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ORIGINAL ARTICLE

Evaluation of Pulmonary Function After Radiotherapy Using Helical Tomotherapy for Breast Cancer Treatment: Prospective Study

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OBJECTIVE
Purpose of the present study was to investigate acute pulmonary changes using pulmonary function tests (PFTs) after breast cancer irradiation with helical tomotherapy (HT).

METHODS
Forty patients were included in this study. Pretreatment and 3 months after completion of radiotherapy (RT), values of forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and FEV1/FVC ratio were measured and recorded.

RESULTS
Restrictive pattern was seen in 4 patients in baseline PFTs and moderate deterioration was observed in their measurements of PFT at 3 months after RT. Obstructive pattern was defined in only 1 patient in baseline PFTs and it remained unchanged after RT. Mild obstructive pattern in 4 patients and mild restrictive pattern in 3 patients had developed at 3 months after RT.

CONCLUSION
Minimal changes that result in mild restrictive and obstructive pattern in PFTs can be seen in acute phase after RT with HT.

Keywords: Breast cancer; radiation pneumonitis; tomotherapy.

Introduction

Radiation-induced lung disease (RILD) is one of the most common clinical toxicities resulting from thoracic radiotherapy. The cells in the alveolar space are damaged by radiation and early damage progresses to an acute exudative inflammation process. In this way, radiation pneumonitis (RP) is manifested within 4–12 weeks after completion of radiotherapy.[1] Subclinical acute lung injury is experienced by most of these patients. Pulmonary function test (PFT) is a useful tool to assess the respiratory impairment and pulmonary function is com-

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monly measured by evaluating the FVC, FEV1, FEV1/FVC.[2] The main factors responsible for pulmonary toxicity are irradiated lung volume and radiation dose. Although the strong correlations between the different dosimetric parameters, there is no sharp threshold dose (Vdose) associated with RP risk due to different radiation techniques and applications.[3] Conventional 3D conformal radiotherapy (3DCRT) that use parallel-opposed tangential beams is most common technique in breast cancer irradiation and it's complications are well documented. In breast cancer irradiation, the increased use of recent more sophisticated radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) and helical tomotherapy (HT) allows complex treatment plan according to patient's anatomy. Particularly HT use all gantry angles because of rotational delivery and it could cause low doses to a greater volume of healthy tissues, especially the contralateral breast and lung. The current question is how these techniques will impact clinical outcomes. These techniques have been evaluated and demonstrated dosimetric advantages in many studies.[4–6] However, to our knowledge, presence of acute lung injury in breast cancer irradiation using HT has been investigated prospectively in very few studies,[7] although many studies[8–14] including different RT techniques have shown changes in pulmonary functions after breast and mostly lung cancer irradiation. The purpose of this prospective study was to investigate acute pulmonary changes that could be caused radiotherapy using pulmonary function tests (PFTs) in breast cancer patients treated with HT.

Materials and Methods

Patients

Between April 2015 and September 2015, proven histopathologic features of breast cancer, age 18–75 years and stage I–III, female patients who were performed breast conserving surgery or mastectomy and required adjuvant radiotherapy were intended to include in this prospective study after obtaining informed consent. The exclusion criteria were a history of chronic respiratory disease, previous RT to thorax, concomitant malignancy, the presence of respiratory symptoms for more 2 weeks within previous one year. Ultimately, 56 patients met the selection criteria for this study that was approved by local research ethic board. Forty patients completed both PFTs at two time points. All patients underwent complete blood count, chest radiograph and PFTs pre-RT and 3 months after completion of RT to evaluate baseline status and acute pulmonary changes.

