Cardiotoxicity of radiation therapy for breast cancer and other malignancies

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INTRODUCTION

The use of radiation therapy (RT) has contributed to significant improvements in disease-specific survival for patients with early stage breast cancer, Hodgkin lymphoma (HL), and other malignancies involving the thoracic region. (See "Treatment of favorable prognosis early (stage I-II) classic Hodgkin lymphoma" and "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)

These successes with RT, used either alone or in combination with other modalities, resulted in large cohorts of cancer survivors, who are subject to late complications from treatment. Analyses have shown that the therapeutic benefits from RT may be offset to some extent by delayed effects on the heart, thereby reducing the benefits of RT.

Irradiation of a substantial volume of the heart to a sufficiently high dose can damage virtually any component of the heart, including the pericardium, myocardium, heart valves, coronary arteries, capillaries, and conducting system. Pericarditis is the typical acute manifestation of radiation injury, while chronic pericardial disease, coronary artery disease, cardiomyopathy, valvular disease, and conduction abnormalities can manifest years or decades after the original treatment. These complications can cause significant morbidity or mortality.

The data on the late cardiovascular toxicity of RT come primarily from survivors of breast cancer and HL, diseases in which RT is a frequent component of the initial management and

in which survival is often prolonged. Similar effects may be present in other cancer survivors who receive thoracic RT, although data are more limited.

An awareness of the potential cardiotoxicity of RT led to the application of improved RT techniques that minimize irradiation to the heart. These contemporary techniques appear to have significantly decreased the incidence of delayed complications, but have not completely eliminated this risk.

The pathophysiology of RT-induced cardiac injury and the clinical data on the magnitude of risk are presented here. RT-induced cardiotoxicity associated with Hodgkin lymphoma and pediatric malignancies is discussed separately. (See "Cardiotoxicity of radiation therapy for Hodgkin lymphoma and pediatric malignancies".)

PATHOPHYSIOLOGY

The pathophysiologic pathway responsible for most manifestations of cardiotoxicity appears to involve damage to blood vessels. This injury is thought to be due to the generation of reactive oxygen species that disrupt DNA strands. Secondary inflammatory changes then lead to fibrosis.

The histologic hallmarks of radiation-associated cardiotoxicity are diffuse fibrosis in the interstitium of the myocardium with normal-appearing myocytes and narrowing of capillary and arterial lumens [1]. Irregularities of the endothelial cell membranes, cytoplasmic swelling, thrombosis, and rupture of the walls are present. The ratio of capillaries to myocytes is reduced by approximately 50 percent, and this leads to myocardial cell death, ischemia, and fibrosis. Dense collagen and fibrin replace the normal adipose tissue of the outer layer of the heart, leading to pericardial fibrosis, effusion, and rarely, tamponade [2].

These changes can have several consequences:

- Coronary artery disease (CAD) results from injury to the intima of the coronary arteries. This initiates a cascade of events that is typical of atherosclerosis, including replacement of damaged cells by myofibroblasts and deposition of platelets [1]. The distribution of arteries affected by RT reflects the dose distribution. As an example, the left anterior descending and the right coronary arteries are most often involved in patients receiving mediastinal RT for Hodgkin lymphoma (HL), and the left anterior descending artery receives more radiation during treatment for left-sided breast cancer. Arterial narrowing is typically proximal and often involves the coronary ostia [3,4].

- The cusp and/or leaflets of valves may undergo fibrotic changes with or without calcification. Changes to valves on the left side are more common than those on the

right, regardless of the relative dose distribution of RT [5]. This suggests that the higher pressures in the systemic circulation contribute to the pathogenesis of these lesions.

- Myocardial fibrosis can compromise cardiac compliance, leading to diastolic dysfunction [6].
- Fibrosis of cells in the conduction system can predispose to dysrhythmia [7,8].

A number of risk factors for the development of RT-induced cardiac toxicity have been identified, including the total radiation dose, the dose per fraction, the volume of heart irradiated, and the concomitant administration of cardiotoxic systemic agents (eg, anthracyclines, trastuzumab). Patient-related factors that may increase the risk of radiation-induced cardiotoxicity include younger age at the time of treatment and the presence of other risk factors for coronary heart disease (eg, hypertension, smoking).

BREAST CANCER

Incidental radiation to the heart as part of the initial treatment of breast cancer can result in a range of cardiotoxic effects including coronary artery disease, cardiomyopathy, pericardial disease, valvular dysfunction, and conduction abnormalities. Cardiotoxicity is related to both the volume of heart irradiated and the radiation dose delivered to that volume.

