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Impact of Chemoradiation on Lung Function in Breast Cancer Survivours

Authors
Lone Mansoor Ul Haq[1], Wani Shahid Bashir[2], Refut Arah Banoo[3], Shah Saqib Ahmad[4] Sofi Mushtaq Ahmad[5], Teli Mohd Ashraf[6], Lone Mohd Maqbool[7]
[1,2,4,5]Senior Resident, Radiation Oncology SKIMS Srinagar
[3]Senior Resident, General Surgery, GMC Srinagar
[6]Ex Professor Radiation Oncology, SKIMS Srinagar
[7]Professor Radiation Oncology, SKIMS Srinagar

Abstract
Introduction: *Both earlier diagnoses of the breast cancer and novel chemo radiation therapy strategies have resulted in a considerable improvement in breast cancer survival. This study was intended to assess the long term impact of these treatment modalities on pulmonary functions in survivors of carcinoma breast patients in Kashmir valley of Indian subcontinent.*
Material and Methods: *A prospective study in which breast cancer patients treated by combined modality treatment protocol with curative intent were taken for study. Patients with any co-morbid medical conditions like chronic lung disease, hypertension, asthma or drug intake for the same or any were not included in the study. Patients included in the study group had histopathological documentation of Carcinoma Breast, female sex, age greater than 18 years and geographical location of Kashmir Valley. Respiratory status assessment was done by pulmonary function test (spirometry) according to the guidelines prescribed in the American Thoracic Society (ATS) guidelines. The pulmonary function test values were compared with the patient's predicted values and percentage change was calculated*
Observations: *While assessing pulmonary functions in the study group cases, revealed slight restrictive ventilatory impairment in contrast to control group cases in the form of reduction in various spirometric parameters. Radiation and chemotherapy have synergistic effect on reduction in the spirometric parameters. The follow up time was less, need more follow up time.*
Conclusion: *Apart from the clear benefits of adjuvant chemo radiation, we should be aware of the potentially increased risk of pulmonary sequelae following specific radiotherapy regimens in long-term breast cancer survivors.*
Keywords: *breast cancer, long term toxicity, fibrosis, chemo radiation, pulmonary sequelae.*

Introduction

Early presentation coupled with delivery of improvised treatment modalities has resulted in a steep increase in breast cancer survival. Advances in diagnosis and treatment have created a population that we need to figure out how to

provide quality care for. The population of breast cancer survivors will continue to increase due to widespread use of mammography and adjuvant therapies [1].As we improve the outcome of patients with breast cancer, the long-term toxicities of various regimens and treatment protocols used takes a paramount importance. Recognition of adverse effects of older radiotherapy techniques led to the development of alternative approaches such as intensity modulated radiotherapy and 3D-based conformal therapy and partial breast irradiation protocols that deliver more precise radiation doses and fraction sizes that minimize lung exposure. Radiation in combination with chemotherapy is associated with a greater risk of toxicity than with radiotherapy only. Although modern radiation techniques provide lower mortality than older techniques, pulmonary damage does nonetheless occur. Prospective studies report radiological evidence of irreversible lung fibrosis and associated pulmonary disorders with left sided breast cancer 6 to 24 months after radiotherapy [2, 3]. Although an initial metaanalysis of adjuvant breast cancer radiation trials showed that improved disease-free survival was counteracted by excess cardiac mortality[4], a recent metaanalysis that included trials with modern radiation techniques found that increased overall survival was associated with radiotherapy[5].

Breast cancer patients treated with adjuvant chemo-endocrine therapy (CET) have a significantly and markedly lower respiratory fitness compared with age- and sex-matched controls. Adjuvant loco-regional radiotherapy, a common practice in breast cancer treatment, is associated with irreversible lung function parameters[6]. Tamoxifen treatment during post-mastectomy radiotherapy in breast cancer patients significantly increases the risk of the development of lung fibrosis along with the patient age and menopausal status[7].Radiation to the whole breast for early breast cancer does not place women at increased risk for long-term pulmonary toxicity, compared with mastectomy and patients with radiation-induced pneumonitis at the time of treatment are not at increased risk for pulmonary complications later[8].

Breast cancer is emerging as a major concern in female population of Kashmir valley with its incidence showing an increasing trend. Keeping in view the increasing incidence and better survival with treatment modalities of breast cancer and the associated toxicities, this study was intended to study the long term impact of these treatment modalities on respiratory status in survivors of carcinoma breast patients in Kashmir valley of Indian subcontinent.

