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Decreased Lung Perfusion Following Breast/Chest Wall Irradiation: Quantitative Results from a Prospective Clinical Trial

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Abstract

Purpose/Objective—To quantify lung perfusion changes following breast/chest wall radiotherapy (RT) using pre- and post-RT SPECT/CT attenuation-corrected perfusion scans; and correlate decreased perfusion with adjuvant RT dose for breast cancer in a prospective clinical trial.

Methods/Materials—As part of an IRB-approved trial studying the impact of RT technique upon lung function in node-positive breast cancer, patients received breast/chest wall and regional nodal irradiation including superior internal mammary node (IMN) RT to 50–52.2 Gy with a boost to the tumor bed/mastectomy scar. All patients underwent quantitative SPECT/CT lung perfusion scanning pre-RT and one year post-RT. The SPECT/CT scans were co-registered and the ratio of decreased perfusion after RT relative to the pre-RT perfusion scan was calculated to allow for direct comparison of SPECT/CT perfusion changes with delivered RT dose. The average ratio of decreased perfusion was calculated in 10 Gy dose increments from 0–60 Gy.

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Conflict of Interest Statement:

The remaining authors report no conflicts of interest.

Results—50 patients had complete lung SPECT/CT perfusion data available. No patient developed symptoms consistent with pulmonary toxicity. Nearly all patients demonstrated decreased perfusion in the left lung using voxel-based analyses. The average ratio of lung perfusion deficits increased for each 10 Gy increment in radiation dose to the lung with the largest changes in regions of lung that received 50–60 Gy (ratio 0.72 (95% confidence interval (0.64, 0.79), $p < 0.001$) compared to the 0–10 Gy region. For each increase in 10 Gy to the left lung, the lung perfusion ratio decreased by 0.06 ($p < 0.001$).

Conclusions—In the assessment of 50 patients with node-positive breast cancer treated with RT in a prospective clinical trial, decreased lung perfusion by SPECT/CT was demonstrated. Our study allowed for quantification of lung perfusion defects in a prospective cohort of breast cancer patients where attenuation-corrected SPECT/CT scans could be registered directly to RT treatment fields for precise dose estimates.

Summary

Radiation for breast cancer has been associated with increased risks of pulmonary toxicity such as radiation pneumonitis and changes in pulmonary function testing. We assessed 50 patients enrolled in a prospective, clinical trial to quantitatively correlate changes in lung perfusion with radiation dose by directly registering treatment planning scans with attenuation-corrected single photon emission computed tomography perfusion scans. Nearly all patients assessed showed sub-clinical decreased lung perfusion one year after breast or chest wall irradiation.

Introduction

Adjuvant radiation therapy (RT) for patients with breast cancer is known to decrease local recurrence and increase overall survival for patients following lumpectomy and mastectomy^{1,2}. Furthermore, the addition of regional nodal irradiation (RNI) including targeting of the internal mammary nodal (IMN) chain in appropriately selected women has been proven to provide significant benefits, including reduction in distant metastases and improved breast cancer specific survival in recently reported prospective randomized trials, as well as increased overall survival in a prospective cohort study^{3–5}.

Unfortunately, adjuvant radiation can also be associated with increased risks of long-term toxicities. Cardiac toxicity has been repeatedly demonstrated following breast cancer irradiation using largely outdated radiation techniques^{6–8}. More recent studies using modern radiation techniques assessing cardiac exposure to radiotherapy using single photon emission computed tomography (SPECT) perfusion changes as an earlier measure of potential cardiac toxicity have either not shown cardiac perfusion deficits following breast cancer irradiation or have not shown an association between perfusion defects and late cardiac toxicity^{9,10}. Additional studies examining long-term effects of radiation-associated SPECT/CT scan findings are on-going.

Though the risks of cardiac toxicity following breast cancer RT have garnered the most attention, pulmonary toxicity is also a concern. Prior attempts to characterize pulmonary toxicity following RT have focused on the reporting of rates of pneumonitis and changes in pulmonary function testing (PFT). In a randomized study assessing the potential impact of

regional nodal plus local RT versus local RT alone on lung toxicity, a small but statistically significant increase in the rate of grade 2 radiation pneumonitis was demonstrated (1.2% vs. 0.2%)⁴. In a recent separate study assessing PFT changes in 41 women at 6, 12, 24, and 84 months following adjuvant breast cancer irradiation, worsening of PFT values 24 months after RT was demonstrated, although at 84 months these PFT values returned to baseline¹¹.