Older RT techniques for treating the breast, chest wall, and/or draining lymph nodes delivered relatively high doses of radiation to portions of the heart. Contemporary techniques expose a smaller volume of the heart and are associated with a reduced risk of cardiotoxicity. However, it is unclear if there is a "safe dose" with no increased risk. Low radiation doses may initiate an inflammatory cascade that persists and augments the risk for cardiovascular events [9]. A case-control study suggested that an increased risk of cardiac disease can be seen after relatively low doses of radiation (approximately 2 Gy averaged across the heart from higher doses to small cardiac volumes), that the clinical manifestation of this increased risk can be seen throughout a broad continuum of follow-up durations (eg, from <5 years to ≥20 years), and the absolute magnitude of the effects of radiation are higher in patients with cardiac risk factors since the presence of cardiac risk factors markedly increases the baseline risk [10,11]. Despite this, the absolute risk associated with RT is small and appears to be outweighed by the benefits in patients for whom radiation is typically recommended.

Randomized trials conducted over the last 40 years demonstrate the overall positive impact of post-lumpectomy/mastectomy radiation on local control and survival [4]. These benefits were achieved despite the use of some older radiation techniques. With more modern approaches, the absolute benefits of radiation may be increased, as has been suggested in

some reports [12]. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer".)

Older evidence of cardiovascular toxicity — The cardiovascular toxicity of chest wall irradiation following mastectomy was initially identified in a retrospective analysis of 1461 long-term survivors of breast cancer who were treated from 1949 to 1955 and then followed for up to 34 years [13]. The women in this cohort had originally been randomly assigned to RT given immediately or delayed RT until the time of a local recurrence. After 15 years, there was a significantly increased mortality in those given immediate RT (relative risk [RR] 1.43) that was attributable to excess deaths from cardiovascular disease.

Subsequent meta-analyses confirmed these initial observations [1,3,4]. The largest, which explored the impact of RT on breast cancer mortality and on mortality from other causes, was conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which evaluated 19,582 women enrolled in 40 randomized trials of RT versus no RT that were begun before 1990 [3,4]. Although the use of RT decreased the annual mortality rate from breast cancer by 13 percent, the annual mortality rate from other causes was increased by 21 percent. The increased nonbreast cancer-related mortality was primarily due to an excess number of deaths from vascular causes (death rate ratio 1.30, compared with those not receiving RT).

Most, if not all, of the individual trials in the meta-analyses were initiated before 1975 and used RT techniques that would now be considered suboptimal because of excessive cardiac irradiation.

Modified RT techniques — Once the potential cardiotoxicity of RT was recognized, treatment techniques were modified and continue to be altered to minimize incidental cardiac irradiation. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer".)

Although the data from more recent studies suggest a decreased incidence of cardiotoxicity from decreased dose-volumes [14], the evidence indicates that there is at least some residual risk.

Approaches to assessing the relative risk of cardiotoxicity in breast cancer patients treated with modified RT techniques have included:

- Comparison of the incidence of cardiac morbidity and/or mortality in those treated with RT (breast or chest wall) with those not receiving RT following surgery. (See 'Meta-analyses and randomized trials' below.)
- Analyses of the effect of radiation dose to the heart on the incidence of cardiac morbidity and/or mortality. These have included case control studies comparing those

who did and did not develop coronary events after RT for breast cancer, as well as studies comparing women with left-sided versus right-sided breast cancers (since the dose to the heart is generally less in patients irradiated for right-sided tumors). (See 'Effect of radiation dose to the heart' below.)

- Radiographic assessment of cardiac injury following RT. (See 'Surrogate endpoints of myocardial injury' below.)

Meta-analyses and randomized trials — Data have shown that radiation exposure of the heart increases the risk of ischemic heart disease and cardiac mortality, though the absolute risks are small, and less than the risk of omitting radiation for appropriately selected patients.

In a meta-analysis of 39 studies involving almost 1.2 million patients with breast cancer, those receiving radiotherapy experienced an increased risk of coronary artery disease (relative risk [RR] 1.3, 95% CI 1.13-1.49) and cardiac death (RR 1.38, 95% CI 1.18-1.62) [15]. However, the absolute risk increase for coronary artery disease and cardiac death was only 76 and 126 cases, respectively, per 100,000 person-years. For coronary artery disease, the risk increased within the first decade, and for cardiac mortality, it increased in the second decade.

