Pulmonary toxicity of hypo-fractionated chest wall irradiation in breast cancer patients post mastectomy

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Abstract

Background: Patients' chances of surviving breast cancer have increased thanks to multimodal therapy. After breast-conserving surgery, hypofractionated radiation (RT) is quickly becoming one of the alternatives for breast cancer patients (BCS).

Objectives: The present study aimed to assess the thoracic radiotherapy's effects on patients with breast cancer's ability to breathe normally and engage in physical activity.

Patients and methods: This was a prospective study which was carried out at Oncology Department & Chest Department of Qena University Hospitals. Spirometry was performed to all included patients to assess their lung function.

Results: The mean and range of spirometer values 3 months after radiotherapy. The mean FEV1 was 65 % predicted, the mean FVC was 62.7 % predicted, the mean FEV1/FVC was 83.7% and the mean $FEF_{25\%-75\%}$ was 70.27 % predicted.

Conclusion: In radiotherapy, the lung is a major organ at risk because of the risk of radiation-induced lung injury. Silent radiation pneumonitis is a common side effect of radiotherapy. FEV1 and FVC parameters are decreased after radiotherapy due to acute radiation-induced lung injury. Spirometry can be used in assessing lung functions after radiotherapy. N3 stage showed significant decrease in FEV1 and FVC compared to other lower N stages. Max. lung dose was found to be the best predictor of the occurrence of radiation pneumonitis.

Keywords: Radiotherapy; Breast cancer; Radiation pneumonitis; Respiratory function; Pulmonary toxicity.
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Introduction

Globally, cancer is remains the biggest cause of mortality. One of the most prevalent malignant tumours in women worldwide is breast cancer. Breast cancer, which accounts for around 32% of all female cancer cases in Egypt, is also the leading cause of cancer-related mortality. **(Yehia et al., 2019).**

There is increased attention to women in our country. For example, the Egyptian Women's Health Initiative, launched by President Abdel Fattah Elsisi, which aims to promote women`s health nationwide. The main objectives of this initiative, regarding breast cancer, intended to raise awareness of breast cancer, the value of early detection, breast cancer screening, and the need to treat cases of the disease in accordance with current guidelines. Participants are not charged for suspected cases that are forwarded for additional examination and treatment. **(Alorabi and Elghazawy, 2021).**

In the early stages, after surgery, used to remove any remaining cancer cells and that improve recurrence. It even may be used intra-operative as one high dose to tumor or tumor bed with breast-conserving surgery in early-stage patients. It may be used also in the late stages when the breast cancer is unresectable or metastatic to bones, lungs, brain, and liver. In that stage, RT is used to reduce complications e.g. to reduce pain, decrease bleeding risk, improve breathing and relieve spinal cord pressure symptoms **(Hennequin et al., 2016).**

The main short-term side effects are fatigue, breast swelling, and skin changes like redness, soreness, skin peeling, or darkening of the skin**(Emami, 2013).**The majority of side effects progressively subside in the weeks or months following treatment, however long-term side effects can persist or may begin a few months later. or even years later on such as lymphedema (arm swelling), breast shrinking, breastfeeding problems, breathing problems, heart problems, ribs fracture and very rarely development of another cancer **(Hennequin et al.,2016).**

Common symptoms of RP include shortness of breath, cough, chest pain, blood-tinged sputum, low-grade fever, and generalized weakness. Frequently symptoms go away on their own, although steroids treatment is required in some patients. Most cases respond well and recover with steroids, but if the condition persists that means pulmonary fibrosis unfortunately developed **(Hanania et al., 2019).**

Spirometry, as a tool, is non-invasive, objective, reproducible, and sensitive to early changes, besides measuring lung volumes and capacities. It also presents information about the responsiveness of airways, the influence of disease on lung function, the prognosis of the disease, and response to therapeutic interventions **(Graham et al., 2019).**

Patients and Methods

This was a prospective study which was curried out at oncology Department & Chest Department of Qena University Hospitals. Total dose of chest wall irradiation 4272 cGY. Dose/ fraction 267 cGY Tumour involvement is more than 95%.

