Full Breast Ultrasonography of Malignant Lesions

8

8.1 Major Risk Factors for Breast Cancer and Breast Cancer Prevention

8.1.1 Major Risk Factors for Breast Cancer

The major risk factors for development of breast cancer in women are as follows:

- Positive family history of breast cancer in a first-degree relative
- History of benign breast disease
- Age over 40 years
- Late-age birth of first child or nulliparous
- Use of long-term estrogen replacement therapy or oral contraceptive pills
- Radiation exposure
- Alcoholic beverage consumption
- Smoking (increases the risk of metastases in lungs)

Today, it is widely acknowledged that breast cancer is found three to five times more often in women with benign lesions of the breast and 30–40 times more often in women with a nodular form of mastopathy with signs of epithelial proliferation. About 10–15 % of breast cancers are thought to be hereditary. Normal cells become cancerous as a result of certain mutagenic genes: BRCA1 in about 45 % cases and BRCA2 in about 35 % cases (*BReast CAncer Gene 1* and *BReast CAncer Gene 2*).

8.1.2 Control of the Risk Factors of Breast Cancer: Dishormonal Changes

Because benign conditions and breast cancers have many similar etiologic factors and pathologic processes, they have common risk factors, most related to dishormonal changes. The hypothalamus–hypophysis system plays an important role in the development of dishormonal hyperplasias of the breast. Some authors consider a risk factor to be the activation of the proliferative process in the hormone-dependant organs, including the tissues of breast, which are target areas for the steroid hormones of the ovaries, prolactin, placental hormones, and, implicitly, other endocrine hormones.

Estrogens have major impacts on the proliferation of the epithelial acini, lobules, and interlobular ducts. Their role is, therefore, overestimated, and the use of progesterone-based creams as an “antidote” treatment is illogical because a breast cancer may be both estrogen-receptor (ER) and progesterone-receptor (PR) positive. Therefore, the level of estrogens is correlated in ductal echography (DE) with breast parenchyma, especially with ductal diameter and the size of the lobules. In ovarian precocious insufficiency, bradimenorrhea, primary or secondary amenorrhea, or after ovariectomy, postmenopausal-type changes of the breast occur. With hormonal substitution therapy, assisted fertility treatment, or other cases of hyperestrogenism and “true” gynecomastia, the breast parenchyma presents more or less as ductal-lobular thickening.

Fibrocystic changes, considered dishormonal hyperplasias of mammas, represent one of the most common benign conditions, affecting more than 50 % of women with palpably irregular breasts, cyclic pain, and tenderness. Some findings are considered as congenital pathology, the most severe being Reclus’ disease. The “sick lobe theory” of Tot considers the whole lobar unit damage present at birth [1], but the branching of the mammary bud begins at puberty, and many women develop mammary dysplasia later in adulthood or in the postmenopausal stage as result of complex dishormonal changes.

High levels of prolactin may cause breast-feeding changes similar to, but less intense than, normal pregnancies: diffuse breast hypervasculature, lobular hypertrophy, and duct ectasia with milky secretions. In chronic disorders, such as prolactinoma, chronic overinfection may be present. However, not all cases of duct ectasia present hyper-prolactin levels, and not all cases of high prolactin are associated with a pituitary lesion, found on the magnetic resonance imaging (MRI) examination. Elevated prolactin level seems to be correlated in Doppler DE with diffuse increase in the number and size of breast vessels, but no vascular changes were found in chronic secreting galactophoritis [2]. Androgens have more impact on the fibrotic process [3].

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Mastodynia/cyclic mastalgia usually occurs premenstrually and may not demonstrate any changes in the breast anatomy in DE, neither ducts nor lobules being influenced in size or aspect. In the premenstrual breast, increased tenderness and reduced elasticity seem to be determined by the stromal reaction, as is frequently demonstrated by Sonoelastography (SE), which can better delineate the differences in the strain of the stroma (harder) and parenchyma (softer, score type 1 Ueno).

Breast cancer has a significant correlation with thyroidal lesions [4, 5]. Not only is the nodular goiter usually associated with breast diseases but also the diffuse goiter. In many cases, the autoimmune thyroiditis, Hashimoto's disease, is present. Thus results the recommendation to explore the thyroid by ultrasonography, in all cases, with breast screening or breast symptomatic examination.

Food hormones are associated with precocious thelarche, "true" gynecomastia, and duct ectasia. Although this correlation is accepted worldwide, there are few studies employing systematic observation in large populations of food-induced breast pathology. More evident are the effects of therapeutic hormonal intake on breast morphology. Birth control pills may aggravate or ameliorate breast dysplasia, and substitution hormonal therapy increases breast density in postmenopausal woman, increasing the risk of breast cancer. More frequent reports present breast cancer following repeated treatments for assisted fertility.

In cases of adrenal or gonadic hormonal-secreting tumors, breast changes are present in male and female patients. In children with precocious thelarche or pathological gynecomastia (at different ages than physiological breast development), in addition to food-intake of steroids and hormone-secreting tumors as causes, genetic disorders correlated with neuroendocrine imbalance, such as neurofibromatosis (von Recklinghausen disease) [6], hydrocephaly, and brain tumors may be found.

8.1.3 Prevention of Breast Cancer

Despite pathological reports of various types of ductal or lobular hyperplasias, preoperatory noninvasive diagnosis was unable to detect these changes until the advent of DE. Prevention of breast cancer was not considered before the last decade, and it is still a subject of discussion because premalignant lesions are usually not diagnosed by "classical" methods of radiological-imaging diagnosis. Mammography cannot detect any premalignant lesion, except some cases of ductal carcinoma in situ (DCIS) that are suspected because of their suggestive branching or extensive microcalcifications. The sectional methods in use do not respect the branching architecture of the ductal tree or the relationship of the lesions inside the same lobe and with the nipple. Thus, abnormal small proliferative lesions are difficult to detect and characterize. However, there are many possibilities for prevention of breast cancer, and this new vision offers better chances for patients both with and without risk factors.

8.1.3.1 Prevention by Therapy: Immunotherapy

An antitumor vaccine would be ideal for prevention, at least in high-risk patients. RESAN is one such novel drug that has been proposed to be administered in combination with surgical and oncological methods. The aim of the so-called vaccine is to destroy small metastases and prevent relapses after surgical treatment of breast cancers, which may result in absolute cures. The immune action of the drug is a result of the glycoproteins that are analogous to fragments of tumor-associated antigens of breast cancer [7]. These glycoproteins, included in the composition of the vaccine, imitate 6–50 different peptide fragments (each with 7–30 amino-acids) of each of the cancer antigens listed below:

1. Ovarian carcinoma antigen CA125 (1A1-3B) (KIAA0049)
2. Mucin 1 (tumor-associated mucin)
3. Breast carcinoma-associated antigen Df3
4. Cancer associated surface antigen
5. Adenocarcinoma antigen ART 1
6. Serologically defined breast cancer antigen NY-BR-15
7. Serologically defined breast cancer antigen NY-BR-16
8. CA 19-9

Tumor markers such as CEA, CA 125, CA 19-9, CA 15-3, and tumor-associated mucin can be used to monitor the treatment of breast cancer. The risk of recidivism could be reduced by using such a vaccine in patients with dishormonal mastopathy or benign tumors such as fibroadenomas. It could prevent malignant tumors in healthy people and those with positive heritable anamnesis or tumor markers that are higher than in normal. Moreover, it has been proposed as a complementary treatment in preventing and curing endometriosis [8].

Another vaccine that is currently in stage 3 of trials is NewVax (Nelipepimut-S), which is the immunodominant nine amino-acid peptide derived from the extracellular domain of the oncogene HER2, present in 85 % of breast cancer cells. The vaccine binds to antigen-presenting cells (APCs) that migrate in the lymph nodes and, after binding the cytotoxic t lymphocytes (CTLs), which rapidly replicate and migrate in the whole body "attracted" by the antigen HER2, recognize, neutralize, and destroy the HER2-expressing cells. Long-term protection against tumor recurrence is promising. Nevertheless, there is much more research aimed at the true prevention of primitive breast cancer. The results are far from satisfactory because the etiology of the disease is multifactorial and some causes are still unknown.

8.1.3.2 Prevention of Breast Cancer by Diagnosis of Premalignant Lesions

A true screening method must diagnose both premalignant and malignant breast lesions. Unfortunately, except for DE, no current method of radiological or imaging diagnosis is able to detect normal ducts and lobules, essential in depicting small abnormal changes. The methods in use for screening are intended for early diagnosis of breast cancer that is already developed but clinically unapparent. Thus, the real incidence of the breast cancer will not decrease with the use of these techniques, but at least the survival rate should increase.

Techniques used worldwide for the early detection of the breast cancer are, in decreasing order of their accuracy, as follows:

- Breast MRI
- Breast tomosynthesis
- Digital mammography and computed aided diagnosis
- Analogue mammography
- Classical ultrasonography

Ductal ultrasonography, which the authors refer to as DE, being the only anatomical imaging method, has an intrinsic high sensibility in detecting the breast's normal ductal-lobular tree and its physiological and pathological changes, with a resolution up to 0.4 mm for the actual transducers. The use of Doppler increases the specificity, without any supplementary contrast agent, and the sonoelastography is a complementary tool in differential diagnosis, resulting in higher overall accuracy.

8.2 Histologic Aspects of Breast Cancer and Correlation with Mammography and Ductal Echography

There are histological characteristics of breast cancer that determine some specific features of the radiological and ultrasonographic images and are not adequately understood by radiologists and, consequently, by clinicians. Therefore, understanding the anatomical basis of the image's formation is important in diagnosis and therapeutic decision making.

8.2.1 The Large-Format Section in Surgical Pathology: The Best Pathological-Imaging Correlation of Breast Carcinoma

The large-format section (LS) of breast pathology has, for more than a century, been a research tool to better understand breast microanatomy and the relationship between radiological images and pathological features [9]. Beginning in 1906, Cheatle used LS in cases of breast cancer to better understand the relation between a neoplastic mass and the surrounding normal tissue and the possible existence of premalignant changes [10, 11]. Furthermore, many researchers have used this method to study the early phases of breast cancer development, proving the importance of analysis with large sections of the branching ducts. Thus, in 1973, Wellings and Jensen concluded that most breast carcinomas arise in the terminal duct lobular unit (TDLU), the main site of the different morphological malignant features [12]. The precise location of the lesion in a TDLU can be visualized only by full breast ultrasonography (FBU) in all cases, because the radial scan allows the detection of all TDLUs at the intersection of the main ductal axis with Cooper's ligament, and Doppler can illustrate the nourishing vessels arising from the superior or inferior segments of that Cooper's ligament. The mammogram, being a volumetric projection to a surface, can visualize only the peripheral TDLUs located to the radius 9:00 and 3:00 for the cranial-caudal view, or to the radius corresponding to the medial-oblique-lateral view (e.g., between 7:00–8:00 and 1:00–2:00, for the left breast). Similarly, MRI examination can visualize the TDLUs located only to the radius 12:00, 3:00, 6:00, and 9:00, the rest of the scans being oblique to the main ductal axes.

More recently, many authors have highlighted the value of LS in the diagnosis of breast malignancy, especially in the precise determination of tumor size, multifocality and cancer extension, vascular invasion, and extension of the DCIS and lobular carcinoma in-situ (LCIS) [13], with good cost/benefit evaluation [14]. However, most authors performed randomly large sections, omitting the radial distribution of the breast ductal tree, and the relationship between their findings and breast anatomy was incomplete.

The best application of LS in the analysis of breast pathology is represented by the *theory of the sick lobe* of Tibor Tot [1, 15]. Indeed, the breast lobes are individual units, without peripheral delimitations by septae or other structures, but with unitary function and pathology (either benign or malignant).

The use of large-format histological sections redefined the terms *multifocality* and *multicentricity* of breast cancer. Their better understanding allowed better evaluation of prognosis and treatment [16]. In classical ultrasonography, used as a complementary tool with mammography, the distinction between multicentric and multifocal cancer is arbitrarily defined, according to the breast quadrants, the unique radiological feasible segmentation of the breasts, which is easily to realize by combining the acquisitions of the cranial-caudal and medial-lateral views. The lesions located in the same quadrant are "multifocal," whereas the lesions located in different quadrants are "multicentric." These arbitrary definitions are dangerous in therapeutic decision making because the lobes with individual ductal trees may overlap in the same quadrant. As a consequence, there can be present in the same quadrant different cancers in different lobes, with different cellular-types and evolution, representing true multicentric cancers. In addition, a mammary lobe may extend to a few adjacent quadrants, and thus the same tumor may disseminate intraductally in two adjacent quadrants, determining multiple monoclonal lesions, or true multifocal cancers.

Tot's classification of breast cancers, based on the sick lobe theory, is logical and offers a better basis for decision making about therapy [17]:

1. *Unifocal cancer* – better prognosis
2. *Multifocal cancer* – in the same lobe (lobar cancer), with worse prognosis, usually with axillary lymph node involvement (in 75 % of cases)
3. *Multicentric cancers* – in different lobes, in the same breast or bilateral
4. *Diffuse cancer* – (5 % of cases) extension is present in many lobes and quadrants, with greater aggressiveness

The number of the lesions was found to be higher in the cases of examinations of large sections than in small, conventional blocks. It is logical that the use of large, anatomical radial scanning in ultrasonography is better than small scans used as a complementary examination of the lesion and of its proximity. The large pathological section is obtained after surgery, but the large scan, with dedicated, long, linear transducers, allows better diagnosis in vivo, with the possibility of measuring the size of the lesion and the extent of disease by locating the multifocal and multicentric breast cancers. Nevertheless, the accuracy of the available ultrasound devices is lower than that of microscopic analysis, but it allows a significant improvement in the preoperatory diagnosis.

Large sections were used in the last century for understanding, diagnosis, and management of pathological lesions of the breast and organs such as lung, brain, kidney, ovary, and colon [9]. The limitations of their availability are related to the manufacturing of the adapted cryothome.

8.2.2 The Main Pathological and Imaging Classifications of Breast Carcinoma

Because the radiological imaging methods of diagnosis of breast cancer have a logical and physical similarity to gross appearance on pathological examination, we have chosen the classification of Martin, which has been well known since 1882 [18]:

Pathological Classification of Breast Cancer Based on Martin (1882)

A. Usual Breast Carcinoma
   - In situ carcinoma (ductal, lobular)
   - Mass-forming carcinoma (invasive)
   – Knobby carcinoma
   – Stellate carcinoma
   – Circumscribed masses (pseudo-benign appearances):
     1. Medullary carcinoma
     2. Mucinous carcinoma
     3. Poorly/undifferentiated carcinoma
     4. Cystosarcoma phyllodes
     5. Mixed carcinomas (usually intraductal and medullary or mucinous)
   – Invasive lobular carcinoma
B. Unusual Malignant Breast Lesions
   - Carcinomas: inflammatory, tubular, metaplastic and anaplastic, apocrine, adenocytic, fibroadenoma and carcinoma, invasive colloid, recurrent
   - Carcinosarcoma
   - Sarcomas: cystosarcoma, liposarcoma, angiosarcoma
   - Metastatic malignant lesions: metastatic carcinomas, melanoma, carcinoid, hypernephroma, angiosarcoma, neuroectodermal tumor, lymphoma
   - Paget's disease
   - Breast carcinoma in children
   - Breast carcinoma in pregnancy

"Knobby" carcinoma is a term proposed by Gallager and Martin [19, 20] to describe the type of invasive breast carcinoma made up of innumerable, tiny, circumscribed masses as small as 1 mm, which coalesce but do not fuse into groupings, each knob remaining separate from the others. As a consequence, when analyzing the whole tumor, we see the knobs protruding from the edges. The edges of the knobby carcinoma become indistinct, with unsharp borders in mammography and and a multilobular/multi-cyclic appearance in ultrasonography. This form of breast was found by the authors to be the most common, comprising up to 47.7 % of all invasive cancers, and its major extensions are in the mammary ducts, usually proximally toward the mammary areola, following the line of minimal resistance. That corresponds to the demonstrations of Teboul, which proved by DE the intraductal dissemination of multistep evolution, the metastases decreasing in size proportionally with the distance from the main tumor. The centripetal or centrifugal dissemination is explained by the minimal resistance of the ductal content. This manner of malignant spreading is confirmed by Tot and colleagues in the sick lobe theory [1]. Gallager and Martin, in 1969, used serial whole organ sections with gross and microscopic viewing, which were easily compared with mammograms. Tot and coworkers, in 2007, used large-format histologic sections, from the nipple to the periphery, similar to radial scanning of the DE, to demonstrate the lobar architecture and the intraductal dissemination of BC.

Stellate carcinoma usually arises in older women, has a distinctive shape with peripheral spicules, and represents the best-known type of breast cancer. However, stellate cancer, with its peripheral stromal reaction determining the spicules, has a better prognosis than knobby cancer, with an absolute survival rate of 70.8 % versus 57.6 % cases based on Martin [18].

Circumscribed masses are mostly represented by medullary and mucinous cancers, which account for less than 5 % of cases. Medullary cancer may develop in young or older women and tends to be located at the periphery of the breast, mimicking a benign lesion on the mammogram. It can be connected to a dilated duct with centripetal orientation toward the nipple.

The mucinous carcinoma tends to lie superficially, has a low density on a mammogram, and the centripetal ducts may be distended by mucin and tumoral cells. The skin may be infiltrated, up to exophytic lesions, but the axillary lymph nodes are rarely involved. Survival rate is higher than in the knobby and stellate forms. However, survival depends on the precise preoperatory diagnosis of the extent of disease, because the whole organ pathological reports may present associated dilated tumor-filled ducts, dilated lymphatic vessels, and other satellite small cancers, unapparent on mammography. Mucinous cancers may present both multifocal and multicentric lesions, and before the use of DE, no preoperatory method could demonstrate the real extent of the disease. Breast MRI may demonstrate the multiple lesions, but the arbitrary scanning planes do not allow the illustration of their connections.

8.2.3 Multifocal and Multicentric Breast Carcinoma

According to Tot, the real local extent of disease can be classified in three major types of breast cancer that can be found by pathologic examination using large sections, which are related to the ductal tree:

- Unifocal lesion, usually located in a TDLU, with various sizes and local extension
- Lobar cancer, with secondary dissemination intraductally, following minimal resistance
- Diffuse cancer

A study by Tot et al. (2011), performed on 574 consecutive cases diagnosed using large sections, found that invasive carcinomas were multifocal in 24 % and diffuse in 5 % of cases, percentages that are largely superior to those published in paper based on conventional blocking [17]. Simultaneously, Teboul recommends following the anatomic criteria and observing the epithelial structures in vivo using DE, which allows for assessment of cancers, and presuming localization in vivo and the type of malignancy (2010). According to his classification, there are three main types of breast cancer [21]:

- Lobular carcinoma (10 % of cases)
- Diffuse carcinoma with involvement of a duct, its branches ,and terminal lobules (25 % of cases); this corresponds to lobar cancer in Tot's classification
- Ductal-lobular and ductal focal cancers (65 % of cases), corresponding to unifocal lesion in Tot's classification

Multifocality has a great impact on survival, as the risk of death from breast cancer is higher in patients with multifocal and/or diffuse carcinomas when compared with those with unifocal carcinomas. Multifocality can be useful in the evaluation of the risk of axillary involvement by breast cancer metastases. According to Baldovini [22], 71.42 % of patients with multifocal tumors exhibited axillary lymph node metastases, whereas 40.54 % of those with unifocal tumors showed axillary nodal involvement.

Radiological differential diagnosis of multifocal and multicentric cancer was established arbitrarily, by necessity, to standardize localization of a mass on orthogonal projections: cranial-caudal and medial-lateral (oblique) views. As a consequence, the mammographic distinction is established by the location in a quadrant: inside the quadrant there are "multifocal" cancers, and in different (even adjacent) quadrants there are "multicentric" cancers. This classification does not reflect the breast anatomy and, therefore, is not concordant with pathologic reports. Nevertheless, this classification is still in use and is important in the surgical treatment of breast cancers, accompanied by the risk of missing foci and recurrence of the disease.

Because of the intralobar dissemination of breast cancer, and the unapparent connection between two lobar branching trees, it is logical for multifocal cancer to spread initially in the same lobe, with similar types of malignant cells (monoclonal). Cancers present in different breast lobes may have more probable different malignant-type cellularity, being multiclonal lesions. Because the lobes may overlap, it is possible using ultrasonograpy to visualize different lobar structures in the same quadrant, even on the same radius, with the potential to develop multicentric cancers. The arbitrary division of a breast in quadrants, while useful for reporting lesions, is not correlated with the lobar distribution. As a consequence, it is possible for a mammary lobe to lie at the border of two quadrants, extending to both sides, as has been proved by Cooper's models [23], with presence of some multifocal cancers simultaneously in different quadrants.

Mammography (analogue or digital) is not suitable for the detection of multiple cancers. Even breast tomosynthesis and breast MRI, which are used more frequently to detect multiple lesions, are not accurate in the differential diagnosis of multifocal and multicentric malignancies. DE, being an anatomical *in vivo* examination, changes the arbitrary delimitation and is able to detect lobar multiple lesions, the multifocal cancers connected to the same ductal tree, whatever the quadrant. Diffuse cancer is easily recognized by MRI examination, but DE findings may be suspect, especially when adding Doppler and sonoelastography, with further evaluation by biopsy or MRI evaluation.

8.2.4 Size and Extent of Breast Cancer

Determining the size of the lesion is important for the characterization of T value of the TNM (tumor, nodes, metastasis) staging of the breast cancer. When the lesion is unique, with well-shaped borders, such as knobby cancer and pseudo-benign rare types, the largest diameter is considered the lesion's size. For the most accurate measurement, the volumetric measurement is more conclusive, especially when preoperatory treatment is intended.

The size of the stellate form of breast cancer is difficult to measure. Some authors recommended measuring the size of the central mass, ignoring the surrounding spicules and the halo as they are determined by the stromal reaction. Others believe that the spicules are the way tumoral cells spread, and the real extent calls for measurement of the whole visible lesion.

To measure the local extent of the disease, multifocal cancer requires evaluation of all distinguishable lesions (determining each lesion's size) and calculation of the global volume of these masses. The best methods for evaluation are breast MRI and FBU with the ductal tree analysis. According to Teboul, the DE technique indisputably shows that malignancies often demonstrate a greater spatial extent than has been suspected by other techniques. Indeed, this method allows direct perception of a malignant diffusion by sprinkling or distinct fragmentation of the main detected malignant masses. The fragmentation into several malignant tiny nodules or malignant clusters is found close to the main malignant lesion or at a distance along the affected duct, as demonstrated by the theory of the sick lobe [21].

8.3 Breast Cancer and Ultrasound Diagnosis Applying Old and New Criteria

Breast cancer staging using the Union for International Cancer Control (UICC) TNM classification was issued in 1960 (joined since 1987 with the staging system of the American Joint Committee on Cancer, or AJCC) and includes five stages [24]:

- *Stage 0*: The cancer has not spread farther than the ducts, DCIS, the lobules, LCIS.
- *Stage I*: The tumor measures 2 cm or less and has not spread to the lymph nodes or other tissues.
- *Stage II*: The tumor is between 2 and 5 cm in size, and/or the cancer has spread to one to three auxiliary lymph nodes on the same side; tumors of 5 cm without any metastases to lymph nodes are also included.
- *Stage III*: Tumors less than 5 cm in size with metastases to four to nine auxiliary lymph nodes; tumors bigger than 5 cm with metastases to one to nine auxiliary lymph nodes; tumors that have spread locally (close to the breast) and usually involve the skin, chest wall, or nine or fewer auxiliary lymph nodes.
- *Stage IV*: A cancer of any size that has spread to the other parts of the body, most often the bones, lungs, liver, brain, or distant lymph nodes.

The most common breast malignancies are of ductal epithelial origin (almost 80 %) and are either confined to the duct (in situ or intraductal) or infiltrative (invasive). Lobular cancer represents 10–15 % of cases, usually as multifocal disease; stromal cancers and rare forms, including atypical cancers and metastases, are less common (5–10 % of cases).

