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Effects on Lung Tissue After Breast Cancer Radiation: Comparing Photon and Proton Therapies

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ABSTRACT

Purpose: In breast cancer, improved treatment approaches that reduce injury to lung tissue and early diagnosis and intervention for lung toxicity are increasingly important in survivorship. The aims of this study are to (1) compare lung tissue radiographic changes in women treated with conventional photon radiation therapy and those treated with proton therapy (PT), (2) assess the volume of lung irradiated to 5 Gy (V5) and 20 Gy (V20) by treatment modality, and (3) quantify the effects of V5, V20, time, and smoking history on the severity of tissue radiographic changes.

Patients and Methods: A prospective observational study of female breast cancer patients was conducted to monitor postradiation subclinical lung tissue radiographic changes. Repeated follow-up x-ray computed tomography scans were acquired through 2 years after treatment. In-house software was used to quantify an internally normalized measure of pulmonary tissue density change over time from the computed tomography scans, emphasizing the 6- and 12-month time points.

Results: Compared with photon therapy, PT was associated with significantly lower lung V5 and V20. Lung V20 (but not V5) correlated significantly with increased subclinical lung tissue radiographic changes 6 months after treatment, and neither correlated with lung effects at 12 months. Significant lung tissue density changes were present in photon therapy patients at 6 and 12 months but not in PT patients. Significant lung tissue density change persisted at 12 months in ever-smokers but not in never-smokers.

Conclusion: Patients treated with PT had significantly lower radiation exposure to the lungs and less statistically significant tissue density change, suggesting decreased injury and/or improved recovery compared to photon therapy. These findings motivate additional studies in larger, randomized, and more diverse cohorts to further investigate the contributions of treatment modality and smoking regarding the short- and long-term radiographic effects of radiation on lung tissue.

Introduction

Over 280,000 women are diagnosed with breast cancer in the United States each year.[1] Through improved early detection and treatment, there are now over 3.5 million breast cancer survivors nationally.[2] Many patients with breast cancer receive radiation therapy (RT) to the affected breast and/or chest wall to minimize the risk of recurrence. Unfortunately, lung tissue and the vascular endothelium (in

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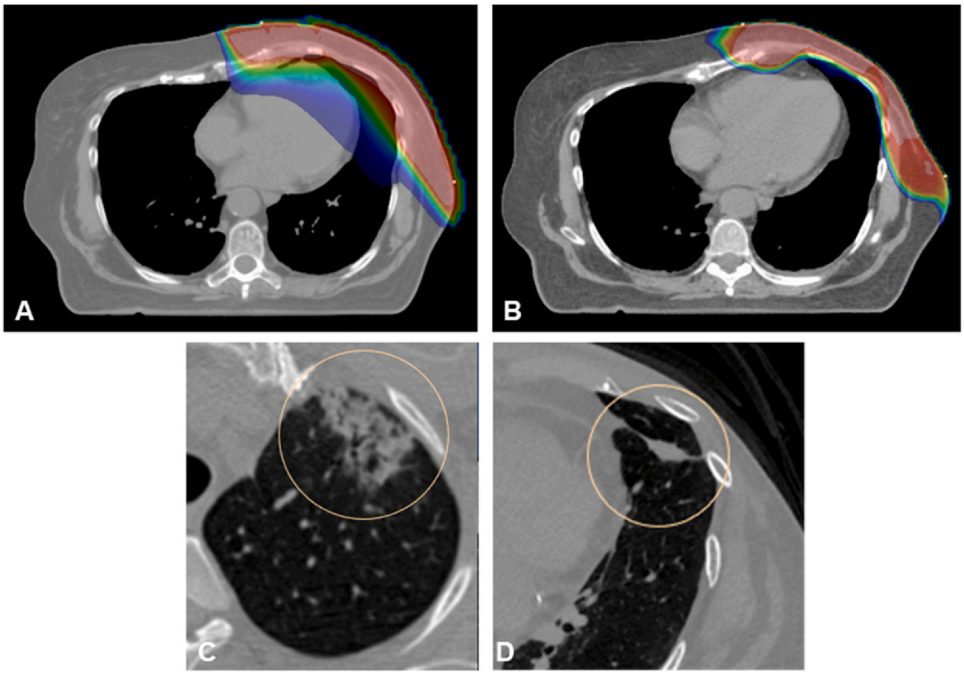