Although previous randomized trials have not suggested a difference between irradiated patients and controls in regards to cardiac morbidity or death, this may be due, in part, to a relatively shorter follow-up. For example, in randomized trials conducted by the Danish Breast Cancer Cooperative Group (DBCG 82b and 82c), among 3083 patients with high-risk stage II or III primary breast cancer randomly assigned to adjuvant systemic treatment with or without RT following mastectomy, there were no significant differences between irradiated patients and controls with respect to either death or morbidity from ischemic heart disease or acute myocardial infarction at a median follow-up of 10 years [16].

Importantly, in these studies, postmastectomy chest wall irradiation improved survival in high-risk women with breast cancer, and the benefit of chest wall irradiation more than outweighed any increase in cardiac morbidity and mortality. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Patients treated with breast-conserving surgery'.)

Effect of radiation dose to the heart — There does not appear to be any minimum radiation dose that is entirely safe, and the effects of radiation on the heart increase with increasing doses of radiation [10]. The increased risk can be seen within the first five years and remains elevated for at least 20 years. Women with significant risk factors for an acute coronary event may be at a particularly increased risk.

This effect of RT was demonstrated in a population-based case-control study that included 2168 women who were treated for breast cancer with surgery and RT in Sweden and Denmark between 1958 and 2001. The study included 963 women who experienced a significant coronary event (myocardial infarction, revascularization, or death from ischemic heart disease) following their treatment for breast cancer. These women were compared with 1205 matched controls who received similar therapy for their breast cancer but did not have a cardiac event following breast cancer treatment. RT records were reviewed for all patients, and the dose of radiation to the heart estimated for each patient.

Results included the following [11]:

- There was increased risk of major coronary events following RT for all time periods from the period less than five years through greater than 20 years.
- The estimated mean dose of radiation to the heart was 4.9 Gy (calculated by averaging a high radiation dose to a small cardiac volume across the entire heart); the dose of radiation to the heart was greater in those with a left-sided breast cancer (6.6 versus 2.9 Gy). The risk of a coronary event increased progressively with the radiation dose, with a relative increase of 7.4 percent for each 1 Gy of radiation to the heart.
- A history of ischemic heart disease before cancer therapy was associated with an increased risk of a cardiac event after treatment for breast cancer (ratio 6.67, $p < 0.001$). Other factors associated with a significantly increased risk included other circulatory disease, diabetes, or a left-sided breast cancer (risk ratios 1.88, 3.23, and 1.32, respectively).

Only a very limited number of patients received potentially cardiotoxic medications (eg, anthracyclines, trastuzumab), which might substantially increase the risk associated with RT. However, this analysis did not take into account other cardiac complications of radiation (cardiomyopathy, valvular heart disease, arrhythmias).

The impact of radiation dose on the risk of ischemic heart disease was confirmed in a smaller study that analyzed cardiac outcomes in a population treated with a consistent RT technique [17].

Even in the relatively-modern era (eg, in patients treated from 1992 to 2012 when 3D planning was largely available), higher cardiac events are seen in a Swedish population study of women receiving left- versus right-sided RT (hazard ratio 1.18), thus suggesting that some modern technologies alone may not fully mitigate the risk [18].

Additional evidence comes from observational studies that have analyzed the rate of cardiac complications in breast cancer survivors [12,19-26]. These studies have yielded conflicting results but suggest that there is an increase in cardiac events in women with left-sided breast

tumors compared with right-sided cancers since the latter received lower doses of irradiation to the heart. Three of the larger registry studies illustrate the potential impact of RT based upon the laterality of the tumor:

- In one report, outcomes were analyzed from 115,000 women in the Surveillance, Epidemiology, and End Results (SEER) database who received adjuvant RT in the United States between 1973 and 2001 [19]. For patients irradiated between 1973 and 1982, cardiac mortality was significantly higher in women with left-sided breast cancers and the difference was more pronounced with longer follow-up (cardiac mortality ratio [CMR] for left-sided versus right-sided cancers 1.20, 1.42, and 1.58, at <10, 10-14, and >15 years, respectively). However, for women treated from 1983 to 1992, the differences were less pronounced and not statistically significant, and none of the patients treated from 1993 onward had 10-year follow-up. This decrease in excess mortality may reflect improvements in RT techniques, shorter follow-up, or other unknown factors.

- In a second SEER database study, the risk of death from ischemic heart disease was analyzed in a cohort of 27,283 women with breast cancer whose treatment included adjuvant RT during the period 1973 to 1989 [12]. For women diagnosed between 1973 and 1979, there was a significantly higher 15-year mortality rate from ischemic heart disease for women with left-sided versus right-sided tumors (13.1 versus 10.2 percent). For those diagnosed from 1980 to 1984, and from 1985 to 1989, the differences in 15-year mortality rates for women with left-sided versus right-sided tumors were not significant (9.4 versus 8.7 percent and 5.8 versus 5.2 percent, respectively). The overall incidence of death from cardiac disease decreased substantially with the later cohorts.

