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Ultrasound Findings After Breast Cancer Radiation Therapy: Cutaneous, Pleural, Pulmonary, and Cardiac Changes

Orlando Catalano[1], Roberta Fusco[2], Serena Carriero[3], Stefania Tamburrini[4], Vincenza Granata[2]

[1]Department of Radiology, Istituto Diagnostico Varelli, Naples, Italy
[2]Radiology Division, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples, Italy
[3]Fondazione IRCCS Ca' Granda, Ospedale Maggiore, Milan, Italy
[4]Department of Radiology, Ospedale del Mare, ASL Na1 Centro, Naples, Italy

External beam radiation therapy (RT) can induce toxicity in patients surgically treated for breast cancer. Modern irradiation techniques have lowered the incidence and severity of radiation-induced injuries; however, their side effects on normal tissues remain challenging. This review illustrates early and late changes observed using ultrasound (US) imaging, including echocardiography, at the skin, muscle, pleura, lungs, and heart levels. The US findings and the potential role of this technique in detecting and grading early and late complications of RT are highlighted in this article. US has proven useful in the differential diagnosis of post-RT complications, including but not limited to cancer recurrence and toxicity from other sources, such as anticancer drugs. Additionally, considering the progressive nature of RT-induced injury, early detection of toxicity may be helpful in the individual stratification of damage risk and serve as a tool for patient screening and management. In these cases, US can be used as a radiation-free biomarker of RT side effects at the subclinical stage.

Keywords: Ultrasound; Echocardiography; Breast cancer; Skin; Pleura; Lung; Heart; Radiation therapy

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide. However, mortality rates have steadily decreased over the past decades due to earlier detection and improved treatment. External-beam radiation therapy (RT) after breast-conserving surgery reduces breast local recurrence and disease-related mortality [1,2]. Therefore, adjuvant irradiation has become the standard treatment modality for breast cancer [3].

The 5-week treatment protocol uses a standard fractionation of 50 Gy in 25 fractions plus a boost [4]. Higher RT dose, increased RT volume, and tumor bed boost, especially if sequential, are associated with late radiation toxicity [5]. Moreover, approximately 30% of patients request breast reconstruction following surgery [6]. RT is believed to negatively influence the results of breast reconstruction in terms of late complications and unsatisfactory aesthetic outcomes [6]. New RT approaches and techniques have been developed, such as intensity-modulated RT, 3D conformational RT, volume-modulated arc therapy, intra-operative RT, partial breast irradiation, simultaneous boost technique, artificial intelligence application, improved prediction of single patient radiosensitivity, lateral decubitus position, deep inspiration breath hold, and hypofractionation [7-12]. The hypofractionation approach is estimated to bear equal tumor control as the standard approach. Consequently, moderate (3 weeks) hypofractionation has become the new standard and is now being recommended for women of any age, whether they have received chemotherapy or not [4,13,14].

The large number of breast cancer survivors calls for an improved understanding of the late effects of anticancer treatments. All anticancer treatments have their own toxicities that sometimes overlap [15]. RT is no exception.

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Corresponding author: Orlando Catalano, MD, FAIUM, Department of Radiology, Istituto Diagnostico Varelli, 65 Via Cornelia dei Gracchi, Naples 80126, Italy
• E-mail: orlando.catalano@istitutovarelli.it

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Damage occurs in healthy tissues through which radiation beams travel once the radiation dose surpasses their DNA repair capability. Owing to its high cellular turnover, the skin is especially prone to radiation toxicity, but all tissues involved in the irradiation field may experience side effects, including the pectoralis muscle, costal pleura, peripheral lung, and heart (Fig. 1).

Ultrasound (US) has undergone dramatic technological improvements in the last decades and has become a multimodality technique based on morphology and vascularization, stiffness, and contrast media perfusion [16-18]. US can be a useful tool for assessing and grading the side effects of RT as part of specific protocols. However, US should be routinely used in the locoregional follow-up of patients with a history of breast cancer. In these patients, the main targets of examination were the breast parenchyma and axillary lymph nodes. However, this follow-up US examination is an opportunity to detect other changes, including RT-induced injuries, in tissues that are placed superficially or deeply in the area of interest [19,20].

