AD________________

Award Number: DAMD17-02-1-0374

TITLE: Treatment Related Cardiac Toxicity in Patients Treated for Breast Cancer

PRINCIPAL INVESTIGATOR: Lawrence B. Marks, M.D.

CONTRACTING ORGANIZATION: Duke University
Durham, NC 27710

REPORT DATE: June 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	June 2005	Annual (1 Jun 2004 - 31 May 2005)

4. TITLE AND SUBTITLE
Treatment Related Cardiac Toxicity in Patients Treated for Breast Cancer

5. FUNDING NUMBERS
DAMD17-02-1-0374

6. AUTHOR(S)
Lawrence B. Marks, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Duke University
Durham, NC 27710

E-Mail: marks@radonc.duke.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)
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: 153 patients underwent pre-RT single photon emission computed tomography (SPECT) cardiac perfusion imaging. Post-RT images were obtained in 121, 88, 49, 31, 22, 27, 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, and 24 months post RT is 34%, 37%, 36%, and 42% respectively. In the 44 pts who have longer follow-up beyond 2 years, 30/44 (68%) exhibit perfusion defects. New defects occurred in approximately 10–30% and 40–60% 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 12 -29% 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.

14. SUBJECT TERMS
Breast cancer, cardiac toxicity, radiation oncology, chemotherapy, doxorubicin

15. NUMBER OF PAGES
15

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Table of Contents

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 25-36

a. **Enroll 15 new African American (AA) patients onto study, obtain baseline scans.** Between 5-24-04 and 5-20-05 we have enrolled 10 new patients on the study, one was AA. Overall, during the last 3 years, 39 patients were enrolled, 6 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 42 follow-up scans have been obtained over the last year on the 153 patients entered into the study. There were fourteen scans obtained 6-months post-RT, 15 scans obtained at 12-months post-RT, seven at 18 months, one 24-month scans, one 36-month scans, ten 48-month scans. We now have 21 pts that scans obtained 60-months post-RT and two 72 months post-RT. Five new patients enrolled on the study over the last year have been enrolled within the last 6 months; therefore none of them have undergone a 6-month scan yet.

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 2 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, 8/11 (73%) 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), 10/14 (71%) 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)	100% (1/1)	63% (12/19)
All abnormal	80% (4/5)	83% (5/6)	75% (6/8)	-	73% (8/11)
Intermittent defects	50% (4/8)	83% (5/6)	50% (2/4)	100% (1/1)	71% (10/14)

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 102 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 35%, 37%, 36%, 42%, 52%, 70%, and 75%, 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 =0.0002). 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				
	< 1%	**1-5%**	**5-10%**	**> 10%**	***p*-value**
6	10% (3/30)	29% (6/21)	54% (7/13)	59% (17/29)	0.001
12	15% (3/20)	29% (5/17)	40% (4/10)	62% (13/21)	0.025
18	20% (2/10)	25% (2/8)	57% (4/7)	43% (6/14)	1
24	0/3	20% (1/5)	63% (5/8)	50% (5/10)	0.20
36	71% (5/7)	50% (3/6)	50% (1/2)	33% (2/6)	1
48	80% (4/5)	80% (4/5)	83% (5/6)	43% (3/7)	1
60	0	60% (3/5)	80% (4/5)	83% (5/6)	1

*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), 54% (58/107) 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. 49% (44/89) of Caucasian patients (p=0.035). Similarly, 67% (44/65) of patients with BMI ≥ 25 kg/m^2 (overweight and obese) developed a defect compared to 33% (14/42) of patients with BMI < 25 kg/m^2 (p=0.0007).

