ORIGINAL ARTICLE

Radiation induced pneumonitis following whole breast radiotherapy treatment in early breast cancer patients treated with breast conserving surgery: a single institution study

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Abstract

Background: Hypofractionated Radiotherapy (RT) regimens for breast cancer, although reduce cost and time for patients and health care systems, could have a negative impact on normal underlying lung tissue. We studied and compared lung function and the post–RT radiological changes using High-Resolution Computed Tomography (HRCT) in early breast cancer patients, treated with 3-Dimentional conformal whole breast radiotherapy (WBRT) using either conventional or hypofractionated regime.

Patients and Methods: Between 2008 and 2009**,** 61 early breast cancer patients (T1-2N0M0) were randomised into two groups .Group A (n=31) received standard radiotherapy with 50Gy/25f/5w plus boost 10Gy/5f/1w to tumour bed. Group B (n=30) received 43.2Gy/16f/22d plus boost 10Gy/5f/1w to tumour bed. Patients of both groups were subjected to dynamic lung testing, using spirometry and gas diffusion tests on Day 0 (D0, before RT), during RT and after completion of RT at 3 and 6 months. HRCT scans were performed in all patients at baseline, and 3,6,12 months after completion of RT. Respiratory symptoms were recorded at 3 and 6 months post completion of RT. Dosimetric factors, such as Central Lung Dose (CLD), lung Volume receiving more 20 Gy (V20), D25 and Mean Lung Dose (MLD) were calculated for all patients.

Results: At 3 months after RT, the pulmonary changes were classified at HRCT as follows: 91.8 % were Grade 0, 8.19 % Grade 1, and 0 % Grade 2. At 6 months, 86.98 % were Grade 0, 11.47 % Grade 1, and 1.6 % Grade 2. At 12 months, 88.52 % were Grade 0, 9.19 % Grade 1 and 3.27% Grade 2. Univariate analysis showed strong association between radiation pneumonitis, age and all dosimetric parameters. There was no association between fractionation type and incidence of RN. FEV1, FVC, FEV 25, FEV 50 and DLCO showed no statistically significant reduction in both treatment groups in 3 and 6 months following completion of RT, compared to baseline. Multivariate analysis showed no relation between HRCT findings and other variables (age, smoking, chemotherapy, hormonotherapy, V20)

Conclusion: Lung toxicity, as assessed with HRCT and PFTs, was minimal in both treatment arms and our results are in consistency with other published data. Hypofractionated RT was a safe modality and well tolerated by the majority of the patients. Longer follow-up is required for robust assessment of incidence of late lung fibrosis in our series.Hippokratia 2013; 17 (3): 233-238

Keywords: Hypofractionated breast radiotherapy, whole breast radiotherapy, radiation pneumonitis, spirometric tests, high resolution computed tomography

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Introduction

Adjuvant radiotherapy following breast conserving surgery is a well established treatment, resulting in decreased local and loco-regional recurrence and mortality rates[1,2]. Although post-operative radiotherapy is an established treatment, there is still no consensus regarding the optimal radiotherapy fractionation regimes, particularly in the group of early – stage breast cancer patients. Conventional radiotherapy treatment consists of 50 Gy in 25 fractions and is widely used, whilst a lot of centres adopt accelerated hypofractionated radiotherapy schemes.

Whelam et al compared conventional whole breast radiotherapy (WBRT) with a hypofractionated regime of 42.5 Gy in 16 fractions in a randomised trial and reported equivalent results in both arms in terms of local control, survival and radiation related toxicity[3]. Moreover, the use

of hypofractionated radiotherapy at a dose of 40 Gy in 15 fractions is the standard schedule in the UK[4,5]. Nevertheless, clinical oncologists raise concerns regarding the toxic effects of radiation therapy when larger doses per fraction are delivered.

Particularly, in breast radiotherapy, one of the main and critical organs at risk is the underlying lung. A number of published studies have shown that radiotherapy following lumpectomy can lead to radiological changes and alterations in pulmonary function. However, most of these studies evaluate toxicity related to either conventional radiotherapy alone, or hypofractionated radiotherapy alone. Although lung damage is clinically asymptomatic in the majority of patients, therefore often under-diagnosed, this clinical entity should be further explored given the longevity of early breast cancer patients and the potential impact of lung injury to their quality of life[6,7].

