

Lucy Kettlewell. *Boats, Michigan #2*. Oil on board. From the personal collection of John Horton.

*Current radiation techniques are showing promise by being less harmful to the heart while still helping to reduce local and regional recurrence of breast cancer.*

## Cardiac Mortality and Morbidity After Breast Cancer Treatment

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**Background:** Breast conservation treatment for early-stage breast cancer has been demonstrated to be equivalent to mastectomy in a large number of randomized trials. A number of earlier studies of surgery with or without radiation did not show an improvement in overall survival despite large reductions in local recurrence rates. Numerous randomized trials have demonstrated that postmastectomy radiation to the chest wall and regional nodes in high-risk early-stage patients provides improvements in local-regional control and overall survival.

**Methods:** This article reviews the medical literature pertaining to long-term cardiac toxicity in early-stage breast cancer patients treated with either breast conservation or postmastectomy radiation.

**Results:** A decrease in breast cancer deaths associated with postoperative irradiation was offset by an increase in cardiovascular deaths in early studies. Cardiac toxicity of breast irradiation is a late event, manifesting clinically 10 or more years after breast cancer treatment. The excess deaths were directly related to radiation techniques that exposed excessive volumes of the heart, leading to the development of new techniques designed to shield the heart and reduce the risk of cardiac toxicity.

**Conclusions:** This review examines the original and contemporary studies of radiation for postmastectomy and breast conservation treatment for early-stage breast cancer, discusses the long-term cardiac mortality and morbidity data from these studies, and reviews the known risk factors associated with cardiac toxicity after irradiation for breast cancer.

### Introduction

Postoperative radiation in early-stage breast cancer is used to eradicate microscopic deposits of residual disease. Breast conservation treatment for early-stage breast cancer is defined as the surgical removal of gross or radiographically detected disease with a partial mastectomy (or lumpectomy), usually followed by radiation therapy to the breast. This treatment approach has been demonstrated to be equivalent to mastectomy in a large number of randomized trials.<sup>1</sup> Breast conservation treatment has become the standard of care and the preferred treatment for the majority of breast cancer

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**Abbreviations used in this paper:** MI = myocardial infarction, SEER = Surveillance, Epidemiology, and End Results, CAD = coronary artery disease.

patients with stage 0, I, or II breast cancer. Postmastectomy radiation to the chest wall and regional nodes has also been extensively studied in randomized trials; in high-risk stage II patients, particularly those with positive nodes, it has been associated with improved local-regional control and an overall survival benefit.<sup>2,3</sup>

The earliest trials validating the use of breast conservation and postmastectomy treatment date to the 1960s, and numerous randomized trials comparing mastectomy or breast-conserving surgery, with and without radiation, have been conducted through a more contemporary era. The majority of these trials have demonstrated not only a significant improvement in local control with the use of irradiation, but also a survival benefit associated with the addition of radiation on the order of 5%.

These same trials also raised concerns about the risks of whole breast or chest wall irradiation. A number of earlier studies did not show an improvement in overall survival despite large reductions in local recurrence rates. The decrease in breast cancer deaths associated with postoperative irradiation was offset by an increase in cardiovascular deaths in some studies. In particular, radiation techniques that incorporated large volumes of the heart in order to encompass the chest wall, breast, and nodal targets appeared to be detrimental to overall survival outcomes.<sup>4</sup> Refinements in radiation techniques were developed with the goal of reducing the radiation exposure of the intrathoracic structures, especially the heart and lungs. Subsequent studies have examined the impact of evolving radiation technique on the risk of cardiac morbidity and mortality.

Cardiac toxicity of breast irradiation is a late event that manifests clinically 10 or more years after breast cancer treatment. Data regarding the interaction of left breast irradiation and cardiotoxic systemic therapies, such as doxorubicin and trastuzumab, are limited since these agents have been in use a shorter time and thus lack long-term outcome data. Several investigators have conducted prospective imaging studies to assess cardiac perfusion and follow patients for subsequent events. Such studies continue to provide valuable insight into the time course and risk factors for radiation-induced cardiac toxicity in breast cancer patients. While most studies have examined primarily mortality events, morbidity is also an important endpoint for cancer survivors, as treatment-related toxicities may affect quality of life.

The goal of radiation treatment in breast cancer therapy is to eradicate areas of residual microscopic disease in order to reduce local and regional recurrence and potentially improve overall survival while minimizing the risk of acute and late treatment-related toxicities. The goals of contemporary studies are to further modify the technical delivery of left breast or chest wall radiation to minimize or eliminate cardiac toxicity and to better understand the risk of radiation-induced

cardiac sequelae for the benefit of the many breast cancer survivors who may be at risk for cardiac toxicity.

## **Radiation Technique in Breast Cancer Treatment**

Beginning in the 1960s, clinical trials examining the concept of breast conservation treatment as an alternative to radical or modified radical mastectomy were conducted concurrently with postmastectomy trials for high-risk early-stage patients. The Halstedian era was punctuated by the concept that radical extirpation was required to adequately treat breast cancer, and radiation techniques were correspondingly initially designed to treat wide areas of the breast, chest wall, and regional nodes. In addition, radiation planning and treatment equipment in that era possessed limited capabilities to identify and avoid normal structures. The cobalt-60 treatment machine that was commonly used encompassed a larger volume of intrathoracic structures due to the characteristics of its beam. As the megavoltage linear accelerator became increasingly used, it was possible to refine the techniques for treatment of the breast. However, the use of comprehensive nodal fields including the internal mammary nodes that reside in the medial intercostal spaces, particularly with anterior photon fields, resulted in the exposure of large volumes of the heart to radiation. By the 1980s it was commonplace to use tangential fields delivered by a megavoltage linear accelerator. However, it was not until the late 1990s that computed tomography (CT)-based 3-D conformal treatment planning was routinely used. Only with the availability of 3-D planning with CT-generated contours can dose-volumes of critical normal structures like the heart and lungs be precisely analyzed and the beam orientation and shaping be individually customized to maintain target coverage of the breast or chest wall and regional nodes while protecting the normal tissues.

