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Original research article

Changes in lung volume parameters regarding the received dose in the lobes of the lungs after locoregional radiotherapy of breast cancer

Mahsa Abdemanafi[a,*], *Mohammad Bagher Tavakoli*[a], *Ali Akhavan*[b], *Iraj Abedi*[a]

[a] *Department of Medical Physics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
[b] *Department of Radiotherapy Oncology, Seyed Alshohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*

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ABSTRACT

Aim: The purpose of this study was to evaluate ΔLVP[1] and correlate them with MLD[2] and V20[3] in the lobes of the lung.
Background: Radiation-induced lung injury after breast irradiation is controversial. The incidence of such an injury could have negative consequences on breast cancer patients.
Materials and Methods: Twenty-three women treated with Breast-conserving surgery, chemotherapy, and locoregional RT[4] underwent body plethysmography pre-RT and 3 and 6 months post-RT. Statistical analysis was used to evaluate ΔLVP over time and relate them with MLD, V20, age, and concurrent hormonal therapy.
Results: LVP decreased after 3 months and then showed a slight improvement by returning partially to their pre-RT values after 6 months. The mean ΔLVP was −0.64% for one Gy increase of MLD and −0.34% for one percent increase of V20 after 3 months. After 6 months, only ΔVC[5] showed 0.45% reduction with MLD in the upper lobe. Finally, there was no significant correlation between ΔLVP with respect to age and concurrent hormonal therapy.
Conclusions: The results of this study showed that lung volume changes were not a cause for concern in breast cancer patients. There are three reasons to support this conclusion. Lung volume changes and percentage reductions in LVP for each Gy increase of MLD and each percentage increase of V20 in each lobe were small; patients were asymptomatic during the follow-up period; and LVP showed partial improvements after 6 months.
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* Corresponding author.
E-mail addresses: m_abdemanafi@yahoo.com (M. Abdemanafi), mbtavakoli@mui.ac.ir (M.B. Tavakoli), ali52akhavan@yahoo.com (A. Akhavan), I.abedi@med.mui.ac.ir (I. Abedi).
[1] Changes in lung volume parameters
[2] Mean lung dose
[3] The percentage of lung volume receiving 20 Gy
[4] Radiation therapy
[5] Vital Capacity
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1. Background

Breast cancer is the most common type of malignancy in females. Nowadays, breast cancer is often detected at an early stage and managed with surgery, RT[6] and systemic therapy.[1,2] Adjuvant radiotherapy following BCS[7] is a well-established treatment, resulting in decreased local and loco-regional recurrence and mortality rates.[3] Chemotherapy, on the other hand, reduces the rate of disease progression and is generally offered to women with the involvement of axillary lymph nodes, large tumor size, high-grade histological type, and extensive lymphovascular permeation.[4] During radiotherapy, a larger part of the lung is typically included within the radiation field and may result in lung toxicity.[5] Radiation-induced lung injury is usually presented with two distinct clinical stages: radiation pneumonitis (developing 1–6 months post-RT) and fibrosis (developing from 6 months onward).[6] The probability and severity of early and late pulmonary damage are related to factors such as total radiation dose, irradiated volume[7] and radiotherapy techniques.[8,9] However, pulmonary function is not only limited by the previously mentioned factors, and is also affected by some clinical factors such as chemotherapy,[6] smoking[10] and pre-treatment pulmonary function.[9] The correlation between lung volume changes with tamoxifen and letrozole was studied previously. Some studies showed increased rates of lung fibrosis with concurrent tamoxifen and RT.[11,12] However, other studies showed that concurrent hormonal therapy neither influenced disease control or survival rate nor increased the risk of pulmonary fibrosis.[13,14] Therefore, the relationship between lung fibrosis and concurrent hormonal therapy is still a matter of debate.

