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Investigation of Pulmonary Complications Induced by Radiotherapy and Chemotherapy in Patients with Breast Cancer through Spirometry, CT Scan Imaging Patterns, and Clinical Criteria in a Six-Month Follow-Up

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Abstract

Background: The aim of this study was to determine pulmonary complications induced by radiotherapy and chemotherapy in patients with breast cancer in a six-month follow-up.

Method: 80 patients with breast cancer who were referred to the Radio-oncology Center in Kerman were included in the current cohort study.

At the baseline, spirometry and lung scan were obtained and all the patients were asked about their respiratory symptoms. After designing the patient's treatment, dose volume histogram data was extracted. All the tests were repeated six months after radiotherapy. The prevalence of pneumonitis and fibrosis in radiographs were determined clinically and the reduction in the values of pulmonary function test parameters was determined.

Results: In 40% of the patients, pulmonary volume was reduced and in 10%, pulmonary fibrosis occurred. Regarding pulmonary function before and six months after radiotherapy, the results revealed that FeV1 (l/s) parameter decreased from 2.68 to 2.48 ($P < 0.0001$) six months after radiotherapy. FVC parameter also showed a decrease from 3.14 to 2.91 ($P < 0.0001$) in the same span of time. The odds of developing clinical symptoms in people with pulmonary fibrosis was five times higher than of those without this condition, (odds ratio: 5.51, 95% confidence interval: 1.10 - 27. 42), which was statistically significant ($P = 0.03$). None of the factors, including mean lung dose, tamoxifen, and age, affected Fev1 and pulmonary fibrosis.

Conclusion: Our results indicated that 10% of the patients undergoing treatment for breast cancer developed pulmonary fibrosis and 40% of the patients suffered from reduced pulmonary volumes, which was not associated with chemotherapy regimen or the use of tamoxifen.

Keywords: Radiotherapy, Chemotherapy, Breast neoplasms, Complications

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Introduction

Breast cancer is the most prevalent non-skin cancer, the most common malignancy, and the second leading cause of death from cancer among women after lung cancer.[1, 2] In Iranian women, breast cancer is the second most common cancer following skin cancer. Among the different types of cancer in women, 23% of cancer deaths are due to breast cancer.[3, 4]

Postoperative regional radiotherapy is an important factor in the treatment of breast cancer reducing regional recurrence and increasing overall patient survival. Reducing the complications of radiotherapy is important since most patients with breast cancer have a long-term survival.[5] Once radiotherapy is given to the chest or breast, radiation to a part of the lung is unavoidable and this accidental exposure can increase the possibility of pneumonitis and fibrosis.[6] The prevalence of radiation-induced pneumonitis has been reported to be 1%-80% in various studies; this wide range of incidence is due to the variety of simulation techniques, treatment program, total dose, use of photons/electrons, and the use of different sample grading systems. In a recent meta-analysis of 10 different studies on the prevalence of early pulmonary complications of radiotherapy in patients with breast cancer, the overall incidence of clinical and radiological pneumonitis was reported to be 14% and 42%, respectively.[5]

In addition to reducing the quality of life, radiation-induced pneumonitis can lead to oxygen dependence.[7-9]

On the other hand, chemotherapy drugs can cause pulmonary complications, such as asymptomatic radiological changes to severe respiratory problems, which is almost a common symptom. In fact, some types of pulmonary complication occur in 10%-20% of all the patients receiving any type of antineoplastic drug.[10]

Radiation-induced pneumonitis could occur 4-12 weeks after radiotherapy. In most cases, radiation-induced pneumonitis regress spontaneously or with steroid treatment although it can also develop into radiation-induced fibrosis as a long-term complication.[7] Diagnosis of radiation-induced pneumonitis is based on the radiological images and non-specific clinical signs with or without changes in pulmonary function tests (PFTs). In conventional radiotherapy, if PTV lung-v20 is higher than 30% and GTV lung-v20 is higher than 33%, it is considered to be a predictive factor of symptomatic pneumonitis. An average lung dose greater than 20 Gy is also a predictor. Although the rate of lethal pneumonitis is low, it is seen in large daily fractions.[12] Considering the importance and prevalence of radiation-induced pneumonitis, the objective of this research was to evaluate the pulmonary