It is widely accepted that, although mammography is the primary imaging modality for the early detection of breast cancer, classical ultrasonography (for the majority, the only known ultrasound technique), used in conjunction with mammography, can further increase the cancer detection rate.

There are different pathologic characteristics that account for some variability in ultrasound appearance. Most invasive ductal carcinomas exhibit irregular or ill-defined margins related to infiltrative and reactive fibrotic desmoplastic components. Carcinomas of uniform cell type or types that do not invade aggressively may appear as well-circumscribed masses, such as mucinous or papillary carcinomas; intracystic carcinomas are rare but usually noninvasive with well-defined margins, mimicking benign lesions on mammography.

Because early diagnosis is desirable in the fight against breast carcinoma (allowing faster treatment that is more effective, less aggressive, and has a great probability of cure), it is essential to have at our disposal a technique making possible to detect with certainty all the variations, abnormalities, or lesions of the breast at an infracentimetric stage. Moreover, it would be ideal to detect premalignant lesions, the most important factor in reducing the incidence of a malignancy. For example, by using the Papanicolaou test to detect and treat cervical dysplasias, cervical cancer incidence was reduced [25], and prostate cancer incidence was reduced after the introduction of PSA (prostate-specific antigen) screening [26]. This will be possible using DE as a technique of examination and guidelines for the diagnosis of breast diseases, combined with Doppler and sonoelastography for the full characterization of the lesions. This is the concept of full breast ultrasonography, as introduced by Amy [27].

In a study by Amy that included 5,010 cases, all patients were investigated systematically by mammography and DE. The study concluded that DE score detection is higher than that of radiological examination [28]. Moreover, contrary to other published studies, the author claims to have never encountered mammographic-visible lesions that were not detected by DE. In addition, we consider that lesions visible only in one mammographic projection, cranial-caudal or oblique, usually called "opacities" (to differentiate them from "masses," visible on two to three projections), are better characterized by DE because of the anatomical scanning. Moreover, Amy's report highlights the significant number of multifocal cancers diagnosed with DE, which consequently involve surgical and chemotherapeutic treatment changes.

DE diagnosis applies to anatomical scans the same Stavros criteria of breast lesions that are used in classical ultrasonography, which are the basis for the ultrasound Breast Imaging Reporting and Data System (BI-RADS) assessment [29, 30]. Stavros reported a 98.4 % sensitivity for diagnosis of malignant masses using classical ultrasonographic criteria for malignancy, including spiculation, nonparallel orientation, angular margins, marked hypoechogeneicity (relative to fat), shadowing, calcification, duct extension and branching pattern, and microlobulations. These results reflect the high resolution of state-of-the-art equipment and expanding skills of radiologists, but classical ultrasonography should be assumed as a complementary examination of a precise area with suspect clinical or mammographic findings.

In classical ultrasonography, suspicious masses identified on ultrasound should always be correlated with mammography, or more recently with MRI, which can depict the lesion and eventually the multicentric/multifocal malignancy.

The halo sign, proposed by Takehara in 1976 and reaffirmed by the Japan Society of Ultrasound in Medicine in 2005 [31], represents the hyperechoic marginal zone that is the expression of a scirrhous carcinoma that invades and spreads into the surrounding tissues. In recent years, the Japan Association of Breast and Thyroid Sonology refined the description and defined a peritumoral "boundary zone," existing on a "border" between the "tumoral margin" at the inside part and the "periphery" at the outside [32].

The complete characterization of a malignant breast lesion is presented in the previous Chap. 5, Sects. 5.2 Ultrasound Diagnostic Criteria and 5.3 Lexicon for Breast Lesions in the fundamentals of ultrasound breast BI–RADS classification. However, the criteria for the differentiating benign from malignant breast lesions are not specific and, even when they are used in combination, the specificity of the method is modest, less 70 % according to most authors.

The use of three-dimensional/four-dimensional (3D/4D) acquisitions as a second step in ultrasound examination may be useful. It is proven that spiculations are more easily seen in the coronal view than in other variant orthogonal views. Moreover, 16 % of benign cases and 90 % of malignant cases are detected with spiculations [33]. Siemens presented a technique of automatic breast volume scanning (ABVS), which offers the coronal plan with accuracy. However, in this technique the sagittal and transverse plan are not useful in screening and detecting premalignant changes because there is no anatomical relationship with the nipple and the ductal tree.

The characterization of the vasculature represents one of the most important criteria of diagnosis, more important than shape, orientation, posterior effects, and so on. Although FBU demonstration of a normal or an abnormal duct or lobule is not difficult with state-of-the-art ultrasound instruments, the demonstration of the intraductal or periductal vasculature cannot be always successful with conventional color Doppler or power Doppler acquisitions. However, the absence of detectable vessels in a solid-type lesion is a negative predictor for malignancy. When visible, the vasculature of the benign masses has less three poles, with a peripheral arcuate course and oblique plunging angle, described by some authors as "basket-type new vasculature." On the other hand, malignant lesions show new vasculature with the number of poles depending on the lesion's size. In the case of small malignancies, new vessels are visible beginning when the tumor reaches 3–4 mm diameter, with the poles increasing progressively. Malignant lesions usually present larger vessels than the surrounding glandular tissues, with higher velocity compared with the normal vasculature in the surrounding regions and sometimes demonstrating an aliasing effect. In addition, the most important sign of malignant new vasculature is the incidence angle of the plunging vessels, which is almost pathognomonic [34].

Three-dimensional Doppler ultrasound may better demonstrate the differences between benign and malignant vascular patterns [35]. The technical evolution of ultrasound machines, including software development, will allow rapid and reproducible volumetric acquisitions, available even for examination of small parts. Actually, the 3D/4D transducers have only small resolution for Doppler reconstruction in breast tumors.

In some cases, there are cysts with echoic content that may mimic a solid benign lesion. Otherwise, a small cancer, usually a second or a third intraductal dissemination of the main tumor, may have undetectable vasculature, but they conserve the irregular shape and the posterior acoustic shadowing of the main tumor and are connected with the same ductal tree. In such cases, the evaluation of periductal angiogenesis using contrast-enhanced ultrasound is recommended. A study by Chou [36] of the efficacy of contrast-enhanced ultrasound (CEUS) in the identification of ductal pathology in women with abnormal nipple discharge found that CEUS has 100 % sensitivity. For intraductal papillomas or carcinomas, ultrasound detected 12 pathologies out of 13 patients, and CEUS showed positive results (i.e., either intra- or periductal contrast flow signal) in all patients (13/13), whereas the specificity was 71.4 % (positive CEUS in periductal mastopathy and occasionally fibrocystic changes).

The use of CEUS was found to be correlated with MRI wash in–wash out curves and with a CEUS specificity of 87.5 % (similar to ultrasound alone) and a sensitivity of 100 % [37]. However, there were some lesions with a false-positive diagnosis: two hypervascular fibroadenomas in young women and a phyllodes tumor. This study demonstrates that evaluation of the vasculature as a single descriptor is not sufficient in positive and differential diagnosis, which is an argument for using FBU as a complete examination utilizing the assets of US. In addition, the use of CEUS has some limitations, the most important being its invasiveness (there are proved side-effects), costs, and lack of an observer agreement regarding vascularization patterns [38].

The use of Doppler techniques has proved useful as a follow-up exam in treated breast cancer, with reduction of vasculature as response of chemotherapy [39–41] or reduced vascular pattern in post-radiotherapy mastitis. Contrarily, an increased number and diameter of vessels are present in developing breast cancer. Most authors agree with Kumar et al. [42], who proved that Doppler scoring correlates well and can be accurately used to objectively predict the pathological response to chemotherapy in patients with locally advanced breast cancer.

8.4 Particular Clinical–Imaging Aspects of Breast Carcinoma

There are some particular clinical and imaging aspects of breast carcinoma that have incomplete descriptions in the typical model of malignancies, but there are some specific findings that are presented in the following.

8.4.1 Inflammatory Breast Carcinoma

Inflammatory breast carcinoma is also called carcinomatous mastitis. Clinically it has an acute appearance, with painful tenderness, orange peel-like skin thickening, hyperthermia redness involving more than a third of the breast, increase in size and heaviness, and lymph node enlargement, mimicking inflammation. These signs are not determined by infection or injury as in real mastitis. Sometimes an inverted nipple occurs. More often, no mass can be felt. This form of breast cancer is caused by malignant cells blocking lymph vessels in the skin and premammary fatty tissue.

Carcinomatous mastitis accounts for about 1 % of all breast cancers in United States, but the diagnosis and reporting seems to be an underestimation. This cancer occurs usually in young women after birth control treatment abuse or in the older women, in whom it is easier to eliminate a nonmalignant mastitis. It is more common among African-American women and in overweight and obese women.

The prognosis is the worst, as it is more aggressive than the common types of cancer. In fact, there is never an early stage with this breast cancer, being diagnosed at least in stage IIIB (locally advanced) or even stage IV, with distant metastases. However, some cases have no findings on the mammogram, or the edema may be present but unspecific. The affected breast may be larger and denser than the contralateral breast, similar to the clinical findings. Moreover, tenderness and swelling can make it difficult to perform a mammogram. The clinical presentation being in the advanced stage, the screening mammogram is not useful.

Characteristic classical ultrasound findings with inflammatory breast carcinoma are diffuse, irregular thickening of the skin and subcutaneous layer. Sometimes it is possible to identify a tumoral mass with irregular margins and internal hypoechoic necrosis in the parenchymal layer. The subcutaneous fatty tissue becomes more echogenic, and the distinction with the hyperechoic glandular stoma is less defined.

Dilated branching pattern of lymphatics in subcutis fatty tissue could be more distinctively evaluated on ultrasound than on MRI. Most authors believe that the association between a tumor with lymphatic dilatation on ultrasound and enhancement of thickened skin and parenchyma on MRI could be useful for the diagnosis of the inflammatory breast cancer [43, 44]. However, the description is vague and nonspecific, and, in the absence of the clinical examination and patient's history, differential diagnosis with infectious mastitis or inflammatory changes after radiotherapy is difficult to make by radiological and classical sonographic examination. MRI can detect abnormal regions not visible on mammogram and it is used to guide the biopsy.

In DE, the aspect is less specific. The thickening of the skin and fatty tissue, which has a hyperechoic aspect with the dilated hypoechoic branching pattern of lymphatics, make it difficult to examine the ductal-lobular structures, which may present ectasias (in benign mastitis the enlarged ducts are better delineated). Cooper's ligaments are thickened with increased posterior acoustic shadowing. The hyperemia is diffuse, as in inflammatory benign mastitis, whereas in post-radiotherapy mastitis the vasculature is reduced. The differential diagnosis between benign-type mastitis and inflammatory breast cancer may be possible by adding sonoelastography. There are few observations about its application for carcinomatous mastitis, but in our experience the benign type presents an inversion of the strain ratio. The skin and subcutaneous fatty tissue present increased strain compared with the glandular lobar structures that are "softer." The malignant type has less strain of the thickened skin and subcutis layer, with increased diffused hardness of the glandular lobes, such as in diffuse lobar cancer. An additional observation about the malignant type is that the axillary lymph nodes are almost always involved with malignant characters. If the breast biopsy is not accurate in such cases, an axillary lymph node biopsy is easier to perform and offers a quick diagnosis.

Staging of the inflammatory breast cancer needs further investigations, by with multi-detector computed tomography or PET-CT. According to the American Cancer Society, after the TNM staging, all inflammatory breast cancer is classified T4. If the collarbone (supraclavicular or infraclavicular) lymph nodes or the internal mammary lymph nodes are involved, without distant metastases, then it is the stage IIIC. If no more than the axillary lymph nodes are involved, it is the stage IIIB. The presence of distant spreading of the disease is stage IV.

8.4.2 DCIS and LCIS

Despite the pathological examinations that make differences between ductal and lobular carcinoma in situ, in the literature there are some disagreements concerning the start zone of these cancers and the imagistic findings. It is widely accepted that DCIS arises in the hormone-sensitive epithelial cells of the peripheral ducts, in the area of TDLUs, so in the proximity of the lobule. There are also locations in the peripheral segments of the main ducts, which allow easier intraductal centripetal/centrifugal dissemination. DCIS may be associated with the ductal papilloma centrally located in a large duct, but the evolution and pathogeneses are different, the papilloma being a benign lesion without risk of malignancy, whereas DCIS may develop in invasive carcinoma [45]. There are some papillomas with apocrine, squamous, mucinous, clear cell, and sebaceous metaplasia with benign prognoses. They are usually not detected by mammography because microcalcifications are usually absent. Sclerosing papillomas may mimic a pseudoinvasive pattern [46] and in sonoelastography may present increasing strain ratio, but there is not a pathological new formation vasculature. Some papillomas may display focal proliferations of a mildly atypical, monotonous cell population identical to grade 1 DCIS or atypical hyperplasia, rarely grades 2 and 3. These lesions were designated as *atypical papillomas*, with excellent prognosis, estimated at nearly 100 % survival at 10 years [47].

Papillomatosis, or peripheral/multiple papillomas, is represented by papillary proliferations within multiple TDLUs or in the ductules. Usually it is an incidental microscopic finding, because mammography cannot distinguish them from the other breast opacities, except in cases with microcalcifications or nodular masses [48]. Even in DE, differential diagnosis with adenosis or small LCIS is difficult, except in cases with nipple discharge, when associated duct ectasia is visualized and cytological tests are performed from the nipple surge.

In DCIS and LCIS, neoplastic growing cells fill and distend the duct without disrupting it. DCIS is an incidental discovery in an asymptomatic woman or in a woman with a painful breast. Rarely it is discovered in nipple discharge cases or after suspect microcalcifications in mammography. The clinical incidence is only 1–3 %, whereas the mammographic incidence is 8–25 %, and practically it could be more because not all DCIS present microcalcifications. With nipple discharge, DCIS was found in 26.8 % of cases with bloody discharge, 13 % of cases with serous discharge, and in no cases with discharge of other types, according to Hou et al., as quoted by Svane [49].

A study by Takebe and Izumory from 1997 to 2003 confirmed a DCIS that was nonpalpable and without discharge or mammographic calcification, which they named "3 non-DCIS." They found well-defined 3–10 mm masses connected to the ducts, without posterior attenuation or other malignant well-known findings [50]. This aspect can be detected with best accuracy only by following the normal anatomy, ductal size, and distribution, as done in DE, and not randomly checking an eventual clinical or mammographic negative abnormality, as in classical ultrasound.

DCIS may involve a unique segment of a duct, but sometimes it extends to multiple ducts by the unfolding process or develops in many sites simultaneously. DE can demonstrate the ductal connection between the lesions, which appear as thickened ducts, with loss of the central hyperechoic line sign, sometimes with inhomogeneous ductal content. The new periductal vasculature is rarely found with the actual transducers, but the elasticity of the whole area and of the ductal tree inside the pathological region may be reduced compared with the healthy lobes. Without treatment, this lesion may develop in few years into an invasive ductal carcinoma (IDC). The problem is hunting it out. DCIS is asymptomatic and painless in this stage and not all cases have an invasive evolution. The high-grade DCIS has the most risk.

Morphological aspects of DCIS are classified as follows:

- Comedocarcinoma
- Papillary carcinoma
- Cribriform carcinoma
- Solid carcinoma

Doppler DE can at least suspect a DCIS when demonstrating a segment with abrupt margins, well-shaped thickening of a duct, with or without shadowing, but with a local periductal detectable vasculature or/and an increased stiffness. Positive diagnosis becomes difficult when the lesion is associated with ductal hyperplasia, as is usually presented in the pathological reports, but a short-interval follow-up (2–3 months) is more useful without any more risk than an ultrasound-guided biopsy. With ultrasound equipment it is not possible to differentiate the atypical ductal hyperplasia from the DCIS. The value of Doppler DE has yet to be demonstrated because there are few encouraging reports regarding the actual state-of-the-art.

High-grade DCIS may present characteristic microcalcifications at pathology as well as mammographically. However, with ultrasound there are few visible microcalcifications with the usual high-frequency probes (7–12 MHz). Hyperechoic spots without shadowing (less than 0.4 mm in diameter) are nonspecific findings. When transducers of 18 MHz or more will become available, they will improve the vascular pattern detection. In ultrasound this is more useful than blind identification of microcalcifications (the manufacturer technical development will allow to the US to become the examination of first-intention). Mammographically, the microcalcifications appear in DCIS as numerous, with segmental distribution and irregularities in size, density, and shape (linear or branching shape, suggesting ductal spreading of the malignant cells and the calcification of the necrotic material).

Although DCIS is considered noninvasive, neoplastic cells have been observed in the sentinel nodes, so the systematic examination of all axillary, subclavicular, and internal mammary lymph nodes must always be performed.

There is not a control interval guideline in suspected DCIS on ultrasound, but, in our experience, performing a follow-up control in 3 months is useful, with increasing intervals if stationary or regressing lesions classified as ultrasound BI-RADS category 3 are found. If the developing evolution of the suspect DCIS is proved, a change of the assessment to ultrasound BI-RADS category 4 is justified and can be supported by the possibility of developing a well-known "interval cancer" encountered in the screening mammography. As a consequence, there are some recommendations for complementary examinations (mammography, breast MRI, serological tumor markers determination, or guided biopsy).

A particular form of DCIS arises with sclerosing adenosis. In classical ultrasound, sclerosing adenosis is usually difficult to detect because of the neglect of the normal anatomy with the connection of the pathological findings to the ductal-lobular tree. However, ultrasound still seems to be useful in the diagnosis of DCIS, which appears as an irregularly shaped hypoechoic lesion, usually as a non-mass-forming lesion (nonpalpable), whereas mammography misinterprets sclerosing adenosis with DCIS as an invasive carcinoma (emphasized diagnosis) [51]. Doppler DE is able to provide more diagnostic accuracy because sclerosing adenosis is easy to visualize in postmenopausal women with normal atrophied parenchyma associated with segmental ductal-lobular hyperplasias. Any supplementary abnormal structure connected to the ductal-lobular tree, with suspect features such as irregular shape, shadowing, abnormal increasing vasculature, or increasing size on short follow-up interval, require further investigation and is referred to as ultrasound BI-RADS category 4. Further research is needed on sonoelastography of sclerosing adenosis associated with malignant lesions because of the risk of emphasized diagnosis, but if it is correlated with the other sonographic descriptors, the diagnostic could be more appropriate. Quantitative sonoelastography seems to be more accurate than the qualitative modality, and the FLR (fat-to-lesion ratio) with the cut-off level 4.70 (5.00) as results from the Amy's reports and from our researches proved more specific. The greater the ranges of the FLR, the greater risk of malignancy. FBU might be able to solve one of the most important causes of false-positive ultrasound diagnosis.

LCIS is the other noninvasive breast cancer. It is limited to the lobule area without breaking the basement membrane, but it can develop into an invasive form. As with DCIS, there have been observed involvements of the sentinel lymph nodes [52]. Usually there are multiple simultaneous lobular involvements in young women, which may be misdiagnosed in FBU as adenosis because of their small sizes and lack of malignant characteristics. In the accentuated forms of adenosis, a 3-month-interval follow-up ultrasound is recommended, associated with dynamic evaluation of tumoral markers. It would be erroneous to consider FBU as a method of differential diagnosis of the pathological type of lesions, but the intention of the method must be limited to finding lesions as early as possible, determining their precise location, and classifying them in a risk category.

Invasive lobular cancers (ILC) are characterized by the multiplicity of their foci. Because of their small size, usually less than 1 cm, they are more easily recognized in FBU. Because there is no evidence of important secondary features on the skin and superficial fascia, ligaments or fatty signs, or architectural disorders, lobular cancers may be missed on mammography, especially in dense breasts. After Teboul, lobular carcinomas appear in DE preferentially located in TDLUs, as a few hypoechogenic lobular enlargements on the skin side of the duct, growing perpendicularly to the duct, isolated from each other and measuring about 5 mm in longitudinal diameter. If Doppler examination is added, the regional vasculature may be increased according to the size and extension of the lesions. The sonoelastographic aspect is not typical, but the overall elasticity is reduced compared with the rest of the breast areas.

8.4.3 Diffuse Breast Carcinomas

Diffuse breast malignancies are difficult to recognize in mammography in the absence of microcalcifications. MRI examination is more sensitive, but it is not a first intention examination. Classical ultrasound has low sensitivity and specificity.

The pathological examination demonstrates a lack of focal arrangement and evidence of spreading of the malignancy in and along ductal-lobular structures. DE illustrates the normal and abnormal ductal tree and thus is able to display two types of patterns of diffuse cancers at initial stages [21]:

1. Anatomical, showing a thick and long linear spreading of malignancy in ductal-lobular structures (slow-growing cancers).
2. Brambles, showing a rather more restricted diffusion, displayed as a thin and irregular tree network developing into some local terminal ductal branches or the close interstitial space and fatty tissue (acute diffuse malignancies and recurrences in scars).

In the intermediate stages of the diffuse malignancy, the lobules enlarge with diameter up to 15 mm, in small number as dominant foci upon Teboul, with small enlargement of adjacent lobules as new foci; their orientation initially perpendicular to the main duct and skin, as in normal lobules, progressively becomes oblique. In advanced stages, these diffuse malignancies appear as extended, hypoechogenic areas, with acoustic shadowing, developed in the whole lobe with almost no remaining recognizable organized ductal-lobular structures. Sonoelastography may add valuable information with diffuse increasing of the lobar strain in a large volume of the breast.

8.4.4 Carcinomas with Pseudo-Benign Appearance

The best-known circumscribed masses with pseudo-benign appearance are presented in the above classification. However, there are multiple malignancies with false appearance on ultrasound. There are a few (less 5 % of all of carcinomas) with pseudo-benign appearance on two-dimensional (2D) ultrasound, both in classical ultrasound and in DE. This means that they can have an oval width-to-depth shape, with more or less regular but clear borders, without malignant shadowing or even with posterior echo enhancement and small lateral shadowings, such as benign posterior findings described by Kobayashi. The most important lesions with these ultrasound findings are mucinous and medullary carcinomas, which have regular internal architecture with low attenuation, and breast lymphomas and leukemic infiltrations, usually in acute leukemia, which may appear as a solid-type infiltration or as a diffuse mixed echo-texture. The pseudo-benign, well-delimited masses may become suspect in FBU by their new formation of rich vasculature demonstrated by Doppler evaluation. Furthermore, the diagnosis can be reinforced by sonoelastography, which is highly sensitive. These lesions, classified with the score 4 Ueno, appear in blue without a peripheral light blue boundary zone (because of the lack of desmoplastic reaction, as in infiltrating carcinomas). It results that FBU can address one of the most important causes of false-negative ultrasound diagnosis in breast cancer management.

8.4.5 Nipple and Retroareolar Carcinomas

The nipple and the retroareolar volume must be distinctly explored by ultrasound, in multiplanary acquisitions, with water-bag probe or adequate echo jelly, which is used to fill the skin irregularities and to offer an image without relief deformation. There are many types of malignancies related to this initial developing root and final functional station of the lobar trees.

The most important lesion involving the nipple is Paget's disease, with a long benign evolution and sometimes malignant changes. The mammographic findings are nonspecific in Paget's disease, because the nipple and areola rarely have nonspecific changes, and the examination is limited to an evaluation of the extent of a primary carcinoma, which may be obscured in dense breasts [52]. The sonographic findings in Paget's disease are more various and correlated with the clinical signs. A study by Choi et al. detailed the most important clinical manifestations compared with the ultrasound findings, with remarkable results considering the technology of 2001:

- Nipple retraction
- Bloody nipple discharge
- Nipple eczema
- Subareolar mass

Ultrasound was better than clinical examination in detecting the mass as a hypoechoic lesion with irregular borders. The second important finding was the irregularly dilated major lactiferous ducts associated with a mass, specific to ultrasound examination and never demonstrated by mammography [54]. Other findings such as calcifications and parenchymal distortion were rarely described and seem to be imitations in interpretation borrowed from the mammographic lexicon. Otherwise, the most frequent mammographic findings were increased subareolar density, parenchymal distortion, microcalcifications (branching and granular shapes), and the presence of a mass. Mass detection was superior on ultrasound, which detected 12 of 13 masses, compared with mammography, which detected 4 of 12 masses.