Radiation therapy planning techniques utilize anatomical landmarks and target volumes to delineate the organs at risk and localize the borders of the irradiation fields. In breast cancer treatment, the tissues targeted for full-dose irradiation include the whole breast or chest wall. Whole breast or chest wall irradiation reduces the risk of in-breast recurrence by approximately one half to two thirds compared to partial mastectomy (lumpectomy) alone. The most commonly used technique to treat the whole breast is currently called a tangent beam (Fig 1). This field arrangement is designed to minimize radiation exposure of the intrathoracic structures, the heart, and particularly lung. However, due to the curvature of the breast and chest wall, some volume of lung (and the heart in left-sided breast cancers) is included in the radiation beam.

In many studies, inclusion of the internal mammary nodes in a comprehensive breast or chest wall field was standard, although today routine inclusion of this

nodal region is controversial. The anatomical location of the internal mammary nodes, lying in the intercostal spaces of the first five ribs and crossing the patient's midline, increases the volume of the treatment field and the volume of heart at risk for exposure in both right- and left-sided patients. Several studies have demonstrated a higher risk of cardiac disease when the internal mammary nodes were included in the treatment fields.<sup>5-8</sup> Older techniques used anterior photon fields or wide tangents to cover the internal mammary nodes, significantly increasing the volume of irradiated heart. For that reason, many radiation oncologists currently do not routinely treat these nodes unless there are specific factors indicating a high risk of internal mammary node involvement. Those who believe these nodes should be covered in order to maximize treatment benefit utilize 3-D CT-based treatment planning in order to precisely target the area with any of several available techniques, dictated by the patient's individual anatomy. Internal mammary nodes should not be treated with 2-D techniques in which the cardiac dose volumes cannot be measured.

Several studies have demonstrated that radiation technique affects the volume of irradiated heart and, as a result, the incidence of both short-term and long-term cardiac sequelae. In a dosimetric comparison of seven different postmastectomy techniques for treatment of the chest wall, Pierce et al<sup>9</sup> noted that the volume of heart receiving greater than 30 Gy (V30) was significantly higher with cobalt-60 treatment than other linear accelerator-based methods. The heart V30 was lowest with the technique known as partially wide tangents, in which the internal mammary nodes are covered in the superior aspect of the field, which is then narrowed in

the inferior portion of the field to block the heart. Gyenes et al<sup>10</sup> evaluated the irradiated heart volumes among 100 consecutive stage I left-sided patients treated with tangent fields to 50 Gy after lumpectomy. For the whole group, the mean irradiated heart volume that received at least 25 Gy was 5.7% but was 12% among patients with the highest cardiac volumes, demonstrating that despite 3-D treatment planning, some patients will have substantial cardiac volumes in the radiation field.

In a prospective study from Duke University in which patients had preradiation and serial postradiation cardiac imaging, Lind et al<sup>11</sup> reported that in patients treated with tangential fields, short-term changes in perfusion following treatment correlated with the percent of left ventricle irradiated to greater than 25 Gy. These investigators examined the factors that most affected left ventricular volume irradiated and the likelihood of the development of perfusion defects posttreatment. They found that body mass index (BMI) and setup errors resulting in fields that set up deeper than planned were both associated with significantly higher rates of perfusion defects.<sup>12</sup> Higher BMI was believed to be associated with deep setup errors, demonstrating that even when treatment plans are deemed acceptable, accuracy of treatment delivery also affects the risk of cardiac injury. In a long-term follow-up study of early-stage patients treated with breast conservation therapy, Correa et al<sup>13</sup> reported that among patients who underwent postirradiation cardiac testing, such as echocardiogram and myocardial perfusion imaging, a larger median central lung distance (the distance from the posterior chest wall to the posterior field edge) was significantly associated with a higher risk of cardiac diagnostic test abnormalities and for diagnoses of coronary artery disease (CAD) and congestive heart failure. The 2-D parameter of central lung distance is correlated with the volume of heart irradiated. Newer techniques for reducing cardiac volumes are discussed below.

## Cardiac Mortality

A number of postmastectomies or postlumpectomies conducted in the 1950s to 1970s randomized women to no further local treatment vs chest wall or breast irradiation. In a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group that included 78 randomized trials of breast or chest wall irradiation after surgery, more than 23,000 women were randomized to receive radiation or no radiation.<sup>1</sup> In this analysis, there was an excess of non-breast cancer deaths among women who received radiation, mainly due to heart disease and lung cancer and mainly in older trials. The excess mortality was seen only after 5 or more years following treatment. These older trials used outdated radiation techniques that exposed more volume of heart and lung to larger doses of irradiation than current stan-

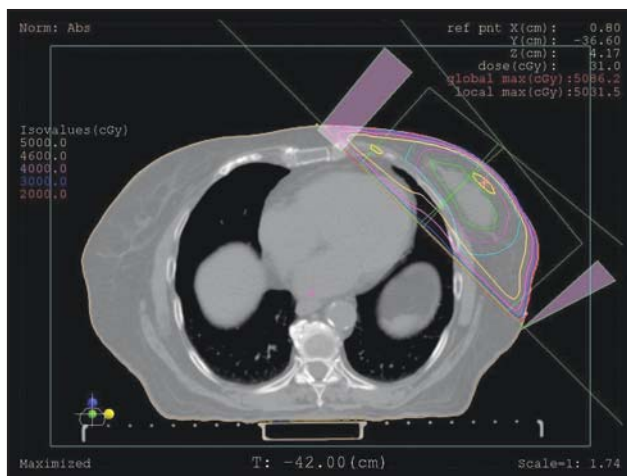


Figure. — Axial slice from a CT simulation treatment plan for a left-sided breast cancer being treated with tangential fields. The values on the left-hand side correspond to the thicker colored isodose lines that overlay the breast volume. A typical prescription dose to the whole breast is 46 to 50 Gy. The thinner colored lines demonstrate the target volumes. Also demonstrated is a segment of heart that is included in the radiation fields. Despite the use of tangent beam arrangements, in left-sided patients it is often not feasible to completely exclude the heart from the treatment field.

dard tangential beams,<sup>2</sup> leading to excess cardiovascular toxicity and mortality.

