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Hypofractionated Radiotherapy Induced Pulmonary Function Changes and Toxicity Analysis in Breast Cancer Patients Post-mastectomy Chest Wall Irradiation

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Abstract

Pulmonary complications post-radiotherapy to chest wall are inevitable. There are plethora of studies on pulmonary complications following conventional radiotherapy delivering 50 Gy in 25 fractions ± boost in early stage breast cancer. However, the data on how hypofractionated regimes used post-mastectomy effects normal pulmonary tissues is still limited. In this trial we studied the impact of hypofractionated RT, used post-mastectomy, on pulmonary function tests.

Keywords: Breast Cancer, HypofractionatedRadiiotherapy, Pulmonary Function Tests, Postmastectomy

INTRODUCTION

Radiation has an important role in the management of breast cancer. Post mastectomy radiotherapy (RT) is highly effective in decreasing chest wall recurrences [1], and it has been shown in multiple prospective randomized trials that addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces the loco regional recurrences and prolongs survival in high- risk women with breast cancer and reduces mortality [2,3]. Historically,

conventional RT delivering 50 Gy in 25 fractions, with or without a subsequent boost to tumor bed has been recommended, adhering to the radiobiological principles whereby larger fraction sizes can lead to increase rate of late tissue damage [4].

Using Linear Quadratic model two components of cell killing can be described, α- which is proportional to dose and, β- proportional to square of dose. The components of cell killing that are proportional to dose and square of dose are equal if, $\alpha D = \beta D^2$ or $D = \alpha/\beta$. Lower the ratio, greater the effect of change in RT fraction size on normal and malignant tissues. Healthy tissues of breast and rib cage are sensitive to fraction size with α/β values 5Gy or less [5]. Use of hypofractionated RT is gaining popularity based on the solid results from various randomized trials conducted in United Kingdom and Canada. These trials have equated hypofractionated RT with conventionally fractionated regime as adjuvant treatment following breast conserving surgery. As for toxicity concerns the results were comparable. However, the data on how hypofractionated regimes used post-mastectomy effects the normal tissues is still limited. Pulmonary complications post-RT are inevitable still the incidence remains unclear [6]. Majority of patients are clinically asymptomatic and so are under diagnosed. Given the long favorable overall survival post treatment in breast cancer patients, the impact on quality of life of patients due to pulmonary complications should be quantified and reported.

Lung is an intermediate to late responding tissue. Two waves of damage post RT can be identified: acute pneumonitis at ≤6 months after treatment, and fibrosis, which may develop slowly over a period of several months to years. The lung is among the most sensitive of late responding organs. The severity depends on three factors: volume irradiated, dose, and fraction size. Lung is particularly sensitive to fractionation, with α/β estimated to be about 3 Gy.

The impact of hypofractionated RT post-mastectomy, in breast cancer patients, on pulmonary function tests (PFT) has been examined in this present study.

MATERIALS and METHODS

Patients 59 female patients of breast cancer, treated by mastectomy, were enrolled from June 2011 to June 2012 after having obtained informed consent. The study was approved by local research ethic board. Eligibility criteria included female patients aged >20 years, StageI, II, III, histologically proven, who have undergone mastectomy. Exclusion criteria: positive margins, chronic pulmonary disease, previous breast cancer, pregnant or lactating, those with chest malformations, and patients who had undergone breast conserving surgery.

All patients had PFT`s before the start of RT, then at 3 monthly intervals to assess the baseline status and the early and late effects. The median follow up was 19 months. Pulmonary function tests were determined utilizing spirometer device installed at

IGMC, Shimla. The Common Terminology Criteria for Adverse Events, version 3.0 was employed to evaluate early and late effects of RT on PFT`s.

Radiotherapy

All patients received postmastectomyhypofractionated RT either 40 Gy in 15 fractions (dose per fraction 2.65 Gy, total time 22 days) or 42.5 Gy in 16 fractions (dose per fraction 2.66 Gy, total time 19 days) depending on treating physician`s preference. External beam RT was administered by TeletherapyTheratron 780e and Equinox Cobalt60 machines. The intention was to treat the chest wall post-mastectomy along with the regional lymph nodes, if need be. Separate fields were placed to irradiate the chest wall and supraclavicular/ axillary area. Patients were placed on wedged breast board. Radiation fields were drawn on the skin and contours were taken. Tangential RT portals were used for chest wall irradiation and direct portal for supraclavicular/ axillary fields. Two dimensional planning was done.