A study of nipple malignancies explored using 3D sonogram multiplanar images and volume-rendering transparent minimum projection mode in 184 histologically proven breast cancers and reported that 41 breast cancers were suggestive of Paget's disease ($n=3$) and pagetoid extension of breast cancers ($n=38$) [55]. The following were found: nipple duct dilatations (41/41), nipple parenchymal stromal distortion (40/41) (sic), calcifications in nipple duct or lactiferous sinus (20/40), disrupted high echoic nipple skin (40/41), and mass in the nipple and subareolar area (12/41). False-positive lesions were breast cancers with duct ectasia ($n=5$), breast cancer with chronic perivascular inflammation ($n=1$), and focal post-inflammatory dermal fibrosis ($n=1$). This study is important because it describes the most frequent findings in Paget's disease, but some findings are unclear (nipple parenchymal stromal distortion) or useless because of clinically evident signs (disrupted high echoic nipple skin). Otherwise, it is important to note that other cancers with a nipple-areolar location may present the same aspect. Ultrasound is useful, especially in the differential diagnosis of a malignant lesion from an inflammatory one, such as infected cysts or ductal-ampullary systems, and also for a summary examination of the whole breast.

For the differential diagnosis of retroareolar lesions, especially for the assumption of malignancy or benign-type mass or dilated ducts, FBU is recommended as the most-performed, noninvasive, and available technique. Because the normal nipple has a high strain, appearing in blue, sonoelastography is useful in detecting retroareolar and periareolary abnormal stiffness, allowing better guidance for biopsy in suspect cases.

8.4.6 Breast Cancer with Nephrotic Syndrome

Paraneoplastic nephropathy/membranous glomerulopathy refers to glomerular disease without specific etiology that develops in parallel with cancer evolution phases (improvement, remission, recurrence) [56]. The most common neoplasias associated with paraneoplastic glomerular disease are Hodgkin's lymphomas and lung and gastrointestinal tract carcinomas. A few cases of nephrotic syndrome and breast cancer have been reported.

Membranous glomerulopathy is caused by immune complexes that build up in the kidney, resulting in a thickening of the vessel walls within the kidney filters. Despite the small number of cases with this association reported in the literature, it is possible that some cases are underdiagnosed or neglected. The ethyological-pathological diagnosis is important because the surgical and chemotherapeutical treatment of breast cancer can resolve the nephrotic syndrome, and, inversely, the resolution of proteinuria with hypoproteinemia might be a measure of cancer control [56]. An important aspect of the reported cases with paraneoplastic membranous nephropathy associated with breast cancer was the advanced local stage, with most cases presenting invasive ductal cancer, with or without any lymph node involvement [56].

The nephrotic syndrome is considered a rare complication of breast carcinoma, but the incidence may be underestimated because of either a missing diagnosis, misinterpretation as different etiologies, or even because of the metachronous association of proteinuria and hypoproteinemia with advanced breast cancer. In a report of Valcamonico et al. [57], the nephrotic syndrome appeared 5 years after the diagnosis of breast cancer. Despite the absence of a widely accepted experimental model of the association of glomerulopathy and cancer, the remission of proteinuria after complete healing of the neoplasia represents clinical proof of etiological correlation.

The differential diagnosis must include the irreversible renal injuries induced by the oncological treatment, such as pamidronate treatment in advanced breast cancer [58]. In these cases, the glomerulopathy associated with tubular-interstitial damage determines irreversible renal failure that does not improve after discontinuation of the treatment.

8.5 Satellite Lymph Node Metastases in Breast Cancer

8.5.1 Diagnosis of the Satellite Lymph Node Metastases by Classical Methods and FBU

Physical examination and plain ultrasound of axillary lymph nodes offer an evaluation that is not always precise. The metastasis in the sentinel lymph node can be detected in some cases only by Doppler imaging [59]. Contrast-enhanced interstitial ultrasound lymphography, with subcutaneous injection, was successfully tested in 2003 as an alternative to the sentinel node biopsy, with 85–94 % sensitivity [60].

Not all axillary findings are lymph nodes and not all lymph nodes detectable with ultrasound or mammography are malignant. Usually, there are more than 15 axillary lymph nodes, but not all normal axillary lymph nodes are detectable because of their small size and because their features are similar to the lobules of the fatty tissue. As a consequence, if some lymph nodes are salient, they must be characterized as well as possible. Those that are undetectable are assumed as benign/normal [61].

A study by a Korean group, presented in 2003, included 114 patients with axillary abnormalities and found 35 cases with benign lymphadenopathy: 21 nodal hyperplasias, 8 tuberculosis, and 6 histiocytic necrotizing lymphadenitis. The malignant lymph nodes ($n=20$) were represented by nine nodal metastases from breast carcinoma and one lymphoma. Other non-lymphadenopathy structures included accessory breast and its related abnormalities in 28 cases, 17 cases of benign skin lesions, a cystic lymphangioma, and a lipomatous tumor [62].

Before the widespread use of the sonoelastography, Doppler imaging was the first technique added to classical ultrasound that proved to be useful for determining whether sentinel lymph node biopsy is indicated [59].

The risk of false-negative results in axillary lymph node biopsy is proportional with the stage of the breast cancer and the location in the upper outer quadrants [63]. In a study of 512 women with breast cancer, axillary lymph node metastases were present in 6.1 % of T1a-b cases, 25.1 % of T1c, 28.7 % of T2, and 35 % of T3. The probability of nodal involvement in negative lymph node biopsy (false negative) was calculated between 1.3 % for T1a-b, up to 6.3 % in T1c, up to 7.5 % for T2, and 9.7 % for T3. The authors concluded the patient may be better informed about the axillary lymph node dissection decision based on the calculated risk of metastases, but the evaluation is only statistical, not case related.

The evaluation of the satellite lymph nodes is important before therapeutic decision making. Mammographic detection has a low sensitivity and poor specificity. MRI has a high sensitivity but low specificity, which increases the biopsy rate. Ultrasound detection of the lymph nodes has a variable accuracy according to different authors, because the technique and the criteria for diagnosis are different. It is important to discriminate between "benign-type" and sentinel lymph nodes in patients with breast cancer. The node seen as the most malignant looking or located closest to the tumor was defined as a sentinel node on ultrasound. Sentinel node biopsy will be a standard technique in breast cancer treatment. Therefore, preoperative examination of axillary lymph nodes needs reevaluation.

In gray-scale ultrasonography it is often difficult to judge lymph node metastasis only by the morphologic assessment, the general sensitivity being less 45 % and the specificity less than 70 %. A classical ultrasound description of a lymph node with a round shape rather than an oval shape, a ratio of the wide to the long axis greater than 0.5, or a wide axis larger than 1 cm is suggestive of a malignant lymph node, in addition to hypoechoic internal structure, with loss of hyperechogenicity of the node's sinus.

Better results are obtained using ultrasonography with Doppler and sonoelastography. Salient new vasculatures, especially in the cortical regions, combined with low elasticity are the most important findings with high accuracy for malignancy. Often, the sentinel node appears as a focal thickening of the cortical region, with asymmetrical shape and local cortical hyper vasculature, the aspect is more specific than the lymph node diameters. These observations related to partial lymph node involvement are confirmed by a study by Britton et al. that presented the results of core biopsies in different ultrasound types of axillary lymph nodes:

- No visible nodes had normal histology after surgical biopsy.
- Normal ultrasound lymph nodes presented micrometastases in 3 of 70 cases.
- Uni-lobulated cortex lymph nodes were malignant in 7 of 17 cases.
- Multilobulated cortex lymph nodes were malignant in 17 of 31 cases.
- Absent hilum with smooth cortex were malignant in 7 of 9 cases; those with absent hilum with lobulated cortex were positive in 5 of 6 cases [61].

When the characterization of axillary lymph nodes was based on 2D assessment of their size, shape, vasculature with Doppler exam, and internal echoes using THI (Tissue Harmonic Imaging), the accuracy was good, up to 95.8 %, with sensitivity 90.8 % and specificity 97.6 %, according to Kusama et al. [64]. The value of Doppler ultrasound was proved in cases with axillary metastases in no palpable lymph nodes, with high accuracy (the sensitivity, specificity, positive and negative predictive values, and accuracy of ultrasonography were 86.49 %, 93.62 %, 91.43 %, 89.8 %, and 90.48 %, respectively, according to Esen and colleagues [66]).

Because of the lack of standardization, the correlation between the ultrasound size and the histopathologic size of the lymph nodes has low value, but Doppler examination is useful in determining response after chemotherapy, with a significant increase in the resistance index and pulsatility index values, according to Rashmi et al. [67].

The normal aspect of the axillary lymph nodes is described in Chap. 3.

8.5.2 Differential Diagnosis of Armpit Lumps

A. *Benign* Armpit Lumps

Some axillary lymphadenomegalies with transverse diameter greater than 10 mm, which may be benign findings, are wrongly designated on mammography as adenopathies because of their increased size. The main differential diagnosis must refer to the following:

- *Normal lymph nodes*, usually with transverse diameter less than 8 mm, but may be enlarged, with diameter up to 12–13 mm and longitudinal axis up to 25 mm, with normal internal structure: hyperechoic sinus, thin hypoechoic cortex, few/absent vessels in the hilum, absent pericapsular and cortical Doppler signal, and scoring 1 or 2 Ueno.

- *Histiocytic necrotizing lymphadenitis/benign histiocytosis*, the most frequent lymphadenomegalies: the lymph nodes present central hypoechoic medullary (sinus), with preservation of a peripheral hyperechoic medullary rim, surrounded by the intense uniform hypoechoic cortical zone. Doppler is normal with few vessels in the hilum, without cortical new vasculature. Sonoelastography corresponds to scoring 2 or 3 Ueno. The benign lymph node histiocytosis is usually associated with plasma cell mastitis, chronic galactophoritis, or rheumatoid arthritis.
- *Chronic granulomatosis*, non-suppurative such as sarcoidosis: the unspecific aspect preserves the benign features of the enlarged lymph nodes, with usually poor or undetectable vasculature. In suppurative chronic lymphadenitis the diffuse borders and perinodal infiltration may mimic malignancy, especially because of the presence of caseum or calcifications that increase the strain ratio. Patient history may be useful in the differential diagnosis. A specific pathology is referred to as silicone-induced granulomatous adenitis.
- *Acute lymphadenitis*, which is less frequent, is characterized by thickening of the cortex, increasing of the vasculature with centrifugal orientation of the benign type, and scoring 1 or 2 Ueno. The clinical signs are useful and patients present with pain and swelling of the small parts in the axilla. There may be an allergic reaction, an unspecific upper limb bacterial infection, cellulitis, lymphadenitis in viral infections, or specific lymphadenitis such as Lyme disease after a tick bite. Cat scratch fever and brucellosis may cause acute axillary lymphadenitis.
- *Other axillary small parts infections*: acute hidrosadenitis and cellulitis.
- *Breast tissue*: hypertrophy of the axillary prolongation of the mammary gland or supernumerary mammary gland.
- *Other axillary benign tumors*: lipomas, cysts, fibroadenoma.

B. *Malignant Armpit Lumps*

The differential diagnosis of malignant-type axillary lymph nodes must include the following:

- *Other metastases*: primary malignancy in ipsilateral arm with the start point from skin tumors, such as malignant melanoma (usually intense hypoechoic with hypervasculature), epithelioma, adenocarcinomas, or sarcoma; or more frequently from metastasis of distant tumors from the head and neck (larynx, thyroid, pharynx, etc.); or, rarely, from the internal thoracic, abdominal, or pelvic organs or other lymph nodes metastases with unknown primary origin.
- *Systemic malignancies*: leukemia, lymphomas. Usually the lymph nodes are small, less 10 mm in the short axis, with hypoechoic aspect, without significant vasculature, and may present reduced elasticity with scoring 4 Ueno.
- *Primary malignant tumors* with armpit involvement: osteosarcoma especially in young, angio-pericitosarcomas, liposarcoma, rhabdomyosarcoma, etc.

Sonoelastography is easier to perform than a biopsy and is more specific than MRI findings of lymph nodes. Thus, lymph node biopsy would become unnecessary, and, in the future, sonoelastography and higher-resolution probes will increase the precision.

Internal mammary lymph node (IMLN) metastases are one of the two most important pathways of lymphatic dissemination in breast cancer. Metastases to the IMLN occur in up to 20 % of patients with clinically operable malignant breast tumors [67]. Although dissection of the axillary nodes is still a widely employed staging strategy for breast carcinoma, staging of disease by dissection of the internal mammary lymphatic chain is rarely performed. Real-time ultrasonography with a high-frequency linear-array transducer has been used to localize the internal mammary artery and veins and to demonstrate lymphadenopathy.

The examination is easily to perform because the internal mammary artery and its two satellite veins are located just laterally of the right and left sternal borders, behind the cartilaginous transonic ending ribs, and, together with the surrounding tissues, are completely visualized with the Doppler technique. The normal IMLNs are not distinct, but pathological lymph nodes appear as round or oval-shaped, well-delineated hypoechoic nodules, usually infracentimetric in size, with the vasculature more or less salient.

IMLNs suspected by ultrasonography can be proven by ultrasound-guided fine needle aspiration cytology (US-FNAC), which is considered to be useful because the evaluation of metastasis to IMLNs is required in TMN classification by the UICC (2002). US-FNAC could be performed comparatively safely and easily, with low-risk of complications of neither pneumothorax nor bleeding.

Only ultrasonography and MRI mammography are able to detect IMLN, which is another limitation of mammography. Whether occurring alone or combined with axillary metastases, IMLN metastases have a substantial negative effect on long-term survival and disease-free interval. According to TNM staging, ipsilateral IMLN metastases are considered as stage 3b, which is accepted as inoperable. The presence of IMLN involvement also affects the area that should be irradiated.

(Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 8.10, 8.11, 8.12, 8.13, 8.14, 8.15, 8.16, 8.17, 8.18, 8.19, 8.20, 8.21, 8.22, 8.23, 8.24, 8.25, 8.26, 8.27, 8.28, 8.29, 8.30, 8.31, 8.32, 8.33, 8.34, 8.35, 8.36, 8.37, 8.38, 8.39, 8.40, 8.41, 8.42, 8.43, 8.44, 8.45, 8.46, 8.47, 8.48, 8.49, 8.50, 8.51, 8.52, 8.53, 8.54, 8.55, 8.56 and 8.57).

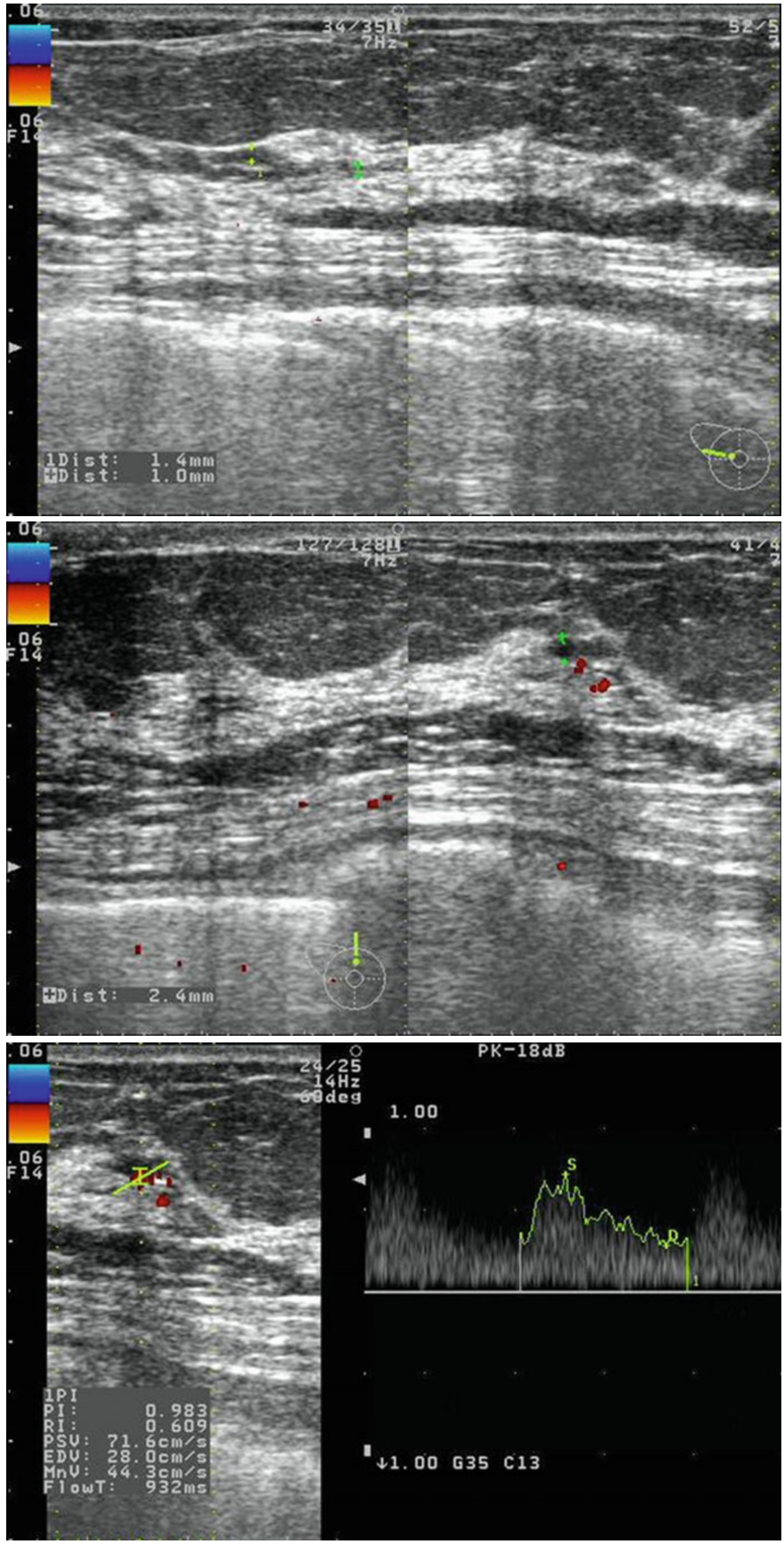


Fig. 8.1 Suspect lobular hyperplasia at R12:00 in a TDLU location in a dense breast of a 52–year-old patient whose mother had breast cancer. Doppler exam makes the differential diagnosis of these multiple lesions of focal ductal/lobular hyperplasia

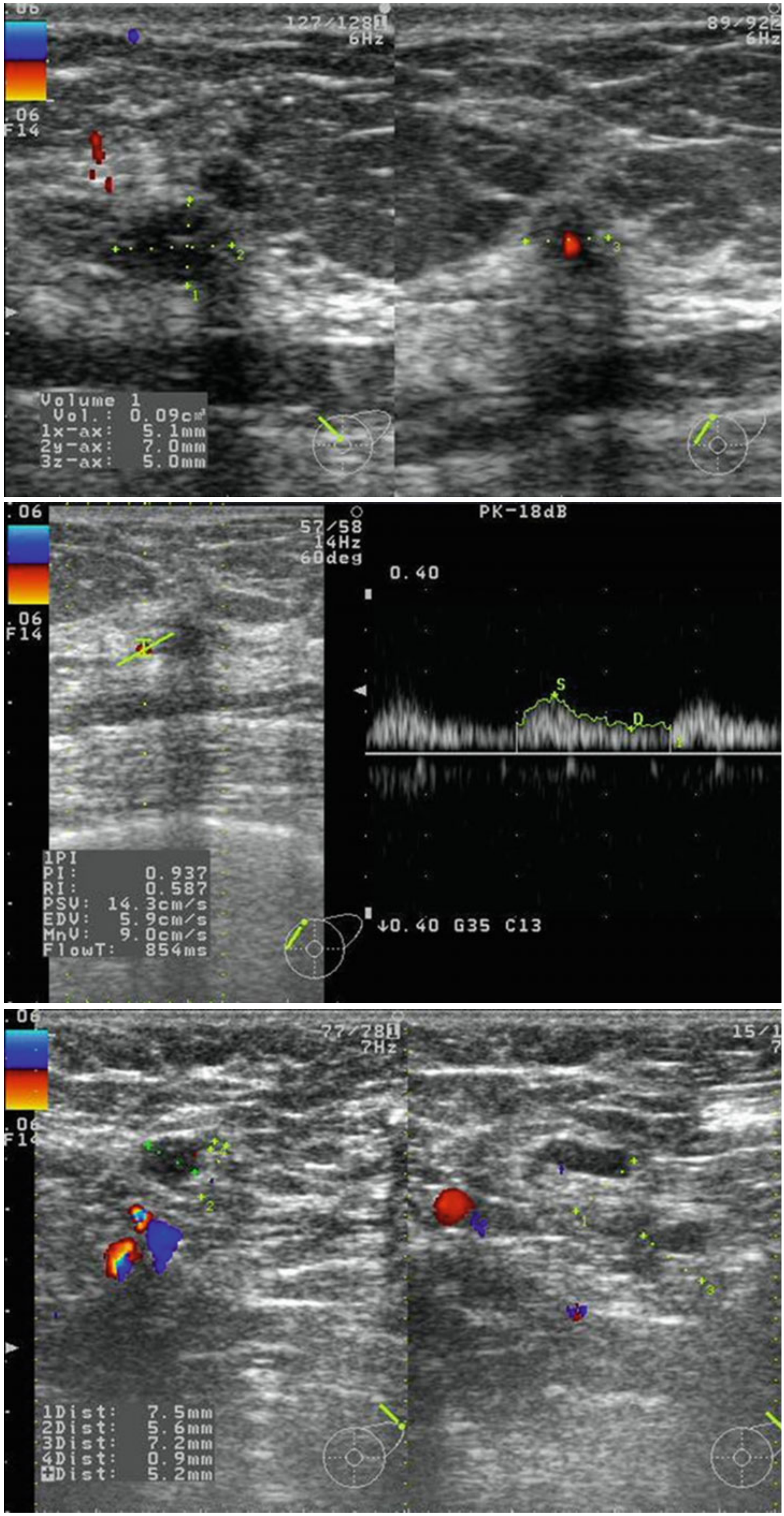


Fig. 8.2 Fifty-one-year-old patient who underwent ultrasound screening over 4 years for family history of breast cancer (mother). DE detected a 5/7 mm lesion in a TDLU localization, with irregular shape, heterogeneous hypoechoic structure, acoustic shadowing, and new vasculature in color and spectral Doppler. A few axillary lymph nodes presented focal cortical thickening, suggesting sentinel nodes. Ultrasound BI-RADS category 4C

