Scintigraphic, Spirometric, and Roentgenologic Effects of Radiotherapy on Normal Lung Tissue*

Short-term Observations in 14 Consecutive Patients with Breast Cancer

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The effects of radiotherapy on lung function, ventilation/perfusion scans, and chest radiography were studied prospectively in 15 patients who underwent either modified radical mastectomy or tumorectomy, followed by radiotherapy for breast cancer. In all patients, pulmonary function studies, chest x-ray films, and lung scintigraphic studies were performed prior to and at the end of radiotherapy as well as three months later. No consistent or significant alteration in either parameter was detected. No patient developed clinical symptoms suggestive of radiation-induced lung changes, although in one of them, major radiologic features were found that were consistent with radiation pneumonitis; those changes disappeared completely in the course of the subsequent months. It is concluded that the tangential beam technique for postoperative irradiation as used in these patients is largely safe as regards pulmonary function, perfusion, and ventilation. (Chest 1990; 97:97-102)

For certain types of breast cancer situations, radiotherapy (RT) is an accepted postoperative treatment modality. More and more patients are likely to undergo irradiation with substantial doses to their chest wall since the rising acceptance of tumorectomy as a conservative surgical technique; concurrently, concern has been growing about the potential risk of RT in these patients. It is well known that the lung is one of the more sensitive organs to irradiation. Studies addressing this problem have been performed mainly in animals and after single doses but also in patients with malignant neoplasms of the thoracic cavity. However, most of the studies dealing with humans have been retrospective in nature, although a few well-controlled prospective observations on the occurrence of radiation pneumonitis in patients with mammary cancer have been published.

The purpose of this study was to evaluate prospectively the changes in pulmonary function, regional perfusion and ventilation, and chest x-ray films after irradiation of the thoracic wall and regional lymph node sites in patients with breast cancer in view of the possibility of applying some form of preventive treatment. These findings were correlated with the irradiated lung volume and in this respect, to the best of our knowledge, this study is the first one to be reported. Since in the past we have, although exceptionally, seen cases of radiation pneumonitis, we were concerned about the risk that an unacceptable burden might, in some patients, be imposed to the lung with our present RT technique. In this technique we systematically include the internal mammary chain in the tangential field treatment volume, so that a larger lung volume is included than if these lymph nodes are left out. In obese women, the tangential field technique is inapplicable, since too large a lung volume would be included and in these cases a direct beam technique of the internal mammary chain is usually preferred. Routine follow-up chest roentgenograms usually do not show any alteration. Furthermore the symptoms associated with radiation pneumonitis are nonspecific and mostly have little or no correlation either with radiographic damage or with the results of pulmonary function tests at least where only small lung volumes are involved. This study is not concerned with the question whether and to what extent postoperative RT in these patients produced any regional lung fibrosis: it is well known that doses in excess of 2000 to 4000 rad will lead to lung fibrosis. Rather, our purpose was to detect early significant pulmonary changes, if any, at an earlier moment and with more sensitive methods.

At the histopathologic level, there is still considerable controversy about the primary site of damage that

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may involve either the capillary endothelial cells or the alveolar epithelial type 2 cells. However, whichever the site or biochemical substrate, most investigators agree that these changes occur at an early stage and, if extending over a sufficiently large volume, should reflect in functional and radiologic changes.2