Figure 1. Representative photon and proton therapy plans and radiographic changes for representative left-sided breast cancer patients. (A) and (B) Chest computed tomography slices through the center of the thorax, including the heart, with the color overlay representing the radiation dose to the tissues. A photon treatment plan is shown in (A), and a proton therapy plan for the same patient is shown in (B). The highest dose in red corresponds to the treatment target dose of approximately 50 Gy, lowering through the color spectrum, with 20 Gy at approximately green and 5 Gy at approximately purple. The lymph nodes in the axilla and internal mammary region were included in the treatment. (C) and (D) The typical radiographic appearance of lung tissue effect (inside yellow circles). Lung tissue reaction was most commonly observed superiorly and laterally (C) and occasionally along pleural surfaces between and around the lung lobes (D).

particular) are highly sensitive to radiation. A meta-analysis from 2013 found that up to 14% of patients with breast cancer treated with RT develop clinical pulmonary toxicity (evidenced by pain, shortness of breath, decreased ability to exercise, and/or fever), with 4% overall experiencing high-grade clinical toxicity requiring medical intervention and severely compromising their quality of life.[3]

Proton therapy (PT) is emerging as a favored modality in the treatment of breast cancer due to its potential for high-dose conformality and low radiation exposure to the surrounding critical organs,[4-6] including the lungs. As particles, protons are entirely absorbed within the tissue rather than passing through the body to affect deeper tissues, as do photons. Although breast cancer is an approved diagnosis for the use of PT by Medicare and Medicaid,[7] level 1 data do not yet exist to guide treatment practices or support requests for coverage to private insurers.

During RT for breast cancer, small portions of the ipsilateral lung are inadvertently exposed to low and moderate doses of radiation (Figure 1A and B). This radiation exposure can lead to asymptomatic radiographic changes (Figure 1C and D) and/or symptomatic clinical presentation. Radiation-induced lung injury is known to follow 2 distinct phases: it can occur within approximately 6 to 12 months of treatment as radiation pneumonitis or > 6 to 12 months as radiation fibrosis. The lungs are composed of parallel functional subunits; hence, a threshold volume must be irradiated before a significant clinical response is observed. In a recent large multi-institutional trial randomizing patients with early-stage breast cancer to standard whole breast RT with or without regional nodal radiation, the rate of grade 2 or higher pneumonitis was 1.2% with regional nodal radiation versus 0.2% without regional nodal radiation.[8] Some chemotherapeutic agents can also enhance the effects of radiation and increase the rates of symptomatic pneumonitis, confounding estimates.[9-11] Risks of radiation pneumonitis appear highest when these agents are delivered concurrently with radiotherapy. For example, using paclitaxel concurrently with radiation for breast cancer is associated with a 14% rate of pneumonitis compared to 1.1% without paclitaxel.[10]

Grade 1 pneumonitis is defined as radiographic changes in the absence of clinical symptoms. The incidence of grade 1 pneumonitis among patients treated for breast cancer is not known precisely because national cancer care guidelines do not recommend that patients with breast cancer undergo surveillance imaging such as chest x-rays or x-ray computed tomography (CT) of the chest in follow-up. Although radiographic changes indicating asymptomatic radiation-induced lung injury can be seen as early as 3 to 6 months after radiation, prospective chest CT scans have not been used previously to quantify clinically relevant endpoints or identify high-risk patients early in the progression of normal tissue injury. Computed tomography imaging can be used to observe ground-glass opacities, consolidation, fibrosis, cicatrization, atelectasis, pulmonary volume loss, and pleural thickening. Grade 2 pneumonitis includes mild to moderate symptoms (including dyspnea and cough) that require medical intervention (typically steroidal anti-inflammatories) but do not require hospitalization. Grade 3 and 4 pneumonitis are defined as severity that requires hospitalization and can be life-threatening.[12]

Previous studies have shown that smoking can impact the observed radiation response of lung tissue. Long-term exposure to tobacco smoke leads to the replacement of living elastic tissue with a fibrotic structure. In contrast to the causative role of smoking and lung cancer, tobacco use leads to a decrease in the severity of pneumonitis in lung cancer patients treated with chemotherapy and radiation.[11,13] In 576 patients with stage III nonsmall cell lung cancer treated with radiotherapy, the incidence of grade 3 or higher radiation-induced pneumonitis was greater in nonsmokers (37% at 1 year) than in smokers (14% at 1 year).[14]

The primary goal of our study was to assess whether modern PT is safer for the lungs (reduces total lung tissue damage) compared to photon therapy. Our approach uses an objective quantitative assessment of overall tissue density change from serial chest CT scans. We introduce normalization of CT pixel intensity changes, using the contralateral hemilung as internal control, to account for differences in scan parameters and techniques across patients and time points. Our findings consider key treatment variables (modality and lung dose) and the patient's smoking history. Our long-term objective is to establish tools and protocols to identify patients with breast cancer at high risk for pulmonary toxicity to tailor treatment and provide early intervention to mitigate adverse effects.

