PULMONARY CHANGES AFTER RADIOTHERAPY FOR CONSERVATIVE TREATMENT OF BREAST CANCER: A PROSPECTIVE STUDY

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Purpose: Radiotherapy (RT) after conservative surgery for breast cancer involves part of the pulmonary parenchyma with a potential detrimental effect of reducing the normal functional reserve. Such an effect deserves to be studied in depth, considering the given long life expectancy of these women. We prospectively analyzed high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) with correlation with dosimetric data from RT.

Methods and Materials: Lung HRCT and PFTs were performed in 41 women who had undergone conservative surgery for breast cancer before and 3 and 9 months after postoperative RT. The PFTs included forced vital capacity, forced expiratory volume in 1 s, total lung capacity, maximal expiratory flow at 50% and 25% of vital capacity, and the diffusion capacity of carbon monoxide. HRCT was matched with the RT treatment plan images to analyze the dosimetric correlation.

Results: At 3 months after RT, the lung alterations were classified at HRCT as follows: 46.3% were Grade 1, 24.4% Grade 2, and 7.3% Grade 3, and at 9 months, 58.5% were Grade 1, 19.5% Grade 2, and 0% Grade 3. The PFTs showed a significant decrease at 3 months, with only partial recovery at 9 months. Chemotherapy, but not hormonal therapy, was associated with PFT changes. The grade of fibrosis increased with increasing lung volume treated to a dose ≥25 Gy.

Conclusion: Lung changes, mainly related to damage to the alveolar–capillary barrier and smallest airway ramifications, were observed at 3 months, with only partial recovery at 9 months after RT. Minimizing the lung volume receiving ≥25 Gy could reduce pulmonary toxicity. © 2008 Elsevier Inc.

INTRODUCTION

Radiation lung injury is a well-known event after radiotherapy (RT) for different tumors in and around the thorax and typically presents with two distinct, subsequent clinical phases: pneumonitis and fibrosis (1, 2). Radiation pneumonitis is due to acute exudation in the alveolar space and migration of inflammatory cells. It occurs 4–12 weeks after RT completion and can be clinically silent, although some patients may experience cough, dyspnea, fever, and chest discomfort. These alterations can regress to complete restitution or evolve into fibrosis when present in a more severe grade. Pulmonary fibrosis is a late injury due to interstitial damage involving the parenchyma and pleura as well. Its severity seems to be related to a number of factors, including the volume of irradiated lung, radiation dose, fractionation, and concomitant use of some chemotherapy regimens (3, 4).

In the conservative treatment of breast cancer, the respiratory apparatus is involved at the level of the parietal and visceral pleurae and the pulmonary subpleural parenchyma of the retromammary region. Although the damage to these structures rarely reaches the clinical threshold and thus is not revealed, it has a potential detrimental effect of reducing the normal functional reserve and should be taken into consideration given the long life expectancy of patients with early-stage breast cancer (5).

A number of published studies, including a preliminary report from our institution, have shown that RT after breast surgery can result in radiologic changes and alterations in pulmonary function in most patients, although asymptomatic, especially when the lymph node areas are included in the treatment volume (4, 6–14). However, most of these studies assessed pulmonary changes only using pulmonary function tests (PFTs), chest X-rays or high-resolution computed topography, Pulmonary function tests.

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tomography (HRCT), often without correlation with the dosimetric data, and mixing patients who had undergone local and locoregional RT.

The present prospective study investigated the radiologic and functional changes using HRCT and PFTs 3 and 9 months after tangential field RT in women who had first undergone conservative surgery for breast cancer and analyzed the possible correlations with the dose–volume parameters.

**METHODS AND MATERIALS**

**Patients**

Between July 2002 and January 2003, 45 consecutive female patients, treated by quadrantectomy or wide tumorectomy for breast cancer, were enrolled after they had provided informed consent. The local research ethic board approved the protocol. The eligibility criteria included proven histologic features of breast cancer, female gender, age 18–70 years, Stage II or less, with fewer than four positive lymph nodes, and baseline normal PFT parameters. The exclusion criteria included Karnofsky performance status <90, a history of chronic respiratory disease, the presence of respiratory symptoms for >2 weeks within the previous 12 months, the need for RT to regional lymph nodes, and previous or concomitant malignancies. Chemotherapy and hormonal therapy with tamoxifen (associated with luteinizing hormone-releasing hormone analogue in 2 patients) were given sequentially and concomitantly with RT, respectively.

