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Therapy on the Heart of Patients Treated for Breast Cancer

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13. ABSTRACT (Maximum 200 Words) Purpose: To determine the incidence and dose dependence of regional cardiac perfusion abnormalities in patients with left-sided breast cancer treated with radiation therapy (RT) with and without doxorubicin (Dox). Methods: Thirty-three patients with left-sided breast cancer underwent cardiac perfusion imaging using single photon emission computed tomography (SPECT) pre-chemotherapy, pre-RT, and 6 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. A decrease in regional cardiac perfusion was assessed subjectively by visual inspection and objectively using image fusion software. Results: Overall there was a 55% incidence in new visibly detectable perfusion defects at 6 months post-RT. In patients receiving chemotherapy (CTx) this incidence was 71% versus 38% in patients having RT only. A dose-dependent perfusion defect is seen at 6 months with no defect appreciated at 0-10 Gy, whereas there was a 20% decrease in regional cardiac perfusion identified between 41-50 Gy. One of thirty-three patients had a decrease in left ventricle ejection fraction of greater than 10% at 6 months, and 2/33 patients developed transient pericarditis. No events of myocardial infarction (MI) or congestive heart failure (CHF) have occurred. Conclusions: RT causes cardiac perfusion defects 6 months post-RT in most patients. Dox-based CTx may increase the frequency of this effect. Long-term follow-up is needed to assess whether these perfusion changes are transient or permanent and to determine if these findings are associated with changes in overall cardiac function and clinical outcome.				
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FOREWORD

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P. Hurdentz 7/31/00
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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. Some randomized series evaluating patients irradiated post-mastectomy report an excess number of cardiovascular deaths in the irradiated group (1). Additionally, radiotherapy to the heart in conjunction with the chemotherapy drug doxorubicin (Dox) appears to increase the risk of developing cardiac damage (2). New 3D radiation treatment planning tools provide the opportunity to know the 3D RT dose distribution in any tissue. Doses can be calculated for complex field arrangements and differences in tissue density may be considered (3). 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 (4). Using 3D treatment planning tools and nuclear medicine perfusion imaging of the heart, we attempted to define 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: **Statement of Work**

Task 1: Preparation for data collection, Months 1-2

- a. Computer program to register CT scan and SPECT images was written and is currently being used to evaluate radiation dose distribution in the heart.
- b. Data collection sheet was created for acquisition of baseline information, results of scans and ejection fractions, and cardiac dose distributions and clinical follow-up. This information is entered into a patient profile database.
- c. We have established a database to maintain patient profiles, treatment information, cardiac risk factors, perfusion scan results, follow-up information, and patients' physician's contact information. We have 90 patients currently entered into the database.
- d. Institutional Review Board approval has been obtained from DUMC. We have had the protocol approved and renewed annually.

Task 2: Subject Recruitment and Data Collection, Months 2-39

- a. Patients with left-sided breast cancer have been enrolled. As of June 30, 2000, 98 patients with left-sided breast cancer have been enrolled on the study.
- b. The baseline perfusion scans will serve as a reference for all follow-up scans. Scanning information has been stored on an optical disc.
- c. After completion of both CT and perfusion scans, 3D simulation dose volume histograms have been generated and stored in patient profile database.
- d. At each follow-up point the new SPECT scan has been compared to previous scans and data has been reanalyzed with respect to dose distribution and cardiac function. Findings are entered into patient profile database and stored on a continuing basis.
- e. Relevant information from clinical follow-up has been recorded on data collection sheet and entered into patient profile database.

Task 3: Interim Analyses, Months 12-39

- a. Data entry and quality control measures have been on-going.
- b. Interim analyses from patient profile data base have been performed.
- c. Annual reports are being written.
- d. Preliminary results have been presented at a national meeting and a manuscript has been submitted.

Task 4: Final Analyses, Months 40-45

- a. Final analyses of data from patient profile database will be performed.
- b. A final report and initial manuscripts will be prepared.

Data presentation (Results)

Reference : See attached manuscript on the Preliminary Results at 6 months which has been accepted for publication in The International Journal of Radiation Biology and Physics, 2000.

The following is an update of our study since the submission of the above manuscript:

Of 33 patients analyzed to date, overall 55% had visible perfusion abnormalities at 6 mos follow-up. For patients receiving RT only (without chemotherapy) this incidence was 38% versus 71% in patients who received Dox-based chemotherapy. There is a decrease in cardiac perfusion as the regional RT dose increases. Figure 1. There may be a trend suggesting that patients who have received Dox-based chemotherapy have a greater decrease in cardiac perfusion when compared to patients who have received RT only. Figure 2.

Of 15 patients analyzed to date with 12 mos follow-up, the overall incidence of visible perfusion defects remained the same for patients receiving RT only (38%) but improved slightly for patients who had received Dox-based chemotherapy (57%). The 12 mo dose response curve suggests a slight worsening over time of perfusion abnormalities when compared to the dose-response curve at 6 mo. Figure 3.

There have been no cardiac events defined by MI or CHF. Two of 33 patients have suffered from transient pericarditis. Both of these patients received Dox-based chemotherapy. One patient has had a decrease in her left-ventricle ejection fraction of greater than 10 %.

Difficulties in accomplishing tasks

Registering SPECT images on CT scans

Our original method of registering SPECT cardiac perfusion images on CT scans was time-consuming. We have altered our procedure for contouring the left ventricle on our 3-dimensional system. Before we instituted these changes, we consulted one of the creators of the PLUNC program, Dr. Julian Rosenman, M.D., Ph.D. In addition, we did a comparison study to assess if our new method produced different results from the original method. We contoured our first 20 patients with each method and found that both procedures yielded the same results. Our new contouring procedure utilizes a faster and more objective autointouring feature of the computer program to contour the left ventricle region as defined by the SPECT image. We then superimpose the SPECT-defined contour onto the CT to verify that the contour as defined by the functional image corresponds with the anatomical image. If the automated contour includes regions that are not left ventricle, such as lung or rib, we alter the contour to exclude these regions.

Statistics

Please see attached manuscript for statistics performed on the first 20 patients with 6 mo follow-up.

Recommended changes or future work

Future work consideration will be given to using an additional imaging modality of the heart, the MRI. Both functional and anatomical information can be obtained from the MRI.