Material and Methods

A prospective study titled *assessment of pulmonary functions in survivors of breast cancer*, treated by combined modality treatment protocol (i.e, operated followed by chemo radiation ± hormonal therapy) with curative intent was conducted from 2009 to 2011 in the Department of Radiation Oncology, Sher-i-Kashmir Institute of medical Sciences (SKIMS) Srinagar.

Patients having following characteristics were excluded:

- Co-morbid medical conditions like chronic lung disease, hypertension, asthma or drug intake for the same.
- Previous history of any chest wall irradiation or chemotherapy other than for carcinoma breast.
- Active smoker, ex-smoker.
- Geographical location other than Kashmir valley like high altitude (Ladakh) or, low altitude (Jammu).

Patients included in the study group had:

- Histopathological documentation of Carcinoma Breast.
- Female sex.
- Age greatr than 18 years.
- Geographical location; Kashmir Valley.

In the study group fifty patients were taken for analysis and reviewed at six monthly intervals during their follow-up. In the control group, fifty subjects were included and evaluated. These

included age and sex matched healthy volunteers from general population. Written informed consent was taken from all the participants enrolled in the study. In study group of patients, all were operated (lumpectomy or mastectomy) and had received post operatively chemoradiation. Chemotherapy given to the patients included three types of regimens; FEC (5-Fluorouracil, Epirubicin, Cyclophosphamide), CMF (Cyclop-hophamide, Methotrexate, 5-Fluorouracil) and FAC (5-Fluorouracil, Adriamycin, Cyclophophamide). All patients had received radiation dose of 45 Grey to primary chest wall, ipsilateralaxilla and supraclavicular area $\pm$ 40 Grey to internal mammary area in 20 fractions.

Respiratory status assessment was done by pulmonary function test (spirometry). The pulmonary function test values were compared with the patient's predicted values and percentage change was calculated. The spirometer used during the study was a PC based. The spirometry testing was performed according to the guidelines prescribed in the American Thoracic Society (ATS) guidelines[9]. While performing spirometry the following steps were adopted:

- Tight clothing was loosened and prosthetic loose dentures (if any) were removed.
- The patient was seated comfortably.
- The patient was asked to take a deep breath.
- A mouth piece was inserted in to the mouth with lips closed tightly.
- The patient was asked to blow out the air as rapidly, forcibly and completely as possible.

While doing FVC maneure a cough, an inspiration a valsalvamaneure, a leak, or an obstructed mouth piece disqualified the trial and the test was repeated. To ensure validity, each patient was asked to perform a minimum of three acceptable maneuvers and the best reading was noted provided the largest and second largest FVC from the acceptable trials did not vary by >5% or 200 ml, so as to ensure reliability. The largest FVC, measured from a set of three acceptable trials was taken as patient's FVC. During FVC maneure several other measurements including FEV1 were also made.

Definitions of various parameters in spirometry are:

a) Forced Vital Capacity (FVC): The maximal volume of air exhaled with maximally forced effort from a position of maximal inspiration. In obstructive lung disease it is normal or mildly decreased. In restrictive lung disease it is mildly to severely decreased.

b) Forced Expiratory Volume in one second (FEV1): The volume of air expelled in the first second of the FVC. In obstructive lung it is mildly to severely decreased. In restrictive lung disease it is moderately to severely decreased.

c) FEV1 to FVC Ratio (Normally over 75%): It is not useful if both FEV1 and FVC are normal. In obstructive lung disease it is moderately to severely decreased. In restrictive lung disease it is normal or increased.

d) Forced Expiratory Small Airway Flow (FEF25-75): It is effort Independent. It is more variable than FEV1 or FVC.

Interpretations of spirometric parameters include:

I. Normal
- FEV1 to FVC Ratio >0.7
- FEV1 >80%
- FVC >80%

II. Obstructive Lung Disease: (FEV1 to FVC Ratio <0.7) Severity assessment of Obstructive Lung Disease:
- FEV1 over 80%: Normal.
- FEV1 over 60%: Mild obstructive lung disease.
- FEV1 over 40-50%: Moderate obstructive lung disease.
- FEV1 under 40%: Severe obstructive lung disease.

III. Restrictive Lung Disease: (FEV1 to FVC Ratio >0.7) Severity assessment of Restrictive Lung Disease:

- FVC over 80%: Normal.
- FVC over 60%: Mild restrictive lung disease.
- FVC over 40-50%: Moderate restrictive lung disease.
- FVC under 50%: Severe restrictive lung disease.