Materials and methods

Study population and recruitment

We conducted an observational study of 41 females with breast cancer aged 18 or older who had either American Joint Committee on

Cancer Eighth Edition anatomic stage II or higher disease or node-positive invasive disease and who were scheduled to receive conventional photon radiation treatment or PT to the breast or chest wall for the treatment of breast cancer. The study exclusion criteria comprised patients who had previously had radiation treatment where any portion of the lung received > 5 Gy and women with bilateral breast cancer or metastatic disease to sites near the chest where additional radiation exposure of 5 Gy or more was anticipated to any portion of the lung. The study protocol was approved by our Institutional Review Board (IRB201600387) and was registered at ClinicalTrials.gov as NCT02725840. All participants were required to provide informed written consent to participate. All patients completed treatment between 2016 and 2020. In the final analysis, 1 participant received radiation prior to chemotherapy; this patient presented with early severe radiation recall dermatitis and radiation-induced organizing pneumonia that affected both hemilungs (a case report was published for this participant).[15] Because of this participant's differing treatment protocol, her data were excluded from the analyses. Whereas all patients treated with PT had planned treatment to the regional lymphatics, 5 photon patients did not; thus, these participants were excluded from the analyses that compared proton versus photon therapies to prevent confounding by the smaller target volume.

Imaging protocol

All enrolled participants were to receive a chest CT at 1 or 3 months and 6, 12, and 24 months after completion of RT. The standard-of-care treatment planning CT data sets were used for the baseline comparator unless a pretreatment diagnostic-quality scan was available. A 2-week acquisition window was allowed for the 1- and 3-month follow-ups, and an 8-week window was permitted for the longer time points. If a chest CT scan was obtained per standard of care or as part of another research study and was within the acquisition window of a planned study-related scan, then the existing scan was used, and the study scan was not acquired. Because IV contrast is not routinely used at our institution for RT planning CTs, the contrast was not planned for the study-directed follow-up scans. Scans obtained per standard of care for diagnostic purposes often involve injected contrast. The CT imaging was acquired using best-practice diagnostic imaging protocols, typically involving 64-slice CT systems with $1 \times 1 \times 3$ mm or smaller voxel dimensions and breath-holding for motion correction. Diagnostic-quality follow-up CT scans are preferred for quantitative voxel-wise analyses over typical RT planning CTs because the latter typically use thicker slices and lack breath-holding, which degrade voxel-wise assessment of tissue density change. These differences reflect the requirements for RT planning versus radiologic diagnosis, for which the latter requires high-fidelity scans to identify small anatomic anomalies. Normalization using the contralateral hemilung is intended to correct for varying uses of contrast and differing imaging techniques across time points.

Image review and handling

The image sets were professionally read by a thoracic radiologist for any clinically significant findings to be added to the patient's medical record. The percent volume of lungs receiving at least 5 Gy dose (V5) and at least 20 Gy (V20) was exported from the treatment planning system along with a Digital Imaging and Communications in Medicine RT dose file of the 3-dimensional dose distribution computed on a $1 \times 1 \times 1$ mm grid across both hemilungs. The chest CT data sets were processed and analyzed using custom software developed in-house and built on the National Institutes of Health ImageJ program platform.[16] The steps in the lung segmentation process are modified versions of those published previously[17-20] and are detailed in Supplemental Figure 1.

Primary outcome

The key outcome was normalized tissue radiographic density change, defined as the ratio, R, of the average pixel intensity (in Hounsfield units: Hu) in the hemilung on the treated (ipsilateral) side of the body over that of the nontreated (contralateral) hemilung. Since healthy lung parenchyma is approximately −800 Hu and the value increases toward 0 for more dense (edematous or fibrotic) tissue, a lower ratio reflects a more severe tissue response. This normalization was used to control for variability of imaging parameters (eg, slice thickness, in-plane pixel dimensions, use of injected vascular contrast, use of breath-holding, and acquisition filter), the presence of normal anatomical features (eg, blood vessels and airways), and overall image quality across patients and time points. An alternative interpretation is that $(1–R)$ is the effective volume of the treated hemilung (as a percentage) that exhibits maximal effect (achieves a density value of solid tissue, which is 0 Hu). Thus, R is a means to compare a patient with a small change in tissue density over a large volume with another patient exhibiting a large tissue density change over a small volume. Changes over time for the normalized pixel intensity relative to baseline prior to RT were computed at all available time points after RT. Independent analyses were performed 6 and 12 months after RT, as the larger number of measurement points made this possible compared to the time points beyond 12 months. For comparison with prior publications, we applied to each patient and time point the 5-level visual radiographic grading scheme of Linda et al[21] from most to least severe, as follows: (1) diffuse consolidation, (2) diffuse ground-glass opacity, (3) patchy consolidation and ground-glass opacity, (4) patchy ground-glass opacity, and (5) no change.

