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ORIGINAL ARTICLES AND REVIEWS

Ultrasound B-lines for detection of late lung fibrosis in breast cancer patients after radiation therapy

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Abstract

Background and purpose. Radiation therapy (RT) for breast cancer after conservative surgery can be life-saving but remains associated with significant late side effects, including lung fibrosis, detected by chest CT. Aim of this study was to assess whether lung ultrasound (LUS) may detect late lung fibrosis through the biomarker of B-lines.

Materials and methods. We evaluated 30 women (median age 67 years, range 46-80 years) about 3-8 years after RT (follow up 38-101 months, median 58 months) for left (n = 12) or right (n = 18) breast cancer (stage 1, n = 24; stage 2, n = 6), treated with total dose 40.5 – 50.00 Gy with/without boost dose). In all, both treated and contralateral hemithorax were evaluated. LUS was performed and B-lines evaluated with a 28-region antero-lateral scan, from second to fifth intercostal spaces, along the mid-axillary, anterior axillary, mid-clavicular, and parasternal lines. In each space, the B-lines were counted from 0 = black lung to 10 = white lung. The sum of B-lines in all spaces generated the B-line score of each hemithorax.

Results. Median B-line score was higher in the irradiated site than in the contralateral control hemithorax (9, 1st-3rd quartiles: 2-23 *vs* 3, 1st-3rd quartiles: 1-4; $P < 0.05$). In the treated hemithorax, higher mean lung doses (> median value of 2.7 Gy) were associated with more B-lines when compared to lower doses (< 2.7 Gy): 9 *vs* 5, $p < 0.001$.

Conclusion. RT in female breast cancer survivors is associated with increase in B-lines in the targeted hemithorax, likely due to lung fibrosis, and related to the lung mean dose. LUS can provide a simple "echo-marker" of lung fibrosis.

Key words
- breast cancer
- lung toxicity
- thorax radiation exposure
- lung ultrasound methodology

INTRODUCTION

Adjuvant radiation therapy (RT) following breast conserving surgery has been shown to reduce the rates of local recurrence and death in breast carcinoma. Despite recent efforts to decrease irradiation volumes, pulmonary toxicity remains one of the main restrictions in breast RT because of the exposition to high doses of radiation to the chest [1] and typically presents with two distinct, subsequent clinical phases: acute pneumonitis and late fibrosis.

A number of published studies have shown data regarding late radiological changes and alterations in pulmonary function tests after breast RT and the reported incidence of radiation-induced lung injury varies between 4.5% and 63% in prospective studies and between 0.9% and 30% in retrospective studies [2]. The heterogeneity of the data in world literature can be attributed to the different treatment techniques, different sites treated (regional or loco-regional RT), different detections tests (functional tests, chest X-rays, computed tomography or high-resolution computed tomography).

Although late lung damage is clinically asymptomatic in the majority of patients and often under-diagnosed due to the absence of screening protocols, this clinical entity has a potential detrimental effect of reducing the normal functional reserve considering the long life ex-

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pectancy of patients with early-stage breast cancer [3].

Lung ultrasound (LUS) has been proven to be accurate in diagnosing extravascular lung water, pulmonary fibrosis and pulmonary interstitial syndrome because these lung disorders produce a peculiar "echo-marker" called B-lines [5-8]. Use of ultrasonography in emergency department, critical care and cardiac care units is becoming popular because this imaging modality is easily available, real time and free of radiation hazards in comparison to conventional radiological modalities [9]. Accordingly, LUS could offer promising tools for an accurate diagnose of pulmonary complications induced by RT and identification of patients at risk.

In a previous study a combined strategy of lung ultrasound and biochemical analysis was evaluated to diagnose RT-induced complications few months after RT completion. LUS showed effective in detecting early lung damage in breast conserving radiotherapy with minimal dose to the lung [10].

The current study hypothesis is that RT-induced lung fibrosis can be detected through B-lines at LUS, since this finding has previously been shown to be very sensitive and specific for detection geographic localization and quantification of lung fibrosis, with accuracy comparable to the gold standard of chest CT.

In this new study, we explore lungs of women who underwent breast RT post conservative surgery years (about 3-8) after RT completion in order to verify late subclinical effect and its possible relationship with dose and other individual parameters.

MATERIALS AND METHODS

Patient characteristics

A total of 30 women with breast cancer (median age 67 years, range 46-80 years) who underwent adjuvant radiotherapy (stage I-II) were enrolled after 38-101 months (median 58 months) after the end of RT. Eighteen of these patients were treated for right and twelve for left breast cancer.

