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ORIGINAL RESEARCH ARTICLE

Evaluation of delayed changes in pulmonary perfusion scan and pulmonary function tests after radiotherapy for breast cancer

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ABSTRACT

Introduction: The application of radiotherapy after performing surgery plays a vital role in the breast cancer treatment. In the current study, we investigated the effects of the radiotherapy for breast cancer on pulmonary perfusion scan (PPS) and pulmonary function tests (PFTs).

Methods: Fifty patients diagnosed with breast cancer with no history of lung diseases who had received radiotherapy after breast surgery and chemotherapy were selected. Mean lung dose (MLD) and volume percentage of the ipsilateral lung receiving a dose equal to or greater than 20 Gy (V20) were calculated for all patients. Quantitative PPS along with SPECT imaging as well as PFTs were performed on each patient before and 6 to 9 months after radiotherapy. For Data analysis, independent Samples t-Test and Pearson's correlation coefficient were used.

Results: There were 27 and 23 patients with right and left breast cancer, respectively. In both groups, the relative perfusion of the lung on the radiotherapy side decreased by an average of 5%, which was significant (P-value<0.05). Among 27 patients (54%), lung perfusion defects were observed in the SPECT images. No significant changes were observed between the PFTs before and after radiotherapy (P-value>0.05). No significant relationship was investigated between V20 and mean lung dose (MLD) with relative perfusion of the irradiated lung (P-value>0.05).

Conclusion: In this investigation, we demonstrated that quantitative PPS and lung perfusion SPECT were are more reliable than PFTs for evaluating lung following radiotherapy for breast cancer. However, the relative lung perfusion bore no relevancy to V20 and MLD.

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INTRODUCTION

Breast cancer is the most common cancer in women [1]. In the United States, one in every eight women would be diagnosed with this malignancy during their lifetime [2]. The researches show that the average age of individuals' being diagnosed with breast cancer in the Middle East [3], China [4], and Africa [5] is 48-49 years. Moreover, the early diagnosis of breast cancer has reduced mortality rate and increased the life expectancy of the patients [6, 7]. The patients diagnosed with breast cancer with favorable molecular subtypes have above 95% chance of survival over five-year period [8]. Therefore, reducing treatment-induced complications is of utmost importance in maintaining the quality of life among such patients.

Adjuvant radiotherapy after lumpectomy and mastectomy takes a prominent role in reducing the local recurrence of breast cancer and increasing the life expectancy of the patients [9]. Some studies have shown that radiotherapy of axillary lymph nodes improves disease-free life expectancy, even in the case of partial involvement [10]. The lung is a sensitive tissue to radiation, and pneumonitis, which can be clinically asymptomatic, but has been reported in about 13% of the patients after receiving radiotherapy [11, 12]. Lung fibrosis may develop months to years after the application of radiotherapy and can lead to progressive chronic shortness of breath in case of significant involvement [13]. In addition, the possibility of secondary lung cancer in patients with breast cancer who undergo radiotherapy is significantly higher than those who do not receive the therapy [14].

High-resolution computed tomography (HRCT) is a method with high sensitivity for diagnosing pneumonitis after radiotherapy in the early stages, but it is not usually used in follow-up of the patients [15]. Different results regarding pulmonary function tests (PFTs) following radiotherapy in the patients with breast cancer have been reported. AlSaeed et al. demonstrated that three months after the completion of radiotherapy in patients who underwent a mastectomy, there was a significant decrease in PFTs [16]; however, the study by Jaén et al. showed that the decrease in PFTs after radiotherapy was slight and indexes returned to the previous values in two years [17].

Pulmonary perfusion scan (PPS) has been used to detect radiation-induced pulmonary injury [18, 19]. Radiation leads to the destruction of epithelial and endothelial cells in the alveolar-capillary complex of the lung, resulting in hypoxia and decreased perfusion in the radiation area. Thus, PPS as a functional method may be helpful for the diagnosis of radiation pneumonitis [20]. Inasmuch as there is lack of consensus regarding the changes in PFTs after the application of radiotherapy for breast cancer and since there are few research articles on the evaluation of PPS in such patients, the results of PFTs with the findings of PPS are compared in this investigation.