In addition among complete lung volume, total lung capacity (TLC) is normal or has a mild change in obstructive lung disease and is decreased in restrictive lung disease, residual volume (RV) is increased in obstructive lung disease and is decreased in restrictive lung disease.

Within the study group, changes in the pulmonary parameters with respect to patient characteristics (age, laterality of disease , tumor size, menopausal status, hormonal status, time period since diagnosis) and treatment characteristics (cumulative anthracyline dose received, inclusion of internal mammary portal in radiation therapy,) were also studied.

The data collected was recorded on a CRF (clinical record form). Data was described as percentages and averages. Intergroup comparison of the metric variables was done by students t-test where non metric variables were compared by Chi-square, Man-whitney u test and Fredman's test. P-value of <0.05 was considered significant.

Observations

The personnel habits and characteristics between the two groups were comparable. As for as the menstrual parameters were concerned no significant difference were observed with regard to age at onset of menarche, frequency and duration of menstrual cycles. Menopausal status between the two groups was also comparable. All cases in both groups were multiparous. Majority (70%) of the patients had tumour location on left side. Most of the patients had T2 stage (70%) and positive nodal status (90%).

With regard to receptor status 18/50 (36%) were positive for estrogen receptor, 8/50 (16%) were negative for same and its status was unknown in 24/50 (48%). Progestrone receptor status was positive for 30%, negative 22% and unknown for 48%. HER-2 NEU receptor status was available in 15 patients out of whom only one patient was positive and rest 14 were negative.

The main surgical procedure undergone by patients was mastectomy in 43/50 (86%) while as breast conservation surgery was done in seven patients. All patients received external beam radiotherapy to primary tumour site/chest wall, ipsilateralsupraclavicular area and axilla, but 32/50 (64%) patients had also received radiation to internal mammary as well. 47/50 patients had received anthracycline based chemotherapy. The most common agent being epirubicin in 37/50 (74%) followed by adriamycin 10/50(20%). Total cumulative mean dose of epirubicin and adriamycin was 645 mg and 320 mg respectively.

Table1: Distribution of cases in two groups according to their mean spirometric parameters at baseline (0 month).

Spirometric Parameter	Study Group Mean±SD	Control Group Mean±SD	p-value
VC Measured (L)	2.2 ± 0.6	2.6 ± 0.6	0.002 (Sig)
VC Percentage	89.4 ± 17.2	107.2 ± 32.3	0.001 (Sig)
FVC Measured (L)	2.4 ± 0.7	2.8 ± 0.5	0.002 (Sig)
FVC Percentage	97.7 ± 15.3	108.9 ± 36.0	0.045 (Sig)
FEV1 Measured (L)	1.9 ± 0.6	2.2 ± 0.6	0.004 (Sig)
FEV1 Percentage	93.8 ± 15.7	99.0 ± 31.4	0.300 (NS)
FEV1/FVC Measured	77.8 ± 10.3	96.5 ± 14.9	0.000 (Sig)
FEV1/FVC Percentage	98.6 ± 13.7	99.8 ± 15.2	0.686 (NS)

Abbreviations: VC = Vital Capacity, FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume at one second, L = litre;

At the beginning of study various spirometric parameters were compared between study group and control group cases. There was statistically significant difference in most of the spirometric parameters at base line (0-month). Average vital capacity of study group was 2.2 litres (89.4%)

while as in control group it was 2.6 litre (107.2%)(p<0.05). Average forced vital capacity in study group wads 2.4 litres (97.7%)compared to 2.8 litres (108.9%) in control group (p<0.05). Average FEV1 in study group was 1.9 litres (93.8%) compared to 2.2litres (99%) in control group (p<0.05).

Table 2: Comparison of serial spirometric parameters at six monthly intervals in study group cases (n =50)