Clinical, demographic, and dosimetric characteristics are described in *Table 1*.

A detailed history was collected; all patients underwent a clinical visit with a complete LUS analysis. The exclusion criteria were history of chronic respiratory disease, need for radiotherapy to regional nodes, previous concomitant malignancies.

Ten patients had arterial hypertension treated with drug therapy.

Only a patient underwent chemotherapy, while 25 patients (83.3%) were susceptible to treatment with hormonal therapy.

At the time of the LUS, no patient showed respiratory symptoms. Two patients showed mild interstitial thickening.

A written informed consent was obtained from all study participants.

Table 1
Clinical and dosimetric features of study patients

Patients characteristics	N = 30	Min-max (median)
Age (years)		46-80 (67.6)
RT side		
-Left	*12 (40%)*	
-Right	*18 (60%)*	
Grading		
G1	*9 (30%)*	
G2	*14 (46.7%)*	
G3	*7 (23.3%)*	
Stage		
I	*24 (80%)*	
II	*6 (20%)*	
BMI		19.5-43 (26.7)
Systemic Therapies		
CHT	1 (3.8%)	
HT	25 (96.2%)	
Hypertensive Cardiopathy	10 (33.3%)	
Smokers	5 (16.6%)	
Dosimetric variables		
Total dose to the breast(Gy)		*40.05-50 (40.05)*
Boost	*18 (60%)*	
Boost dose(Gy)		*10-13.35 (10.7)*
V95%(%)		0.0-2.4 (0.2)
V90%(%)		0.0-4.4 (0.8)
V50%(%)		1.6-9.7 (4.6)
V20Gy(%)		1.8-10.5 (4.6)
V5Gy(%)		42.9-16.2 (7.2)
LMD (Gy)		1.2-5.3 (2.67)
PTV (cc)		200-1779 (553)
LV (cc)		1457-3768 (2276)

RT = radiotherapy; BMI = body mass index; CHT = chemotherapy; HT = hormone therapy; V95%(%), V90%(%), V50%(%) = lung volume percentage that absorbed at least respectively 95%, 90% and 50% of the dose delivered to the target; V20Gy(%) and V5Gy(%) = lung volume percentage that absorbed at least 20 Gy and 5 Gy respectively; LMD (Gy) = lung mean dose; PTV (cc) = planning target volume; LV (cc) = lung volume; data are numbers of patients unless otherwise indicated.

Radiotherapy

The planning target volume (PTV) total dose (TD) prescription respectively for 16 patients and for 2 patients was of 40.05 Gy and 42.7 Gy with fraction dose (FD): 2.67 Gy/day for 5 days/week; for 3 patients TD of 45 Gy (FD: 2.5 Gy x 5 days/week) and for 9 patients DT of 50 Gy (FD: 2.0 Gy x 5 days/week). In 18 patients the PTV irradiation was followed by a boost phase to the tumour bed with a median dose of 10 Gy (range: 10-13.35 Gy) and a median daily dose of 2.5 Gy (range: 2-2.67 Gy) for 4-6 fractions.

The clinical target volume (CTV) and the PTV were defined according the International Commission on Radiation Units and Measurements (ICRU 50) [11].

Further details about radiotherapy characteristics have been previously published [10].

To evaluate the dose received by organs at risk, in-

tegral dose-volume histogram were used, and some dosimetric parameters were calculated according to the International Commission on Radiation Units and Measurements (ICRU 83) [12].

Dose-volume parameters considered for the lung were as follows: (I) D_{mean}(Gy) that is mean dose; (II) V_{YYGy} (%), which indicates the percentage of organ volume that receives at least a YY dose expressed in Gray (in particular were considered 5 and 20 Gy); (III) $V_{YY\%}$ (%), which indicates the percentage of organ volume that receives at least a YY percentage of dose (in particular were considered 50, 90 and 95%).

Lung ultrasound

The normal lung reflects ultrasound almost completely and in normal conditions reverberation phenomena is characterized by regular horizontal lines, at regular intervals and these are known as lines A. Instead, the alteration of the normal lung structure (*eg*, interstitial edema, fibrous thickening of the interlobular peripheral septa) induces the creation of perpendicular artifacts called B lines *(Figure 1)*. B lines, also called "ultrasound lung comets" are defined as laser-like vertical hyperechoic reverberation artifacts (previously described as "comet tails") that arise from the pleural line extend to the bottom of the screen without fading, and move synchronously with lung sliding [5, 13, 14].