Changes to original statement

1. We have included the analysis and report of detecting visible wall motion abnormalities to the evaluation of each cardiac perfusion scan. This will enable us to further study the functional implications of the perfusion abnormalities and predict clinical relevance to visible defects. This additional parameter has increased the cost of each scan by \$100. However, it does not increase the time of the scan for the patients.
2. If a patient has an abnormal scan, as determined by the radiologist, we refer this patient to a cardiologist at Duke University Medical Center, Dr. Carolyn Donovan Landolfo, MD. Abnormal results are defined as a change in ejection fraction of greater than 10% since a patient's previous scan or as a conclusion of "infarct" determined by the radiologist. We notify the patient as well as send a letter to the patient's primary care provider regarding the abnormal result and suggest that the patient see Dr. Landolfo. A copy of the letter sent to the PCP is also sent to the patient's medical oncologist and radiation oncologist. Results from the patient's visit with the cardiologist are recorded into our database.

3. We have used the radiologist's visual reading of the patient's scans to calculate scores for each scan. This number is calculated as follows:

Score = (# of locations in the left ventricle with a perfusion defect) + (sum of severity of each defect)

The number assigned to defect severity is:

0 – no defect

1 – mild defect

2 – moderate defect

3 – severe defect

We have used the sum rest scores to evaluate numerically the perfusion changes in our patients.

KEY RESEARCH ACCOMPLISHMENTS:

- We have established the first dose-response curve for radiation therapy to the heart. This helps define the dose tolerance of the heart to radiation therapy and is a spring board to apply our technique to any patient receiving RT to the thoracic region.
- We are showing the importance of sophisticated radiation therapy treatment planning (3-D) for patients with left-sided breast cancer. This may be particularly relevant for patients with left-sided breast cancer who have received chemotherapy.

REPORTABLE OUTCOMES:

Manuscript:

- 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*, accepted, June 2000.

Abstract/Platform Presentation:

- 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. American Society for Therapeutic Radiology and Oncology, 41st Annual Meeting, 1999.
- Based on the results of this work, we are submitting a NIH-R01 research grant entitled: Physical Predictors of Radiation-induced Cardiac Dysfunction. The purpose of this study is to broaden our understanding of effects on cardiac irradiation in all patients (not just breast cancer patients) undergoing thoracic radiation therapy.
- Based on this work in breast cancer we have submitted a proposal to study the effects of cardiac irradiation on pediatric patients.

Outcomes:

- 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.
- The understanding of treatment -induced (with Dox-based chemotherapy and RT) cardiac dysfunction may become better understood.
- Based on the results of this work, we are submitting a NIH-R01 research grant entitled: Physical Predictors of Radiation-induced Cardiac Dysfunction. The purpose of this study is to broaden our understanding of effects on cardiac irradiation in all patients (not just breast cancer patients) undergoing thoracic radiation therapy.

CONCLUSIONS:

The perfusion injury observed in this study estimates a decrease in blood flow to the region of the heart in the RT field and suggests that microvascular damage has occurred. The observed rates of abnormal perfusion in this study do not correlate with the expected clinical cardiac outcome in left-sided irradiated breast cancer patients (with or without CTx) based on current literature. Hence, RT appears to cause subclinical perfusion injury at 6 months of unknown significance.

Radiation therapy appears to cause dose-dependent regional cardiac perfusion defects 6 months after treatment. Dox-based CTx may increase defects at corresponding RT dose levels. The 2 events of reversible pericarditis occurred in patients

receiving CTx and RT. These findings suggest that RT and Dox together may have a greater negative impact on treatment-related cardiac changes. The new perfusion defects have not predicted for a clinical event of CHF or MI, albeit follow-up is short.

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2. Shapiro CL, Hardenbergh PH, Gelman R, Blanks D, Hauptman P, Recht A, Hayes DF, Harris J, Henderson IC. Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. *J Clin Oncol*. 16:3493-3500, 1998.
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Appendices

6-month Cardiac Dose Response Curve (n=32)

