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14. ABSTRACT Purpose: To determine the incidence, dose/time-dependence, and functional significance of regional cardiac perfusion abnormalities in patients with left-sided breast cancer treated with radiation therapy (RT) with and without doxorubicin. Methods: 160 patients underwent pre-RT single photon emission computed tomography (SPECT) cardiac perfusion imaging. Post-RT images were obtained in 125, 95, 56, 43, 24, 28, 21 and 2, patients at 6, 12, 18, 24, 36, 48, 60, and 72 months post-RT. SPECT perfusion images were registered onto 3-dimensional (3D) RT dose distributions. The volume of heart in the RT field was quantified and the regional RT dose was calculated. Changes in regional and global cardiac function were assessed. Results: The incidence of new perfusion defects 6, 12, 18, 24, 36, 48, and 60 months post RT was 38%, 35%, 38%, 42%, 52%, 71%, and 67% respectively. In the 44 patients who have longer follow-up beyond 2 years, 30/44 (68%) exhibit perfusion defects. New defects occurred in approximately 0-80% and 30-80% of patients with < 5% and > 5% of their left ventricle included within the RT fields, respectively. Perfusion defects were associated with changes in regional wall motion 8-26% of the time and possibly with the development of chest-pain. Patients with extensive perfusion defects may have subtle reductions in ejection fractions. Conclusions: RT causes volume-dependent perfusion defects in approximately 42% of patients within two years of RT. These perfusion defects largely persist beyond 2 years and are associated with corresponding wall motion abnormalities and possibly reductions in ejection fraction.					
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INTRODUCTION:

With the increasing use of radiotherapy in the management of primary breast cancer, there has been rising concern about long-term side effects of radiation therapy (RT). Some randomized series evaluating patients irradiated post-mastectomy report an excess number of cardiovascular deaths in the irradiated group. Additionally, radiotherapy to the heart in conjunction with the chemotherapy drug doxorubicin (Dox) appears to increase the risk of developing cardiac damage. New three-dimensional (3D) RT planning software permit us to calculate the 3D radiation dose distribution in any tissue. Doses can be calculated for complex field arrangements and differences in tissue density may be considered. Single-photon emission computed tomography (SPECT) cardiac perfusion imaging provides a noninvasive assessment of myocardial perfusion and function. Advances in image registration allow us to superimpose the 3D dose distribution onto noninvasive nuclear medicine 3D cardiac imaging studies. Using 3D treatment planning tools and nuclear medicine perfusion imaging of the heart, we determine the volume of left-ventricle in the RT treatment field, and correlate regions of post-RT perfusion changes with both the RT dose and the use of Dox-based chemotherapy.

BODY:**Data Presentation, Research Results:****Task 1: Subject recruitment, Data Collection and Analyses, Months 37-48**

- a. Enroll 15 new African American (AA) patients onto study, obtain baseline scans.**
Between 5-20-05 and 5-19-06 we have enrolled 4 new patients on the study, two being AA. Overall, during the last 4 years, 46 patients were enrolled, 10 of whom are AA. Baseline SPECT scans have been obtained on all of these patients.
- b. Register SPECT and treatment planning CT scans.**
All baseline and follow-up SPECT scans performed within the last year have been registered with the treatment planning CT scans
- c. Perform 3D dose calculations on new patients.**
3D dose calculations have been performed on all new patients entered into the study within the past year.
- d. Obtain follow-up scans on patients from prior study period, and on new patients.**
A total of 29 follow-up scans have been obtained over the last year on the 160 patients entered into the study. There were four scans obtained 6-months post-RT, seven scans obtained at 12-months post-RT, seven at 18 months, twelve 24-month scans, two 36-month scans, one 48-month scans. We now have 21 pts that scans obtained 60-months post-RT and two 72 months post-RT.

- e. At each follow-up point, the new SPECT scan will be compared to previous scans and data will be reanalyzed with respect to dose distribution and cardiac function. Findings to be entered into patient profile database and stored for analyses.**

The results of all follow-up SPECT scans performed in the last year have been entered into the patient profile database, where they are stored for future analyses.