METHODS

The current prospective study was approved by the ethical committee (code: IR.MUK.REC.1396/305) and conducted on women diagnosed with breast cancer for the first time and referred to the hospital to receive radiotherapy from January 2020 to November 2021. Patients with early breast cancer (stage I) and patients with a locally advanced disease (T4) or distant metastasis (stage IV) were excluded. Patients with current smoking or history of lung-disease were also excluded. The present study was the result of the research with ethics code/file number IR.MUK.REC.1396/305 approved and financed by the Kurdistan University of Medical Sciences. Sufficient explanations were given to the patients about PPS and PFT and written informed consent was obtained. All patients underwent breast-conserving surgery or modified radical mastectomy and received Adriamycin, Cyclophosphamide, and Paclitaxel. Four weeks after the completion of chemotherapy, conventional (3D-conformal) breast radiotherapy with four field single isocenter technique including supraclavicular and axillary nodal irradiation with a fixed dose of 50 Gy in 25 fractions (5 days per week) was applied to all patients. No boost dose was given to the patients. Mean lung dose (MLD) and volume percentage of the ipsilateral lung receiving a dose equal to or greater than 20 Gy (V20) were calculated for all patients. PPS and PFTs were taken for all patients before radiotherapy and 6 - 9 months (average 7.5 months) after the completion of radiotherapy. FEV1 (forced expiratory volume 1), FVC (forced vital capacity), and FEV1/FVC ratio were measured using a MIR Spirolab spirometer (MIRmedical, Roma, Italy). PPS was taken following IV injection of 185 MBq [^{99m}Tc]Tc-MAA (Macro-Aggregated Albumin) in the supine position. Planar imaging (1000 k counts per view, 256x256 matrix) and SPECT (64 views in a 360-degree rotation, 15 seconds per view, 64x64 matrix) were taken utilizing a dual-head ECAM Scintron (MiE Medical Imaging Electronics, Hamburg, Germany) using a low energy high-resolution collimator. SPECT images were processed following OSEM (ordered subsets expectation maximization) iterative reconstruction method (8 iterations and 4 subsets). Using Scintron7 software, relative perfusion in upper, middle, and lower regions of each lung in anterior and posterior views of planar images were automatically calculated. The geometric means of the relative perfusion automatically calculated from the anterior and posterior values by the software were used to compare quantitative relative perfusion of each lung before and after radiotherapy (Figure 1). The SPECT images were reviewed by a nuclear medicine specialist in a single-blinded manner. PFT results before and after radiotherapy were also recorded in a single-blinded manner. Using SPSS software, mean and standard deviation indices were calculated, an Independent Samples t-Test was administered to compare variables, and Pearson's correlation coefficient was measured to determine the extent of correlation between variables with quantitative PPS results after radiotherapy.