Patients and Methods

Study Design and Treatment Technique

Informed consent was obtained from 15 consecutive female patients with breast cancer to participate in this prospective series to study the effects of postoperative RT on pulmonary function. None of the patients had a history of lung disease. Their mean age was 51 years (range, 40 to 75 years). One patient did not attend the third and last evaluation for personal reasons. She has been followed up until 21 months after RT and did not show any pulmonary complaints or chest roentgenogram changes. Her spirometry and pulmonary scintigraphy data immediately after RT were completely normal. She has, nevertheless, been excluded from our analysis, leaving 14 cases in study. Among these 14, ten patients were referred for irradiation after modified radical mastectomy, four were referred after tumorectomy. Irradiation was delivered by a linear accelerator (8 MV Philips SL75) at FSD of 100 cm. Patients were treated each day with opposing wedged tangential breast fields, encompassing the ipsilateral internal mammary nodes and thoracic wall. An anterior field covered the supraclavicular fossa together with the upper section of the internal mammary chain and, in N+ patients, the axilla was treated with opposed anterior and posterior fields. Care was taken to adequately include the ipsilateral internal mammary chain in the irradiated volume, and individual treatment plans were obtained in every single case (Fig 1), using computed tomographic (CT) scans at the level of the field center and assuming a uniform lung density of 0.33. The dose aimed at was 4500 rad in 180-rad fractions, five days a week, followed by an additional boost of 2000 rad to the remaining breast tissue in patients who had undergone tumorectomy. Since the end of the study, two patients have developed bone metastases and a third has died of carcinomatous meningitis. The 11 other patients are without evidence of disease.

Estimation of Irradiated Lung Volume

Irradiated lung volumes were calculated individually, based on a CT scan through the tangential field center. Using a planimeter, the volume, encompassed externally by the inner aspect of the thoracic wall and internally by the edge of the tangential beam, was estimated. The volume irradiated by the supraclavicular field was omitted in our calculations.

Pulmonary Function Tests

These included resting measures of total lung capacity (TLC) and all of its subdivisions, the various flow rates resulting from forced expiratory flow curves, maximum voluntary ventilation (MVV), and steady state diffusing capacity (Table 1).2

Capillary blood gas determinations were obtained in all patients. Pulmonary function test data were described as percentages of predicted values, based on individual weight, height, and body surface area. Spirometry was performed on an expirograph (Godart). Inspiratory vital capacity and forced expiratory volume in 1 s ( FEV1) were measured three times and the best result was used.6 Total lung capacity and residual volume (RV) were measured by means of the helium dilution method and the carbon monoxide diffusion capacity (Dco) by means of a single breath method.

Regional Lung Function

Each patient had a baseline ventilation-perfusion study to establish normality. Patients had a 99mTc-perfusion study and a 81Kr ventilation study in four positions (posterior, anterior, right profile, and left profile), using a large-field-of-view scintillation gamma camera (Toshiba) and a medium energy collimator with an effective field of view of 350 mm, 9,500 holes, and an energy range up to 300 keV.

Table 1—Lung Function Parameters

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>1st Before RT</th>
<th>2nd After RT</th>
<th>3rd 3 mo after RT</th>
<th>χ²</th>
<th>1st-2nd</th>
<th>2nd-3rd</th>
<th>1st-3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRC</td>
<td>105.93</td>
<td>107.00</td>
<td>100.00</td>
<td>2.714</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>MVV</td>
<td>63.57</td>
<td>63.36</td>
<td>64.96</td>
<td>0.428</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1</td>
<td>98.36</td>
<td>97.64</td>
<td>92.64</td>
<td>10.857</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>102.50</td>
<td>104.86</td>
<td>100.79</td>
<td>1.750</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TGV</td>
<td>99.57</td>
<td>96.29</td>
<td>90.00</td>
<td>13.285</td>
<td>NS</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TLC</td>
<td>97.36</td>
<td>98.07</td>
<td>94.93</td>
<td>1.107</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RV</td>
<td>108.64</td>
<td>113.14</td>
<td>104.29</td>
<td>1.321</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VC</td>
<td>91.71</td>
<td>91.50</td>
<td>90.43</td>
<td>4.000</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>102.43</td>
<td>102.29</td>
<td>98.71</td>
<td>12.000</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dco</td>
<td>103.46</td>
<td>97.38</td>
<td>92.54</td>
<td>8.115</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Kco</td>
<td>79.08</td>
<td>76.38</td>
<td>77.38</td>
<td>1.846</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Abbreviations are explained under "Patients and Methods" (pulmonary function tests).
†NS indicates not significant.
keV. Its overall sensitivity was 230 cpm/μCi.