In the present prospective randomised study, we investigated the radiotherapy – induced lung toxicity in women with early stage breast cancer with node negative disease, primarily treated with breast conserving surgery, comparing two different radiotherapy franctionated regimes.

Materials and Methods

Patients

Between 2008 and 2009, 61 female patients treated with conservative surgery for early stage node negative breast cancer (T1,T2N0M0) were recruited into the present study. Informed consent was obtained for all patients. Trial protocol was approved by the local research ethics committee. The eligibility criteria included histologicaly proven breast cancer, female gender, age 18 to 70, stage T1,T2N0M0. The exclusion criteria included N+ disease, history of chronic respiratory or heart disease, need for radiotherapy to regional nodes, previous concomitant malignancies and mental or other serious co-morbidities that according to the investigators could affect follow-up and compliance. Data on smoking habits were recorded and patients were categorised as non - smokers or past/ present smokers.

All patients were allocated following randomisation into two radiotherapy treatment arms: group A received conventional radiotherapy (50Gy/25#/5w) and group B received hypofractionated radiotherapy (43.2 Gy /16#). High resolution Copmuted Tomography (CT) was performed at baseline and at 3, 6 and 12 months post completion of RT. PFT s were obtained at baseline and post completion of radiotherapy. Pulmonary and heart symptoms were monitored using a trial specific questionnaire, following Common Terminology Toxicity Criteria for Adverse Events (Version 3.0)[8].

Radiotherapytreatment techniques and dose

All patients underwent radiotherapy planning CT at treatment position and underwent 3-D treatment planning (Theraplan, Nucletron, Canada). Patients were treated in the supine position with the ipsilateral arm raised above their shoulder. The Clinical Target Volume (CTV) comprised of the soft tissues of the whole breast down to the deep fascia, excluding muscle and underlying rib cage of the breast parenchyma and Target Volumes were defined according to the criteria of the International Commission of Radiation Units and Measurements[9]. The Planning Target Volume (PTV) was obtained by adding an 8mm margin to the CTV. Organs at risk (OARs) were contoured and included ipsilateral lung, heart and contralateral breast. Prescribed OAR dose constrains were as follows: the volume of ipsilateral lung receiving at least 20Gy (V20) less than 25%, and the volume of ipsilateral lung receiving 25Gy less than 25%. (D25% = 25Gy). We accepted Central Lung Distance (CLD) <= 3 cm and Mean Lung Dose (MLD) < 20 Gy, based on literature data[9-13]

All patients were treated on a linear accelerator (Mevatron, KDS-2; Siemens AG, Berlin, Germany) and radiotherapy was delivered in five fractions per week. In the control arm, patients had 50Gy /25# and in the hypofractionated arm they had 43.2Gy in 16#. A boost dose of 10 Gy in 5# was given using 6 - 9 MeV electron field, depending on the location of the tumour.

Monitoring of symptomatic pneumonitis

Respiratory symptoms, i.e. cough, dyspnoea with or without fever were monitored for all patients at 3weeks, 3, 6 and 12 months post completion of RT. We used the CTC-Criteria (version 3.0)[8] for symptom grading as follows:

0. no complications: no registered respiratory symptoms monitored by the clinician

1. mild reaction: cough and /or dyspnoea with or without fever judged to be radiation pneumonitis

2. moderate reaction: same as 1, however with impaired daily functions and treated with corticosteroids.

Radiological assessment

All patients underwent High Resolution Computed Tomography as per study protocol. The following acquisition protocol was used: patients were scanned in the supine position and in full inspiration; Images were reconstructed in time and displayed at the standard lung window settings (width/level 1200/-600 Housfield/Units) 1mm thickness at 10mm intervals with registration.

One experienced radiologist assessed and evaluated any lung changes and reported relation to the radiation field, using the Nishioka et al[14] scoring system.

Pulmonary Function Tests

All patients underwent PFTs as per protocol, using a PF/DX dense (Medical Graphics tm, St Paul, MN). Forced Vital Capacity (FVC), Forced Expiratory Volume 1 (FEV1) and Carbon Monoxide Diffusing Capacity (DLCO) by single breath technique were monitored and recorded as percentages of predicted values after adjustment for age, gender and height. We also recorded the values of KCOc, FEF25 and FEF50 at baseline, and 3weeks, 3months and 6 months post completion of radiotherapy treatment.