Several authors attempted to assess the relationship between irradiated lung volume and radiation dose with PFTs[8] in patients with breast cancer,[15] malignant lymphoma[16] and lung cancer.[17] Moreover, some studies analyzed the influence of treatment-related factors such as age, gender, smoking, chemotherapy and MLD[9].[6,10] A number of other published studies assessed pulmonary changes and correlated them with dose-volume parameters by using PFTs and high-resolution computed tomography.[15,18]

2. Aim

In the present study, lung volume changes of the breast cancer patients were evaluated with body plethysmography, pre-RT and 3 and 6 months post-RT, and their correlation with MLD and V20[10] were studied in the upper and lower lobes of the lung. The reason for separating the lobes of the lung in this study was the difference between each lobe and the variation in the V[11] /Q[12] ratio at the apex and base of the lung.[19] Pulmonary symptoms of the patients i.e. cough, dyspnoea, and fever were assessed using a questionnaire, following Common Terminology Criteria for Adverse Events (version 3.0).[20]

3. Materials and methods

3.1. Study design

Twenty-three consecutive women with T1-T2 and node-positive breast cancer undergoing BCS and at least six cycles of chemotherapy with anthracycline- and/or taxane-containing regimens were incorporated in this study from January to August 2018. The average age was 48 years (ranging between 32 and 62), and the majority of the cohort (14 patients; 61%) had left-side breast cancer. The inclusion criteria were histologic evidence of breast cancer, female gender, and non-smokers. The exclusion criteria were previous chronic respiratory or heart disease, history of collagen vascular disease, and recurrence of breast cancer or distant metastasis. Of all the patients, 65% received concurrent hormonal therapy with tamoxifen (60%) and letrozole (40%) concurrently with RT. A written informed consent was obtained from the patients before inclusion in the study.

3.2. CT-simulation

CT simulation of the patients was carried out by a 64-slice MDCT[13] covering the entire thoracic region from the skull base to 3 cm below the breast with 5-mm slice thickness and 5-mm interval.

3.3. Contouring

The target and OAR were contoured according to the criteria of the International Commission on Radiation Units and Measurements Reports 50 and 62[21] and RTOG breast contouring atlas.[22] Dose-volume constraints in patients treated with locoregional RT were defined as V20 of the lung <35%.[23] The ipsilateral lung was divided into its lobes (upper and lower), and each lobe was contoured separately. The right middle lobe was included in the right lower lobe. The data were then imported to the TiGRT, a 3D-radiation therapy treatment planning system.

3.4. Radiation therapy

Three-dimensional conformal radiotherapy plans were created. All the patients received locoregional RT with a Siemens Primus linear accelerator consisting of two tangential fields and two supraclavicular fields designed for each patient, as shown in Fig. 1. Half-beam blocking was used to avoid overdosing or underdosing at the junction of the fields and dose inhomogeneity.

A total dose of 50 Gy to the PTV along with 50 Gy to the axillary and supraclavicular fossa was delivered in 2 Gy/fraction, 5 days/week, using 6-MV photon beams. A boost dose of 10 Gy

[6] Radiation Therapy
[7] Breast Conserving Surgery
[8] Pulmonary Function Tests
[9] Mean Lung Dose
[10] The percentage of lung volume receiving 20 Gy
[11] Ventilation
[12] Perfusion
[13] Multi-detector computed tomography