Spirometric Parameter	Baseline Mean±SD	6 month Mean±SD	12 month Mean±SD	18 month Mean±SD	24 month Mean±SD	p-value
VC Measured (L)	2.2 ± 0.6	2.2 ± 0.6	2.1 ± 0.7	2.2 ± 0.7	2.1 ± 0.7	0.419 (NS)
VC Percentage	89.4 ± 17.2	100.7 ± 63.2	85.1 ± 15.4	87.1 ± 16.3	89.1 ± 17.4	0.521 (NS)
FVC Measured (L)	2.4 ± 0.7	2.4 ± 0.7	2.3 ± 0.8	2.2 ± 0.6	2.4 ± 0.7	0.506 (NS)
FVC Percentage	97.7 ± 15.3	100.0 ± 16.0	98.8 ± 18.1	98.9 ± 14.9	96.4 ± 14.8	0.233 (NS)
FEV1 Measured (L)	1.9 ± 0.6	1.9 ± 0.5	1.8 ± 0.6	1.9 ± 0.6	1.8 ±0.6	0.167 (NS)
FEV1 Percentage	93.8 ± 15.7	94.0 ± 12.8	93.0 ± 17.7	94.9 ± 14.6	93.4 ± 14.8	0.425 (NS)
FEV1/FVC Measured	77.8 ± 10.3	77.2 ± 10.7	76.7 ± 12.9	78.1 ± 9.9	76.1 ± 9.7	0.888 (NS)
FEV1/FVC Percentage	98.6 ± 13.7	97.1 ± 14.2	96.4 ± 15.5	99.1 ± 13.1	97.6 ± 13.2	0.595 (NS)

Abbreviations: VC = Vital Capacity, FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume at one second, L = litre.

Serial spirometry performed in study group patients revealed no significant change in any parameters over two years period (p>0.05). The base line vital capacity was 89.4% and 89.1% at two years. The FVC was 97.7% at base line and 96.4% at two years. No significant change in FEV1 and FEV1/FVC was also noted.

Table 3: Distribution of cases in two groups according to their spirometric parameters at their last follow up (24 month)

Spirometric parameter	Study Group Mean±SD	Control Group Mean±SD	p-value
Mean VC Measured (L)	2.1 ± 0.7	2.6 ± 0.5	0.000(Sig
Mean VC Percentage	89.1 ± 17.4	109.1 ± 29.7	0.000(Sig)
Mean FVC Measured (L)	2.4 ± 0.7	2.7 ± 0.5	0.015(Sig)
Mean FVC Percentage	96.4 ± 14.8	102.3 ± 33.4	0.622(NS)
Mean FEV1 Measured (L)	1.8 ±0.6	2.2 ± 0.6	0.006(Sig)
Mean FEV1 Percentage	93.4 ± 14.8	96.4 ± 31.0	0.530(NS)
Mean FEV1/FVC Measured	76.1 ± 9.7	95.3 ± 14.9	0.000(Sig)
Mean FEV1/FVC Percentage	97.6 ± 13.2	100.5 ± 13.5	0.264(NS)

Abbreviations: VC = Vital Capacity, FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume at one second, L = litre;

When compared study group and control group cases there was statistically significant difference in most of the spirometric parameters at the end of study. Average vital capacity of study group was 2.1 litres (89.1%) while as in control group it was 2.6 litres (109.1%) (p<0.05). Average forced vital capacity in study group wads 2.4 litres (96.7%) compared to 2.7 litres (102.3%) in control group (p<0.05). Average FEV1 in study group was 1.8litres (93.4%) compared to 2.2 litres (96.4%) in control group (p>0.05).

Table 4: Comparison of baseline (0 month) and final (24 month) spirometric parameters in control group cases (n = 50)

Spirometric Parameter	Base line (0 month) Mean±SD	Final (24 month) Mean±SD	p-value
VC Measured (L)	2.6 ± 0.6	2.6 ± 0.5	0.824 (NS)
VC Percentage	107.2 ± 32.3	109.1 ± 29.7	0.286 (NS)
FVC Measured (L)	2.8 ± 0.5	2.7 ± 0.5	0.050 (NS)
FVC Percentage	108.9 ± 36.0	102.3 ± 33.4	0.075 (NS)
FEV1 Measured (L)	2.2 ± 0.6	2.2 ± 0.6	0.169 (NS)
FEV1 Percentage	99.0 ± 31.4	96.4 ± 31.0	0.534 (NS)
FEV1/FVC Measured	96.5 ± 14.9	95.3 ± 14.9	0.424 (NS)
FEV1/FVC Percentage	99.8 ± 15.2	100.5 ± 13.5	0.722 (NS)

Abbreviations: VC = Vital Capacity, FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume at one second, L = litre;

Comparison of various spirometric parameters in control group between baseline and closure time of study at an interval of about 2 years revealed insignificant change and were in the normal range.