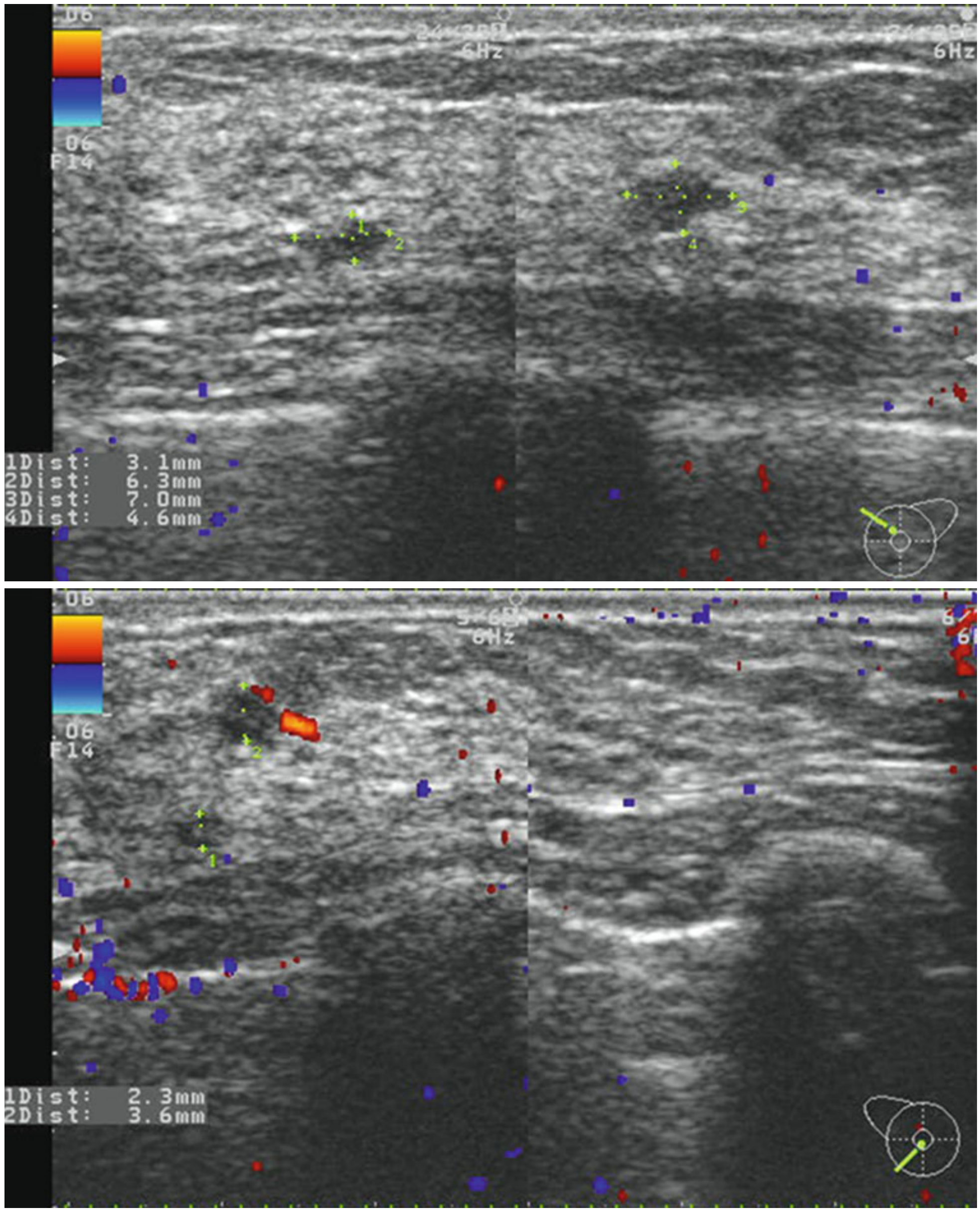


Fig. 8.3 Patient is 39 years old: Doppler DE presents at R7:00 a suspect micronodule less than 5 mm, with a double pole of new formation vasculature. It is similar in appearance, size, and aspect to L10:00 lobular hyperplasias but without salient vasculature. The suspect lesion was classified ultrasound BI-RADS category 4, and short-term follow-up was recommended. After 1 month the lesion doubled its diameter, increased its vasculature, and surgical biopsy confirmed DCIS

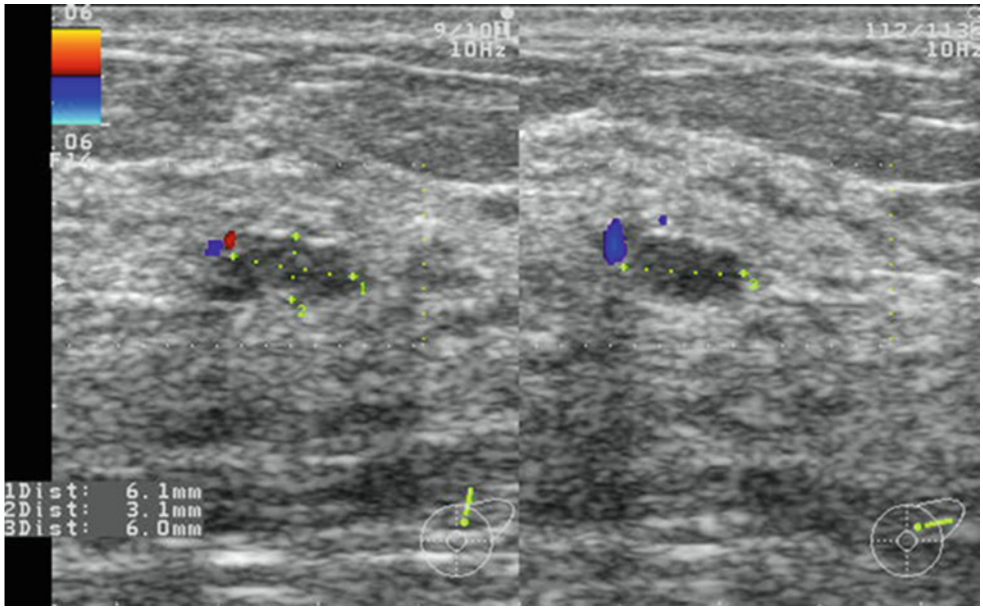


Fig. 8.4 Suspect infracentimetric lesion at Doppler DE: hypoechoic, with irregular shape and new formation vasculature. Radial and antiradial scans are used to demonstrate its ductal connection and to estimate its volume. U ltrasound BI-RADS category 4

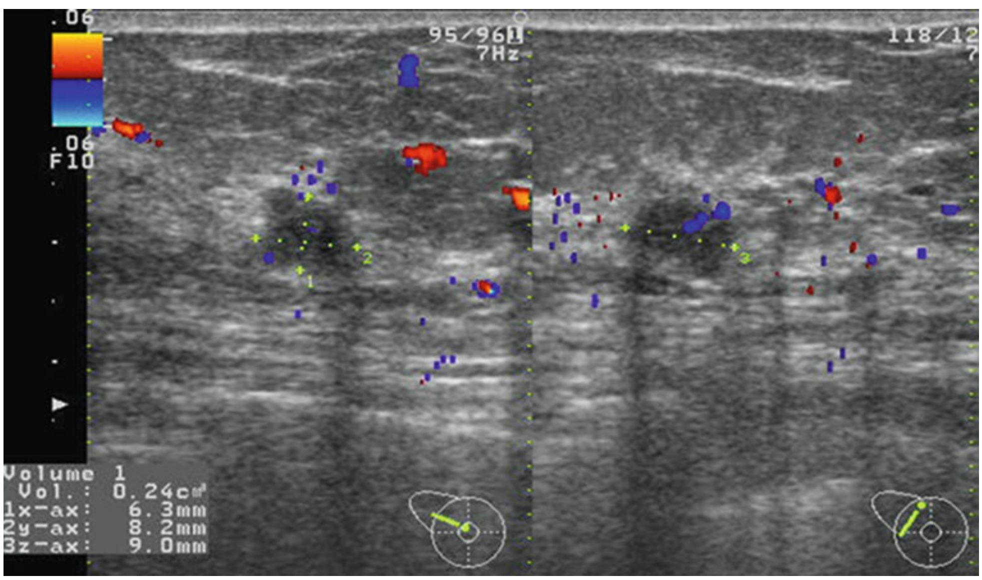
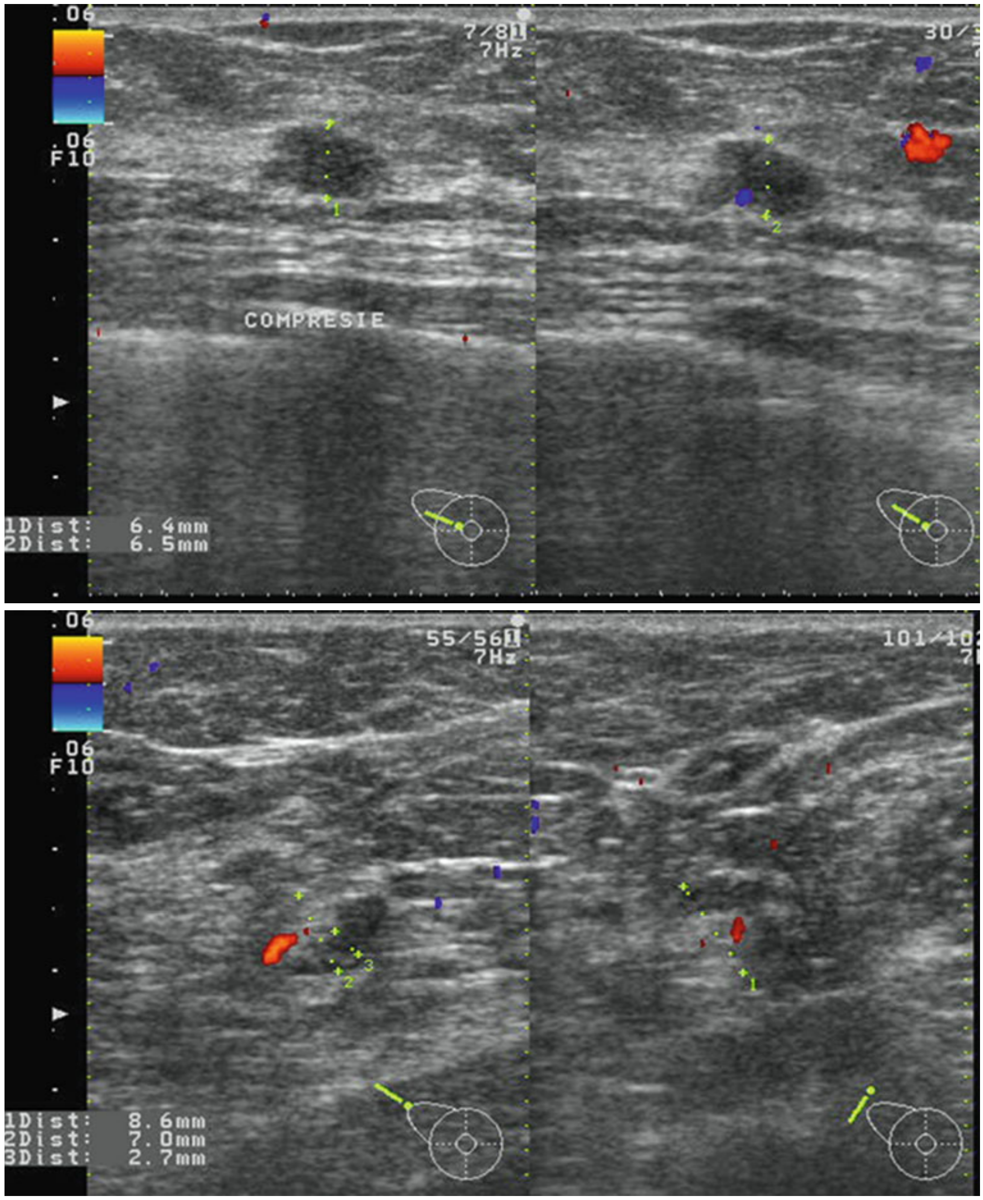


Fig. 8.5 Patient is 53 years old with a family history of breast disease (a sister died of breast cancer and her mother had breast dysplasia). DE detected an infracentimetric mass at R10:00 in a TDLU location, with polycyclic shape, hypoechoic texture, unequal lateral shadowing, and a centripetal vasculature. Adjacent small hypoechoic foci with shadowing suggest intraductal early spreading or multifocal malignancy. Without sonoelastography, the simple compression suggests a stiff lesion. The focal thickening of the cortical of an axillary lymph node is suggestive of a sentinel node. Based on the collateral history and the DE, the findings were assessed as ultrasound BI-RADS category 4. The pathological report presented lobular multiple micro-invasive carcinoma

Fig. 8.5 (continued)



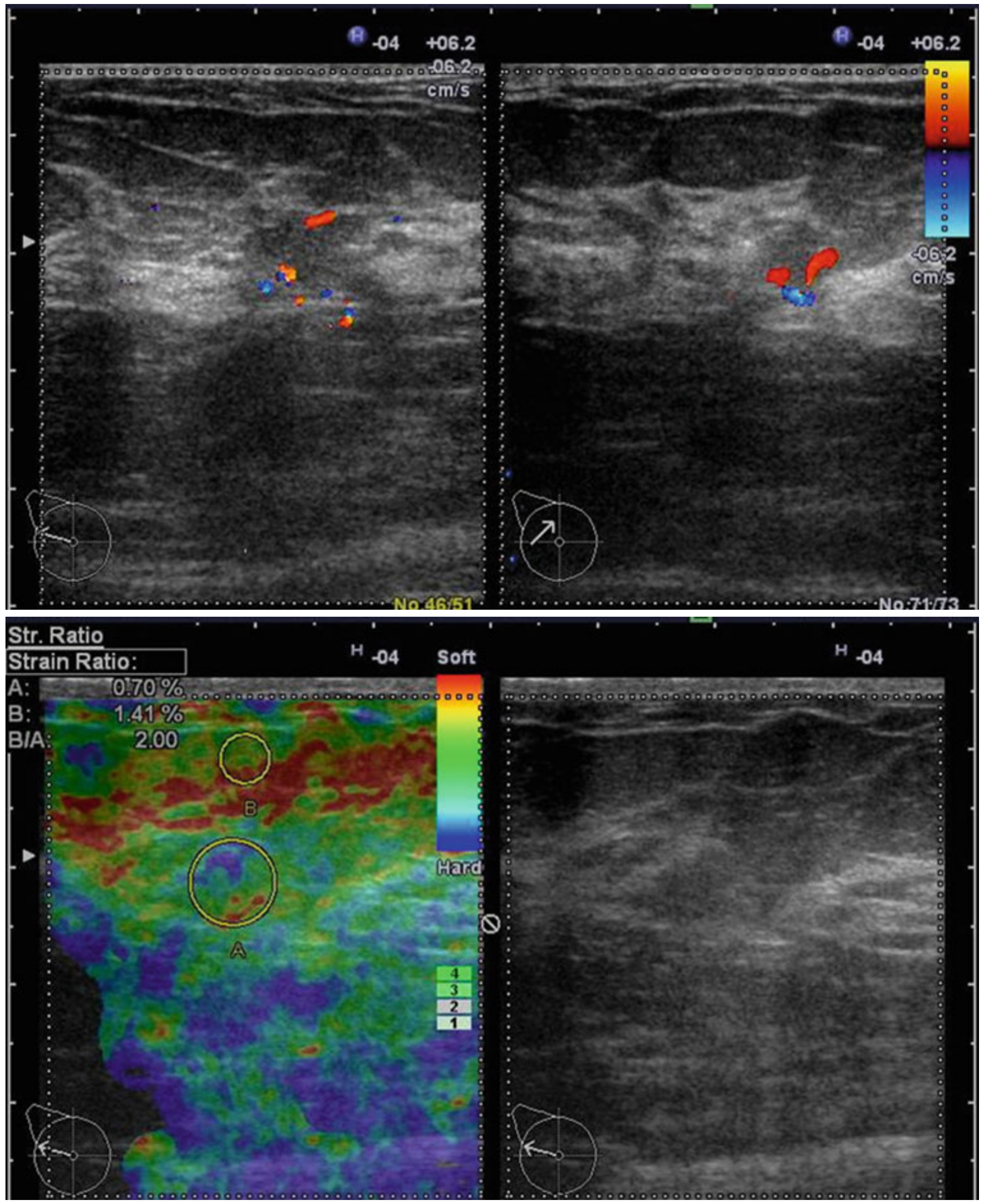


Fig. 8.6 Patient is 53 years old, with negative mammography 8 months earlier. A complementary FBU demanded for mastalgia demonstrated at R10:00 segmental ductal thickening without abnormal Doppler or sonoelastography. The same location developed in the interval an infracentimetric mass with isoechoic structure, no posterior effects, diffuse borders with irregular shape and thickened duct connections, and salient new formation vasculature but benign sonoelastography type BGR scoring. In this case, the sonoelastography is false negative, but the most important point is the local evolution and the verified new formation vasculature, which were concordant with an interval DCIS

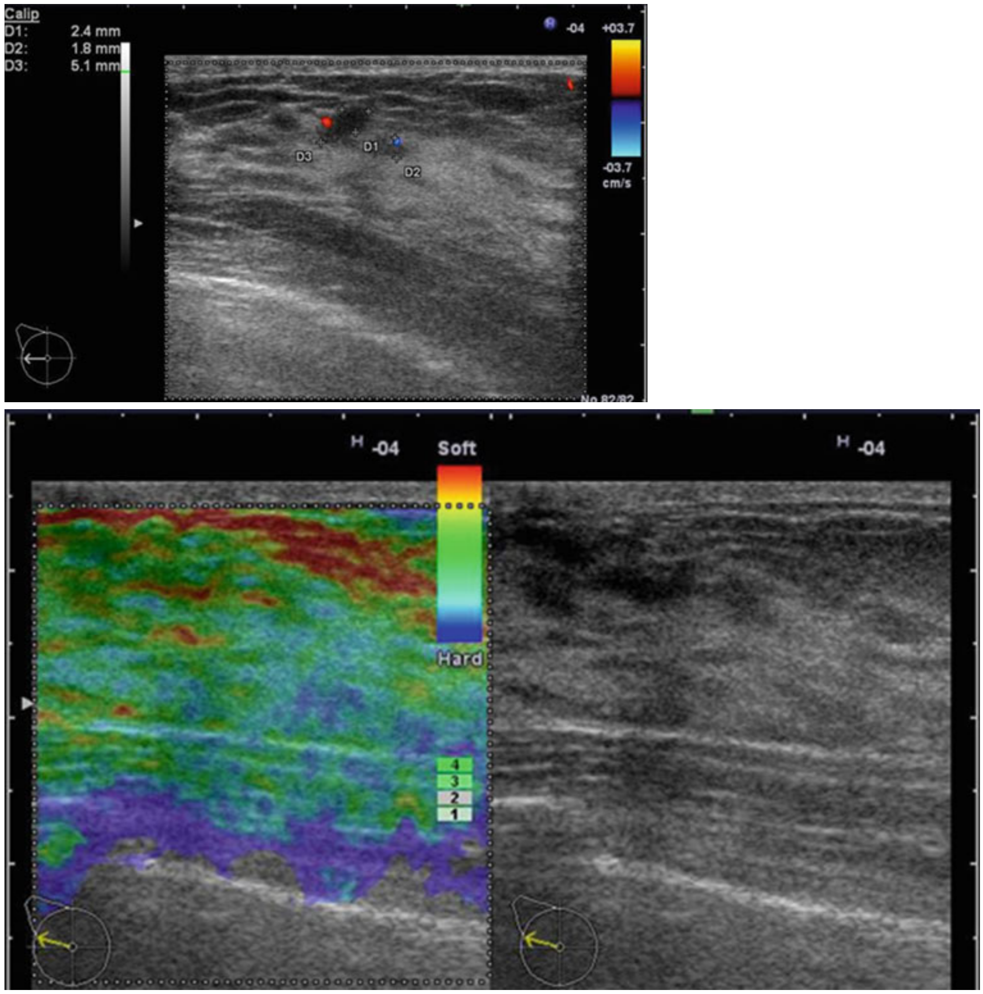


Fig. 8.7 The early stage of lobular carcinoma in FBU: multiple lobules enlarged up to 5 mm, with increased hypoechoic aspect and oblique orientation toward the ducts. The new formation of tiny vessels may be considered an alarm sign, but SE presents an initially benign score because of the small size of these lesions (false-negative sonoelastography)

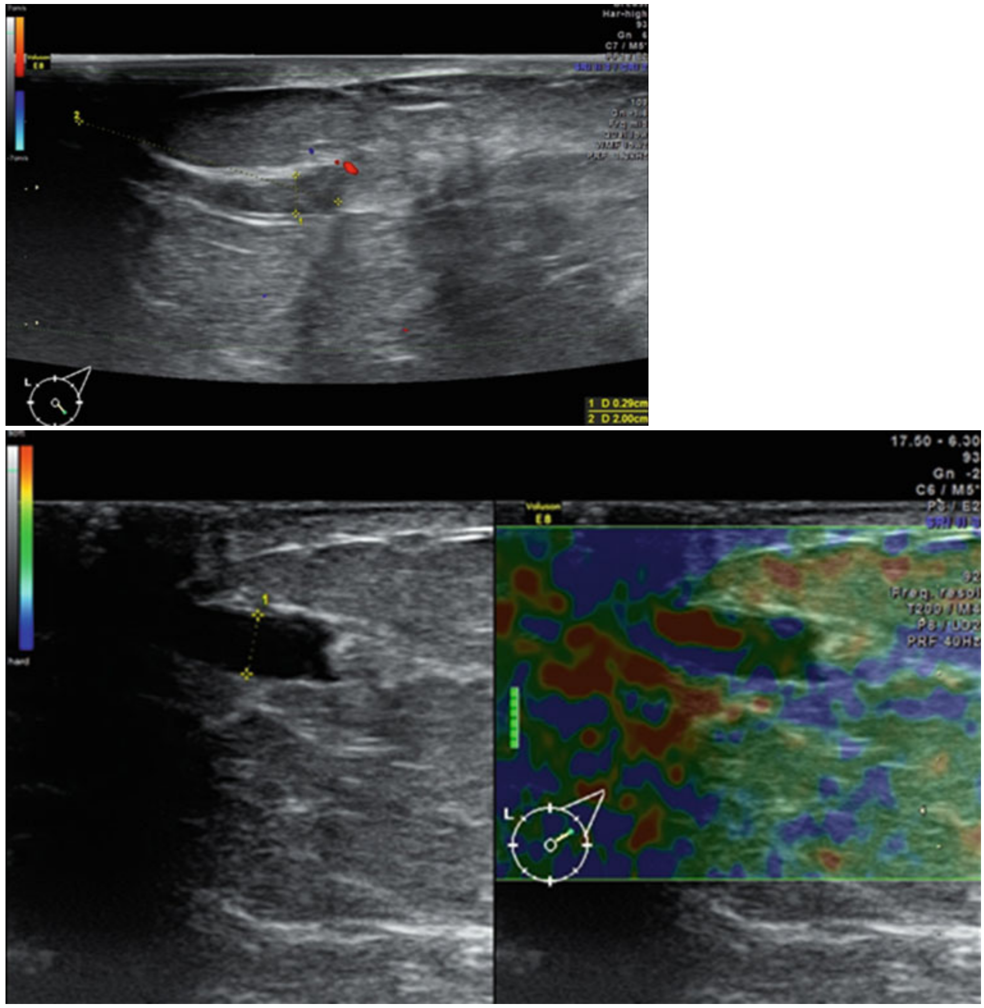


Fig. 8.8 Duct ectasia ended by an isoechoic intraductal mass, with nourishing vessel, suspect according to the small duct diameter and small mass, despite the benign SE. A short follow-up is recommended for the differential diagnosis of the ductal papilloma with a DCIS

