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Is There a Dose-Response Relationship for Heart Disease With Low-Dose Radiation Therapy?

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Summary

Although long-term cardiac morbidity after radiation therapy for left-sided breast cancer is well established, a dose-response relationship using modern treatment techniques is still undefined. Thirty-two patients underwent cardiac SPECT-CT scans before and 1 year after radiation therapy. No clinically or statistically significant changes in perfusion or function were seen after radiation. No correlations were found between cardiac doses and changes in perfusion or function.

Purpose—To quantify cardiac radiation therapy (RT) exposure using sensitive measures of cardiac dysfunction; and to correlate dysfunction with heart doses, in the setting of adjuvant RT for left-sided breast cancer.

Methods and Materials—On a randomized trial, 32 women with node-positive left-sided breast cancer underwent pre-RT stress single photon emission computed tomography (SPECT-CT) myocardial perfusion scans. Patients received RT to the breast/chest wall and regional lymph nodes to doses of 50 to 52.2 Gy. Repeat SPECT-CT scans were performed 1 year after RT. Perfusion defects (PD), summed stress defect scores (SSS), and ejection fractions (EF) were evaluated. Doses to the heart and coronary arteries were quantified.

Results—The mean difference in pre- and post-RT PD was $-0.38\% \pm 0.32\%$ ($PZ.68$), with no clinically significant defects.

To assess for subclinical effects, PD were also examined using a 1.5-SD below the normal mean threshold, with a mean difference of $2.53\% \pm 12.57\%$ ($PZ.38$). The mean differences in SSS and EF before and after RT were $0.78\% \pm 2.50\%$ ($PZ.08$) and $1.75\% \pm 7.29\%$ ($PZ.39$), respectively. The average heart Dmean and D95 were 2.82 Gy (range, 1.11–6.06 Gy) and 0.90 Gy (range, 0.13–2.17 Gy), respectively. The average Dmean and D95 to the left anterior descending artery were 7.22 Gy (range, 2.58–18.05 Gy) and 3.22 Gy (range, 1.23–6.86 Gy), respectively. No correlations were found between cardiac doses and changes in PD, SSS, and EF.

Conclusions—Using sensitive measures of cardiac function, no clinically significant defects were found after RT, with the average heart Dmean <5 Gy. Although a dose response may exist for measures of cardiac dysfunction at higher doses, no correlation was found in the present study for low doses delivered to cardiac structures and perfusion, SSS, or EF.

Introduction

Adjuvant radiation therapy (RT) has been demonstrated to improve local control and survival after both mastectomy and breast-conserving surgery (1, 2). However, the benefits of RT may be offset by increased nonbreast cancer mortality, especially in regards to cardiovascular injury. Numerous studies have documented the increased incidence of coronary artery disease (CAD) and myocardial infarction after left-sided compared with right-sided radiation (3–6). Furthermore, a large meta-analysis demonstrated a significant increase in death from heart disease after radiation, with the overall survival benefit of RT decreasing over time in women who received postmastectomy radiation therapy (1).

With the increased concern for cardiovascular injury, radiation techniques have changed over time, resulting in decreased heart doses. Giordano et al (7) demonstrated that heart disease mortality for left-sided versus right-sided disease has decreased over time, with no difference observed in women diagnosed after 1988. This finding may partially be attributed to limited follow-up, with longer follow-up needed to estimate long-term cardiac injury. The prolonged latency for cardiac disease highlights one of the difficulties in determining the effects of RT on cardiac function and mortality.

More recently, evidence of early radiation-associated cardiac changes has been identified using perfusion scintigraphy (8). In the largest series using single-photon emission computed tomography (SPECT-CT) perfusion scans, Evans et al (9) demonstrated the development of perfusion defects (PD) in 59 of 108 patients within 24 months after RT for left-sided breast cancers (9). Although PD have been associated with regional wall motion abnormalities (10), they have yet to be associated with changes in ejection fraction (EF), and longer follow-up is required to determine their physiologic importance. However, perfusion scintigraphy provides a metric to quantify radiation exposure to the heart and its effects on the coronary microvasculature.

Although the increase in PD after RT has been demonstrated, previous reports used treatment techniques whereby portions of the anterior heart were directly in the tangential fields (8, 9), resulting in significant left ventricle (LV) doses. More contemporary treatment techniques use CT-based planning to further minimize cardiac exposure (11). In 2006, we initiated a prospective, randomized trial of 3-dimensional conformal radiation therapy (3D-CRT) versus intensity modulated radiation therapy (IMRT), with the primary goal of determining any incremental cardiac sparing with IMRT. Here we report the initial results of our study correlating myocardial perfusion SPECT-CT scan findings with doses received to the heart and cardiac substructures.