The purpose of this review was to illustrate the changes detected by US in patients with a history of postoperative breast RT. Abnormalities encountered at the levels of the skin, muscular plane, pleura, lungs, and heart are described (Table 1). The authors chose to address the cardiac findings briefly because radiologists do not typically perform echocardiography.

US Approach

An appropriate US examination requires adequate knowledge of the patient's history, particularly regarding the

Table 1. Key abnormalities than can be encountered after breast radiation therapy

Anatomic location	Ultrasound changes
Skin	Epidermis line: Normal
	Dermis: Thickened and hypoechoic, with decreased visibility of dermis-hypodermis boundary. Increased Doppler signals (acute phase)
	Subcutis: More echoic than normally (acute phase edema). Increased elasticity ratio
Pectoralis muscle	Decreased thickness and increased stiffness
Pleura	Pleural line thickening and/or irregularity
Lung	Increase number of B-lines. Subpleural consolidations
Heart	Septum: Thickening
	Left ventricle: Posterior wall thickening and volume decrease. Increased myocardium reflectivity

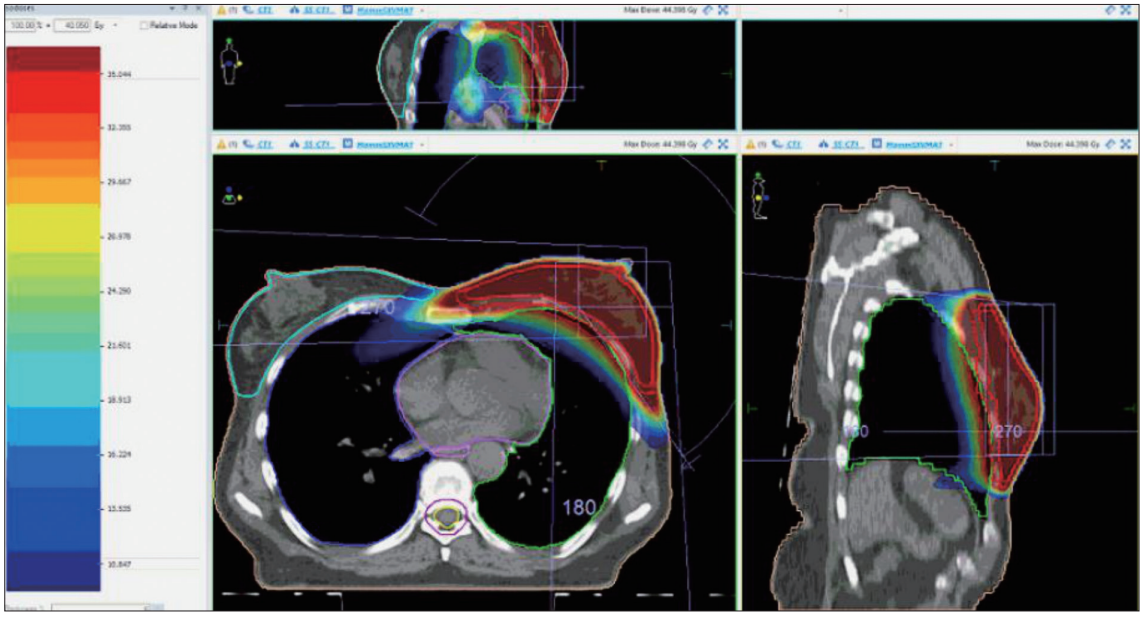

Fig. 1. Schematic diagram of isodose curve distribution in left-sided breast cancer radiation therapy plan.

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time between surgery and RT. For all chest examinations, the patients had to remove their clothes. The area must be preliminarily inspected, with special reference to the surgical scar location. A comparison between the irradiated patient and the contralateral sides is mandatory to assess the presence and severity of skin, pleura, and lung changes.