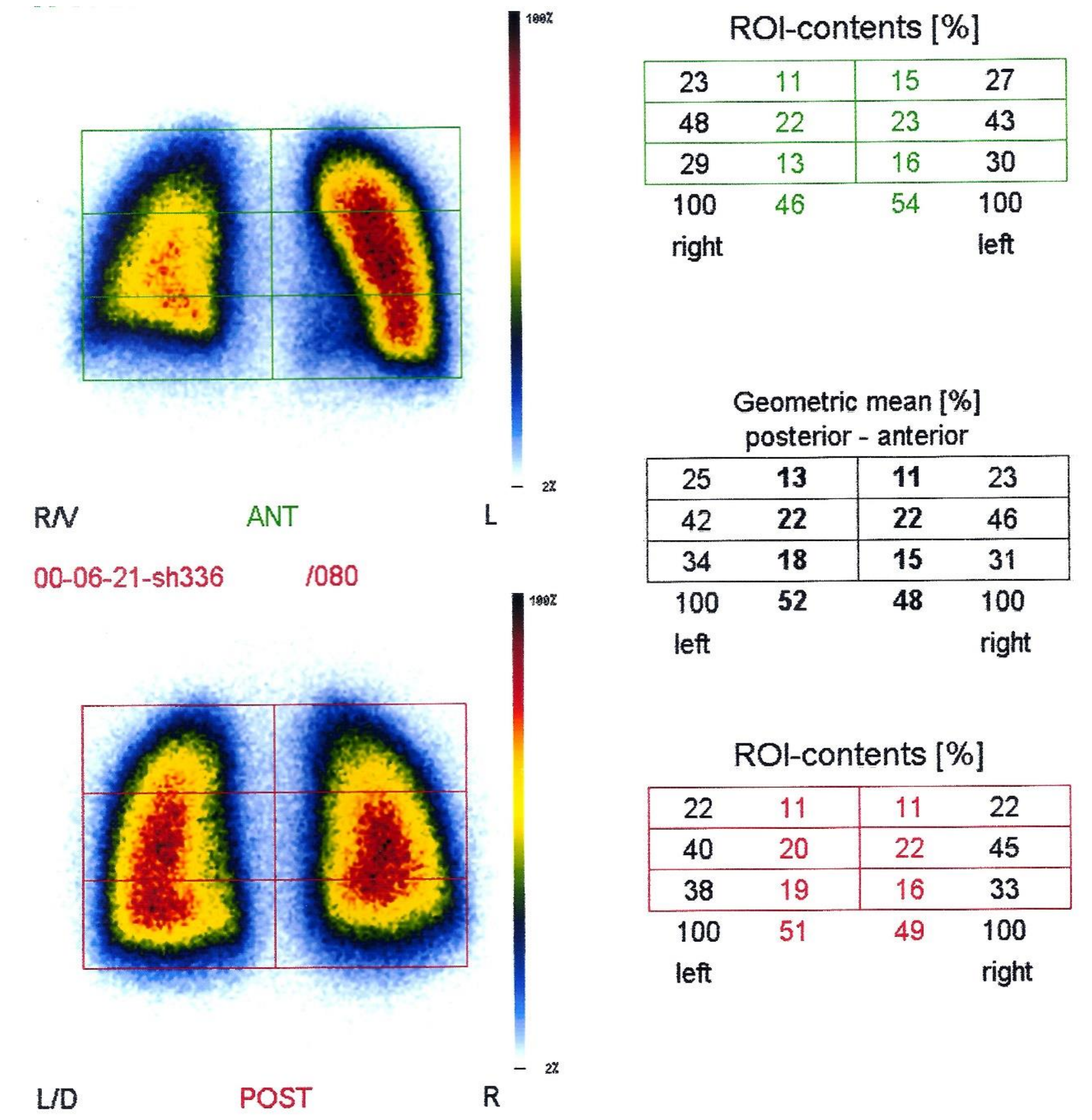

Figure 1. Automatic calculation of geometric means of relative perfusion in upper, middle, and lower regions of the lungs

RESULTS

Fifty women with breast cancer (27 right breast cancer, 23 left breast cancer) were evaluated. The demographic characteristics of the patients are shown in Table 1. Thirty-six patients (72%) were less than 50 years old. Twelve patients (24%) had normal BMI (18.5 to 24.9), and 38 patients (76%) had high BMI (≥25).

Table 1. Demographic characteristics of the patients

	Mean ± standard deviation	Minimum	Maximum
Age [years]	48.1 ± 10.1	29	73
Height [cm]	159.0 ± 6.2	138	175
Weight [kg]	71.0 ± 12.3	45	96
BMI	28.1 ± 4.9	18.7	39.8

No significant difference was observed between patients diagnosed with right and left breast cancer regarding the age, height, weight, BMI, V20, and MLD (P-value>0.05). Only four patients (8%) had V20 less than 20%, but in 34 patients (72%), MLD was less than 20 Gy. Twenty-two patients were in stage 2 and 28 were in stage 3. Twenty-one patients underwent breast-conserving surgery (BCS) and 29 underwent modified radical mastectomy (MRM). Patients with right and left breast cancer showed no significant difference in the stage of cancer and surgical method (P value>0.05). PFTs before and after radiotherapy showed no significant change in patients with right and left breast cancers (Table 2).

Table 2. The results of pulmonary function tests before and after radiotherapy

			Mean ± standard deviation	t-statistic	P-value
Right breast cancer	FEV1 [liter]	Before After	2.16 ± 0.68 2.11 ± 0.56	0.383	0.608
	FVC [liter]	Before After	2.81 ± 0.94 2.75 ± 0.61	0.505	0.618
	FEV1/FVC	Before After	78.2 ± 13.4 76.2 ± 13.4	0.596	0.556
Left breast cancer	FEV1 [liter]	Before After	1.93 ± 0.73 2.11 ± 0.79	-1.226	0.233
	FVC [liter]	Before After	2.71 ± 0.82 2.73 ± 0.80	-0.179	0.860
	FEV1/FVC	Before After	73.5 ± 20.8 77.4 ± 12.8	-1.087	0.289

Quantitative PPS showed a significant decrease (5%) in the relative perfusion of the ipsilateral irradiated lung. All three regions of the irradiated lung showed significant reduction in the relative perfusion (Tables 3 and 4).