- f. Relevant clinical follow-up information obtained and recorded on all patients and entered onto data sheets and database.**

Datasheets have been filled out for each follow-up visit that has occurred over the last year and the data contained on these sheets entered into the database.

- g. With a larger number of patients now evaluable, and some with longer follow-up (>4 years), assess for:**

1) persistence of perfusion changes

Forty-four patients with follow-up scans > 2 years from RT were analyzed. Patients with pre-RT abnormal perfusion were excluded from this analysis. Twenty-one, 24, 18, and 7 patients are evaluable at 36-, 48-, 60-, and 72-months post-RT, respectively. These 44 patients are divided into 3 subgroups based on their 6-24 month post-RT scans. In those patients whose 6-24 month post-RT scans were consistently abnormal, 8/10 (80%) had persistent abnormalities 3-6 years post-RT. In patients whose 6-24 months post-RT scans were intermittently abnormal (i.e. some scans normal, others abnormal), 10/15 (67%) had abnormal scans 3-6 years post RT. In patients whose scans 6-24 months post-RT were all normal, 12/19 (63%) had abnormal scans 3-6 years post RT. For details see Table 1.

Table 1: Rates of Defects in Patients with Prior Perfusion Normal or Abnormal at 3 – 6 Years Follow-up

6-24 month perfusion scan	Incidence of Defects on later scans (3-6 years post-RT)				
	36 mos	48 mos	60 mos	72 mos	36-72 mos
All normal	38% (3/8)	58% (7/12)	67% (4/6)	67% (2/3)	63% (12/19)
All abnormal	80% (4/5)	100% (5/5)	86% (6/7)	50% (1/2)	80% (8/10)
Intermittent defects	50% (4/8)	72% (5/7)	40% (2/5)	50% (1/2)	67% (10/15)

Thus, RT-induced perfusion defects can persist 3-6 years post-RT. Somewhat concerning is the observation that new perfusion defects may present 3-4 years post-RT. The clinical relevance of these perfusion defects remains unclear. However, it is possible that such RT-induced perfusion defects represent subclinical microvascular injury, which

may render the patients at increased risk for ischemic heart disease. Additional follow-up and study is required.

Further, we performed additional analyses to better understand the temporal nature and volume dependence of RT-induced left ventricular perfusion defects. This portion of the analysis included 110 patients for whom scans were performed ≥ 6 months post-RT and had available data for the amount of left ventricle in the RT field. Two-tailed Fisher's exact test and the chi-square test were used for statistical analysis.

The incidence of new perfusion defects 6, 12, 18, 24, 36, 48, and 60 months post RT was 38%, 35%, 38%, 42%, 52%, 71%, and 67%, respectively. New defects occurred in approximately 0-80% and 30-80% of patients with $< 5\%$ and $> 5\%$ of their left ventricle included within the RT fields, respectively ($p=0.0015$). The details are shown in table 2.

Table 2: Incidence of new perfusion defects in patients with normal pre-RT SPECT scan

Months Post RT	Percent of left ventricle in RT field				* <i>p</i> -value
	< 1%	1-5%	5-10%	> 10%	
6	18% (6/33)	30% (7/23)	54% (7/13)	60% (18/30)	0.0004
12	14% (3/21)	28% (5/18)	40% (4/10)	59% (13/22)	0.018
18	33% (4/12)	22% (2/9)	57% (4/7)	43% (6/14)	0.52
24	0/4	33% (2/6)	56% (5/9)	50% (6/12)	0.25
36	71% (5/7)	50% (3/6)	50% (1/2)	33% (2/6)	0.21
48	80% (4/5)	83% (5/6)	83% (5/6)	43% (3/7)	0.021
60	0	50% (3/6)	67% (4/6)	83% (5/6)	0.47

*Chi-square p-value

2) The effect of patient-specific factors on the incidence of perfusion defects

One hundred seven patients with normal pre-RT perfusion scans, and available follow-up data, were analyzed to address this issue. With a median follow-up of 18 months (range 6-60 mos), 55% (59/108) of patients developed new perfusion abnormalities 6-60 months post-RT. Race and BMI (body mass index) appear to be associated with an increased rate of perfusion defects. Overall, 78% (14/18) of African-American patients developed new perfusion defects vs. 50% (45/90) of Caucasian patients ($p=0.038$). Similarly, 68% (45/66) of patients with BMI ≥ 25 kg/m² (overweight and obese) developed a defect compared to 33% (14/42) of patients with BMI < 25 kg/m² ($p=0.0005$).