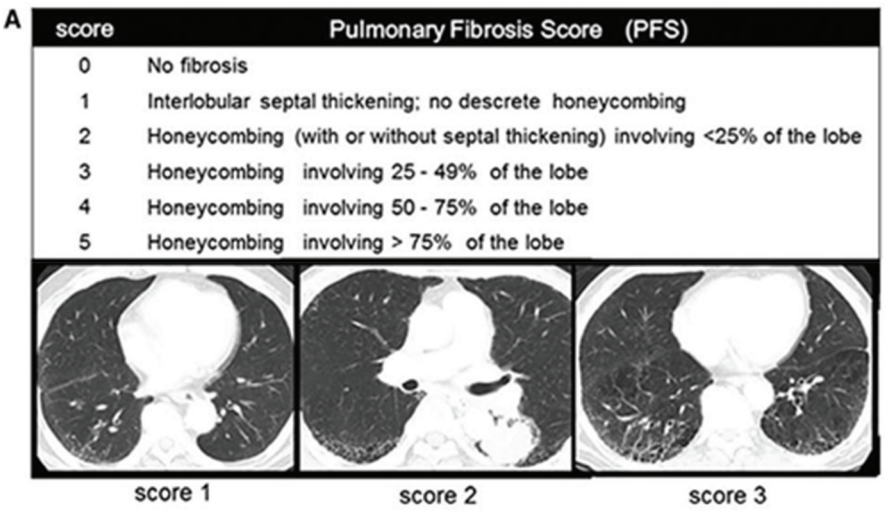

Figure 1. This figure shows pulmonary fibrosis scoring.

Table 1. Demographics and clinical information of patients at baseline

Variables	Level of variables	Patients with breast cancer (n=80)
Age, mean ± SD		50.79 ± 11.81
Chemotherapy type (%)	ACT	65 (81.3)
	CMF	15 (18.7)
Surgery (%)	BCT	39 (48.8)
	MRM	41 (51.2)
Side (%)	Right	48 (60)
	Left	32 (32)
Chemotherapy time (%)	Adjuvant	37 (46.3)
	Neoadjuvant	43 (53.8)
HER2 (%)	Negative	56 (70)
	Positive	24 (30)
ER/PR (%)	Negative	23 (23.8)
	Positive	57 (71.2)
Stage	Early	53 (66.25)
	Advance	27 (33.75)

ACT: Adriamycine, cyclophosphamide, paclitaxel; CMF: Cyclophosphamide-methotroxate-5fu; BCT: Breast conservating surgery; MRM: Modified radical mastectomy; HER2: HER2 NEU receptor; ER: Estrogen receptor; PR: Progesterone receptor; SD: Standard deviation

complications of radiotherapy and chemotherapy in patients with breast cancer via imaging, spirometry, and clinical models.

Methods

This work was performed as a prospective cohort study. The study population consisted of patients with breast cancer who referred to the Radio-oncology Medical Center of Afzalipour Hospital in Kerman. The present study was approved by the Ethics Committee of Kerman University of Medical Sciences (ethics code: 97000427).

In this cohort work, 80 patients with breast cancer referring to the Radio-oncology Center of Afzalipour Hospital were included from the beginning of treatment after being given comprehensive information about the study and obtained informed consents. Patients with a history of asthma, previous radiotherapy, metastasis, smoking, metastasis during follow-up, or death during follow-up were excluded from the study. Before radiotherapy, a questionnaire comprising demographic characteristics, history of chemotherapy, the affected breast side, family history, comorbidities, and patient's height and weight was completed. Information about the stage of the disease, type of surgery, the number of chemotherapy sessions and drugs, progesterone (PR) and estrogen receptors (ER), human epidermal growth factor receptor-2 (HER2), and histological data were extracted from the patient's medical record. We performed basic spirometry for the patients and a respiratory symptoms questionnaire was completed. After designing the specific treatment for the patients, several variables, including volume of the lung receiving 20 Gy or more (V20), dose determined for the treatment of the patient (DOSE), mean lung dose, dose volume histogram, number of fields, and the presence or absence of boost, were extracted. Following radiotherapy, the patients were followed up for six months and computed tomography (CT) scan and spirometry were performed. In addition, a questionnaire for clinical diagnosis of pneumonitis was completed again. At the end of the follow-ups, the prevalence of pneumonitis and fibrosis in radiographs and reduced levels of PFT parameters were determined. Grading criteria for radiation pneumonitis in lung CT scan was as follows: 0 for no change; 1 for ground glass opacities without fuzziness of the subjacent pulmonary vessels; 2 for the findings which may vary from ground glass opacities, extending beyond the radiation field to consolidation; 3 for clear focal consolidation ± elements of fibrosis; 4 for dense consolidation, cicatrisation atelectasis, (traction bronchiectasis), significant pulmonary volume loss and thickening. Fibrosis is defined as figure 1. The results of spirometry before and