To appropriately assess the changes in the breast skin, it is necessary to use high-spatial-resolution transducers with a frequency above 15 MHz, possibly 22 MHz or more [21,22]. This allows adequate spatial resolution to assess any dermatological abnormality optimally. Spacers were employed in the past, but most operators currently use a thick layer of US gel to increase the probe-to-skin ratio and maximize US beam focalization [22,23]. Probe pressure on the skin should be minimized [22,23]. Standard or hockeystick linear transducers were used. Real-time extended field-of-view scans may help display changes in the entire breast skin area [24]. If available, the newer microvascular software should be used with an increased sensitivity to slow flows [25,26]. Both strain elastography and shear-wave elastography may help assess changes in the stiffness of irradiated tissues.

The pleural line was best evaluated using linear transducers at a 7.5–13 MHz frequency. The lungs were explored using linear, high-frequency probes, which allow optimal exploration of more peripheral pulmonary regions, and convex, lower-frequency probes, which allow investigation of deeper regions. For the lung, as well as for the pleura, exploration is essentially limited to grayscale imaging.

The heart was evaluated particularly in the case of left breast irradiation, and it is typically studied using 2–4 MHz microconvex probes. Grayscale (2D and 3D) spectral analysis and color Doppler assessment are necessary. However, echocardiography is not always performed by a radiologist in many countries. In such cases, using US for cardiac examination can be challenging.

Cutaneous Changes

Changes in body image due to multimodal breast cancer treatment can be extensive and enduring, affecting the patient's quality of life. In many women, these changes are the most challenging aspects of the disease [6]. Between 74% and 100% of patients receiving RT for breast cancer experience a certain degree of cutaneous toxicity [27]. Factors associated with cutaneous side effects include a higher RT dose, increased RT volume, and an additional boost to the tumor bed [5]. Moreover, there are concerns regarding the current hypofractionation regimen that could be associated with an increased incidence of post-radiation breast fibrosis [4]. Patient-related risk factors include high body mass index, advanced age, diabetes, immunocompromised state, breast implants, chemotherapy, smoking, and connective tissue disorders [27-29].

Postradiation disorders include acute and chronic radiation dermatitis, fibrosis, and morphea. Acute radiation dermatitis occurs during the second week of RT and presents as a dry, erythematous patch localized in the radiation field (Fig. 2). Further changes developed thereafter owing to

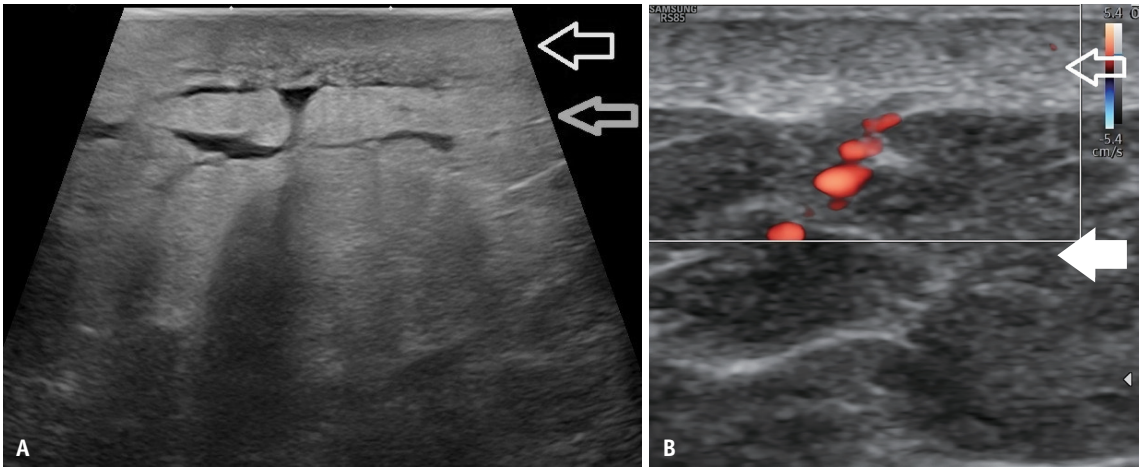

Fig. 2. Post-radiation therapy acute radiodermatitis. Ultrasound scan at 22 MHz. **A:** The dermis is thick and hypoechoic (white arrow). The subcutaneous fat lobes below are hyperechoic, with septal fluid accumulation (gray arrow). **B:** Normal skin appearance for comparison (power-Doppler scan), with the echoic dermis (white open arrow) and the hypoechoic subcutis (white arrow). The dermal-hypodermal boundary is well-defined, and flow signals are limited to the subcutaneous layer.