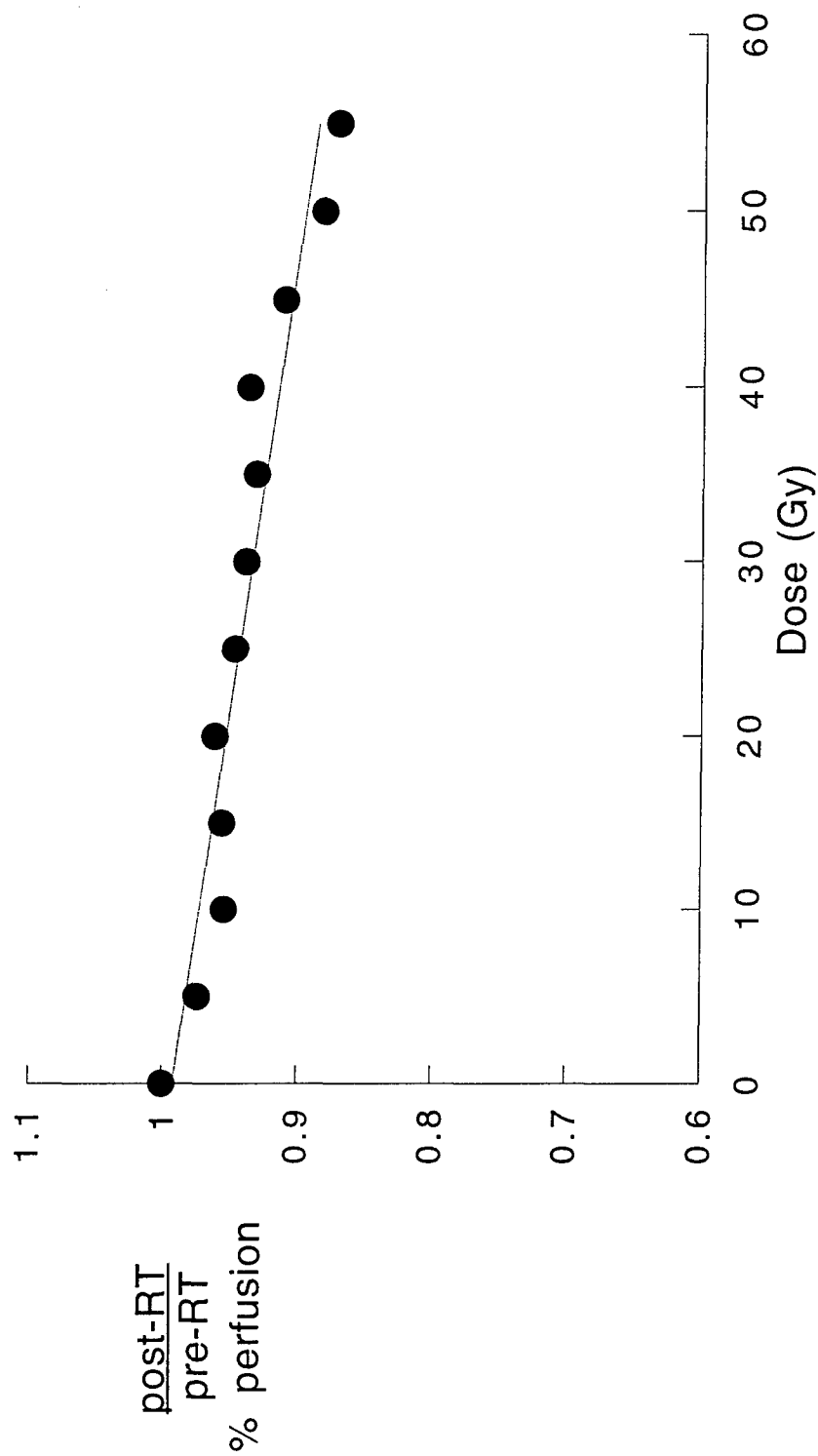


FIGURE 1

Comparison of Cardiac Dose Response between Patients Treated +/- Chemotherapy

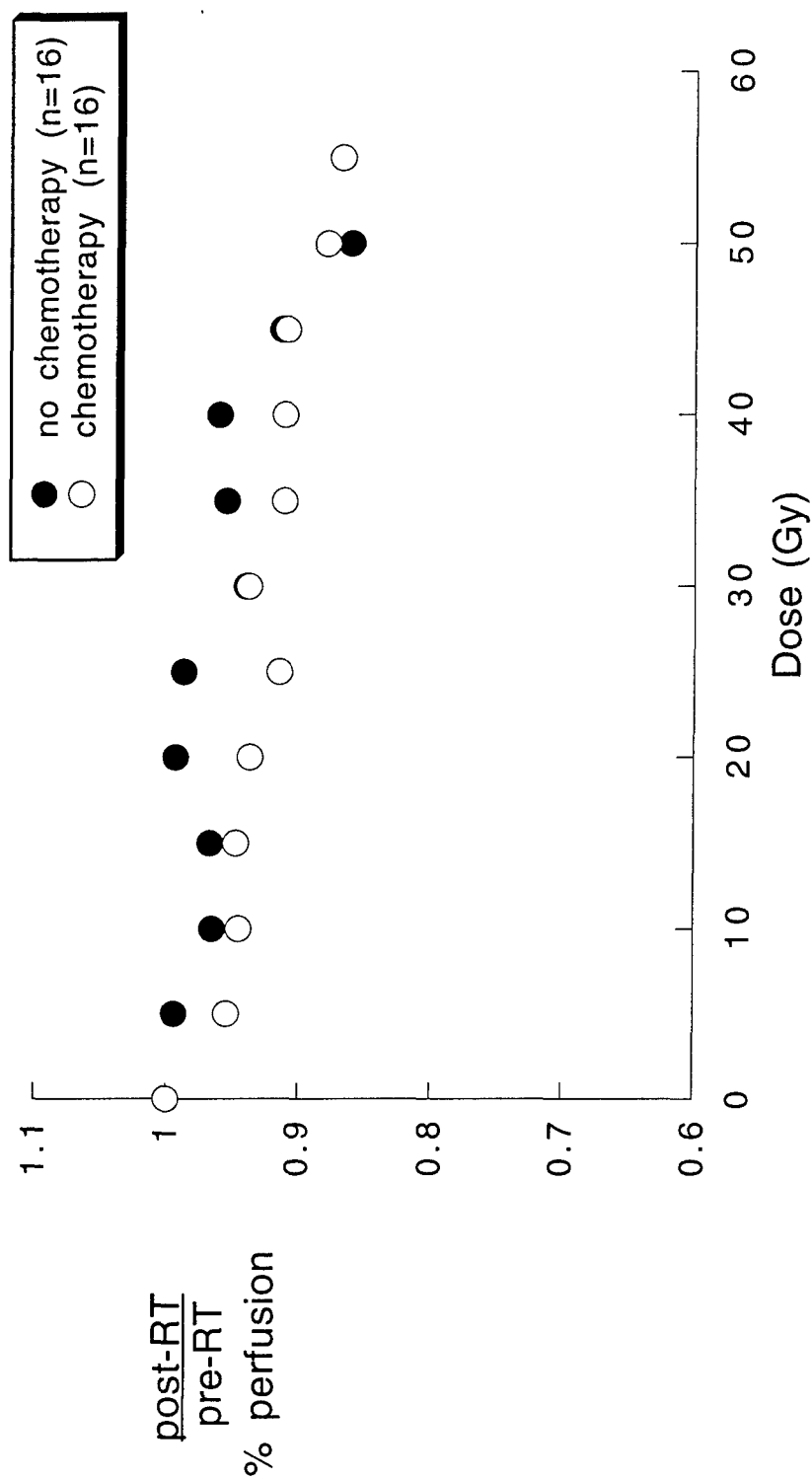


FIGURE 2

Comparison of Cardiac Dose Response between 6- and 12-month Follow-up Data (n=9)