Lung perfusion SPECT/CT scanning is a means of quantifying changes in lung function following chest radiotherapy. Dose-dependent perfusion deficits following thoracic radiation have been described using SPECT imaging, but these studies did not allow for direct registration of treatment planning CT data to lung perfusion data as patients were not immobilized in the same exact position during the treatment planning CT and the SPECT/CT scans^{12,13}. We conducted a prospective, randomized trial of 3-dimensional conformal radiation therapy (3D CRT) versus intensity modulated radiation therapy (IMRT) for patients with left-sided, node-positive breast cancer. As part of this study, all patients underwent lung SPECT/CT perfusion scans prior to RT and one year following RT and these scans were directly registered to the RT treatment planning scans. The objective of the current analysis is to report the association of radiation dose to changes in left lung perfusion among patients treated on this trial.

Methods and Materials

Patients

Patients with left-sided, node-positive breast cancer were enrolled in an institutional review board-approved prospective trial with patients randomized to IMRT using active breathing control (ABC) or 3D CRT treated with free-breathing. Patients were eligible if they had histologically confirmed, node-positive, left-sided breast cancer requiring local-regional irradiation following lumpectomy or mastectomy. All patients received chemotherapy. Pre-existing pulmonary comorbidities and history of smoking was recorded for all patients.

Radiation Therapy

At time of CT simulation, the clinical borders for the tangent fields were marked on the patients using wires prior to scanning. The superior border of the supraclavicular field and the first three intercostal spaces were also clinically marked. All patients were simulated on a breast board. Patients underwent two RT treatment planning scans; a free-breathing CT scan was performed, followed by a second scan using ABC to suspend breathing at approximately 75% of vital capacity. A 3D CRT treatment plan was created using the free-breathing scan and an IMRT plan was created using the ABC scan for all patients using a radiation treatment planning software program developed in-house (XXXX). Randomization occurred after both plans were created using a pulmonary dose constraint allowing no more than 33% of the left lung to receive 20 Gy. The breast or chest wall (CW), supraclavicular and infraclavicular nodes, and internal mammary nodal region in the first three intercostal spaces were targeted. The breast/CW and nodal regions were prescribed 50 Gy in 2 Gy fractions followed by a lumpectomy cavity or chest wall scar boost to an additional 10 Gy in 2 Gy fractions for the 3D CRT plans. The breast/CW and nodal regions were prescribed 52.2

Gy in 1.74 Gy fractions with a concomitant boost to the lumpectomy cavity or chest wall scar prescribed to 60 Gy in 2 Gy fractions for the IMRT plans.

Lung perfusion imaging

Lung perfusion SPECT/CT was performed with patients positioned supine in the same position as RT simulation using a breast board allowing for direct registration of the SPECT/CT scans and RT treatment planning scans. The lung SPECT/CT scans were performed at baseline prior to RT and at one year following completion of RT. SPECT/CT was performed after intravenous injection of 5 mCi of [^{99m}Tc]macroaggregated albumin (MAA). SPECT/CT imaging consisted of acquisition of 64 projection views covering 360° with a dual-head, hybrid tomograph (Siemens Symbia T6, Siemens Medical, Hoffman Estates, IL, USA). CT imaging of the field-of-view employed 70 mAs, 130 kVp, pitch 0.8, 2.5 mm axial reconstruction. The radiotracer projection views were reconstructed tomographically employing the CT data for attenuation correction using an iterative algorithm (OSEM, with 8 iterations and 4 subsets; FLASH 3D, Siemens Medical, Hoffman Estates, IL, USA). Use of attenuation correction in SPECT reconstructions renders the data linearly proportional to the voxel-wise concentration of radiotracer. Co-registered MAA perfusion images and X-ray CT images were provided for further analyses. All pre-RT and one year post-RT lung perfusion SPECT/CT scans were read by the same expert nuclear medicine physician. These two scans were compared for each patient and qualitative perfusion changes were recorded.