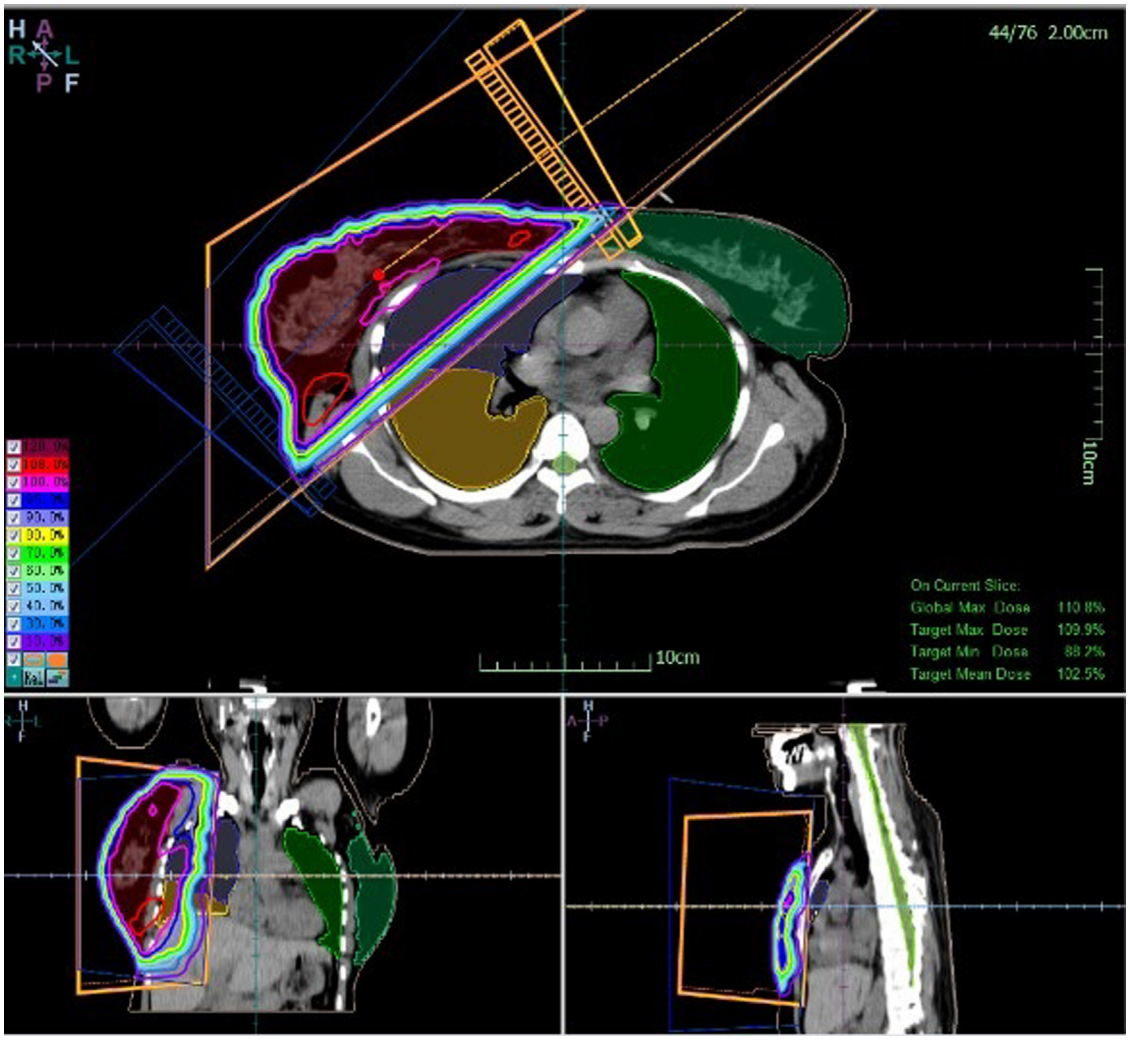

Fig. 1 – Planning and dose distribution in axial (top), coronal (left) and sagittal (right) views. Treatment planning of a random patient receiving 3-D conformal RT for breast and supraclavicular fields.

was given to the tumor bed of all the patients with the same fractionation and energy. Wedges were used to reduce dose inhomogeneity.[24]

3.5. *Body plethysmography*

For each patient, measurements of dynamic and static lung volumes were carried out by a body plethysmograph (ZAN-500, nSpire Health GmbH Germany). Vital capacity (VC) and forced vital capacity (FVC) measure lung volumes in litres.[25] Forced expiratory volume in one second (FEV1) is a mechanical property of large and medium-sized airways (bronchi). Residual volume (RV) is the volume of air remaining in the lungs after full exhalation. Total lung capacity (TLC) is a total amount of respiratory volume. Maximum expiratory flow (MEF) is a sensitive measure of small airways (bronchioles) and can be used as a diagnosis for obstructive lung disease.[26]

According to clinical findings, the GOLD[14] concluded that for detection and classification of lung diseases, FEV1/FVC had higher sensitivity whereas FEV1/VC had higher accuracy.[27] Therefore, we considered the analysis of Mirsadraee et al.,[28] who recommended to report both FEV1/FVC and FEV1/VC values and choose the best result according to clinical findings.