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dose accumulation. After 3–4 weeks, dry desquamation may occur, followed by edema, tenderness, moist desquamation, full-thickness necrosis, and ulceration [27,29]. Most cases of acute radiation dermatitis resolve after completion of RT. Chronic radiation dermatitis can present months to years after treatment. Patients show hyper- or hypopigmentation of the skin, xerosis, hyperkeratosis, breast pain, skin atrophy, telangiectasias, subcutaneous fibrosis, and disappointing cosmetic results [5,27,29]. Radiation-induced cutaneous fibrosis is a severe, progressive, and irreversible late complication of RT (Fig. 3), and it develops gradually within the first three months after treatment and continues to progress over the years, especially during the first two [27]. Skin retraction, induration, and scarring have been observed in patients with global breast deformities. Fibrosis can be diagnosed by palpation or using a tissue compliance meter. However, a biopsy may be necessary to rule out mimickers such as secondary cancers, angiosarcoma, and morphea [29]. The true incidence of post-radiation morphea is debatable because of the misdiagnosis of infection in the early stage and radiation-induced fibrosis in the late stage [29,30]. Localized morphea presents as an abrupt-onset circumscribed inflammation of the breast skin and underlying tissue, progressing to a chronic stage of fibrotic transformation and deformity [27,30]. In most cases, the onset is within one year after the completion of RT, but shorter and longer intervals have also been reported [30].

Radiation-related skin toxicity is currently clinically evaluated by radiation and medical oncologists. Although an international grading system was adopted [31], this assessment was subjective. Additionally, the naked eye cannot adequately assess or quantify changes in the subcutaneous dermis. Cutaneous reactions after breast RT can be reliably evaluated using ultrasonography.

On US imaging, the skin includes a very thin, regular, hyperechoic line of the epidermis and a thicker, homogeneous, and less echoic dermis [22]. Below the skin is the subcutis, or subcutaneous tissue, whose fat lobules are hypoechoic compared with the overlying dermal layer. Breast edema after conservative surgery is already present before RT, particularly in patients who have undergone axillary dissection, but it increases during treatment and usually decreases after that [32,33]. Objective changes in thickness and subjective changes in echogenicity can be estimated using US by comparing the treated breast with the untreated breast [32,33]. Due to the increased fluid content, the dermis showed increased thickness and reduced echogenicity [34]. The contrast gradient between the dermis and subcutaneous layer decreases, which may create difficulty in precisely measuring skin thickness [35].

Wernicke et al. [36] quantified architectural distortion of the surgical bed in women treated with hypofractionated RT. The average size of the distortion on US was 4.1 cm. No correlation was observed between this measurement and the assessment using palpation and a tissue compliance meter.

Other preliminary attempts investigated radiation-induced skin fibrosis but were based on sophisticated calculation systems [37-40]. Yoshida et al. [39] evaluated skin thickness using US. Women treated for breast cancer were scanned at 10 MHz [39] or at 12 MHz [40]. The