However, irradiated left ventricular volume is known to be a major predictive factor for the development of a perfusion defect. Using multivariate logistic regression to control for irradiated left ventricular volume, BMI remained a significant predictor for new perfusion defects ($p = 0.0091$), (see table 3). Other factors patients-specific factors were not significant.

Thus, patient-specific factors may influence the risk for RT-induced cardiac dysfunction. Longer follow-up and additional study involving larger numbers of patients are needed to better study this issue.

Table 3: Analysis of the Impact of Patient-Specific Factors on the Cumulative Incidence of Perfusion Defects 6-60 Months Post-RT.

Variable	Univariate		Multivariate	
	Odds Ratio	p-value*	Odds Ratio	p-value*
Age	0.99	0.46		
Race (white vs. non-white)	0.29	0.038	0.29	0.24
Chemotherapy	1.44	0.37		
BMI (≥ 25 kg/m ² vs. < 25 kg/m ²)	4.28	0.0005	4.45	0.0091
Adjuvant Hormonal Therapy	1.05	0.94		
Menopausal Status	0.58	0.19	0.75	0.63
Hypertension	1.16	0.70		
Hypercholesterolemia	0.92	0.88		
Diabetes Mellitus	0.82	0.81		
Tobacco History	2.04	0.088	1.58	0.47
%LV in RT Field	1.09	0.0058	1.03	0.49

*Logistic regression Wald chi-square statistic probability.

†Unit of analysis was a 1-year change in age.

§Unit of analysis was a 1% change in %LV.

3) Changes in regional and global function

Regional Dysfunction: The rates of wall motion abnormalities in patients with and without perfusion defects were 8-26% vs. 0–10%, respectively; p -values 0.018 – 1, depending on the post-RT interval (see table 4). Thus, RT causes volume-dependent perfusion defects in approximately 40% of patients following RT, and these perfusion defects are associated with corresponding wall motion abnormalities.

Table 4; Rates of wall motion abnormalities in patients with and without perfusion abnormalities post-RT

Months post-RT	Rate of Wall Motion Abnormalities:		p-value*
	If Perfusion Defects Absent	If Perfusion Defects Present	
6	7.6% (5/66)	26% (10/38)	0.018
12	6.4% (3/47)	12% (3/25)	0.41
18	0% (0/26)	13% (2/16)	0.14
24	0% (0/19)	23% (3/13)	0.058
36	10% (1/10)	18% (2/11)	1
48	0% (0/7)	18% (3/17)	0.53
60	0% (0/6)	8.3% (1/12)	1
72	0% (0/3)	0% (0/4)	1

*two-tailed Fisher's Exact Test

All patients in this analysis had normal pre-RT SPECT scans.

At all of the follow-up intervals, the rates of wall motion defects appear greater in patients with perfusion abnormalities than in patients with normal SPECT scans. The location of wall motion defects in the majority of patients was the anterior portions of the LV, corresponding to the region of the heart within the RT field. The wall motion defects in most of these patients were scored as hypokinetic and involved small portions of the wall.

Wall motion abnormalities were seen in 14% (3/21), 13% (3/24), 6% (1/18), and 0% (0/7) of patients at 3, 4, 5, and 6 years post-RT. The wall motion defects in all of these patients were scored as hypokinetic and involved small portion of the wall.

Global Cardiac Function (Ejection Fraction)

The absolute change in EF following RT is similar in patients with and without new perfusion defects 6–60 months post-RT.(Figure 1). In patients with new perfusion defects 6-24 months post-RT, the rate of decline in EF \geq 5 percentage points was 40% (21/53), while in patients without a new perfusion defect, the rate of decline in EF \geq 5 percentage points was 29%% (17/59) (p=0.24). Of patients studied 3–6 years post-RT, 13/44 (30%)

have declines in EF $\geq 5\%$ (each patient counted once). Among patients with and without perfusion defects 3-6 years post-RT, the rates of decline in EF $\geq 5\%$ are 27% (8/30) and 36% (5/14), respectively (p=0.72).