- A large Danish registry-based study of patients treated from 1970 to 2009 suggested that both irradiation of the internal mammary nodes (IMN) and anthracycline-based chemotherapy can increase the risk of cardiotoxicity (in at least an additive manner, and perhaps synergistically). For example, overall, the hazard ratio for cardiovascular disease among those receiving radiation to the internal mammary chain without anthracyclines was 1.54 (95% CI 1.4-1.8) relative to those receiving neither internal mammary chain radiation nor anthracyclines, and 2.1 if anthracyclines were also administered (95% CI 1.6 -2.7) [27]. Absolute risk rates were increased over time and in patients with pre-existing cardiac risk factors. The authors of the study suggest that patients treated with these techniques might warrant more careful surveillance for cardiac disease.

The applicability of these studies to more recently treated patients is unclear since the cardiac radiation doses seen in the era studied were typically much higher than those seen in contemporary series using more modern techniques. Nevertheless, about 29 percent of the

patients in the third study received radiation after 1999 (ie, with relatively modern techniques). This study highlights the ongoing controversy surrounding IMN RT as several contemporary prospective trials suggest that IMN RT can improve overall outcomes [28-30], but their follow-up is not as long as in this large population-based study.

The absolute increase in risk of a major coronary event or death from ischemic heart disease is small. In the case control study comparing women given RT who had a major coronary event with those did not have a coronary event [11], the authors calculated that the risk that a 50-year-old women with no other coronary risk factors would die of ischemic heart disease prior to age 80 years would increase from 1.9 to 2.4 percent if she received a mean dose of radiation of 3 Gy to her heart; the risk of having at least one major coronary event would increase from 4.5 to 5.4 percent. If the mean dose to the heart were 10 Gy, the risk of dying would increase from 1.9 to 3.4 percent, and the risk of having at least one acute coronary event would increase from 4.5 to 7.7 percent.

Data suggest that the cardiac risk associated with breast cancer radiation is higher for smokers than for nonsmokers, though still low for both groups. In a patient data meta-analysis including approximately 41,000 breast cancer patients randomly assigned to receive or not receive adjuvant radiation in 75 trials, those receiving radiation had an increased cardiac mortality (relative risk [RR] 1.3, 95% CI 1.15-1.46) [31]. The risk of radiation-associated cardiac mortality was higher for smokers, translating to an absolute increase of 1.0 percent, versus 0.3 percent for nonsmokers.

Numerous other studies, using either overall morbidity and mortality frequencies or less detailed individual patient data, confirm that the effect of radiation on the heart is small compared with the benefit potentially derived from such treatment in appropriately selected patients [32-38].

Surrogate endpoints of myocardial injury — Changes in the incidence of cardiac morbidity and mortality represent the "gold standard" endpoints for evaluating the risk of RT-induced cardiotoxicity. However, there are several drawbacks to this approach:

- Cardiac injury is typically a "late effect" that may only become apparent many years or even decades after RT. Without prolonged follow-up, cardiac events attributable to RT are unlikely to be observed.
- Coronary artery disease is frequent in North America and Europe. Thus, analysis of large numbers of patients is required to detect a statistically significant difference in the ratio of observed to expected events in women who have or have not received RT for breast cancer.
- Competing causes of death (breast cancer itself, other noncardiac causes, age-related illnesses) are likely to obscure any increase in cardiac mortality observed following RT

unless a cohort of relatively young, favorable-prognosis breast cancer patients is studied.

To provide an early assessment of possible myocardial injury, studies have used radionuclide myocardial perfusion imaging to look for RT-induced cardiac changes. In the largest prospective series, 160 women were treated with tangential photons to the left breast or chest. Patients underwent serial single-photon emission computed tomography (SPECT)-gated cardiac myocardial perfusion scans for up to six years [39].

The following findings were noted:

- The incidence of new perfusion defects was related to the volume of myocardium included in the radiation field. When greater than 5 percent of the left ventricle was included in the RT field, the incidence of perfusion defects was significantly higher (approximately 55 percent in the first two years versus 25 percent in those with less than 5 percent of the left ventricle in the RT field).

- Among patients who develop a perfusion defect 6 to 24 months after RT, those defects largely persist at longer follow-up intervals.

- The patients with perfusion defects were slightly more likely to have an abnormality in wall motion, but there were no evident reductions in ejection fraction. Thus, the clinical significance of these perfusion defects remains unclear.