Table 2. Pulmonary function tests performed before and six months after radiotherapy

Indexes	Baseline (Mean ± SD)	Six months later (Mean ± SD)	*P*-value
FEV1 (l/s)	2.68 ± 0.30	2.48 ± 0.35	<0.0001
FVC	3.14 ± 0.32	2.91 ± 0.38	<0.0001
FEV1/FVC	85.12 ± 2.12	84.81 ± 2.1	0<0.0001
PaO2	94.30 ± 1.71	94.15 ± 1.85	0.210

FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PaO2: Pressure arterial o2; SD: Standard deviation

after treatment were demonstrated as mean, median, and standard deviation. Their alterations were examined through SPSS software with paired t-test and their association with complications was examined employing logistic or linear regression. $P = 0.05$ was considered to be the level of significance.

Results

Herein, 80 patients with breast cancer were assessed. The mean age of the patients was 50.79 ± 11.81 years (age range: 28-72). The mean body mass index (BMI) of the subjects was 24.49 ± 4.23 kg/m^2 (BMI range: 17.60-34 kg/m^2). ACT was the frequent chemotherapy type among patients with breast cancer (n = 65, 81.3%). For more than half of patients, cancer occurred in the right breast (n = 48, 60%). HER2 and ER/PR were positive for 30% (n = 24) and 71.2% (n = 57), respectively. We applied chemotherapy before surgery (neoadjuvant) for more than half of patients (n = 43, 53.8%). The demographic and clinical information of patients is represented in table 1.

The results of our study revealed that pulmonary indexes significantly changed for patients after six months. FEV1 (forced expiratory volume in one second) and FVC (forced vital capacity) statistically decreased for the patients ($P \leq 0.001$), but FEV1/FVC increased six months later ($P \leq 0.001$). PaO2 did not experience any significant changes during this period ($P = 0.210$). Table 2 illustrates the pulmonary functions of the patients before and after the six-month follow-up.

According to bivariate logistic regression, the mean lung dose ($P = 0.011$) and radiologic fibrosis ($P = 0.032$) were related to develop clinical fibrosis following radiotherapy. The results showed that with each unit increased in mean lung dose, the odds of developing clinical fibrosis also increased (odds ratio (OR): 1.26, 95% confidence interval (CI): 1.03 - 1.53). Additionally, the patients with radiologic fibrosis had greater odds of developing clinical fibrosis versus the other patients (OR: 5.51, 95% CI: 1.10 - 27.42) (Table 3). The results of multivariable logistic regression model revealed mean lung dose to be the only predicting factor of developing clinical fibrosis after six months of radiotherapy (OR: 1.26, 95% CI: 1.03 - 1.53, $P = 0.011$).

Table 2 shows the results of paired t-test related to pulmonary function before and six months after radiotherapy. As shown in this table, FeV1 (l/s) decreased significantly six months after radiotherapy. Additionally, FVC also demonstrated a significant decrease during the same period of time. FeV1/FVC had a significant increase. Although a slight increase was reported for PaO2 parameter, the difference was not statistically significant.