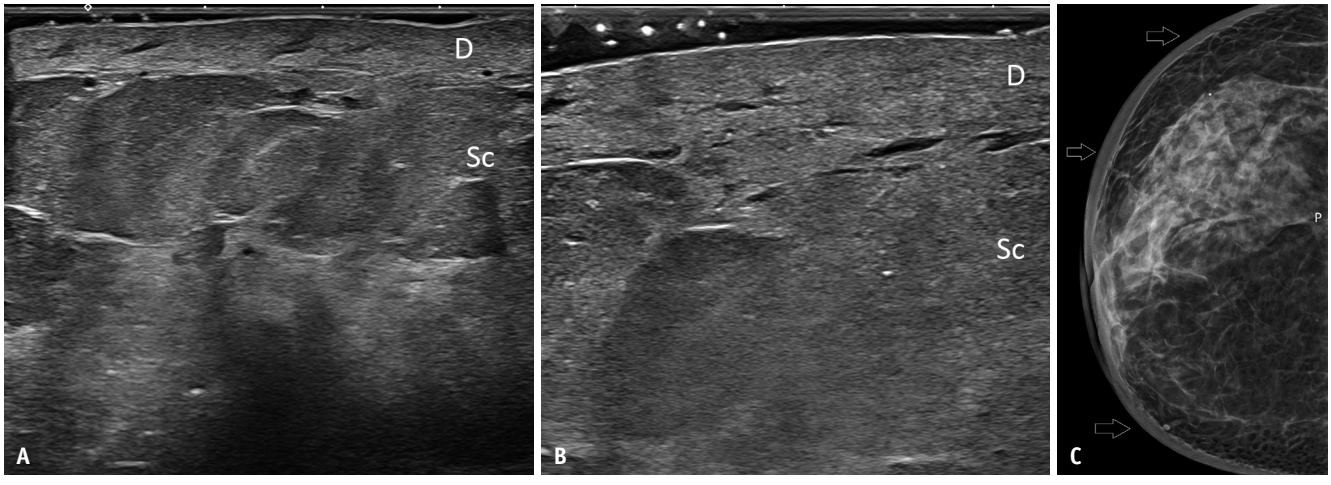

Fig. 3. Post-radiation therapy cutaneous fibrosis. **A:** US scan at 15 MHz. The dermis is thick and echoic. The subcutis is hypoechoic. **B:** US scan at 24 MHz. The dermis is thick and echoic. The subcutis is hypoechoic. **C:** The two layers cannot be distinguished from each other. Cranio-caudal mammographic view in the same patient. Diffuse skin thickening (arrows). US = ultrasound, D = dermis, Sc = subcutis

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interval between RT completion and US ranged from 6 to 92 months. The parameters computed from backscattered US radiofrequency signals were used. Skin thickness was determined from the product of the US wave propagation speed in the breast tissue and the time interval between the radiofrequency signal interaction between the epidermis and hypodermis. The Pearson correlation coefficient and mid-band fit of the hypodermis were calculated. The average skin thickness of the treated breast was 2.6 mm, whereas that of the untreated breast was 2.05 mm. The mean increase in the thickness was 27%.

Landoni et al. [41] used US to evaluate skin fibrosis after hypofractionated RT. The median time between the end of RT and the US examination was 20.5 months. The transmission frequency was in the range of 8–15 MHz. The skin thickness was estimated as the maximum vertical measure of the epidermis and dermis. The mean increase in thickness of the irradiated breast compared to that of the contralateral breast was 0.52 ± 0.52 ± 0.67 mm. In the boost region, the increase was greater at 0.62 ± 0.74 mm.

Chen et al. [42] focused on acute radiodermatitis. The skin thickness on US and elastic modulus at shear-wave elastography were measured in women who underwent RT after conservative breast surgery. At the end of treatment, the increase in skin thickness was significantly greater in patients with clinically severe skin reactions than in those with milder skin reactions. Similar changes were demonstrated in a previous study using 18 MHz and 20 MHz probes [43]. This may allow the prediction of parenchymal edema 12 months after irradiation. Chen et al. [42] did not find any significant difference in the elastic modulus of breast skin between patients with mild and severe radiodermatitis. Another study used elastography before and after breast-conserving surgery and irradiation [44]. The elasticity ratio of the subcutis of the treated breast increased in 89% of patients and was significantly higher than that before surgery, unlike that of the contralateral breast.

Wong et al. [23] evaluated patients with a history of post-mastectomy RT at 14 MHz. The median interval between the RT and US scans was 27.5 months. The mean total skin thickness of the right-irradiated chest wall was 0.17 mm compared with the epidermis and dermis, which was 0.1845 mm. The left irradiated chest wall had a mean skin thickness of 0.18 mm compared with the right non-irradiated breast of 0.1835 mm.