Inclusion criteria: Breast cancer patients underwent modified radical mastectomy or breast conservative surgery with

- T3 (>5 cm tumor), T4 (skin/chest wall invasion) or stage III tumor
- Involvement of axillary lymph nodes
- Positive surgical margin
- Gross extracapsular invasion in axilla
- Gross residual disease
- Invasion of pectoral muscle fascia
- Inadequate axillary dissection (<6 or <10 lymph nodes excised)
- Multiple primary tumors (multicentricity)

and no age limitation

Exclusion criteria: Other causes of pneumonia and other causes of lung fibrosis.

All of the participants will be subjected to the following: Full history (demographic data. personal history, drug, family, and surgery history), general examination including vital signs, body mass index (BMI) and systematic examinations.

This study has been given approval by the Ethics Committee of Faculty Of Medicine, south valley University, Qena, Egypt. (Ethical approval code is SVU-MED-ONM027-1-21-7-219).

- **Investigations: pulmonary function test**: radiographic investigation (CT chest , X-ray chest)

Research outcome measures: Primary (main): Assessment of pulmonary toxicity after chest wall irradiation. **Secondary (subsidiary): early &late pulmonary complication of chest wall irradiation & TTT**

Statistical analysis

The collected data was, tabulated, and statistically analyzed using SPSS program (Statistical Package

for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1. Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) and minimum & maximum of the range and for numerical non parametric whereas they were completed for categorical data as number and percentage, data as median and first and third interquartile range. Chi square test for independent groups was used for inferential analyses of qualitative data. P values under 0.05 were used to determine significance; values beyond this threshold are non-significant. The p-value is a statistical indicator of the likelihood that the findings of a study may have been the result of chance.

Limitation of the study

This study was done among 30 patients with Breast cancer according to sample size equation and low rate of patients as most patients were metastatic and indeed of adjuvant radiotherapy

Results

This prospective cohort study was done among 30 patients with Breast cancer after mastectomy at Oncology Department of Qena University Hospital. **Table (1)** shows 30 female patients' baseline characteristics.

Table 1. Baseline characteristics among the studied patients

Variables	**Patient characteristics**		**Studied patients (n=30)**	
			No.	**%**
Age (years)	**Range**	(35 - 79)		
	Mean ± SD	54.57 ± 11.42		
Body mass index (BMI) (Kg/m2)	**Range**	(19.5 - 29.85)		
	Mean ± SD	25.12 ± 5.16		
Menopause	Pre-menopausal		13	43.3
	Post-menopausal		17	56.7
Comorbidity	Hypertension (HTN)		11	36.7
	Diabetes mellitus (DM)		7	23.3
	Chest diseases		13	43.3
Side	Right		18	60.0
	Left		12	40.0
Pathology	Invasive ductal carcinoma		28	93.3
	Invasive lobular carcinoma		1	3.3
	Ductal carcinoma in situ (DCIS)		1	3.3
Chemotherapy received	Adjuvant (after surgery)		23	76.7
	Neoadjuvant (before surgery)		7	23.3
	Hormonal		12	40.0
TNM staging	**T-stage**	T0	1	3.3
		T1	0	0.0
		T2	23	76.7
		T3	6	20.0
	N-stage	N0	9	30.0
		N1	8	26.7
		N2	8	26.7
		N3	5	16.7
Type of surgery	Modified radical mastectomy		23	76.7
	Breast conservative surgery (BCS)		7	23.3

Most patients on clinical examination were asymptomatic (grade 1) , (**Table.2**). The mean (± SD) of lung dose was 3306.13 ± 774.94 while the mean (± SD) of volume 20 was 1475.60 ± 508.39 (**Table.3**).

Table 2. Incidence of clinical radiation pneumonitis in the studied patients

Variables		NO.(30)	%
CTCAE v.5 pneumonitis*	Grade 1	25	83.3%
	Grade 2	5	16.7%

*CTCAE v.5 means Common Terminology Criteria for Adverse Events (CTCAE) v5. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated while grade 2 means Symptomatic; medical intervention indicated; limiting instrumental ADL

Table 3. Maximum lung dose in the studied patients

Variables		Studied patients (n=30)
Maximum lung dose	Range	(1506 – 4945)
	Mean ± SD	3306.13 ± 774.94
Dose of Volume 20 (D20)	Range	(327.0 – 2647.0)
	Mean ± SD	1475.60 ± 508.39

Table 4. CT chest finding of pulmonary toxicity of hypo fractionated radiotherapy on chest wall in breast cancer patients

Variables	Basal		After 6 months	
	N	%	N	%
Metastasis	0	0.0%	1	3.3%
Lymphadenopathy	0	0.0%	5	16.7%
Lung fibrosis	0	0.0%	13	43.3%

** SD=standard deviation*

CT chest finding showed no pulmonary toxicity of hypo fractionated radiotherapy on chest wall in breast cancer patients. Meanwhile, after 6 months of radiotherapy one case developed metastasis, five cases had lymphadenopathy and thirteen cases developed lung fibrosis (**Table.4**).