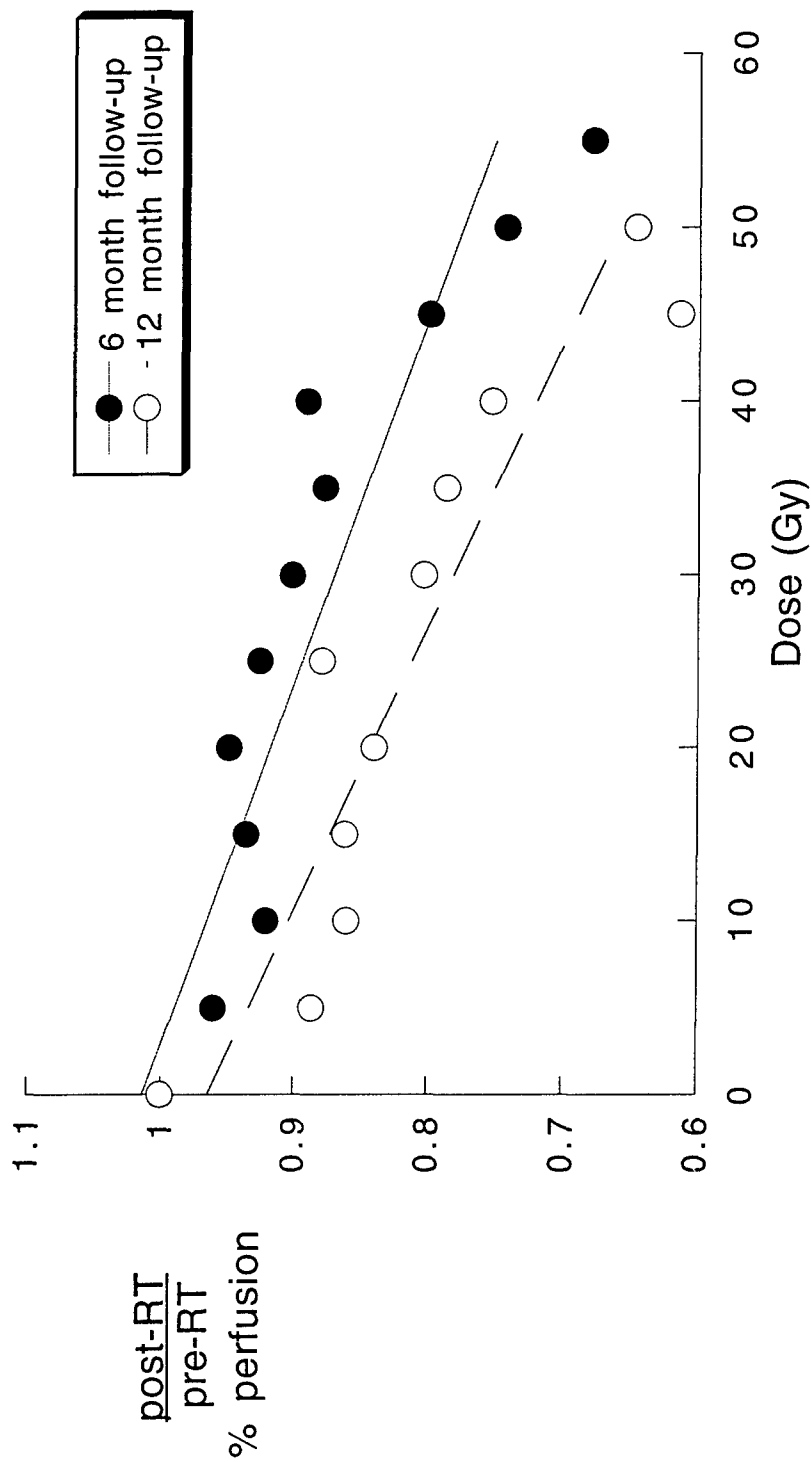


FIGURE 3

**Cardiac Perfusion Changes in Patients Treated for Breast Cancer with Radiation Therapy and
Doxorubicin: Preliminary Results**

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We wish to thank the Department of Radiation Oncology, University of North Carolina for the use of the 3-D radiation planning system, Plan UNC.

Abstract

Purpose: To determine the incidence and dose dependence of regional cardiac perfusion abnormalities in patients with left-sided breast cancer treated with radiation therapy (RT) with and without doxorubicin (Dox).

Methods: Twenty patients with left-sided breast cancer underwent cardiac perfusion imaging using single photon emission computed tomography (SPECT) pre-chemotherapy, pre-RT, and 6 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. A decrease in regional cardiac perfusion was assessed subjectively by visual inspection and objectively using image fusion software. Ten patients received Dox-based chemotherapy (total dose 120-300 mg/m²) and 10 patients had no chemotherapy. RT was delivered by tangent beams in all patients to a total dose of 46-50 Gy.

Results: Overall 60% of the patients had new visible perfusion defects 6 months post-RT. A dose-dependent perfusion defect was seen at 6 months with minimal defect appreciated at 0-10 Gy, and a 20% decrease in regional perfusion at 41-50 Gy. One of twenty patients had a decrease in left ventricle ejection fraction (LVEF) of greater than 10% at 6 months, 2/20 patients had developed transient pericarditis. No instances of myocardial infarction (MI) or congestive heart failure (CHF) have occurred.

Conclusions: RT causes cardiac perfusion defects 6 months post-RT in most patients. Long-term follow-up is needed to assess whether these perfusion changes are transient or permanent and to determine if these findings are associated with changes in overall cardiac function and clinical outcome.

Key words: radiation therapy, chemotherapy, doxorubicin, cardiac toxicity, breast cancer

Introduction

Radiation therapy (RT) is widely used to treat patients with breast cancer. Breast conserving surgery combined with RT to the breast is standard practice in the management of early stage breast cancer. Mounting evidence suggests that post-mastectomy radiation therapy provides benefits in local control and overall survival (1,2). 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. Some randomized series evaluating patients irradiated post-mastectomy report an excess number of cardiovascular deaths in the irradiated group (3). In the overview analysis by Cusick et al., the reduction in cause-specific deaths from breast cancer afforded by post-mastectomy radiation therapy was offset by an excess cardiac mortality in the irradiated patients, resulting in no change in overall survival (4). The cardiac complications secondary to RT are thought to be primarily ischemic heart disease with a time of onset of many years following RT (5).

The concern for cardiotoxicity is heightened by the widespread use of adjuvant systemic therapy, in particular, anthracycline containing drug regimens. Doxorubicin is a well known cardiotoxin, the principle effects being on the myocardium with an increasing incidence of congestive heart failure (CHF) correlated with increasing doses (6). The time to onset of doxorubicin-induced CHF is typically 1-3 months but has been reported to be as long as 20 years in the pediatric population (7). Radiotherapy to the heart in conjunction with doxorubicin appears to increase the risk of developing cardiac damage (8,9,10).

Recent advances in radiation treatment planning and functional cardiac imaging provide an opportunity to quantitatively study changes in regional and global heart function and relate them to radiation dose. New 3D radiation treatment planning tools can calculate accurate 3D dose distributions throughout the heart (11). Gated cardiac SPECT perfusion imaging provides a noninvasive assessment of myocardial perfusion and function. Herein we report the initial results of a prospective study

exploiting these technologies (12), to assess RT-induced changes in cardiac function in 20 patients treated for breast cancer.

METHODS:

All patients with left-sided breast cancer who planned to undergo radiation therapy to either the chestwall or breast $\pm$ regional lymph nodes at Duke University Medical Center (DUMC) and affiliated institutions were eligible. The protocol was approved by the DUMC Institutional Review Board. Appropriate informed consent was obtained.

Baseline Studies

The following studies were performed prior to initiation of radiotherapy: resting gated perfusion SPECT imaging to determine left-ventricular ejection fraction (LVEF) and to provide a 3D map of regional cardiac perfusion; thoracic computerized tomogram (CT) in the treatment position for 3D treatment planning and dose calculation.

Gated SPECT Cardiac Perfusion Study

Resting gated SPECT myocardium perfusion imaging studies were performed after the administration of 25-30 mCi of Tc-99m sestamibi. SPECT images were acquired 60 minutes post tracer administration over a 180° circular orbit using a dual head detector gamma camera with the detectors placed at right angles and equipped with high resolution collimators (Elscint, Cardial). Images were acquired from 60 projections at 30 seconds. The camera was set for a 140 kev photopeak with a 20% window. Acquisition was obtained with a matrix size of 64 x 64 x 8. During acquisition, images were gated for 8 frames per cardiac cycle with 100% beat acceptance. Images were reconstructed with filtered back-projection; no attenuation correction was applied. After reconstruction of the transaxial images, the short axis images undergo a preprocessing for gated left ventricular ejection fraction quantification using previously validated software (13,14). The data set was also processed for

qualitative interpretation of the perfusion image. The images provided a 3D map of myocardial perfusion of the left-ventricle.