Table 3. The results of quantitative pulmonary perfusion scan before and after radiotherapy in patients with right breast cancer

			Mean ± standard deviation	t-statistic	P-value
Relative perfusion of the right lung	Upper zone	Before After	13.0% ± 1.0% 12.0% ± 2.0%	4.315	0.001
	Middle zone	Before After	25.0% ± 2.0% 23.0% ± 2.0%	4.359	0.001
	Lower zone	Before After	15.0% ± 1.0% 14.0% ± 2.0%	1.663	0.018
	Total	Before After	55.0% ± 3.0% 50.0% ± 4.0%	5.161	0.001
Relative perfusion of the left lung	Upper zone	Before After	12.0% ± 1.0% 13.0% ± 1.0%	-2.934	0.007
	Middle zone	Before After	19.0% ± 2.0% 20.0% ± 2.0%	-2.937	0.007
	Lower zone	Before After	14.0% ± 2.0% 15.0% ± 2.0%	-2.571	0.016
	Total	Before After	45.0% ± 4.0% 50.0% ± 4.0%	-4.210	0.001

Table 4. The results of quantitative pulmonary perfusion scan before and after radiotherapy in patients with left breast cancer

			Mean ± standard deviation	t-statistic	P-value
Relative perfusion of the right lung	Upper zone	Before After	12.0% ± 1.0% 13.0% ± 2.0%	-2.699	0.013
	Middle zone	Before After	24.0% ± 1.0% 26.0% ± 1.0%	-6.092	0.001
	Lower zone	Before After	17.0% ± 1.0% 19.0% ± 2.0%	-2.599	0.016
	Total	Before After	54.0% ± 2.0% 59.0% ± 3.0%	-5.727	0.001
Relative perfusion of the left lung	Upper zone	Before After	12.0% ± 1.0% 11.0% ± 1.0%	3.441	0.002
	Middle zone	Before After	19.0% ± 1.0% 17.0% ± 2.0%	4.335	0.001
	Lower zone	Before After	13.0% ± 2.0% 12.0% ± 1.0%	3.648	0.001
	Total	Before After	46.0% ± 3.0% 41.0% ± 3.0%	4.868	0.001

In 27 patients (54% of all), lung perfusion defect was observed in the SPECT images (Figure 2) among whom 19 patients (38%) had right breast cancer and eight patients (16%) had left breast cancer demonstrating a significant difference (P-value=0.012). In 15 of the 19 patients with right breast cancer, the defects were seen in the right middle lobe. In patients with left breast cancer, the defects were not dominant in a particular area of the left lung.

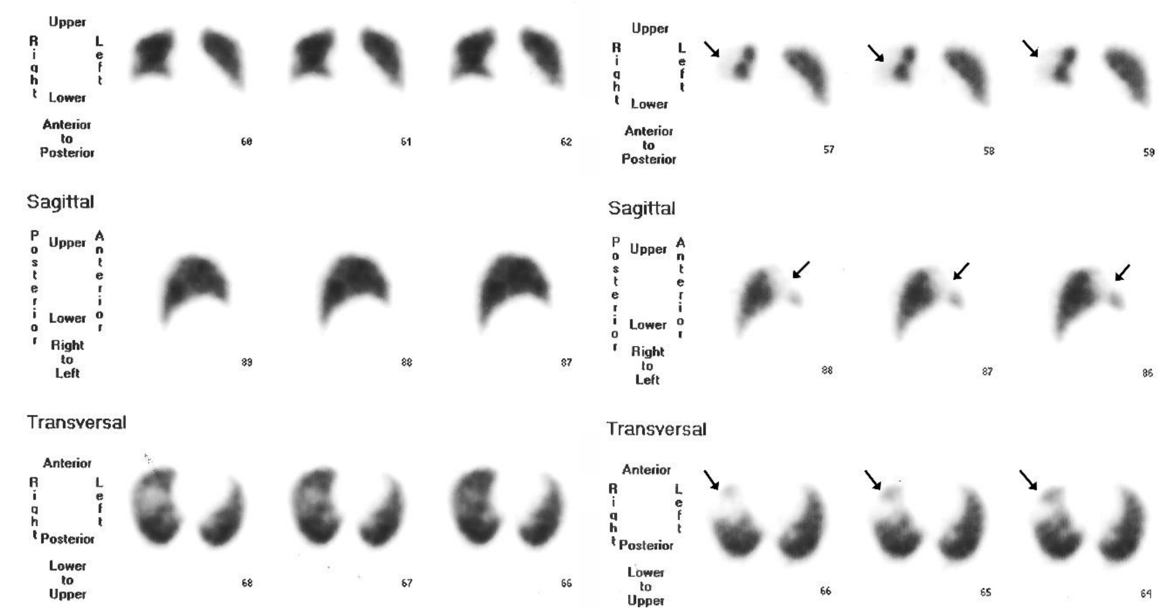

Figure 2. The lungs perfusion SPECT before (left) and after (right) radiotherapy of right breast cancer representing post-radiotherapy perfusion defects (arrows) in the middle and upper regions of the right lung

There was no significant relationship between the stage of cancer and surgical method with changes in relative perfusion of the irradiated lung (P-values>0.05). Besides, there was no correlation between MLD and V20 with the relative perfusion of the irradiated lung (P-values>0.05).