Modeling the time course of response

To identify the time point at which the maximum tissue density change occurred, a mathematical model of injury repair was created that was reminiscent of the models proposed by Rubin and Casarett.[22] Details of the model are provided in Supplemental Figures 1 and 2.

Statistical analyses

The demographic and clinical characteristics of the study patients at baseline were collected and compared using descriptive statistics such as median and range for continuous data and frequency and proportion for discrete data. At baseline, treatment group comparisons were carried out using an exact Wilcoxon rank-sum test or Fisher's exact test. The primary statistical analyses were the associations of the normalized tissue radiation response with time, treatment modality, V5, V20, and smoking history. The statistical tests of associations were carried out using nonparametric tests such as exact Wilcoxon signed rank-sum tests or exact Wilcoxon rank-sum tests, depending on the prespecified hypothesis and the data distribution.[23] Pearson correlation coefficients were used to assess the significance of differences in tissue response at 6 and 12 months after treatment and in V5 and V20. Multivariable regression models for the response were fitted to evaluate the effects of treatment modality (photon vs proton), time as a continuous variable, and smoking history (previous or current smokers vs never-smokers). No adjustment for the multiplicity and no imputations for missing data were considered due to the scope of the study. All tests were 2-sided, and the alpha level was 0.05.

Results

Patient population

Of the 41 participants initially enrolled, 10 were omitted from the final analysis: 1 who received radiation prior to chemotherapy, 5 who did not have planned treatment to the regional lymphatics (as noted

earlier), and 4 who withdrew before the 6-month CT scan. Most (35) of the evaluable patients received 50 Gy over 25 fractions (at 2 Gy/fraction). Two photon patients received 28 fractions of 1.8 Gy; 1 photon patient received 29 fractions of 2 Gy (including a 5-fraction electron boost); 1 photon patient received 30 fractions of 2 Gy (including a 5-fraction photon boost); 1 proton patient received 45 fractions of 1.5 Gy; and 1 proton patient received 30 fractions of 2 Gy. For the 6-month time point, the acquisition window was 4.7 and 7.1 months after RT, and for the 12-month time point, between 10.7 and 15.0 months after RT. Thirteen patients provided 24-month follow-up data, with the acquisition window being 21.3 to 25.4 months. One patient had an additional standard-of-care (out-of-study) chest CT scan at 30.1 months. In another patient, COVID-19 delayed the 24-month follow-up acquisition to 32.4 months. The final data set contained 16 patients treated with PT and 15 treated with photon therapy. Baseline CT imaging and V5 and V20 data points were available for 31 patients, 6-month post-RT CT scans were available for 28 patients (15 proton and 13 photon), and 12-month post-RT CT imaging was available for 27 patients (13 proton and 14 photon).

Lung radiation exposure: V5 and V20.

Figure 2 displays box plots of the V5 and V20 distributions for each treatment modality. The numerical median and range values are given in Table 1. Proton therapy resulted in significantly lower V5 and V20 ($P < .001$ for each) compared to conventional photon therapy.

Radiographic appearance

Visual radiographic changes were most apparent in the superior aspects of the lung, adjacent to the pleural surfaces (Figure 1C and D) and within the radiation field. Of the 31 participants, 26 (84%) presented with visual grade 2 (moderate opacity[21]) or higher radiographic changes.

Modeling time course of tissue response

Figure 3A shows the time evolution of the radiographic density change ratio for each participant using all time points, with the maximum being 32.4 months. An initial downward trend in this response ratio, indicative of radiation damage, is followed by a leveling and, commonly, partial recovery out to 30+ months. Figure 3B plots the change in response ratio from baseline for all patients individually (blue dots). Negative values indicate increased tissue density indicative of a greater radiation tissue effect. There is high variability in the data that limit statistical power for comparisons. A generalized regression model with independent variables of time, time squared, smoking, treatment modality, and cross terms thereof showed that only the time and time-squared terms were significant contributors to this continuous time response ratio. In each formulation, the time coefficient was negative, indicating a significant net tissue density increase over time, while the time-squared term was positive, indicating a significant recovery effect.

