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ORIGINAL ARTICLE

Long-term functional and radiological pulmonary changes after radiation therapy for breast cancer

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ABSTRACT

Background. We assessed late functional and radiological pulmonary changes in breast cancer patients after a median of 11 years following radiotherapy (RT).

Material and methods. Seventy women who received adjuvant loco-regional RT for breast cancer during November 1994–May 1998 accepted to participate in this follow-up study. Pulmonary function tests (PFTs) ($n = 56$) were compared to pre-RT examinations and diagnostic computer tomography (CT) of the lungs ($n = 70$) were performed and compared to four months post-RT examinations.

Result. The median-matched vital capacity (VC), forced expiratory volume in one second (FEV1), and total lung capacity (TLC) were reduced 15%, 9%, and 7%, respectively, at the long-term follow-up ($p < 0.001$). We could not, however, detect a correlation between ipsilateral V_{20} and VC-changes. Diffusion capacity (DLCO) appeared to improve compared with the pre-RT baseline level probably due to transient chemotherapy-induced toxicity. The median-matched percentage of the predicted DLCO 11 years after RT was, however, only 86%, indicating a chronic therapy-induced reduction also of this metric. According to the Arriagada classification, ipsilateral V_{20} and long-term CT-changes showed a significant correlation (r_s: 0. 57; $p < 0.001$) in a small subset of the women.

Conclusion. A chronic clinically significant reduction of PFTs compared to pre-RT values and CT-changes four months after RT were still detectable after a median follow-up of 11 years. There was a statistical correlation between V_{20} and abnormalities on CT but no statistical correlation between V_{20} and VC-changes.

Many women are today breast cancer (BC) survivors. Radiotherapy (RT) is an effective method for preventing loco-regional recurrence and BC death [1,2]. However, RT is also known to cause early and late side effects in surrounding tissues, e.g. heart [3] and lung [4]. Incidental RT to the lung parenchyma can cause acute or sub acute pneumonitis typically occurring after 1–6 months. From eight months radiation fibrosis may develop and progress over several years. Long-term survivors may, thus, experience late pulmonary side effects. Presently, relatively few reports on the long-term consequences of BC RT on the respiratory function have been published [5–10]. Some reports indicate that pulmonary changes follow a biphasic pattern, an early reaction with a maximum after six months and thereafter a partial recovery after one year followed by a late progressive worsening after 5–10 years [6,7,9] (Supplementary Table I, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.934967).

The most important factors for development of RT-induced toxicity are dose to and volume of incidentally irradiated lung tissue. A potential influence of several other co-variates has, however, also been evaluated in earlier studies. We have previously reported an association between short-term radiological and clinical pneumonitis and age [11,12]. Other groups have found relations between RT-induced lung toxicity and chemo-

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therapy [13,14] and tamoxifen intake [15]. Smoking has been reported to reduce the risk of RT-induced pneumonitis [16]. Thus, data on the long-term consequences of RT in BC are limited. Few studies have both pre- and post-RT examinations with lung function tests and radiological examination. In this study we aimed to assess long-term pulmonary side effects as changes in pulmonary function tests (PFTs) and radiological changes on chest computer tomography (CT) in irradiated BC patients after a median follow-up of 11 years. The results of the examinations were compared with each patient's pre-RT PFTs and dose planning CT, and radiological abnormalities were classified with the Arriagada method [17].

Material and methods

This is a long-term follow-up of two previous studies [18,19]. The study was approved by the local ethics committee. Participating women gave informed consent before study enrolment.

Study population

We have previously reported on the incidence of short-term symptomatic pneumonitis in 475 patients who were referred to the Radiotherapy Department at Stockholm Söder Hospital 1994–1998 for adjuvant RT following surgery for early BC [12]. CT was performed prior to and four months after RT in 105 of these patients [18], and the pulmonary function was re-examined five months after completion of RT in 144 women [19]. From 2007 to 2008, we contacted 107 of these patients for participation in this follow-up. Seventy women, of the median age 65 years (range 46–83 year), consented to participate and underwent the chest CT examination. Twenty-nine of these women had also undergone a chest CT four months post-RT. Fifty-six women performed the repeated PFTs (Table II). One of the non-consenting patients had a hip fracture and was therefore not able to participate. Ten women reported a good physic and chose to abstain from participating, and the rest of the non-participating women choose to give no reason for not participating. Data on potentially confounding co-variates, i.e. a history of cardiovascular or pulmonary co-morbidity, smoking habits, reduced functional level (not being able to climb three flights of stairs without a rest due to shortness of breath) were collected both at the short-term (Table I) and long-term follow-ups. Adjuvant chemotherapy had generally been concluded 3–4 weeks before RT. Endocrine treatment with tamoxifen, either 20 or 40 mg/day for five years, was given concomitantly with RT. The typical adjuvant chemotherapy regime consisted of CMF (cyclophoshamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-Fu 600 mg/m^2, day 1 and 8 q 4 wks $\times$ 6) or FEC or dose intensified FEC (5-Fu 600 mg/m^2, epirubicin 60 mg/m^2, cyclophoshamide 600 mg/m^2 up to 600, 120 and 1800 mg/m^2, respectively, day 1 q 3 wks) with or without high-dose chemotherapy CTC (cyclophoshamide 6 g/m^2, thiothepa 500 mg/m^2 and carboplatin 800 mg/m^2 as continuous infusion over 4 days) and stem cell rescue [20].