DISCUSSION

Chest organ irradiation during breast cancer radiotherapy is inevitable [21]. Considering that radiation-induced pulmonary side effects in most cases are asymptomatic in the first year after radiotherapy [22], imaging methods or PFTs should be used to evaluate possible lung injury.

In the current study, no significant change was observed in PFTs after radiotherapy for breast cancer. Considering that the patients were followed up to 9 months after radiotherapy, the findings confirm Jaen et al. study [17] wherein the change in PFTs was shown to occur 24 months after radiotherapy for breast cancer. The present study is also consistent with Elmas et al. [23] findings which revealed that PFTs did not change 6 and 12 months after breast cancer radiotherapy. However, the findings of the present research are in contrast to the studies showing a significant decrease in FEV1 and FVC and an increase in the FEV1/FVC ratio following breast cancer radiotherapy in the first few months after radiotherapy [13, 15, 16, 17, 23, 24]. It has been shown that the dose received by the lungs in breast cancer radiotherapy varies considerably worldwide [18] which, in turn, might explain the lack of consensus among different studies. Thus, other diagnostic methods, such as PPS or HRCT, should be considered in evaluating radiation-induced lung injury in such patients [15, 22].

Quantitative PPS in the current study showed a significant decrease in relative lung perfusion of the irradiated lung. In line with the research by Liss et al. [25] showing a reduction in relative lung perfusion in quantitative SPECT/CT one year after radiotherapy for patients with node-positive breast cancer. Likewise, Elmas et al. [23] revealed a significant decrease in relative lung perfusion in PPS on the side of breast cancer radiotherapy. They also demonstrated that the effect is directly related to the radiation dose as a more significant decrease in lung perfusion was observed in patients with V20>20%. However, in the current study, there was no relationship between V20 and relative perfusion of the irradiated lung. This inconsistency may be due to the fact that 92% of the patients had V20 greater than 20%.

The study also showed that relative perfusion decreased in all three regions of the irradiated lung; however, the vast majority of visible perfusion defects in the SPECT images of the irradiated right lung were observed in the middle lobe. Perfusion defects in the SPECT images of the irradiated left lung were significantly lesser prevalent than patient with right lung irradiation, possibly due to the absence of the middle lobe in the left lung. To the best efforts of the current researchers, no studies were found wherein perfusion changes in different lung regions were evaluated.

In the current study, no correlation was investigated between V20 and MLD with changes in relative lung perfusion after radiotherapy. The findings are consistent with the study by Muttath et al. [26] in which no relationship was shown between V20 and MLD with radiotherapy-induced pneumonitis in breast cancer. On the other hand, some studies demonstrated a significant correlation between high V20 values with decreased PFT [17] and radiation-induced pneumonitis [15]. However, in both studies, the evaluation was done during the first three months after radiotherapy indicating the maximum prevalence of the acute phase of pulmonary inflammation after radiotherapy, while in our study, the evaluation was carried out 6 to 9 months after radiotherapy at the time of late complications of radiotherapy. Ideally, MLD<20 Gy and V20<20% are acceptable to decrease lung irradiation [27]. Although the average MLD was less than 20 Gy in the current research, 92% of the patients had V20>20% probably explaining why the reduction of relative lung perfusion showed no significant correlation with V20.

The current study had some limitations, too. First of all, the study failed to evaluate the possible structural lung changes after radiotherapy due to lack of combined CT scan with the SPECT images. Second, additional imaging was not obtained to exclude pulmonary emboli as differential diagnosis of post-radiotherapy perfusion defects. However, the perfusion defects were mainly non-segmental which were in contrast to typical segmental pattern of perfusion defects in pulmonary emboli. The relatively small number of patients was the other limitation probably explaining the lack of relationship between the variables in the current study and the post-irradiation relative lung perfusion. In addition, the follow-up period was up to 9 months. However, Zhang et al. [28] showed that the decrease in lung perfusion after radiotherapy may occur in the first year and can worsen up to 18 months after radiotherapy. Therefore, evaluating a larger number of patients and follow-up evaluation for 1 to 2 years after radiotherapy may be more appropriate.

CONCLUSION

Few months after radiotherapy for patients with breast cancer, relative perfusion of the ipsilateral lung was decreased and perfusion defects were observed in the lungs perfusion SPECT in more than half of the patients while PFTs showed no significant changes. Hence, pulmonary perfusion scan could have a role in evaluation of radiation-induced lung injury in such patients. There was no significant relationship between the relative lung perfusion after radiotherapy with V20 and MLD.

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