Statistical Analysis

Descriptive statistics and simple proportions were used

to present the data. Pearson correlation coefficient was used to assess correlation of numerical variables. We performed logistic regression analysis to investigate correlation between HRCT findings with other variables (age, smoking, radiotherapy treatment arm, dosimetric parameters). In particular we investigated the association between HRCT and MLD, CLD, V20 and D25. Chi squared test was implemented to investigate association between fractionated treatment regime (conventional vs hypofractionated), smoking and HRCT findings. Association between age, and dosimetric variables was investigated using the student's t-test.

Results

Patient demographics and treatment characteristics are shown in Table1. Demographics and clinical characteristics were well balanced between treatment groups. Symptomatic pneumonitis in our study was rare.

Findings in HRCT

HRCT obtained at 3 months post completion of radiotherapy treatment showed no radiological signs of lung injury for 53 patients (86.8%). The degree of lung changes within the irradiated volume assessed by HRCT 3 and 12 months after RT is shown in Table 2. All patients scored Grade 0 at the baseline HRCT scan before RT. Of the 61 patients, 7 (11.47%) patients (3 patients from Group A and 2 patients from Group B) had pulmonary changes between the baseline measurements and 3 months after RT. At 6 months, 10 (16%) and 3 (4.9%) patients scored Grade 1 and Grade 2 pneumonitis on HRCT respectively. At 12 months, One patient with Grade 1 pneumonitis on HRCT at 6 months from group A progressed to Grade 2 at 12 months, whereas 2 patients with Grade 1 pneumonitis (one patient from Group A and one patient from Group B) recovered to Grade 0 at 12 months. None of the patients in both treatment arms developed Grade 3 radiation pneumonitis based on radiologic criteria (Table 2).

Correlation between radiation induced pneumonitis on HRCT and age, fractionation treatment type, smoking and dosimetric variables, as based on treatment planning calculations are shown on Table 3. There was a strong association between pneumonitis on imaging and age (p= 0.02). On the contrary, there is no correlation between fractionation type, smoking and radiation pneumonittis.

Table 1: Patients' demographic characteristics and treatment related parameters in group A (Conventional Radiotherapy treatment) and Group B (Hypofractionated Radiotherapy treatment).

Characteristics	All Patients	Group A	Group B
Age			
Mean	55.16	57.06	53.2
Range	31-69	42-69	31-67
Menopausal status			
Pre	18 (29%)	7 (11.5%)	11 (18%)
Post	43 (70.5%)	24 (39.3%)	19 (31.1%)
Left	38 (62.3%)	18 (29.5%)	20 (32.8%)
Right	23 (37.7%)	13 (21.3%)	10 (16.4%)
T Stage			
T1	48(78.7%)	25 (41%)	23 (37.7%)
T2	13 (21.3%)	6 (9.8%)	7 (11.5%)
Histology			
Ductal	60 (98.4%)	30 (49.2%)	30 (49.2 %)
Lobular	1 (1.6%)	1 (3.2%)	0 (0%)
Grade			
1	38	20	18
2	20	10	10
3	3	1	2
ER Status			
+	56 (91.8%)	27 (44.3%)	29 (47.5%)
-	5 (8.2%)	4 (6.6%)	1 (1.6%)
PR Status			
+	48 (78.7%)	22 (36.1%)	26 (42.6%)
-	13 (21.3%)	9 (14.8%)	4 (6.6%)
HER2 Status			
+	10 (16.4%)	6 (9.8%)	4 (6.6%)
-	51 (83.6%)	25 (41%)	26 (42.6%)
Chemotherapy			
Yes	16(26.2%)	6 (9.8%)	10 (16.4%)
Hormonotherapy			
Yes			
AI	38 (62.3%)	20 (32.8%)	18 (29.5%)
Tamoxifene	18 (29.5%)	7(11.5%)	11 (18%)
No	5 (8.1%)	4(6.5%)	1 (1.6%)
Smoking			
Yes	25 (41 %)	11 (18%)	14 (23%)
No	36 (59%)	20 (32.8%)	16 (26.2%)

AI: Aromatase Inhibitors

Table 2: Grading of pneumonitis on High-Resolution Computed Tomography (HRCT), bases on Nishioka et al scoring system at 3, 6 and 12 months post completion of radiotherapy in the two treatment arms.