Radiotherapy

All patients were positioned using a breast board (CIVCO) with their head turned to the contralateral side and the ipsilateral arm raised above their head in a supine position and computed tomography (CT) images with 3.0 mm thickness were obtained for RT planning. For whole breast or chest wall RT with or without lymph nodes, the planning target volume (PTV) and critical structures including the ipsilateral and contralateral lung, heart, esophagus, spinal cord, contralateral breast and skin were defined and contoured according to the recommendations of the breast cancer atlas for radiation therapy planning consensus definitions of RTOG (the Radiation Therapy Oncology Group) (available at: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx). The lumpectomy bed was also contoured as a boost PTV with 1cm expansion in the patients were performed breast-conserving surgery and 10 or 16 Gy was prescribed as boost dose for 13 lumpectomy cavity and 4 incision scar. In the case of lymph node positivity, lymphatic PTV was created. Loco-regional RT volume was defined as the axillary and supraclavicular lymph nodes with or without ipsilateral internal mammary nodes additional to the chest wall or breast. Local RT was defined as target volume of the chest wall or breast. The volume contours and CT images were transferred to the Tomotherapy H system (Accuray Inc., Sunnyvale, CA) to create treatment plans. TH plans were created with a field width of 5.048 cm, fixed jaw mode and a pitch of 0.287. The median modulation factor was 3.0 and it ranged from 2.0 to 3.5. Dose prescription was 50 Gy in 25 fractions of 2.0 Gy daily.

Evaluation of Radiation Doses

As dose constraints for the PTV, 1) D95 was defined as the minimum dose delivered to 95% of the PTV and D95 ≥95% of the prescribed dose were satisfied. 2) V95% (V47.5 Gy) was defined as the percentage of the PTV receiving at least 95% of the prescribed dose and V95% ≥ 95% were satisfied. For PTV, the parameter V107 (V53.5 Gy) was defined as the percentage of the PTV receiving at least 107% of the prescribed dose and was used to assess the maximum doses. Dose-volume histograms (DVHs) for the PTV, lung and the heart were calculated for each patient. Ipsilateral and total mean lung dose (MLD), ipsilateral lung volume receiving 5 and 20 Gy (V5 and V20), values of mean dose, V5, and V30 of the heart derived from DVHs were evaluated.

The Conformity Index (CI) was calculated as the ratio of the V95% over the volume of breast or chest

Table 1 Baseline patient and treatment characteristics

Variable		n	%
Age			
Mean±SD	47.47±10.12		
Range	25–71		
<50 y		22	55.0
≥50 y		18	45.0
Smoking history			
Smokers		10	25.0
Non smokers		30	75.0
Histology			
Invasive ductal carcinoma		32	80.0
Invasive lobular carcinoma		3	7.5
Tubulo-lobular carcinoma		2	5.0
Others		3	7.5
Stage			
IA		3	7.5
IIA		9	22.5
IIB		10	25.0
IIIA		12	30.0
IIIB		4	10.0
IIIC		2	5.0
Tumor side			
Right breast cancer		22	55.0
Left breast cancer		18	45.0
Surgery			
Partial mastectomy		15	37.5
Modified radical mastectomy		25	62.5
Chemotherapy			
Adjuvant		34	85.0
Neo-Adjuvant		3	7.5
Both		2	5.0
No chemotherapy		1	2.5
Chemoterapy regime			
AC+Taxan		19	47.5
Taxan		11	27.5
FEC+Taxan		7	17.5
AC		1	2.5
FEC		1	2.5
No chemotherapy		1	2.5
Hormone therapy			
Aromatase inhibitor		11	27.5
Tamoxifen		20	50.0
No hormone (Receptor negative)		9	22.5
Concurrent trastuzumab			
Yes		17	42.5
No		23	57.5

AC: Adriamycin, cyclophosphamide; FEC: 5-Fluorouracil, epirubicin, cyclophosphamide.

wall PTV. The Homogeneity Index (HI) was calculated by the following formula.

HI=(D2%–D98%)/D50%

Chemotherapy and Hormone therapy

Thirty nine patients had been given neoadjuvant and/or adjuvant chemotherapy including anthracycline and/or taxan-containing regimens. The patients had hormone receptor positivity were given aromatase inhibitor or tamoxifen with or without luteinizing hormone-releasing hormone (LHRH) analogue after completion of RT. One patient with partial mastectomy received tamoxifen plus LHRH analogue but not chemotherapy because she had stage IA disease. The patients whose were Her2 (3+) and Silver Enhanced In Situ Hybridization (+) (SISH+) in the case of Her2 (2+) received concomitant Trastuzumab with RT and were continued 1 year after completion of RT.