The echographic examination was conduct using a commercially available echographic equipment top of the range Toshiba Aplio 500 (Toshiba America Medical Systems, Inc. 2441 Michelle Dr, Tustin, CA 92780, United States) with a 1.9-6.0 MHz convex probe, used to 3.5-5.0 MHz.

Further details about the echographic examination's methods have been published in a previous study [10]. An experienced sonographer performed all examinations.

In this work, LUS was performed and B-lines were evaluated with a 28-region antero-lateral scan, from second to fifth intercostal spaces, along the midaxillary, anterior axillary, mid-clavicular, and parasternal lines. B-lines score per patients was scored as follows: score 0 "absent" (< 5), score 1 "mild" (5-14), score 2 "moderate" (15-29), score 3 "severe" (> 30) [5]. A number of B-lines larger than 5 is considered abnormal. The sum of B-lines in all spaces generated the B-line score of each hemithorax. Both diseased and contralateral hemithorax were evaluated, in order to compare the chest area exposed to irradiation compared with the contralateral side.

Statistical analysis

Data are expressed as mean ± standard deviation (normally distributed data), median and inter-quartile (25^{th}, 75^{th}) range (non-normally distributed data, such as B-lines) or per cent frequency (categorical data).

Normality of the data distribution was assessed both visually and through Shapiro-Wilk test. With no evidence against the null hypothesis, i.e. normally distributed data, the following tests were planned to be applied: one sample Student's t-test, in order to test the null hypothesis of means of B-lines equal to 0; paired samples t-test for the comparison of the mean numbers of B-lines showed by the lungs in both irradiated and not-irradiated sides; F-test of Snedekor-Fisher to test the equality of two variances. Paired samples t-test was adopted since we could, indeed, not assume the independences of the samples.

With strong evidence against null hypothesis of normality of the data distribution we adopted non-parametric tests: Mann-Whitney test, if the hypothesis of equal variances was satisfied or, otherwise Wilcoxon test. Correlation between two variables was evaluated through Pearson correlation coefficient.

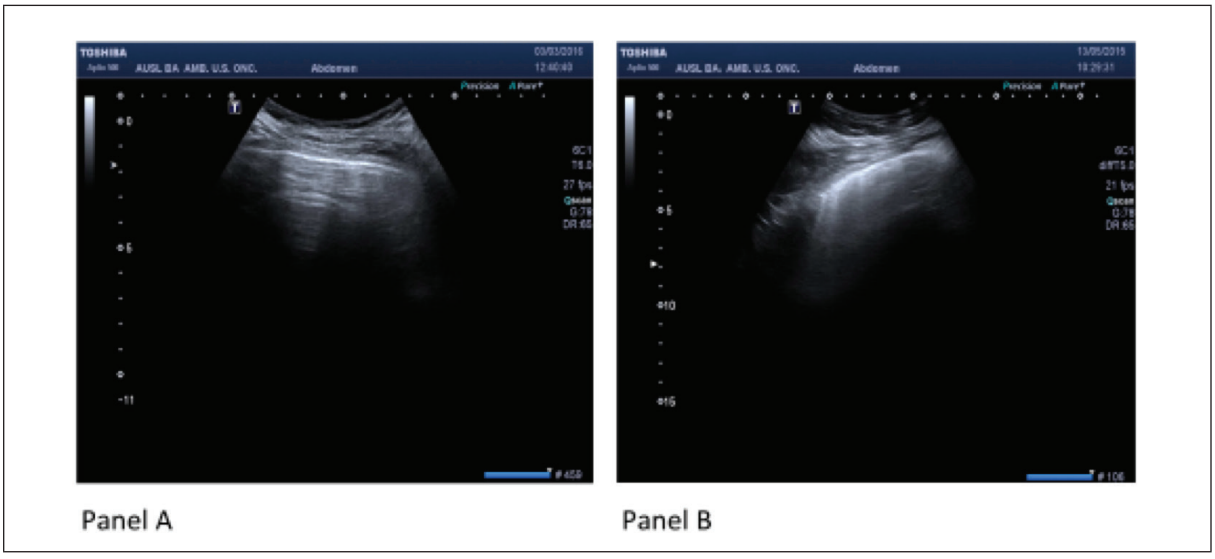

Figure 1
Images of an unirradiated (panel A) and contro-lateral irradiated lung (panel B). Panel A: normal lung appareance with A-line. Panel B: B-line or ultrasound lung comet (ULC): laserlike vertical hyperechoic reverberation artifacts that arise from pleural line extended to the bottom of the screen without fading.