Grade of pneumonitis On HRCT	Baseline		3 months post RT		6 months post RT		12 months post RT	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
0	100%	100%	28 (90.32 %)	28 (93.33 %)	26 (83.8 %)	27 (90 %)	27 (87 %)	27 (90 %)
1	0%	0%	3 (9.67 %)	2 (6.66 %)	4 (12,9 %)	3 (10 %)	3 (9.67 %)	2 (6.66 %)
2	0%	0%	0%	0%	1 (3,22 %)	0%	1 (3.22 %)	1 (3.33 %)
3	0%	0%	0	0	0	0	0	0

HRCT= High Resolution Computed Tomography

Table 3: Association between radiation induced pneumonitis on High-Resolution Computed Tomography and demographic variables (age, smoking), treatment parameters (conventional vs hypofractionated RT) and dosimetric variables.

	No Pneumonitis on HRCT	Pneumonitis on HRCT	p
Age	54.11	61.75	^p=0.02469
Smoking Status			
Smokers	34	6	p=0.054*
Non-Smokers	19	2	
RT Fractionation type			
Conventional	27	4	p=1*
Hypofractionated	26	4	
MLD	11.24	14.08	^p=0.026
V20 Gy	16.77	20.71	^p=0.006
D25%	16.55	22.98	^p=0.014
CLD	2.01	2.97	^p= 0.0189

HRCT: High Resolution Computed Tomography, MLD: Mean Lung Dose, V20: Lung Volume receiving 20 Gy, D25: Dose received by 25% of lung volume, CLD: Central Lung Distance.

Table 4: Variation in pulmonary function tests in Group A (Conventional Radiotherapy treatment).

PFT	**Group A** (paired t test)						
	Before RT (D0)	3weeks	3months	6months	D0 vs 3 m	3m vs 6m	D0 vs 6 m
	Mean (SD)				p value		
FVC	105.80 (12.7)	105.4 (13.01)	105.2 (12.61)	105.2 (12.87)	0.6	0.00	0.6
FEV1	103.60 (10.4)	103.43 (10.3)	103.2 (10.4)	103.0 (10.41)	0.32	0.28	0.6
FEV25	103.0 (12.1)	102.30 (12.3)	102.4 (12.7)	102.7 (13.0)	0.6	0.3	0.3
FEV50	94.0 (15.9)	91.98 (15.73)	93.1 (15.4)	92.8 (15.01)	0.9	0.3	1.2
DLCO	94.8 (10.2)	94.8 (10.17)	93.3 (10.38)	92.7 (9.61)	1.5	0.6	2.1
KCOc	99.7 (10.00)	98.7 (10.97)	94.9 (10.37)	94.0 (10.3)	4.8	0.9	5.7

PFT: pulmonary function tests, RT: radiotherapy, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, FEF 50: forced expiratory flow at 50% of vital capacity, FEF 25: forced expiratory flow at 25% of vital capacity, DLCO: carbon monoxide diffusing capacity.
Data presented as mean, with standard deviation in parentheses, of percentage of predicted lung function; all measurements expressed as percentage of predicted values adjusted for age, gender, and height.

(p= 1 and 0.05 respectively). All dosimetric parameters (CLD, V20, MLD and D25) were found to have strong statistically meaningful correlation with radiation – induced pneumonitis (p= 2.08, 0.006, 2.48e-05, 2.08e-13 respectively).

Pulmonary function tests

The results of the PFTs 3 weeks, 3 and 6 months after RT are summarized in Table 4 and Table 5. The differences among the examined periods in group A were not statistically significant for FVC, FEV. In group B, none of the PFT parameters showed a significant decrease at 3 months, compared with the baseline measurements. All

Table 5: Variation in pulmonary function tests in Group B (Hypofractionated Radiotherapy treatment).

PFT	Group B (paired t test)						
	Before RT (D0)	3weeks	3months	6months	D0 vs 3 m	3m vs 6m	D0 vs 6 m
	Mean (SD)				p value		
FVC	104.75 (11.2)	104.3 (11.57)	103.2 (11.3)	104.25 (8.46)	1.55	1.05	0.5
FEV1	101.65 (7.73)	101.53 (7.70)	101.42 (7.65)	101.33 (7.66)	0.23	0.09	0.32
FEV25	98.5 (14.2)	97.85 (13.03)	96.85 (14.14)	96.65 (14.08)	1.65	0.2	1.85
FEV50	93.0 (15.1)	92.75 (14.78)	92.1 (14.9)	91.85 (14.62)	0.9	0.25	1.15
DLCO	93.0 (10.95)	92.85 (10.97)	92.45 (11.01)	92.1 (10.87)	0.55	0.35	0.9
KCOc	93.1 (9.98)	92.6 (9.22)	91	91.5 (8.66)	1.75	0.15	1.6

PFT: pulmonary function tests, RT: radiotherapy, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, FEF 50: forced expiratory flow at 50% of vital capacity, FEF 25: forced expiratory flow at 25% of vital capacity, DLCO: carbon monoxide diffusing capacity.
Data presented as mean, with standard deviation in parentheses, of percentage of predicted lung function; all measurements expressed as percentage of predicted values adjusted for age, gender, and height.

these measurements are expressed as a percentage of the predicted values, adjusted for age, gender, and height.