Pulmonary Function Tests

Evaluation of pulmonary function was based on spirometric measurement (ZAN 300: ZAN Messgerate GmbH, Oberthulba, Germany). Pre-treatment and 3 months after completion of RT, values of forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and FEV1/FVC ratio were monitored and recorded as percentages of predicted values. All tests were assessed the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS).[15]

Statistical analysis

Data were analyzed using SPSS version 16.0 statistical software (SPSS, Chicago, IL, USA). All data were expressed as median and/or mean±standard deviation. Patients' demographic, clinical and dosimetric data were analyzed using Kolmogorov-Smirnov to test whether for normal distribution. Since variables were non-normally distributed and/or were ordinal, correlation coefficients and their significance were calculated using Spearman test to examine the strength of the relationship between variables at two time points. The Wilcoxon test was used to test the significance of dependent variables between pre-treatment and 3 months after RT. Mann–Whitney U test was used to identify the relation between independent groups such as age (<50 and ≥50 years), RT volume (local RT and loco-regional RT), ipsilateral lung volume receiving dose ≥20 Gy (V20, ≥20% and <20%, ≥25 and <25, ≥30 and 30), use of tamoxifen (yes and no) and also use of concomitant Trastuzumab (yes and no).

Results

Baseline patient and treatment characteristics were summarized in Table 1. Dosimetric parameters of

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Table 2 Dosimetric parameters of PTV and organs at risk

Parameter	Mean±SD	Median	Range
Treatment time (min)	6.82±3.03	6.10	3.8–17.9
PTV			
Dmean	52.19±1.48	51.67	50.30–56.37
Dmin	35.95±4.79	36.58	18.14–42.49
Dmax	59.10±4.44	56.86	54.37–70–18
V95	97.44±2.14	97.45	87.63–100.00
V107	26.34±25.11	19.17	0.42–75.96
CI	0.97±0.25	0.97	0.88–1.05
HI	0.20±0.09	0.18	0.07–0.38
Ipsilateral lung			
Dmean	14.94±2.57	15.22	6.93–20.52
V5	83.16±16.64	84.94	22.45–100.00
V20	24.30±5.55	25.35	10.41–34.68
Contralateral lung			
Dmean	7.00±2.25	7.09	1.24–11.25
V5	56.53±22.44	56.03	0.00–100.00
V20	2.23±3.15	1.12	0.00–13.23
Total lung			
Dmean	11.29±2.07	11.54	4.36–16.22
Heart			
Dmean	9.32±2.14	9.25	0.50–13.42
V5	77.87±24.70	83.71	0.00–100.00
V25	2.94±2.74	2.61	0.00–9.74
V30	1.52±1.75	0.65	0.00–6.50
Contralateral breast			
Dmean	6.30±1.84	6.51	0.46–9.81

SD: Standart deviation; Vx: Volume (%) receiving x dose (Gy) or higher; Dmax: Maximum dose; Dmin: Minimum dose; Dmean: Mean dose; CI: Conformity index; HI: Homogeneity index.

PTV and organs at risk were presented in Table 2. The target dose homogeneity and conformity index were perfect in this study. PFTs measurements pre-RT and 3 months after RT and comparison of parameters between two time points were presented in Table 3. Means of percent of decrease in FEV1 and FVC was found as 0.06±0.07 and 0.06±0.06, respectively. There were statistically significant changes in PFTs at 3 months after RT ($p<0.05$). We compared the means of percent decrease in FEV 1 and FVC from before RT to 3 months after RT in subgroups (Table 4). In the patients were given concurrent Trastuzumab with RT and the group had the value of ipsilateral lung V20 was ≥30, mean of percent decrease in FVC at 3 months after RT was significantly higher ($p= 0.022$ and $p=0.019$, respectively). However, age, RT volume and use of tamoxifen had no effect on means of percent decrease in FEV 1 and FVC from before RT to 3 months after RT. In correlation analysis, there was no statistically significant correlation between irradiated lung volumes including values of total lung Dmean, ipsilateral lung Dmean, V5 and V20 and measurements of PFT at 3 months after RT ($p>0.05$). However, there was negative correlation between age and FEV1/FVC at 3 months after RT ($r=-0.321$ and $p=0.043$). The patients were diagnosed with neither clinical nor radiological pulmonary complications after RT during the study period. According to baseline measurements of PFT, restrictive pattern was seen in 4 patients and a moderate deterioration was observed in their measurements of PFT at 3 months after RT. In the evaluation at 3 months after RT, mild restrictive pattern newly developed in 3 patients additional to 4 patients at baseline. The obstructive pattern was defined in only one patient in baseline PFTs and it remained unchanged after RT. Additional to this patient, mild obstructive pattern was developed in 4 patients at 3 months after RT. Table 5 shows characteristics of these restrictive and obstructive patients.