Methods and Materials

Patients

We enrolled patients with node-positive, left-sided breast cancer in an institutional review board approved prospective phase 2 trial. Patients were randomized to adjuvant radiation with either 3D-CRT or IMRT with active breathing control (ABC). All patients had

histologically confirmed breast cancer requiring comprehensive locoregional irradiation. Both postmastectomy and intact breast patients were eligible. Of 32 patients, 31 received chemotherapy before RT. All pre-existing cardiac disease and major risk factors for development of CAD were recorded.

Radiation therapy

All patients underwent free-breathing CT simulations with catheters placed in the locations expected for the field borders of standard tangent fields before scanning. A second CT scan using ABC to suspend breathing motion at deep inspiration breath-hold, approximately 75% of vital capacity, followed. Two treatment plans were developed for each patient, a 3D-CRT plan on the free-breathing scan and an IMRT plan on the deep inspiration breath-hold scan, with randomization occurring after physicians had approved both plans to be clinically acceptable. No portion of the heart was allowed to be within the primary beam for either treatment plan. Targets included the breast/chest wall (CW) and supraclavicular (SCV), infraclavicular, and internal mammary nodes in the first 3 intercostal spaces.

The 3D-CRT plans included lateral and medial tangents matched to an SCV field. The breast/CW and lymph nodes were treated to 50 Gy in 2-Gy fractions. A 10-Gy boost was delivered to the tumor bed or mastectomy scar (Fig. 1). Tangential beamlet IMRT plans were developed as previously described (12). The target volume was treated to 52.2 Gy in 1.74-Gy fractions, which is approximately biologically equivalent to 50 Gy in 2-Gy fractions. A concomitant boost was incorporated to deliver 60 Gy to the tumor bed or mastectomy scar (Fig. 1). For both planning techniques, electron beams were used when needed to minimize cardiac doses (Table 1). For IMRT plans, electron doses were considered during optimization.

Dose calculations

The breast/CW contours excluded the pectoral musculature, excluded 5 mm of skin and tissue from the external surface, and extended to 5 mm inside the medial and lateral catheters. The heart, left main coronary artery (LCA), and left anterior descending artery (LAD) were contoured according to a heart atlas previously developed at our institution (13). The mean dose (Dmean) and dose to 95% (D95) of the heart, LCA, and LAD were determined.

Cardiac Imaging

Baseline pre-RT and 1-year post-RT adenosine stress myocardial perfusion SPECT-CT scans were performed to assess PD, EF, and cardiac wall motion abnormalities. Patients were scanned in the treatment position on a breast board to aid in registration of SPECT-CT datasets to treatment planning scans. One hour after infusion of 15 to 30 mCi of Tc-99m sestamibi, stress-gated myocardial perfusion images were acquired using a SPECT-CT system (Siemens Symbia, Malvern, PA). The CT volumes were obtained with typical exposure settings of 130 kVp and 70 mAs. Computed tomography scans near end-expiration, approximately 25% of vital capacity, were acquired and used to correct SPECT data for photon attenuation correction. For patients randomized to IMRT, a second CT scan using ABC was obtained for registration with treatment planning models. The SPECT

projection data were acquired over 180° in 128×128 matrices using a 15% energy window centered at 140 keV. All SPECT image acquisitions were acquired gated to the cardiac cycle at 16 frames per cycle using forward-backward gating with bad-beat rejection to ensure accurate assessments of cardiac function. The SPECT images throughout the cardiac volume were reconstructed into 128x 128 matrices at a resolution of 4.80×4.80×4.80-mm voxels. Images were reconstructed with attenuation correction for most patients (28 of 32) owing to the improvement in discrimination of abnormal from normal (14). Filtered back-projection reconstructed images were used for 4 patients owing to artifacts seen after attenuation correction.