All patients underwent lung HRCT and PFTs before and 3 and 9 months after RT completion to assess the baseline status and the early and late changes. Pulmonary symptoms were measured using a specific questionnaire, following the Common Terminology Criteria for Adverse Events, version 3.0 (15).

**Radiotherapy**

All patients underwent postoperative RT planned using the three-dimensional treatment planning system, Pinnacle (Philips, Eindhoven, The Netherlands). CT images were obtained by helical CT (Prospeed, General Electric Medical Systems, Milwaukee, WI), covering the entire thoracic region from the apex of the lung to the diaphragm, with the patient in the treatment position. The target and nontarget volumes were outlined according to the criteria of the International Commission of Radiation Units and Measurements Reports 50 and 62 (16, 17). The clinical target volume consisted of the breast parenchyma. The planning target volume was obtained by adding an 8-mm margin to the clinical target volume, taking into account the variations in size, shape, and position during treatment. Each lung was automatically outlined from the apex to the base. The lung border was defined as the points at which the CT number of pixels crossed approximately −600 Hounsfield units. These automatic contours were reviewed by a radiation oncologist expert in breast treatment. The treatment technique consisted of two opposed wedged tangential 6-MV photon beams. The angle of the beams was adjusted to minimize irradiation of lung parenchyma. The total dose prescribed to the International Commission of Radiation Units and Measurements point was 50 Gy, delivered with 2 Gy/fraction, 5 d/wk. A boost dose of 10 Gy in five fractions was given using a 6–9-MeV electron field, depending on the location of the original tumor site in all but 3 patients diagnosed with ductal carcinoma in situ. Dose calculation with a grid of 3 mm was performed using a collapsed cone convolution algorithm, including the correction for tissue heterogeneity. For each patient, dose–volume histograms (DVHs) for the target, lung, and left ventricle for left-sided cancers, were calculated. The 25-Gy isodose encompassing the lung volume receiving >50% of the prescribed dose was chosen to correlate the grade of pulmonary fibrosis and the PFT changes with the radiation dose.

**High-resolution CT**

High-resolution CT of the lungs was performed using NX/I equipment (General Electric Medical Systems). The acquisition protocol of images was as follows: 1 mm thickness and 10 mm interval from the apex to the base of the lung with the patient in the supine position with both arms stretched out beyond the head in full inspiration. The images were reconstructed with a high-spatial frequency algorithm (i.e., an algorithm that reduces image smoothing and increases spatial resolution) and displayed at the lung window setting (width/level 1,800/-600 Hounsfield units). The whole lung was carefully analyzed by a radiologist with specific expertise, who was unaware of the PFT results, to identify radiation-induced changes, in particular in the subpleuric parenchyma adjacent the irradiated breast. The lung alterations were scored according to the scoring system of Nishioka et al. (18): Grade 0, no significant changes in the radiation fields; Grade 1, only pleural thickening in the radiation fields; Grade 2, pulmonary changes (plaque-like or heterogeneous density) in <50% area of radiation fields; and Grade 3, pulmonary changes in >50% area of radiation fields. The HRCT scan before RT was used as a reference study to assess and score the radiation-induced changes 3 and 9 months after RT. The HRCT images obtained 3 and 9 months after RT were matched and fused with the treatment plan images to correlate the pulmonary changes with the isodose curves using a dedicated software program (Syntegra, Philips) (Fig. 1). The image fusion was performed by an interactive method with three-dimension rigid body transformation, and the accuracy of the procedure was verified by the correspondence of the anatomic bony and soft-tissue structures.

**Pulmonary function tests**

The measurement of dynamic and static lung volumes was done using plethysmography at a constant volume with Masterlab equipment (Jaeger, Würzburg, Germany). The following parameters were assessed: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), total lung capacity (TLC), maximal expiratory flow at 50% (MEF 50) and 25% (MEF 25) of the vital capacity, and the diffusing capacity of carbon monoxide (DLCO). The FVC is a measure of lung volume, the FEV₁ reflects the mechanical properties of large and medium-size airways, the TLC is a sum of the respiratory volumes, the MEF 50 and the MEF 25 measure the average rate of airflow in the bronchioles, and the DLCO represents the diffusing capacity through the alveolar–capillary barrier. All these parameters are reduced in the case of pulmonary fibrosis. All measurements are expressed as a percentage of the predicted values adjusted for age, gender, and height.