Table 5. Spirometric parameters 3 months after radiotherapy

Variables	Mean	SD	Minimum	Maximum
Forced expiratory volume (FEV1) (% predicted)	65.00	12.01	35.00	96.00
Forced vital capacity (FVC) (% predicted)	62.70	13.76	35.00	110.00
FEV1/FVC (%)	83.70	16.12	35.00	105.00
Forced expiratory flow (FEF25-75%) (% predicted)	70.27	24.26	6.00	109.00

** SD=standard deviation*

The mean and range of spirometer values 3 months after radiotherapy. The mean FEV1 was 65 % predicted, the mean FVC was 62.7 % predicted, the mean FEV1/FVC was 83.7% and the mean $FEF_{25\%-75\%}$ was 70.27 % predicted (**Table.6**).

Table 6. Validity of Max. lung dose, V20, FVC change (%) and FEV1 change (%) to predict the occurrence of radiation pneumonitis

Variables	Cutoff value		Specificity	Sensitivity	P-value
Max. lung dose	>3679	0.784	76%	80%	0.007 S
Volume 20	>1372	0.548	56%	80%	0.636 NS
Forced vital capacity (FVC) change (%)	>0.0	0.580	28%	100%	0.536 NS
Forced expiratory volume (FEV1) change (%)	>20	0.724	68.00	80%	0.724 NS

ROC curve analysis for the optimal cutoff values of Max. lung dose, d20, FVC change (%) and FEV1 change (%) to predict the occurrence of radiation pneumonitis. The max. lung dose was significantly associated with RP. The largest area under the ROC curve was that of max. lung dose followed by FEV1 change

Discussion

With multimodality therapy, breast cancer patients' survival has increased (**Von Minckwitz et al., 2021**). After breast-conserving surgery (BCS), hypofractionated radiotherapy (RT) is quickly becoming one of the alternatives for breast cancer patients (START Trialists, 2008), yet there is a dearth of information on hypofractionated postmastectomy radiation treatment (PMRT). Concerns about RT's long-term effects are constant, especially when regional nodal irradiation is involved (RNI). Locoregional radiation's potential survival advantage must be weighed against its long-term side effects (**Early Breast Cancer Trialists' Collaborative Group, 2000**).

Following mastectomy, **Wang et al. (2019)** carried out a randomised study in high-risk people. After five years, they demonstrated equivalent clinical outcomes and late toxicity with standard and hypofractionation. Similar dose fractionations were used in a PMRT situation with a small number of patients in a few trials from Canada and the United States, albeit RNI was not utilised in those research (**Whelan et al., 2010**).

Therefore, global data on PMRT and RNI are required to confirm their long-term safety in breast cancer patients. As a result, many radiation oncology organisations are reluctant to recommend hypofractionated RNI. There might also be research on breast cancer radiation. Our clinical outcomes for patients with breast cancer who received local and RNI at 3 weeks after surgery have previously been published. (**Yadav and others, 2015**)

The major objective of this study was to assess the effects of thoracic radiation on exercise tolerance and respiratory function in breast cancer patients. This prospective cohort study was done among 30 patients with Breast cancer after mastectomy at Oncology Department of Qena University Hospital. 3D radiotherapy technique was used for all studied cases. The present study showed that the mean age of the studied females was 54.57 ± 11.42 years. Mean BMI was 25.12 ± 5.16. According to the menopausal state, 43.3% were pre-menopausal, and 56.7% were post-menopausal. 36.7% had hypertension, 23.3% had diabetes and 43.3% had Chest diseases. 60% were right sided. The majority (93.3%) had Invasive ductal carcinoma. Chemotherapy received was receive pre-surgery in 76.7% and post- surgery in 23.3%, Hormonal therapy received in 40%. As regard T staging, there were 76.7% had T2 stage and 20% had T3. As regard N-stage N0, N1, N2 and N3 were found in 30.0%, 26.7%, 26.7% and 16.7% respectively. Type of surgery was 76.7% Modified radical mastectomy and 23.3% were treated with Breast conservative surgery (BCS).