Radiotherapy treatment techniques

Dose planning was performed with the Theraplan Vo 5B-system (Theratronics International Limited, Kanata, Ontario, Canada) with inhomogeneity correction. All patients were placed in a supine fixed position, with both arms elevated above their head. The treatment techniques have been described in detail in an earlier report [18].

Loco-regional radiotherapy (LRRT) after modified radical mastectomy

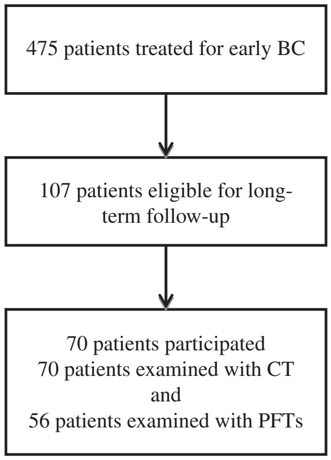
For LRRT following modified radical mastectomy, the target was defined as the chest wall and internal mammary lymph nodes (IMN), axillary- and supra-

Table I. Baseline patients' characteristics.

	n	Mean age years	Cardio vascular disease no.	Pulmonary disease no.	Adjuvant chemotherapy no.	Adjuvant tamoxifen no.	Smokers no.	Reduced functional level no.
Local RT	9	50	Slight*: 1 Severe**: 0	2 0	CMF: 9 FEC: 0	4	1	Slight°: 1 Severe°°: 0
Loco-regional RT Modrad. mastectomy	41	53	Slight: 8 Severe: 0	6 1	CMF: 16 FEC: 14	25	6	Slight: 5 Severe: 1
Loco-regional RT Part.mastectomy	20	57	Slight: 4 Severe: 0	2 0	CMF: 7 FEC: 9	11	4	Slight: 3 Severe: 0

*slight, hypertension or uncomplicated heart disease; **severe, cardiac failure; °slight, shortness of breath after 1 flight of stairs; °°severe, shortness of breath walking on flat ground.

Table II. Flowchart.



clavicular lymph nodes. The treatment was delivered with an anterior electron beam (median 11 MeV; range: 6–16 MeV) covering the chest wall and the lower IMN. The energy was selected so that the 95% isodose covered one-half of the rib thickness of the chest wall. Bolus material was used to even out differences in the thickness of the chest wall. The supraclavicular fossa, axilla, and upper IMN were covered with an anterior-posterior (AP) 8 MV photon beam, including the most lateral part of the chest wall. The prescribed dose was 2 Gy at the depth of 3 cm in the supra-clavicular fossa. A total dose of 46 Gy was given; 2 Gy/day, 5 fractions/week. A small posterior axillary field was added with an 8 MV photon beam based on the thickness of the axilla, to avoid overdose in the anterior part. The reference dose of these fields was approximately 0.37 Gy.

Loco-regional radiotherapy after partial mastectomy including the IMN

The breast parenchyma was treated with two tangential photon beams (4–8 MV) and the regional lymph nodes were irradiated in a similar way as described above. The lower IMN were irradiated with a separate oblique electron beam (9–12 MeV). The dose to the lymph nodes was 46 Gy and the dose to breast parenchyma was 50 Gy with a daily fractionation of 2 Gy/day, 5 fractions/week. The border between the AP (supraclavicular, axillar) and tangential fields was chosen on clinical grounds, and varied between the lower border of clavicle to the first intercostal space.