**Statistical analysis**

Analysis of variance was performed to identify the relation between the lung fibrosis grade and the volume of irradiated lung receiving a dose of ≥25 Gy using the data derived from the DVHs. Analysis of variance for repeated measurements was used to assess the differences in PFT values at different times. It was also used to identify a possible relation between age (two classes according to a median value: >58 years vs. ≤58 years), smoking history (current and exsmokers vs. nonsmokers), chemotherapy (yes vs. no), hormonal therapy (yes vs. no), and the irradiated lung volume with the PFT values at different times. All statistical analyses involving the measurements of irradiated lung volume (to a dose ≥25 Gy)
were performed twice, using either the absolute value of the irradiated volume or the percentage of the total volume. The significance between the pairs of measurement results before and 3 and 9 months after RT was also calculated. \( p \) Values were considered statistically significant when \(<0.05\). Statistical Analysis Systems software, version 8.02 (SAS Institute, Cary, NC), was used to perform all statistical analyses.

**RESULTS**

The main patient and treatment characteristics are reported in Table 1. Of the 45 patients screened, 4 (8.9%) refused HRCT and PFT after RT and were excluded from the post-RT analysis. At the end of RT, 2 (4.9%) of 41 patients had developed Grade 1 (Common Terminology Criteria for Adverse Events, version 3.0) respiratory symptoms consisting of cough and mild fever that persisted at 3 months and required treatment with steroids and antibiotics. Their symptoms had resolved 6 months after RT completion. The remaining 39 patients (95.1%) were completely asymptomatic during and after RT and throughout the follow-up period.

**High-resolution CT**

The degree of lung changes within the irradiated volume assessed by HRCT 3 and 9 months after RT is shown in Table 2. All patients scored Grade 0 at the baseline HRCT scan before RT. Of the 41 patients, 32 (78.0%) had pulmonary changes between the baseline measurements and 3 months after RT and 14 (34.0%) between the measurements at 3 and 9 months after RT. Three cases (7.3%) classified at 3 months as Grade 0 had changed to Grade 1 after 9 months, and three (7.3%) had changed from Grade 1 at 3 months to Grade 0 at 9 months. Of 10 patients with Grade 2 at 3 months, 5 had recovered partially and were classified as having Grade 1 alterations at 9 months. Of the 41 patients, 3 (7.3%) were classified as having Grade 3 at 3 months, with a ground glass appearance and parenchymal opacities related to alveolar filling on an air bronchogram inside the irradiated volume (Fig. 2). Two of these patients developed symptoms of pneumonitis after RT completion. The lung injury had partially recovered in all 3 patients and was scored as Grade 2 at 9 months after RT completion.

The volume of lung tissue encompassed by the 25-Gy isodose curve (representing 50% of the prescribed dose) was chosen as a threshold to study the relation between lung fibrosis, rated according to Nishioka et al. (18), and the radiation dose to the lung. The mean lung volume treated to a dose of \( \geq 25 \) Gy was 98.5 cm\(^3\) (range, 13.0–219.4 cm\(^3\)). The mean proportion was 7.5% (range, 2.0–16.8%). We observed a statistically significant difference in the mean volumes of the irradiated lung in the four groups as defined according to the Nishioka score (19). The difference was statistically significant using either the absolute lung volume (at 3 months, 67.8 cm\(^3\) for Grade 0, 86.0 cm\(^3\) for Grade 1, 131.9 cm\(^3\) for Grade 2, and 157.6 cm\(^3\) for Grade 3; and at 9 months, 70.4 cm\(^3\) for Grade 0, 92.6 cm\(^3\) for Grade 1, and 147.5 cm\(^3\) for Grade 2; \( p < 0.01 \)) or the proportion of the total lung volume (at 3 months, 0.05 for Grade 0, 0.07 for Grade 1, 0.10 for Grade 2, and 0.10 for Grade 3; and at 9 months, 0.05 for Grade 0, 0.07 for Grade 1, and 0.11 for Grade 2; \( p < 0.001 \); Table 3). A greater irradiated lung volume was observed for patients with greater grades (Fig. 3). No patient receiving a dose of \( \geq 25 \) Gy to a volume <100 cm\(^3\) developed changes greater than Grade 1 at 9 months. On pairwise analysis, the mean values of lung volume treated to a dose of \( \geq 25 \) Gy were significantly different 3 months after RT between those with Grade 2 and those with Grade 0 (\( p = 0.01 \) for volume in cubic centimeters and \( p = 0.0007 \) for volume in percentages) and Grade 3 vs. Grade 0 (\( p = 0.02 \) for volume in cubic centimeters and \( p = 0.02 \) for volume in percentages). The mean values of the lung volume treated to a dose of \( \geq 25 \) Gy were also significantly different 3 months after RT between those with Grade 2 vs. Grade 0 (\( p = 0.002 \), volume in cubic centimeters; and \( p = 0.0005 \), volume in percentages) and between Grade 2 vs. Grade 1 (\( p = 0.01 \), volume in cubic centimeters; and \( p = 0.0069 \), volume in percentages) 9 months after RT.