US was used for serial follow-up of patients with breast cancer treated conservatively. These patients may develop local recurrence within the breast parenchyma, with special reference to the peri-cicatricial area or at the skin level [45]. Cutaneous recurrence is less common than that of parenchymal and should be differentiated from RT-related complications, particularly chronic post-radiation dermatitis and fibrosis. However, from both clinical and sonographic points of view, tumor recurrence is usually focal, appearing as discrete, hypoechoic, dermal, and/or hypodermal nodules with irregularly arranged internal and external vessels. Elastography usually reveals increased stiffness at the nodule level.

Pectoralis Muscle Changes

However, the toxicity in the muscular plane has received limited attention. However, RT is associated with pectoralis major muscle fibrosis and atrophy. A histopathology and immunohistochemistry study reported significantly increased neutrophil migration in irradiated muscle tissue, with elevated levels of proteins responsible for muscular atrophy and apoptosis. DNA microarrays detected immunological upregulation and myodifferentiative disorders [46].

Wolfram et al. [47] assessed the pectoralis major muscle with B-mode US and shear-wave elastography. The decrease in pectoralis major muscle thickness and increased stiffness began one month after radiotherapy. The sternocostal region was more affected than the clavicular region.

Pleural Changes

The pleural surface normally appears on US imaging as a thin and regular hyperechoic line between the chest wall and aerated lung. The abnormal pleural line becomes thickened (>3 mm) and/or irregular, with loss of the normal linear contour (Fig. 4) [48,49]. These changes are common after breast RT and can be observed alone or in combination with pulmonary abnormalities, especially B-lines (see below).

Pulmonary Changes

The reported incidence of radiation-induced lung injury, as demonstrated by radiological changes and alterations in pulmonary function tests, ranges from 4.5% to 63% in prospective studies and from 0.9% to 30% in retrospective studies [50]. A recent CANTO-RT cohort reported X-rays or CT evidence of lung injury in 2.4% of patients with breast cancer treated with adjuvant 3D RT [51]. Factors

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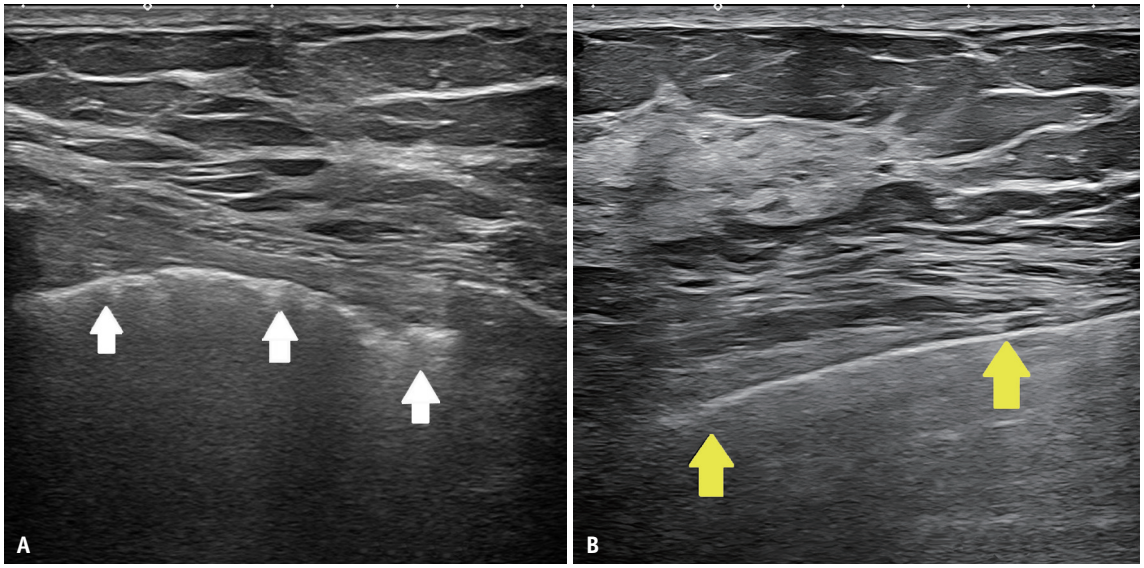