Discussion

Both earlier diagnoses of the breast cancer and novel chemo radiation therapy strategies have resulted in a considerable improvement in breast cancer survival. Apart from the clear benefits of adjuvant chemo radiation, we should be aware of the potentially increased risk of pulmonary sequelae following specific radiotherapy regimens in long-term breast cancer survivors. The purpose of this study was to analyze and assess the pulmonary implications in survivors of carcinoma breast patients treated with postoperative chemo radiation and ±hormone therapy. This was a prospective case control study in which fifty breast cancer patients and fifty healthy volunteers from general population were included. Patients who refused to consent and had other co morbidities were not included the study. Lung function was evaluated by spirometry at six monthly intervals over a period of two years.

The study group and control group cases were comparable according to their personnel habits and characteristics. Most of them were middle aged at presentation. The age at presentation among the studied breast cancer patients was 47.3±5.8 years, this age of presentation was in accordance with the study of Sunita Sexana et al[10], Raina V. et al[11], Fakhro A.E. et al[12], Priya Hazrah et al[13]. In our study most of the patients (70%) belonged to rural area where as 30% belonged to urban area. This was probably due to the reason that more than 75% of population of Kashmir reside in the rural areas. With regard to the parity among the breast cancer patients, all the patients in our study were multiparous and married, although nulliparity is a risk factor for breast cancer. This was comparable to figures shown by Sexana et al[10].

The tumour location for most 35/50 (70%) of patients was on the left breast. Left breast tend to be more involved in breast cancer compared to the right breast and the most common location being upper outer quadrant[14]. A palpable lump was present in 100% patients while discharge from the nipple was the commonest symptom 14 (28%) patients, followed by pain in breast in 6 patients, comparable with figures of A. Mehmood et al[15]. Majority 36/50 (72%) of the patients had tumour size between 2cm and 5 cm. Lymph node positive status was present in 45/50 (95%) of cases. These findings of advanced disease presentation in the form of node positivity were in accordance with the study conducted by Arshad Mehmood et al[15]. All the patients were treated with surgery followed by chemo radiation. All patients had intraductal carcinoma on histology, figures comparable with the study conducted by Arshad et al[91]. Mastectomy with lymph node dissection was the surgical procedure done in majority of patients 44/50 (88%), and in six (12%) patients breast conservation surgery was done. Breast conservation surgeries are done for early stage localized breast cancer while as modified radical mastectomy is the surgical procedure of choice for locally advanced disease[91].

At the beginning of study various spirometric parameters were compared between study group and control group cases. There was statistically significant difference in most of the spirometric parameters at base line (0-month). Average vital capacity of study group was 2.2 litres (89.4%) while as in control group it was 2.6 litre (107.2%)($p<0.05$). Average forced vital capacity in study group wads 2.4 litres (97.7%)compared to 2.8 litres (108.9%) in control group ($p<0.05$). Average FEV1 in study group was 1.9 litres (93.8%) compared to 2.2litres (99%) in control group ($p<0.05$). These findings were in accordance with the prospective study of CC Ooiet al, (2001), which had showed that adjuvant loco-regional radiotherapy, a common practice in breast cancer treatment, is associated with irreversible lung function parameters. The changes were accompanied by radiological evidence of persistent lung injury. FEV1, FVC, TLC and

DLC, progressively declined after radiotherapy and was irreversible at 12 months. Patients who received chemotherapy did not have significantly different lung function indices compared with their counterparts at all times points[6].

While assessing pulmonary functions in the study group cases, revealed slight restrictive ventilatory impairment in contrast to control group cases in the form of reduction in various spirometric parameters, as concluded by May Brit Lund MD, et al[16]. Radiation and chemotherapy have synergistic effect on reduction in the spirometric parameters as reported by Jacqueline C.M. Theuws, et al[54]. The restrictive ventilatory impairment in breast cancer patients is due to the radiation induced pulmonary fibrosis as evaluated by Huang EY, Wang CJ, et al[17].

Conclusion

Apart from the clear benefits of adjuvant chemo radiation, we should be aware of the potentially increased risk of pulmonary sequelae following specific radiotherapy regimens in long-term breast cancer survivors. Adjuvant therapies have been shown to have a significant impact on reducing the risk for breast cancer recurrence and overall mortality, associated with adverse events which are frequently over shadowed by the well demonstrated clinical efficacy. Awareness of long term sequelae will help oncologists contribute to their "cured" patients' lifelong well being during long term follow-up and improve their quantity and quality of life[4]. It is important to realize that our role as oncologists is not only to treat the tumour but also to improve the quality of life of our patients by preventing and treating the long term toxicities induced by chemo radiation.

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