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**CLINICAL INVESTIGATION** **Breast Cancer**

# CHANGES IN PULMONARY FUNCTION UP TO 10 YEARS AFTER LOCOREGIONAL BREAST IRRADIATION

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**Purpose: To evaluate the long-term impact of locoregional breast radiotherapy (RT) on pulmonary function tests (PFTs).**

**Methods and Materials: This study included 75 women who underwent postoperative locoregional breast RT. PFTs were performed before RT and 3, 6, and 12 months and 8 to 10 years after RT. By use of univariate and multivariate analyses, the impact of treatment- and patient-related factors on late changes in PFTs was evaluated.**

**Results: During the first year after RT, all PFTs significantly worsened at 3 to 6 months after RT ($p < 0.05$). At 12 months, forced vital capacity (FVC), vital capacity (VC), and forced expiratory volume in 1 second ($FEV_1$) recovered almost to baseline values, whereas total lung capacity (TLC) and diffusion capacity of carbon monoxide ($DL_{CO}$) recovered only slightly and were still found to be decreased compared with baseline ($p < 0.05$). At 8 to 10 years after RT, mean reductions in $FEV_1$ of 4% ($p = 0.03$) and in VC, $DL_{CO}$, and TLC of 5%, 9%, and 11% (all $p < 0.0001$), respectively, were observed compared with pre-RT values. On multivariate analysis, tamoxifen use negatively affected TLC at 8 to 10 years after RT ($p = 0.033$), whereas right-sided irradiation was associated with a late reduction in $FEV_1$ ($p = 0.027$). For $FEV_1$ and $DL_{CO}$, an early decrease was predictive for a late decrease ($p = 0.003$ and $p = 0.0009$, respectively).**

**Conclusions: The time course of PFT changes after locoregional RT for breast cancer follows a biphasic pattern. An early reduction in PFTs at 3 to 6 months with a partial recovery at 12 months after RT is followed by a late, more important PFT reduction up to 8 to 10 years after RT. Tamoxifen use may have an impact on this late decline in PFTs.** © 2012 Elsevier Inc.

**Radiotherapy, Breast cancer, Lung toxicity, Pulmonary function tests.**

## INTRODUCTION

The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group showed the need for locoregional radiotherapy (RT) in node-positive breast cancer patients by showing a reduction in the 5-year local recurrence rate from 23% to 6% and in the 15-year risk of breast cancer mortality from 60% to 55% (1). Despite these proven benefits of locoregional RT for breast cancer patients, the appropriate selection of patients and RT volumes remains uncertain. It is clear that the addition of RT fields to encompass the regional lymphatics increases the risk of subacute and late side effects, including predominantly pulmonary and cardiovascular toxicity.

Two types of lung injury are described after RT, according to the time of appearance and physiopathology. Radiation pneumonitis typically occurs 1 to 6 months after completion of RT. If symptomatic, it presents as dry cough, dyspnea, and fever. In a later phase, lung fibrosis may develop. The incidence of symptomatic radiation pneumonitis, requiring corticosteroids, increases from less than 1% after breast-only treatment to 4% to 11% after locoregional RT (2, 3). Even if not symptomatic, a decrease in pulmonary function tests (PFTs) is often observed within the first 3 to 9 months after thoracic RT, which most frequently disappears 12 to 18 months after RT (4–8). Whether pulmonary function parameters fully recover or not largely depends on the amount of lung fibrosis that occurs. Lung fibrosis is known to be a progressive pathologic entity, but to date, little is known about the pulmonary function several years after breast RT. However, long-term follow-up data would be valuable, especially for breast cancer patients because they have a long life expectancy.

The aim of this study is to determine the long-term impact of locoregional breast RT on pulmonary function parameters.

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## METHODS AND MATERIALS

### *Patient and treatment characteristics*

From February 1998 to January 2000, 75 patients with breast cancer were consecutively enrolled in this prospective study at the University Hospital Gasthuisberg, Leuven, Belgium. All patients needed postoperative RT to the internal mammary and medial supraclavicular lymph nodes according to the criteria of European Organisation for Research and Treatment of Cancer (EORTC) Protocol 22922 (medially or centrally located tumors or axillary lymph node invasion) combined with breast or chest wall RT. Exclusion criteria were previous malignancy or serious chronic respiratory disease. The study was approved by the hospital's ethics committee, and all patients provided informed consent. Three patients were excluded from the analysis, one because of poor baseline PFTs and two because they refused to undergo the planned post-RT examinations.

Patient characteristics are summarized in Table 1. Chemotherapy was administered in 35% of patients, either concomitant with RT (25%) or before RT (10%). Concomitant chemotherapy consisted of 6 cycles of cyclophosphamide (600 mg/m$^2$), methotrexate (40 mg/m$^2$), and 5-fluorouracil (600 mg/m$^2$) (CMF). Preoperative chemotherapy consisted of CMF in 4 patients and an anthracycline-based combination in 4 patients. Hormonal therapy (tamoxifen, 20 mg/d) was started in 50% of patients, either concomitant with RT (40%) or after RT (10%). In all patients, RT to the internal mammary and medial supraclavicular lymph nodes was performed by an anterior mixed beam, consistent with the requirements of EORTC Protocol 22922 (9). Tangential photon fields were used to irradiate the breast, and an anterior electron field was used for chest wall irradiation. The latter was prescribed at the dose maximum, and the electron energy was chosen such that the chest wall was covered by the 85% isodose. Dose prescription was 50 Gy in 25 fractions. In case of breast-conserving surgery, an additional dose of 16 Gy was delivered to the tumoral cavity by electrons (92%) or brachytherapy (8%).