Pulmonary function tests

All patients underwent PFTs as per protocol. The following parameters were assessed: forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1) and diffusing capacity of carbon monoxide (DLCO). FVC is the volume of air that can forcibly be blown out after full inspiration measured in liters, an is an index of lung volume, FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration and reflects the mechanical properties of large and medium sized airways, while DLCO is the carbon monoxide uptake from a single inspiration in a standard time (usually 10 sec), representing the diffusing capacity through the alveolo- capillary barrier. All measurements recorded as percentages of predicted values after adjustment for age, gender and height.

Statistical analysis

Descriptive statistics were used to present the data. For repeated measurements analysis of variance (ANOVA) was used to assess the differences in PFT values at different times, as well as to correlate PFT values at different times with age, smoking history, chemotherapy and hormonal therapy use and addition of supraclavicular/ axillary field. Pearson chi- square test was used to assess correlation of numerical variables.

RESULTS

In our present study a total of 59 patients were screened. Patient, tumor, and treatment characteristics are reported in Table 1. Majority of the patients were in 41 to 60 years age group (67.8%), with a median age of 49 years. Average length and width of tangential field were 19.0 $\pm$ 1.2cm and 7$\pm$1.26cm respectively. Average central lung distance measured was 1.8 $\pm$ 1.5cm. Median follow up was 19 months. Symptomatic pneumonitis was very rare in our study. The mean of FEV1, FVC, and DLCO before and after

radiotherapy are summarized in Table 2. showing no statistically significant difference. All measurements being expressed as a percentage of predicted values adjusted for age, gender, and height. The CTC (v 3.0) adverse effects grading is depicted in Tables 3. and 4, reported as percentage decline of predicted values of pulmonary functions.

Table 1. PATIENT, TUMOR AND TREATMENT CHARACTERISTICS

Age	
<45yrs	20
>45 yrs	39
Smoking	
Smokers	6
Ex-smokers	3
Non-smokers	50
Histology	
Ductal	57
Lobular	2
Others	1
Nodal dissection	
Adequate (≥10)	32
Inadequate (<10)	27
T stage	
T1	3
T2	29
T3	21
T4	6
N stage	
N0	19
N1	18
N2	16
N3	6
Stage grouping	
I	2
II	31

III	26
Grade	
I	18
II	31
III	10
LVSI	
Present	16
Absent	43
ECE	
Present	5
Absent	54
Receptor status	
ER/ PR +	39
ER and PR -	20
HER 2neu	
Positive	11
Negative	13
Unknown	35
Chemotherapy used	
CAF	11
TAC	16
AC→ TC	32
Supraclavicular field	
Yes	
No	36
	23

Table 2. Variation in mean(SD) values of pulmonary function tests(PFT)

PFT	Before RT (a)	3 months (x)	6 months (y)	2 years (z)	p value x vs. a	y vs. a	z vs. a
FEV1	106.63 (3.52)	101.5 (3.4)	101.0 (4.41)	100.31 (8.92)	0.79	0.08	1.0
FVC	108.43 (4.18)	106.0 (3.8)	106.0 (4.24)	106.10 (4.94)	0.47	0.91	0.20
DLCO	94.6 (4.8)	95.3 (5.1)	93.3 (5.3)	91.6 (9.2)	0.64	0.45	1.7

Data presented as Mean with standard deviation in parenthesis (expressed as percentage of predicted lung fuction)

Table 3.Acute pulmonary toxicity (CTC v 3.0)

Grade	No. of patients
Gr 0	50 (84.7%)
Gr 1	9 (15.3%)
TOTAL	59

Table 4. Late pulmonary toxicity

GRADE	No. of patients
Gr 0	44
Gr 1	10 (16.9%)

Gr 2	4 (6.8%)
Gr 3	1 (1.7%)
TOTAL	59

Table 5. Association between demographic variables and ≥ Grade (Gr) 2 lung toxicity

	No ≥ Gr2 toxicity	With ≥ Gr2 toxicity	p- value
Age			
<45 years	19	1	0.16
>45 years	35	4	
Smoking			
Smokers/ Ex-smokers	9	2	0.03
Non-smokers	47	1	
Supraclavicular RT			
Yes	32	4	0.36
No	22	1	
Chemotherapy used			
CAF	10	1	0.16
TAC	13	3	
AC→TC	31	1	
Hormonal therapy			
Tamoxifen	10	0	0.29
Aromatase inhibitors	26	3	

DISCUSSION

To ease the burden of patients and hospitals alike, hypofractionated RT was introduced in mid-1960s. However, later in almost all publications unacceptably high percentage of severe complications after hypofractionation has been reported [7-9]. Fractional size of >2 Gy produce unacceptable late adverse sequelae [10]. In this present study hypofractionated RT (40 Gy/ 15 fractions or 42.5 Gy/ 16 fractions) was utilized in adjuvant settings postmastectomy. While modeling the schedules α/β values of 3 Gy for late changes and 10 Gy for early changes were considered. Using these values the biologically effective doses estimated are as follows; early/ late effects→ 53.8 Gy/ 80.3 Gy and 50.6 Gy/ 75.3 Gy for 40 Gy and 42.5 Gy schedules respectively.