Smaller retrospective studies from other groups have generated conflicting results, with some showing a similarly high incidence of RT-associated perfusion defects, and others not identifying such an association [40-43]. A systematic review of six SPECT perfusion studies performed between 6 and 12 months post RT for left-sided breast cancer concluded that perfusion defects were dose dependent [44]. Additional research will be required to establish the long-term clinical and functional significance of these perfusion defects, but the defects and their increase in frequency from time since therapy (over different studies) correlate with the increase in frequency of events in survivors over time.

Effect of radiation after lumpectomy versus mastectomy — Any associations of RT with cardiotoxicity are not dependent on the presence or absence of a breast, but on the radiation volume. Thus, cardiotoxicities associated with RT should be very similar in the postlumpectomy and postmastectomy settings, if the irradiated volumes are similar. However, this is usually not the case; in the postmastectomy setting, the RT field often includes the nodal tissues, and these nodes are not always targeted in the post-lumpectomy setting. Thus, postmastectomy RT is more often associated with cardiac disease (compared with postlumpectomy RT), but this is likely a result of the usually-larger irradiated volumes in the former.

Details of adjuvant radiation therapy are discussed elsewhere. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)

Time course and risk factors — Early studies with RT in breast cancer patients established a link between incidental radiation to the heart and an increase in the frequency of cardiovascular disease. These cardiac effects have been manifested as coronary artery disease (myocardial infarction, need for revascularization, death from ischemic heart disease), cardiomyopathy, pericardial disease, valvular dysfunction, and conduction abnormalities.

Improvements in RT technique significantly decreased the amount of incidental radiation received by the heart. These technical advances substantially reduced the incidence of cardiovascular complications compared with older studies. However, cardiovascular complications still appear to be more frequent in patients with left-sided compared with right-sided tumors, suggesting that the risk has not been entirely eliminated.

The key factors that appear to influence the risk of delayed cardiovascular toxicity include:

- **The RT field and dose –** This determines the amount of incidental irradiation to the heart. As an example, studies that separately analyzed the risk in patients who received internal mammary lymph node irradiation partially or entirely with anterior photon fields found an increased risk of cardiovascular complications compared with those in whom the internal mammary lymph nodes were not included in the field [32]. (See 'Effect of radiation dose to the heart' above.)

  The controversy surrounding whether the internal mammary nodes should be included in the radiation field is discussed elsewhere. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer", section on 'Regional field'.)

- **The time interval between RT and cardiac events –** Most studies in patients irradiated for breast cancer have suggested that latency is generally long (eg >10 years). For example, most of the studies that have not found an increased risk of cardiovascular disease were characterized by a follow-up of approximately 10 years [16,20,22,33-35]. By contrast, those analyses that looked at cohorts with longer follow-up have observed an increase in toxicity [2,12,19,32,35].

- As an example, one pooled analysis of randomized trials evaluated overall survival in patients treated with mastectomy with or without RT [45], and found equivalent outcomes in the 10 years post-RT, but decreased overall survival (attributed to cardiac disease) seen only at later follow-up durations.

However, there are several lines of evidence suggesting that RT-associated cardiac injury can be clinically pertinent at earlier time points, including the following:

- A large case control study suggested an increased rate of cardiac events within a few years of RT [11].
- Studies looking at imaging-based measures of cardiac toxicity in these patients note events as early as 6 to 24 months post-RT [46,47].
- Studies in patients irradiated for esophageal cancer, lung cancer, and Hodgkin lymphoma suggest a shorter latency period for RT-associated heart disease [48,49]. (See 'Esophageal cancer' below and 'Hodgkin lymphoma and pediatric malignancies' below.)

Reasons for these discrepant observations include the likelihood that differences in subclinical endpoints (eg, imaging changes) and non-lethal clinical events may arise sooner than survival endpoints, as well as improvements in RT technique over time [12,45,50]. A contemporary case control study found a rise in the rate of cardiac events relatively faster than is typically ascribed to RT [11]. (See 'Modified RT techniques' above.)

Other risk factors for cardiovascular disease (hypertension, hyperlipidemia, smoking, obesity) and preexisting cardiovascular disease may increase the risk of cardiotoxicity following RT [11,32]. In a study of 236 breast cancer survivors (median age 51 years [range 30 to 70], median observation time 12 years [range 9.2 to 15.7]) treated with four-field RT of 50 Gy (median cardiac dose 2.5 Gy [range 0.5 to 7]), there was no correlation between measures of cardiac dose and coronary artery calcification as measured by Agatston score. However, Agatston score was associated with attained age at time of coronary artery calcification assessment and baseline total cholesterol on multivariate adjustment [51].