Patients underwent PFTs before RT and 3, 6, and 12 months and 8 to 10 years after RT. The examinations at 3 and 6 months were performed in 71 patients (in 1 of 72 patients, the 3-month PFT was not performed, and in another patient, the 6-month PFT was missing).

Table 1. Patient characteristics ($n$ = 72)

| | Data |
|---|---|
| Age [mean (range)] (y) | 53 (32–78) |
| Radiotherapy [$n$ (%)] | |
| Chest wall + IM–MS LN | 24 (33) |
| Breast + IM–MS LN | 48 (67) |
| Adjuvant therapy [$n$ (%)] | |
| Hormonal therapy concomitantly | 29 (40) |
| Hormonal therapy sequentially | 7 (10) |
| Chemotherapy concomitantly | 18 (25) |
| Chemotherapy before radiotherapy | 7 (10) |
| None | 13 (18) |
| Smoking history [$n$ (%)] | |
| Active (baseline) | 14 (19) |
| Ex-smoker (baseline) | 10 (14) |
| Active (10-y follow-up) | 2 (3) |
| Menopausal status [$n$ (%)] | |
| Premenopausal | 33 (46) |
| Postmenopausal | 39 (54) |

*Abbreviation:* IM–MS LN = internal mammary and medial supraclavicular lymph nodes.

At 12 months, 66 patients were evaluable:1 received chemotherapy for tumor relapse and 5 refused further participation. At 8 to 10 years after RT, 48 patients remained evaluable: 11 patients relapsed and 15 were lost to follow-up or refused further particip-ation.

### *Pulmonary function tests*

The measurement of dynamic and static lung volumes was done by spirometry and plethysmography (bodybox; Sensor Medics San Diego, CA, USA), according to American Thoracic Society and European Respiratory Society guidelines (10). Parameters assessed included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), total lung capacity (TLC), and diffusion capacity of carbon monoxide ($DL_{CO}$). The PFT results were expressed as percentage predicted of normal values (*i.e.,* adjusted for age, gender, and height) so that serial studies over time are not confounded by the effects of aging (11). All patients' sequential PFTs were compared with the pre-RT result, and a percentage of the baseline value was calculated. $DL_{CO}$ was corrected for hemoglobin (Hb) level: Corrected $DL_{CO}$ = Measured $DL_{CO} \times (10.22 + Hb)/(1.7 \times Hb)$.

### *Statistical analysis*

A general linear model for repeated measures is used to evaluate the evolution of each PFT parameter. Time is treated as a categorical predictor in the analysis (*i.e.*, no parametric form is assumed for the PFT evolution). An unstructured form is used for the covariance matrix of the five repeated measures (12). Dunnett adjustments for multiple testing are used for the comparisons with baseline. The PFT values have been transformed (natural logarithm) to meet the distributional assumptions of the model. Results are presented after back-transformation to the original scale.

Furthermore, it has been verified whether the evolution over time, and more specifically, the late change in PFT, differs as a function of treatment- and patient-related factors. To this purpose, the aforementioned linear model is extended with the specific factor and its interaction with time as additional predictors. Treatment-related factors included RT side, use of chemotherapy, and use of concomitant tamoxifen. Patient-related factors included baseline smoking status, menopausal status, age, and body mass index. Furthermore, the influence of an early reduced PFT on the late change in PFT was examined. An early reduced PFT was defined as a reduction in PFT at 3 or 6 months larger than the mean reduction at 3 or 6 months. We performed a multivariate analysis taking into account all factors showing a relation at the $p < 0.1$ level in the univariate

Table 2. Baseline PFT values for patients receiving chemotherapy before RT and patients who were not

| PFT | Chemotherapy before RT ($n$ = 7) | No chemotherapy before RT ($n$ = 65) | $p$ Value (Student $t$ test) |
|---|---|---|---|
| VC | 108 ± 10 | 115 ± 16 | 0.31 |
| FVC | 109 ± 10 | 113 ± 15 | 0.51 |
| $FEV_1$ | 104 ± 12 | 105 ± 19 | 0.85 |
| TLC | 113 ± 8 | 111 ± 12 | 0.78 |
| $DL_{CO}$ | 89 ± 24 | 91 ± 16 | 0.82 |

*Abbreviations:* PFT = pulmonary function test; RT = radiotherapy; VC = vital capacity; FVC = forced vital capacity; $FEV_1$ = forced expiratory volume in 1 second; TLC = total lung capacity; $DL_{CO}$ = diffusion capacity of carbon monoxide.

Data are shown as mean ± SD of percent predicted lung function.