Null hypothesis was rejected with p value less than 0.05. Statistical analyses were performed using R [32].

RESULTS

We counted the number of B-lines in treated anterior hemithorax and compared it with the number in untreated anterior hemithorax.

B-lines were more numerous in treated (median 8.5, range: 0-53) *vs* untreated (median 3; range: 0-13) hemithorax (Wilcoxon Signed rank test: p = 0.0192).

B-lines distribution in the treated and untreated hemithorax is shown in *Figure 2*.

In the same way as described in our previous article, we analysed B-line score per patients and we found abnormal score (B-lines > 5) was present in 17/30 (51%) in treated *vs* 7/30 (21%) in untreated hemithorax.

Median B-line score per hemithorax was higher in the RT-targeted (9; 1st-3rd quartiles: 2-23) than in the contralateral control (3; 1st-3rd quartiles: 1-4) hemithorax (Wilcoxon Signed rank test: P < 0.05).

The patients suffering from acute broncopathy (cough and cold) at the time of the first echo pulmonary were 9 over 30 (30%) and their median of B-lines was 4 (1st-3rd quartiles: 3-10) in the treated side and 2 (1st-3rd quartiles: 1-4) in the untreated side.

We considered mean lung dose (MLD) and identified two groups, MLD > 2.7 Gy and MLD < 2.7 Gy observing that median number of B-line in the treated side was higher for higher median doses, 13 and 5 respectively for the two groups.

The median number of B-lines in the treated side was higher for patients with V95%, V90%, V50%, V20% and V5% over the median number.

Although not statistically significant, we found a trend to higher number of B-lines in older patients with a BMI over 25.

We found no significant correlation with age and some dosimetric variables *(Table 2)*.

DISCUSSION

Radiation lung injury is a well- known event after breast RT and its natural history can be divided into 5 phases: immediate phase (hours to days); latent phase; acute exudative (4-12 weeks post-RT); intermediate phase with resolution of exudate and deposition of fibroblasts and the final phase when fibrosis is established (usually 6-12 months post-RT) [16, 17].

Pulmonary fibrosis involves parenchyma and pleura and its severity seems to be related to a number of factors, including the volume of irradiated lung, radiation dose, fractionation and concomitant use of some chemotherapy regimens. Additional risk factors that may increase the degree of damage include age, cigarette smoking, and pre-existing lung disease.

There are a number of studies in the literature describing pulmonary changes following adjuvant RT in patients that underwent conventional surgery for breast cancer [18-23].

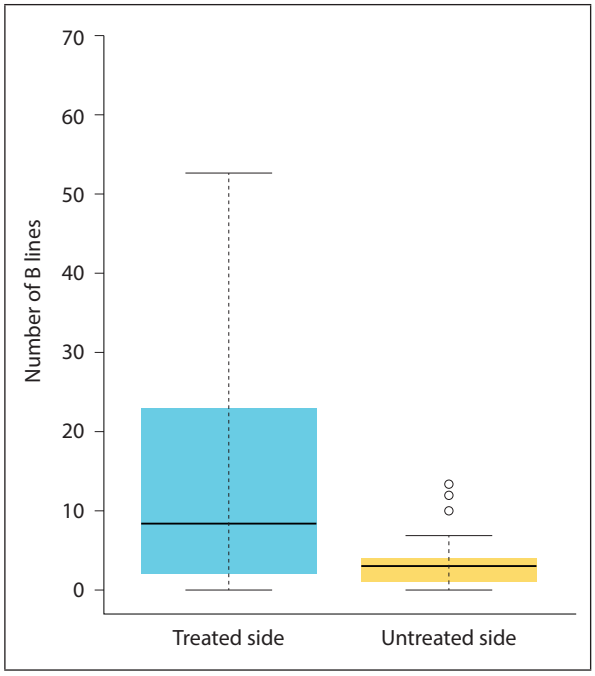

Figure 2
Number of B lines in the comparison between treated and untreated hemithorax for each patient. Data are expressed as the median value (25th-75th percentiles and outliers, in a box and whiskers plot). Whiskers represent the maximum and minimum value of the collected data, and, with reference on the box related to the untreated side, that the individual points refer to outliers.