Evaluation of lung doses

At the start of our trial, we did not have three-dimensional (3D) dose planning data in all patients. Mean cumulative lung dose-volume histograms (MDVH) with the used RT-techniques were therefore created based on 84 patients from the latter part of the study and have been reported earlier [12]. Studies of dose-volume histograms (DVH) inform us about the percentage of a particular structure that receives a specified dose. From the DVH, dose-volume parameters, such as maximum dose (D_{max}), mean dose (MD), and dose-volume constraints (V_{xGy}) are defined. Regarding symptomatic pneumonitis, several of the DVH parameters, e.g. V_{30}, V_{20}, V_{13}, and MD correlate with incidence data. The V_{20} of the total or ipsilateral lung volume are commonly used dosimetric descriptors in clinical practice. The different V_{XGy} are highly correlated to one another. The calculated mean ipsilateral lung V_{13}, V_{20}, and V_{30} for all patients with 3D planning data and long-term follow-up in the present report (n = 33) and for those undergoing loco-regional RT only (n = 27) (Supplementary Table II, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.934967).

CT evaluation

Computer tomography was performed before, four months after, and at a median of 11 years after RT. Slices at three different levels of the lung, i.e. a central, a slice just above the heart contour, and an apical slice at the level of the clavicle, were examined. The density of the lung on the treated side was examined using a standard lung window (mean -600; width 1000 Hounsfield's Units). A CT-adaptation of the Arriagada classification of RT-induced radiological changes was use [17,18]. The lung was divided in three regions; apical-lateral, central-parahilar, and basal-lateral. Increases in density were graded as 0 = no change; 1 = low opacity in linear streaks; 2 = moderate opacity; and 3 = complete opacity. The highest density grade in each volume was added together. Scores of 1–3 represented slight radiological reactions and scores of 4–9 represented moderate to severe reactions.

Seventy women were re-examined with thoracic CT 9–13 years after RT. The women were placed in the identical treatment position with the arms above their heads at the re-scanning.

The patients were re-scanned with CT slices every 3 mm. An evaluation of the identical, above mentioned, three standard cross-sections was used both at the short- and long-term follow-up. The same radiologist (G. S.) assessed the CT slices in both the previous and present studies.

Pulmonary function tests

Pulmonary function tests were performed prior to 5 months and at a median of 11 years after completion of RT in 56 patients, using a Sensor Medics Vmax Encore equipped with a body box (Sensor Medics, Yorby Linda, CA, USA). Lung function parameters including vital capacity (VC), forced expiratory volume in one second (FEV1), functional residual capacity (FRC), total lung capacity (TLC), and residual volume (RV), as well as lung diffusion capacity for carbon monoxide (DLCO), were measured according to criteria of the American Thoracic Society. The diffusion capacity was corrected for hemoglobin level and the better of two acceptable measurements was used. All parameters were expressed as a percentage of the predicted normal values, and adjusted for sex, age, height, and in some cases also weight. The same physiology laboratory was used for the PFTs in both the present and in our previous reports.

Statistics

Changes in PFTs at different time-points were tested with the Wilcoxon matched pairs test. Correlations between ipsilateral V_{20} and radiological changes and VC-changes were tested with Spearman's rank-order correlation. P-values of < 0.05 were considered statistically significant.

Results

We were able to detect a chronic clinically significant reduction of PFTs (Figure 1). The distribution of the VC in percentage of the predicted values (% predicted) at baseline and at the long-term follow-up is shown in Figure 1 [all patients (n = 56); median 105% vs. 92%; median matched change −13%; p < 0.001]

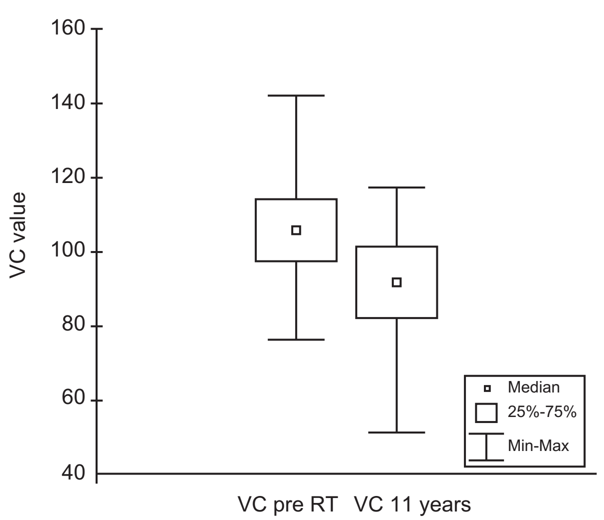


Figure 1. Box-and-whisker plots of the distribution of the percentage of the predicted VC values at baseline and at the long-term follow-up in all patients (n = 56); median 105% versus 92%; median-matched change −13%: p < 0.001.

