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ORIGINAL ARTICLE

Evaluation of pulmonary complications of radiotherapy in breast cancer patients

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Summary

Purpose: *To study the early and late pulmonary complications of radiotherapy (RT) in patients with operated breast cancer who received postoperative RT.*

Patients and methods: *Radiation pneumonia (RP) and radiation fibrosis (RF) rates were evaluated after 3 and 18 months from the end of RT, using the Radiation Therapy Oncology Group and the European Organization for the Research and Treatment of Cancer (RTOG/EORTC) combined toxicity classification scale. Evaluation included physical examination, high resolution computed tomography (HRCT) of the thorax, and pulmonary function tests (PFTs). The incidence of RP and RF, the relationship between RP and RF and possible predisposing factors and the impact of RT on the PFTs were analyzed.*

Results: *Between December 2000 and March 2001 35 patients were included in the study. Due to several reasons 29 patients were evaluable for RP and 25 for RF. On the 3rd month post-RT, 17 (59%) patients developed RP. Three (18%) of the cases were grade 1, 13 (76%) grade 2 and 1 (6%) grade 3. One patient was radiologically diagnosed with early RF. When evaluated for RF, 9 (36%) of 25 patients were found to have RF. Four (45%) of them were grade 1, and 5 (55%) grade 2. FEV1, FEV1/FVC, VC, FVC values showed different degrees of decline on the 3rd month. The most prominent change occurred with DLCO/VA ratio which decreased by 20%. On the 18th month, all values returned to at least the pretreatment levels.*

Conclusions: *RT-induced RP and RF are quite frequent. As clinical findings are generally nonspesific, radiological findings of RP and RF should be known. Early and late effects on PFTs are generally mild and transient.*

Key words: breast cancer, radiation fibrosis, radiation pneumonitis, radiotherapy

Introduction

Due to adverse effects of RT on non-target normal tissues, its use in cancer treatment is restricted. Pulmonary complications of high dose irradiation were first described by Groover et al. in 1922 in the USA [1].

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Breast cancer is the most common cancer in women. Close anatomical relationship causes frequent pulmonary complications in patients receiving RT for breast cancer. Good prognosis and long-term survival for breast cancer patients necessitate minimizing these complications. Irradiation causes mainly two types of lung damage: RP in the early post-RT period and RF in the long-run. RP typically occurs 2-6 months after completion of RT, frequently followed by RF. The latent period between RP and RF is usually 3-6 months. Symptomatic RP has an incidence of 1-34 % as compared with 13-100% radiologic changes [2-9].

There are fewer studies concerning the incidence of RF. Symptomatic RF occurs in 0-14% of patients whereas 1-57% develop radiological evidence of fibrosis [2,3,5,7,9].

In the present study, we aimed at finding the incidence of RP and RF in breast cancer patients,

predisposing factors for pulmonary RT toxicity and clinical, radiographic and functional changes in the lungs following RT.

Patients and methods

Thirty-five previously operated breast cancer patients who received RT at Dr. Lütfi Kırdar Kartal Education and Research Hospital, Radiation Oncology Clinic, between December 2000 and March 2001 were included in this study, the aim of which was to evaluate the early (RP) and late (RF) RT complications.

The study exclusion criteria included patients receiving chemotherapy for a malignancy other than breast cancer, prior exposure to RT, use of medication known to possess pulmonary toxicity, and patients not being able to perform PFTs for any reason including operation-related pain. All of the patients were evaluated with personal medical history and physical examination, followed by complete blood count, serum biochemistry and chest X-rays.