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 ($p = 0.018$), and several other factors had p-values of borderline significance (race 0.14, and tobacco use 0.08). (see table 3). Other factors (age, chemotherapy exposure, adjuvant hormonal therapy, menopausal status, hypertension, hypercholesterolemia, and diabetes mellitus) 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†	0.52		
Race (white vs. non-white)	0.28	0.035	0.37	0.14
Chemotherapy	1.41	0.40		
BMI (≥ 25 kg/m^2 vs. < 25 kg/m^2)	4.19	0.0007	2.97	0.018
Adjuvant Hormonal Therapy	1.02	0.98		
Menopausal Status	0.61	0.23		
Hypertension	1.10	0.81		
Hypercholesterolemia	1.50	0.35		
Diabetes Mellitus	0.84	0.83		
Tobacco History	1.95	0.11	2.32	0.080
%LV in RT Field	1.09§	0.0047	1.08§	0.021

*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 12–29% vs. 0–8%, respectively; p-values 0.007 – 0.66, 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	7.7% (5/65)	29% (10/34)	0.007
12	6.5% (3/46)	12% (3/25)	0.66
18	0% (0/26)	14% (2/14)	0.12
24	0% (0/16)	27% (3/11)	0.06
36-72	4.3% (1/23)	15% (6/40)	0.41

*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% (3/22), 13% (3/24), 6% (1/18), and 0% (0/2) 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 charge 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 46% (21/46), while in patients without a new perfusion defect, the rate of decline in EF $\geq$ 5 percentage points was 29% (17/58) (p=0.10). Of patients studied 3–6 years post-RT, 17/43 (40%) have declines in EF $\geq$ 5%. Among patients with and without perfusion defects 3-6 years post-RT, the rates of decline in EF $\geq$ 5% are 41% (12/29) and 36% (5/14), respectively (p=1).

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 (10/34 vs. 7/58; p = 0.052).

