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Chapter

Strain Elastography in Invasive Lobular Carcinoma

Angelica Rita Chiorean, Roxana Pintican, Diana Feier,
Dan Eniu and Maria Magdalena Duma

Abstract

Breast cancer remains the second cause of mortality in women, even if the mortality rates linked to it have drastically dropped at the present time. Invasive lobular carcinoma (ILC) accounts for 5–15% of the breast cancers and it is the second most encountered type among invasive carcinomas. There has been reported a high rate for bilateral lesions (6–47%), multifocality/multicentricity (21%), all affecting ILC overall survival. Due to its nonspecific symptoms and to the fact that it does not invoke a vigorous desmoplastic response and has a low likelihood of producing calcifications, the ILC tends to be insidious on mammography. Contrast enhanced MRI has the lowest false negative rate in detecting ILC and it is the most accurate method of determining the lesion extension, though it is expensive and not widely available. Therefore, the ultrasound (US) plays a significant role in the diagnosis of ILC. US elastography imaging (EI) individualizes malignant breast lesions with high sensitivity and specificity. Recent studies suggested that US elastography can even diagnose lobular cancers that have benign findings on conventional imaging. Goal: present various US aspects and exemplify the added diagnostic value of strain elastography—how it may change the BIRADS category and further therapeutic management?

Keywords: breast cancer, invasive lobular carcinoma, elastography, ultrasound, BI-RADS

1. Introduction

Breast cancer remains the second cause of mortality in women, even if the mortality rates linked to it have drastically dropped at the present time. Based on the origin of the cancer cells, there are two types of breast cancer subtypes: ductal and lobular. Both include an "in situ" and an "invasive" form, depending on their extension to the neighboring tissues. We will further address invasive lobular cancer (ILC), which accounts for 5–15% of the breast cancers and is the second most encountered type among invasive carcinomas.

2. Epidemiology

ILC has an estimated incidence of 2.7 per 100.000 people, with a mean diagnostic age higher than for invasive ductal carcinoma. About two-thirds of women are 55 or older at the time of the diagnosis, ILC tending to occur even later in life [1].

3. Pathology and ILC subtypes

The tumor develops at the terminal ductal-lobular unit (TDLU), and it is composed of cancer cells that are individually dispersed or arranged in a single-file pattern. Often, the cells form a target-like configuration around normal breast ducts. Two main histology findings are characteristic for invasive lobular cancer: the noncohesive cell pattern and the minimal desmoplastic response. The first is an effect of the E-cadherin (CDH1) germline mutation encountered in about 85% of the tumors, which results in the loss of adhesion proteins and a discohesive morphologic pattern [2]. The second is due to the fact that malignant cells grow in the mammary stroma and adipose tissue and induce less desmoplastic reaction than ductal carcinoma, which has important repercussions on the imaging aspects [3].

As it regards the ILC subtypes, occasionally the classic single-file formation is absent, and there is a different pattern encountered: solid (large sheets with little stroma), alveolar (groups of 20 cells), or tubular-lobular (tubelike structures together with single-file pattern) [2, 3].

The classic ILC presents with tumor cells that are usually small, uniform, and round with minimal pleomorphism. Otherwise, a less often subtype cell might be reported: pleomorphic or signet-ring cells.

The majority of ILC are positive for estrogen and progesterone receptors and are negative for the HER2 amplification (consistent with a luminal A category).

4. Signs and symptoms

The invasive lobular carcinoma may be asymptomatic. Due to the typical spread pattern, some of the patients may present with the first sign of ILC as a skin thickening or hardening of the breast rather than a distinct lump. Basically there are no ILC-specific signs or symptoms; the patients' physical examination may reveal general breast cancer-related changes such as a swelling area, skin irritation or dimpling, breast or nipple pain, nipple discharge (other than breast milk), and even an axillary lump [4].

Due to the lack and nonspecific symptoms, up to 10% of the patients present with metastatic disease at the time of diagnosis [1].

5. Diagnosis of ILC

Breast cancer in general might be diagnosed using different complementary methods or techniques, starting with a physical breast examination; whether we are using screening or diagnostic mammography (Mx), ultrasound, or magnetic resonance (MRI), it is well known that imaging often underestimates this disease's extension. The tissue analysis remains the gold standard for tumor diagnostic, regardless if the tumor tissue originates from a biopsy or a surgical excision.

Regarding the tumor appearance, a high rate for bilateral lesions (6–47%) has been reported, multifocality/multicentricity (21%), all affecting the ILC overall survival (**Figure 1**) [1].

5.1 Mammography

The sensitivity of mammography is reported to be lower for ILC than for invasive ductal carcinoma, ranging from 34–72%, and it is frequently seen in only one view (often on cranio-caudal compared to mediolateral oblique) [5]. Most commonly, the tumor presents as a spiculated mass lesion without calcifications.
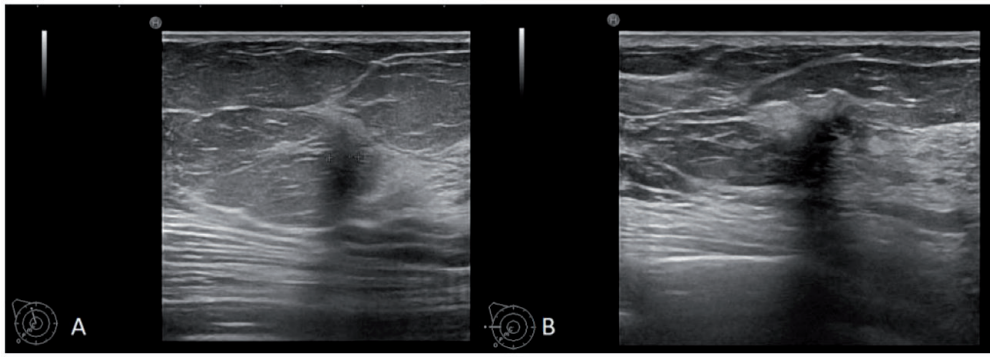
Figure 1.
Multifocal ILC. Ultrasound suspect lesions located in the right breast, first at 11 o'clock (A) and second at 9 o'clock (B).