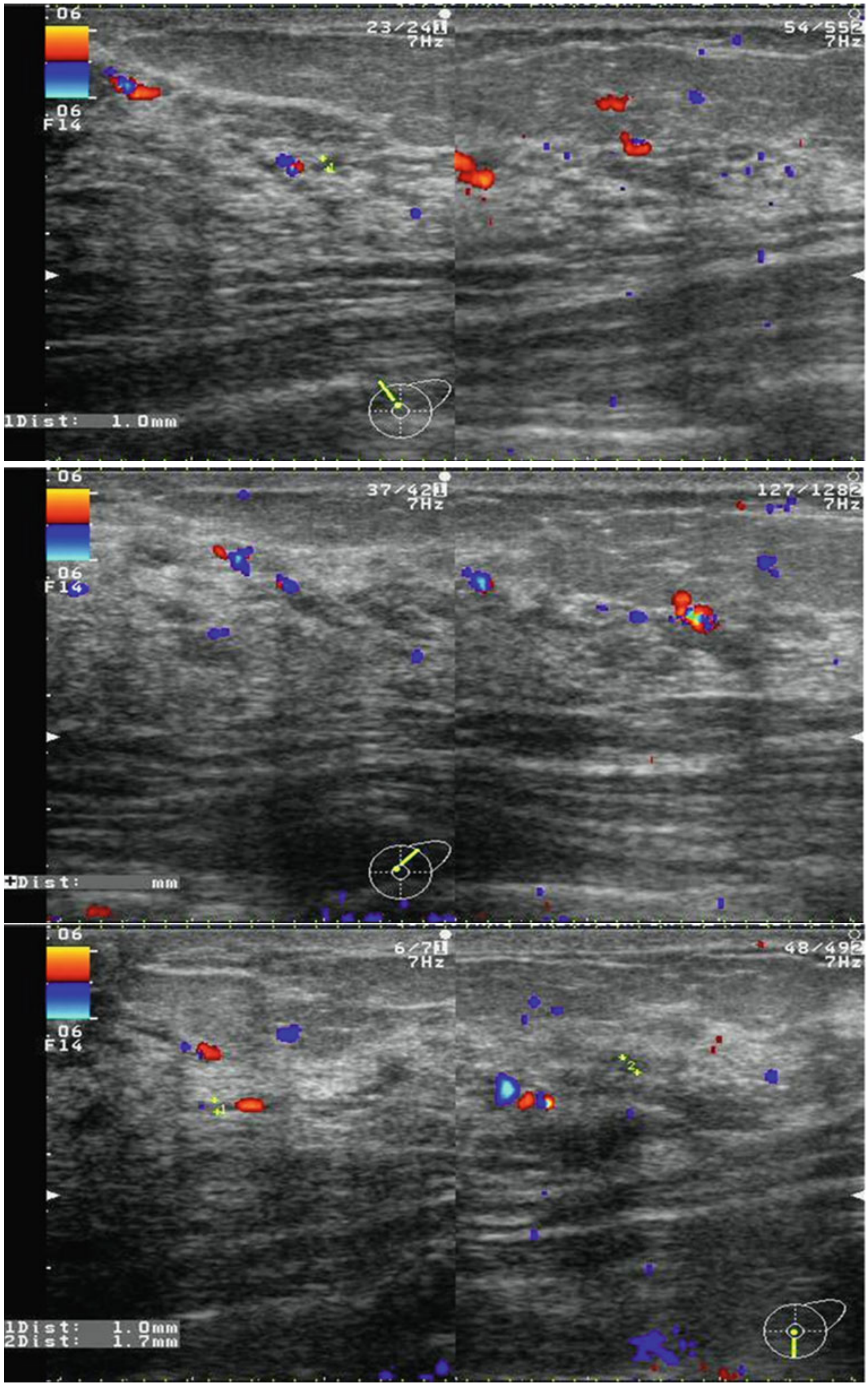


Fig. 8.9 Patient is 35 years old: the left breast stings and a lump is present on the upper-outer quadrant; mammogram is negative. The first important finding on Doppler DE is a gentle diffuse lobular hyperplasia with important periductal and perilobular hyper vasculature

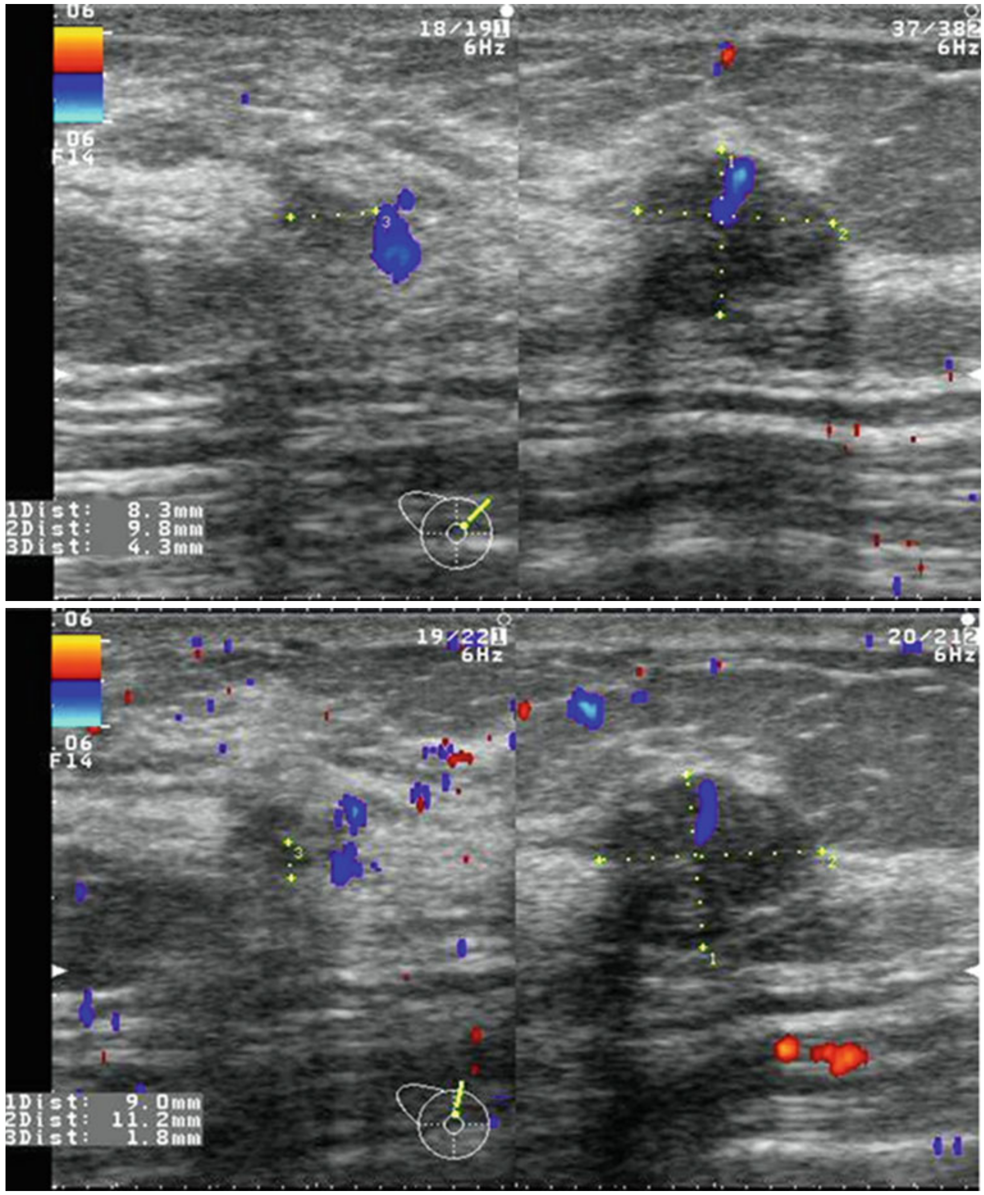
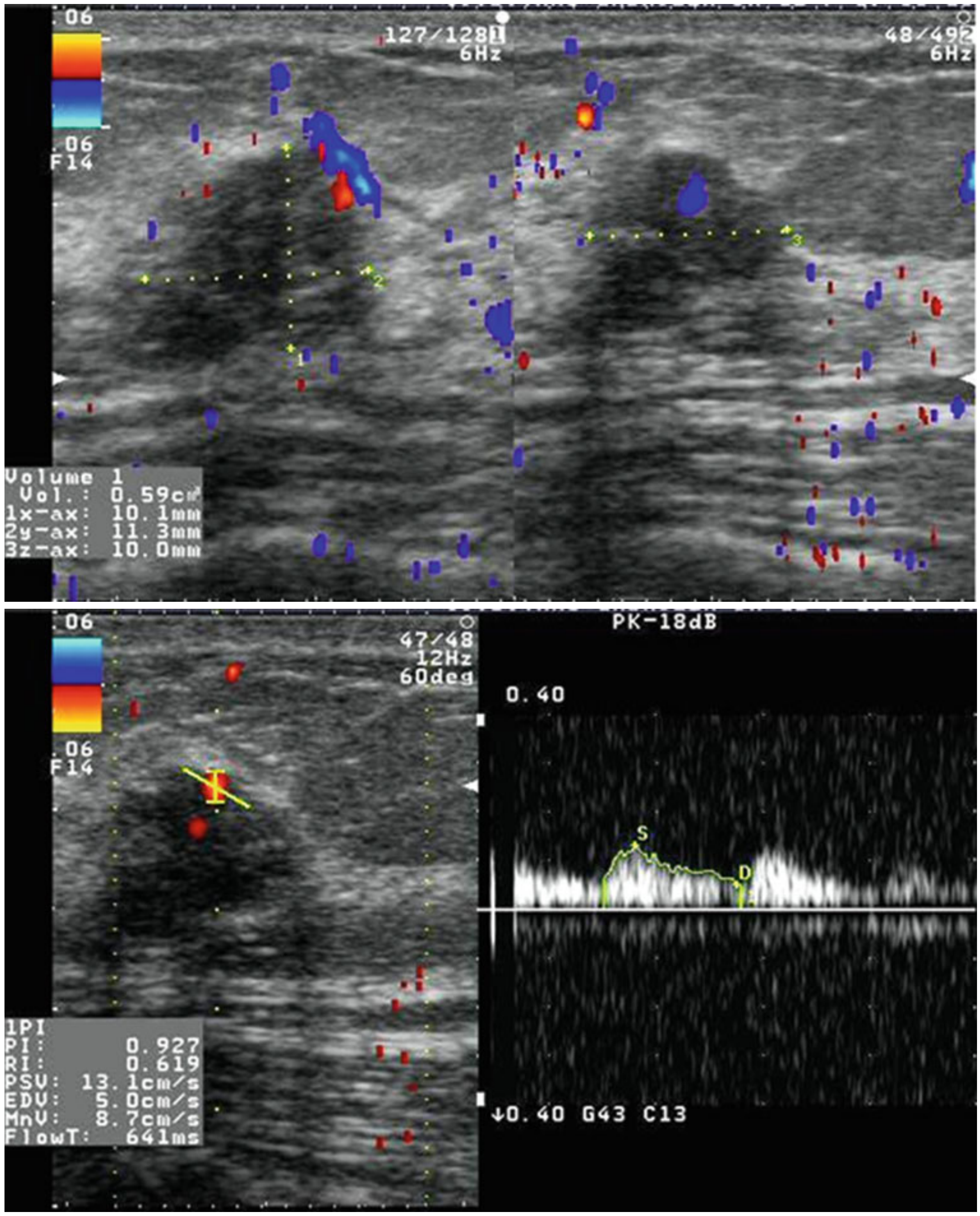


Fig. 8.10 Patient is 35 years old, same case as in Fig. 8.9: Doppler DE presents at R12:30-13:00 an impalpable 11 mm asymptomatic mass, polylobated, hypoechoic with posterior peripheral asymmetrical shadowing and centripetal plunging suspect vasculature. A second lesion, smaller and located centripetal to the nipple on the same radius, presenting similar characteristics including new vasculature, raises the suspicion of malignity. The qualitative color and power Doppler are more useful than the quantitative spectral Doppler because, in this case, with minimal stromal reaction the velocity indices are intermediate, as in the most benign masses (pulsatility index (PI) 0.927, resistive index (RI) 0.619). "Knobby carcinoma" type assessed as ultrasound BI-RADS category 5

Fig. 8.10 (continued)



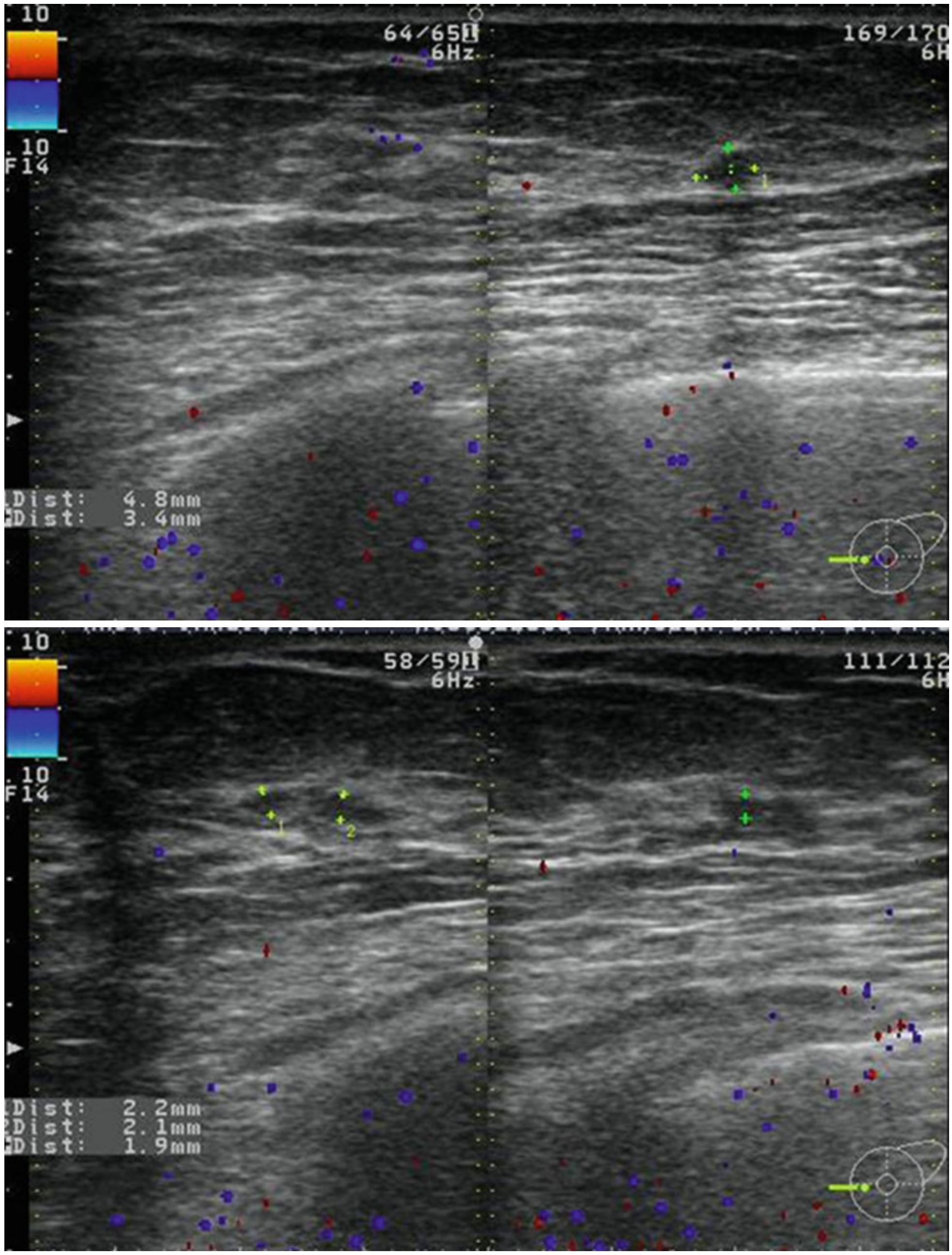
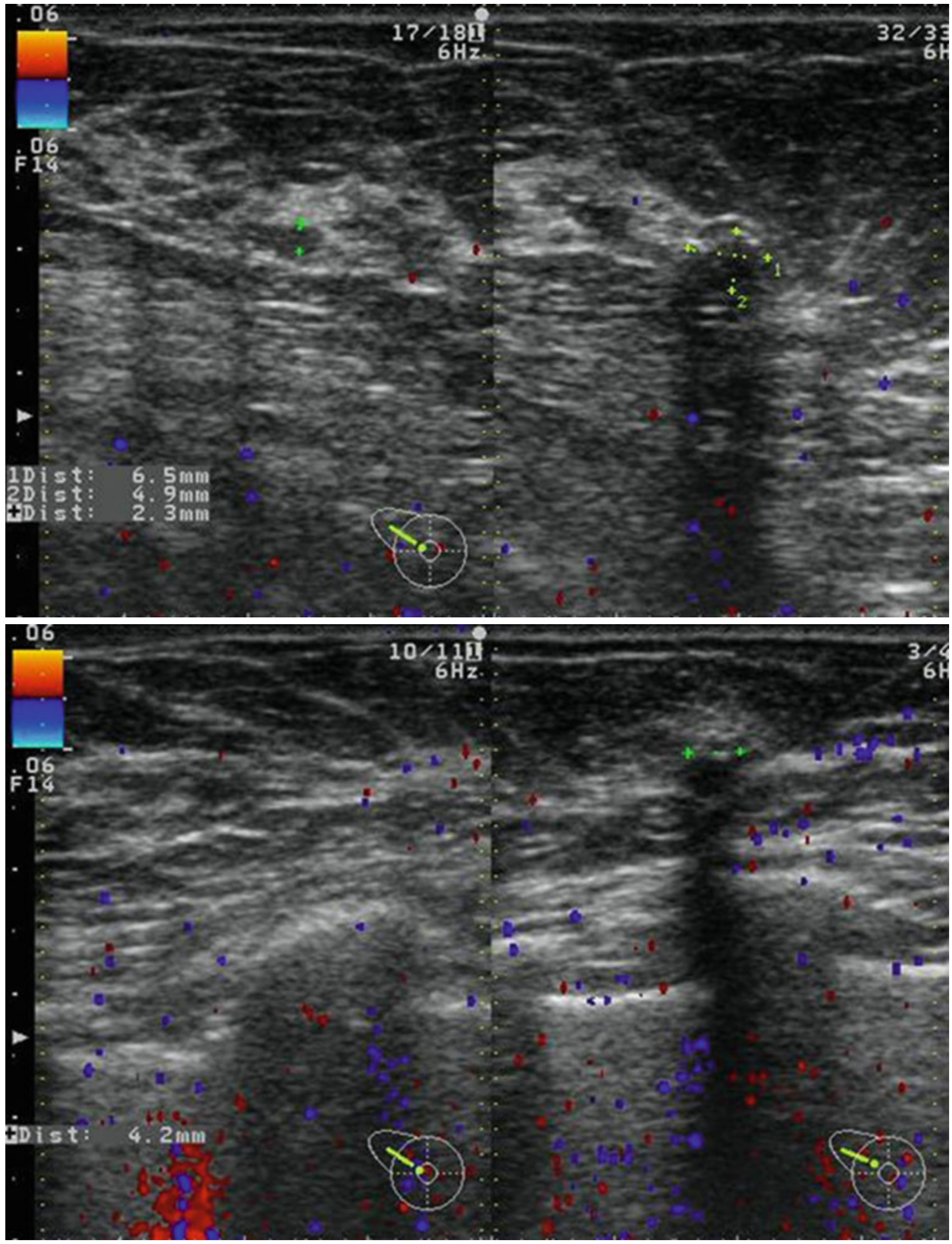


Fig. 8.11 A 67-year-old patient: predictable breast cancer or high-risk breast cancer may be assumed based on the dense breast in advanced menopause, with lobular hyperplasia as pseudo-nodules, some with acoustic shadowing, suggesting small sclerosing adenosis lesions. No abnormal vasculature maintains a benign characterization

Fig. 8.11 (continued)



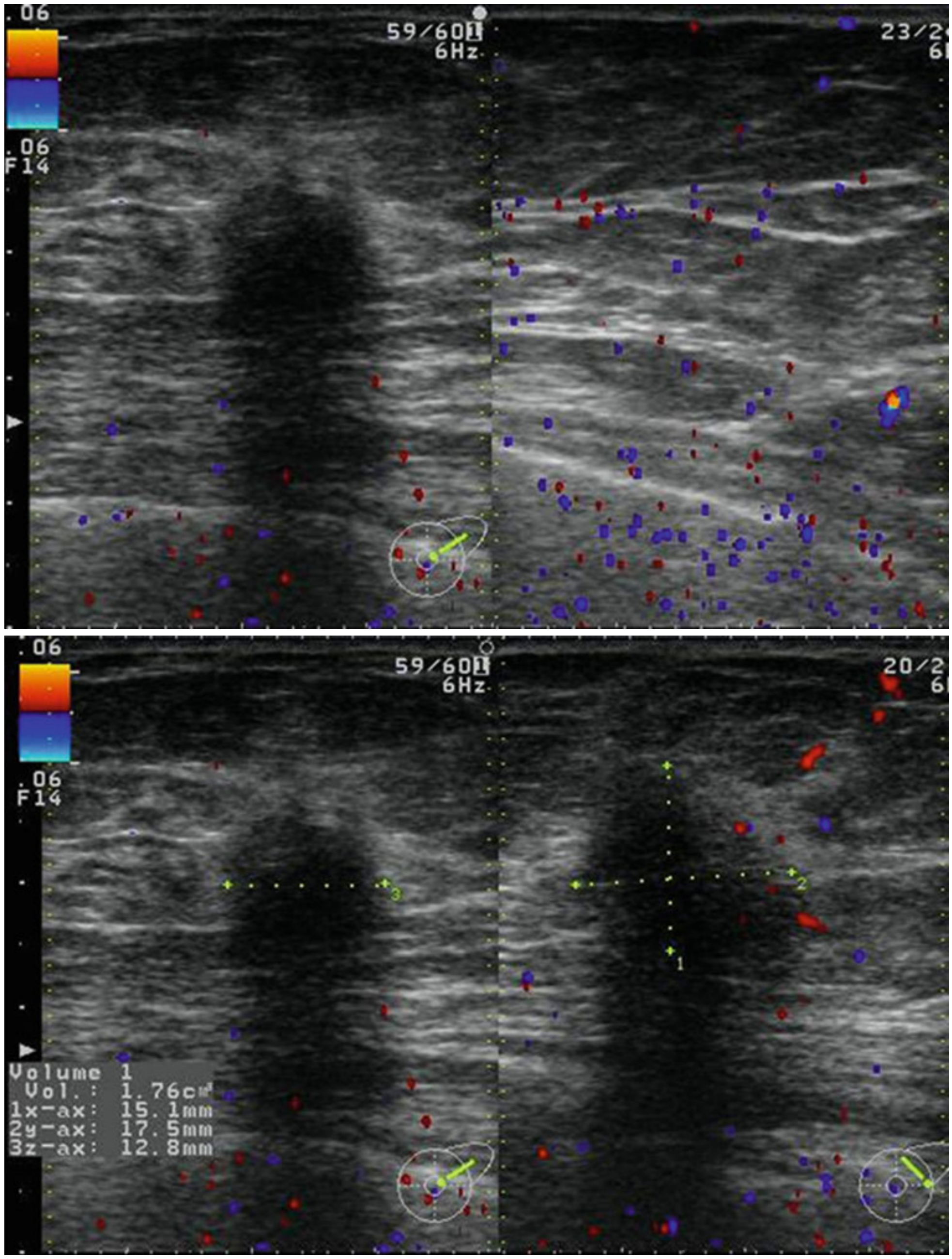
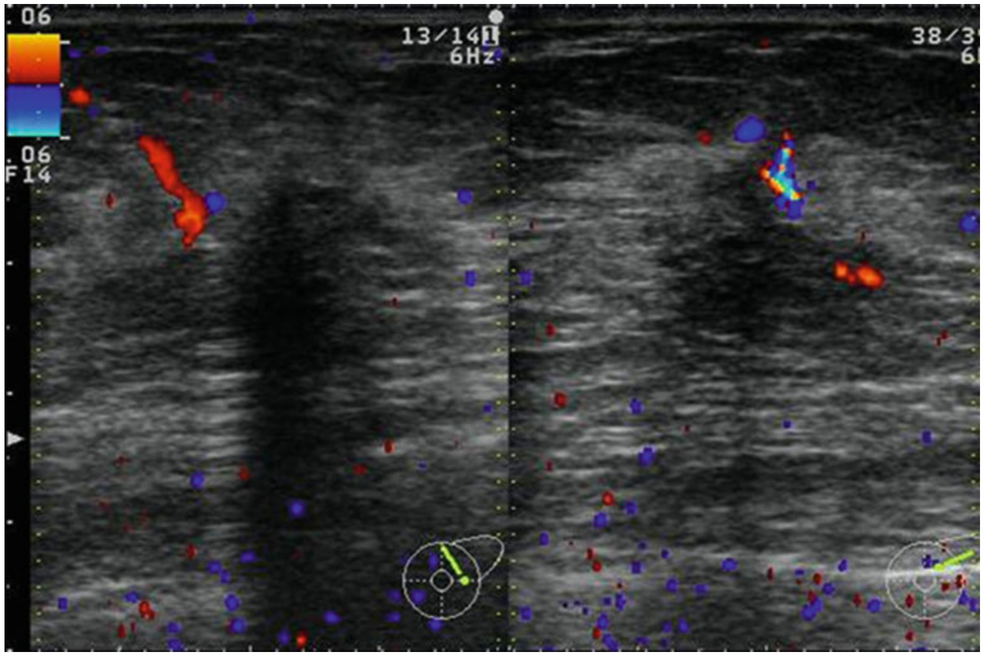