The test was performed pre-RT and 3 and 6 months post-RT using the same technique and equipment for all the patients. All the measurements were expressed as a percentage of the predicted value adjusted for age, gender, weight, and height. Changes in LVP[15] were expressed as the difference between pre- and post-RT values divided by previous values in percentages 3 (ΔLVP_3) and 6 months (ΔLVP_6) post-RT.

[14] Global Initiative for Chronic Obstructive Lung Disease
[15] Lung Volume Parameters

Table 1 – Characteristics of the study population.

Variables	N (%)
Age(y)	
Mean (Range)	48 (32–62)
Side of the cancer	
Left-sided	14 (61%)
Right-sided	9 (39%)
T-stage	
T1	6 (26%)
T2	17 (74%)
Histological type	
Invasive Ductal Carcinoma	21 (91%)
Invasive Medullary Carcinoma	2 (9%)
Hormone receptors	
Positive	15 (65%)
Tamoxifen	9 (60%)
Letrozole	6 (40%)
Negative	8 (35%)
Chemotherapy	Anthracycline- and taxane-containing regimens

3.6. *Statistical analysis*

The paired sample t-test was used to compare the average MLD and V20 in the lobes of the lung and analyze ΔLVP over time. Moreover, the repeated measures ANOVA (RM-ANOVA) was used to compare the mean LVP (as percentages of normal values adjusted for age, weight, and height) during the study period. However, LSD[16] was used for the two-by-two comparison of the mean LVP pre-RT and 3 and 6 months post-RT. Further, linear regression analysis was performed to assess the relationship between irradiated lung volume and absorbed dose by each lobe of the lung, derived from DVHs, taking ΔLVP_3 and ΔLVP_6 as dependent values and MLD and V20 as independent variables. The Pearson correlation was performed to study the correlation between age and ΔLVP. A correlation between positive or negative hormone receptors and ΔLVP was observed by the independent t-test. All statistical analyses were carried out using SPSS 22.0 (SPSS, Chicago, IL, USA). A P-value of 0.05 was considered statistically significant.

4. Results

Demographic characteristics, T-stage, histological types, hormone receptors, and chemotherapy regimens in the study population are presented in Table 1.

4.1. *DVH-data*

The paired sample t-test showed statistically significant differences in both MLD and V20 in the upper and lower lobes of the lung ($P < 0.001$). The average MLD was 21.62 Gy (SD 5.45) and 4.28 Gy (SD 2.20) in the upper and lower lobe of the lung, respectively. Moreover, the average V20 was 42.28% (SD 10.8) and 6.68% (SD 4.41) in the upper and lower lobe of the lung,

[16] Least significant difference

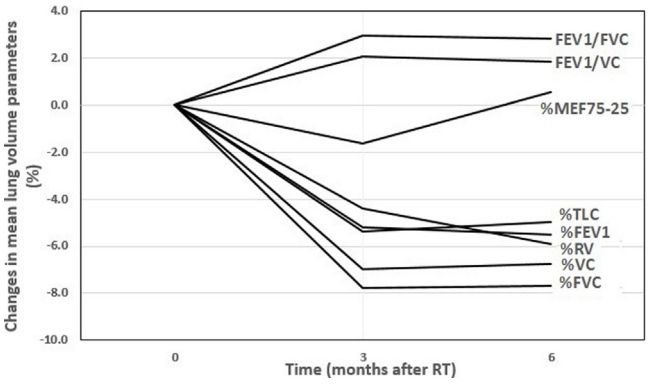

Fig. 2 – Changes in the mean LVP 3 and 6 months post-RT relative to pre-RT values as a percentage of pre-RT values (ΔLVP_3 and ΔLVP_6).

respectively. The average MLD and V20 values of the upper lobe were twice the MLD and V20 values of the entire lung (12.09 Gy and 22.87%). However, the average MLD and V20 values in the lower lobe were almost one third of the MLD and V20 values of the entire lung.