In line with the present study **AlSaeed et al., (2017)** was to evaluate the effects of locoregional post-mastectomy radiotherapy on the pulmonary function tests (PFTs) in 20 breast cancer patients (PMRT).

The median age of the group was 44.95 years (range: 25–68). Three patients (15%) had comorbidities that were known (hypertension and diabetes). 85% of the cohort, or 17 individuals, had breast cancer on the left side. 65% of the sample had N2 status, and 85% had progressed primary (T3 and T4 stages). Additionally, **Yadav et al. (2020**) used a two-dimensional (2D) technique to assess the late-term results of 1770 patients with stage II and stage III breast cancer who received hypofractionated local and RNI 3 weeks after mastectomy. 48 years old on average (range, 19 to 75 years). The majority 72% were more than 40 years. 55% were right sided. As regard T staging, there were 51% had T1 stage and 37% had T2. As regard N-stage N0, N1, N2 and N3 were found in 37.0%, 34%, 22% and 8% respectively.

Chemotherapy received in 64% and hormonal therapy received in 74%.As well, **Khan et al., (2014)** aimed to assess the impact of hypofractionated RT postmastectomy, in breast cancer patients, on pulmonary function tests (PFT). The study enrolled 59 female patients of breast cancer. Majority of the patients were in 41 to 60 years age group (67.8%), with a median age of 49 years. 84% of patients were T3- stage. As regard N-stage N0, N1, N2 and N3 were found in 19/59,

18/59, 16/59 and 6/59 respectively. Also, **Mehnati et al., (2021)** had a median age of 49.37 years in their work. Fifteen with right breast cancer and 17 with left-sided. Twenty had modified radical mastectomy and the remaining 12 had breast-conserving surgery.

The study by, **AlSaeed et al., (2017)** reported that most patients were positive Estrogen receptor (70%), positive progesterone receptor (50%) and negative Human epidermal growth factor receptor 2-neo (Her2/neu) (75%). While, **Yadav et al., (2020)** revealed thatpositive Estrogen receptor (49%) and positive progesterone receptor (41%)

As regard the incidence of clinical radiation pneumonitis in the studied patients, the present study showed that most patients (83.3%) on clinical examination were asymptomatic (grade 1). However, **AlSaeed et al., (2017)** reported that all patients were found asymptomatic (grade 1). **Abdali et al., (2018)** after completion of RT, 46 (90.1%), and 5 patients (9.8%) exhibited, Grades 0 and 1 pulmonary functional abnormalities, according to the Common terminology criteria CTC Version 2.

Pneumonitis of grade 1 patients exhibited symptoms. Their results are rather comparable to ours. The results of the current investigation showed that the mean (SD) of volume 20 was 1475.60 508.39 and the maximum (SD) lung dosage was 33.06 7.74 (Gy). In agreement with the present study **Abdali et al., (2008)** reported that the maximum (± SD) of lung dose was 32.35 (Gy) while the mean was 7.22 Gy

The study by **Mehnati et al., (2021)** reported that the mean lung dose was 10.76 ± 3.11 Gy. Furthermore, the study by **Fragkandrea et al., (2013)** reported that the mean lung dose and V20 were significantly associated with the incidence of Pneumonitis in patients received hypofractionated RT. Pre- radiotherapy treatment the present study showed that the mean FEV1 was 75.77 % predicted, the mean FVC was 66.13 % predicted, the mean FEV1/FVC was 88.17% and the mean FEF25%-75% was 69.77 % predicted. At 3 months post-treatment the mean FEV1 was 65 % predicted, the mean FVC was 62.7 % predicted, the mean FEV1/FVC was 83.7% and the mean FEF25%-75% was 70.27 % predicted. At 6 months post-treatment the mean FEV1 was 57 % predicted, the mean FVC was 54.13 % predicted, the mean FEV1/FVC was 82.37% and the mean FEF25%-75% was 64.13 % predicted. Statistical analysis of these data showed that there was a highly statistically significant decline in FEV1 and FVC after radiotherapy compared to before radiotherapy. Concerning Forced expiratory volume (FEV1), the delta change FEV1 was 10.77 between basal and after 3 months of radiotherapy, 18.6 between basal and after 3 months of radiotherapy and 7.83 between 3 and 6 months after radiotherapy.