Assessment of cardiac function

Single photon emission computed tomography image quantification was performed using Corridor 4 DM (INVIA Medical Imaging Solutions, Ann Arbor, MI) software. One-year post-RT SPECT-CT scans were compared with baseline scans to assess changes in cardiac perfusion and function. Perfusion defects were assessed by comparing normalized perfusion distributions against normal polar map databases using thresholds of 2.5 and 1.5 SD below the normal mean. On the basis of intertest variability, PD increases greater than 5% and 10% were considered significant for 2.5- and 1.5-SD thresholds, respectively. Summed stress defects scores (SSS) were evaluated using the standard 17-segment model semiquantitative method, with perfusion tracer uptake scored from 0 (normal) to 4 (no myocardial uptake) for each segment. A cumulative SPECT-SSS was obtained by summing the score from each segment. Increases in SSS greater than 1 point between post- and pre-RT scans were considered clinically significant. Left ventricular EFs were automatically calculated using the standard Corridor 4 DM algorithm. In brief, LV endocardial surface estimates throughout the cardiac cycle were used, with LV volumes calculated as the sum of the voxels within the contours for each frame. The end-diastolic and end-systolic volumes were determined from LV volume curves, and EFs were calculated.

Statistics

All patients, regardless of surgery type or radiation planning arm, were combined for the current analysis. Inpatient differences in PD, SSS, and EF between before and after RT were calculated. Significant differences for the entire cohort of patients were tested for using paired *t* tests. Patients with differences greater than the clinical meaningful thresholds were identified as illustrating the potential for cardiac damage. Patients with and without evidence of potential cardiac damage were compared for differences in Dmean and D95 to the heart, LCA, and LAD. Statistical comparisons were made using 2-sample *t* tests. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), with *P* values at or below .05 considered as evidence for significant difference.

Results

From 2006 to 2010, 32 patients completed both pre- and post-RT SPECT-CT scans. The baseline patient and treatment characteristics are shown in Table 1. Besides family histories of cardiac disease and prior smoking histories, there were few CAD risk factors. The majority of women were Caucasian, and 30 patients received doxorubicin-based

chemotherapy regimens. The average Dmean and D95 to the heart, LCA, and LAD are shown in Table 2. Overall heart doses were low, with only 3 patients receiving a mean heart dose greater than 5 Gy.

Post-RT SPECT-CT scans were compared with pre-RT scans to quantify changes in PD in the distribution of the LAD. At our institution, a 2.5 SD below the normal mean threshold is clinically used to assess for PD, and therefore this level was initially selected (Fig. 2). The mean difference in pre- and post-RTPD was $-0.38\% \pm 3.20\%$, with no clinically or statistically significant increase ($P=.68$) (Fig. 3). To determine whether subclinical changes were potentially excluded at the 2.5-SD level, PD were examined using a 1.5-SD threshold (Fig. 2). The mean difference in PD at the 1.5-SD level was $2.53\% \pm 12.57\%$ ($P=.38$) (Fig. 3). Changes between SSS and EF between pre- and post-RT SPECT-CT scans were subsequently analyzed. The mean difference in SSS was 0.78 ± 2.50 , which was not clinically or statistically significant ($P=.08$). Similarly, there was no difference in EF, $1.75\% \pm 7.29\%$ ($P=.39$). No evidence of wall motion abnormalities was observed any SPECT-CT scan.

Although there were no significant differences in PD, SSS, or EF after RT, we attempted to correlate differences in cardiac function with doses to the heart, LCA, and LAD. For PD, patients were stratified using the 1.5-SD threshold. Patients with an increase in PD $>10\%$ were categorized as having “worse” ($n=5$) perfusion; all other patients were categorized as having “no change” ($n=27$). There was no correlation in doses to the cardiac structures and changes in PD (Table 3). Similarly for SSS, patients were stratified as “worse” ($n=11$) if the SSS increased by 2 or more points, and “no change” for all other patients ($n=21$). There was no correlation in doses to the cardiac structures and changes in SSS (Table 3). Finally, no significant correlations were found between changes in EF and heart doses (Table 3).

Discussion

Although the survival advantage provided by adjuvant radiation has been demonstrated (1, 2), the increased rates of cardiac morbidity and mortality have been well described (3–6). To adequately predict the cardiac risks of modern radiation techniques, the determination of a relationship between cardiac doses and long-term morbidity and mortality is necessary. Previous reports have attempted to correlate the risk of cardiac injury with doses received by the heart (5, 15, 16). Hooning et al (15) retrospectively reviewed the incidence of cardiovascular disease in 10- year survivors of breast cancer treated from 1970 through 1986. Although the risk of cardiovascular disease increased with increasing estimated mean heart doses, the risk was decreased with more modern treatment techniques. More recently, Nilsson et al (5) demonstrated with coronary angiography that the location and severity of coronary artery stenosis correlates with the expected regions of high-dose radiation, especially for left-sided radiation or inclusion of the internal mammary nodes.