4.2. *Outcomes of body plethysmography over time*

A comparison between ΔLVP with their standard deviation and minimum/maximum values is shown in Table 2. Significant changes were observed in the mean percentages of VC, FVC, FEV1, and FEV1/FVC, TLC and RV. The LSD analysis showed statistically significant between-group differences in VC, FVC, FEV1, TLC, and RV between pre-RT and 3 months post-RT and pre-RT and 6 months post-RT and in FEV1/FVC between pre-RT and 3 months post-RT. However, none of the parameters showed any significant difference between 3 and 6 months post-RT.

Fig. 2 shows ΔLVP_3 and ΔLVP_6 over time. All the parameters except for FEV1/VC and FEV1/FVC decreased 3 months post-RT. The major descent was related to FVC with the mean equal to −7.78% (SD = 4.37). Six months post-RT, FEV1 and RV continued to decrease at a slower rate, FEV1/VC and FEV1/VC decreased but remained within their normal range (between 80–120%), and the rest of the parameters increased partially.

An association between ΔLVP with MLD (Gy) and V20 (%) is: ΔLVP_3 or $\Delta LVP_6 = (\alpha_0) * \text{MLD or V20} \pm \text{constant}$. The slope of the regression analysis is α_0 and the constant in the equations is ignored by considering that only RT brings about changes in LVP. The results are shown in Table 3.

4.3. *Correlation between ΔLVP with MLD and V20*

Three months post-RT, ΔVC, ΔFVC, and ΔTLC showed statistically significant correlation with MLD and V20. The mean reduction in LVP ranged from 0.39% to 0.84% for each Gy increase of MLD and from 0.28% to 0.42% for each percentage increase of V20. Six months post-RT, only VC reached a significant level and showed a reduction of 0.45% per each Gy increase of MLD in the upper lobe. The correlation between ΔVC and each Gy increase of MUD in the upper lobe, the entire lung, and the lower lobe 3 months post-RT is shown in Fig. 3.

Table 2 – Changes of the mean LVP.

LVP* (Unit)	Percentage of the predicted values Pre-RT min-max Mean*** (SD)	3 Months after RT min-max Mean (SD)	6 Months after RT min-max Mean (SD)	P-value**
VC (L)	65–97 79.39 (9.92)	58–91 73.87 (9.96)	56–96 73.96 (10.52)	**<0.001**
FVC (L)	66–98 80.04 (8.53)	60–90 73.82 (8.81)	59–89 73.74 (7.89)	**0.012**
FEV1 (L)	67–96 82.17 (7.2)	64–94 77.86 (6.69)	63–95 77.65 (8.07)	**0.023**
FEV1/VC (%)	81–129 104.47 (11.36)	79–138 106.73 (14.06)	73–146 106.39 (14.54)	0.118
FEV1/FVC (%)	65–94 103.60 (13.17)	57–91 106.69 (13.95)	56–90 106.43 (15.57)	**0.017**
MEF 25-75 (L/S)	59–94 75.83 (11.84)	53–95 74.22 (13.62)	57–97 75.74 (11.70)	0.788
TLC (L)	58–97 82.43 (13.02)	55–101 76.24 (14.43)	52–105 78.86 (15.98)	**0.031**
RV (L)	63–128 91.95 (17.85)	61–110 86.95 (13.45)	59–118 85.95 (15.92)	**0.013**

* Abbreviations: VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; MEF, maximum expiratory flow; TLC, total lung capacity; RV, residual volume.
** Analysis of variance for repeated measurements (RM-ANOVA). Statistically significant values are in boldface type.
*** Mean values expressed as percentages of predicted values adjusted for age, gender, and height with the standard deviation in parentheses.

Table 3 – Correlation between ΔLVP with MLD and V20 in each lobe and the entire lung.