Symptoms such as dyspnea, cough and sputum production were registered. Operation performed for breast cancer, tumor TNM stage, chemotherapy and hormonotherapy were recorded. Patients were classified according to the ECOG performance status scale. HRCT and PFTs were performed pre-RT and 3 and 18 months after the completion of RT. Three patients died before the 3rd post-RT month and 3 refused follow-up, leaving 29 patients eligible for RP evaluation. On the 18th month, one patient was lost to follow-up and 3 had died, leaving a total of 25 patients for RF evaluation. HRCT scans were obtained with a GE CT sytec 3000 scanner with 1 mm thickness and a dose of 120 kV-160 mA. CT scans were radiologically evaluated for RP and RF by radiologists and pneumonologists of our hospital. All PFTs and DLCO measurements were performed by the same technician using a Vmax Series 2130, Sensor Medics Corp USA apparatus. DLCO was measured by single breath technique. Expected values were calculated according to the European Respiratory Society 1994 Update. Considering the size of the tumor, axillary lymph node metastases and the type of the operation performed, patients were treated either locally with two opposing tangential fields (n=5) or local-regional RT to the parasternal region, supraclavicular fossa and internal mammary lymph nodes (n=24). Patients who had undergone partial mastectomy were administered an additional 10 Gy/5 fr (200 cGy/day) electron (9 meV) boost with 2 cm safety margin. The total prescribed dose was 46-50 Gy/23-25 fr with conventional fractionation (200 cGy/day) for patients who had undergone radical mastectomy plus axillary lymph node dissection. RT was delivered with CO60 GE Alcyon 11 machine. Four cycles of AC (doxorubicin, cyclophosphamide) were administered to 15 patients, whereas 14 received 6 cycles of CAF (cyclophosphamide, doxorubicin, fluorouracil) with 2 cycles being administered post-RT. Following RT, RP and RF rates were registered on the 3rd and 18th month using the RTOG/EORTC combined toxicity classification scale (Tables 1,2) [10].

Changes in PFTs comparing pre-RT values and after 3 and 18 months were evaluated. PFTs functional changes were compared between patients in whom RP and RF were detected and those without RP and RF.

Table 1. Acute changes due to radiotherapy according to RTOG/EORTC combined toxicity classification scale

Grade 0	None
Grade 1	Mild symptoms or dry cough or dyspnea on exertion.Slight radiographic changes
Grade 2	Persistent cough requiring narcotic antitussive agent or dyspnea with minimal effort but not rest.Patchy radiographic appearances
Grade 3	Severe cough unresponsive to narcotic antitussive agent or dypnea at rest/symptoms of acute pneumonitis /intermittent O2 or steroid may be required.Dense radiographic changes
Grade 4	Severe respiratory insufficiency with continuous O2 need
Grade 5	Death directly related to radiation toxicity

Table 2. Late changes due to radiotherapy according to RTOG/EORTC combined toxicity classification scale

Grade 0	None
Grade 1	Asymptomatic or slight radiographic changes
Grade 2	Severe cough, moderate symptoms of fibrosis or pneumonitis, low grade fever, patchy radiographic changes
Grade 3	Severe symptoms of fibrosis or pneumonitis, radiographic changes
Grade 4	Severe respiratory insufficiency
Grade 5	Death directly related to radiation toxicity

Table 3. Patient parameters

Parameter		*n*	*%*
Smoking	Yes	6	17.1
	No	29	82.9
Stage of	I	1	2.9
breast cancer	II A	4	11.4
	II B	11	31.4
	III A	14	40
	III B	4	11.4
	IV	1	2.9
Tamoxifen	Yes	9	25.7
	No	26	74.3
Radiotherapy	Local	7	20
	Local + regional	28	80
Chemotherapy	4 cycles	15	51
	6 cycles	14	49

Statistics

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) for Windows 10.0 programme. In addition to descriptive statistical methods (mean, standard deviation) Oneway Anova, Kruskal Wallis analysis, independent samples T-test, paired samples T-test, and Mann Whitney U test were used. Comparison between quantitative data was done using McNemar, Ki-square and Fisher exact test. P values < 0.05 were considered significant, with 95% confidence limits.

Results

The median age of the patients was 48.7 years (range 25-76). No co-existing pulmonary diseases were recognized and all patients were ECOG 2 performance status in their first visit. Descriptive characteristics of the patients are shown in Table 3.

In 17 of 29 patients (59%) RP was detected at the 3rd month. Three (18%) of these were grade 1, 13 (76%) grade 2 and 1 (6%) grade 3. One patient demonstrated early radiologic evidence of RF.

RF was identified in 9 of 25 patients (36%) 18 months post-RT. Four of them (45%) were grade 1 and 5 (55%) grade 2.

Local irradiation (5 patients) and local-regional irradiation (24 patients) showed no statistically significant difference ($p > 0.05$) considering the occurrence of RP and RF.

No statistically significant difference was detected between 15 patients receiving 4 cycles of chemotherapy as compared with 14 patients to whom 6 cycles were administered.

There was no correlation between smoking and RP and RF occurrence.

The susceptibility to RP and RF was not increased in patients who used tamoxifen ($p > 0.05$).