The perfusion scans were performed using intravenously injected microspheres of albumin labeled with technetium-99m in a dose of 3 mCi. Three regions of interest (ROIs) were inscribed over each lung on both the anterior and posterior images and six ROIs were inscribed on each lateral lung image (Fig 2). The activity in each ROI during each subsequent examination was determined and compared with the values before RT.

For the ventilation scans, 133-krypton was eluted off the rubidium generator by oxygen and flowing directly to the patient, usually at a rate of 0.3 L/min. Patients breathed at their own pace through a mouth-nose mask open to room air, connected by the oxygen line to the generator. Depending on the generator’s strength, its elution efficiency and the lung ventilation of the patient 150,000 to 300,000 counts were collected in each view.29

Chest X-ray Films

Anteroposterior and profile roentgenograms of the chest were taken at the time that the total lung function tests were performed. All roentgenograms were evaluated independently by two observers (J.T. and J.B.).

Clinical Evaluations

Patients were questioned and examined weekly during radiotherapy sessions concerning evidence of related symptoms. They were also examined three months after radiotherapy and at two-monthly intervals thereafter.

Statistical Methods

To compare results of the pulmonary function tests and the scintigraphy data at the time before, immediately after, and three months after radiotherapy we used the Wilcoxon signed rank test for paired data in the SPSS statistical package.29

Time Schedule of Assessment

All tests described were performed on all patients several weeks after mastectomy or tumorectomy scars had healed and incisional pain was no longer present11 and before RT was started. They were repeated shortly after RT and, again, three months later.

RESULTS

Irradiated Lung Volumes

Lung volumes covered by the tangential breast or chest wall fields (Fig 1) were estimated to fall between 185 and 522 ml (mean, 391 ml), corresponding to 18 to 38 percent (mean, 30 percent) of the entire lung (Table 2).

Pulmonary Function

Analysis of covariance testing of the changes in pulmonary function parameters with time showed a moderate decrease of the FEV1, FEV1/VC, steady state diffusion capacity (Dco), and thoracic gas volume (TGV) (Table 1). No changes were noted in vital capacity, RV, TLC, RV/TL, MVV, and transfer fraction (Kco). The figures recorded that a small loss in functional lung parenchyma occurs as a result of this treatment. This suggestion is deduced from the small but significant decrease in TGV and Dco. The observation that the Kco does not change is an argument in favor of the absence of any specific alteration of the lung interstitium. In general, there was little change in lung function parameters as one would expect from the small volume of radiation-exposed tissue.22

Lung Scintigraphy

Analysis of the consecutive perfusion and ventilation

Table 2—Tangentially Irradiated Lung Volumes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Volume Estimate, ml</th>
<th>Irradiated Volume in % of Total Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>491</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>413</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>393</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>522</td>
<td>38</td>
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<td>5</td>
<td>399</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>185</td>
<td>19</td>
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<tr>
<td>8</td>
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<td>32</td>
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<td>9</td>
<td>343</td>
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<tr>
<td>10</td>
<td>426</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>354</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>194</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>453</td>
<td>31</td>
</tr>
<tr>
<td>14</td>
<td>396</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>391</td>
<td>30</td>
</tr>
</tbody>
</table>
scintigrams did not show any significant alteration in either ROI. More particularly, the upper region on the anterior and posterior scans and the anterior region on the profile images were scrutinized in detail and no significant perfusion or ventilation defect could be detected. As previously mentioned, even the one patient with radiographic signs of radiation pneumonitis did not develop any associated scintigraphic changes.