Independent variables	Units	Upper lobe*	P-value	Entire lung	P-value	Lower lobe	P-value
(ΔVC_3 / MLD**) ±SE	(%/Gy)	**−0.92 ± 0.38**	**<0.001**	**−0.63 ± 0.23**	**0.014**	−0.58 ± 0.32	0.125
(ΔVC_3 / V20***) ±SE	(dimensionless)	**−0.42 ± 0.06**	**0.001**	**−0.23 ± 0.17**	**0.021**	**−0.20 ± 0.10**	**0.036**
(ΔVC_6 / MLD) ±SE	(%/Gy)	**−0.45 ± 0.25**	**0.009**	−0.43 ± 0.63	0.135	−0.29 ± 0.46	0.339
(ΔVC_6 / V20) ±SE	(dimensionless)	−0.32 ± 0.32	0.145	−0.20 ± 0.32	0.188	−0.15 ± 0.19	0.433
(ΔFVC_3 / MLD)±SE[α_0±SE]	(%/Gy)	**−0.60 ± 0.41**	**0.025**	−0.45 ± 0.29	0.135	−0.38 ± 0.15	0.156
(ΔFVC_3 / V20) ±SE	(dimensionless)	**−0.31 ± 0.08**	**0.014**	−0.21 ± 0.21	0.150	−0.16 ± 0.12	0.178
(ΔTLC_3 / MLD) ±SE	(%/Gy)	**−0.99 ± 0.21**	**0.016**	**−0.78 ± 0.25**	**0.005**	−0.39 ± 0.50	0.06
(ΔTLC_3 / V20) ±SE	(dimensionless)	**−0.54 ± 0.09**	**<0.001**	**−0.41 ± 0.08**	**<0.001**	**−0.37 ± 0.18**	**0.048**

Statistically significant values are in boldface type.
** The slope of the regression line (α_0) with each percent increase in MLD ± SE (standard error).
*** The slope of the regression line with each percent increase of V20.

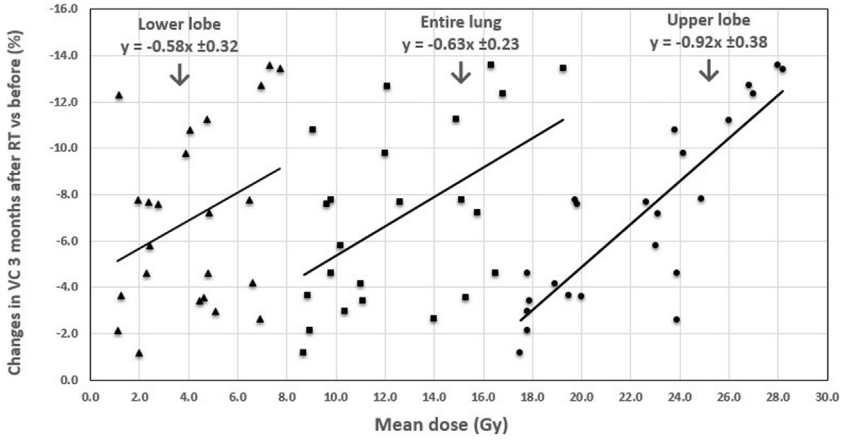

Fig. 3 – VC_3 relative to each Gy increase of MLD in the upper lobe (circle dots), the entire lung (square dots), and the lower lobe (triangular dots) with P-values <0.001, 0.014, and 0.125, respectively.

Other possible factors for developing lung disorders are age and hormonal therapy. However, in this study, no significant association was observed between these two variables and ΔLVP.

5. Discussion

A number of studies described lung volume changes in breast cancer patients undergoing different treatment modalities by comparing local and locoregional RT, different radiotherapy fractioned regimens, or different chemotherapy regimens.[15,18,26] Moreover, few studies assessed lung volume changes using body plethysmography,[18,26] which measures static lung volumes accurately (VC, TLC, and RV) and leads to a better diagnosis of restrictive or obstructive diseases.[29]

In the present study, patients with similar treatment procedures underwent body plethysmography pre-RT and 3 and 6 months post-RT. Changes in LVP were assessed, and the correlation between ΔLVP with MLD and V20 was studied in the upper lobe, the entire lung, and the lower lobe. To our knowledge, this was the first study separating the upper and lower lobes of the lung. The reason for considering the lobes of the lung separately was the difference between the lobes and the variation of the V/Q ratio throughout the lung.