Comparative mortality risks attributable to irradiation are available from randomized trials of surgery alone vs surgery with breast or chest wall irradiation. A number of these trials have reported increased rates of cardiac death in irradiated groups. While these studies are primarily in the postmastectomy setting or include both breast conservation and mastectomy patients, they provide important information on the long-term cardiac risks of irradiation that is applicable to the breast conservation patient. The earliest randomized trials of postmastectomy radiation are mainly of historical interest. These studies were the first to demonstrate the risk of cardiac toxicity from chest wall irradiation, which is directly related to the large volume of heart irradiated in these older studies.

One of the first such studies was conducted by the Christie Hospital from 1949 to 1955, in which 1,461 patients were randomized after radical mastectomy to postoperative radiation or observation. Jones and Ribeiro<sup>14</sup> reported on a follow-up period of 34 years and found no difference in survival between the two groups until 15 years after treatment, when a significant increase in mortality was observed in the irradiated group ( $P=.003$ ). The excess mortality in irradiated patients compared to those with surgery alone was due to deaths from cardiovascular disease, with no differences seen between right- and left-sided irradiated patients. The Oslo study reported by Høst et al<sup>5</sup> took place between 1964 and 1972 and randomized women with operable breast cancer after radical mastectomy to receive radiation or no further treatment. Radiation was delivered at first using 200 Kv X-rays, then with cobalt-60. The entire chest wall, axilla, and internal mammary nodes were targeted. This study showed a survival benefit for stage II but not stage I patients compared to unirradiated controls ( $P=.15$ ). With a minimum follow-up of 11 years, there was a significant increase in deaths from acute myocardial infarction (MI) among the irradiated group ( $P=.004$ ), with the majority of deaths occurring in left-sided patients. Haybittle et al<sup>15</sup> reported on causes of death in the Cancer Research Campaign trial for early breast cancer conducted from 1970 to 1975, which randomized women with clinical stage I and II breast cancer postmastectomy to radiation or no further treatment. Some women in the observation arm later received radiation at the time of local or regional recurrence. At 18 years of follow-up, there was a small excess overall mortality in the irradiated group, with a relative risk (RR) of 1.04, while the RR of death from breast cancer was 0.97. This benefit was offset by an increased RR of 1.37 of death from other causes, mainly seen in left-sided patients (RR = 1.61) and those treated with orthovoltage (RR = 1.85). The RR of death from cardiac causes more than 5 years after treatment was 2.67.

Cuzick et al<sup>16</sup> collated information from 8 randomized trials of surgery with or without radiation conducted prior to 1975, and they reported 10-year mortality outcomes. An excess of cardiac deaths was seen in these trials ( $P<.001$ ), which was offset by a reduced rate of breast cancer deaths in irradiated groups. Gyenes et al<sup>17</sup> reported long-term outcomes for the Stockholm Southern Hospital randomized trial between 1971 and 1976 of 960 women with operable breast cancer who were allocated to surgery alone vs either preoperative or postoperative radiation. There was no significant difference in the incidence of MI among the three groups. The investigators calculated cardiac dose-volumes in irradiated patients and separated the participants into three dose-volume groups. Patients in the highest dose-volume group had a hazard ratio (HR) for MI of 1.3 compared to surgical controls and a HR for death from ischemic heart disease of 2.5.

Other randomized and institutional series have found no impact of left-sided irradiation on overall cardiac mortality. These studies generally were conducted in a more contemporary era, using megavoltage tangential treatment technique, although still preceding the use of 3-D treatment planning. Højris et al<sup>6</sup> reported on mortality from ischemic heart disease in patients who participated in the Danish Breast Cancer Cooperative Group (DBCG) 82b and 82c randomized trials for high-risk postmastectomy patients. High risk in these studies was defined as one or more positive axillary lymph nodes, tumor size greater than 5 cm, or skin or pectoral fascia invasion. Between 1982 and 1990, 3,083 women were randomized after mastectomy and chemotherapy to receive chest wall and regional nodal irradiation vs no further treatment. The nodal regions, which lie superior to the heart, were treated with anterior photon fields. The chest wall was treated with two anterior electron fields, including the internal mammary nodes, and custom blocks were used to shield the heart and lung caudal to the first rib. All diagnoses of morbidity and mortality from ischemic heart disease were recorded during follow-up, excluding 37 women with preexisting ischemic heart disease. At a median follow-up of 10 years, overall survival was significantly better in the radiotherapy group (46% vs 36%,  $P<.0001$ ), while similar proportions in each group died of ischemic heart disease: 0.8% in all radiotherapy patients; 0.9% in no radiotherapy patients; 0.7% in left-sided radiotherapy patients; and 0.9% in right-sided radiotherapy patients. Similar rates were seen for death from acute MI. When patients were censored at the time of local or distant cancer recurrence, deaths from ischemic heart disease appeared to be associated with a higher relative hazard in left-sided radiotherapy patients, but the overall rates were relatively low: left-sided radiotherapy = 0.7%, left-sided no radiotherapy = 0.3%, relative hazard 2.18.