Fitting the model of Equation 3 from Supplemental Figure 2 to the data gives values for the 3 coefficients of $a_0 = 0.971$, $a_1 = 1.57$, and $a_2 = 0.015$. The model-estimated response at each measured time point is shown as orange dots in Figure 3B. The maximal observative response ratio occurs at 3.01 months for these values of a_1 and a_2 with this model formulation. Given the high variability in tissue response ratio, there is considerable uncertainty in these coefficients and the maximum time estimate.

Tissue response at 6 and 12 months after treatment

The baseline (pretreatment) ratio of pixel intensity between treated and untreated hemilungs was not significantly different from 1.0 across all participants and individually for the photon and proton cohorts and the ever-smoker and never-smoker cohorts. All cohorts had similar average pixel intensity across the hemilungs, with no detectable differences prior to the start of radiotherapy. At both the 6- and 12-month time points, the radiation response ratio was significantly different from 0 for all patients combined and for the photon cohort but not for the PT cohort (Table 2). A direct test for the difference in tissue response ratio between photon and PT cohorts found no apparent difference ($P = .89$ at 6 months and $P = .38$ at 12 months). The PT cohort had a larger interpatient variability in response ratio at both time points compared to the photon patients, contributing to the lack of statistical significance for changes in this cohort.

Tissue response by V5 and V20.

At the 6-month posttreatment time point, the lung tissue density changes significantly correlated with V20 but not V5 (Figure 4). At the 12-month posttreatment time point, the lung tissue density changes trended with V20 but did not reach significance for either V20 or V5 (Figure 4).

Effect of smoking on tissue response

In our study population, 11 of 31 participants had currently or previously smoked, with the most ($n = 8$) treated with photon therapy. The difference in the number of never- and ever-smokers across treatment modalities was not significant but close ($P = .07$). At the 6-month

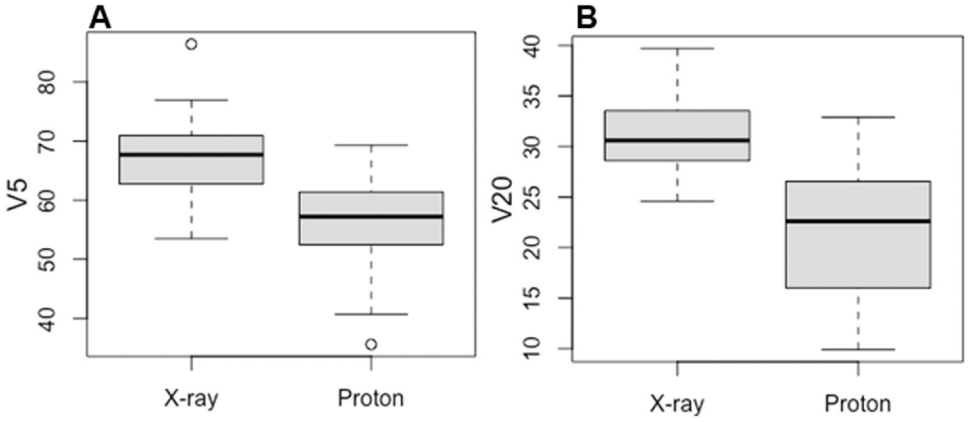

Figure 2. Box plots of the percent volume of lung receiving at least 5 Gy dose (V5) (A) and at least 20 Gy (V20) (B) for the photon ($n = 15$) and proton therapy ($n = 16$) cohorts. The median volumes were significantly less for the proton therapy cohort ($P < .001$ for each). The Y-axis scale differs between the V5 and V20 plots.

Table 1
Baseline patient and treatment characteristics (n = 31).

	Overall (n = 31)	Photon (n = 15)	Proton (n = 16)	P value[a]
Median age (years, range)	50 (31-68)	52 (31-67)	48.5 (33-68)	.87
Smoking history				.07
Never	20 (64.5%)	7 (46.7%)	13 (81.2%)	
Previous/current	11 (35.5%)	8 (53.3%)	3 (18.8%)	
Median % lung V5 (range)	60.6 (35.6-86.4)	67.7 (53.5-86.4)	57.2 (35.6-69.3)	< .001
Median % lung V20 (range)	26.8 (9.9-39.7)	30.6 (24.6-39.7)	22.6 (9.9-32.9)	< .001

[a] The P value refers to statistical comparison between photon and proton cohorts for each characteristic.

posttreatment time point, the radiation response ratio was significantly different from 0 for both the ever-smoker (P = .004) and never-smoker (P = .049) cohorts, but there was no significant difference in tissue response ratio between cohorts. A 2-variable regression model of tissue response ratio as a function of both treatment modality and smoking history found no significant association for either attribute at 6 months after RT (Table 2).