Fig. 8.12 The same patient as Fig. 8.11: L13:00 breast cancer less than 2 cm diameter with typical malignant descriptors after Stavros, acoustic shadowing and malignant-type new vasculature, with multipolar vessels having an incident plunging angle. "Stellate" carcinoma-type

Fig. 8.12 (continued)



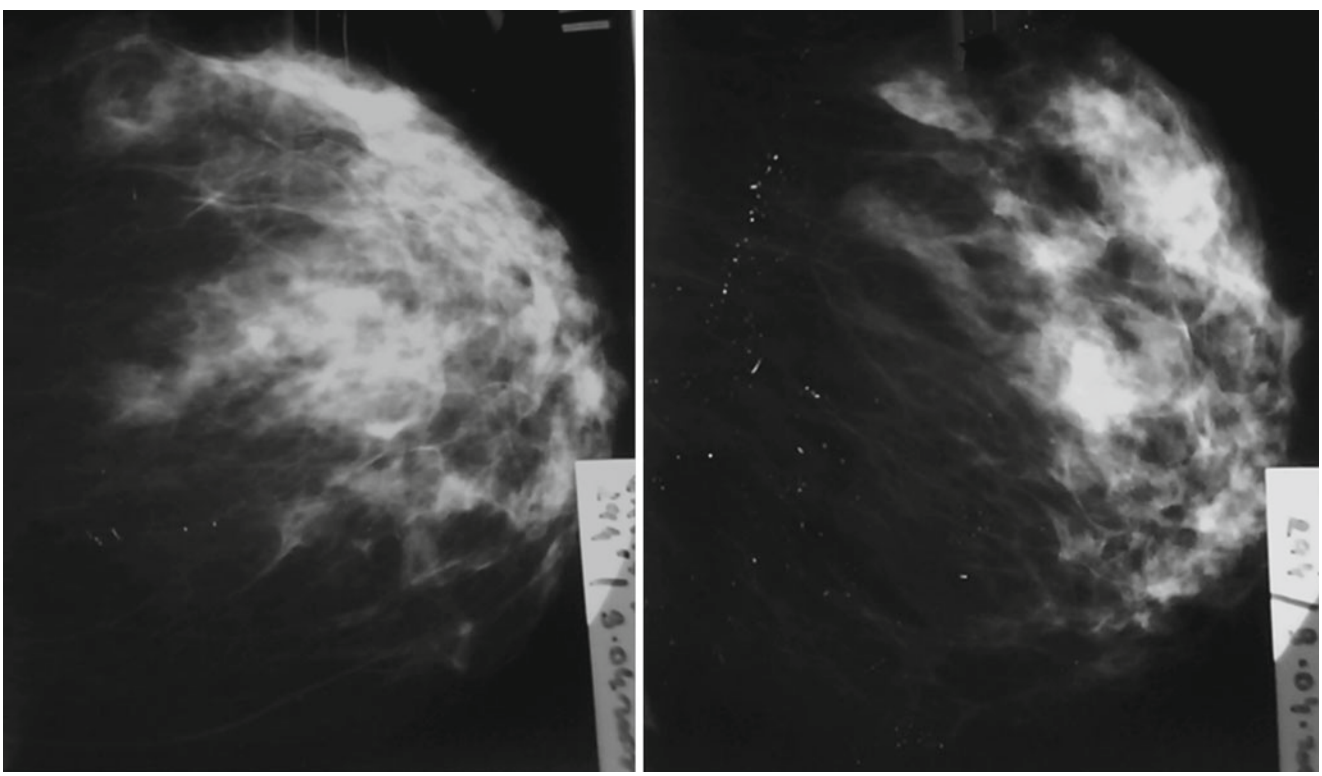


Fig. 8.13 Patient is 57 years old: follow-up mammograms 4 years (*upper*) and 5 years (*below*) after right breast cancer, treated with mastectomy, chemotherapy and radiotherapy. Large left dense breast post hormonal therapy for primary infertility, without significant changes on mammography, classified as BI-RADS category 2.3. We will not comment on the quality control of these films

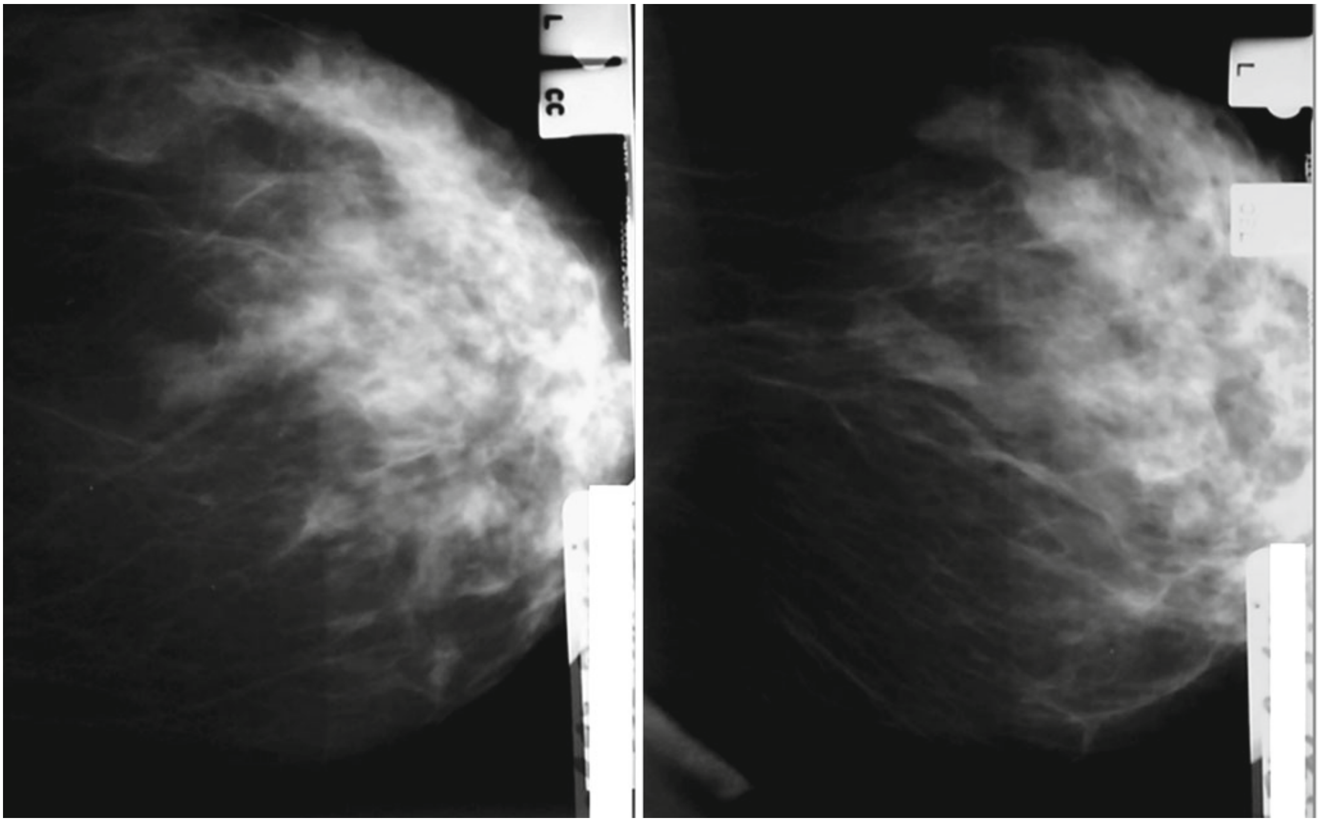


Fig. 8.13 (continued)

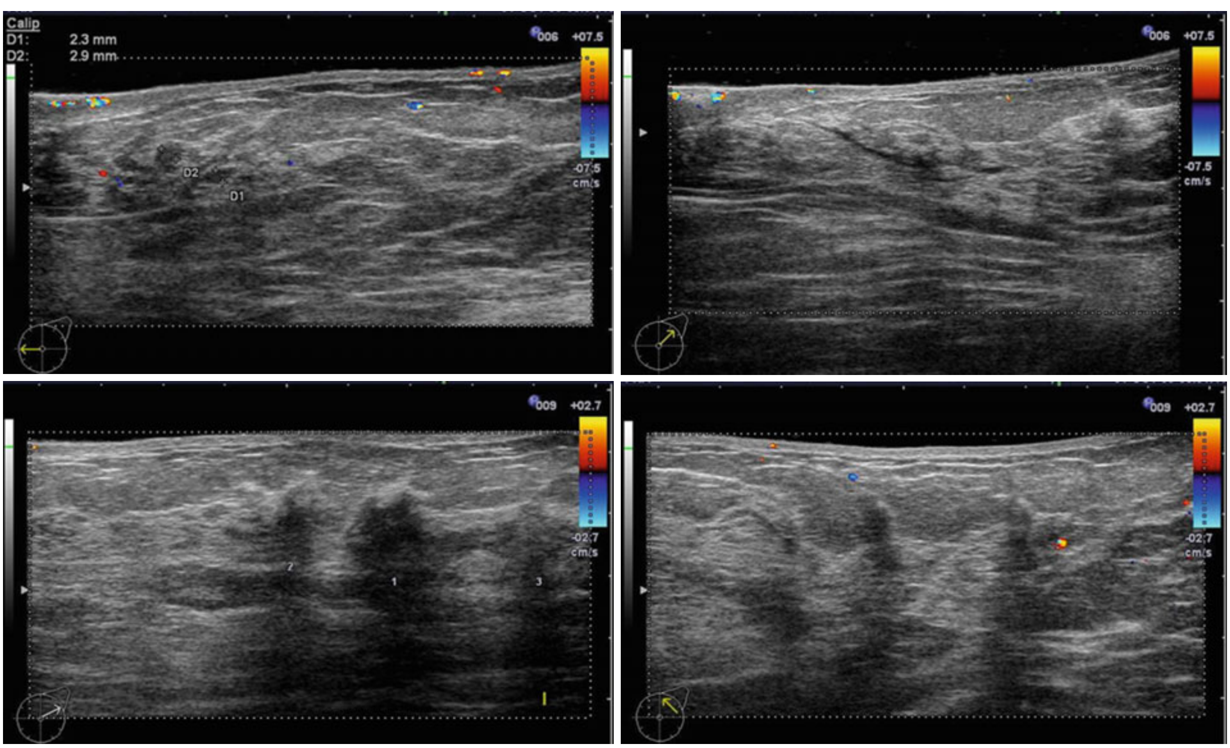


Fig. 8.14 Patient is 57 years old, same case as in Fig. 8.13: DE with long probe shows lobular hyperplasia and ductal ectasias, as remnant marks of the hormonal treatment of infertility. L1:00-2:00 multifocal cancers on radial and antiradial large scans, with malignant descriptors after Stavros (less salient vasculature with 7 MHz long probe, especially after chemotherapy)

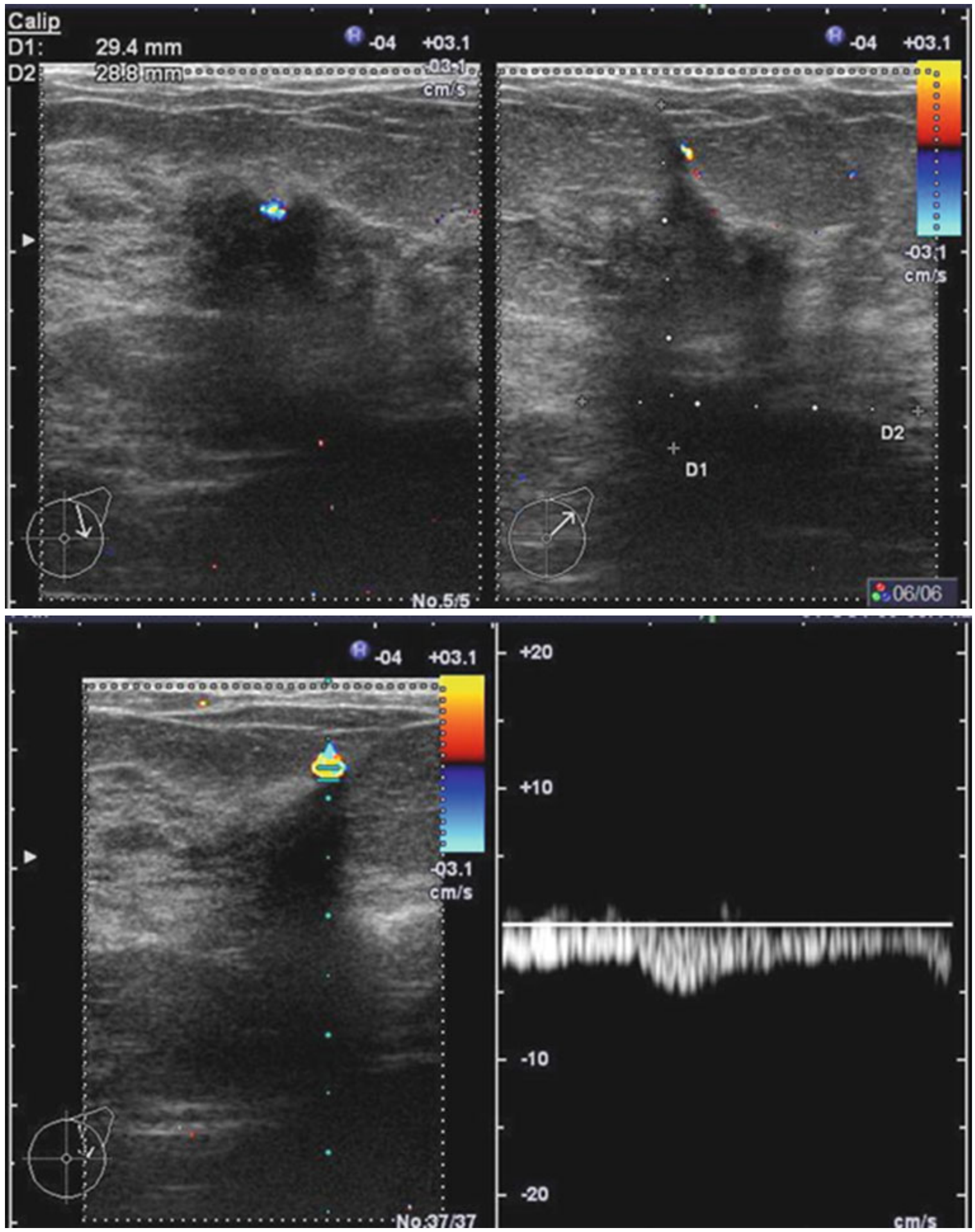
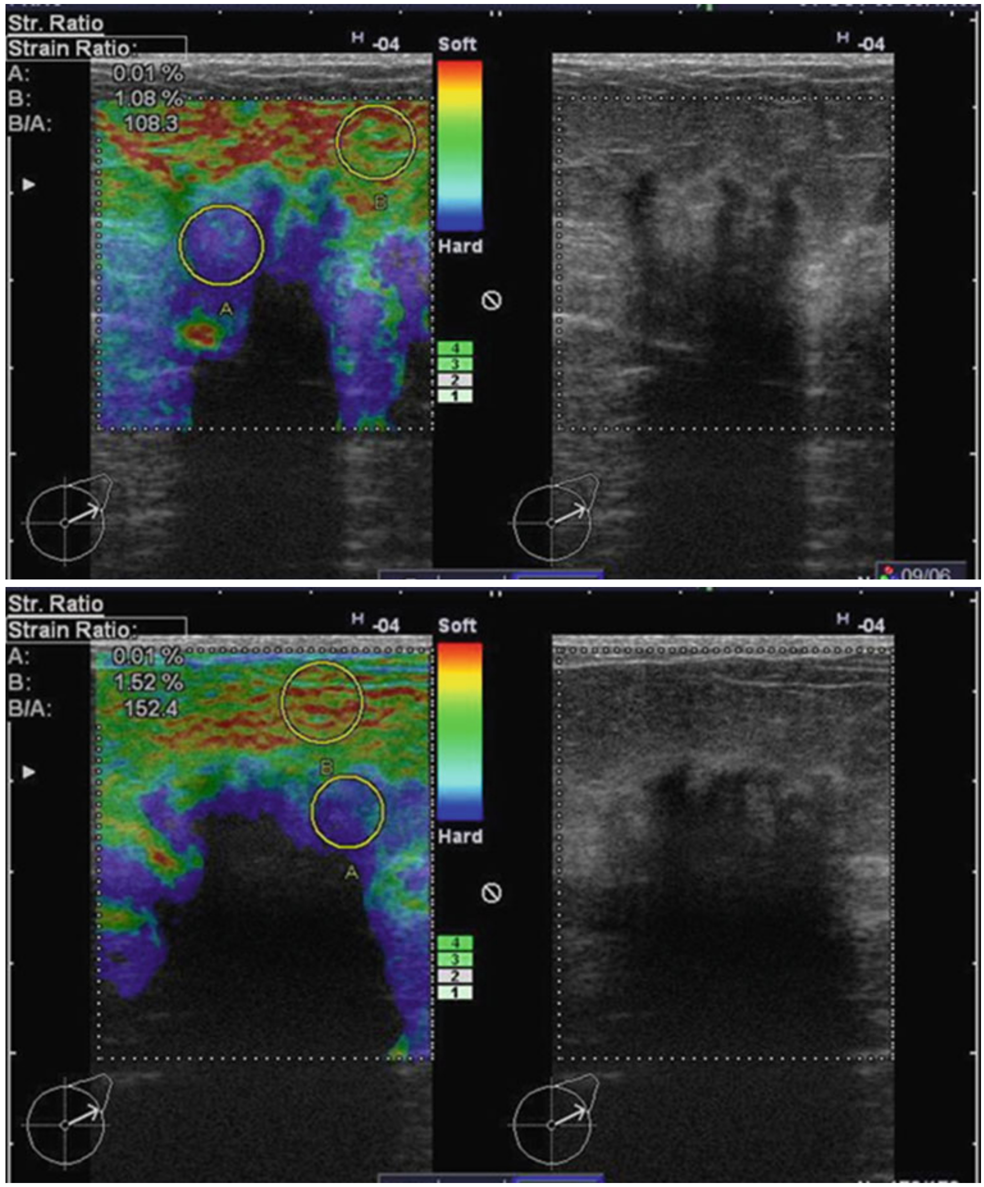


Fig. 8.15 Patient is 57 years old, same case as in Fig. 8.13: FBU demonstrates the spreading of the cancer by infiltration of the Cooper's ligament, with new vasculature on Doppler, and a desmoplastic reaction illustrated by a score 5 Ueno. The high stiffness is suggested by the black artifact and the huge FLR, over 108.00. "Stellate" cancer type

Fig. 8.15 (continued)



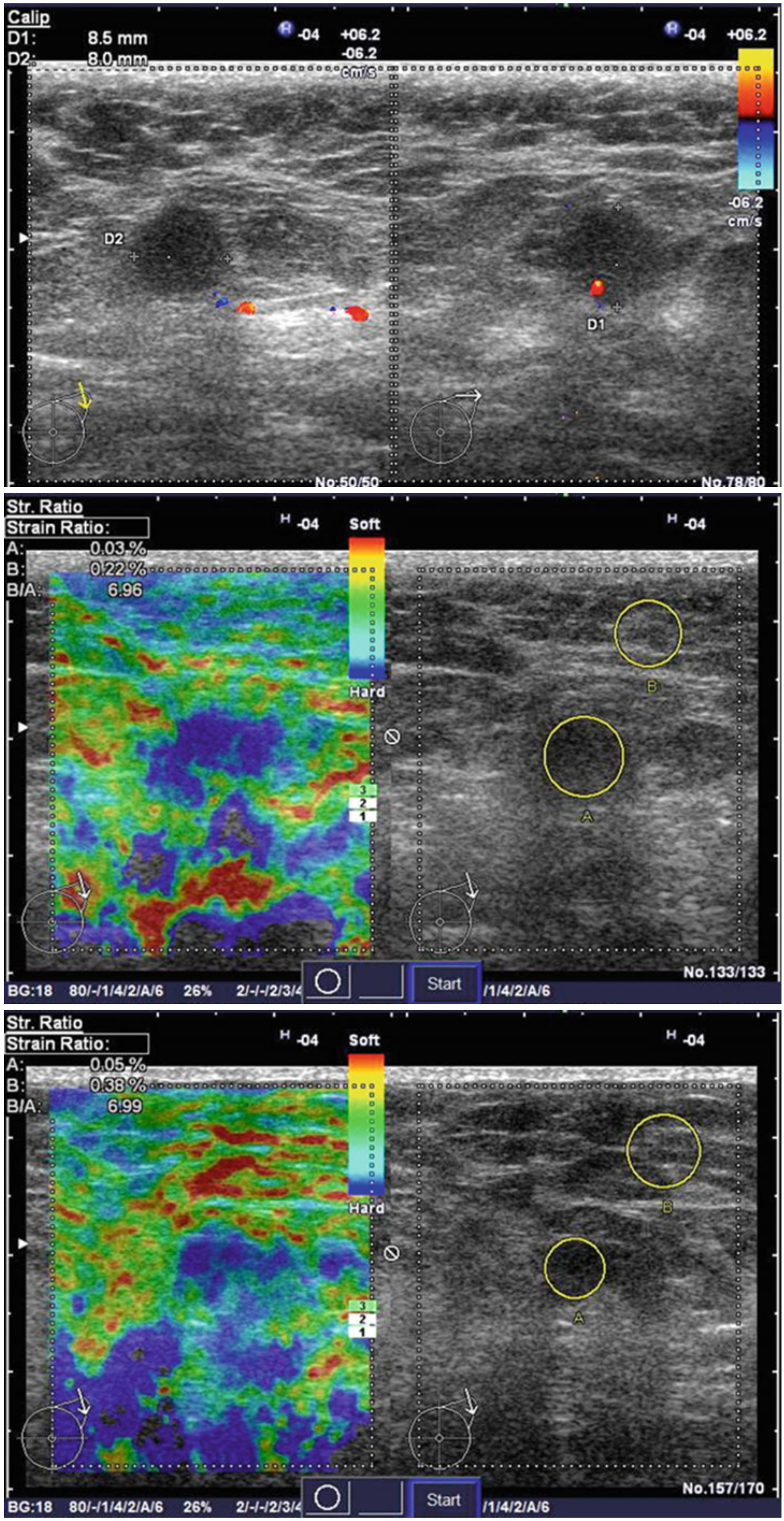
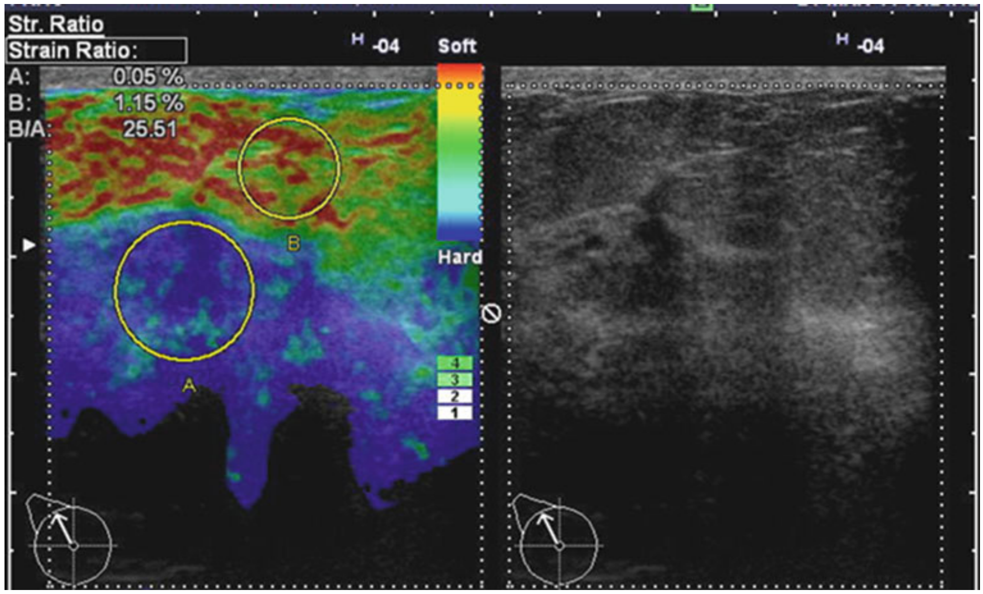