In some cases, architectural distortions or asymmetrical densities are observed; moreover, up to 16% of ILC remains mammographically occult or are attributed to benign lesions (**Figure 2**).

5.2 Ultrasound

The studies reported a sensibility of 98% in the ultrasound diagnostic of ILC [6]. The tumor usually presents as a hypoechoic mass, with ill-defined margins and posterior acoustic shadowing (58%), occasionally without shadowing (27%) [6]. Contrary to ductal carcinoma, which commonly presents as a lesion perpendicular to the surface, ILC may exhibit a so-called "wider than tall" shape, a tumor that is parallel to the skin. In some cases, the mass might be heterogeneous with an iso- or hyperechoic halo (**Figure 3**).

5.2.1 B-mode

Two classic signs of ILC were described using B-mode of ultrasound. First, the Golden Gate sign resulted from 2 to 3 adjacent Cooper's ligaments involved by cancer so that the shadowing area (hypoechoic area) resembles the shape of a suspension bridge seen from the profile. The second one, named the picket fence sign, is observed when more numerous and more closely spaced Cooper's ligaments are involved in cancer and the shadowing area resembles the profile of a picket fence (**Figure 4**).
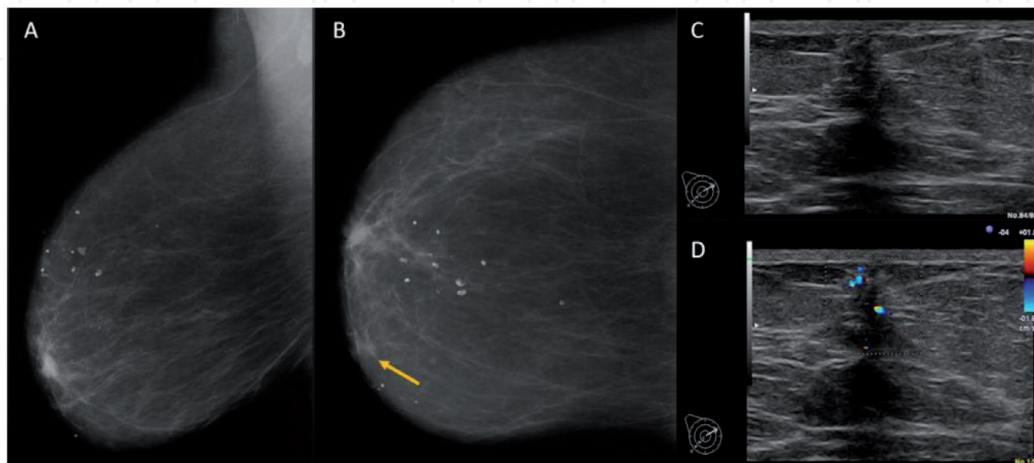
Figure 2.
Subtle ILC mammographic findings: An asymmetry of density is seen on the CC view (B, arrow), without a correspondent on MLO projection (A). Note the same density of the lesion as of the normal tissue breast. The ultrasound (CD) revealed a 5 mm, spiculated, hypoechoic lesion with vascularization on color Doppler.
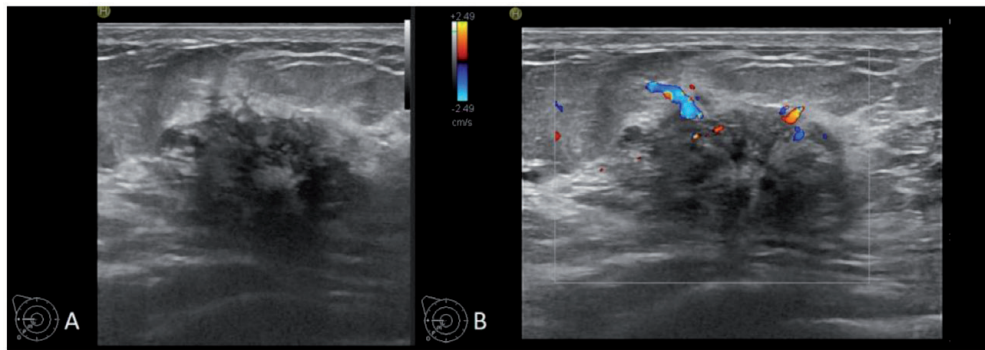
Figure 3.
ILC presented as a heterogeneous mass, with small cystic areas included and ill-defined margins (A), vascularized on color Doppler (B). Note the mass orientation, parallel to the surface, with a "wider than tall" appearance.
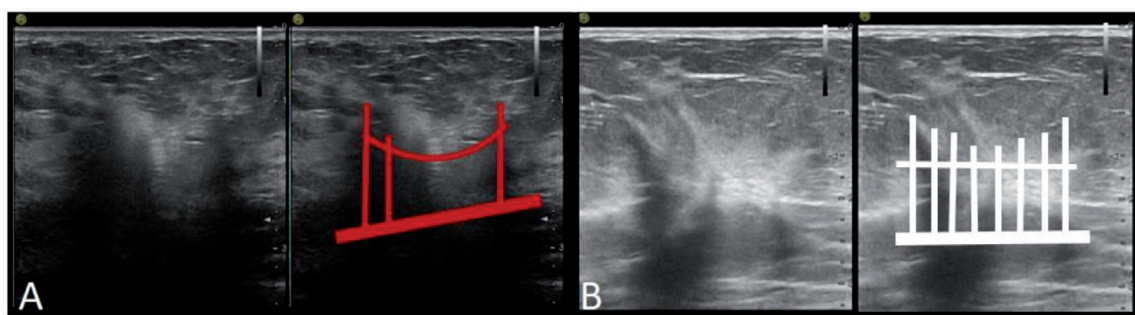
Figure 4.
Classic sign of ILC: Golden Gate bridge (A) and picket fence (B).