In an attempt to correlate cardiac dose with long-term morbidity, the Radiation-Associated Cardiovascular Events (RACE) collaboration retrospectively reviewed population-based disease registries and related the mean cardiac dose to the risk of developing heart disease (17). The risk of heart disease was greater with left-sided versus right-sided breast cancer,

and the risk correlated with increasing heart doses. A major limitation of these retrospective studies has been the lack of patient-specific radiation data to accurately calculate cardiac exposure, with estimates of dose made according to phantoms or virtual simulations of a representative patient. However, a representative patient would not account for differences in cardiac positioning and anatomy, which can be substantial (18). Confounding the accurate estimation of radiation-induced cardiac toxicity are the changes in dose per fraction and treatment techniques used over time.

Although the applicability of previous estimates of long-term cardiovascular injuries are uncertain with contemporary treatment planning and techniques, recent data demonstrate that decreases in cardiac perfusion are present even with minimal cardiac radiation. Using cardiac SPECT-CT perfusion scans, Marks et al (10) reported new defects in 10% to 20% of patients who had less than 5% of their LV within the radiation fields. The percentage of patients with new defects increased to >70% to 80% in patients who had more than 5% of the LV irradiated. In addition to in-field cardiac volume, dose to the heart was also found to impact incidence of PD. Hardenbergh et al (19) reported differences in cardiac perfusion 6 months after RT, with the relative decrease in regional LV perfusion seeming to be linearly related to the dose received. There were minimal PD in regions of the LV receiving 0 to 10 Gy, whereas regions receiving 41 to 50 Gy demonstrated a 20% decrease in perfusion.

Similar to the report by Hardenbergh et al, our results suggest no clinically or statistically significant increases in PD after low-dose exposure. Unlike previous reports interpreting cardiac perfusion scans (8, 19), we used attenuation correction for visual and quantitative analyses of cardiac SPECT-CT scans in 30 of 34 patients. Although attenuation correction has been demonstrated to significantly improve SPECT-CT specificity and accuracy (14), we still did not detect an increase in PD after RT. Furthermore, even when the threshold for detecting PD was decreased to 1.5 SD below the normal mean to identify subclinical defects, no significant increases were identified.

In addition to changes in PD, we also evaluated myocardial perfusion with a semi-quantitative method by comparing pre- and post-RT SSS. Similar to our PD results, no significant increases in SSS were observed. As expected with minimal changes in PD and SSS, there were no changes in wall motion abnormalities or EF. The lack of functional deficits is consistent with previous findings demonstrating a correlation between wall motion abnormalities and PD (10).

As previously discussed, the RACE collaboration reported a dose-response relationship between the risk of heart disease and the mean heart dose (17). Compared with women who had estimated heart doses <5 Gy, the relative risks of heart disease in women with estimated doses 5 to 14 Gy and >15 Gy were 15% and 108%, respectively. Although there was a calculated 4% increase in risk for every 1-Gy increase in estimated mean heart dose, it is unclear whether this linear relationship exists after very low cardiac doses. In the present study, no relationship was found between heart doses and cardiac perfusion or function.

There may be several potential explanations why neither an increase in PD nor a dose-response relationship was demonstrated. The mean heart dose in our study was 2.82

Gy(range, 1.11–6.06 Gy), which is considerably lower than the mean estimated heart dose of 6.6 Gy (range, 0–20.4 Gy) reported by the RACE collaboration. Furthermore, because patient-specific dose calculations were not available to the RACE collaboration, actual doses delivered to the heart may have been higher. Additionally, unlike prior studies that treated at least a portion of the LV, none of our treatment plans allowed any portion of the heart to be within the tangential beams. There are several limitations to the present study. First, only 32 patients have been analyzed, and the sample size may be too small to detect significant differences in perfusion. Second, obtaining perfusion scans 1 year after RT may be too early to detect all PD. In a report by Prosnitz et al (20), 12 of 19 patients who had normal scans during the first 2 years of follow-up developed new PD during years 3–6 (20).