Fig. 8.16 Fifty-seven year, the same case: axillary lymphadenopathy, with hypoechoic cortical thickening, few vessels because of previous chemotherapy, but sonoelastography with a score 4 Ueno and FLR over 5.00 is high, suggestive of a sentinel node

Fig. 8.17 Peripheral R: 11:00 "stellate" cancer, scored 5 Ueno, without axillary lymphadenopathy



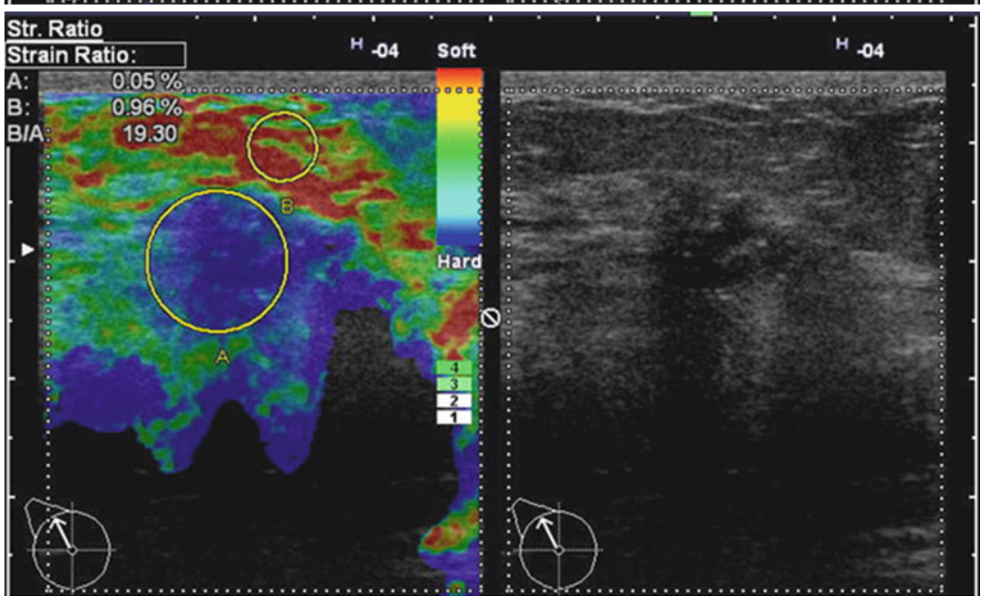
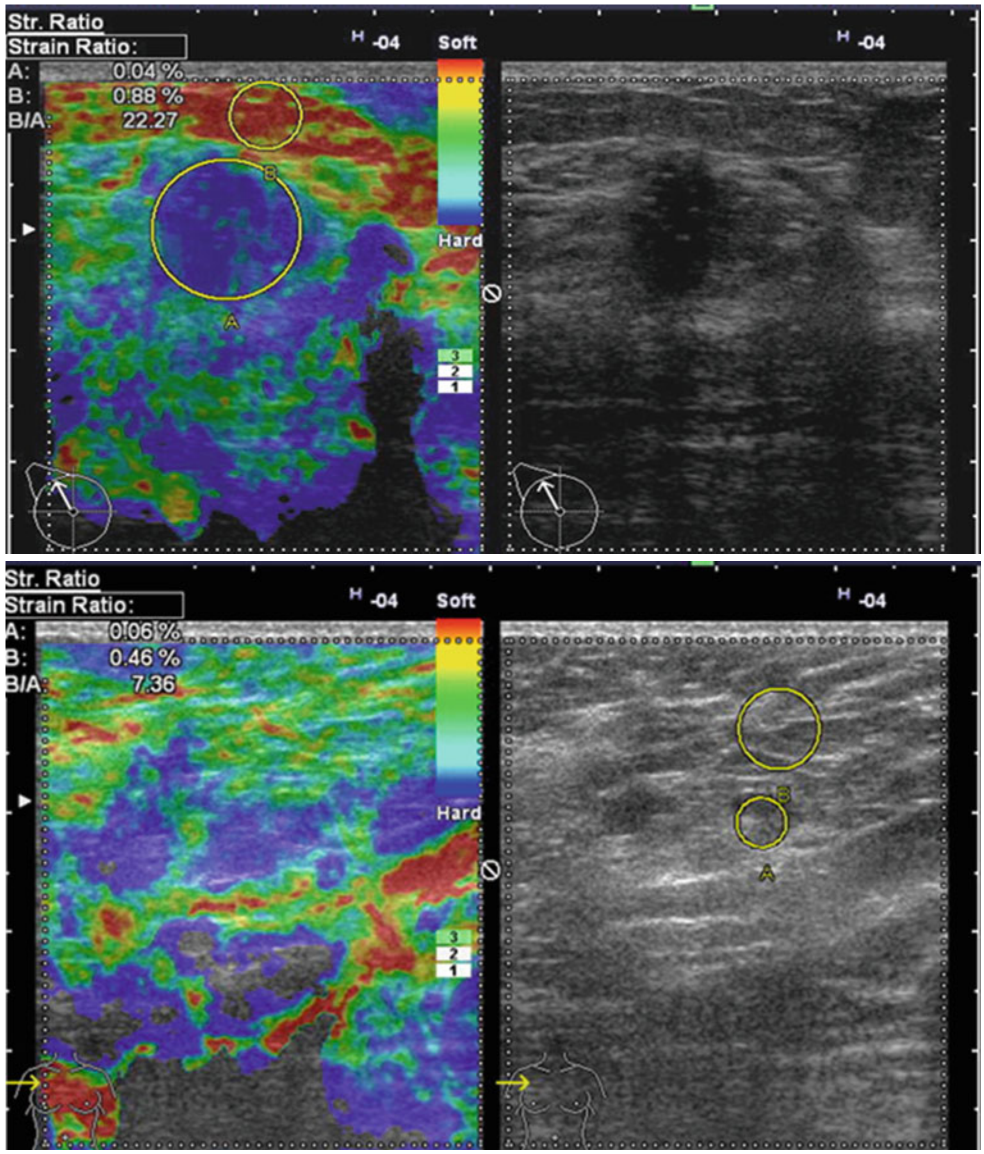


Fig. 8.17 (continued)



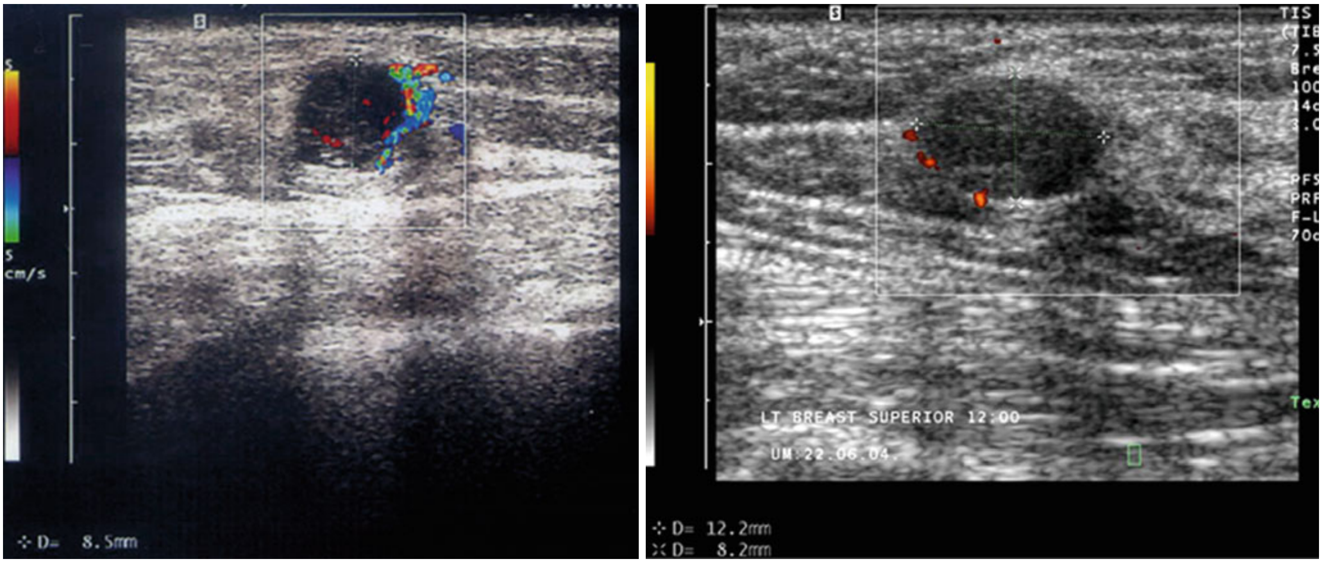


Fig. 8.18 Infracentimetric DCIS with pseudo-benign ultrasoundfeatures (*above*): posterior acoustic enhancement and marginal shadowing, similar to the fibroadenoma (*below*), but with peripheral and centripetal intense large new vasculature; otherwise, the malignant lesion is more hypoechoic. Both masses present adjacent hyperplasic lobule connected to the ductal tree

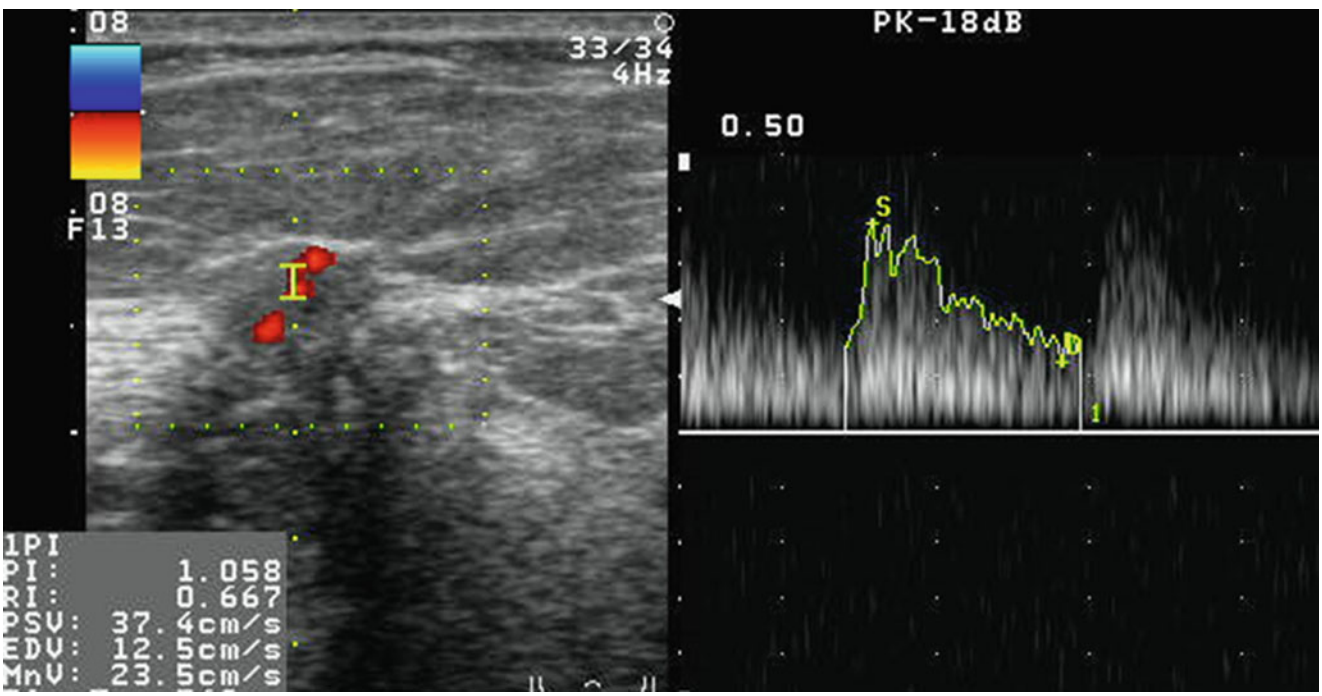


Fig. 8.19 Typical infracentimetric IDC, with ductal connection, spiculated irregular shape, acoustic shadowing, taller-than-wide, and with internal vasculature

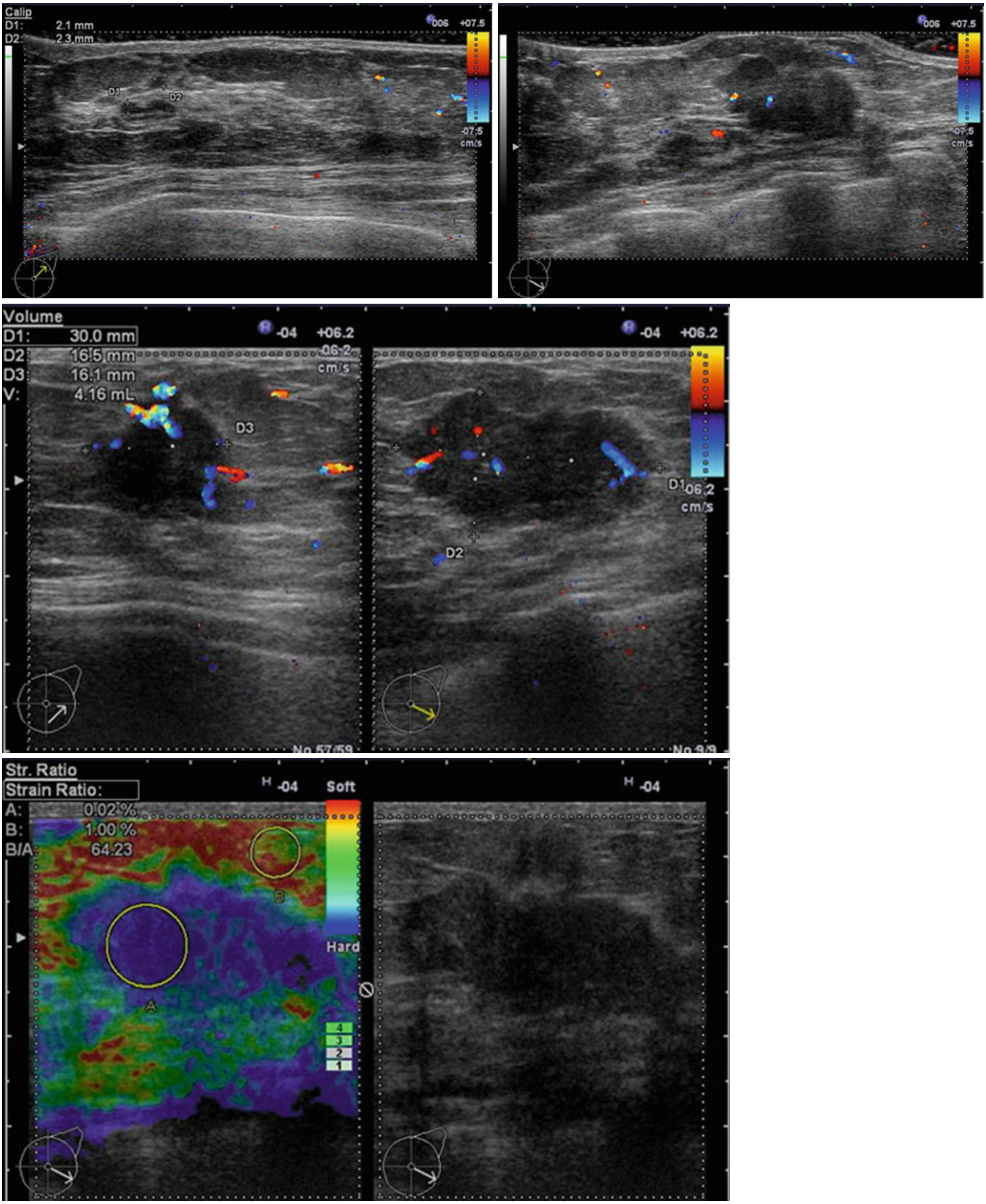


Fig. 8.20 Fourty-nine-year-old patient: presence of ductal-lobular hyperplasia with salient new vasculature is considered as a premalignant disease (upper), an "alarm sign" for possible associated malignancy, which must systematically be researched. At L:4:00 FBU illustrates a hypoechoic mass without significant acoustic shadowing, without hallo, the longer axis horizontal as in benign tumors. However, the irregular shape, with multilobulated contour, the Doppler malignant characters, and the sonoelastography scored 4 Ueno with high FLR are concordant with the presence of a medullary breast carcinoma, a rare tumor that demonstrates some pseudo-benign finding in classical ultrasound

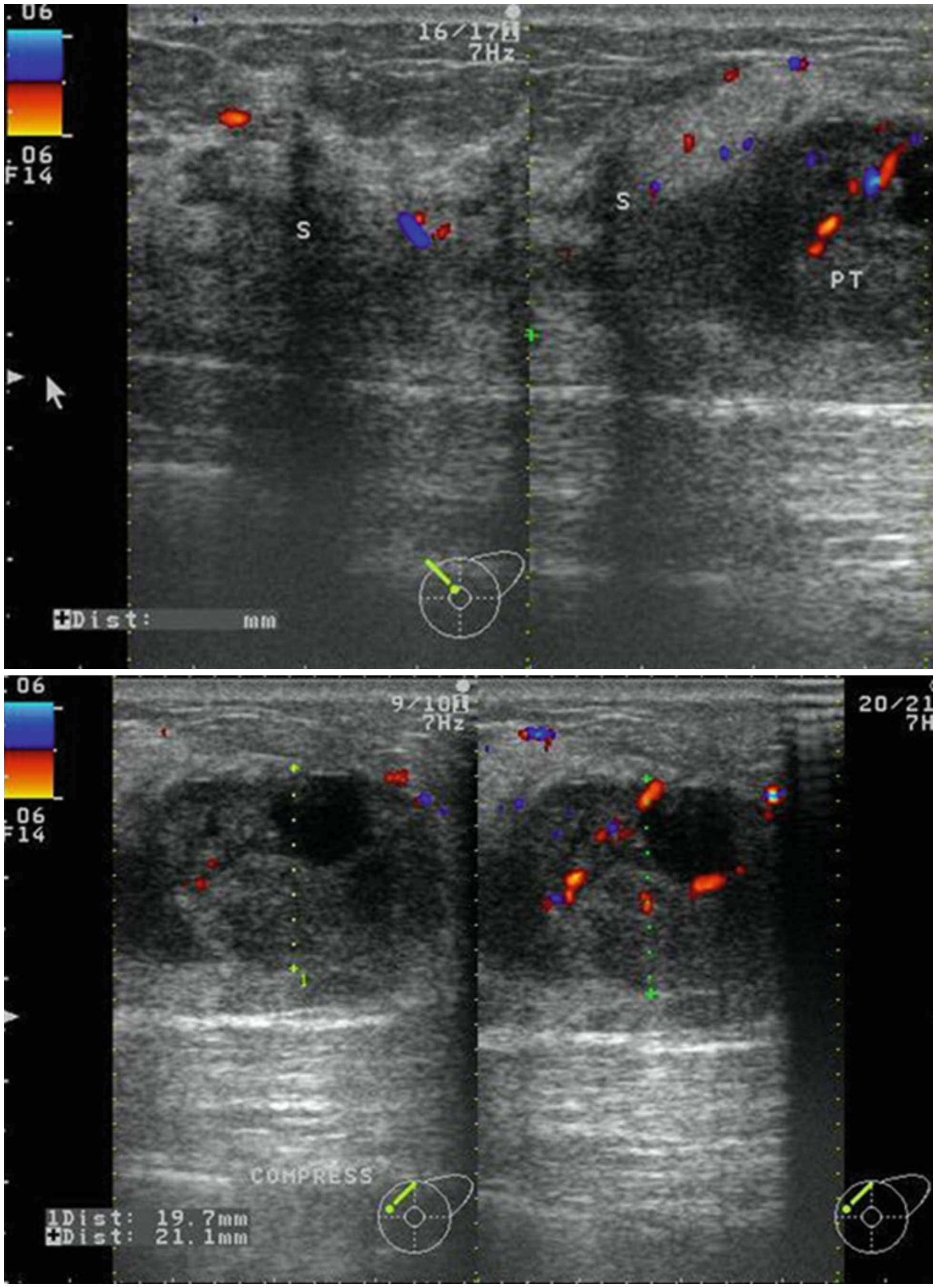


Fig. 8.21 Forty-year-old patient: palpable lump present for 2 years, enlarged in the last 3 months; Doppler DE visualizes the main pathological mass in the lobar periphery at L10:00, with pseudo-benign descriptors. and a cystic internal component, but with a few secondary centripetal lesions (s), and a new formation vasculature of malignant-type, originated from the internal mammary artery – multifocal cancer

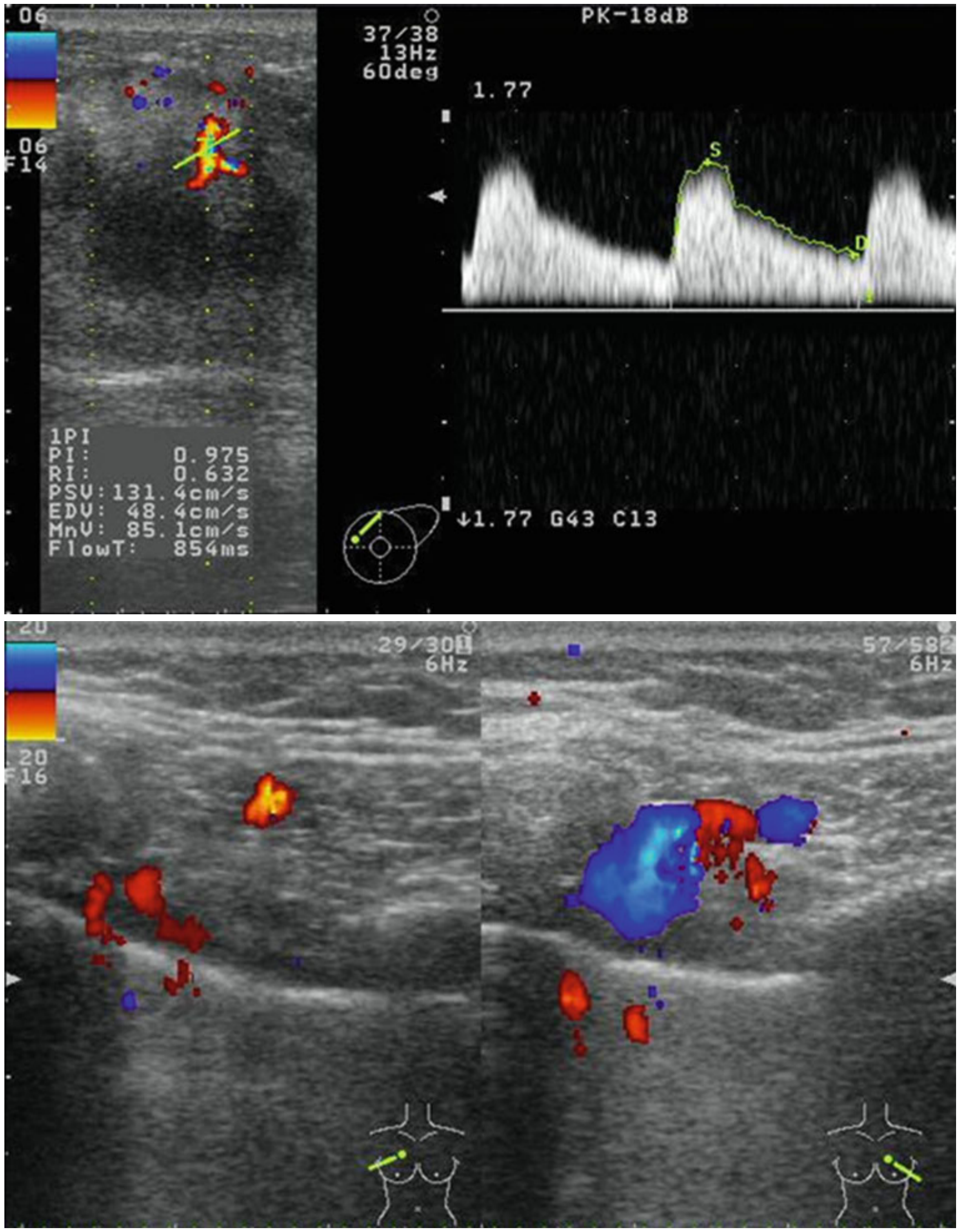


Fig. 8.21 (continued)