**Pulmonary function tests**

The results of the PFTs 3 and 9 months after RT are summarized in Table 4. The differences among the three periods
were all statistically significant. Compared with the baseline measurements, all PFT parameters showed a significant decrease at 3 months and none showed a return to baseline at 9 months. The most significant changes (p < 0.0001) were observed for MEF 25 (baseline, 104.4; 3 months, 65.4; and 9 months, 66.9), MEF 50 (baseline, 93.8; 3 months, 83.2; and 9 months, 84.6), and DLCO (baseline, 114.3; 3 months, 100.0; and 9 months, 100.2). All these measurements are expressed as a percentage of the predicted values, adjusted for age, gender, and height.

The PFT values at 3 and 9 months did not correlate significantly with the irradiated lung volume, in particular, that encompassed by the 25-Gy isodose. The role of other covariates was also assessed. The values of MEF 25 and MEF 50 were significantly different in the group receiving chemotherapy compared with the group who did not. The mean value of MEF 25 was 63.0 (standard error [SE], 2.3) in the chemotherapy group and 82.0 (SE, 2.5) in the nonchemotherapy group (F = 6.6; p = 0.01). The mean value of MEF 50 was 79.0 (SE, 1.3) in the chemotherapy group and 96.6 (SE 1.4) in the nonchemotherapy group (F = 7.2; p = 0.01). The interaction between chemotherapy and the time of measurement was not statistically significant. Hormonal therapy did not show an association with the PFT values. The study included only 6 smokers and 3 exsmokers. Among the PFTs, a difference was observed for MEF 25 and DLCO, but these did not reach statistical significance. The PFT values at 3 and 9 months did not differ significantly according to age class.

**DISCUSSION**

Lung changes following RT after conservative surgery for breast cancer have been described in a number of studies (3, 6, 7, 12, 14, 19–22), but only few series have prospectively analyzed the radiologic and functional modifications using HRCT and PFTs in relation to the dosimetric data from the treatment plans (8, 11, 14). Radiation-induced changes have been assessed in most studies using plain chest radiography or CT with a conventional technique, both are less sensitive and detailed than HRCT (23). Pulmonary function was typically assessed by analyzing the main dynamic and static vital respiratory parameters, as we did in the present study, determining the presence of restrictive (FVC, FEV1, TLC) and/or obstructive (FEV1, FVC/FEV1) deficits and the decrease in the diffusing capacity due to alveolar–capillary barrier impairment (DLCO).

Because the large majority of patients are asymptomatic, the clinical significance of HRCT and PFT changes is represented by a reduction in the pulmonary functional reserve that could become relevant only in the case of increased respiratory workload.

In our study, 4.9% of patients developed Grade 1 symptoms of pneumonitis that resolved after medical treatment. In previously published studies, the onset of radiation-induced symptoms during or after postoperative RT for breast cancer was a relatively variable event, accounting for <1–23%, mainly depending on whether the irradiated volume included the regional lymph nodes (3, 14).
We scored the radiologic changes using the classification of Nishioka et al. (18), a scoring system that takes into account the alterations detectable by HRCT. In contrast, the classification proposed by Arriagada et al. (24) is typically used for describing changes detectable by chest X-ray. Pulmonary changes were detected in the irradiated volume by HRCT at 3 months after RT in 78% of our patients, reaching Grade 3 in 7% of cases. Localized pulmonary fibrosis at 9 months was found by HRCT in 78% of patients, with a 24% rate of improvement and 7% rate of worsening between 3 and 9 months. A quite similar incidence of lung changes was reported by other investigators using HRCT. Nishioka et al. (18) reported a 90% incidence of radiation-induced pneumonitis after 1 year at HRCT in a series of 52 patients. Localized pulmonary fibrosis at 9 months was found by HRCT in 78% of patients, with a 24% rate of improvement and 7% rate of worsening between 3 and 9 months. A recent prospective study by Jarvenpaa et al. (14) reported an incidence of lung changes in 51% of 202 patients on plain radiography and 87% on HRCT, performed in 15 patients at 6 months after RT.