At the 3rd month evaluation, HRCT revealed that 18 of 29 patients (62%) showed radiographic changes, the most common being patchy infiltrates (72%), followed by minimal infiltration (22%) and dense consolidation (5.5%). We found that 9 of 25 (36%) patients had radiographic changes after 18 months. RF presented with mild linear opacities in 4 (45%) patients and patchy infiltrates in 5 (55%) patients (Table 4). The radiographic manifestations were characteristically conformed to the radiation portals.

FEV1, FEV1/FVC, VC, FVC values showed different degrees of decline on the 3rd month evaluation.

The most prominent change occurred with DLCO/VA ratio which decreased by 20%. On the 18th month, all of the values returned to at least the pre-RT values. Comparison of the PFTs at each evaluation is shown in Table 5.

Table 4. HRCT findings at 3 and 18 month evaluation

HRCT findings at 3rd month	*n (%)*	*HRCT findings at 18th month*	*n (%)*
Radiographic changes	18 (62)	Radiographic changes	9 (36)
Patchy consolidation	13 (72)	Mild linear densities	4 (45)
Mild changes	4 (22)	Patchy infiltrates	5 (55)
Dense consolidation	1 (5.5)	Traction bronchiectasis	6 (66)
Air bronchogram	2 (11)	Volume loss	5 (55)
Volume loss	5 (27)	Pleural thickening	2 (22)
Pleural effusion	2 (11)	Pleural effusion	3 (33)

Table 5. Comparison of pulmonary function tests at each control

	1st measurement	*2nd measurement*	*3rd measurement*	*1-2 measurements p*	*1-3 measurements p*	*2-3 measurements p*
FVC (lt)	2.91 ± 0.79	2.83 ± 0.73	3.09 ± 0.69	0.300	0.136	0.027*
FEV1 (lt)	2.41 ± 0.64	2.34 ± 0.62	2.63 ± 0.64	0.300	0.013*	0.008**
FEV1/FVC	83.31 ± 7.98	80.76 ± 7.09	84.20 ± 5.54	0.025*	0.410	0.019*
VC(lt)	2.97 ± 0.74	2.80 ± 0.80	3.10 ± 0.69	0.011*	0.365	0.015*
FEF (lt/sec)	2.60 ± 0.93	2.47 ± 0.81	2.93 ± 0.91	0.363	0.004**	0.005**
DL_{CO} (lt)	19.63 ± 6.65	1590 ± 545	21.10 ± 6.29	0.001**	0.186	0.001**
DL_{CO}/VA (lt)	4.47 ± 0.99	4.01 ± 1.03	4.46 ± 0.90	0.001**	0.100	0.001**
VA (lt)	4.30 ± 1.41	3.90 ± 0.87	4.63 ± 0.94	0.034*	0.079	0.001**

*p <0.05 significant, **p <0.01 highly significant

Discussion

RP and RF are the most common pulmonary complications of RT. Previous studies revealed various incidence rates for RP (1-100%) and RF (0-57 %) [2-9]. In our study, the incidence of RP was 59% and of RF it was 36%. Variations in diagnostic methods and criteria constitute the cause of such differences. Either radiological or radiological plus clinical data are used for diagnosis. In order to prevent such a confusion, th RTOG/EORTC toxicity grading scale was developed in 1995. A group of lung cancer patients were classified as grade 1 (38.2%), grade 2 (5.6%) , grade 3 (9%) and grade 5 (5.6%) by Roach et al. using this scale for RP [11]. Another study revealed that 52 of 89 (58%) lung cancer patients developed RF and were classified as grade 1 (65%), grade 2 (10%), grade 3 (15%) and grade 5 (10%) [10]. In our study 17 of 29 patients (59%) developed RP. Of these, 3 (18%) were grade 1, 13 (76%) grade 2 and 1 (6%) grade 3. The absence of grade 4 and 5 cases can be explained by the fact that they had received lower doses of radiation than lung cancer patients. In a similar way, no death due to radiation-induced toxicity was reported in breast cancer patients [2,12,13], whereas another study revealed a 33% mortality rate of lung cancer patients [14]. No study about the use of RTOG/EORTC toxicity scale in RF could be found in the literature. We evaluated RF at the 18th month and diagnosed 9 (36%) RF cases. These were classified as grade 1 (4 patients, 44%) and grade 2 (5 patients, 55%).