Regarding Forced vital capacity (FVC), the delta change FVC was 3.43 between basal and after 3 months of radiotherapy, 12 between basal and after 3 months of radiotherapy and 8.57 between 3 and 6 months after radiotherapy.

Regarding FEV1/FVC, the delta change was 4.47 between basal and after 3 months of radiotherapy, 5.8 between basal and after 3 months of radiotherapy and 1.33 between 3 and 6 months after radiotherapy.

These results are in agreement **AlSaeed et al., (2017)** who worked on 20 breast cancer female patients with a dose of 50 Gy in 25 fractions (5 weeks) was prescribed to the chest wall, SC, and level III axillary nodes. Spirometry has been done before treatment with radiation and repeated after 30 and 90 days. A significant decrease in FVC and FEV1 after 3 months of completion of radiotherapy (p-value = 0.033 and 0.042, respectively), the same parameters when measured after 1 month of radiotherapy decreased but without statistical significance. FEF25-75% and FEF50% were not affected at 1 month or 3 months.

Also, in line with our study **Mehnati et al., (2021),** who assessed FVC and FEV1 on 32 patients, found that the spirometry parameters showed significant reductions after 3 and 6 months of radiotherapy end (50 Gy in 25 fractions), especially in the patients who presented with grades 1 and 2 radiation pneumonitis.

In contrast, **Khan et al., (2014)** investigated PFTs before the start of RT, then at 3 and 6 monthly intervals to assess the baseline status and then early and late effects on lung functions. The mean of FEV1 and FVC before and after radiotherapy (19-22 days course) showed a decrease in the values with no statistically significant difference.

As well, **Jeba et al., (2015)**as comparison to the baseline, there was a substantial decline in the mean FEV1, mean FVC, and mean TLC after

12 weeks (p 0.001). The decline in pulmonary function parameters was less severe in those who did not develop radiation pneumonitis (RP). The mean FEV1 and FVC fell by 9% and the TLC dropped by 14% in those with RP. However, there was a statistically significant difference in TLC between the two groups (p=0.02). Similarly, N3 showed significant decrease in FEV1 compared to other lower N stage (p<0.001). There is no statistically significant difference in mean values of change in FEV1 and groups classified according to age, menopause, comorbidity, site of mass, T-stage, as well as chemotherapy (p>0.05)These results are in line with **Mehnati et al., (2021),** when they assessed age, tumor location, stage, and surgery type found that there is no correlation between patient and treatment-related factors with pulmonary function decrease at 3 and 6 months after radiation treatment.

Abdali et al.,(2018), also observed no correlation between age, tumor site, the surgery type, and stage with change in spirometry parameters values.

Khan et al., (2014),claimed that rising radiation lung injury was not influenced by either age orchemotherapy. The best cutoff values for the variables Max. lung dose, V20, FVC change (%), and FEV1 change (%) to forecast the development of radiation pneumonitis were determined via ROC curve analysis.

Maximum lung dosage and RP were substantially correlated. Max. lung dosage and FEV1 change had the two areas under the ROC curve that were the biggest. In keeping with our findings, **Abdali et al. (2018)** revealed that only the Mean lung dosage parameter was statistically significant (P value 0.05), together with the ROC curve, Mean lung dose, and V20 risk factors. Our results were supported by **Fragkandrea et al., (2013)** who found that the incidence of Pneumonitis on hypofractionated CT was significantly associated with higher Mean Lung Dose, and V_{20}.

Conclusion

In radiotherapy, A main organ at danger from radiation-induced lung injury is the lung.. Silent radiation pneumonitis is a common side effect of radiotherapy. FEV1 and FVC parameters are decreased after radiotherapy due to acute radiation-induced lung injury. Spirometry can be used in assessing lung functions after radiotherapy. N3 stage showed significant decrease in FEV1 and FVC compared to other lower N stages. Max. lung dose was found to be the best predictor of the occurrence of radiation pneumonitis. It will take more research with a larger sample size and a longer follow-up period to confirm our findings and pinpoint the risk factors for unfavourable outcomes.

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