5.2.2 Doppler mode

The Doppler mode highlights the presence of the blood vessels within the tumor, whether it is a mild, moderate, or intensely vascularized tumor mass. The vessel's spreading pattern is not characteristic, usually the tumor presenting with diffusely distributed vascularization. Rarely, a malignant mass may present as an avascular tumor, due to the present-day limitation of the technique (vessels too small to be highlighted).
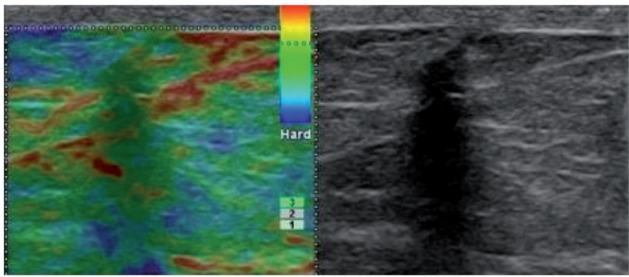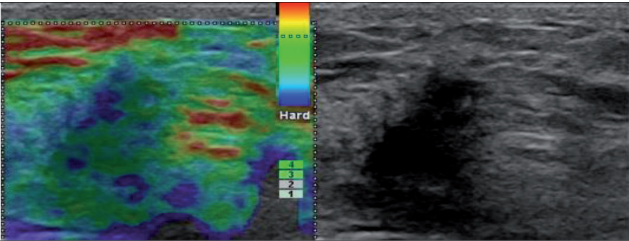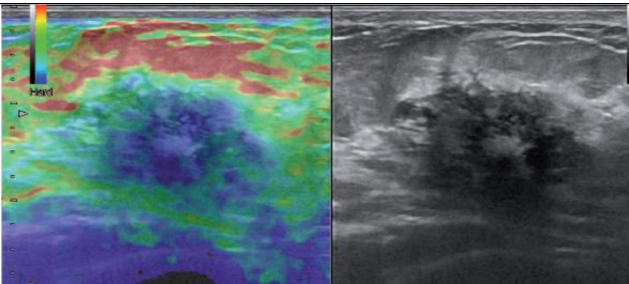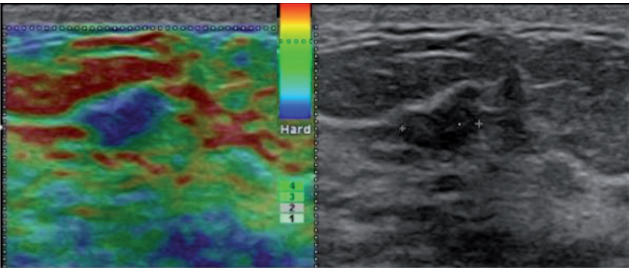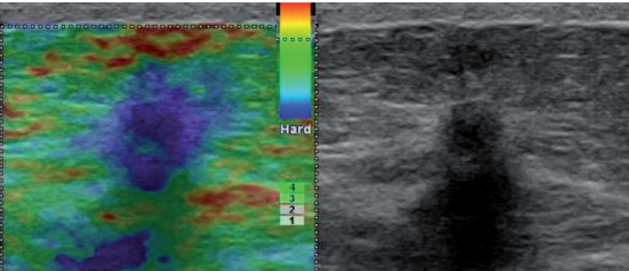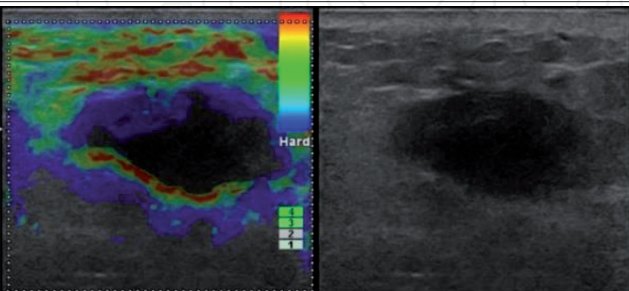
5.2.3 Elastography

In breast ultrasound, both strain (static) and shear wave (dynamic) elastography are used. Ultrasound elastography of the ILC masses exhibits various patterns, from soft to mosaic and predominantly hard tumors. Tsukuba score (TS) is often used to qualitatively classify the elasticity of the masses, from 1 (soft) to 5 (extensively hard lesions) (**Table 1**).

The elasticity varies between different lobular cancer masses, which may even have an elastography score similar with the normal adjacent breast tissue. An important take-home message lies in the lesion's grayscale aspect: if the B-mode indicates any sign of malignancy, a normal hardness should not delay the following biopsy.

ILC commonly presents as hard masses (Tsukuba 4 or 5 score). Sometimes a mosaic pattern might be obtained, and rarely a blue-green-red (BGR) appearance may be noted.

A topic of interest nowadays is represented by the US prediction regarding the breast cancer tumor grades. The mean elasticity/B-mode ratio was reported as statistically different between ILC and grade III ductal carcinoma, versus mucinous or grade I and II ductal cancers [7].