Rutqvist et al<sup>18</sup> of the Karolinska Hospital in Stockholm, Sweden, reported on 684 women with early-stage breast cancer treated between 1976 and 1987 with breast conservation therapy using tangential fields compared to a contemporaneously treated group of 4,996 postmastectomy patients who did not undergo irradiation. At a median follow-up of 9 years, 0.7% of the irradiated group had died of MI, with a relative hazard for acute MI of 0.60 in the irradiated group compared with the mastectomy group. The incidence of MI was similar in the right- and left-sided patients. While finding no evidence of increased MI overall, the authors suggested a possible effect in left-sided patients with an anteriorly placed heart. Nixon et al<sup>19</sup> from the Joint Center for Radiation Therapy compared 745 right- and left-sided stage I and II patients treated with breast conservation therapy using contemporary tangential technique. With at least 12 years of follow-up, they found an equivalent incidence of death from non-breast cancer causes in both groups (11%), including 2% in each group who died of cardiac causes, and they did not find an increase in cardiac death over time.

Vallis et al<sup>20</sup> performed a retrospective cohort linkage study of breast cancer patients treated with postlumpectomy radiation at Princess Margaret Hospital in Toronto, Canada, between 1982 and 1988, based on two province-wide health databases for hospitalizations and mortality. The incidence of MI was compared between right- and left-sided patients and also to the general population. The 2,128 patients in the study had a median follow-up of 10 years. There were equal numbers of fatal MI in the right- and left-sided patients ( $P=.66$ ), and there was no difference in the incidence of MI between the irradiated study cohort and the general population. Harris et al<sup>8</sup> reported long-term outcomes for 961 stage I and II breast conservation patients treated with contemporary tangential technique at the University of Pennsylvania between 1977 and 1994. The median follow-up was 12 years. This study found no significant difference in overall mortality from any cardiac cause between right- and left-sided patients up to 20 years after treatment (2% vs 3.5%). However, in a cumulative risk analysis, examining the risk of cardiac mortality over accumulated time, an increase in cardiac deaths among left-sided patients compared to right-sided was noted in the second decade after treatment. There was no effect of era of treatment on risk of cardiac death, likely reflecting a relatively uniform treatment technique over time in this single institution series.

Several large epidemiologic studies of cardiac effects of irradiation in breast cancer patients have been performed using datasets from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) or other cancer registry databases. These cancer registries have the advantage of large numbers of patients and long-term follow-up, allowing

for the potential identification of statistical trends that may not be apparent in smaller cohorts. However, the range of data points available for study is limited, particularly with respect to radiation dose and technique. Radiation use is reported only up to 4 months after diagnosis and has been underreported in the SEER database compared with Medicare records.<sup>21</sup> Paszat et al<sup>22</sup> used the SEER database to study the registry of 206,523 women with locoregional breast cancer diagnosed from 1973 to 1992, comparing the time to fatal MI in right- and left-sided patients with or without radiation among different age groups (less 60 years or 60 years or more) and treatment eras (1973 to 1982 and 1983 to 1992). At a median follow-up of 6 years, they found a greater likelihood of fatal MI in left-sided irradiated patients compared to right-sided (RR = 1.17) but no difference by laterality among nonirradiated women (RR = 1.04). The increased risk of fatal MI was seen only in the 60 years or younger age group at diagnosis (RR = 1.98), and especially among those with regional-stage disease (RR = 2.24). The risk was significantly greater for this younger age group at longer follow-up times of 10 to 15 years, while not seen before 10 years. There also appeared to be a higher RR for women treated in the older era, though there were insufficient data to examine the younger age group in the more recent era.

Giordano et al<sup>23</sup> also used the SEER 12-registry 1973–2000 dataset, which included 27,283 women treated with radiation for breast cancer between 1973 and 1989. In order to assess whether presumed changes in radiation technique over time had an impact on the incidence of cardiac mortality, the cohort was divided into treatment eras of 1973 to 1979, 1980 to 1984, and 1985 to 1989. The investigators found that women with left-sided cancers treated in the 1973 to 1979 era had a higher 15-year mortality rate from ischemic heart disease than right-sided patients (13% vs 10%;  $P=.02$ ). No such difference was seen in the other two eras, although median follow-up was necessarily shorter in the more recent eras. Darby et al<sup>24</sup> also utilized the SEER cancer registry for 1973 to 2001 to examine the risk of cardiac mortality over time, including 308,861 women with early breast cancer, 37% of whom received radiation. For women diagnosed and treated prior to 1983, the cardiac mortality ratio for left- vs right-sided patients was 1.20 at less than 10 years of follow-up, 1.42 at 10 to 14 years of follow-up, and 1.58 at 15 years or more of follow-up. For women diagnosed and treated between 1983 and 1992, cardiac mortality ratio was 1.04 under 10 years and 1.27 at 10 or more years. Follow-up data for the final era group, 1993 to 2001, is under 10 years, with a cardiac mortality ratio of 0.96. While the reduction of cardiac mortality risk for women treated more recently may be related to improvements in radiation technique, there were also improvements in screening and treatment of ischemic heart disease during the study period.

Other registries have been explored for cardiac outcomes in breast cancer survivors. Paszat et al<sup>25</sup> linked records from the Ontario Cancer Registry to hospital discharge records to compare the risk of death from MI between right- and left-sided patients radiated following lumpectomy between 1982 and 1987 (N = 3,006). At a median follow-up of 9 years, there was a higher risk of death from MI in the left-sided group (2%) compared to the right-sided group (1%;  $P=.02$ ; RR = 2.1). In this study, age-stratified analysis showed that the increased risk of MI was seen only after age 60 years, while no difference was seen for patients under 60 years at the time of treatment. The mean dose per fraction in this cohort was about 2.4 Gy, somewhat higher than in series from the US population, and 77% received treatment on cobalt-60 units. The study found that some radiation treatment quality factors were associated with a higher RR of MI in left-sided patients. The authors postulate that differences in available data from the SEER vs the more detailed Ontario dataset, particularly in regard to staging and radiation technique, that may have accounted for the different outcomes seen in their different population-based studies.