At the 12-month posttreatment time point, the radiation response ratio was significantly different from 0 for ever-smokers (P = .002) but not for never-smokers (P = .159). This result suggests that the pulmonary tissue in never-smokers recovered more completely at 12 months compared to that of ever-smokers. However, a direct test for the difference in tissue response ratio between never- and ever-smoker patients did not find significance, in part due to large variability in the nonsmoker response ratio. A 2-variable regression model of tissue response using treatment modality and smoking history found no significant association of the contribution for either attribute 12 months after RT.

Discussion

The goal of this study was to quantify the totality of subclinical pulmonary tissue changes following radiation exposure at early time points and compare the extent of pulmonary tissue effects between patients with breast cancer receiving proton versus photon therapy. The implications are for future national care guidelines for using PT in this setting regarding total lung radiation damage. The primary tissue radiation response metric was defined as the change in the ratio of the average pixel intensity from the pretreatment baseline for the ipsilateral versus contralateral hemilungs. This metric corrects for differing image acquisition and reconstruction parameters and can be used to compare large regions of low-level change to small regions of high-level change. Such normalization is recommended to harmonize CT protocols across patients and time points. For the combined cohort, the tissue response ratio was significantly different from 0 at both the 6- and 12-month post-RT time points. For the photon cohort, there was also a significant change in pulmonary tissue density after radiation, but this effect was not observed for the proton cohort. These results indicate that PT results in less overall structural pulmonary tissue effect compared to photon therapy in the setting of radiotherapy for breast cancer. However, statistical inference is hindered by the magnitude of total density change being small relative to the measured variability in pulmonary tissue effect.

Both ipsilateral hemilung V5 and V20 were significantly higher with photon therapy than with PT. Although there was a trend for increased tissue effect versus V5 and V20 at both 6 and 12 months after treatment, significance was reached only for V20 at 6 months. These data suggest that by 12 months, the tissue experienced recovery.

While both never-smokers and ever-smokers exhibited a pulmonary tissue effect 6 months after RT, only ever-smokers exhibited a persistent tissue effect at 12 months after radiation. Prior to this work, 1 hypothesis was that people with a smoking history would have less volume of viable lung tissue before the start of treatment and, therefore, would exhibit lesser lung radiation-induced changes compared with never-smokers. A competing hypothesis suggested that combined injuries from smoking plus radiation obey Rubin and Casarett's 2-hit model,[22] resulting in persistent long-term effects that cannot be observed with either agent alone. Our data suggest that nonsmokers' lungs are better able to repair by 12 months, thereby supporting the latter hypothesis.

The time course of response consists of an initial downward trend (increasing tissue density reflective of increased tissue damage) followed by a partial recovery that persists to 30 months. The increased pulmonary density is most readily observed at approximately 3 months after treatment, although there is large interparticipant variability in the time course of the tissue effect. In addition, the estimated time of maximal change is influenced by the choice of the mathematical model.

There have been many eloquent studies of the radiation dose-response relationship ("dose-response") of lung tissue aimed to better

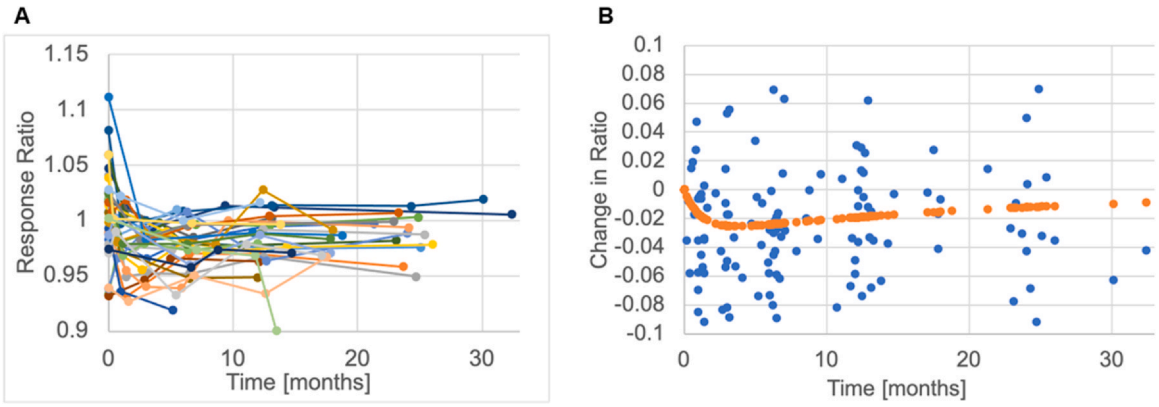

Figure 3. Plots of tissue density response over time for all patients. (A) The response ratio where connected line segments denote the 31 individual participants. (B) The change from baseline in response ratio individually for each participant (blue dots). Shown also in (B) are model-estimated values for each measurement (orange dots) using the model of Equation 3 (Supplemental Figure 2). The minimum of this fitted curve indicates the time point at which the change is maximum, averaged over all participants, which occurs at approximately 3 months.