Image registration

Each post-RT lung perfusion SPECT scan was rigidly registered to the pre-RT lung perfusion scan using the mutual information cost function in the “coreg” process from the NEUROSTAT software package¹⁴. The CT scan acquired with the pre-RT lung perfusion SPECT scan was used to create a lung mask, which was then applied to the co-registered SPECT scans to exclude all non-lung voxels from analyses. The co-registered, masked, SPECT perfusion scans were intensity normalized using the “rnorm” routine from the NEUROSTAT package. This routine determines a scale factor for each image based on maximizing the number of voxels across the entire image volume that are within a fixed percent of one another (comparing each voxel to its counterpart in the other scan). From the normalized images, the post-RT to pre-RT ratio image was calculated. This dataset, which we termed the ratio map, was then converted into DICOM format and imported into our institution’s RT treatment planning system. For patients treated with 3D CRT, the ratio map DICOM file was manually and rigidly registered to the RT treatment planning CT because both the lung perfusion SPECT/CT images and RT treatment planning CT were acquired in a free-breathing state. The registration was verified via 3D image inspection and, if necessary, the registration was biased toward the left lung apex, anterior lung, and lateral lung.

An additional step was required for patients randomized to the IMRT arm because their treatment planning CT was acquired at approximately 75% vital capacity using ABC. For these patients, the ratio map and the treatment planning CT DICOM data were imported into Morfeus which is an in-house software program that uses a finite element model-based

deformable image registration method^{15,16}. The RT treatment planning CT data containing the dose information was deformed to the ratio map and the registration was reviewed. Figure 1 graphically demonstrates the steps used to register the lung perfusion SPECT/CT scans to the treatment planning scans.

We created a program within our treatment planning software to correlate RT dose to the perfusion ratio change with a voxel resolution. We wanted to assess for changes in 10 Gy dose increments for lung volumes of at least 50 cubic centimeters (cc). This program allowed us to obtain the average ratio of perfusion changes as well as standard deviation according to those 10 Gy dose increments and allowed us to calculate the volume of left lung that was included in each 10 Gy dose region.

Statistical Analysis

Rates of decrease in perfusion ratio were modeled using a repeated-measure mixed effects model, where dose was a fixed effect (midpoint of the dose range) and patients were considered random effects, both for their intercept value (perfusion ratio at zero radiation dose) and slope (change by dose). The model was weighted by the proportional lung volume within each dose-range per patient. The mean perfusion ratios and 95% confidence intervals were estimated from this model at the midpoint of each dose range. We used the SAS System Version 9.4 (Cary, NC, USA).

Results

The trial included 50 patients who had complete SPECT/CT lung perfusion data available for our assessment; 25 were randomized to IMRT and 25 were randomized to 3D CRT. The average age of all patients was 50 years-old (range 25–74). Prior to radiation, 27 patients underwent a mastectomy and 23 patients had a lumpectomy. There were 29 patients with stage II breast cancer and 21 patients with stage III breast cancer. All but one patient received chemotherapy prior to radiation with 82% (n=41) receiving dose-dense doxorubicin and cyclophosphamide followed by a dose-dense or weekly taxane. Thirteen patients also received trastuzumab. Approximately half of the patients (n=26) stated they never smoked and nearly half (n=24) had a history of smoking prior to radiation, although only 6 patients had a history of smoking the year prior to treatment and 2 patients were smokers at the start of radiation. The average ipsilateral mean lung dose for all patients was 14.0 Gy. The percent volume of the ipsilateral lung receiving at least 20 Gy (V20) and the volume of ipsilateral lung receiving at least 5 Gy (V5) were 29.3% and 52.8% respectively. Table 1 summarizes these patient characteristics.

All 50 patients were assessed for signs or symptoms of pulmonary toxicity during follow-up appointments (every 3 months for the first 2 years, then every 6 months until 5 years after completing RT), and none were detected in any patient. Additionally, the one year post-RT lung perfusion SPECT/CT scan was compared side-by-side by the same nuclear medicine physician to the pre-RT SPECT/CT for all patients in order to evaluate for qualitative reductions in lung perfusion. A qualitative decrease in lung perfusion one year after RT was detected in 8 patients (16%) using this method. Finally, all 50 patients in this study had quantifiable complete voxel-based attenuation-corrected lung perfusion SPECT/CT data

available for analysis. Though no patient developed any clinical evidence of pulmonary toxicity during follow-up, and only 16% of patients had evidence of decreased perfusion at one year post-RT based on nuclear medicine qualitative assessment of post-RT lung SPECT scans, 94% of patients demonstrated some degree of quantitative perfusion deficit one year after RT using attenuation-corrected, voxel-based assessment of lung perfusion changes. Using our quantitative method, we observed that the areas of greatest perfusion deficit were in the left lung apex and anterior portion of the left lung. Figure 2 demonstrates examples of correlation of radiation dose with regions of decreased perfusion in 2 patients. The results from the dose-based analysis were consistent among nearly all patients (94%), regardless of whether the previously validated image registration method was used.