Paszat et al<sup>7</sup> conducted another population-based case control series of 6,680 women treated with post-lumpectomy or mastectomy radiation between 1982 and 1988 in Ontario, Canada. The investigators identified and validated cases of acute MI by enzyme or electrocardiographic criteria as well as those identified as acute MI on a death certificate. After adjusting for history of smoking and prior MI, the risk of an acute MI among women aged 60 or older with left-sided vs right-sided breast cancers was associated with an HR of 1.96. Treatment of the internal mammary nodal chain was associated with an HR of 1.90. However, examination of other technical factors did not show treatment of an anterior left breast boost to significantly increase the risk of acute MI (HR = 1.02).

Rutqvist and Johansson<sup>26</sup> reported mortality rates by laterality among 54,617 breast cancer patients from the Swedish Cancer Registry for patients treated from 1970 to 1985. At a median of 9 years, no difference was found between right- and left-sided patients for total mortality, total intercurrent deaths, or total cardiovascular mortality. However, the rate of deaths from MI was slightly higher in the left-sided patients (RR = 1.09). This risk became more pronounced with longer follow-up, with an RR for left-sided vs right-sided of 1.06 at 0 to 5 years, 1.13 at 5 to 10 years, and 1.20 at 10 to 17 years ( $P=.22$ ). To assess long-term cardiac mortality in women treated in an older era, Roychoudhuri et al<sup>27</sup> examined the Thames Cancer Registry of 20,871 women with any breast cancer diagnosis between 1971 and 1988 to identify deaths from ischemic heart disease and any cardiovascular disease, comparing right-sided patients who did or did not receive any radiation as controls against

left-sided irradiated patients. The HR of death from ischemic heart disease at 15 years or more after treatment for left-sided patients compared to unirradiated controls was 1.59, and for any cardiovascular death was 1.27. HRs for left-sided patients compared to irradiated right-sided controls were 1.23 and 1.25, respectively.

Few studies have reported on women with pre-existing cardiac disease who received breast irradiation and whether they are at increased risk of additional cardiac events. In fact, these patients have typically been excluded from the studies and trials due to the confounding effect of preexisting ischemic cardiac disease, as they are inherently at higher risk for subsequent cardiac events. The University of Pennsylvania excluded patients with preexisting cardiac disease from the long-term outcomes analysis but did examine the outcomes in these patients separately (R. Gutt, MD, unpublished data, August 2007). Forty-one women treated with breast irradiation had a history of congestive heart failure, CAD, or MI prior to their diagnosis of breast cancer. While there was no difference in overall survival between right- and left-sided patients, the left-sided group had a higher incidence at 10 years after irradiation of cardiac deaths (27% left vs 9% right;  $P=.08$ ), and the right-sided group had a higher rate of breast cancer deaths and noncardiac deaths. This study is small but raises an intriguing question as to whether the risk of subsequent cardiac events in left-sided patients with preexisting cardiac disease is increased by the addition of breast irradiation.

One major limitation of most of the studies of cardiac toxicity is the lack of long-term data in patients who have also received current commonly used cardiotoxic systemic therapies, especially doxorubicin and trastuzumab. Woodward et al<sup>28</sup> reported outcomes in 470 patients who were treated on a series of prospective institutional protocols at M. D. Anderson Cancer Center. They compared the toxicity rates of 470 patients who received doxorubicin-based chemotherapy and radiation and the toxicity rates of 1,031 women with the same systemic therapy who did not receive radiation. While this study includes only postmastectomy patients with more advanced disease, currently it is the only published series with long-term follow-up in patients who received a doxorubicin-based chemotherapy regimen. The investigators looked at chronic toxicities with and without chest wall radiation, including the rates of cardiac-related deaths, primarily from MI. While the 10-year rate of death from MI was higher in the irradiated group (2.4% vs 0.5%;  $P=.057$ ), 2 of 8 patients died of MI during systemic therapy, and only 2 patients who died of MI had left-sided cancers. Consistent with other series not including cardiotoxic chemotherapy, the median time to MI was 9 years after treatment and the overall rate of MI was low. The National Surgical Adjuvant Breast and Bowel Project (NSABP B-31 trial) ran

domized women with node-positive and HER/2-positive breast cancer to doxorubicin, cyclophosphamide, and paclitaxel with or without trastuzumab.<sup>29</sup> Postlumpectomy radiation was required, while postmastectomy radiation was optional. All patients in the trastuzumab arm received the drug concurrently with radiation when given. The cumulative incidence of cardiac events in the trastuzumab arm was 4.1% compared to 0.8% in the chemotherapy alone arm, and most of the cardiac events were congestive heart failure. There are currently no published studies of any possible interactive effects of trastuzumab and radiation; thus concurrent therapy as conducted in the randomized trials is considered acceptable.

Two important factors have emerged from the accumulated data on the risk of cardiac injury after breast or chest wall irradiation. The first is that the greater the volume of heart included in the radiation fields, the higher the likelihood of cardiac injury leading to ischemic heart disease and cardiac mortality. This is evident from the higher rate of cardiac deaths in the older trials, which is less prominent in more contemporary studies. The second is that radiation-induced cardiac injury is a late event. In most studies, cardiac deaths do not appear to be increased among irradiated patients compared to controls, or among left-sided patients compared to right-sided, until 10 or more years after irradiation. Therefore, long-term outcomes are necessary to evaluate the impact of any new techniques.