Score 1 Complete deformability of lesion		Benign
Score 2 Lesion with little stiff areas		Benign
Score 3 Central stiff area with peripheral deformability		Probably benign
Score 4 Completely stiff lesion		Malignant
Score 5 Stiff lesion and surrounding area		Malignant
BGR sign Blue-green-red pattern		Benign/cyst/malignant with necrotic area

Table 1.
Tsukuba qualitative score. The left column displays the elastography score, the middle column shows the elastography/B-mode appearances, and the right column describes the score meaning. All the abovementioned lesions were proven to be invasive lobular cancers.

On the topic of shear wave elastography, the method provides a quantitative assessment and tissue stiffness values, represented in kilopascals (kPa). A value higher than 45.7 kPa for the mean elasticity was attributed to malignant breast tumors (**Figure 5**) [8].
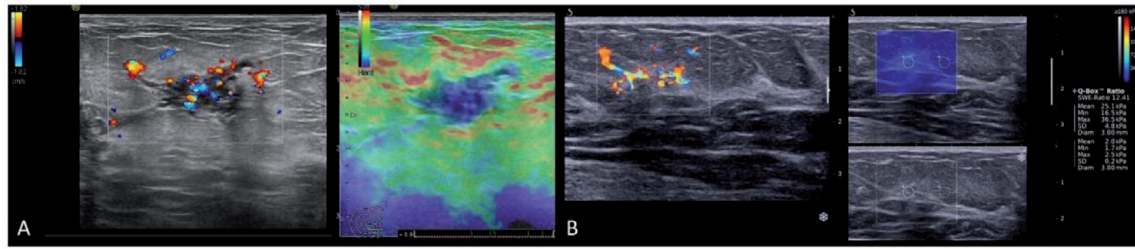
Figure 5.
Breast elastography techniques. (A) Vascularized lesion, hard on strain elastography. (B) Vascularized area, soft on shear wave elastography. Note the difference between stiffness' color coding: Blue in strain EI = hard, blue in share wave EI = soft.

A comparison of strain and shear wave ultrasound elastography in differentiating benign and malignant breast lesions concluded that strain ultrasound elastography is more specific (93.7%) and less sensitive (81.7%), while shear wave ultrasound elastography is more sensitive (95.8%) and less specific (84.8%) in differentiating benign from malignant breast lesions [9].

There are three additional and important EI key aspects that help in the ILC diagnostic:

1. Highlighting hardly visible lesions—Sometimes a breast lesion might be isoechoic to the surrounding breast tissue, scarcely visible in grayscale; in some cases elastography may help us in identifying those hard lesions with greater confidence (the lesions will appear as isoechoic on B-mode and blue on strain EI).

2. Identifying pseudo-benign lesions—EI may indicate lobular cancers that have benign or normal findings on conventional imaging as suspicious [10].

3. Suggesting a larger lesion—It is known that imaging often underestimates ILC. Even so, EI may sometimes suggest a lesion's extension by highlighting a hard area that exceeds the grayscale lesion (lesions with Tsukuba 5 score).

To conclude, whether or not it is a strain or a shear wave, elastography methods are adding value to the ILC diagnostic and should be definitely used in the assessment of every patient. Moreover, it may change the BI-RADS category from a probable benign lesion (score 3) to a suspicious lesion (score 4). Thereby, elastography has an important impact in the patient's therapeutic management, which translates in certain cases, in switching from a short-time follow-up to biopsy.

By educational purposes, all ultrasound characteristics presented above will be highlighted in the following case-based section. The various ILC imaging appearances were grouped in subcategories, as it follows:

a. Hypoechoic mass with posterior acoustic shadowing (**Figure 6**).

b. Hypoechoic mass without posterior acoustic shadowing (**Figure** 7).

c. Architectural distortion (**Figures 8** and **9**).

d. Iso- or hypoechoic area or non-mass lesion (**Figures 10** and **11**).

e. Hyperechoic lesion. Even if the hyperechoic appearance usually represents a benign entity, up to 5% of the ILC were reported as hyperechoic lesions, out of which 48% were associated with posterior acoustic shadowing (**Figure 12**) [11].
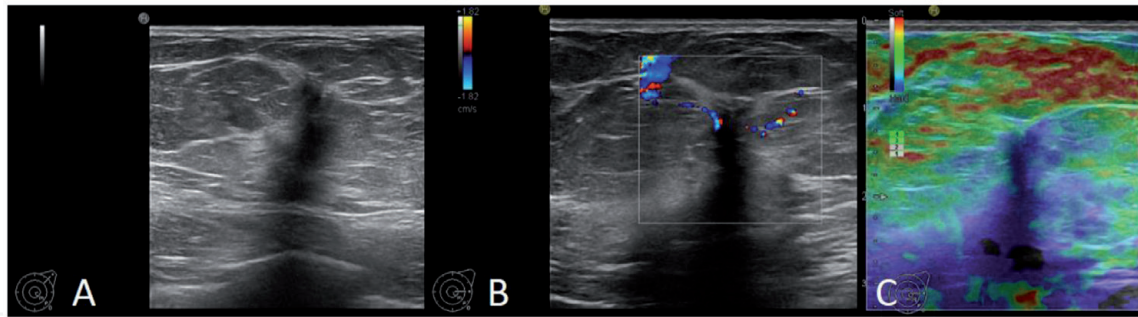
Figure 6.
ILC lesion presents as a hypoechoic mass with intense posterior acoustic shadowing (A), vascularized (B), and hard on elastography (C, TS 5).
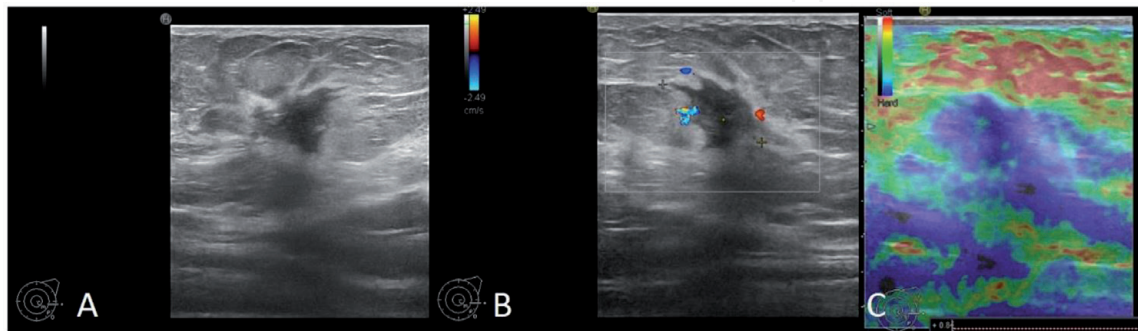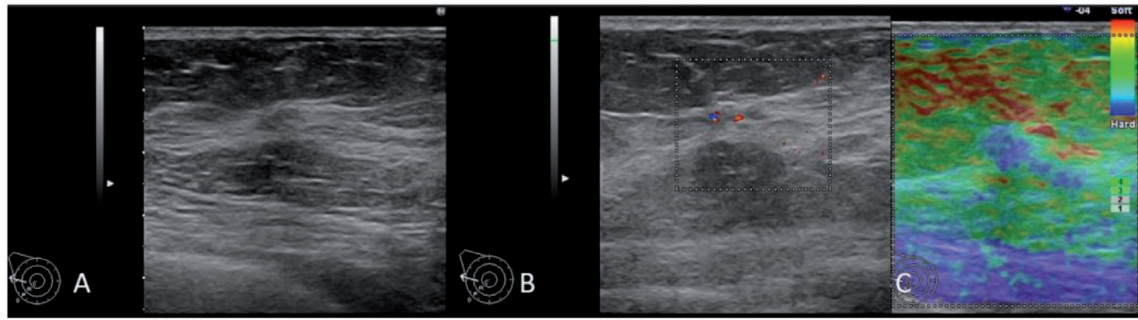