The relationship between the severity of the perfusion defect, measured by the SRS, and the changes in EF 6 months post-RT, is shown in Figure 2. Amongst patients with any new perfusion defects, those with more severe perfusion defects (i.e., SRS greater than the mean), were more likely to have a decline in EF $\geq 5\%$ than were patients with a lesser SRS (11/38 vs. 8/61; p = 0.067).

No patient has had a myocardial infarction or experienced congestive failure.

Figure 1. Decline in Ejection Fraction 6-60 months post-RT

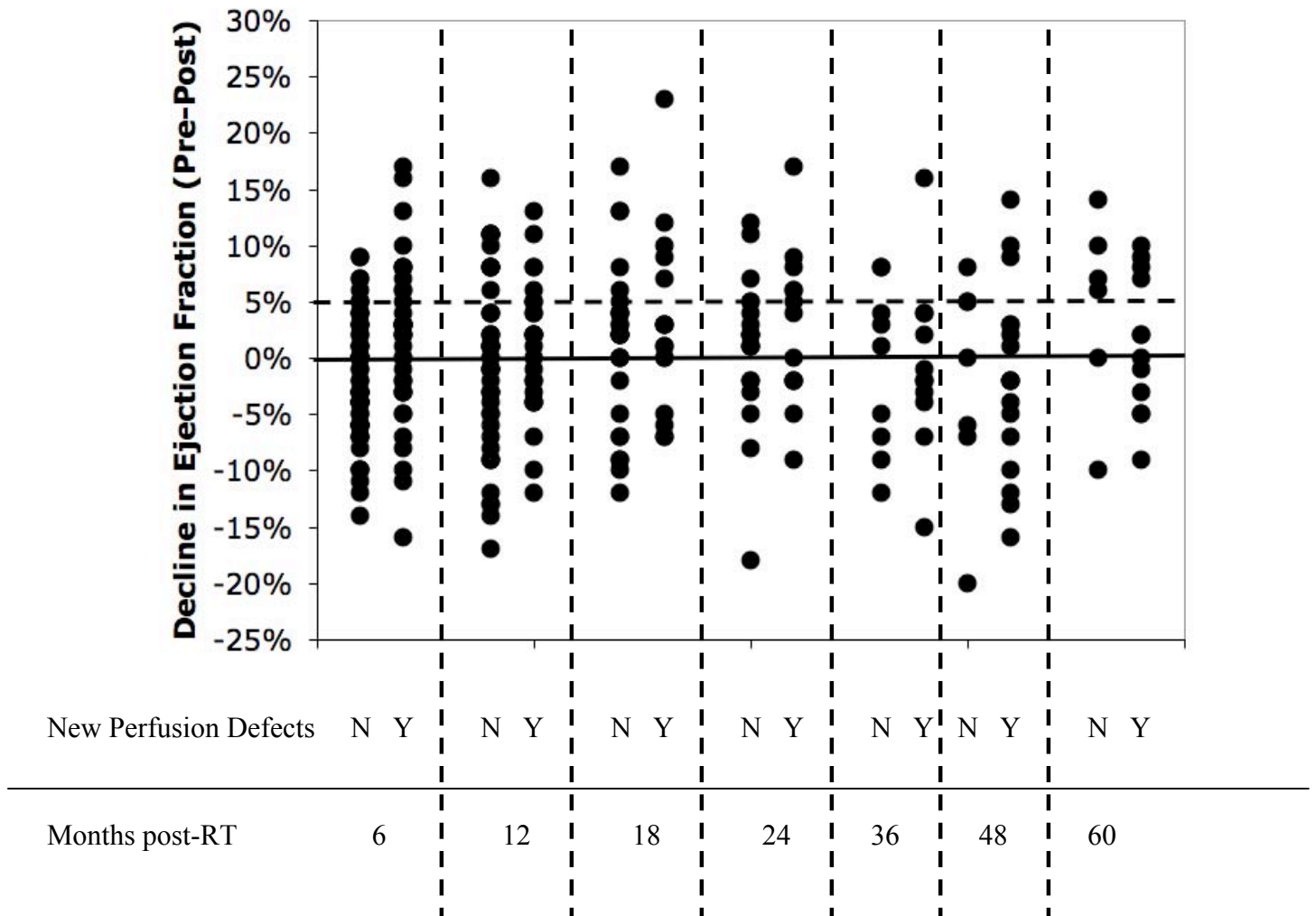
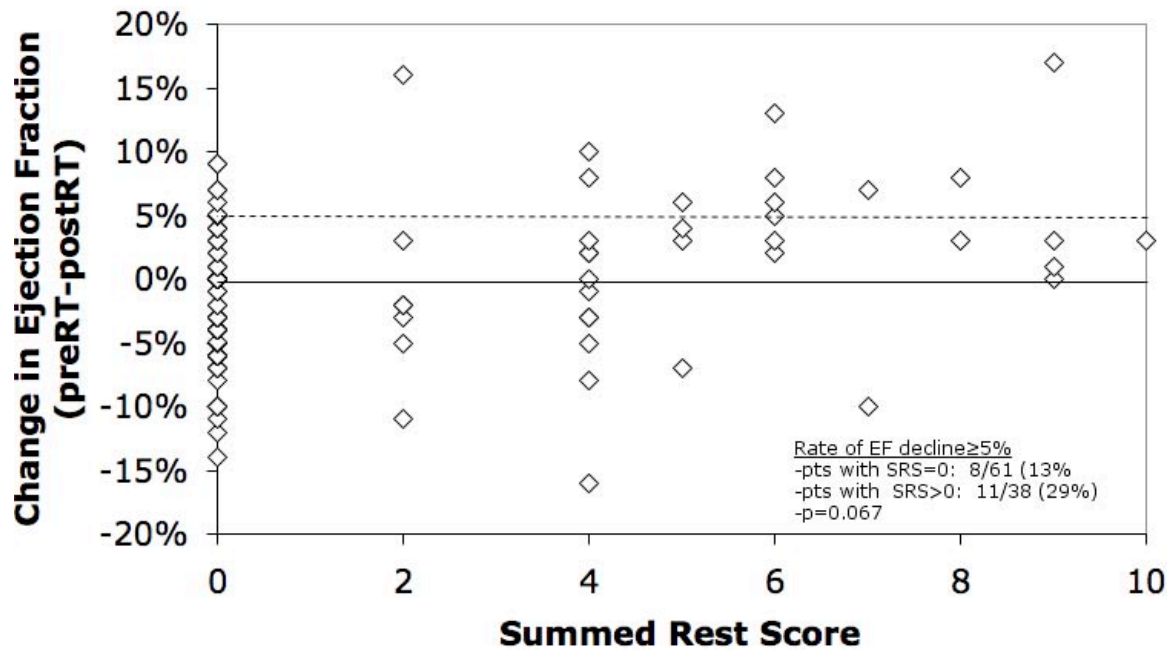