Particular caution is indicated when RT is used in patients who have or will receive known cardiotoxic agents, such as an anthracycline or trastuzumab [52]. The safety of combining RT with agents remains uncertain, and long-term follow-up is required to assess the frequency of late side effects. (See "Clinical manifestations, diagnosis, and treatment of anthracycline-induced cardiotoxicity" and "Risk and prevention of anthracycline cardiotoxicity" and "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

ESOPHAGEAL CANCER

Management of patients with locoregional esophageal cancer of the esophagus generally includes RT or chemoradiotherapy. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus" and "Management of locally advanced, unresectable and inoperable esophageal cancer".)

Because of the proximity of the esophagus to the heart, cardiac exposure is unavoidable and can result in high doses of radiation being administered to the heart and pericardium.

Cardiotoxicity from RT or chemoradiotherapy can cause benign pericardial effusions [53-56] and may have an adverse effect on the left ventricular ejection fraction [57,58].

The potential for pericardial toxicity was illustrated by a series of 167 patients with adequate follow-up who were treated with chemoradiotherapy at a single institution between 2001 and 2010 [56]. The overall incidence of pericardial effusion was 36 percent, occurring at a median of six months after treatment; symptomatic effusions occurred in 14 cases (8.4 percent). The incidence of symptomatic effusions was higher in those treated with two-dimensions versus three-dimensional conformal techniques (11 of 70 [16 percent] versus 3 of 97 cases [3 percent]). Increasing doses of radiation to the pericardium was the strongest risk factor for toxicity.

Timing from therapy to onset of radiation induced heart disease appears faster in patients irradiated for esophageal cancer (versus breast cancer), likely due to much higher cardiac doses/volumes [59]. Additionally, esophageal cancer patients more often have more severe cardiopulmonary comorbidities and risk pre-RT, which likely impacts the incidence of, and time frame for, RT-associated heart disease. A review from 2015 found that the crude incidence of symptomatic cardiac disease (most frequently pericardial effusion, ischemic heart disease, and heart failure) was 10 percent, with a majority of events occurring within two years [60].

LUNG CANCER

Historically, RT-associated cardiac injury in patients with lung cancer has not been considered to be too clinically relevant. However, there are some contemporary data to suggest that clinically meaningful cardiac injury is occurring in patients irradiated for lung cancer.

- **Impact of dose** – The Radiation Therapy Oncology Group (RTOG) examined the role of RT dose-escalation in stage III non-small cell lung cancer (NSCLC) patients receiving concurrent chemotherapy, randomizing patients to receive 60 or 74 Gy (RTOG 0617) [61]. Overall survival was worse in the high dose arm, with the curves separating within six months after RT. On multivariate analysis, the volume of heart receiving ≥5 Gy and ≥30 Gy were independent predictors for overall survival, thus implicating RT-related heart disease as a potential cause for the worsened survival rates seen in the high-dose arm. Unfortunately, heart-specific toxicities were not assessed in this trial. These data suggest that to the degree that the poorer survival in the high dose arm was due to cardiac disease, RT-associated cardiac injury can occur relatively soon after RT.

  In a series of 112 patients treated on several radiation dose-escalation trials, there was an association between the rate of subsequent cardiac events (including acute coronary

syndrome, arrhythmia, symptomatic effusions, and pericarditis) and both heart dose and baseline cardiac risk [62]. The two-year rate of symptomatic cardiac events after adjustment for the competing risk of death was 21 percent with mean heart doses ≥20 Gy versus only 7 and 4 percent with mean heart doses 10 to 20 Gy and <10 Gy, respectively. The median time to event was 26 months (range 1 to 84). These findings are consistent with the findings of RTOG 0617, and support the contention that RT-associated cardiac injury can occur relatively soon following RT for lung cancer and that this might be clinically meaningful. Similarly, other reports in patients with lung cancer noted a correlation between increasing cardiac doses, and increased rates of cardiac toxicity and reduced rates of overall survival [62-66].

Similarly, a report in patients with lung cancer noted a correlation between increasing cardiac doses, and increased rates of cardiac toxicity and reduced rates of overall survival [63]. When stratified by heart V50 less than 25 versus 25 percent or greater, the one-year overall survival rates were 70.2 versus 46.8 percent, and the two-year overall survival rates were 45.9 versus 26.7 percent.