Table 2
Baseline pixel intensity ratio between ipsilateral and contralateral hemilungs and tissue response at 6- and 12-month follow-ups[a].

Group (*N* at baseline, 6 months, and 12 months)[a]	Baseline pixel intensity ratio (range)[b]	6-month tissue response (range)[c]	12-month tissue response (range)[c]
All patients (*N* = 31, 28, 27)	1.008 (0.932, 1.111)	−0.028 (−0.089, +0.069)[d]	−0.019 (−0.123, +0.062)[d]
Photon (*N* = 15, 13, 14)	1.008 (0.939, 1.111)	−0.027 (−0.080, +0.011)[d]	−0.034 (−0.123, +0.029)[d]
Proton (*N* = 16, 15, 13)	1.005 (0.932, 1.082)	−0.033 (−0.089, +0.069)	−0.015 (−0.074, +0.062)
Previous or current smokers (*N* = 11. 9, 10)	1.016 (0.974, 1.111)	−0.028 (−0.080, −0.016)[d]	−0.034 (−0.123, 0.0)[d]
Never-smokers (*N* = 20, 19, 17)	1.003 (0.932, 1.082)	−0.030 (−0.089, +0.069)[d]	0.015 (−0.074, +0.062)

[a] Number of participants differs for each group and time point.
[b] Baseline value of 1.0 indicates no pretreatment difference in treated versus nontreated hemilungs.
[c] A tissue response value < 0.0 indicates an adverse lung tissue response.
[d] Significant difference ($P < .05$) between the follow-up and baseline values.

understand the underlying radiobiology[2] and to model[24] the radiation delivery effects of regional dose magnitude, dose rate, dose volume, fractionation schedule, and type of radiation,[25] among others. Historically, these studies measured rates of cell[26] or animal death[27] and, more recently, have focused on subclinical changes in pixel-wise density observed with chest CT.[28] While analysis of dose-response has important clinical implications, here we sought to answer whether PT is safer (causes less overall lung tissue damage) than photon therapy, given the differences in the underlying radiobiology and modern radiation delivery for each modality. For this objective, total tissue reaction is the more relevant metric. Thus, while protons have a higher radiobiological effect than photons, because the lung V5 and V20 are lower with PT the trend for lower total tissue damage with PT aligns with our expectations.

The measured interparticipant variability in lung tissue response was large relative to the magnitude of the response. This suggests that additional yet unaccounted-for patient factors and/or individual treatment plan details are impactful in dictating lung tissue damage. Measurement variability is likely contributed to by the motion of the chest wall and heart that overlap signal from a neighboring anatomical feature (eg, heart, blood vessel, chest wall, fibrotic region) onto the voxels of interest, and partial volume effects, which are more important with larger voxel dimensions.

This observational study was limited relative to an ideal randomized study by a relatively small sample size and unequal distribution of people who smoked and those who never smoked across the photon/proton cohorts. At baseline, all patients had a similar ratio of pixel intensity for the ipsilateral versus contralateral hemilungs. Within the 12-month follow-up period, only 1 participant experienced grade 3+ clinical radiation pneumonitis, and this was the lone study participant who received chemotherapy after radiation (a radiation recall effect). Clinical pneumonitis was not observed in the remainder of our cohort, confirming a 2015 prospective study that found only a 1.2% incidence.[8] Compared with the 14% incidence rate compiled from breast cancer patients treated between 1997 and 2007,[3] our finding using patients treated between 2016 and 2020 indicates that continued improvements in conformal treatment techniques continue to reduce radiation damage to the lung in breast cancer patients.