Figure 2. Change in Ejection Fraction 6 months post-RT



h. If appropriate, submit paper for publications based on updated data.

This work has been presented in abstract form at several meetings, and several papers have been published or submitted for publication (see appendix).

Difficulties in accomplishing tasks:

We continue having problems enrolling African American patients.

Recommended Changes or Future Work:

In future work, consideration will be given to using additional imaging modalities to measure changes in cardiac perfusion, wall motion, and ejection fraction. Two promising cardiac imaging modalities are magnetic resonance imaging (MRI) and positron emission tomography (PET). We anticipate considering using serial MRI to measure changes in regional microvascular cardiac perfusion (similar to what is provided by SPECT). We also hope to perform MRI-based assessments of regional inflammation, metabolic activity, and coronary artery blood flow. We anticipate using serial PET scans to measure regional metabolism in the heart. Images from either MRI or PET scans could be fused to the 3D radiation dose distribution with with minor modifications to the image fusion software we currently use to map the SPECT scan data onto the 3D dose distribution.

Changes in physiologic cardiac parameters (perfusion, wall motion, ejection fraction) may be associated with the development of cardiac symptoms or events. We have performed a preliminary analysis to address this question over the past year (Yu et al,

Clin Breast Cancer 2003). We plan to follow patients carefully in the coming years to monitor for cardiac symptoms and report our findings with longer FU.

Given the findings of persistent perfusion defects post-RT, we have been further evaluating methods to reduce the incidental cardiac exposure which occurs during RT for breast cancer. We have quantitatively studied the impact of placing a heart block in conventional tangent fields on the coverage of breast tissue (Quaranta et al, San Antonio Breast Cancer Symposium, 2002). Further, we are reviewing the impact of such a heart block on the risk of recurrence of breast cancer (Raj, ASTRO 2004).

KEY RESEARCH ACCOMPLISHMENTS:

- We have enrolled a total of 160 patients on the protocol. We have performed post-RT scans at 6, 12, 18, 24, 36, 48 and 60 months post-RT in many patients and we are continuing to scan patients past 60 months, when possible.
- We have demonstrated that modern RT techniques still result in perfusion defects in many patients irradiated for breast cancer.
- Demonstrated that these perfusion defects persist up to 5 years post-RT.
- We have demonstrated the volume-dependence of such perfusion defects.
- Have demonstrated that these perfusion defects are associated with changes in wall motion.
- Have demonstrated that patient-specific factors such as race, BMI, and tobacco use may increase the risk of RT-induced heart injury.

REPORTABLE OUTCOMES:

Manuscripts and Abstracts:

Hardenbergh PH, Munley MT, Bentel GC, Strickland J, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB: Pathophysiologic impact of doxorubicin (Dox) and radiation therapy (RT) on the heart of patients treated for breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 45(3) (Suppl):197, 1999.

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Xiaoli Yu, M.D.,¹ Su-Min Zhou, Ph.D.,¹ Robert R. Prosnitz, M.D.,¹ Patricia H. Hardenbergh, M.D.,^{1,5} Daniel Kahn, Ph.D.,¹ Michael Blazing, M.D.,² Donna Hollis, B.S.,³ Andrea Tisch, B.A.,¹ Zafer Kocak, M.D.,^{1,6} Terence Wong, M.D., Ph.D.,⁴ Salvador Borges-Neto, M.D.,⁴ Lawrence B. Marks, M.D. Persistence of radiation-induced cardiac perfusion defects; Poster presentation at the 40th Annual Meeting of the American Society of Clinical Oncology (New Orleans, June 2004, Vol 23, #625)

Yu X, Zhou S, Prosnitz RG, Kahn D, Hollis D, Hardenbergh PH, Tisch A., Marks LB. Radiation-associated cardiac dysfunction 1-5 years following radiation for breast cancer: the impact of race. Presented at Radiation Research Society 2004 Annual meeting St. Louis, MO April 24-27, 2004.

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CONCLUSIONS:**Clinical Relevance:**

- RT-induced cardiac injury appears to be common in patients with breast cancer receiving left-sided RT.
- Treatment of left-sided breast cancer may be effected by the results of this study. The development of 3-D treatment planning to limit treatment-induced heart damage may become more widely applied.
- A better understanding of RT-induced cardiac dysfunction (with or without chemotherapy) may help us better plan therapies for women with breast cancer.
- While this study addressed only patients with breast cancer, its findings are applicable to patients with other diseases as well. Recognition of RT-induced cardiac dysfunction, and its dose/volume-dependence, may impact on therapy for patients with cancers of the lung, esophagus, mediastinal tissues and upper abdomen.

Conclusions:

RT induces dose-dependent changes in regional cardiac perfusion within the region of heart irradiated. This suggests that RT may cause microvascular damage to the heart. To date, there have been no clinically-relevant cardio-toxic events observed, and thus the clinical importance of these perfusion changes remains unclear. However, these perfusion abnormalities are associated with wall motion defects. The incidence of these perfusion defects appears higher in African Americans (vs. Caucasians). These defects appear to generally persist up to at least 5 years post-RT. Additional follow-up of the current cohort of patients, plus the study of additional patients, will help determine if these perfusion defects are persistent, if they have long-term clinical significance, and the role of race in their evolution.