This is a report on the first 20 patients with 6 month post-RT perfusion imaging. The median age at diagnosis was 54 (range 42-72). Twelve patients were postmenopausal, 8 patients were premenopausal.

Treatment

Ten patients were treated with CTx and received it prior to RT. All ten patients had cyclophosphamide and Dox with total cumulative Dox doses ranging from 120-300 mg/m². In addition to cyclophosphamide and Dox, 3 patients had 5-fluorouracil (range: 2900-3600 mg/m²), 1 patient had 375 mg/m² of taxotere, and 2 patients had 640 and 700 mg/m² of paclitaxel.

Ten patients had RT without CTx. Radiation therapy was delivered through tangential beams to a total prescribed dose of 46-50 Gy to the breast or chestwall in 2 Gy daily fractions. All patients underwent CT-assisted radiation treatment planning. Fields were shaped with a cardiac block to reduce the volume of heart irradiated (Figure 1). Five patients had the upper internal mammary nodes (IMNs) included in the "partly wide tangent fields" (15).

3D Radiation Dose Calculation

A preradiation therapy CT scan was performed in the treatment position for 3D treatment planning (Plan University of North Carolina) (16). A 3D radiation dose calculation, with tissue density heterogeneity correction, was done to determine the radiation dose delivered to the heart. The volume of heart that received a dose from 0 to the maximum was calculated to create a dose-volume histogram. In general, the bin size used for dose volume histogram calculation = maximum radiation dose/100. Total heart volume was measured on the CT and the left-ventricle volume was measured on both the CT and SPECT scans.

Interpretation of SPECT images

Pre and post treatment perfusion scans were interpreted in the following 2 ways:

1. Qualitative scoring of changes on perfusion scans: The pre and post RT SPECT scans were visually compared independently by an experienced nuclear medicine physician (SB) using a 12 segment model. New perfusion defects were noted and severity of lesions were graded as 0=normal, 1=mildly decreased uptake, 2=moderately decreased uptake, and 3=severe decreased uptake. This analysis was done without knowledge of the patient's treatment, radiation dose distribution, or clinical condition.
2. Quantitative analysis using image fusion: Pre and post treatment SPECT images were superimposed onto the RT dose distribution. Relative perfusion defects were analyzed by computer software as described below.

Registering SPECT Scans with Radiation Dose Distribution

Computer software (Plan University of North Carolina) was used to visually register the pre- and post treatment SPECT cardiac images with the pretreatment CT. After the SPECT scan was registered with the CT data set, the SPECT image was resampled by tri-linear interpolation to match the spatial sampling of the CT data set. The entire 3D radiation dose distribution was then overlaid onto the SPECT scan. By calculating the number of SPECT counts on each radiation dose level, a dose-count histogram was generated.

Correlating Changes in Regional Perfusion With Regional Radiation Dose

By comparing the pre- and post-treatment SPECT scans the reduction in the percent of the SPECT counts at a particular RT dose level was calculated at varying dose levels. On each scan, the percent of counts at each dose level was normalized to the percent of counts in the volume of the heart that received < 2.5 Gy. Normalization is necessary since the SPECT perfusion scans give information regarding *relative*, rather than absolute perfusion.

Follow-up Evaluations

Myocardium perfusion and left-ventricle ejection fractions were assessed by gated SPECT perfusion imaging and were obtained 6 months following radiation therapy. Reductions in LVEF >10% were considered clinically significant as smaller reductions may be due to normal variations. Clinical evaluation to assess tumor status, and any cardiac symptoms or disease was performed 6 months post-treatment.

Statistics

This report of preliminary data is predominantly descriptive at this time. Medians, proportions and percentages have been used to describe the patient population and resulting observations. Comparison of proportions was done using a 2-tailed Fisher's Exact test.

RESULTS:

Twelve patients developed new visibly detectable perfusion defects 6 months post-RT (60%). Among patients receiving Dox-based CTx the incidence was 70% (7/10). Among patients receiving Dox-based CTx with any volume of LV in the RT field, the incidence of new perfusion defects was 100% (7/7). All 10 patients receiving RT alone (without CTx) had some volume of their heart in the RT field, and 5 of the 10 developed new perfusion defects (50%). Figure 2 shows an example of one patient's pre- and post-RT perfusion image. A new defect in the RT field is visible. All patients (5/5) with upper IMNs intended to be included in the tangents had new cardiac perfusion defects compared to 43% (7/15) of patients without IMNs in the RT field ($p = 0.06$). All 5 patients with IMNs treated had received prior CTx. See table 1. The median percent volume of the left ventricle receiving $\geq 50\%$ of the prescribed RT dose for all patients was 5%. This was similar among all treatment groups. See table 2.

The impact of chemotherapy and the volume of LV included in the RT field on the frequency of observing a new perfusion defect was considered. Three of the 10 patients treated with RT and CTx did not have any portion of the LV receive >50% of the prescribed dose. None of these 3 patients had new

perfusion defects. Of the 7 with any fraction (volume range 3-23%) of the LV receiving >50% of the prescribed dose, all had new defects observed. All of the patients treated with RT alone had some of their LV exposed to >50% of the prescribed dose (volume range 1-32%). Of the six patients receiving RT alone with <10% of their LV at >50% of the dose, 2/6 (33%) had new defects versus 3/4 (75%) patients with >10% (range 15-32%) of their LV receiving >50% of the dose. None of these differences were statistically significant. See Figure 3.

The dose-dependence of regional cardiac perfusion changes was assessed using image registration. There were minimal changes in perfusion in regions of the LV receiving 0-10 Gy. In regions receiving 11-20 Gy, there was a 7% decrease in regional perfusion, from 21-30 Gy an 11% change, from 31-40 Gy a 15% change and 41-50 Gy showed a 20% decrease in regional perfusion. See Figure 4.

Cardiac function was assessed by LVEF. One patient who did not have any CTx had a decrease in LVEF > 10%. This patient had only 1% of her LV in the RT field. Her cardiac risk factors include hypertension, hypercholesterolemia, remote 20 pack/year smoking history and age of 72 years. At 6 months, there was no clinical evidence in any patients of a myocardial infarction or congestive heart failure. However, two patients had symptomatic reversible acute pericarditis within 8 weeks after completion of RT. The volumes of left-ventricle irradiated for these 2 patients were 22% and 5%. Both patients had Dox-based CTx regimens consisting of CAF. One patient also had paclitaxel.