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

Figure 1. Decline in Ejection Fraction 6-24 months post-RT

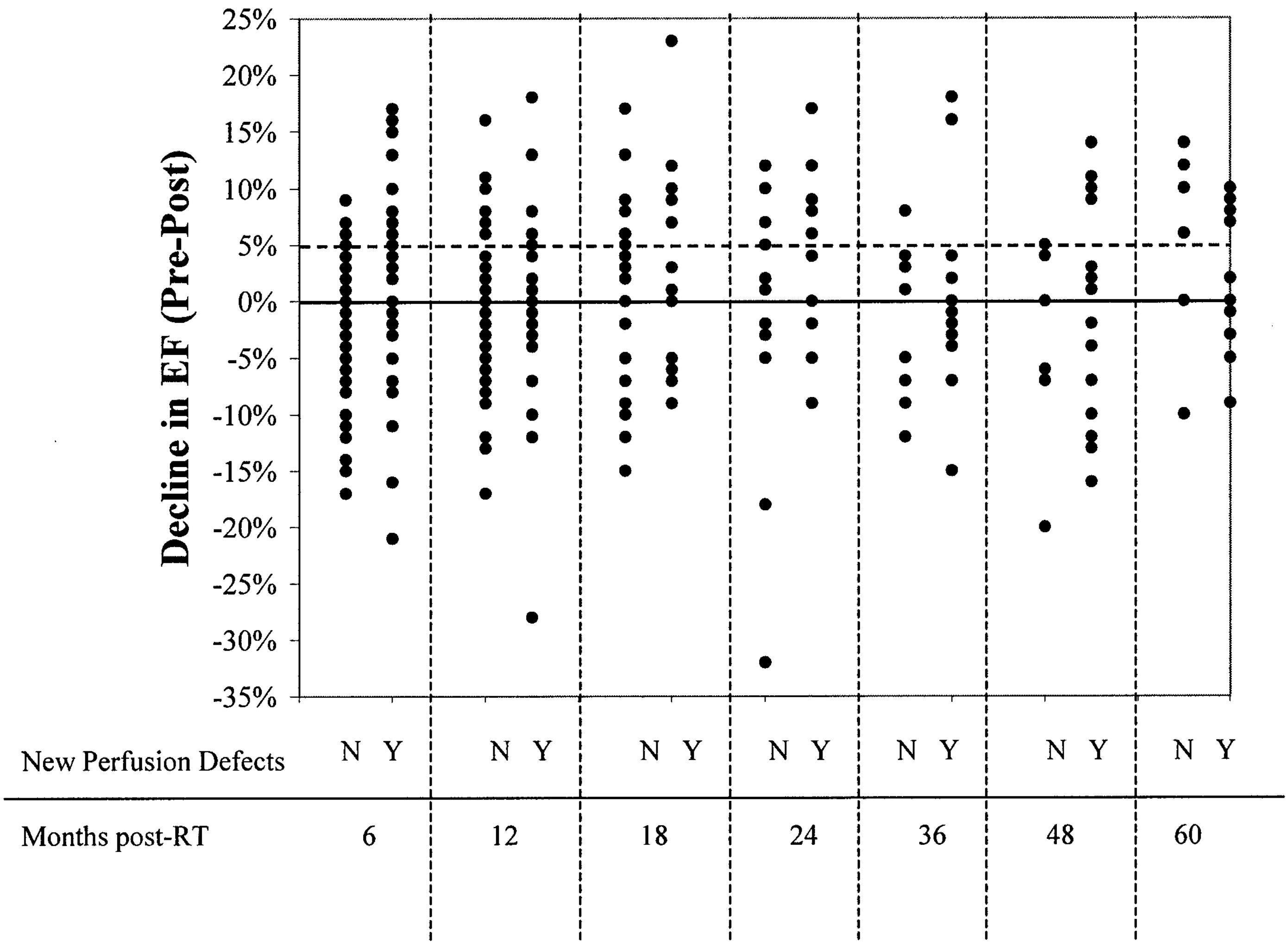
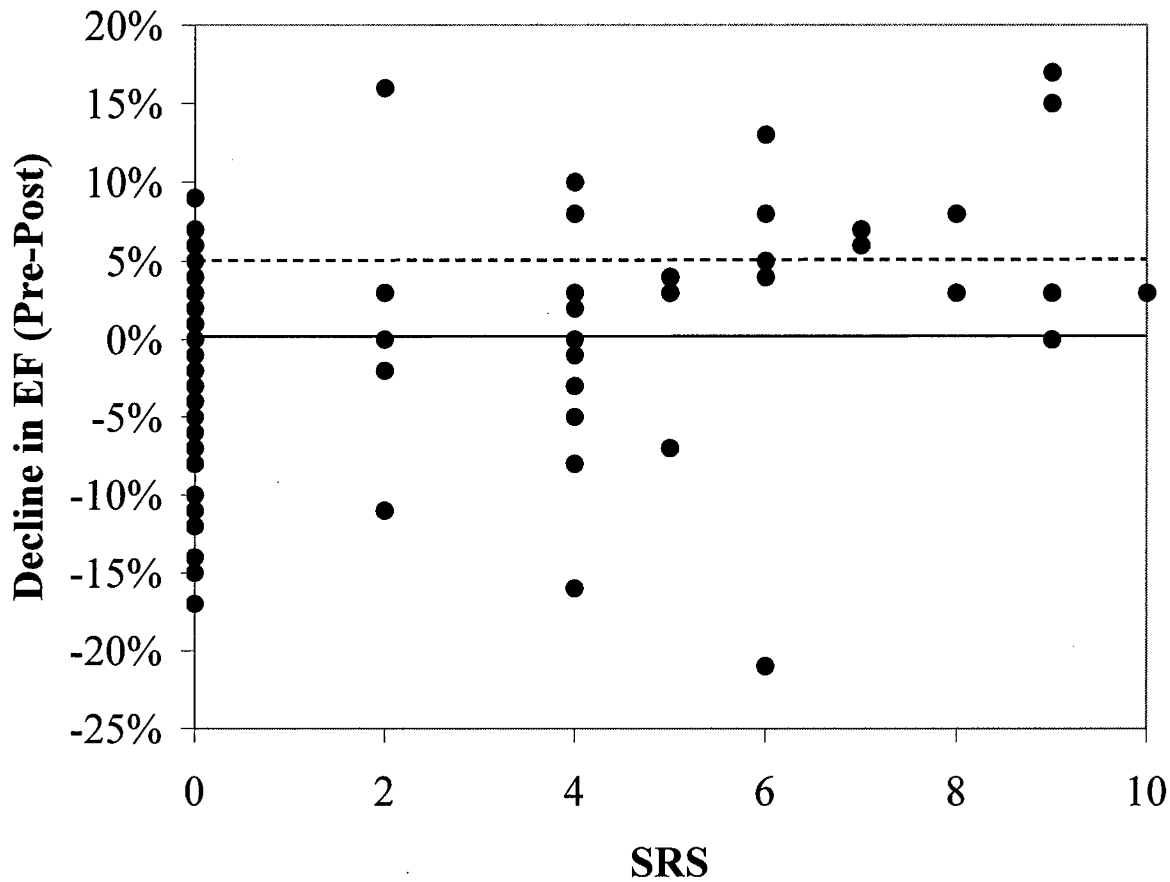


Figure 2. Changes in Ejection Fraction at 6 months post-RT



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).