Table 3 Parameters of pulmonary function tests and hemogram at two time points and results of Wilcoxon Test

PFT	Pre-RT (T0)		At 3 mo after RT (T1)		Comparison of T0 and T1
	Median	Range	Median	Range	p
FVC (%)	93.00	58–117	88.00	49–120	0.000
FEV1 (%)	89.00	52–122	82.50	49–120	0.000
FEV1/FVC (%)	84.0	65–108	84.00	64–106	0.073
Hemoglobin	11.87	7.32–13.40	12.58	10.06–14.28	0.000
WBC	6.90	2.93–40.95	6.01	3.10–9.93	0.002
Platelet	288.35	164.00–478.20	231.15	140.90–307.70	0.000

PFT: Pulmonary function test; FVC: Values of forced vital capacity; FEV1: Forced expiratory volume in first second; WBC: White Blood Cell; RT: Radiotherapy.

Table 4 Comparison of mean of percent decrease in FEV 1 and FVC from before RT to 3 months after RT by using Mann Whitney U Test in subgroups

Group	n	Change in FEV1 p	Change in FVC p
Age		0.22	0.24
<50 y	22		
≥50 y	18		
Concurrent trastuzumab		0.05	0.02
YES	17		
NO	23		
Tamoxifen		0.66	0.25
YES	20		
NO	20		
RT volume		0.07	0.25
Local RT	8		
Loco-regional RT	32		
Ipsilateral lung V20 (Group 1)		0.25	0.73
<20	7		
≥20	33		
Ipsilateral lung V20 (Group 2)		0.74	0.73
<25	19		
≥25	21		
Ipsilateral lung V20 (Group 3)		0.61	0.01
<30	36		
≥30	4		

FVC: Values of forced vital capacity; FEV1: Forced expiratory volume in first second.

Discussion

One of the primary concerns for breast cancer RT is the issue of pulmonary toxicity. Data related pulmonary toxicity has been obtained mostly from studies on lung cancer irradiation because lung exposure is lower in breast irradiation than that in lung cancer. Although it was found strong correlation between RILD and Vdose in lung cancer irradiation, this relationship is smaller in local or loco-regional breast cancer RT.[16] To our knowledge, this is the first study investigating prospectively the acute pulmonary toxicity linked to breast radiotherapy in covantional doses with helical tomotherapy although there are a lot of study[7–9,16–18] including different RT techniques. Van Parijs et al.[7] evaluated pulmonary function of

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Table 5 The characteristics of restrictive and obstructive patients

Patient	Age	RT field	Total MLD	Ipsilateral lung MLD	Ipsilateral lung V5	Ipsilateral lung V20	PFT					
							BeforeRT			At 3 mo. After RT		
							FEV1 (%)	FVC (%)	FEV1 /FVC	FEV1 (%)	FVC (%)	FEV1 /FVC
R1**	58	LR	8.45	11.25	70.31	10.41	84	88	82	73	78	78
R2**	71	LR	12.22	15.22	92.30	27.78	92	88	84	79	76	82
R3**	33	L	10.47	14.92	76.70	22.68	87	85	89	77	69	98
R4*	60	LR	9.54	12.08	73.80	19.50	89	79	93	71	69	84
R5*	44	LR	12.88	15.87	99.0	25.34	57	72	67	52	67	66
R6*	33	LR	14.21	20.52	100.0	33.26	52	58	77	49	48	88
R7*	38	LR	12.07	17.07	99.84	22.75	75	78	101	75	78	101
O1**	60	LR	13.20	13.20	89.91	28.45	96	107	75	78	93	71
O2**	41	LR	10.38	10.38	83.22	23.87	80	93	74	78	91	74
O3**	50	LR^{im}	16.22	16.22	100.0	34.68	96	101	80	71	81	74
O4**	51	LR	12.30	12.30	94.77	24.70	91	97	79	75	81	78
O5*	56	L	9.40	9.40	72.19	15.56	65	86	65	65	86	64