The results of our study showed a significant reduction of all PFT parameters at 3 months, with only partial recovery at 9 months, with different trends for the different parameters. The early changes of FVC, FEV1, and TLC might reflect a partially reversible acute exudative process in the alveolar spaces, and the partial recovery at 9 months might be related to the compensatory effect of residual areas of normal lung reserve. The substantially irreversible reduction of DLCO was most likely the result of interstitial damage due to inflammatory infiltrates in the early phase and collagen deposition in the later phase. The decrease of MEF 25 and MEF 50, which have never been evaluated in other studies, might represent damage to bronchioles related to the inflammatory infiltration in the early phase and fibrosis with loss of elasticity in the later phase. Some investigators reported on the onset of “bronchiolitis obliterans organizing pneumonia” after RT for breast cancer with patchy alveolar infiltrates on air bronchograms, which are an expression of damage to the smallest airway ramifications (25). In addition to MEF 25 and MEF 50, similar modifications of PFTs have been reported by other investigators, who have described significant changes in FVC, FEV1, and DLCO a few months after RT. However, data have shown some differences between patients who received RT only to the breast and those treated to the breast and regional lymph nodes. In a study of 144 women with Stage II breast cancer who had undergone either locoregional or local RT, a statistically significant reduction (3–5%) in

<table>
<thead>
<tr>
<th>Grade</th>
<th>3-mo Assessment</th>
<th>9-mo Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung volume*</td>
<td>Proportion of lung volume</td>
</tr>
<tr>
<td>0</td>
<td>67.8 (39.2)</td>
<td>0.05 (0.02)</td>
</tr>
<tr>
<td>1</td>
<td>86.0 (44.8)</td>
<td>0.07 (0.03)</td>
</tr>
<tr>
<td>2</td>
<td>131.9 (38.7)</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>3</td>
<td>157.6 (50.5)</td>
<td>0.10 (0.01)</td>
</tr>
</tbody>
</table>

Data in parentheses are standard deviations.

* Lung volume is reported in cubic centimeters.
DLCO, FEV1, and FVC was observed in those patients who had undergone locoregional and not local RT (6). In the group who underwent local RT, a reversible reduction of PFT values, ranging from 3% to 22%, was reported 3–4 months after RT completion (6). In a subsequent study of 613 women with breast cancer, Lind et al. (19) observed an increase in lung toxicity in those patients also irradiated to the internal mammary nodes. In recent prospective studies in which irradiation of the regional lymph nodes was performed, an irreversible and even progressive decrease of PFT parameters was described (7, 8, 11). All the patients in our series were treated to the breast only and consequently to a smaller lung volume, this could explain the partial recovery of some PFT parameters.

To study a possible treatment-related factor affecting lung toxicity, we analyzed the correlation between HRCT changes and dosimetric data. The results showed a correlation between the degree of lung changes at 3 and 9 months and the volume included in the 25-Gy isodose. In particular, all patients presenting with Grade 2 pulmonary fibrosis at 9 months had had a mean irradiated pulmonary volume to \( \geq 25 \) Gy of 150 cm\(^3\) but no patient with an irradiated volume <100 cm\(^3\) developed Grade 2 changes. In published data, various thresholds have been reported by different investigators. Marks et al. (20) reported on the use of the volume receiving \( \geq 30 \) Gy considered “whole lung tolerance.” Jaen et al. (11) found a statistically significant correlation between the alteration of lung perfusion at 3 years and the volume receiving a dose between 10 and 20 Gy but not \( > 20 \) Gy. Jarvenpaa et al. (14) observed the onset of pulmonary symptoms in patients with less-favorable dose–volume correlations. In contrast, Hernberg et al. (8) reported the DVH data but did not describe any correlation between dose–volume parameters and a reduction in lung function or CT changes. We chose the 25-Gy isodose because this value was in the range of the other data findings and corresponds to the 50% of the prescribed dose and represents the volume included in the lateral edge of the beams. The relative volume receiving a dose \( \geq 25 \) Gy was calculated on the DVHs of the ipsilateral lung, just as in other data series that focused on the correlation of the radiation dose with post-RT radiologic changes (22). In

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Fig. 3. Lung volume receiving >25 Gy by grade of fibrosis according to Nishioka et al. (19) at (a) 3 and (b) 9 months. \( p \) Values refer to pairwise comparison between different grades of fibrosis.