DISCUSSION:

The Stockholm Group was one of the first to attempt to quantify the volume of heart irradiated and dose received and relate this to cardiac damage. In a 1992 report, Rutqvist et al. (3) retrospectively analyzed cardiac toxicity among the 960 patients in the Stockholm randomized trial of post-mastectomy radiation therapy compared with surgery alone. No patients received adjuvant systemic therapy. Radiation doses to the heart were reconstructed using 3D techniques in four patients. The subset of patients who presumably received the highest doses of cardiac radiation, those treated with tangential

fields for left-sided tumors, were found to have a significantly increased risk of death due to ischemic heart disease compared to surgical controls.

A subsequent study from Stockholm (1996) utilized 3D imaging techniques to prospectively study the volume of heart irradiated and determine if injury had taken place through the use of Tc-99m sestamibi cardiac perfusion imaging (17). Six of the 12 patients with left ventricle within the RT field exhibited new fixed areas of hypoperfusion 13 months after radiation therapy. Among 3 patients who had received Dox-based CTx, only 1 had a new perfusion defect. The location of the defects appeared to correspond well with the irradiated volume of the left ventricle.

Our study uses advances in 3D RT treatment planning to relate the volume of the LV irradiated and the RT dose to perfusion defects. We found that RT appears to cause dose-dependent regional cardiac perfusion defects 6 months after treatment in most patients. Dox-based CTx may increase the frequency and severity of these defects. Among patients treated with RT alone there is a suggestion that new perfusion defects occurred primarily in patients with larger volumes of the LV irradiated. In contrast, among patients treated with Dox-based Ctx and RT new perfusion defects were observed if any volume of the LV was irradiated regardless of size. The new perfusion defects have not been associated with clinical events such as CHF or MI, but follow-up is short. It is not known if these changes will persist with additional follow-up.

The pattern of perfusion injury observed in our study demonstrates a decrease in blood flow to the irradiated region of the heart. It does not correlate specifically with coronary artery blood distribution but rather to the RT field. This suggests damage at the microvascular level. Most reports of ischemic RT-related heart disease note a late occurrence 10 to 15 years after RT (5,18). Since these perfusion abnormalities in our study are seen only 6 months after RT without evidence of a change in LVEF, the clinical significance of these changes is not clear.

The cardiac consequences of administering sequential RT and Dox-based CTx to patients with breast cancer are not well understood. One study by Shapiro et al. reviewed the cardiac outcome

(congestive heart failure or myocardial infarction) in 299 node-positive breast cancer patients who had been randomized to receive cyclophosphamide and either 450 mg/m² of Dox versus 225 mg/m² of Dox (8). A second randomization of radiation therapy to the chestwall and regional lymph nodes was made for 36% of the patients. At a median of 6 years follow-up, patients receiving the higher dose of Dox (450 mg/m²) and left-sided breast or chestwall radiation therapy had a three to four fold increased risk of cardiac events over patients treated with the same dose of Dox without radiation. Interestingly, in patients treated with 225 mg/m² of Dox there was no increase in cardiac events irrespective of the use of radiation.

Six months is a relatively short time for follow-up of RT-related injury. Partial recovery of perfusion abnormalities has been described in studies of RT-related lung injury (24). The Amsterdam group studied the lungs of irradiated breast cancer patients and found that early dose-dependent reduction in local perfusion underwent partial improvement 18 months after treatment. It is possible that local cardiac perfusion injury observed in our population will improve with longer follow-up.

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Visibly detectable new perfusion defects among irradiated left ventricle

Treatment	No.	%
chemo + RT	7/7	100
RT only	5/10	50
+ IMNS	5/5	100
- IMNS	7/15	47
all	12/17	71

Table 1

The percent volume of the left-ventricle receiving $\geq 50\%$ of prescribed dose

	+ chemo N = 10	RT only N = 10	+ IMNS N = 5	- IMNS N = 15	all N = 20
median	4	6.5	5	7	5
volume					
range	0-22	1-32	2.5-22	0-32	0-32