R: Restrictive; O: Obstructive; LR: Loco-regional; L: Local; MLD: Mean lung dose; Vx: Percentage volume of lung receiving ≥x dose. *The patient was restrictive or obstructive at baseline PFTs; **The patient had newly developed restrictive or obstructive lung ingury. ^{im}: Internal mammary nodes were treated additional to whole breast.

patients were treated using HT. They performed total dose 42 Gy in 15 fractions with simultaneous boost as a short course RT but not conventional RT in 50 Gy in HT arm and assessed pulmonary function via FEV1 and diffusing capacity of the lung for carbon monoxide (DLCO) prior to RT and 2 months after completion of RT. In their study, lung toxicity significantly reduced in HT arm according to measurements of DLCO but not FEV1 (p=0.047). We treated 40 patients with breast cancer using HT and found statistically significant reduction in FEV1 and FVC at 3 months after RT (p<0.05). However, in assessment 3 months after RT, restrictive pattern newly developed in 3 patients and obstructive pattern developed in 4 patients based on measurements of PFTs. Except one patient developed restrictive pattern, other obstructive or restrictive patients underwent loco-regional RT. She received concurrent trastuzumab with 50 Gy whole breast and 10 Gy lumpectomy cavity boost RT. The value of ipsilateral lung V20 was 22.68% in this patient and she received concurrent trastuzumab. We found that decrease in FVC at 3 months after RT was significantly more in the patients were given concurrent trastuzumab with RT (p=0.022). The incidence of trastuzumab-induced pneumonitis has been reported in the literature as 0.4–0.6%.[19] Of our patients 97.5% including this restrictive patient had been given taxan-containing regimen although this regimen was not found efficient on PFTs in our study. Paclitaxel cause pneumonitis usually develop 1 week to 3 months after treatment with estimated frequencies of 0.73–12% [20–22]. This suggests to us that new developing restrictive disease may be independent of the lung dose for this patient. One of patients developed obstructive pattern after RT had inner quadrant tumor and multiple high-risk recurrence factors. This patient had also large breast volume (1621.50 cm^3) received adjuvant 50 Gy RT to whole breast and internal mammary nodes on the first three intercostal space and 16 Gy boost to lumpectomy cavity following breast conserving surgery. Therefore, the value of ipsilateral lung V20 was very high with 34.68%. It has been found a correlation between the risk of RP and value of ipsilateral lung V20 in breast cancer irradiation. The incidence of RILD rises up to 7.5–11.5% if the value of ipsilateral lung receiving 20 Gy increase to 20–30%.[18,23,24] Similarly, we found that in the group (n=4) with the value of ipsilateral lung V20 ≥30%, decrease in FVC at 3 months after RT was more (p= 0.019). In our study, in one patient (Table 5, R1**), value of ipsilateral lung V20 was very low with 10.41%. She was Her2 (-) and smoker unlike other restrictive or obstructive patients but she developed newly mild restrictive pattern with minimal reduction in baseline FEV1/FVC. The smoking has been found related to lower incidence of RILD. [25] Ten patients were smoker in our study and only one of them developed restrictive pattern after RT. This finding supports positive effect of smoking on RP.

There are some limitations of this study. First, this study was performed with a single measurement tool to assess the pulmonary function; additionally to PFTs, we may be use DLCO that reflect properties of alveolar-capillary membrane. Second, we present preliminary results of our study. Thus, we cannot comment on long-term effects. However, our study will continue to assess late effects of breast irradiation with helical tomotherapy. Third, the characteristics such as stage and surgery of patients including in this study were heterogeneous. Thus, irradiated volumes were heterogeneous. Finally, the number of patients recruited was too small to allow drawing generalizations.

HT plans provide excellent conformity and homogeneity even in target volumes including lymph nodes in breast cancer irradiations. In very few patients, minimal changes in PFTs can be seen in the acute phase after RT with HT and these changes result in mild restrictive and obstructive pattern. Nevertheless, when considered the risk to benefit ratio, HT can be a viable option for breast cancer patients with complex volumes.

Disclosure Statement

The authors declare no conflicts of interest.

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