Figure 7.
ILC lesion presents as an ill-defined, hypoechoic mass without posterior acoustic shadowing (A), hypovascular (B), and hard on elastography (C, TS 5).
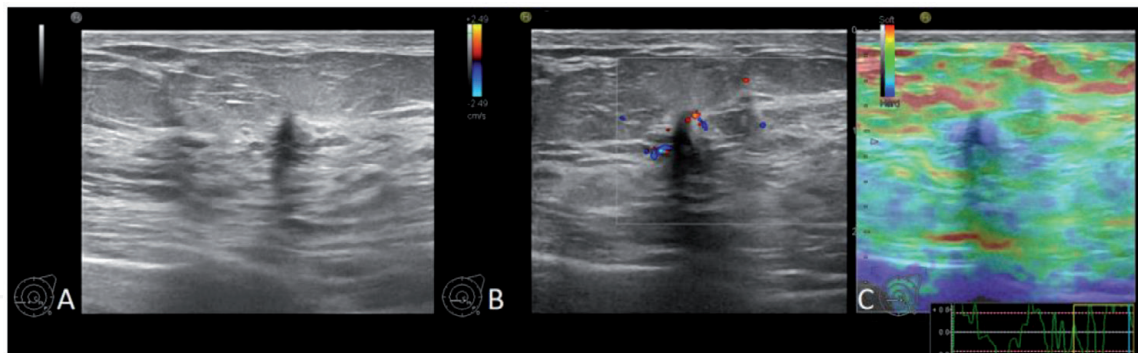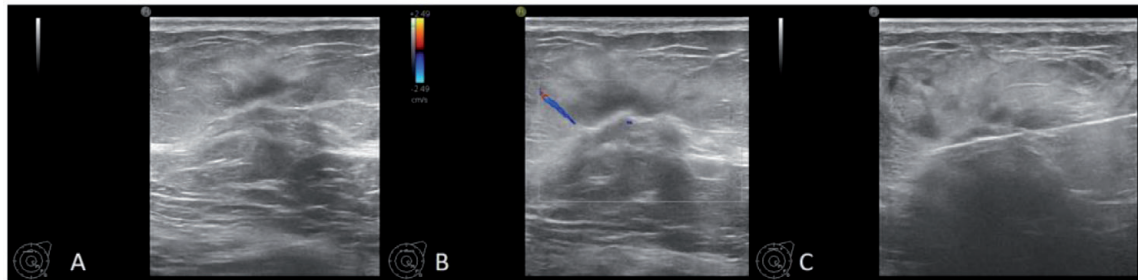

Figure 8.
ILC lesion presents as an architectural distortion with mild posterior acoustic shadowing, hardly visible on grayscale (A). The area is hypovascular (B) and hard on elastography (C, TS 4).

    f. Well-defined nodule. Studies reported up to 2–12% of the ILC cases as a pseudo-benign, well-defined nodule (**Figure 13**) [12].

    g. Occult lesion. Not often, ILC may not be highlighted by ultrasound. Authors report up to 10% of the cases missed on US [12]. Sometimes, a lesion might be detected during a second-look US after an MRI depiction (**Figure 14**).