**Chest X-ray Films**

No changes were observed in ten patients. Minor changes within the radiation field were observed in two patients, and bilateral minor changes were found in one. These consisted of a discrete haze in the basal region of the irradiated lung. The irradiated apex showed no changes. Unequivocal signs of radiation pneumonitis were observed in one patient, who was otherwise symptomfree; they consisted of a diffuse haze over the left upper lobe that was present on the anterior and profile x-ray films (Fig 3). These findings disappeared after six months and were totally absent one year after radiotherapy. All the while, results of her function tests remained normal.

**Clinical Evaluation**

No patient developed signs or symptoms such as cough, shortness of breath, or fever. As mentioned, the one patient who developed radiologic signs of pneumonitis remained subjectively well and without symptoms.

**DISCUSSION**

In this limited series of patients with irradiated breast cancer, the study of functional and imaging parameters did not detect any consistent or symptomatic impairment of the lung, at least in the short term. Roberson et al have shown that for two among the most commonly employed breast irradiation techniques, the standard tangents or the en face internal mammary field, the integral dose to lung is comparable. Although our patients were treated using a “deep tangential” technique, where the internal mammary chain is irradiated en bloc to 4,500 rad and, as a rule, a higher lung volume is being irradiated than with more standard tangential fields, any deleterious effects on pulmonary function, ventilation, or perfusion were not detected.

It is only fair to say that this technique cannot be used in all patients and that—especially in obese women—we apply an en face field technique for adequate coverage of the internal mammary. However, no such patient was included in this series.

As Groth et al have pointed out, the McWhirter technique where the tangential field for the internal mammary chain was used appeared to be safer than a direct anterior field as judged by pulmonary function and ventilation-perfusion scans. In their study, patients were examined three months after postoperative RT and changes in pulmonary function as well as ventilation and perfusion scintigraphy could be found only in those who had been treated by means of a medial chest wall field. This was in contrast with those whose chest wall, lymphatic channels, and regional lymph nodes had been irradiated tangentially. Although we used smaller ROIs than did Groth et al, our findings were similar in that we could not detect any significant alterations in either regional perfusion or ventilation.

In the patients of Alth and Ogris, the thoracic wall was treated with 15 MeV electrons and the internal mammary chain was treated with a 50° rotation technique. Although no changes in pulmonary func-
tion or chest x-ray films were noted, they found a permanent decrease in regional lung perfusion from 1,500 rad upwards, but with a fractionation of 300 rad three times a week.

We conclude that the treatment method, such as described and with the doses and fractionation such as they were applied, appears safe and reliable as regards the lung, at least, on a short-term basis.

As to the single patient who developed an asymptomatic radiation pneumonitis, the most likely explanation would be the estimated size of the irradiated lung volume which, in her case, was the largest of all 14 patients investigated: 522 ml or 38 percent of the total lung. In this connection it might be added that in our population of patients with irradiated breast cancer, this complication is quite infrequent, occurring in well below 5 percent of all treated women. In this particular patient, we failed to demonstrate pulmonary function test or scintigraphic abnormalities that could have been caused by radiation damage and the development of roentgenographic abnormalities could not have been predicted by these tests. Therefore, we do not believe that sequential pulmonary spirometry or ventilation-perfusion scintigraphy are indicated if the possibility or probability of radiation pneumonitis is contemplated.

Careful clinical follow-up, focused on early detection of relevant symptoms and signs, would appear the most reliable measure for the early detection of radiation pneumonitis and subsequent fibrosis. According to Rothwell et al., development of symptoms in the acute phase implies the possibility of permanent damage.

Our findings are in full agreement with previously published reports and we believe that, with adequate fractionation, the inclusion of a small proportion of lung in the irradiated volume is acceptable. However, and in as far as these observations can be generalized, one should strive to keep this volume below the level of one-third of the total lung.

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Magnetic Resonance Imaging

The Department of Radiology, University of California San Diego School of Medicine will present this course March 6-9 at the Hotel del Coronado, Coronado (San Diego), California. For information, contact Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, Georgia 30077-1925 (404):641-9773.