and (Supplementary Figure 1, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.934967) local RT (with no additional fields against regional lymph nodes) excluded (n = 49); median 103% versus 92%; median matched change −15%; (p < 0.001). The different median values for the percentage of the predicted FEV1, TLC, and DLCO for patients undergoing locoregional RT (n = 49) were 94.5% versus 86% (median-matched change −9%), 98.5 versus 90.5% (median-matched change −7%), and 76% versus 86.5% (median matched change + 15%), respectively. We were not able to detect a reduction of radiological changes at the long-term follow-up (Figure 2). Radiological CT-scores four months post-RT (n = 29) and at the long-term follow-up (n = 70) are shown with a box-and-whisker plot in Figure 2A. Figure 2B depicts the scores at these time points for patients treated with all techniques and having undergone both evaluations (n = 29; p = 0.9) and Figure 2C patients who had undergone locoregional RT and both evaluations (n = 23; p = 0.9) CT score 0 = 4, 1–3 = 16 and 4–9 = 3. There was, thus, no statistical difference between the early and late follow-ups. Figure 3 illustrates the correlation relation between V_{20} and CT-scoring at the long-term follow-up (n = 33) (0.57; p < 0.001). We found no statistical correlation between V_{13}, V_{20}, V_{30} and VC-changes nor with any of the studied clinical covariates.

Discussion

In this long-term follow-up, a median of 11 years after BC irradiation, we found that VC, TLC, and FEV1 measurements were reduced 10–15% compared to the pre-RT levels. The magnitude of the decline could be of clinical importance, e.g. in patients with pulmonary co-morbidities, and aims to reduce the volume of incidentally irradiated lung should therefore continue. The lack of a statistical correlation between ipsilateral V_{20} and PFTs changes could be due to the limited sample size. Due to the absence of DLCO-measurements before chemotherapy, the effect of RT on DLCO cannot be fully evaluated in this report. The median percentage of the predicted DLCO at 11 years was, however, only 86%, which probably indicates a similar long-term effect of chemo- and radiotherapy as for VC, as the patients had normal median TLC, VC, and FEV1 at the pre-RT tests (Figure 1). Many chemotherapy drugs, e.g. cyclophoshamide and methotrexate, are known to cause pulmonary toxicity by local inflammation in the lung parenchyma and this affects the gas exchange [21]. Several patients who receive LRRT after BC-surgery will develop radiographic abnormalities [22]. In our series, CT changes visible

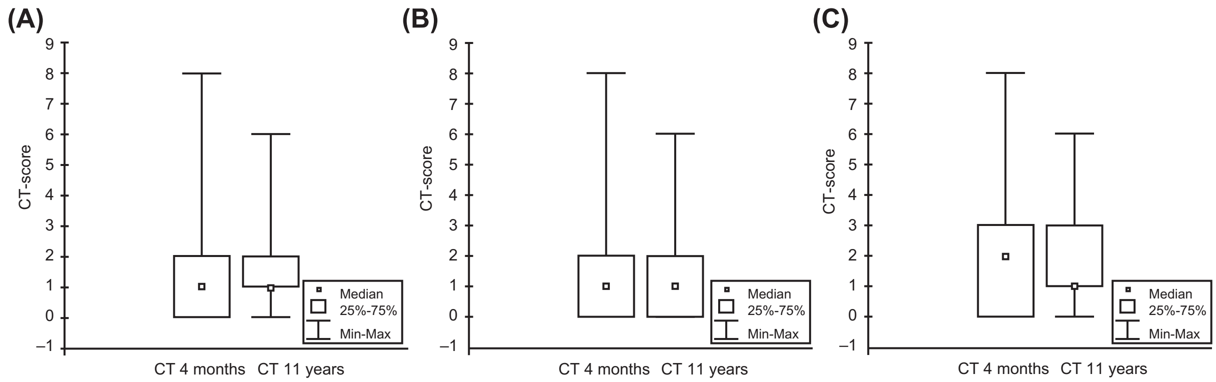


Figure 2. (A) Box-and-whisker plots of radiological CT-scores at baseline (n = 29) and at long-term follow-up (n = 70). (B) Box-and-whisker plots of all patients who underwent both evaluations (n = 29) (n.s). (C) Box-and-whisker plots in patients who underwent LRRT and both evaluations (n = 23) (n.s).

at four months after RT were still detectable in a similar fashion after 11 years. We also detected a correlation between ipsilateral V_{20} and long-term CT-changes. According to Kahan and co-workers, the strongest risk predictors for early radiation sequelae in BC are age > 59 and dose to and volume of the incidentally irradiated lung tissue [23]. The median age at treatment in our study was 54 years. We have in our previous reports also detected an effect of age as a risk factor for short-term lung RT-sequelae [11,12]. Our present report included too few patients to effectively test for potentially confounding effects of patient- or treatment co-variates. Even the performed dosimetric analyses were hampered by the relatively few number of patients with complete 3D dose planning data.