Table 2

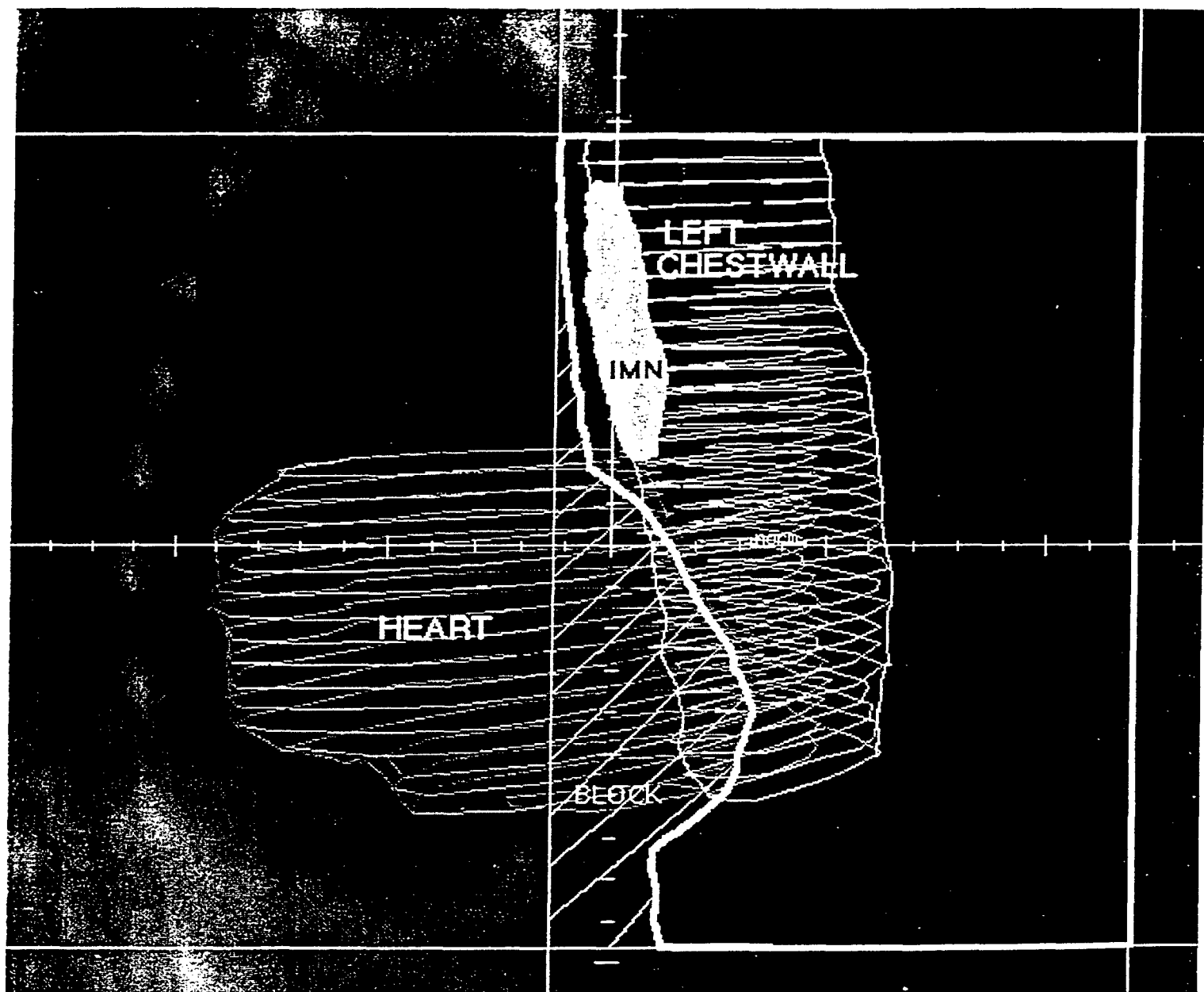


Figure 1: A beam's-eye-view of a medial tangent radiation field to treat the left chestwall. This "wide tangent" includes the IMNs while avoiding the heart.

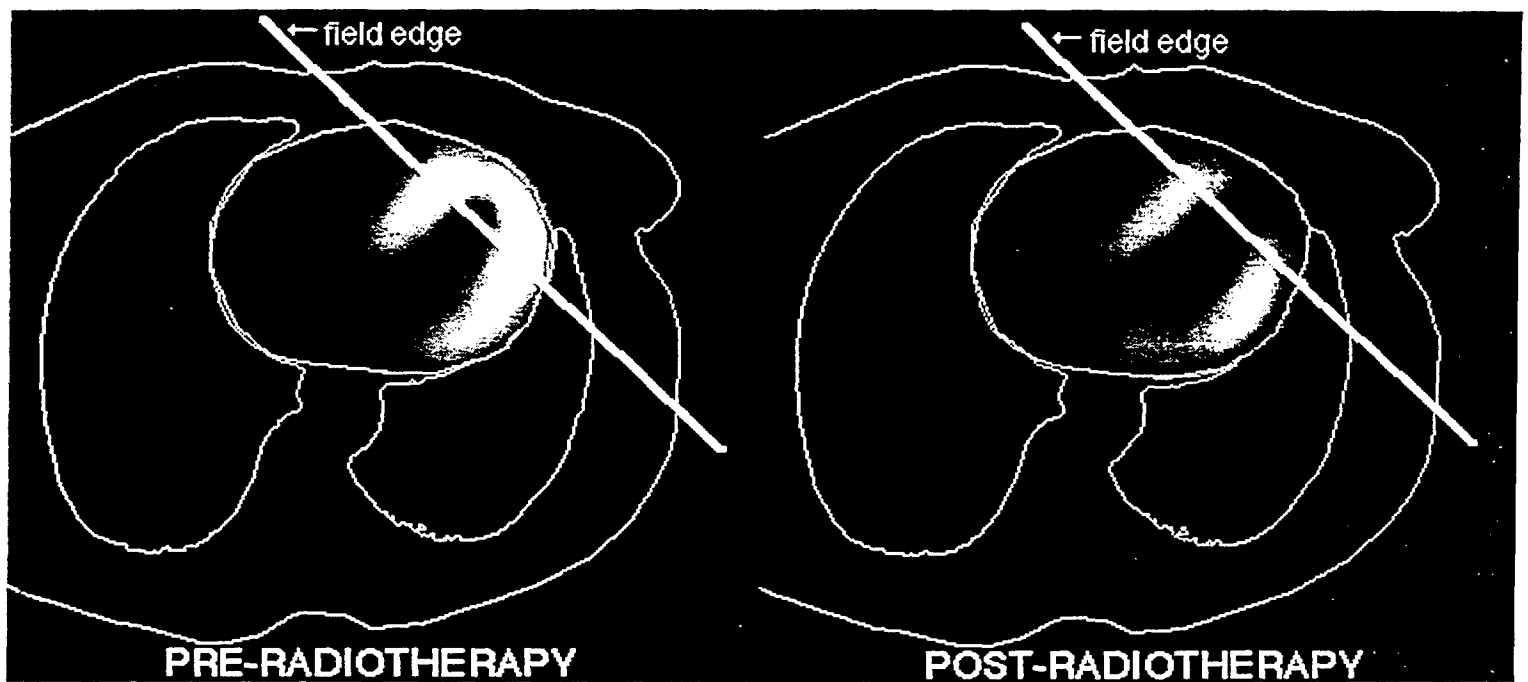


Figure 2: Pre- and post-radiotherapy cardiac SPECT perfusion scans showing a new perfusion defect after irradiation.