In a Surveillance, Epidemiology, and End Results (SEER)-based analysis of over 34,000 patients more than 65 years of age receiving a variety of therapies for NSCLC, the relative risk of cardiac dysfunction in the patients receiving RT alone was 1.5, and the relative risk was 2.4 for those managed with chemoradiotherapy compared with those not receiving RT [67]. The majority of these cardiac events occurred within the first year after treatment.

- **Influence of tumor laterality and treatment modality** – A SEER registry-based study identified 3256 patients ≥65 years of age, with early-stage lung cancer (stage I-IIA; all <5 cm) treated with RT [68]. In the 1506 patients who received stereotactic body radiation therapy (SBRT), there were no differences in subsequent rate of cardiac events in those with left- versus right-sided tumors (median follow-up two years). In the subset of 1750 patients treated with three-dimensional conformal radiation therapy (3DCRT) or intensity modulated RT (IMRT), there was a very select subset of cardiac outcomes (ie, congestive heart failure and percutaneous coronary artery intervention) that were more frequent among those with left- versus right-sided cancers; however, most cardiac outcomes (including composite risk of any cardiac event) were similar. These data are challenging to interpret because the overall rate of cardiac disease was unexpectedly high; the three-year probability of a cardiac event in the SBRT cohort was 61 percent and 62 percent in the 3DCRT/IMRT cohort.

HODGKIN LYMPHOMA AND PEDIATRIC MALIGNANCIES

The RT-induced cardiotoxicity associated with the treatment of Hodgkin lymphoma and pediatric malignancies is discussed separately. (See "Cardiotoxicity of radiation therapy for Hodgkin lymphoma and pediatric malignancies".)

PREVENTION OF CARDIOTOXICITY

Until there are long-term data on the cardiac toxicity associated with modern treatment approaches, we advocate a strategy of minimizing the chance of harm based upon modifying both treatment- and patient-related risk factors whenever possible. The key components of this approach include the following:

- **All patients –** Individualized RT planning and treatment delivery methods that reduce both the volume and dose of incidental cardiac irradiation should be employed whenever possible (balanced with the need to provide adequate target coverage and risks to other organs; eg, involved-site RT, deep inspiration breath holding [DIBH]) [69-72].

- **In breast cancer –** In patients receiving RT for left-sided breast cancer, reducing (and hopefully eliminating) the heart from the primary radiation beams is the optimal/preferred strategy. CT-based planning is critical in reducing incidental cardiac irradiation in these patients and can reduce the risk of RT-associated heart injury [14]. DIBH is a particularly useful approach in this setting as well. Systematic cardiac blocking without DIBH often results in underdosage of portions of the breast/chest wall/internal mammary nodes (IMN) and thus may not be prudent, depending on the clinical setting. With DIBH, the heart is displaced inferior, medial, and posterior (ie, away from the left breast), and thus when the beams are shaped to exclude the heart, the amount of potential targets (ie, breast/chest-wall/IMN) that are underdosed is reduced. Thus, DIBH can improve the therapeutic ratio of RT, and enable cardiac sparing with lesser impacts on target coverage.

  - In two prospective trials, patients receiving RT with DIBH and conformal heart blocking were found to be without post-RT single-photon emission computed tomography (SPECT) cardiac perfusion abnormalities [73,74]. Conversely, in a prospective randomized trial comparing DIBH with no DIBH, but where the heart was not systematically excluded from the RT field, post-RT SPECT cardiac perfusion defects were noted in both groups [75].

  - Gating the RT to be delivered only during the deep inspiratory phases of respiration should yield similar results to DIBH. Other strategies to reduce cardiac exposure include:

- The purposeful treatment to lesser volumes of the breast (eg, accelerated partial-breast RT)
- Intensity-modulated RT (though the volume of heart, lung, and contralateral breast receiving a low dose of RT may increase with this approach)
- Protons
- Prone positioning (though with this approach the heart is displaced anteriorly [76], so the deep field border needs to be at/near the chest wall to block the heart, and thus this approach is likely only appropriate when the target does **not** include the deep aspects of the breast or chest-wall/IMN).

  However, differences in breast cancer control and cardiac outcomes have not been definitively demonstrated.

- Studies demonstrate that the negative cardiac effects from RT in the setting of breast cancer treatment have declined in magnitude over time with such changes in radiotherapy technique. For example, a population-based Danish Breast Cancer Group analysis demonstrated that in patients treated for early breast cancer, among those treated using older (but modified/relatively modern) techniques (eg, without computed tomography [CT]-based planning, 1999-2007, but limited fraction size), the 10-year cardiac event risk in left- versus right-sided breast cancer was 1.4 (95% CI 1.1–1.9, thus demonstrating RT-associated risks); versus a 10-year event risk ratio in left- versus right-sided treatment of 0.90 (95% CI 0.7–1.2) in the most-modern era (eg, with CT-based planning, 2008-2016) [14]. Similar finding have been reported by others.