Fig. 4. Radiation-induced pleural fibrosis. **A, B:** Ultrasound scans at 15 MHz. In the left breast **(A)**, the pleural hyperechoic line is thick and irregular (white arrows). The pleura is thin and regular in the right non-irradiated breast (yellow arrows) **(B)**.

predicting RT-induced lung toxicity include older age, poorer performance status, history of smoking, chronic obstructive pulmonary disease, interstitial lung disease, concurrent chemotherapy or tamoxifen assumption, higher primary tumor size, higher radiation dose, axillary and/or supraclavicular nodal irradiation [51-53].

Lung toxicity can occur early (<6 months), such as radiation-induced pneumonitis, and late (>6 months), such as radiation-induced lung fibrosis [52,53]. Radiation-induced pneumonitis is a subacute inflammatory state that occurs weeks to months after the RT treatment. Increased reactive oxygen species in pulmonary tissue results in chemotaxis of cells, increased cytokine levels, tissue edema, and damage [54]. Minor cases are asymptomatic and incidentally detected during follow-up, whereas major cases result in dyspnea, cough, and fever [55]. Pneumonitis can regress or progress to fibrosis. Radiation-induced fibrosis is a chronic abnormality characterized by lung scarring, volume loss, and permanent structural distortion [55].

CT can diagnose radiation pneumonitis showing homogeneous ground-glass attenuations in the early phases and patchy areas of air-space consolidation in the late phases, with linear scarring and atelectatic volume loss [53,55,56]. However, it should be considered that post-RT pulmonary changes typically involve the cortex and subpleural lung tissue placed right below the breast target field. Consequently, these peripheral abnormalities can be adequately evaluated using US. The main signs of lung injury include an increased number of B-lines and subpleural consolidation. These abnormalities are not specific; however, their location and irradiation timing suggest a correct diagnosis. Changes in pleural lines were typically observed together.

B-lines, or vertical comets, correspond to thickened interlobular septa. These reverberation artifacts are described as hyperechoic, well-defined bands arising from the pleural line, extending deeply in an indefinite way, and moving in concert with the lung sliding [57-59]. B lines are quite common, particularly in older adults, and should be regarded as abnormal only if there are more than three lines between two ribs on a single scan (Fig. 5) [57-59].

Lung consolidations can be seen as hypoechoic areas in the subpleural area (Fig. 6) [57,58]. Signs of lung consolidation include the shred sign, an irregular line opposed to the lung line, a shredded boundary between the consolidated and aerated lung, a tissue-like sign, tissue in continuity with the liver on the right side, and the spleen on the left side (although separated from them by the hemidiaphragm). In contrast to pneumonia, post-radiation consolidation areas usually do not show air bronchograms (linear, arboriform hyperechoic images representing air-filled bronchioles) or at least do not show a dynamic air bronchogram, that is, a change in appearance during inspiration and exhalation [58].

Petruzzelli et al. [60] measured the B-lines in the treated and contralateral lungs of patients with breast cancer 1–3 months after the end of RT and 1 year after the first US

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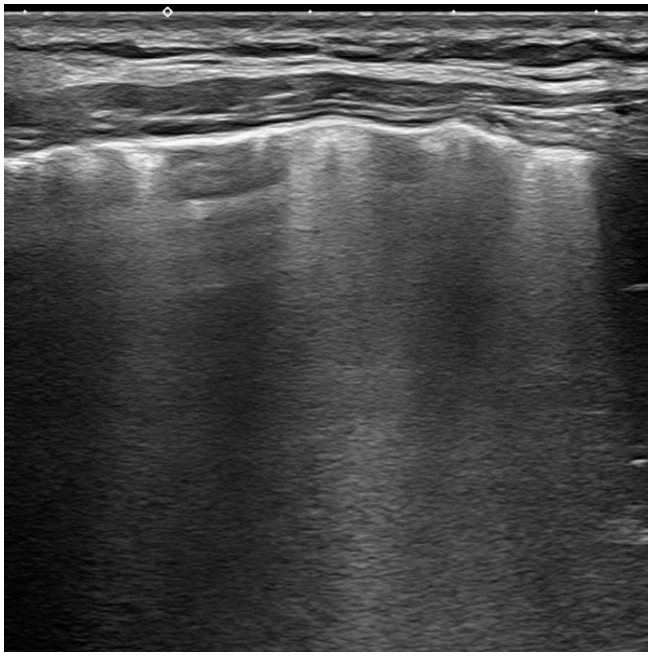