The findings of six previous reports on long-term pulmonary toxicity of BC-RT are summarized [5–10] and compared to the present report (Supplementary Table I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.934967).

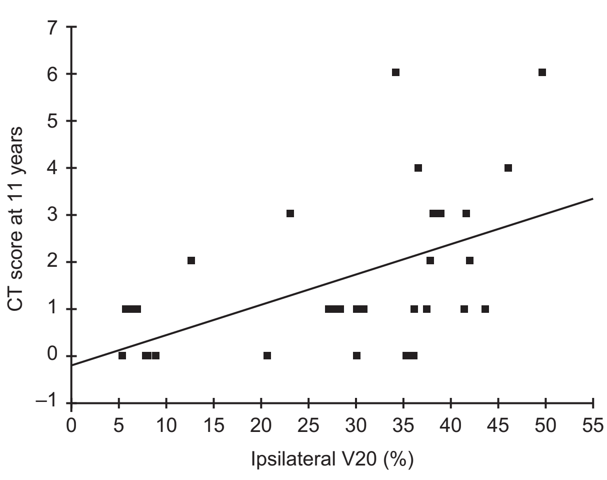


Figure 3. Scatterplot of V_{20} and CT scoring after 11 years of follow-up (n = 33).

Theuws et al. assessed pulmonary injury in BC and lymphoma patients up to 48 months after irradiation. Follow-up data were available only up to 18 months for BC patients. An initial reduction of PFTs was seen in all patients at three months and a recovery at 18 months. Skocylas and co-workers suggested a biphasic lung response, i.e. an early radiological reaction with a maximum around six months and late reactions after one year [6]. This could in some cases even progress for more than five years. Detectable density changes could, however, also decrease over time, probably due to shrinkage of the fibrotic tissue. Similar findings as ours were reported by Dörr and colleagues, i.e. early radiological changes at 15 weeks after RT were also detectable at 4–7 years [7]. Vågane et al. found that the calculated effective dose was a better predictive factor for radiation-induced fibrosis than for changes in overall lung function. The study included 61 BC patients receiving post-operative RT and they were followed for three years or more and also examined with FVC and thoracic CT. In the latter study there was no correlation between local irradiation-induced changes and lung function [8]. Erven and co-workers evaluated patients for changes in lung function for 3–10 years and have also proposed that these changes may follow a biphasic pattern with a partial recovery after 12 months, followed by a late progressive worsening after –10 years [9]. Reductions were seen in TLC and DLCO, and in patients receiving concomitant tamoxifen. A potential effect of tamoxifen use on RT-induced fibrosis was originally described by Bentzen [15]. Jaén and colleageus performed a prospective study with a seven-year follow-up with PFTs (n = 41) [10]. Functional test results decreased in the first two years, but recovered to their baseline values. Non-smokers tended to show larger DLCO and perfusion reductions at three years [24]. Franzen et al. suggested likewise in 1989 that smoking decreased the post-irradiatory inflammatory response and radiographic changes [25]. In our intervention trial in 2002–2005, we studied the short-term lung changes on CT and pulmonary function after applying the ipsliateral lung V_{20} constraint of 30% [26,27]. We plan to perform long-term follow-up in our above mentioned intervention trials [26–28], in which the ipsilateral lung dose-volume constraint of $V_{20} < 30\%$ was applied, to rule out a possible worsening at a later stage, of the initially observed relatively mild short-term lung toxicity, when that strategy was used. We found fewer short-term changes in lung function, symptomatic radiation pneumonitis, and lung changes on chest x-ray compared to our earlier studies [12,18,19].

In conclusion, similar lung changes on CT as four months after RT could still be detected after 11 years in this follow-up study and the median percentage of the predicted VC, FEV1, and TLC were also lowered 10–15%. The DLCO recovery after 11 years was probably due to an in part transient effect of pre-RT chemotherapy, but the median percent of 86% at 11 years indicates a similar decrease also in this metric, as the women had normal VC, FEV1, and TLC before the start of RT. The magnitude of the decrease in lung function could be of importance in patients with lung co-morbidities and pursuits to decrease the amount of incidentally irradiated lung should continue.

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Supplementary material available online

Supplementary Figure 1
Supplementary Tables I and II available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.934967