Many technical factors including volume of lung tissue irradiated, total dose delivered, irradiation rate and duration are found to affect the incidence and severity of radiation damage [9,13,15-20]. All of the patients we evaluated had received similar doses of RT with similar rates. In a previous investigation, patients who were given local-regional RT were found to develop RP in a higher rate compared to patients irradiated locally [21]. However, no statistically significant difference was observed between these 2 groups in our study. This result could have been influenced by the fact that 5 patients received local RT whereas 24 had local-regional RT.

Excluding the technical factors, the most important factor influencing the occurrence of RP is chemotherapy [2,13,19,22-25]. Previous studies revealed that receiving chemotherapy prior to, concurrent with or following RT increases the risk of pulmonary damage. All treatment regimens included doxorubicin and cyclophosphamide, which are known to enhance the adverse effects of RT. No comparison could be made between chemotherapeutic agents. Chemotherapy can disclose subclinical pulmonary damage in a previously irradiated site, a phenomenon called “radiation recall” [1,2,22]. To explore this effect, we compared patients who received 4 cycles of chemotherapy prior to RT (n=15) with those who had 6 cycles of chemotherapy (4 cycles prior to and 2 cycles after RT; n= 14). No statistically significant difference was found between these 2 groups.

Previous studies have shown that smoking decreases the risk of RP by suppressing the immune response [3,26-28]. Johansson et al. showed that 14 of 606 breast and esophagus cancer patients developed RP and all of these patients were non-smokers [26]. Our study included 6 smokers. The occurrence of RP showed no statistically significant association with smoking, presumably as a result of the low num-

ber of smokers. The only patient who developed grade 3 RP was a non-smoker.

In previous studies age was found to have no effect on the development of RP [3,21,29-31]. This was also confirmed in our study. The mean age of patients who developed RF was higher in a study by Koç et al. [32]. Similarly, in our study the mean age of RF patients was 56 *versus* 43 in the other group, with a statistically significant difference ($p < 0.05$).

Pre-RT or concomitant tamoxifen use and impaired PFTs prior to RT also contribute to RP and RF occurrence [3,32-34], though no statistically significant association concerning these parameters was observed in our study.

In the early phases of RT-induced lung damage, HRCT findings are patchy or dense consolidation and ground glass appearance [35]. Chest radiographs of 83 lung cancer patients showed that 90% of the radiographic manifestations became evident within 6 months. These included patchy infiltrates (34%), ground glass opacities (32%), linear densities (21%) and volume loss (43%) [3]. Mah et al. assessed radiographic changes of lung damage in 54 patients with various malignancies and found the incidence to be 66%. Abnormalities included patchy infiltrates (85%), dense infiltrates (65%), air bronchograms (25%), volume loss (15%) and pleural thickening (15%) [7].

In our study, the 3rd month HRCT evaluation revealed that 18 of 29 patients (62%) showed radiographic changes, the most common being patchy infiltrates (72%), followed by minimal infiltration (22%) and dense consolidation (5.5%). In addition, 2 (11%) patients showed air bronchograms and 5 (27%) had volume loss. Radiological findings are characteristically well-defined with sharp boundaries and correspond to radiation portals crossing the anatomical structures [2,29]. Although some reports about RP extending beyond the radiation ports exist [13,36,37], all the radiological changes were limited to the radiation field in our study.

Pleural effusion due to RT occur within 2-6 months with an incidence of 2-25% . Bachman et al. described 3 characteristics for these effusions: occurrence within 2-6 months following RT, co-existence of RP and spontaneous regression of the effusion. Two of our patients developed pleural effusion within 3 months and had co-existing RP. Cytological analysis repeated twice demonstrated no malignant cells. Eighteenth-month evaluation revealed spontaneous regression, supporting the etiology to be RT. One patient was detected to have pleural effusion at the 18th month showing cytological evidence of malignant cells. Moreover, RP did not co-exist, suggesting pleural metastases from breast cancer.

RF occurs not before 3-4 months after completion of RT. It occurs either in the location of previous RP or without pre-existing RP. Only one case was found to have RF without previous RP in our study.