## Cardiac Morbidity

In the studies described in the previous section, the endpoint for analysis was death due to cardiac causes or a specific cardiac disease, particularly death due to MI. However, not all patients will die of MI or CAD. The treatment and prevention of ischemic cardiac disease have improved greatly over the past 2 decades, and many women who develop cardiac disease after treatment for breast cancer, regardless of the etiology, may be successfully treated for cardiac disease for many years. Still, taking medications chronically or undergoing diagnostic and therapeutic procedures for treatment-related morbidities will affect the quality of life of breast cancer survivors. Thus it is important to study the incidence of nonfatal events that affect the heart after cancer treatment in order to inform patients of their risks and follow-up requirements and to improve treatment of these significant morbidities.

Data on cardiac morbidity after breast cancer treatment from randomized trials are limited. From the Stockholm Breast Cancer Trial, Gyenes et al<sup>17</sup> reported the incidence of nonfatal MI among patients with operable breast cancer randomized to preoperative, postoperative, or no radiation after surgery. At a median follow-up of 20 years, the investigators reported no difference in number of acute MI among the three

groups, although no other specific morbidity data were provided. From the Danish Breast Cancer Group randomized trial, Højris et al<sup>6</sup> noted no difference in cumulative incidence of morbidity from ischemic heart disease between the radiotherapy and no radiotherapy groups, including in analyses according to laterality and menopausal status. Ischemic heart disease morbidity was reported as follows: 3% in all radiotherapy patients; 3.2% in all no radiotherapy patients; 2.9% in left-sided radiotherapy patients; and 3.1% in right-sided radiotherapy patients. Acute MI morbidity was also reported as follows: 1.7% in all radiotherapy patients; 1.4% in all no radiotherapy patients; 1.9% in left-sided radiotherapy patients; and 1.6% in right-sided radiotherapy patients. The analysis was also performed censoring at the time of recurrence to account for the confounding effects of treatment for recurrent cancer on the risk of heart disease, and the morbidity-relative hazard for all radiotherapy patients was better than for no radiotherapy patients due to higher rate of breast cancer recurrences in the no radiotherapy group. To assess whether the risk of ischemic heart disease increased over time, hazard rates over follow-up increments showed no increased trend for cardiac events. In the study by Vallis et al,<sup>20</sup> from the Princess Margaret Hospital, the incidence of MI was compared between right- and left-sided breast cancer patients, and the treatment group to the general provincial population. At a median follow-up of 10 years, they found no difference in the incidence of MI between the right-sided (2.1%) and left-sided (2.4%) patients in the treatment group or the general population. Fatal MI occurred in only 0.7% of the treated group, with the remainder of MIs representing nonfatal events. While the study noted no significant difference between right- and left-sided patients for baseline cardiac risk factors (including smoking, hypertension, and history of cardiac disease), no analysis of the association of baseline factors with cardiac morbidity incidence was undertaken.

In a study by Correa et al,<sup>30</sup> the era of treatment was 1977 to 1995, although the treatment techniques were relatively similar throughout the study period and were more consistent with contemporary techniques to avoid excess lung and cardiac dose and with little use of internal mammary nodal fields. However, this study still predated the era of 3-D treatment planning. A comparison of cardiac symptoms and morbidity endpoints between right- and left-sided patients was undertaken, and all analyses were adjusted for year of treatment as well as baseline cardiac risk factors (with no difference compared to unadjusted values). There was no difference between right- and left-sided patients for endpoints including congestive heart failure, palpitations, arrhythmia, and valvular disorders. There were significant differences between right- and left-sided patients for the development of chest pain and for any diagnosis of MI and CAD. At 20 years, CAD was diag-

nosed in 10% of right-sided patients and in 25% of left-sided patients ( $P<.001$ ) and MI in 5% of right-sided patients and in 15% of left-sided patients ( $P=.002$ ). That a difference was seen may be partly attributable to the longer follow-up period compared to some other series. These investigators compared the incidence of CAD after breast conservation treatment among right- and left-sided patients who subsequently had cardiac testing for symptomatic indications. At a median follow-up of 12 years, there was a significantly higher prevalence of stress test abnormalities in left-sided tested patients (59%) than in right-sided tested patients (8%), and the majority of left-sided abnormalities were located in the left anterior descending artery. This is the artery most likely to be in the breast tangent fields, and the rate of abnormalities exceeded that expected in an age-matched population. As seen in other studies, these coronary artery defects were diagnosed 10 or more years after the completion of radiation.

Patt et al<sup>31</sup> utilized the SEER database to examine the risk of cardiac morbidity with “modern adjuvant radiotherapy” in women with nonmetastatic disease treated between 1986 and 1993. They identified 16,270 women with known laterality who had undergone adjuvant radiation after surgery, and they used hospital discharge diagnoses codes to attempt to quantify incidents of ischemic and valvular heart disease and congestive heart failure. At a median follow-up of 9.5 years, the study found no difference between left- and right-sided patients among hospitalizations for ischemic heart disease (9.9% vs 9.7%), valvular heart disease (2.9% vs 2.8%), conduction problems (9.7% vs 9.6%), or heart failure (9.7% vs 9.7%). The HR for left- vs right-sided patients was 1.07 for ischemic heart disease and 1.05 for heart failure. The authors concluded that up to 15 years after radiation, there is no increase in cardiac morbidity for left-sided irradiated patients.