However, because all patients did not routinely undergo perfusion scans after 2 years, the authors acknowledge that a significant selection bias may have been present in recruiting these patients for additional studies. Finally, the present study population has few cardiac risk factors and consists of relatively healthy women. The results of this study may not be generalizable to patients with increased cardiac risk factors receiving thoracic radiation. However, women with breast cancer have been shown to have lower rates of ischemic cardiac events compared with the general population (4), and in this group of women, no significant changes in cardiac perfusion or function were seen.

Conclusion

Using 3D-CRT or IMRT treatment techniques and sensitive measures of cardiac function, no clinically significant perfusion defects were found after RT when the average heart dose was <5Gy. Furthermore, at low heart doses, no correlation was found between doses to the cardiac structures and cardiac perfusion or function. Although the long-term clinical significance of perfusion defects and cardiac disease is unknown, the lack of worsening defects at 1 year after low-dose exposure is encouraging. These results emphasize the importance of using treatment techniques that minimize cardiac irradiation, consistent with the “as low as reasonably achievable” concept, and the need for further study of the long-term clinical impact after low-dose exposure.

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Fig. 1.

Example 3-dimensional conformal radiation therapy and segmental intensity modulated radiation therapy (IMRT) plans. The heart (red) and left anterior descending artery (yellow) are contoured. Given the location and anatomy of the heart for patient 1, steep tangents with medial electron fields were used.

Fig. 2.

Left ventricle polar map reconstructions of cardiac perfusion single photon emission computed tomography (SPECT-CT) scans (A) before and (B) after radiation therapy in an example patient. Perfusion defects were compared against normal polar map databases using thresholds of 2.5 and 1.5 standard deviations (STD) below the normal mean. Defects (in percentages) in the distributions of the left anterior descending artery (LAD), left circumflex (LCX), and right coronary artery (RCA) are shown. Summed stress defect scores (SSS) were evaluated using a 17-segment model, with perfusion tracer scored from 0 (normal) to 4 (no uptake) for each segment. Cumulative SPECT-SSS were obtained by summing scores from each segment.

Fig. 3.
Mean differences in pre- and post-radiation perfusion defects at 1.5 and 2.5 SD below the normal mean threshold. Negative values Represent worse cardiac function.

Table 1

Patient/treatment characteristics

Age (y), median (range)	50 (25–74)
Race	
Caucasian	29
African American	2
Asian	1
BMI (kg/m ²), mean (range)	28.0 (20.7–38.9)
CHD risk factors	
Coronary artery disease	0
Hypertension	6
Diabetes mellitus	0
Hypercholesterolemia	6
Current smoker	0
History of smoking	17
Family history	19
Surgery	
Lumpectomy	15
Mastectomy	17
Pre-RT chemotherapy	31
Trastuzumab	6
Treatment arm	
Standard	14
IMRT	18
IMN Treatment Technique	
Photons Only	9
Photons/electron	23

Abbreviations: BMI Z bodymass index; CHD Z coronary heart disease; IMN Z Internal Mammary Nodes; IMRT Z intensity modulated radiation therapy; RT Z radiation therapy. Values are number unless otherwise noted.

Table 2

Mean doses and D95 to the heart coronary vessels

Parameter	Mean dose (Gy)	Range (Gy)
Heart		
Dmean	2.82	1.11–6.06
D95	0.90	0.13–2.17
LCA		
Dmean	2.49	1.02–4.23
D95	2.31	1.01–3.85
LAD		
Dmean	7.22	2.58–18.05
D95	3.22	1.23–6.86

Abbreviations: LAD Z left anterior descending artery; LCA Z Left main coronary artery

Table 3

Correlation of cardiac perfusion and function with dose to cardiac structures

Parameter	Perfusion defects			Summed stress scores			Ejection fraction		
	No change	Worse	P	No change	Worse	P	No change	Worse	P
Heart									
Dmean (Gy)	2.82	2.8	.98	2.92	2.63	.56	2.99	2.62	.41
D95 (Gy)	0.95	0.61	.26	0.97	0.75	.2	0.87	0.92	.76
LC									
Dmean (Gy)	2.51	2.4	.85	2.55	2.38	.64	2.56	2.51	.65
D95 (Gy)	2.32	2.26	.91	2.38	2.18	.54	2.35	2.26	.76
LAD									
Dmean (Gy)	6.91	8.9	.5	6.81	8.01	.44	8.08	6.25	.14
D95 (Gy)	3.19	3.41	.85	3.14	3.38	.71	3.4	3.02	.45

Abbreviations as in Table 2