Table 2
Correlation between number of B-lines in treated and untreated side and some variables

Spearman correlation coefficient		
Variable	**Treated side**	**Untreated side**
Age	0.28	0.08
Weeks after radiation therapy	0.13	0.83
Total dose	0.12	0.72
Number of fraction	0.09	0.58
Dose per fraction	-0.12	-0.72
Dose of boost	-0.24	-0.61
Number of fraction of Boost	-0.09	0.24
Dose per fraction Boost	-0.12	-0.72
Cumulatice dose (Boost+WB)	0.04	0.64
PTV	0.06	-0.33
LV	0.19	-0.05
V95%(%)	-0.01	0.23
V90%(%)	-0.22	0.09
V50%(%)	0.17	-0.26
V20Gy(%)	0.15	-0.35
V5Gy(%)	0.13	-0.40
MLD (Gy)	-0.21	0.14

PTV = planning target volume, LV = lung volume, MLD = mean lung dose.

Lind *et al*. reported that the addition radiotherapy to the axilla involved an increased incidence of radiation pneumonitis, compared to whole breast radiotherapy alone [24].

Another study by Lingos *et al*. showed that axillary/supraclavicular radiotherapy was correlated with an increased incidence of pulmonary side effects and an increased incidence of radiation-induced lung injury was highlighted in patients receiving CHT concomitantly [25]. In contrast, Ooi *et al*. found no correlation between chemotherapy and pulmonary function or radiological findings [26].

Fragkandrea *et al.* showed the correlation between pneumonitis diagnosed with images, age and dosimetric parameters, but not between pneumonitis, smoking and fractionation type [27].

Another study by Dorr *et al*. showed that higher age and tamoxifen treatment significantly increased the incidence of early pneumopathy [28].

In a meta-analysis study by Gokula *et al*. considering the incidence of early lung toxicity in 3-dimensional conformal irradiation of breast carcinomas, it was observed that patients of age > 55 years have an increased risk of developing radiation pneumonitis [29].

Currently, chest high-resolution computed tomography (HRCT) is considered the "gold-standard" for the diagnosis, disease activity and therapy monitoring of interstizial pulmonary fibrosis (IPF). Its value is remarkable since it has been demonstrated also to be able to detect both early pulmonary changes and subclinical lung involvement. Despite of this, LUS is considered as a reliable alternative in the detection of pulmonary fibrosis. The US assessment of IPF is determined by the detection and quantification of B-lines, which consist of tails generated by the reflection of the US beam from thickened sub-pleural interlobar septa detectable in between the lung intercostal spaces (LIS) [30]

In a previous study we focused on RT-induced acute pulmonary complications after thoracic radiotherapy for breast cancer with the use of ultrasound as a diagnostic non-invasive tool, in about 4-9 weeks after the end of treatment and we showed that LUS is effective in detecting early lung damage after breast conserving radiotherapy [10].

In the present study, with the use of LUS, we examined lung late toxicity in breast cancer patients after RT. To observe a chronic effect we enrolled a new group of 30 patients studied with the same protocol as the previous study. We confirmed that B-lines were more frequent in radio-treated side but, with respect to "acute" study, we observed a lower median number of B-lines in the treated side [median: 9; (1st-3rd quartiles: 2-23) *vs* 21; (1st-3rd quartiles: 11-31)], likely because of repair activity in the meantime, but the residual number of B-lines could be expression of a late and permanent effect.

Considering the dosimetric parameters of the lung, we observed that dosimetric parameters of the lung influenced pulmonary fibrosis and were correlated with LUS changes. We observed a higher number of B-lines in older patients with a BMI over 25 and this seems to be correlated with anatomical changes that occur in overweight and obese patients, especially after a certain age. Furthermore, obese patients have often larger breast size which displace laterally and this may result in increasing the incidental dose delivered to the lung to cover PTV [31].

This is the first study that has shown that breast adjuvant RT gives late sequelae sonographically detectable on treated *versus* untreated hemithorax.

Important limitations of the present study are the small number of patients, the different time of LUS from the end of RT (from three to eight years), and the lack of a subacute evaluation in the early months after RT.

However, the persistence of observed B-lines asymmetry on treated hemithorax *versus* untreated is reasonably due to asymmetry of local radio-induced changes in the lung tissue.

Then, our results could encourage the use of LUS in monitoring patients and detecting late pulmonary toxicity after thoracic radiation treatments for breast cancer and for other cancers which require chest irradiation.

Nevertheless, further prospective studies are needed to evaluate the applications of LUS in detecting lung fibrosis in breast cancer survivors, examining a greater number of patients and monitoring sonographic lung B-lines before and after RT, with a longer follow-up than the one applied in this analysis.

Conflict of interest statement

The authors report no declaration of interest.

Disclosures

None.

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