    h. Axillary abnormality. Regarding the US sensitivity in the metastasis detection, the technique was reported positive in about 50% of the N1 cases. Furthermore, US is able to exclude 96% of the N2 and N3 axillary metastasis (more than four positive lymph nodes). The fine needle biopsy is less sensitive in ILC than invasive ductal carcinoma (IDC vs. ILC; 98.4% vs. 53.6%; p < 0.001) (**Figure 15**) [13].
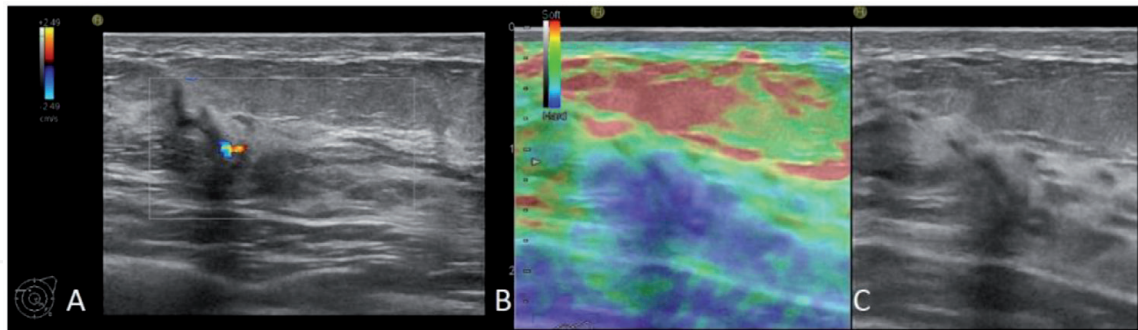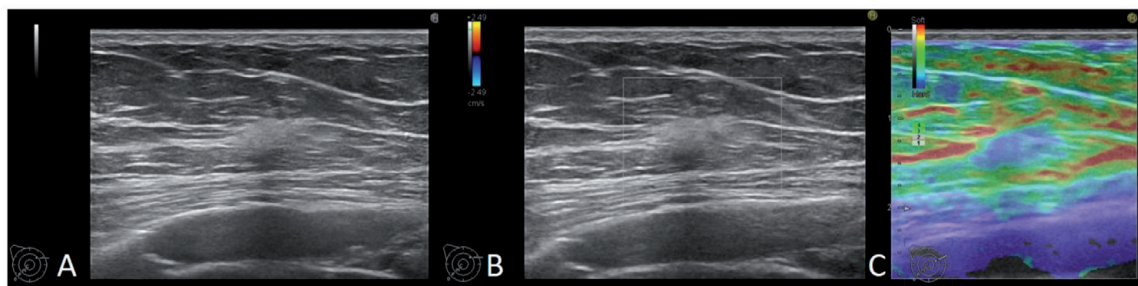
Figure 9.
Hardly visible ILC isoechoic lesion (A) associated with a hypovascular architectural distortion (B). The lesion is easily spotted on elastography, as a hard area (C, TS 4).
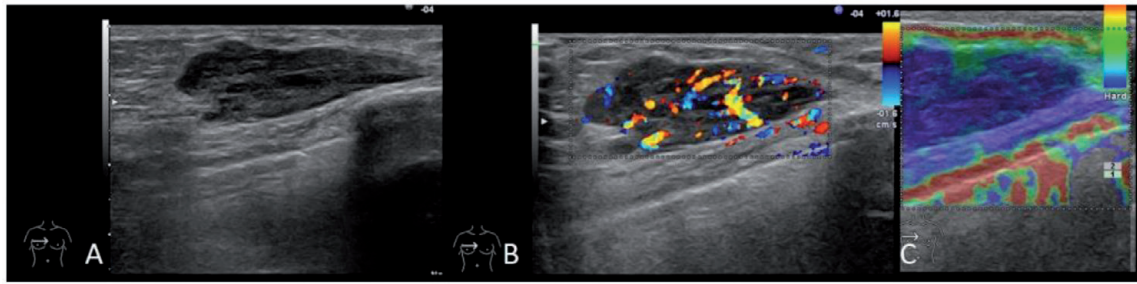

Figure 10.
Hypoechoic area with hyperechoic halo resembling the picket fence sign (A), with minimal vascularization on color Doppler (B). The core needle biopsy (C) revealed an ILC lesion, with positive estrogen and progesterone receptors RE = 100%, RP = 25%, Ki67 = 15%, and HER2 negative.
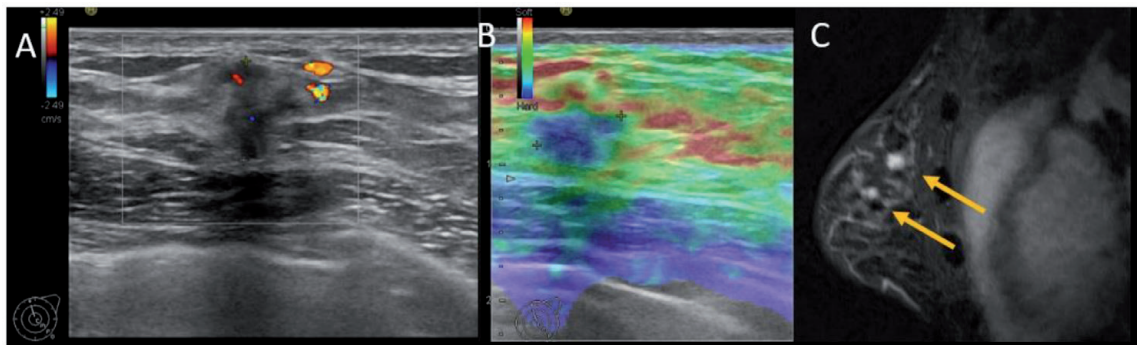