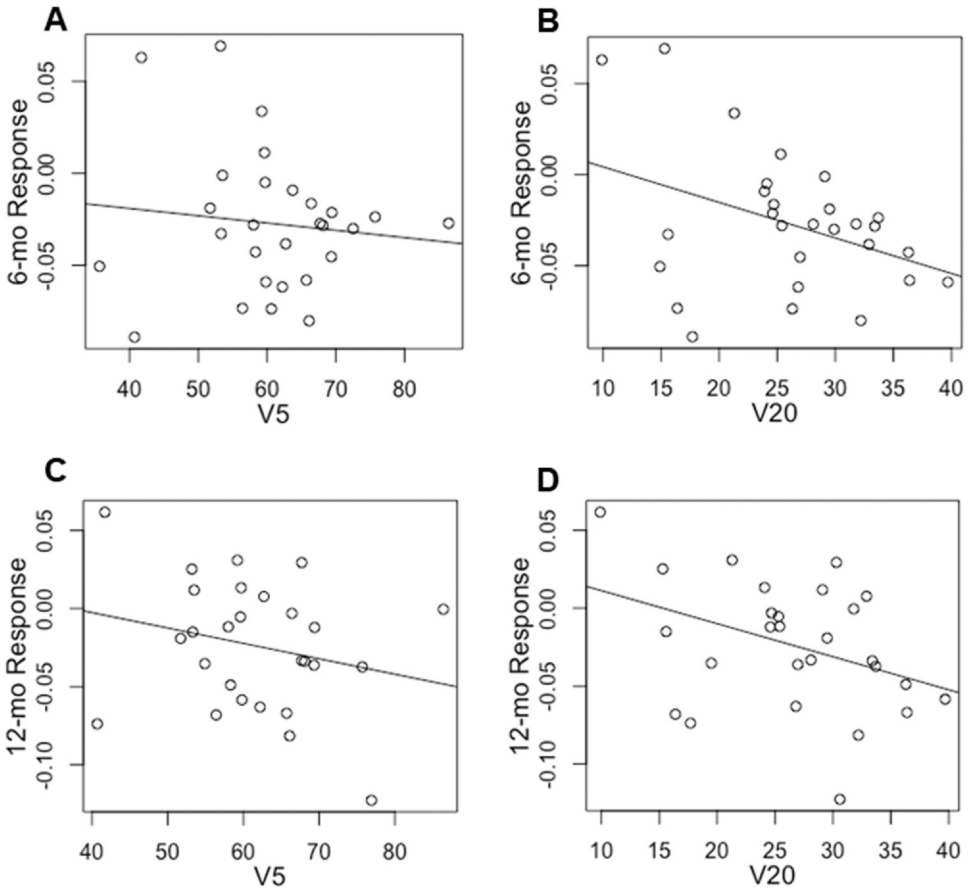

Figure 4. Comparing change from baseline in lung tissue density change to percent volume of lung receiving at least 5 Gy (V5) and 20 Gy (V20). (A) A box plot for the 6-month radiation response ratio (change from baseline of the ratio between the ipsilateral and contralateral hemilungs) as a function of V5. Zero indicates no tissue effect, and a lower value indicates a more severe tissue effect. (B) Six-month tissue response versus V20, which was significantly correlated. (C) and (D) Analogous lots plots for the 12-month pulmonary tissue response ratio, where significance was not reached.

Summary

In patients with breast cancer treated with external-beam radiation to the breast or chest wall and regional lymphatics, PT was associated with significantly lower ipsilateral hemilung V5 and V20 than photon therapy, confirming prior studies. The extent of lung tissue density change (and effective volume of affected lung tissue) measured 6 and 12 months after treatment tended to increase with both V5 and V20 but reached significance only for V20 at the 6-month time point. A significant short-term change in lung tissue density was followed by a partial recovery, with maximal tissue density observed at 3 months after completion of RT. Patients receiving PT had higher inter-participant variability in pulmonary tissue effect than those receiving photon therapy, which hindered statistical comparisons across modalities. Both ever-smokers and never-smokers exhibited significant pulmonary tissue change at 6 months after treatment, while only ever-smokers had persistently significant tissue changes at 12 months, suggesting better recovery in never-smokers. Despite the visible changes in pulmonary tissue density in all patients, clinical pneumonitis was not observed in the analyzed cohort. These findings motivate additional studies in larger cohorts to further investigate the contributions of treatment modality and patient factors on short- and long-term lung tissue changes after radiation.

Ethics

The study protocol was approved by the (anonymized for review) Institutional Review Board and the (anonymized for review) Protocol Review and Monitoring Committee, reference number IRB-201600387, on May 27, 2016, and registered at ClinicalTrials.gov with number NCT02725840 on April 1, 2016. All participants are required to provide informed written consent to participate in this study.

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Author contribution

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Data Availability Statement

The authors agree to share anonymized data upon reasonable request by researchers.

Declaration of Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Walter G. O'Dell, PhD reports financial support was provided by Florida Department of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijpt.2024.02.001.

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