The results of analysis indicated that the odds of developing clinical symptoms in people with pulmonary fibrosis was five times higher than of those without this condition, (OR: 5.51, 95% CI: 1.10 - 27.42), which was of statistical significance ($P = 0.030$). The results also revealed that with each unit decrease in Fev1, the odds of developing clinical symptoms increased more than eight times although this relationship was not statistically significant ($P = 0.203$). Regarding the type of treatment, the CMF diet increased the odds of developing clinical symptoms by 4%, (OR: 1.04, 95% CI: 0.2-5.42), compared with ACT, yet this relationship was not statistically significant ($P = 0.904$). The analysis also proved that age had no effects on the clinical symptoms (OR: 1.01, 95% CI: 0.95 - 1.07). However, it was shown that with

Table 3. The bivariate logistic regression models for developing clinical symptomatic fibrosis after radiotherapy

Variables	Level of variables	Crude odds ratio (95% CI)	*P*-value
Age		1.01 (0. 95 - 1.07)	0.650
FEV1		8.80 (0.29 - 259.56)	0.203
FVC1		0.74 (0.51 - 223.02)	0.121
FEV1/FVC		1.41 (0.56 - 3.57)	0.462
Mean lung dose		1.26 (1.03 -1.53)	0.011
Radiologic fibrosis	Negative1	-	-
	Positive	5.51 (1.10 -27.42)	0.032
Chemotherapy Type	ACT	1	-
	CMF	1.04 (0.2-5.42)	0.904
Surgery	MRM	1	-
	BCT	1.30 (0.36 - 4.69)	0.671
Chemotherapy time	Neoadjuvant	1	-
	Adjuvant	1.47 (0.41 - 5.28)	0.557
Side	Left	1	-
	Right	3.46 (0.69 - 17.22)	0.121
HER2	Negative	1	-
	Positive	2.19 (0.59 - 8.03)	0.232
ER/PR	Negative	1	-
	Positive	0.66 (0.17 - 2.53)	0.550
Stage	Early	1	-
	Advanced	0.39 (0.07 - 1.95)	0.251

ACT: Adriamycine, cyclophosphamide, paclitaxel; CMF: Cyclophosphamide-methotroxate-5fu; CI: Confidence interval; BCT: Breast conservating surgery; MRM: Modified radical mastectomy; HER2: HER2 NEU receptor; ER: Estrogen receptor; PR: Progesterone receptor; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PaO2: Pressure arterial o2

a single unit increase in the mean lung dose, the odds of incidence of decrease of FEV1 increased more than 26%, (OR: 1.26, 95% CI: 1.03 - 1.53), which was statistically significant (P = 0.011) (Table 3).

The results of bivariate logistic regression models demonstrated that developing radiologic fibrosis following radiotherapy was related to age (P = 0.002), FEV1 ($P \leq$ 0.001), FVC ($P \leq$ 0.001), FEV1/FVC (P = 0.041), mean lung dose (P = 0.023), clinical fibrosis (P = 0.030), ER (P = 0.033) and stage (P = 0.003). Based on the finding, by increasing one unit in the age of the patients, the odds of radiologic fibrosis increased (OR: 1.06, 95% CI: 1.02 - 1.11). By increasing 1/10 unit of FEV1, FVC, and FEV1/FVC, the odds of radiologic fibrosis respectively increased greater than five times (OR: 5.06, 95 %CI: 2.57 - 9.95), three times (OR: 3.87, 95% CI: 2.23 - 6.72) and one time (OR: 1.07, 95% CI: 1.00 - 1.14). Increasing one unit in mean lung dose led to increasing the odds of radiologic fibrosis greater than one time (OR: 1.22, 95% CI: 1.02 - 1.46). The results revealed that the patients with clinical fibrosis had higher odds of radiologic fibrosis in comparison with other patients without clinical fibrosis (OR: 5.51, 95% CI: 1.10 - 27.42). In the current work, the patients with positive ER/PR had greater odds of radiologic fibrosis versus the other patients (OR: 3.14, 95% CI: 1.12 - 8.82). The patients with advanced stages also had higher odds of radiologic fibrosis versus the patients in early stages (OR: 4.71, 95% CI: 1.69 - 13.31) (Table 4). Finally, age (P = 0.133), FVC ($P \leq$ 0.001), and FEV1/FVC (P = 0.032) could predict the development of radiologic fibrosis among patients with breast cancer (Table 4).