Perfusion Defect by % LV in RT Field

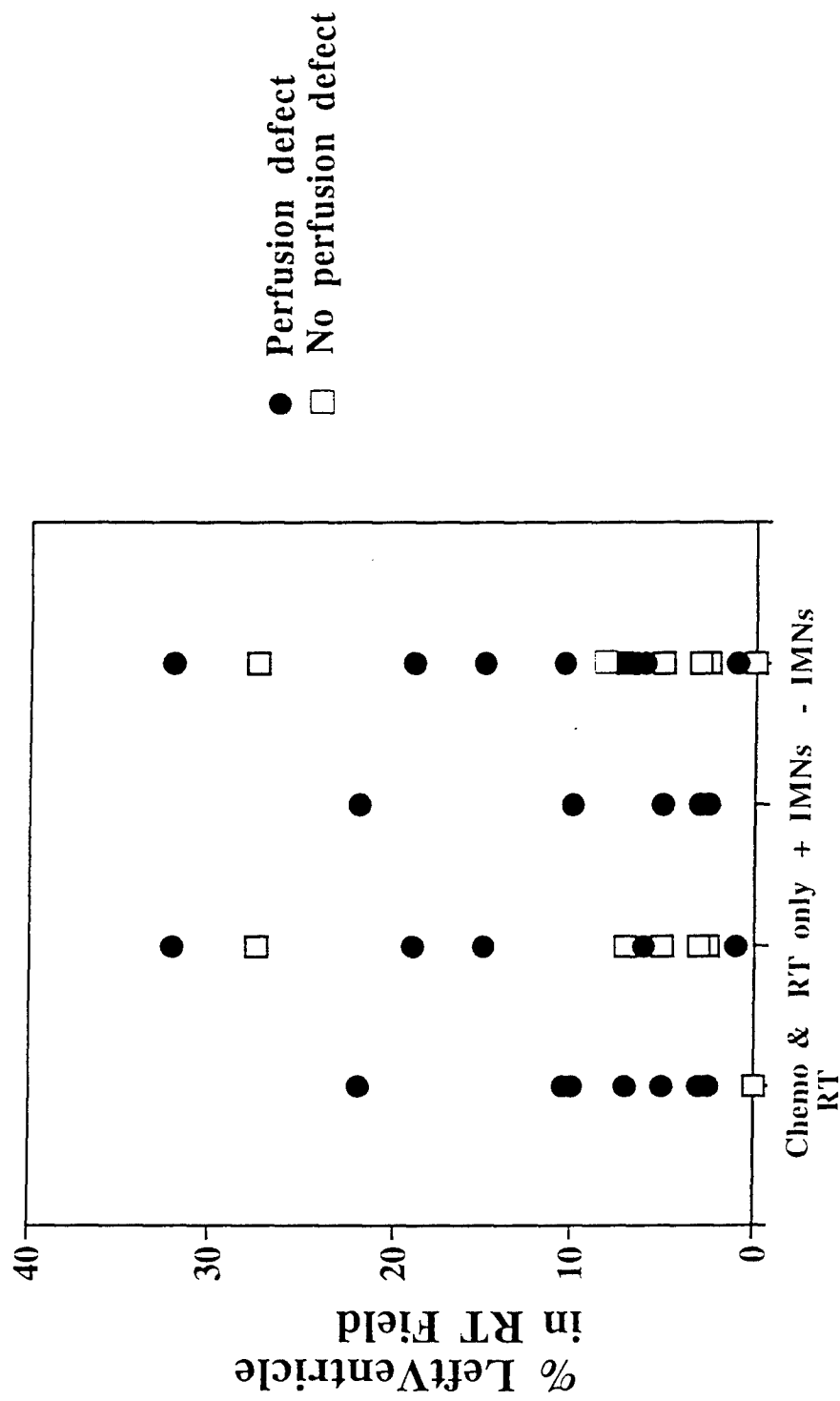


Figure 3: Graph shows the observed perfusion defect 6 months post treatment relative to the volume of LV in the RT field

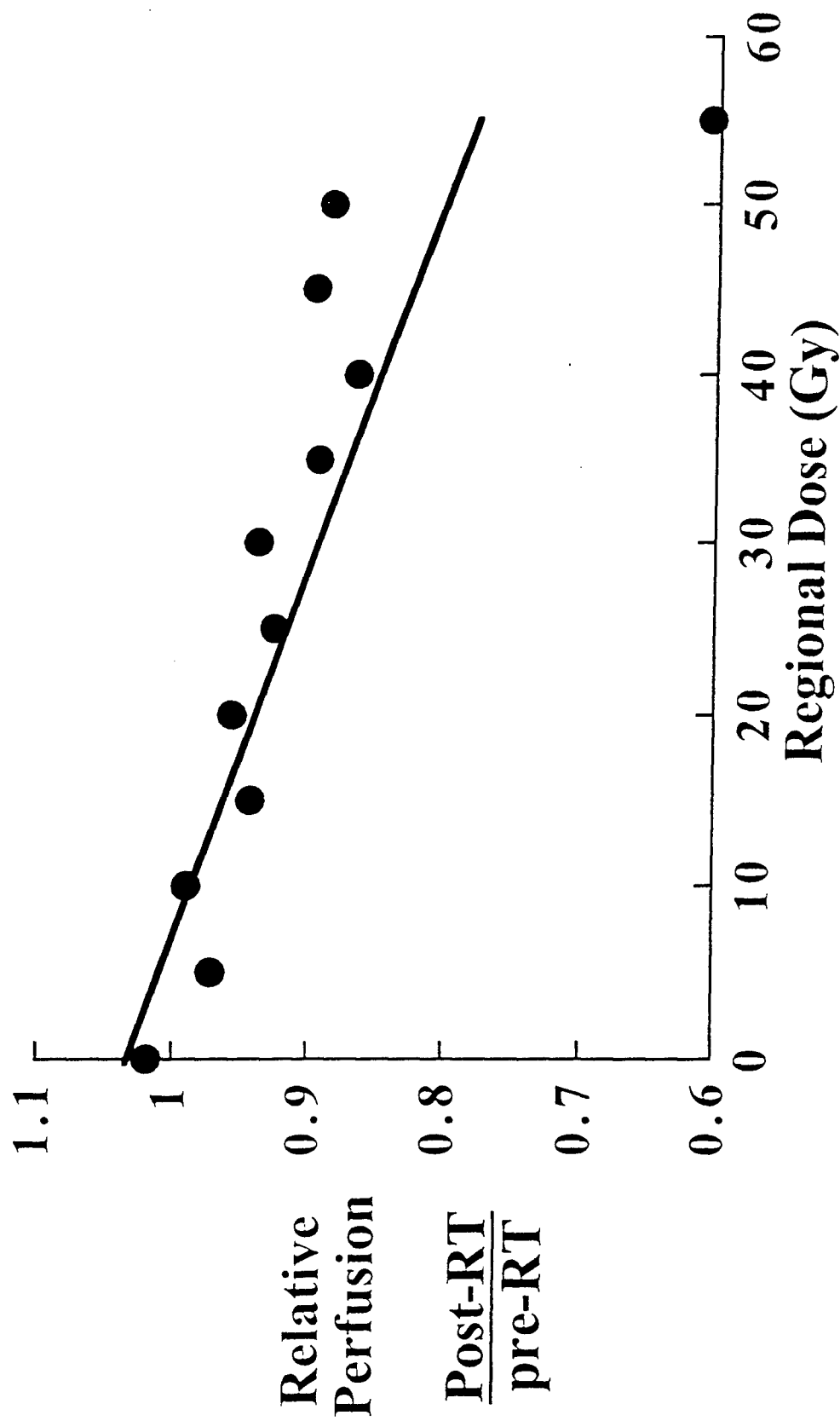


Figure 4: Graph shows relative perfusion change from pre to post imaging. Each point represents the weighted average of all perfusion changes at that regional RT dose.



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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

27 Feb 03

MEMORANDUM FOR Administrator, Defense Technical Information
Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir,
VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to the enclosed list of technical documents. Request the limited distribution statement assigned to the documents listed be changed to "Approved for public release; distribution unlimited." These documents should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Encl


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Deputy Chief of Staff for
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