Table 4. Variations in pulmonary function tests

<table>
<thead>
<tr>
<th>RT</th>
<th>Before</th>
<th>At 3 mo after</th>
<th>At 9 mo after</th>
<th>Global test*</th>
<th>Before vs. 3 mo after</th>
<th>3 mo vs. 9 mo after</th>
<th>Before vs. 9 mo after</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>104.4 (16.5)</td>
<td>100.1 (13.9)</td>
<td>101.4 (12.3)</td>
<td>F = 7.5</td>
<td>( p = 0.001 )</td>
<td>( p = 0.23 )</td>
<td>( p = 0.03 )</td>
</tr>
<tr>
<td>FEV1</td>
<td>105.9 (15.7)</td>
<td>102.5 (16.1)</td>
<td>103.9 (14.6)</td>
<td>F = 7.4</td>
<td>( p = 0.001 )</td>
<td>( p = 0.06 )</td>
<td>( p = 0.05 )</td>
</tr>
<tr>
<td>MEF 25</td>
<td>83.1 (30.4)</td>
<td>65.4 (32.5)</td>
<td>66.9 (25.0)</td>
<td>F = 0.0012</td>
<td>( p = 0.0007 )</td>
<td>( p = 0.67 )</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>MEF 50</td>
<td>93.8 (24.8)</td>
<td>83.2 (25.2)</td>
<td>84.6 (22.5)</td>
<td>F = 10.9</td>
<td>( p &lt; 0.0001 )</td>
<td>( p = 0.3 )</td>
<td>( p = 12.9 )</td>
</tr>
<tr>
<td>DLCO</td>
<td>114.3 (19.2)</td>
<td>100.0 (13.0)</td>
<td>100.2 (15.4)</td>
<td>F = 0.001</td>
<td>( p = 0.0001 )</td>
<td>( p = 0.60 )</td>
<td>( p = 0.0009 )</td>
</tr>
<tr>
<td>TLC</td>
<td>106.7 (14.6)</td>
<td>100.7 (18.6)</td>
<td>102.4 (10.8)</td>
<td>F = 3.6</td>
<td>( p = 0.03 )</td>
<td>( p = 0.49 )</td>
<td>( p = 0.007 )</td>
</tr>
</tbody>
</table>

* Analysis of variance for repeated measurements.
contrast, no correlation was found between the PFT values and irradiated lung volume to a dose ≥ 25 Gy. Such a finding might have been due to the relatively small variations in the irradiated lung volume related to the use of only two tangential fields in all cases. Other investigators (11, 13) found a correlation between the dose–volume parameters and PFT changes for early, but not for late, measurements analyzing series treated by local and locoregional RT and consequently with larger variations of the irradiated lung volume.

Among the other possible risk factors for developing radiation lung injury for breast cancer treatment, data about age, smoking, and administration of chemotherapy and hormonal therapy have been reported (6–8, 19, 26–29). None of these factors was statistically significant in our series when considering the HRCT changes. We observed the expected differences in the pulmonary function tests with respect to smoking, but the sample size was not large enough to detect them as statistically significant. Of the 45 patients in the study population, only 9 were smokers or exsmokers. As expected, the difference was observed for MEF 25, a very sensitive test for early damage to the bronchioles. In respect to age, the PFTs are expressed as the percentages of the expected values for a person of the same age, gender, and height; therefore, an age effect could not be considered in this analysis. An association was observed between chemotherapy and MEF 25 and MEF 50, but chemotheraphy did not modify the relation of the PFTs with time after treatment. Also, hormonal therapy was not significant; however, it should be highlighted that it was administered to a relatively low percentage of patients (36.6%).

**CONCLUSION**

Our results have shown that local RT for breast cancer by two tangential fields can lead to radiologic evidence of radiation lung injury and a significant reduction in lung function parameters at 3 months, with only a partial recovery at 9 months. The most evident damage is directed to the alveolar–capillary barrier and the smallest airway ramifications. This study has confirmed that HRCT and PFTs are sensitive and robust tests and should be recommended to detect radiation-induced pulmonary alteration. The radiologic changes correlated significantly with the dose–volume parameters, showing that a reduction of pulmonary toxicity could be achieved by minimizing, possibly to <100 cm³, the lung volume receiving a dose ≥ 25 Gy.

**REFERENCES**