<u>Difficulties in accomplishing tasks:</u>
We continue having problems enrolling African American patients. We will redouble our efforts in the coming year.

<u>Recommended Changes or Future Work:</u>

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.

We have requested, and been granted a no-cost extension to continue our studies through June 2006. This will enable us to enroll additional patients, obtain additional follow up on our already enrolled patients, and perform additional analysis of the data.

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 ACCOMPLISHEMENTS:

- We have enrolled a total of 153 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.

Munley MT, Marks LB, Hardenbergh PH, Bentel GC: Functional imaging of normal tissues with nuclear medicine: Applications in radiotherapy. *Seminars in Radiation Oncology* 11(1):28-36, 2001.

Hardenbergh PH, Munley MT, Bentel GC, Kedem RR, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB. Cardiac Perfusion Changes in Patients Treated for Breast Cancer with Radiation Therapy and Doxorubicin: Preliminary Results. *Int. J. Radiat. Oncol. Biol. Phys.* 49:1023-1028, 2001.

Hardenbergh PH, Munley MT, Hu CY, Borges-Nesto S, Hollis DR, Marks LB: Breast cancer treatment related myocardial damage appears increased in African-American Women. Proceedings of ASCO 2001, 20 (1 of 2):29a, 2001.

Lind PA, Pagnanelli R, Marks LB, Hu C, Borges-Neto S, Hardenbergh PH. Myocardial perfusion changes in patients treated with left-sided breast cancer and correlation with coronary artery distribution. Proceedings of the 43rd American Society of Therapeutic Radiology and Oncology Annual Meeting. *Int. J. Radiat. Oncol. Biol. Phys.* 5(suppl 1):157-158, 2001.

Hardenbergh P, Munley M, Hu C, Hollis D, Light K., Blazing M, Borges-Neto S, Marks L. Doxorubicin-based chemotherapy and radiation increase cardiac perfusion changes in patients treated with left-sided breast cancer. Proceedings of ASTRO. *Int. J. Radiat. Oncol. Biol.* Phys. 5(suppl 1):158, 2001.

Yu XL, Prosnitz R, Zhou SM, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Hollis D, Wong T and Marks L. Symptomatic "cardiac" events following radiation therapy (RT) for left-sided breast cancer: possible association with RT-induced changes in regional perfusion. *Breast Cancer Research and Treatment.* 2002; 76(suppl. 1), #464.

Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Wong T and Marks L. Long term radiation (RT)-induced cardiac perfusion defects following left sided tangential breast-chest wall irradiation. *Breast Cancer Research and Treatment 2002;* 76 (suppl. 1), #457.

Quaranta BP, Prosnitz, R, Light KL, Steffey B, Hardenbergh P, Marks LB. Customized blocking of tangential radiation (RT) breast fields: excluding the heart vs. covering the breast. Striking a balance. *Breast Cancer Research and Treatment 2002;* 76 (suppl. 1), #460.

Marks L, Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Hollis D, Borges-Neto S, Wong T and Marks L. Functional Consequences of Radiation (RT)-induced Perfusion Changes in Patients with Left-Sided Breast Cancer. *Int J Radiat Oncol Biol Phys* (2) suppl: 3, 2002 (abstract 1).

Marks LB, Yu X, Zhou S, Prosnitz RG, Hardenbergh P, Hollis D, Blazing M, Wong T, Coleman RE, Tisch A, Borges-Neto S. The impact of irradiated left ventricular volume on the incidence of radiation-induced cardiac perfusion changes. *Int J Radiat Oncol Biol Phys* 57(2): S129, 2003.

Xiaoli Yu, Robert R. Prosnitz, Sumin Zhou, Patricia H. Hardenbergh, Andrea Tisch, Michael A. Blazing, Salvador Borges-Neto, Donna Hollis, Terrance Wong, Lawrence B. Marks, Symptomatic "Cardiac" Events Following Radiation Therapy (RT) for Left-sided Breast Cancer: Possible Association with RT-induced Changes in Regional Perfusion. *Clinical Breast Cancer*. 2003 Aug;4(3):193-7.