Due to their close proximity to chest wall, certain organs/ structures suffer radiation induced toxicities. One such toxicity is radiation pneumonitis (RP). RP is directly related to the volume of lung tissue irradiated. The likelihood of pneumonitis increases when the tangential fields are combined with the axillary and / or supraclavicular field and adjuvant chemotherapy. RP is characterized by interstitial inflammation within the irradiated field, a non-productive cough, and/ or low grade fever. Another very rare and unique lung complication is radiation associated bronchiolitis obliterans organizing pneumonia (BOOP). It is characterized by ground glass opacities/ interstitial changes extending beyond the irradiated lung, and appears to be migratory in nature. Lignos et al [11] reported RP in 1% of patients after surgery and radiation. The frequency was 9%, when three fields plus concurrent chemotherapy was administered compared to only 13% when two fields and sequential chemoradiation was used. Plataniotis GA et al [12]evaluated RP in hypofractionation setting (42.5 Gy/ 16#) by HRCT in early breast cancer patients, and reported minimal and minor effects on the underlying lung parenchyma.

Radiation induced pulmonary changes have been investigated in majority of the trials for conventionally fractionated RT. Moreover, these studies provided literature for pulmonary changes in patients who underwent breast conserving therapy [11, 13-17]. Data pertaining to adverse effects of hypofractionated RT on lung function assessed using PFTs in patients post- mastectomy is scarce. In our present study we utilized, pulmonary function tests to assess the pulmonary adverse events following hypofractionated RT.

In our present study, percentage decline of predicted values of FVC, FEC1 and DLCO, were investigated to quantify the hypofractionated RT induced early and late pulmonary toxicity. We observed that the variation in pulmonary function tests presented as mean over a 19 months of median follow up and expressed as percentage of predicted, was not statistically significant. However, regards the individual assessment and bifurcation of acute and late reactions 15.3% of the study population developed Gr 1 acute reactions, late reactions- 16.9% had Gr1, 6.8% Gr2, and 1.7% Gr3 late pulmonary toxicity.

A study by Lind et al [18] reported that as compared to whole breast radiotherapy alone addition of axillary/ supraclavicular radiotherapy portals increased incidence of pulmonary complications. However, in our study Gr2 and above late pulmonary toxicity was observed in 11.11% patients treated with supraclavicular radiotherapy ($p = 0.36$). Lingos et al [11] found increased incidence of radiation induced lung injury in patients receiving chemotherapy concomitantly. In contrast, our trial found no statistically significant late adverse effect in patients receiving chemotherapy, though in almost all patients it was used sequentially, with no influence of the type of regime used. ($p= 0.16$). The impact of hormonal therapy, tamoxifen or

aromatase inhibitors, on radiation pneumonitis has been demonstrated in a number of trials [19,20]. There were 3 patients out of a total 29 receiving aromatase inhibitors who developed ≥ Gr2 lung reactions (p= 0.29).

When considering other risk factors contributing to radiation lung injury, literature about age, and smoking have been reported [18, 21-26]. In our series there were 4 patients out of 39 aged>45 years who had ≥Gr2 late pulmonary toxicity, not statistically significant (0.49). Out of 59 patients, 11 were smokers or ex-smokers with only 2 developing ≥Gr2 late toxicity Table 5.

Opposed tangential portals with or without direct supraclavicular fields exposes lung to significant amounts of radiation doses. And though lung is particularly sensitive to fractionation (α/β= 3Gy), clinically significant incidence of radiation toxicity even after use of hypofractionated RT post-mastectomy was not recorded in our study. Results clearly support the use of hypofractionated RT post-mastectomy with no fear of long term pulmonary toxicity

CONCLUSION

Our study has shown that hypofractionated regimes are not detrimental to the effective and safe delivery of radiation post-mastectomy in breast cancer patients especially when concerning acute or late pulmonary damage, with data in this study revealing no clinically statistically significant acute or late pulmonary toxicity even at a follow up of 2years.

Conflict of interest:

Authors state no conflict of interest.

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