Table 5 describes the factors predicting FEV1 changes. According to the table, mean lung dose, tamoxifen, and age predicted 3%, 0.04%, and 1% of the changes in FEV1, respectively. However, based on the β-coefficient and R2, none of these factors had any effects on FEV1 alternation (P > 0.050).

Discussion

The findings of the present study on pulmonary function before and six months after radiotherapy

Table 4. The bivariate and multivariate logistic regression models for developing radiologic fibrosis after radiotherapy

Variables	Level of variables	Crude odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Age		1.06 (1.02 -1.11)	0.002	1.12 (1.02 - 1.22)	0.133
FEV		15.06 (2.57 - 9.95)	0.001	-	-
FVC		3.87 (2.23 - 6.72)	0.001	6.86 (2.50 - 18.78)	0.001
FEV1/FVC		1.07 (1.00 - 1.14)	0.041	1.19 (1.01 - 1.40)	0.032
Mean lung dose		1.22 (1.02 - 1.46)	0.023	-	-
Clinical fibrosis	Negative	1	-	-	-
	Positive	5.51 (1.10 - 27.42)	0.030	-	-
Chemotherapy Type	ACT	1	-	-	-
	CMF	2.33 (0.71 - 7.58)	0.150	-	-
Surgery	MRM	1	-	-	-
	BCT	0.60 (0.25 - 1.46)	0.260	-	-
Chemotherapy time	Neoadjuvant	1	-	-	-
	Adjuvant	1.35 (0.56 - 3.26)	0.500	-	-
Side	Left	1	-	-	-
	Right	1 (0.40 - 2.44)	1	-	-
Her2	Negative	1	-	-	-
	Positive	0.77 (0.30 - 2.05)	0.620	-	-
ER/PR	Negative	1	-	-	-
	Positive	3.14 (1.12 - 8.82)	0.033	-	-
Stage	Early	1	-	-	-
	Advanced	4.71 (1.69 - 13.31)	0.003	-	-

ACT: Adriamycine, cyclophosphamide, paclitaxel; CMF: Cyclophosphamide-methotroxate-5fu; BCT: Breast conservating surgery; MRM: Modified radical mastectomy; HER2: HER2 NEU receptor; ER: Estrogen receptor; PR: Progesterone receptor; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PaO2: Pressure arterial O2; CI: Confidence interval

indicated that FEV1 (l/s) decreased significantly in half a year. FVC also revealed a significant decrease six months after radiotherapy. Although a slight increase was reported for PaO2, this difference was not of significance. Accordingly, it was found that the reduction of pulmonary volume and pulmonary fibrosis occurred in approximately 40% and 10% of the patients, respectively. On the other hand, no decrease in the oxygen level was observed in any of the patients.

FEV is short for forced expiratory volume. FEV1 is the amount of air you can force from your lungs in one second. Forced vital capacity (FVC) is the total amount of air exhaled during the FEV test. In obstructive pulmonary diseases, the ratio of FEV1/FVC decreases.

As we mentioned above, the results showed a reduction of FEV1 and FVC, but no differences in the proportion of FEV1/FVC. This demonstrates the reduction of these pulmonary volumes (FEV1, FVC) without an obstructive component since there were no differences in the FEV1/FVC ratio before and after radiation.

Mehnati et al. (2020) also implied that FEV and FVC decreased three and six months after radiotherapy, which is consistent with the results of this work. However, only the decrease in FEV1 was significant.[13] In addition, AlSaeed et al. (2017) also reported a significant decrease in FVC, FEV1, and DLCO 90 days after treatment (Baseline 2.94, 2.52, 8.04 versus after 90 days 2.68, 2.30, 7.81, respectively), while VO2 max was not affected significantly. Although the findings indicated a limitation for pulmonary function, none of the patients had any symptom.[7] In another study by Goldman et al. (2014), the findings revealed that FEV1 and TLC after radiotherapy (RT) in long-term follow-up were reduced respectively by 9% and 7% ($P < 0.001$).[14] The findings of Abdemanafi et al. (2019) showed a decreasing trend in pulmonary parameters three months after radiotherapy and a slight improvement six months after treatment. These changes, three and six months after treatment, did not expose the patient to lung disease and irreversible reduction of lung volume.[15] In a study by Hernberg et al. (2002), the prevalence of clinical symptoms was 29% and the changes in CT scan were 48%, which occurred mostly in the first three months following radiotherapy.[16] In a study by Giridhar et al. (2015), a relationship