The results of this study showed that 3 months post-RT, FEV1/VC and FEV1/FVC remained within 80% and 120% of the predicted values while VC, FVC, FEV1, and TLC were reduced. These changes are indicative of a restrictive lung disorder. The decrease in MEF 25–75% might represent damage to bronchioles, which leads to obstructive lung disease.[4] However, as MEF 25–75% did not significantly change in our study, the probability of restrictive lung disease increased.

The results also revealed that 6 months post-RT, FEV1 and RV decreased at a slower rate. The small increase in VC, FVC, MEF 25–75%, and TLC could indicate more probable improvements in LVP over a longer follow-up duration. None of the patients showed any RT-induced respiratory symptoms at the time of the study.

The results of this study were consistent with previous studies[6,13,26] in that LVP was reduced significantly 3 months post-RT and was partially recovered 6 months post-RT. Jaen et al.[30] reported lung volume changes in breast cancer patients at 7 years. They concluded that DLCO, ventilation, and perfusion reduced up to 2 years post-RT and partially recovered at 7 years. However, FVC and FEV1 reduced 6 months post-RT and reached their baseline values at 7 years.

Average MLD and V20 were greater in the upper lobe than in the entire lung and the lower lobe. Consequently, the mean ΔLVP for each Gy increase of MLD and each percentage increase of V20 were greater in the upper lobe than in the entire lung and the lower lobe. This result was also expected by the higher V/Q ratio in the apex of the lung. However, the mean ΔLVP for each Gy increase of MLD and each percentage increase of V20 were obtained <1% in the upper lobe. Similarly, other researchers reported very small changes in LVP with respect to MLD and V20 over time. Jaén et al.[13] obtained a regression equation between the relative reduction of perfusion and V,[10–20] a percentage of irradiated lung volume receiving a dose between 10 and 20 Gy, as follows: $\Delta\text{perfusion} = -1.43 \times \text{pV}$.[10–20] Moreover Theuws et al.[10] found a correlation between pulmonary changes pre- and post-RT and MLD in breast cancer and malignant lymphoma patients. The relative decrease in the LVP (VC, FVC, and FEV1) for each Gy increase of MLD ranged from 0.8% to 0.9% 3 months post-RT and from 0.3% to 0.4% 18 months post-RT. However, Goldman et al.[31] and Dehing-Oberije et al.[32] could not detect a correlation between ipsilateral V20 and ΔVC and MLD with ΔFVC, ΔFEV1, and DLCO, respectively.

In the current study, no correlation was observed between age and concurrent hormonal therapy with ΔLVP 3 and 6 months post-RT. Similar results were reported by other researchers.[13,26]

Determination of a more definitive threshold value for V20 in both the upper and lower lobes of the lung concerning lung fibrosis requires a longer follow-up duration and a larger sample size. It is best to carry out additional tests such as DLCO to better detect pulmonary disorders and their severity over time and also to predict a more accurate model for ΔLVP.

According to the obtained results, in cases where a greater part of the ipsilateral lung is exposed and consequently V20 exceeds 35%, we suggest separating the upper and lower lobes of the lung and calculating V20 for each lobe separately. If V20 is below 42% in the upper lobe (average V20 in the upper lobe) and is not above 6% in the lower lobe (average V20 in the lower lobe), it does not appear to have a major impact on lung volume changes.

6. Conclusion

Radiotherapy can cause lung volume changes. However, as percentage reductions in LVP for each Gy increase of MLD and each percentage increase of V20 in the upper and lower lobes are small and patients are completely asymptomatic during a follow-up period as observed in our study, lung volume changes will not be a cause for concern.

Conflict of interest

None declared.

Financial disclosure

None declared.

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