Yu X, Zhou S, Kahn D, Ahn S, Shafman T, Hollis D, Light K, Tisch A, Folz R, Jaszczak R, Coleman R, Marks LB. Predicting RT-induced pulmonary symptoms based on the dose to the superior vs. inferior lung in patients irradiated for lung cancer. *Int J Radiat Oncol Biol Phys* 57(2): S415, 2003.

Yu X, Prosnitz RR, Zhou S, Hardenberg PH, Tisch A, Blazing MA, Borges-Neto S, Hollis D, Wong T, Marks LB. Symptomatic cardiac events following radiation therapy for left-sided breast cancer: possible association with radiation therapy-induced changes in regional perfusion. *Clin Breast Cancer*. Aug;4(3):193-7.2003.

Marks LB, Yu X, Zhou S, Prosnitz RG, Hardenbergh P, Hollis D, Blazing M, Wong T, Coleman RE, Tisch A, Borges-Neto S. The impact of irradiated left ventricular volume on the incidence of radiation-induced cardiac perfusion changes. *Int J Radiat Oncol Biol Phys* 57(2): S129, 2003.

Xiaoli Yu, Sumin Zhou, Robert R. Prosnitz, Daniel Kahn, Donna Hollis, Patricia H. Hardenbergh, Zafer Kocak, Michael A. Blazing, Salvador Borges-Neto, Terence Wong, Lawrence B. Marks. Radiation (RT)-associated cardiac dysfunction in patients irradiated for breast cancer: The impact of race and results 3-5 years post-RT, Proceedings of Rad Research meeting 2004.

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 presention 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.

Robert G. Prosnitz, Xiaoli Yu, Sumin Zhou, Daniel Kahn, Donna Hollis, Patricia H. Hardenbergh, Michael A. Blazing, Salvador Borges-Neto, Terence Wong, Lawrence B. Marks. Impact of patient-specific factors in the development of radiation (RT)-associated cardiac perfusion defects. Poster presentation at the 40th Annual Meeting of the American Society of Clinical Oncology (New Orleans, June 2004,Vol 23, #673)

Wong T, Zhou S, Prosnitz R, Hardenberg P, Borges-Neto S, Coleman RE, Yu X, Blazing M, Marks LB. Challenges in defining the single photon admission computed tomorgraphy (SPECT) - defined left ventricle: implication in studying radiation (RT)-induced cardiac dysfunction.. Int J Radiat Oncol Biol Phys. Abst. No. 2440, 2004.

Yu Z, Zhou S, Prosnitz RG, Kahn D, Hardenbergh PH, Hollis D, Tisch A, Blazing MA, Wong T, Borges-Neto S, Marks LB. Persistence of radiation (RT)-induced cardiac dysfunction 3-5 years post RT.. Int J Radiat Oncol Biol Phys. Abst. No. 2093, 2004.

Prosnitz R, Yu X, Zhou S, Kahn D, Hollis D, Tisch A, Blazing M, Wong T, Borges-Neto S, Hardenbergh P, Marks L. The importance of daily treatment set-up accuracy in preventing RT-induced cardiac dysfunction in patients irradiated for left-sided breast cancer.. Int J Radiat Oncol Biol Phys. Abst. No. 129, 2004.

Das SK, Baydush A, Zhou S, Miften M, Yu X, Light K, Wong T, Blazing M, Marks L. Comparison of biological models to predict the incidence of breast radiotherapy-induced cardiac perfusion defects. Int J Radiat Oncol Biol Phys. Abst. No. 42, 2004.

Raj KA, Hardenbergh P, Hollis D, Evans B, Prosnitz R, Prosnitz L, Marks L. Local recurrence under the heart block in patients with left-sided breast cancer. Int J Radiat Oncol Biol Phys. Abst. No. 2115, 2004.

Applied for Komen 2005, Duke SPORE in Breast Cancer Full Translational Research Project, Avon Foundation- AACR International Scholar Awards in Breast Cancer Research

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.