Discussion

There are a number of studies in the literature describing pulmonary changes following adjuvant RT in patients that underwent conventional surgery for breast cancer[6,15-21]. Radiation-induced pulmonary changes have been investigated for conventionally fractionated schedules[15,22-26]. Nevertheless, there is a small number of prospective studies investigating the effect of RT in lung function as assessed with the combination of HRCT and PFTs, in particularly comparing two different radiotherapy fractionation regimes[27-29]. In addition, in the majority of the studies, radiographic changes were assessed by plain chest X rays, or with conventional CT scans, which are less sensitive and provide less detailed information about the radiological changes suggestive of radiation induced pneumonitis[27,29].

In our prospective study, we investigated the grade of lung toxicity in early breast cancer patients receiving two different radiotherapy fractionated schedules: group A received conventional RT and Group B received hypofractionated RT. We determined the presence of restrictive (FVC, FEV1, TLC) and/or obstructive (FEV1, FVC/FEV1) deficits, by using the main dynamic and static vital respiratory parameters, as well as the decrease in the diffusing capacity due to alveolar–capillary barrier impairment (DLCO).

Lind et al[16] have reported that the addition radiotherapy to the axilla leads to an increased incidence of radiation pneumonitis, compared to whole breast radiotherapy alone. Another study by Lingos et al[15] has showed that axillary/supraclavicular radiotherapy correlates with an increased incidence of pulmonary side effects and have reported an increased incidence of radiation-induced lung injury in patients receiving CHT concomitantly. In contrast, Ooi et al[24] have found no correlation between CHT and pulmonary function or radiological findings. Another study showed that there was a positive relationship between tamoxifen and radiation pneumonitis, and the results from a randomised study suggested that AI could increase long-term toxicity when combined with RT[28,29]. In a recent study, Jaeg at al investigated the long term effects of breast radiotherapy to the lung with PFTs and reported that changes in PFT values were reversible at a 7 year follow up[30]. Moreover, no correlation between dosimetric factors and spirometry changes were found in this study.

In our series, there was no significant decrease in PFTs, and there was no significant difference between the change in the mean values of FVC, FEV1, and DLCO from baseline to 3 months and from baseline to 6 months between the two treatment groups. Recent prospective studies have shown that irradiation of the internal mammary nodes could lead to an irreversible decrease of PFTs[6,25-26].

All patients recruited in the current study received local breast RT, and consequently had minimal irradiated lung volume, which could explain the non-significant decrease in the PFTs in both groups.

Incidence of radiological radiation pneumonitis was rare in our study and we recorded no incidence of symptomatic pneumonitis. There are published data supporting that the use of more conformal radiotherapy techniques, aiming to minimise the dose to the underlying lung could lead to a significant decrease to the incidence of radiation pneumonitis[26-27,29]. Manavis et al[31]reported no acute and short term late lung toxicity in a number of 32 patients treated with hypofractionted/accelerated RT along with cytoprotection, after a minimum follow up of 24 months. In our series all patients were treated with 3-D treatment planning, with the aim to minimise V20 to the ipsilateral lung to < 25%. Nevertheless, we have no previous data to assess the impact of 2D and 3D treatment planning on lung function changes and radiological findings.

Conclusion

The results of our study show that there is no clinically meaningful and statistically significant difference in the incidence rates of radiation induce pulmonary toxicity between patients treated with conventional and hypofractionated radiotherapy. Nevertheless, assessment of

late lung fibrosis requires longer follow -up compared to the follow-up applied in this study. Our study supports that hypofractionated RT is safe and doesn't lead to higher or unacceptable pulmonary toxicity. Moreover, the use of 3-D treatment planning, aiming to minimise lung dose in accordance to certain constrains, seems to minimise pulmonary injury secondary to radiotherapy.

Conflict of interest

There is no conflict of interest.

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