Table 5. Univariate linear regression analysis of FEV1 changes

Variable	B	R2	*P*-value
Mean lung dose	0.17	0.03	0.131
Tamoxifen	0.06	0.004	0.582
Age	0.1	0.01	0.370

FEV1: Forced expiratory volume in one second

between radiation pneumonitis and the total lung volume, mean lung dose, volume of the lung receiving 20 Gy or more (V20), and volume of the lung receiving 30 Gy or more (V30) was reported.[11] In the study of Lind et al. (2002), no association was found between the clinical symptoms of radiation-induced pneumonitis and its radiological symptoms.[17] Accordingly, it seems that radiation-induced fibrosis and pneumonitis are usually accompanied by factors, such as irradiated lung volume, mean lung dose, fractionation, concomitant use of chemotherapy and radiotherapy, use of supraclavicular field, radiotherapy techniques, cigarette smoking, tamoxifen, age, BMI, central lung distance (CLD), and pulmonary function before radiotherapy.

Inconsistent with the findings of the present work, the results of a study by Fragkandrea et al. (2013) indicated that there were no statistically significant decreases in the parameters FEV1, FVC, FEV 25, FEV 50, and DLCO in the two treatment groups at three and six months after RT completion.[18] A study by Khoshbin et al. (2011) implied that there were no differences between FEV1 and FVC before and after radiotherapy. In addition, no abnormal symptoms were observed in any of the patients.[19] The findings of this study proved that there were no significant relationships between the reduction of respiratory volumes and chemotherapy regimen. Moreover, we observed no significant relationship between tamoxifen consumption and respiratory volumes. However, Vasiljevic et al. (2018) reported that a combination of tamoxifen and Goserelin may increase the risk of developing pneumonitis.[21]

The incidence of pulmonary complications is probable as a result of radiation therapy for breast cancer; however, their severity varies according to different treatment conditions. Clinical complications of radiotherapy are divided into acute and chronic. Acute complications occur about 6-12 weeks after radiotherapy, which are reported as pneumonitis. Chronic complications occur 6-12 months following radiotherapy, which are reported as pulmonary fibrosis.[22, 23] Decreased pulmonary parameters after radiotherapy treatment may be due to incomplete lung expansion and as a result, air accumulation. This indicates restrictive pulmonary diseases.[24] This reduction in lung volume does not seem to have much effect on people's normal lives. Meanwhile, it can reduce a person's respiratory capacity during exercise or surgery, which should be considered seriously.[23] Several similar studies have reported chemotherapy to be a factor affecting the radiotherapy outcomes. Therefore, chemotherapy reduces diffusing capacity of the lung for carbon monoxide (DLCO),[22] which may lead to discrepancies in the findings.

Limitations

The limitations of this study include the small sample size and the limited follow-up time. It is also recommended to utilize additional diagnostic measures, such as high resolution CT (HRCT) or DLCO to assess the pulmonary function in patients more accurately. It is suggested to examine the effect of different radiotherapy methods on pulmonary volumes.

Conclusion

According to the results of this study, 10% of the patients with breast cancer undergoing radiotherapy and chemotherapy, developed pulmonary fibrosis and 40% had a reduction in lung volumes, none of which had any relationship with chemotherapy or tamoxifen consumption. Considering the problems induced by these parameters in the future physical activity and respiratory reservation of the patient, the

importance of paying attention to the design of the field in these patients is emphasized. Radiotherapy is an essential component of breast cancer treatment and cannot be disregarded. Sometimes this beneficial treatment comprises several complications, including pneumonitis and pulmonary fibrosis. In addition to optimal radiotherapy treatment, the prevention of acute and chronic complications, such as pneumonitis and pulmonary fibrosis, is of importance for patients with breast cancer. Thus, the patients' normal life is not affected with these complications and their quality of life does not decrease.

Conflict of Interest

None declared.

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