Figure 11.
Hypoechoic, hypovascular area which presents with mild posterior acoustic shadowing (AC). Note that the hard area is larger on elastography than grayscale (B, TS 5).
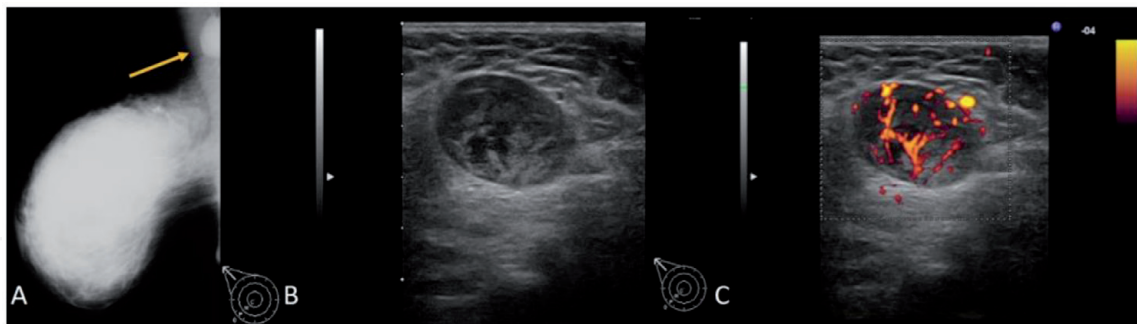

Figure 12.
Hyperechoic, ill-defined lesion (A), apparently avascular (B), but hard on elastography (C, TS 4). At the time of diagnosis, the patient presented peritoneal metastasis.

Figure 13.
A patient with a history of ILC treated with mastectomy 24 years ago. The present US revealed a well-defined, hypoechoic nodule in the area of mastectomy (A). The nodule is intensely vascularized (B) and hard on elastography (C, TS 4). Initially considered a BI-RADS 4a lesion, after EI the lesion has been assigned to a higher BI-RADS 4b score. The core needle biopsy showed an ILC relapse.
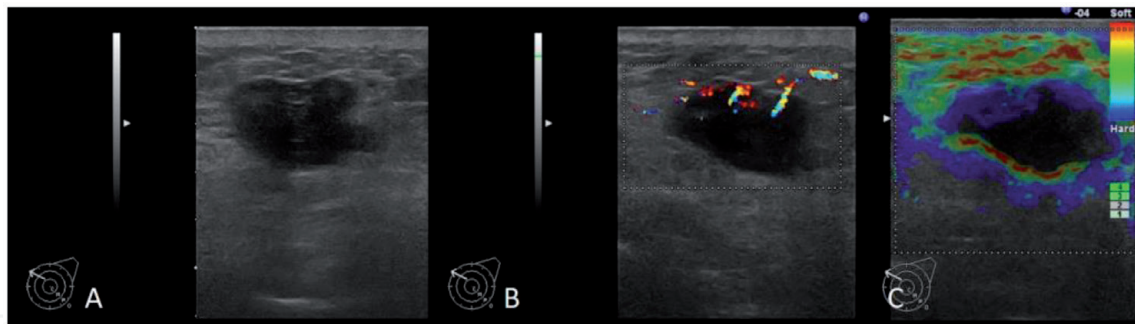

Figure 14.
A breast lesion with suspect features was detected at US and proven to be an ILC (AB). The following staging MRI highlighted not one, but two lesions (C), concluding that one of the lesions was US occult.
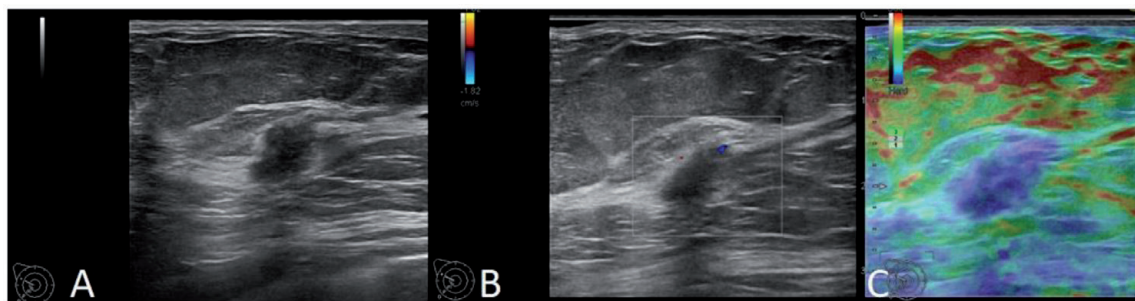

Figure 15.
The mammography shows a highly dense right breast and an abnormal axillary mass (A, arrow). The US revealed an enlarged, rounded lymph node (B), with intense and chaotic vascularization (C). The core needle biopsy concluded an ILC metastasis.

i. ILC with BGR appearance. Rarely, ILC may display a blue-green-red sign due to a necrotic component. Even if the BGR sign is commonly attributed to cysts, its presence in a solid, suspicious mass may never delay a biopsy (**Figure 16**).