Late term HRCT findings include linear opacities, volume loss with homogeneous consolidation and traction bronchiectasis [35]. A study concerning 25 Hodgkin's disease patients revealed that 15 (60%) had radiographic changes within 5-16 years following RT. These manifestations consisted of paramediastinal fibrosis in all, apical fibrosis in 3 (20%), apical pleural caps in 9 (60%) and volume loss in 14 (93%) [38]. We found that 9 of 25 (36%) patients had radiographic changes after 18 months. RF presented with mild linear opacities in 4 (45%) patients and patchy infiltrates in 5 (55%) patients. Traction bronchiectasis developed in 6 of 9 patients (66%), pleural thickening in 2 (22%) and volume loss in 5 (55%). RP can either completely resolve or progress to RF. In an analysis including 1624 breast cancer patients, radiologic evidence of RP was visualised in 17 cases. In the follow-up period 12 (71%) of these patients showed complete resolution compared with only 5 (29%) who progressed to RF [39]. In our study, 7 of 16 (44%) RP patients demonstrated complete regression and 9 (56%) ended with RF without significant association with the grade of RF.

Several investigations concerning the relationship between clinical findings and radiographic changes revealed no evidence of correlation [7,40,41]. By using the RTOG/EORTC toxicity grading scale we conclude that radiographic findings correlate with the severity of symptoms.

We also evaluated the effect of RT on PFTs. Radiation-induced lung damage is seldom long-lasting and severe. Measurable changes generally occur 2-3 months following RT, with a peak at 4-6 months and return to baseline after 8-18 months [4,11]. In a study with a median follow-up period of 48 months, functional and morphological damage after 18 and 48 months were nearly the same. Fibrosis seems to stabilize at the 18th month, therefore PFTs at this time may indicate the degree of probable impairment [42,43].

Most significant changes are recorded in DLCO measurement after RT. This method can also aid in finding out the prognosis of radiation damage. DLCO declines by 20-60% within 3-5 months and returns back to normal values after 12 months [2,9,15,44-46]. Several studies indicate the influencing factor to be the decrease in alveolar volume. In an analysis of 28 cases with Hodgkin's disease significant decreases in DLCO, IC and VC were recorded following radiotherapy. Nevertheless, no changes were observed in

FEV1 and DLCO/VA values. Half of this patient population ended up with persistent functional impairment whereas the other half turned back to normal within one year [45]. Theuws et al. have reported that VA, VC and FEV1 showed near-total improvement in 3-18 months *versus* slight increase in DLCO [43]. Morgan et al. identified changes in PFTs in 16 of 18 patients. Most significant changes occurred in DLCO, compared with slight or no changes in VA, VC and PEF values [39]. According to Kaufman et al. changes concerning small airways were found to occur within 3 months, whereas for larger airways they persisted longer than 3 months. These changes were 15% for FEV1, 10% for FVC, 5% for FEV1/FVC and 20% for DLCO. Full recovery did not occur [47]. Kimsey et al. evaluated FVC, FEV1, FEV1/FVC, TLC, FRC, RV and DLCO values of 34 breast cancer patients. Following RT, all parameters declined 5-10% within 1-4 months, with most prominent change being 22% in DLCO. In the 24th month, evaluation of DLCO values showed complete recovery, unlike other parameters [48].

Comparing baseline and 3rd month FEV1/FVC, VC, DLCO, DLCO/VA and VA values and 3rd and 18th month FEV1/FVC, VC, FVC, FEV1, FEF25-75, DLCO, DLCO/VA and VA values, we obtained statistically significant differences. In the 3rd month evaluation, FVC, FEV1, FEV1/FVC, FEF25-75, and VC reduced by 2%, 2%, 3%, 4% and 6%, respectively. Most prominent change was the reduction by 20% of DLCO/VA, followed by 18% decrease in DLCO and 9% decrease in VA. PEF measurements showed no significant changes in 3 controls. After 18 months, all parameters improved to at least the baseline values.

Several studies reveal correlation between symptoms and PFTs [2,13,19,48] whereas others do not [43,44]. Our study demonstrated no significant difference between PFTs values of RP and RF cases and others.

Our study revealed that RP and RF following RT of breast cancer are quite frequent. Detection of predisposing factors helps prediction of occurence of RP. Changes in PFTs due to RT are generally self-limited and transient. Therefore, unless there is a pulmonary co-morbidity, PFTs are not routinely recommended. Nevertheless, a negative prognostic effect of co-existing chronic obstructive pulmonary disease should be taken into account.

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