### **Risk Factors for Cardiac Morbidity and Mortality**

While the risk of cardiac disease, in particular CAD and ischemic heart disease, may be elevated in some left-sided breast cancer patients after irradiation, it is important to place this risk in context of other cardiac disease risk factors and to understand how preexisting or newly developed cardiac risk factors interact with the use of both irradiation and other cardiotoxic cancer therapies. Clearly, left-sided irradiation for breast cancer in and of itself is a minor contributor to heart disease in comparison to other risk factors such as hypercholesterolemia, hypertension, obesity and sedentary lifestyle, and family history. A few studies have examined the interaction of preexisting cardiac risk factors and cancer treatment, as well as the context of cardiac disease in the breast cancer population compared to the general population.

In the study by Harris et al,<sup>8</sup> the investigators examined the association and interaction of multiple cardiac risk factors with the use of left- and right-sided radiation, including smoking history, family history, Framingham score,<sup>32</sup> hypertension, use of cardiac medications, thyroid disease, alcohol use, and diabetes. Cardiac mortality was associated with several of these known risk factors, including age, smoking history, hypertension, hyperlipidemia, diabetes and Framingham risk score. However, left-sided radiation did not modify the association between these risk factors and the risk of cardiac death. This analysis was also performed for the interaction of the presence of any cardiac morbidities (including chest pain, CAD, and MI) and the use of radiation. There was an interaction with laterality and the presence of hypertension for the development of CAD. The HR was 7.2 for the development of CAD for right-sided patients with hypertension, 4.6 for left-sided patients without hypertension, and 11.4 for left-sided patients with hypertension. This interaction was not seen for the endpoint of MI. While hypertension in itself is a major contributor to the development of CAD, this risk may be further elevated by other sources of cardiac injury. Thus it would be prudent to closely observe women who have received left-sided irradiation for hypertension and other risk factors such as hyperlipidemia and diabetes and also to treat aggressively in hopes of risk reduction.

Preexisting ischemic heart disease might be expected to have an adverse association with left-sided radiation as these patients already have coronary artery compromise. However, this issue has not been widely studied. Doyle et al<sup>33</sup> utilized the SEER database to study the effects of radiation and the impact of preexisting cardiovascular risk factors specifically in an older population of breast cancer patients 65 years of age or greater at diagnosis. The investigators identified 48,353 women of this age range diagnosed with stage I to III breast cancer between 1992 and 2000 who were treated with either mastectomy (55%) or lumpectomy (42%). Use of radiation was associated with later year of diagnosis, younger age, fewer comorbidities, and use of chemotherapy. While MI 10 years or more following treatment was associated with various factors, including age, African American race, advanced stage, hormone receptor-negative tumors, more than one comorbid condition, and preexisting cardiac risk factors or a history of heart disease, it was not associated with the use of radiation. Laterality was not a risk factor for MI in this study. Accordingly, while older women with known cardiac risk factors or previous heart disease are at increased risk of MI, the use of radiation did not appear to affect this risk up to 10 years after treatment. While comorbidities and life expectancy should be considered for any age group, and particularly for elderly women, radiation should not necessarily be withheld when clinically indicated, even in women with cardiac risk factors.

The breast cancer population has been shown to have better overall health than the general population, possibly due to more intensive medical care after a diagnosis of early-stage breast cancer, a disease from which most patients will enjoy long-term survival. In terms of heart disease specifically, population comparisons confirm this phenomenon. Jagsi et al<sup>34</sup> compared the observed rates of cardiac events of 828 patients from the University of Michigan Health System to expected rates from the general population. Expected cardiac event rates were calculated from the National Hospital Discharge Surveys of the US Centers for Disease Control and Prevention from 1989 to 2003. Patients were treated with breast-conserving therapy, including radiation, between 1984 and 2000, with a median follow-up of 6.8 years. This time frame is shorter than the average time to ischemic heart disease after radiation, which typically exceeds 10 years. However, in this study, the median time from treatment to first cardiac event was 3.7 years, with a 10-year cumulative incidence of MI of 1.2% and of any MI or CAD requiring intervention of 2.7%. These observed rates of cardiac events were lower than expected. The standardized incidence rate (SIR) of MI for breast cancer patients vs the expected population rate was 0.44, and the SIR for any MI or CAD event requiring intervention was 0.50. Harris et al<sup>8</sup> compared the study population to the general US female population using statistics from the National Institutes of Health Morbidity and Mortality Chartbook on Cardiovascular, Lung and Blood Disease,<sup>35</sup> analyzed by a standardized mortality ratio (SMR). For all cardiac deaths, the overall rate of death among the breast cancer cases was lower than expected from the population controls. In right-sided patients the SMR was 0.56, and for left-sided patients the SMR was 0.73. For death from MI, the same observation was noted, with an SMR of 0.45 in the right-sided patients and an SMR of 0.73 in the left-sided patients.

## Conclusions

Cardiac mortality and morbidity may be radiation-induced after treatment for breast cancer. Over the past several decades, breast conservation treatment has become more widely used and the indications for post-mastectomy radiation have expanded, resulting in more patients receiving postoperative irradiation. Simultaneous refinements in the delivery of radiation to the breast or chest wall have evolved. The oldest radiation techniques exposed large volumes of the heart to excessive dose, but as this technique was recognized as harmful to the heart, the more contemporary technique of tangential irradiation was developed and widely adopted. Long-term outcome data in the era of tangential radiation have become available; these data show more subtle effects on the heart, demonstrating that the changes in technique were beneficial. In the

current era of 3-D CT-based planning, even further refinements are possible. Other conditions may increase the risk of developing cardiac disease, such as hypertension and other comorbid conditions. Understanding the interaction of left-sided irradiation with these other cardiac risk factors is preliminary. It would appear prudent to advise breast cancer patients to vigilantly pursue routine preventive health measures and to treat any cardiac risk factors appropriately.