The average perfusion deficits in the left lung following radiation were greatest in regions of lung that received the highest dose, although the regions of lung that received the highest dose were of small volume. For example, the average ratio decrease for regions of lung that received 10–20 Gy was approximately 5% as compared to a decrease in the ratio of approximately 30% for regions that received 50–60 Gy. The volume of lung that received each of these doses was 691 cc versus 73 cc, respectively. Each consecutive increase in dose in 10 Gy increments was associated with a larger average decrease in lung perfusion. When compared to regions of left lung that received 0–10 Gy, there was a statistically significant decrease in perfusion incrementally for all other dose ranges. The average ratios of decreased perfusion with 95% confidence intervals and lung volume for each dose range are summarized in Table 2. We created a repeated-measure model fit to perfusion change by dose range after compiling all patient data (Figure 3). For every increase of 10 Gy to the left lung, the lung perfusion ratio decreased by 0.06 ($p < 0.001$).

Discussion

The benefits of adjuvant local RT for breast cancer are clear ^{1,2}. Furthermore, recent studies have provided additional evidence supporting the inclusion of regional nodal irradiation for appropriately selected patients, which increases the volume of lung irradiated compared to treatment of the breast/chest wall only ^{3–5}. Our goal was to associate radiation dose with decreased lung perfusion by directly comparing treatment planning CT data with attenuation-corrected lung perfusion SPECT/CT imaging in a population of patients with node-positive, left sided breast cancer who required breast/chest wall and regional nodal irradiation. To our knowledge, this is the largest study directly correlating RT dose to perfusion defects in the lung in patients treated for breast cancer, CT-planned and immobilized in the treatment position for all scans used in the study. Our study also utilized attenuation-corrected SPECT lung perfusion measures, rendering the data linearly proportional to lung function on a voxel level. With the data obtained, we have established a dose-response relationship for lung perfusion deficits.

The use of SPECT imaging to correlate perfusion deficits to RT dose has been previously studied. Investigators at Duke University have assessed patients for perfusion deficits following irradiation for tumors located in or near the thorax with long-term follow-up ^{12,17,18}. Their most recent study evaluated 123 patients, 11 of whom had breast cancer, and compared changes in pre-RT and post-RT SPECT lung perfusion scans with RT dose

delivered to the lung ¹². Dose dependent reductions in lung perfusion were suggested with the greatest decreases observed in the first 12 months following treatment with a plateau to the dose-response curves after 18 months ¹². They also demonstrated that post-RT changes on soft tissues surrounding the lung were not responsible for the SPECT lung perfusion deficits. However, their results were not corrected for the effects of tissue attenuation or lung geometry on the tracer distributions ¹⁸. Also, though SPECT scans were registered to the RT treatment planning scans, the SPECT scans were not acquired using the same positioning and immobilization as the treatment planning scans. Yet, a relationship was clearly shown between dose and reduction in lung perfusion.

Investigators at the Netherlands Cancer Institute have also extensively studied the effects of radiation on lung perfusion and pulmonary function ^{13,19–21}. Their work included a study of 110 patients, including 51 patients with breast cancer who underwent pre-RT SPECT lung perfusion scanning in addition to scans at 3 months and 18 months post-RT ¹³. A reduction in lung perfusion was noted at 3 months with partial improvement detected at 18 months. For the patients with breast cancer, the partial improvement was approximately 10%. Similar to our study, these investigators noted an almost linear association of dose with perfusion changes ¹³. Though their work included a similar number of patients with breast cancer as were enrolled in our study, it differed from our work in that the SPECT scans and RT treatment planning scans were not acquired in the exact treatment position and therefore not directly registered. However, attenuation-correction was utilized in the analysis of SPECT imaging in their study.

In our study, the only lung constraint was V20 <33%. This is a widely utilized lung constraint and has been shown to correlate with decreased lung complications following RT. A Swedish study compared rates of radiation pneumonitis in a cohort of patients treated without a lung constraint and a cohort of patients treated with a V20 of <30%. They found a significant decrease in the incidence and severity of radiation pneumonitis when adhering to a V20 <30% constraint ²². Another study analyzing possible predictive factors for radiation pneumonitis following thoracic radiation found that dosimetric parameters including mean lung dose and volume of lung that received >30 Gy were the best predictors of symptomatic radiation pneumonitis ²³. The highest doses in our study were associated with the largest perfusion deficits and the most severe changes seemed to occur at doses above 30 Gy. While no patients in our study developed clinically evident pneumonitis, decreased perfusion is a marker of lung injury and based upon our results, could be utilized when comparing treatment planning techniques for breast cancer in future clinical trials.

