienced high dose RT (≥30 Gy) in the area of the heart, or lower doses in combination with anthracycline chemotherapy were considered at increased risk for developing cardiac dysfunction—regardless of prior risk factors. However, suggested preventative strategies were limited in scope owing to an overall lack of robust evidence of efficacy of interventions, with the recommendation of performing a comprehensive assessment of screening for cardiovascular risk factors and avoiding or minimizing the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer outcomes. In regard to RT techniques, it was recommended that clinicians select lower radiation doses when clinically appropriate, use more precise or tailored radiation fields (excluding as much of the heart as possible), include deep-inspiration breath holding for patients with mediastinal tumors or breast cancer, and use intensity-modulated RT that varies the delivery of radiation energy to precisely contour the desired radiation distribution and minimize involving normal tissue.[49]

In closing, wide-scale efforts are needed to capture the dynamic epidemiology of the effects of RT in a diverse spectrum of cancer states and survivors. Such research efforts may involve tracking outcomes in national/international registries, as well as evaluating the effects of cardiovascular interventions and imaging surveillance for cardiotoxicity in prospective, randomized trials. As many effects of RT may not manifest for decades, such registries are crucial toward our understanding of the natural history of RIHD, which has yet to be defined accurately.

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