j. ILC lesions in which elastography changed the BI-RADS score. It was previously established that in order to achieve an accurate breast cancer diagnosis, US B-mode should be combined with Color Doppler and elastography. Regarding EI, there was a positive impact in breast cancer diagnosis, especially for small lesions [14]. Moreover, in invasive lobular cancer, EI demonstrated to improve the BI-RADS classification, particularly for lesions smaller than 13 mm (**Figures 17–19**) [15].
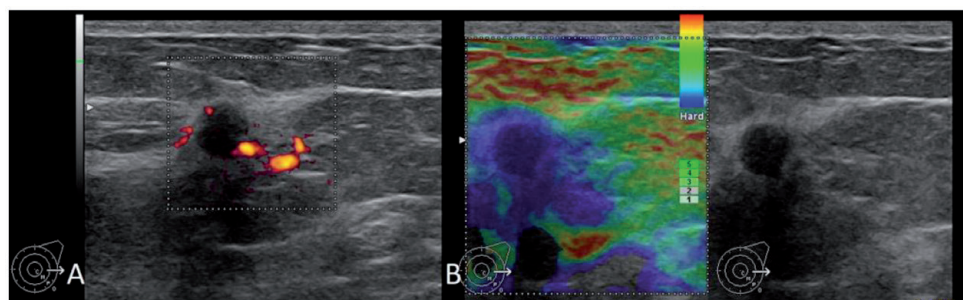
Figure 16.
Intensely hypoechoic nodule with partially well-defined, partially ill-defined margins (A), moderately vascularized on color Doppler examination (B). The elastography displays a blue-green-red appearance (C). Core biopsy revealed an ILC lesion.
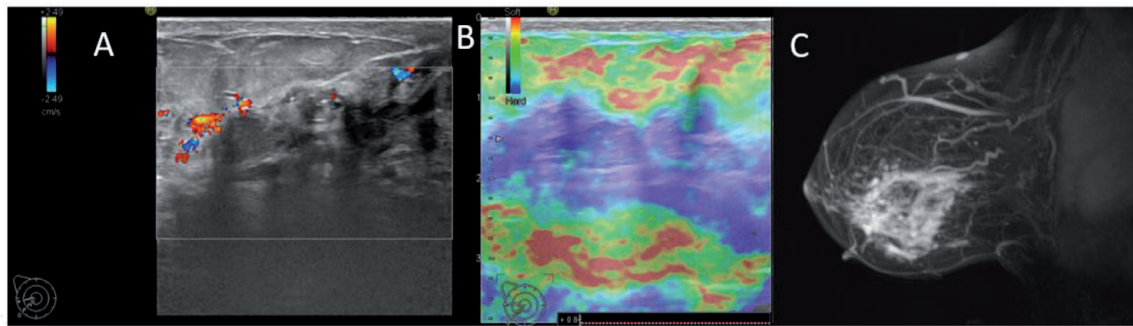

Figure 17.
BI-RADS 3 to BI-RADS 4a. ILC presented as a small hypoechoic lesion with indistinct margins (A), hypovascular (B), and hard aspect on EI (C, TS 4/5). The lesion was upgraded from BI-RADS 3 to BI-RADS 4a after the elastography criterion was added.
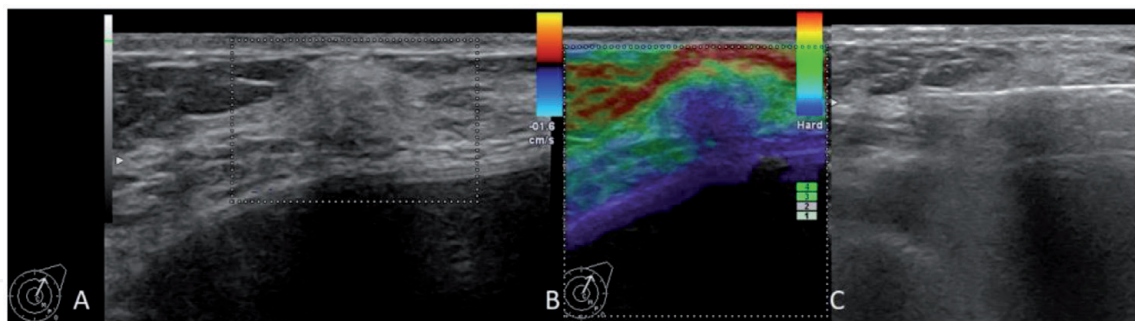
Figure 18.
BI-RADS 4a to BI-RADS 4b. A small, avascular, hyperechoic lesion with indistinct margins (A) and hard on EI (B, TS 4). The core needle biopsy revealed ILC (C). The lesion was upgraded from BI-RADS 4a to BI-RADS 4b after the elastography criterion was added.

Figure 19.
Doppler US reveals a hypoechoic round lesion with partially angulated margins and peripheral vascularity (A). On strain elastography (B), the entire lesion and its surrounding parenchyma were shaded blue (TS 5). The lesion was upgraded from BI-RADS 4B to BI-RADS 4C after the elastography criterion was added.

Figure 20.
Heterogeneous US area of ILC, which is moderately vascularized and hard on elastography (AB, TS 5). The MRI (C) shows a non-mass enhancement, with a regional distribution, larger than the area predicted on US.

5.3 MRI

Due to its propensity for bilaterality and multicentricity, breast MRI is usually recommended when histology of a lesion reveals an ILC. MRI easily highlights occult Mx and US lesions and has the lowest false-negative rate in detecting ILC [16]. In addition, MRI has the highest accuracy in measuring ILC sizes, whether it is a mass or non-mass enhancement pattern. ILC kinetic is rarely a type III curve (washout) or type I curve, more often displaying a type II (plateau) curve (**Figure 20**).

6. Treatment and prognosis

Depending on the disease's stage, there is a local ILC treatment represented by surgery and radiation therapy and a systemic treatment characterized by chemotherapy, hormonal therapy, or targeted therapies. Due to its diffuse invasive nature, positive resection margins are common.

ILC spreads slowly outside the breast, but when it does, it tends to manifests with atypical metastases, affecting the gastrointestinal tract (as a diffuse spreading process of the colon 26%, stomach, or small bowel), ovaries (21%), peritoneum (as Krukenberg syndrome, 30%), retroperitoneum, leptomeningeal, or bone. It may also cause lymph node, lung, or liver metastasis.

Despite the multifocality, the bilateral lesions, and the atypical metastases, the prognosis for ILC patients with a given size and stage is believed to be slightly higher than for patients with invasive ductal carcinoma.

7. Conclusion

The ultrasound plays a significant role in the diagnosis of invasive lobular carcinoma. Ultrasound elastography imaging individualizes malignant breast lesions with high sensitivity and specificity, being sometimes a "problem-solving" method. Moreover, it may change the BI-RADS category and have an important impact on the patient's therapeutic management.

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Conflict of interest

All authors declare no conflict of interest.

Notes/thanks/other declarations

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