We acknowledge limitations in our study. Because our study included only 50 patients, we are unable to correlate the severity of perfusion deficits with treatment and patient factors such as age and smoking history. Our goal, however, of correlating radiation dose as precisely as possible with changes in lung perfusion was achieved. Though perfusion deficits were noted in almost every patient, all of the changes were subclinical and no patient developed clinically significant toxicity. It should be noted that this subclinical damage occurred despite meeting standard lung dose constraints. Deformable registration of the treatment planning CT scans with the SPECT scans for the cohort of patients treated at approximately 75% vital capacity using ABC may have introduced uncertainties, but we

expect these uncertainties to be minor. Finally, post-RT scans were obtained at 1 year. It is unclear whether this is the optimal time to assess post-RT perfusion changes. However, the studies by Zhang et al. and Theuws et al. have demonstrated that the largest decreases in lung perfusion are noted during the first year after treatment with no further worsening of the dose response curve after 18 months¹². It is therefore likely the one-year scans captured the majority of changes.

Conclusion

In the assessment of 50 patients with node-positive breast cancer treated with adjuvant RT in a prospective clinical trial, decreased lung perfusion by attenuation-corrected SPECT/CT was uniformly demonstrated. To our knowledge, this is the largest study quantifying lung perfusion defects in a prospective cohort of breast cancer patients where attenuation-corrected SPECT scans could be registered directly to RT treatment fields for precise dose estimates. While no patient developed lung symptoms even with treatment to the superior IMNs, this study demonstrates the ability to correlate in-field lung dose with subsequent perfusion risk. We suggest this metric be utilized when comparing treatment planning techniques for breast cancer going forward.

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Figure 1.

For each patient the pre-RT SPECT/CT scan was registered to the 1 year post-RT SPECT/CT scan. A perfusion ratio map was created from these two scans. For patients in the 3D CRT arm, the ratio map was rigidly registered to the RT planning CT scan. For IMRT patients, the RT planning CT scan was deformed to match the SPECT/CT, prior to registration of the ratio map.

Figure 2.

A comparison of the SPECT/CT ratio map and the RT treatment planning scan is shown for two patients. Decreased perfusion is noted in one patient in an axial and sagittal image at the lung apex (A). Decreased perfusion is noted of the anterior left lung in a different patient (B).

Figure 3.

The graph demonstrates the average ratio of decreased lung perfusion for each patient in 10 Gy increments. Overall, for every increase in 10 Gy, the lung perfusion ratio decreases by 0.06 ($p < 0.001$). This establishes a dose-response curve of dose to lung perfusion deficits.

Table 1

Patient Characteristics

Average age (range)		50 (25–74)
Treatment arm	IMRT	25
	3D CRT	25
Type of treatment	Mastectomy	27
	Lumpectomy	23
Stage	II	29
	III	21
Chemotherapy	dd AC/ dd T	28
	dd AC/ weekly T	13
	Other	9
Smoking history	Never smoker	26
	Ever smoker	24
	Smoked in year prior to RT	6
	Smoked at start of RT	2
Average mean left lung dose		14.0 Gy
Average left lung V5 Gy		52.8%
Average left lung V20 Gy		29.3%

Abbreviations: IMRT = intensity modulated radiotherapy; 3D CRT = three-dimensional conformal radiotherapy; dd = dose-dense; AC = doxorubicin and cyclophosphamide; T = taxane; Gy = gray; V5 = volume of lung receiving at least 5 Gy; V20 = volume of lung receiving at least 20 Gy.

Table 2

Summary of perfusion changes by dose range by repeated-measures model estimates

Dose (Gy)	Average ratio	95% confidence interval	Volume (cc)
0 – 10	1.01	(0.99, 1.03)	690.5
10 – 20	0.95	(0.93, 0.98)	146.2
20 – 30	0.89	(0.86, 0.93)	105.6
30 – 40	0.83	(0.79, 0.88)	126.7
40 – 50	0.78	(0.72, 0.83)	137.8
50 – 60	0.72	(0.64, 0.79)	72.7

Abbreviations: Gy = gray; cc = cubic centimeters.