The emerging principle of radiation treatment for breast cancer is to minimize the dose to the heart as much as possible. Radiation treatment remains a critical component of comprehensive breast cancer treatment, providing a substantial reduction in local and regional recurrence rates for early-stage and locally advanced breast cancers and contributing to improvements in overall survival. The role of the radiation oncologist is to perform individualized treatment planning using CT-based 3-D planning with careful attention to normal tissue exposure and minimizing these parameters to allow long-term breast cancer survivors the optimal chance of survival without toxicity.

## Disclosures

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## References

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of randomised trials. *Lancet*. 2005;366:2087-2106.
2. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol*. 2006;24:2268-2275. Epub 2006 Apr 17.
3. Ragaz J, Olivetto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst*. 2005;97:116-126.
4. Krueger EA, Schipper MJ, Koelling T, et al. Cardiac chamber and coronary artery doses associated with postmastectomy radiotherapy techniques to the chest wall and regional nodes. *Int J Radiat Oncol Biol Phys*. 2004;60:1195-1203.
5. Høst H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer: long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys*. 1986;12:727-732.
6. Højris I, Overgaard M, Christensen JJ, et al. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. *Lancet*. 1999;354:1425-1430.
7. Paszat LF, Vallis KA, Benk VM, et al. A population-based case-cohort study of the risk of myocardial infarction following radiation therapy for breast cancer. *Radiother Oncol*. 2007;82:294-300. Epub 2007 Feb 5.
8. Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncol*. 2006;24:4100-4106. Epub 2006 Aug 14.
9. Pierce LJ, Butler JB, Martel MK, et al. Postmastectomy radiotherapy of the chest wall: dosimetric comparison of common techniques. *Int J Radiat Oncol Biol Phys*. 2002;52:1220-1230.
10. Gyenes G, Gagliardi G, Lax I, et al. Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. *J Clin Oncol*. 1997;15:1348-1353.

11. Lind PA, Pagnanelli R, Marks LB, et al. Myocardial perfusion changes in patients irradiated for left-sided breast cancer and correlation with coronary artery distribution. *Int J Radiat Oncol Biol Phys.* 2003;55:914-920.
12. Evans ES, Prosnitz RG, Yu X, et al. Impact of patient-specific factors, irradiated left ventricular volume, and treatment set-up errors on the development of myocardial perfusion defects after radiation therapy for left-sided breast cancer. *Int J Radiat Oncol Biol Phys.* 2006;66:1125-1134.
13. Correa C, Harris E, Litt H, et al. Prediction of Nuclear Stress Perfusion Defects and Cardiac Diagnoses from Amount of Heart Irradiated in Primary Radiotherapy for Left-Side Breast Cancer. Presented at: 90th Scientific Assembly and Annual Meeting of the Radiological Society of North America; November 28 - December 3, 2004; McCormick Place, Chicago. Abstract SST18-07. [http://rsna2004.rsna.org/rsna2004/V2004/conference/event\\_display.cfm?em\\_id=4407886](http://rsna2004.rsna.org/rsna2004/V2004/conference/event_display.cfm?em_id=4407886). Accessed February 11, 2008.
14. Jones JM, Ribeiro GG. Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy. *Clin Radiol.* 1989;40:204-208.
15. Haybittle JL, Brinkley D, Houghton J, et al. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *BMJ.* 1989;298:1611-1614.
16. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol.* 1994;12:447-453.
17. Gyenes G, Rutqvist LE, Liedberg A, et al. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. *Radiother Oncol.* 1998;48:185-190.
18. Rutqvist LE, Liedberg A, Hammar N, et al. Myocardial infarction among women with early-stage breast cancer treated with conservative surgery and breast irradiation. *Int J Radiat Oncol Biol Phys.* 1998;40:359-363.
19. Nixon AJ, Manola J, Gelman R, et al. No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol.* 1998;16:1374-1379.
20. Vallis KA, Pintilie M, Chong N, et al. Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. *J Clin Oncol.* 2002;20:1036-1042.
21. Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. *Cancer Epidemiol Biomarkers Prev.* 1999;8:1117-1121.
22. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol.* 1998;16:2625-2631. Erratum in: *J Clin Oncol.* 1999;17:740.
23. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst.* 2005;97:419-424.
24. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol.* 2005;6:557-565.
25. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. *Int J Radiat Oncol Biol Phys.* 1999;43:755-762.
26. Rutqvist LE, Johansson H. Mortality by laterality of the primary tumor among 55,000 breast cancer patients from the Swedish Cancer Registry. *Br J Cancer.* 1990;61:866-868.
27. Roychoudhuri R, Robinson D, Putcha V, et al. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer.* 2007;7:9.
28. Woodward WA, Strom EA, McNeese MD, et al. Cardiovascular death and second non-breast cancer malignancy after postmastectomy radiation and doxorubicin-based chemotherapy. *Int J Radiat Oncol Biol Phys.* 2003;57:327-335.
29. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol.* 2005;23:7811-7819.
30. Correa CR, Litt HI, Hwang WT, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol.* 2007;25:3031-3037.
31. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol.* 2005;23: 7475-7482. Epub 2005 Sep 12.
32. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837-1847.
33. Doyle JJ, Neugut AI, Jacobson JS, et al. Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients. *Int J Radiat Oncol Biol Phys.* 2007;68:82-93. Epub 2007 Mar 2.
34. Jagi R, Griffith KA, Koelling T, et al. Rates of myocardial infarction and coronary artery disease and risk factors in patients treated with radiation therapy for early-stage breast cancer. *Cancer.* 2007;109:650-657.
35. *Morbidity & Mortality: 2004 Chart Book on Cardiovascular, Lung, and Blood Diseases.* National Heart, Lung, and Blood Institute, National Institutes of Health. Bethesda, MD. May 2004.