  Interestingly in this study, the 10-year cumulative cardiac event rate for such patients increased from 1.7 percent in the non-CT based planning to 2.1 percent with CT planning [14]. We surmise that this is most likely due to increasing use of cardiotoxic chemotherapy agents in such patients such as anthracyclines, CAR-T and targeted antibodies, and possibly different patient mix in the two different treatment eras.

- When RT is appropriate in addition to systemic chemotherapy, the minimum necessary total dose of anthracycline should be administered. For patients whose treatment requires an increased number of cycles of anthracycline-based chemotherapy, a lower dose of RT will probably decrease the risk of myocardial infarction, but the higher doses of anthracycline will increase the risk of congestive heart failure and valvular abnormalities. (See "Risk and prevention of anthracycline cardiotoxicity".)

- Because classical coronary heart disease risk factors, such as smoking, elevated lipid levels, obesity, and hypertension, appear to increase the risk of RT-induced heart disease, efforts should be made to screen for and reduce or eliminate these risk factors

in patients who have received cardiac irradiation. (See "Overview of established risk factors for cardiovascular disease".)

- While no guidelines exist specifically for those who received chest irradiation, consideration should be given to echocardiography, cardiac perfusion imaging, stress testing, and/or coronary calcium scoring by CT if the coronary arteries received >35 Gy of irradiation exposure beginning five years after therapy or after age 30 to 35 years, whichever is last. Screening with one of these modalities is especially encouraged for survivors at high risk based upon other coronary artery disease risk factors [77-79]. (See "Overview of stress radionuclide myocardial perfusion imaging" and "Coronary artery calcium scoring (CAC): Overview and clinical utilization".)

  Strain imaging is promising, but is only beginning to be studied specifically in this population. Although several studies have shown dose-related abnormalities uncovered in the acute phase after RT, the prognostic value of these findings remains unknown [80,81]. Only two studies have demonstrated persistent decreased strain at 12 [82] and 36 months [83], respectively, but without significant change in left ventricular ejection nor definitive association with radiation dose. Therefore, we do not suggest strain imaging for routine clinical use, based on limited available data. Further discussion of cardiac strain in patients treated with anthracyclines is found elsewhere. (See "Risk and prevention of anthracycline cardiotoxicity", section on 'Left ventricular function assessment'.)

- In those survivors who received >300 mg/m^2 of doxorubicin as part of their treatment, noninvasive screening with nuclear imaging and/or echocardiography should also be encouraged to evaluate cardiac function and valvular status. (See "Clinical manifestations, diagnosis, and treatment of anthracycline-induced cardiotoxicity" and "Risk and prevention of anthracycline cardiotoxicity".)

COMPLICATIONS AFTER CARDIAC SURGERY

A case series of 59 survivors of thoracic irradiation from a single institution demonstrated that they suffered more complications than would have otherwise been predicted from the Euroscore II (a prognostic tool used for cardiac surgery that considers various risk features, but not thoracic radiation) [84]. For example, although the tool suggested an in-hospital postoperative mortality rate of 3.6 percent (n = 2), these survivors (mostly of breast cancer) suffered a mortality rate of 10.2 percent (n = 6). Along with much earlier case series and reports, this study suggests that extra care needs to be taken in planning and performing cardiac surgery in survivors who received thoracic irradiation. Similarly, other studies have demonstrated that patients undergoing cardiac procedures (eg, cardiac surgery, valve replacement, and percutaneous coronary interventions) for radiation-associated heart

disease have worse survival than those undergoing the same procedures for non-radiation associated heart disease [85]. Almost all these studies were from a single center and included patients treated with older RT techniques and thus had higher dose-volumes than patients receive with modern approaches.

SUMMARY

Older radiation therapy (RT) techniques used to treat patients with malignancies involving the thorax clearly caused an increase in cardiovascular morbidity and mortality. Such treatment involved exposure of large volumes of the heart to high doses of radiation. Newer treatment techniques reduce both the dose of radiation and the volume of heart within the RT field, and appear to reduce the risk of late complications.

When treating a patient with thoracic RT, careful attention should be paid to contemporary techniques that minimize the dose of radiation to the heart, and to other factors that may contribute to subsequent cardiotoxicity. (See 'Prevention of cardiotoxicity' above.)

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