Fig. 5. Radiation-induced lung fibrosis. Presence of multiple B lines and pleural line thickening can be seen.

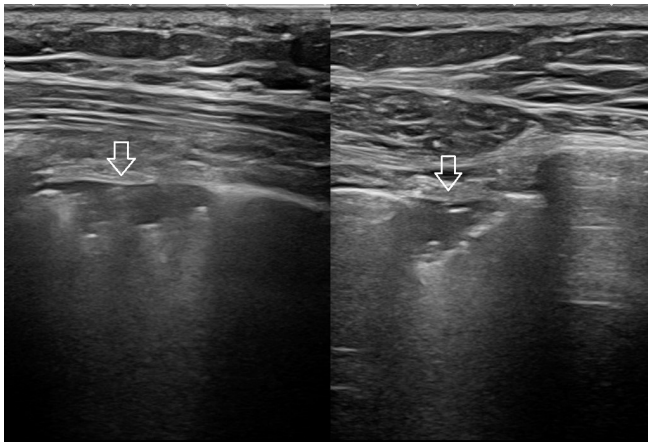

Fig. 6. Radiation-induced lung consolidation. The subpleural hypoechoic area (arrows) and the B lines in the lung parenchyma are indicated.

examination. B-lines were more numerous in the treated versus the untreated hemithorax in both examinations. In addition, within the treated hemithorax, B-lines were more frequent in the anterior aspect of the chest than in the posterior dorsal aspect in both examinations. The presence of B-lines is correlated with the radiation dose to the lung [61].

Cardiac Changes

Particularly in left-sided breast cancer, RT induces slowly evolving fibrotic changes in cardiac structures, which may increase the incidence of heart failure with preserved ejection fraction [62-64]. The risk of heart failure with a preserved ejection fraction increases 16-fold in patients with breast cancer and prior RT [64]. Late changes that develop after several years of latency include coronary artery disease, aortic and mitral valve stenosis and regurgitation, and disturbances in the conduction system [62,65]. B-mode echocardiography revealed thickening of the cardiac septum and left ventricular posterior wall. In the 3D analysis, the left ventricle volume decreases in diastole and systole [62]. RT is associated with increased myocardial reflectivity in ultrasonic tissue characterization analyses [62]. These changes have progressed over the years and are localized, especially in the septal and apical regions.

CONCLUSION

US is useful in diagnosing post-RT complications, improving their differential diagnosis, particularly when clinical assessment is insufficient. Interfering factors such as post-surgical edema, axillary lymph node surgery, chemotherapy, and hormone therapy should always be considered. US is useful in grading the severity of changes and predicting the effects of RT. US qualitative and quantitative parameters may be useful for screening patients who would benefit from post-RT physical therapy or other kinds of treatments, as well as from other precautions, such as radioprotective drugs before RT, topical treatments, or systemic drugs. This may help to prevent or attenuate late irreversible radiation-induced damage.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Funding acquisition: all authors. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: all authors. Supervision: all authors. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

ORCID IDs

Orlando Catalano
https://orcid.org/0000-0003-0188-1236

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Roberta Fusco
https://orcid.org/0000-0002-0469-9969
Serena Carriero
https://orcid.org/0000-0003-2583-4215
Stefania Tamburrini
https://orcid.org/0000-0003-0455-0256
Vincenza Granata
https://orcid.org/0000-0002-6601-3221

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