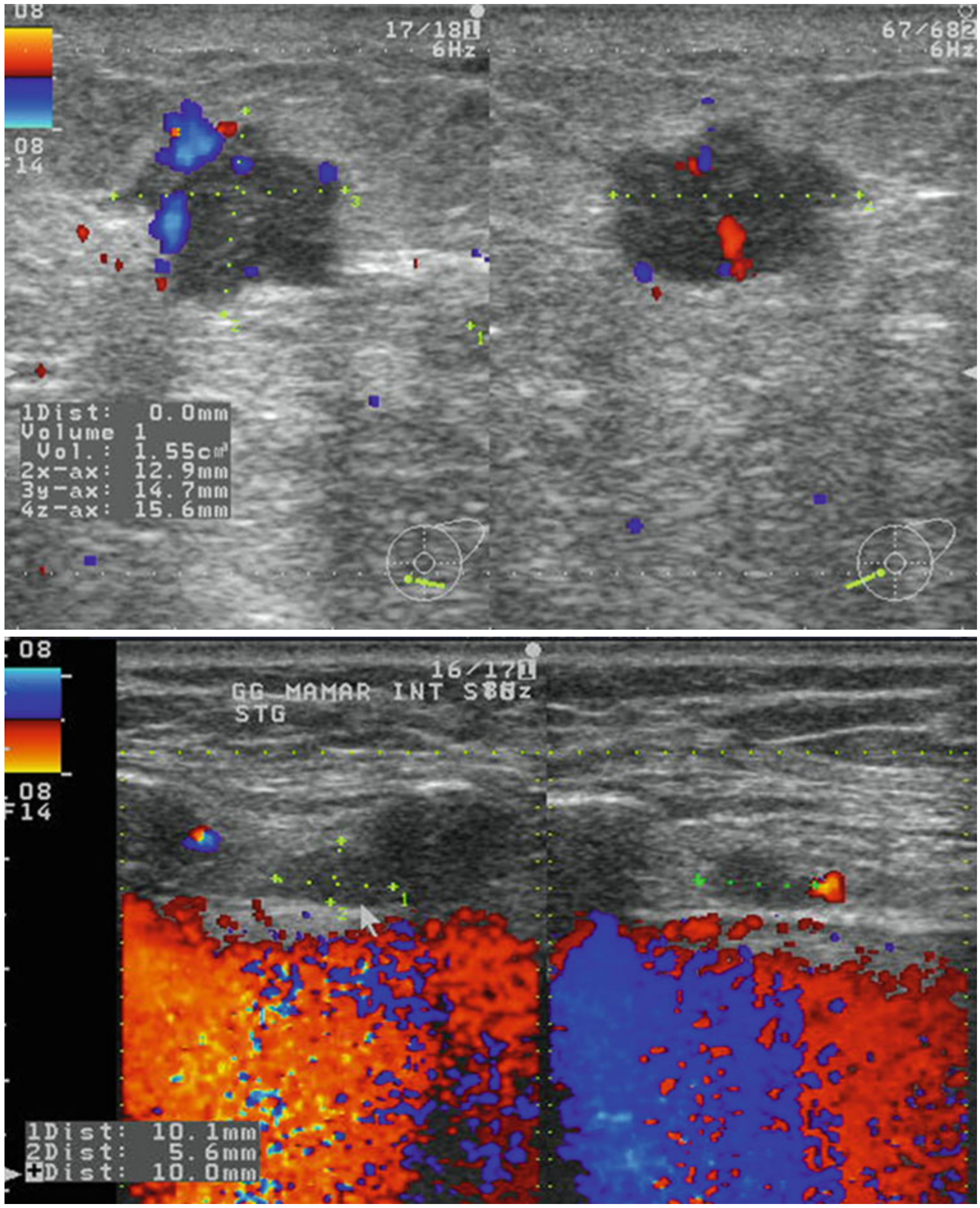


Fig. 8.22 Doppler DE: L8:30 "knobby" carcinoma less 2 cm in size, in a TDLU location, with angular malignant shape, hypoechoic but with posterior enhancement and marginal shadows (Kobayashi benign signs), and malignant new vasculature with incident plunging angle. The malignancy is confirmed by the pathological lymph nodes in the internal mammary chain (more frequent in inner quadrant cancers), and easy to explore by US [68], and axillary and subclavicular adenophathies (see Fig. 8.23). The absence of malignant shadowing and of the hallo is pathologically correlated with absence of any desmoplastic reaction, but the presence of multiple stations of adenophathies is suggestive of high-grade malignancy of this IDC

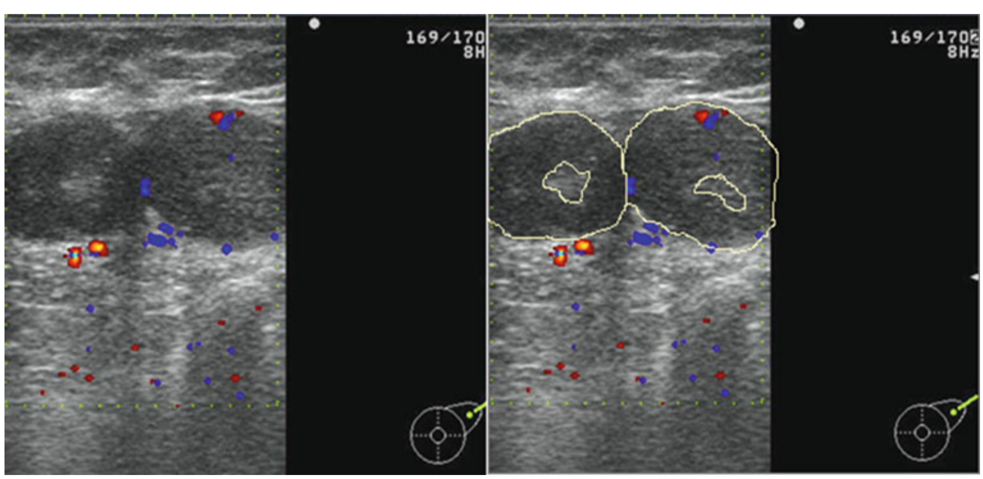


Fig. 8.23 The same case: A few axillary lymph nodes that are rounded-shaped and enlarged by increasing of the cortical hypoechoic thickness and with peripheral new vasculature are highly suggestive of lymph node metastasis

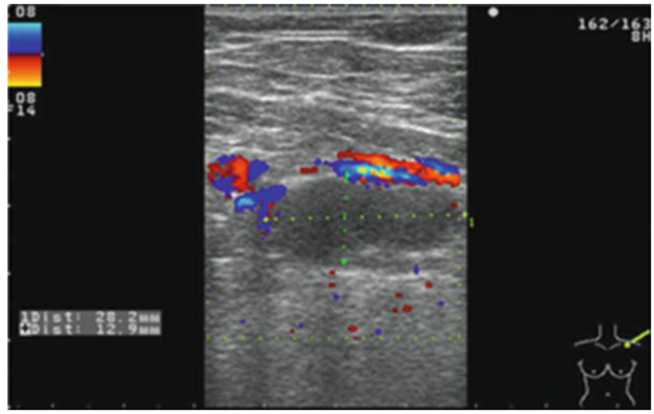


Fig. 8.24 The same case as in Figs. 8.22 and 8.23: supraclavicular lymph node with homogeneous hypoechoic internal texture and pericapsular vasculature. Differential diagnosis with other metastases or with leukemic lymphadenopathy is necessary when unknown breast cancer is present

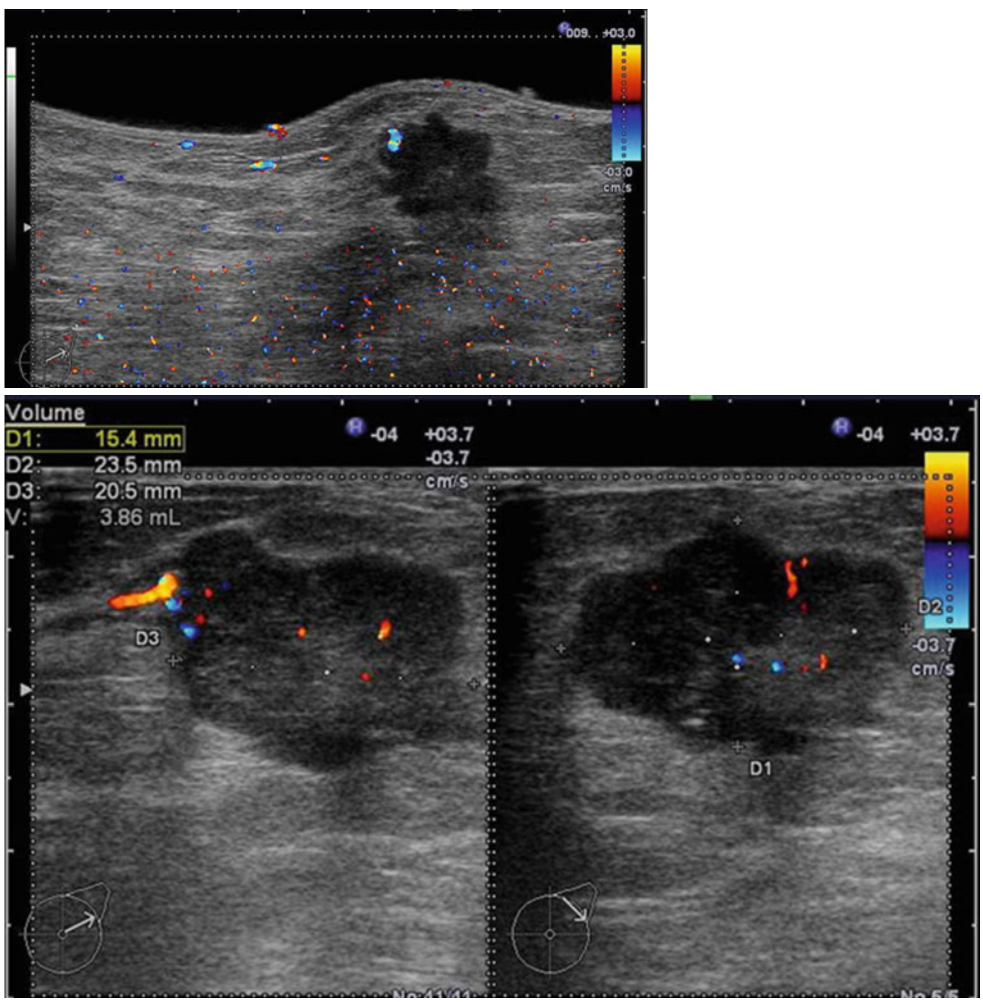
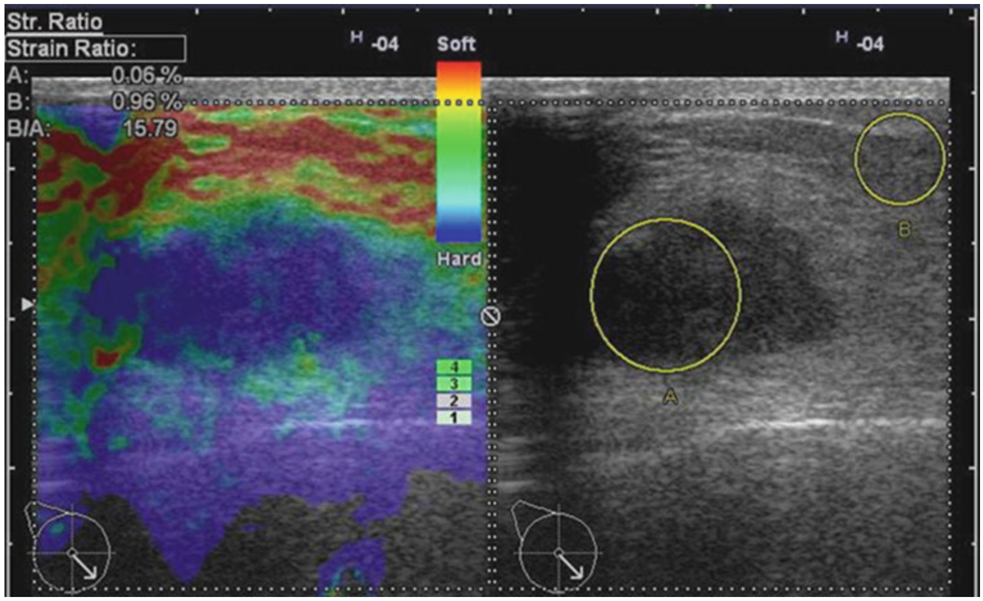


Fig. 8.25 L2:00 malignant mass with pseudo-benign features in 2D ultrasound in a 64-year-old patient, significant as it is a rare type of mucinous breast cancer. The benign findings, such as the largest diameter parallel with the skin and the posterior acoustic enhancement, are accompanied by the polycyclic shape, the incident angle of the plugging arteries, and the score 5 Ueno, all indicative of malignancy. Note the thickening of the emerging ducts with centripetal orientation and hypoechoic aspect, similar to the main tumor, indicative of intraductal spreading of the malignant cells. Sonoelastography and the salient vasculature confirm the associated ductal in situ malignancy, in concordance with the pathological report – “knobby” cancer

Fig. 8.25 (continued)



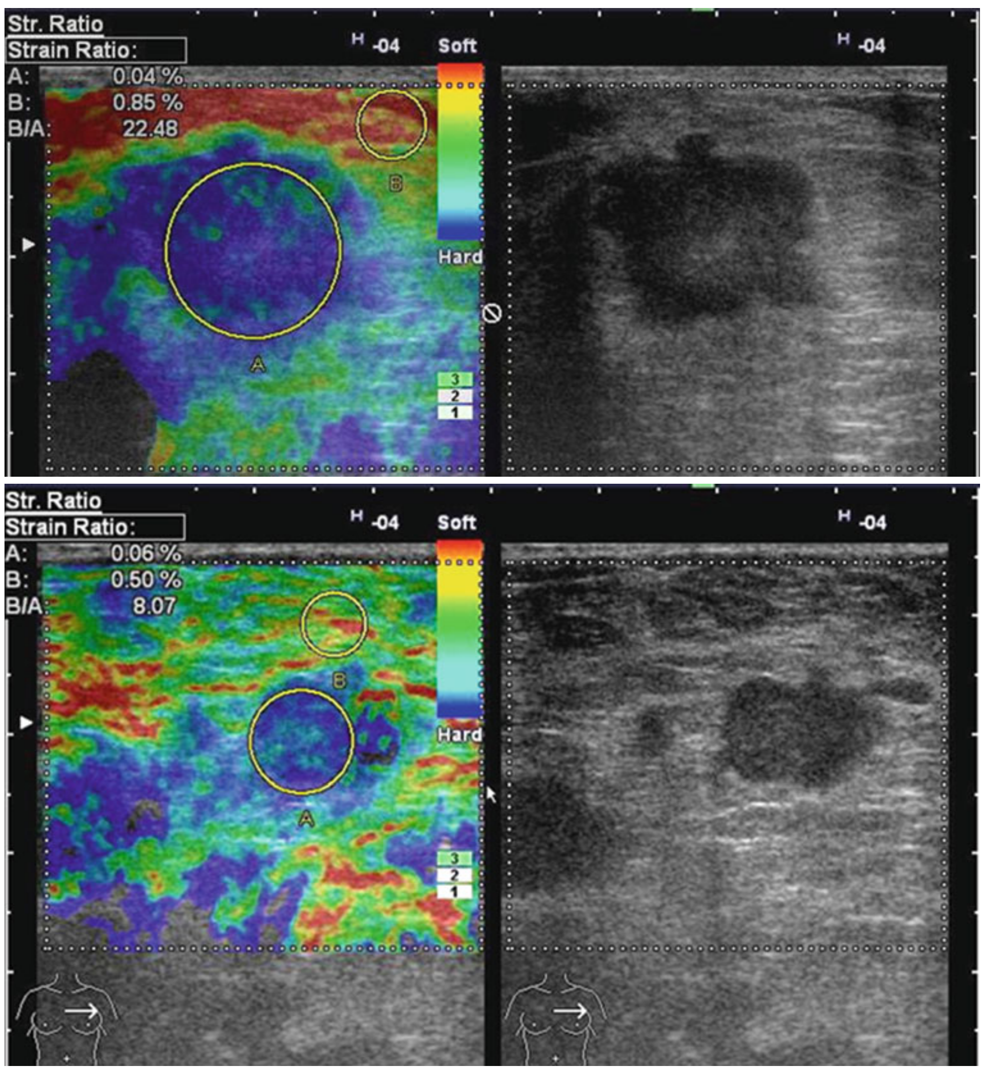


Fig. 8.26 The same case as in Fig. 8.25: note the similarity between the main tumor (*above*) and the multiple axillary lymph nodes metastases (below): polycyclic shape, posterior acoustic enhancement, score 4–5 Ueno with increased FLR

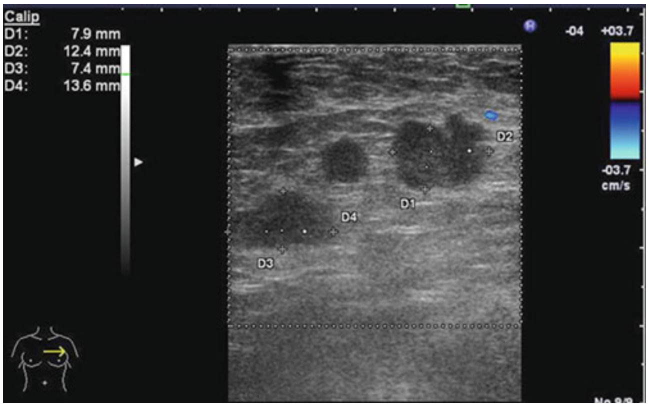


Fig. 8.26 (continued)

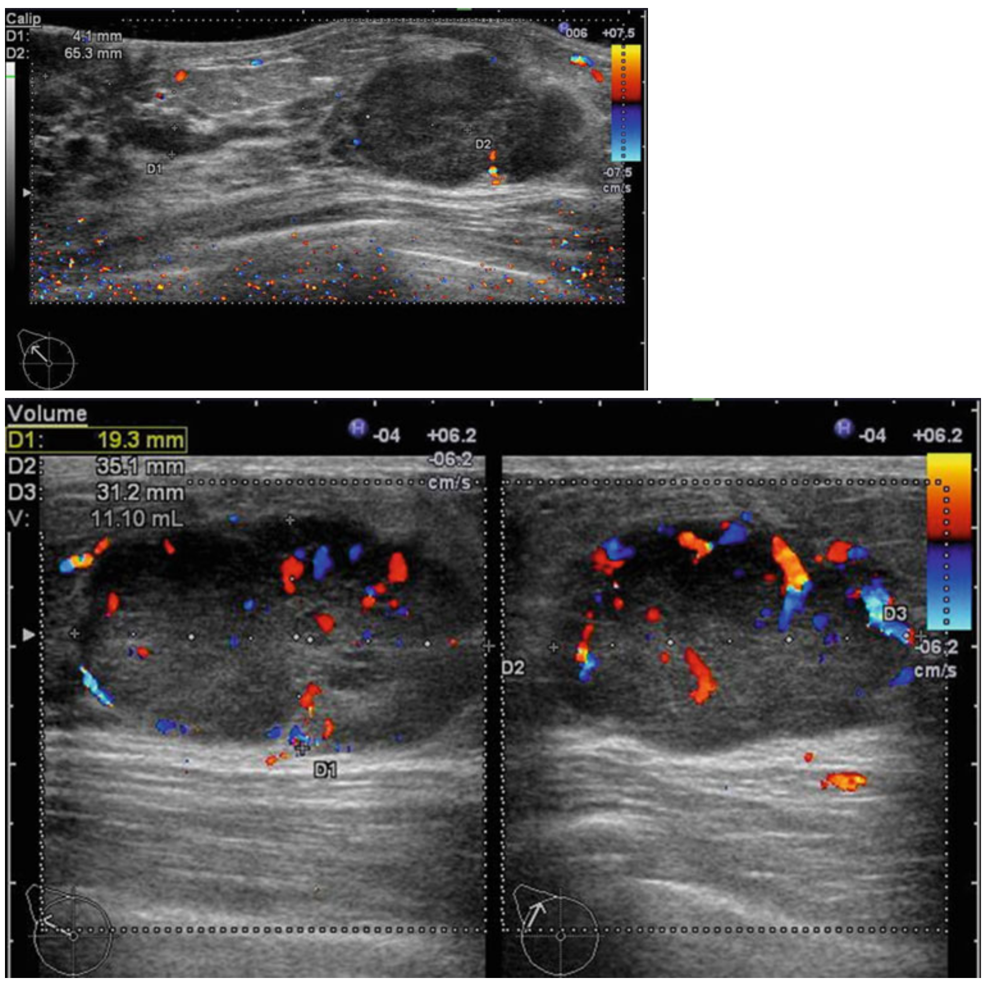
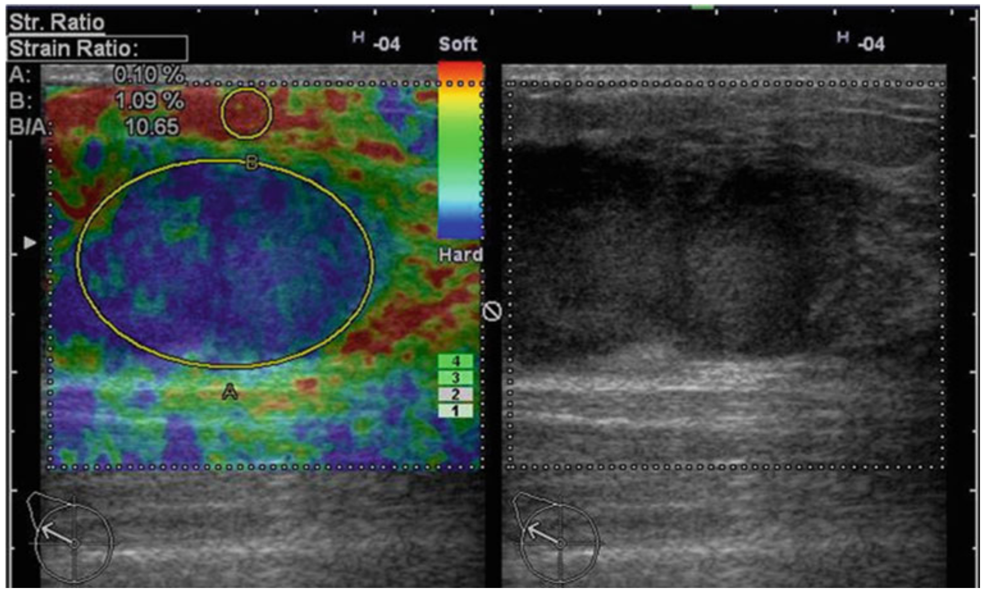


Fig. 8.27 Rare tumor in a 39-year-old patient with a pseudo-benign aspect after the classical criteria of Stavros. Doppler mapping is highly suggestive of malignancy, concordant with the score 4 Ueno and increased FLR over 10.00. The benign posterior features after Kobayashi show the aspect of a mucinous breast cancer

Fig. 8.27 (continued)



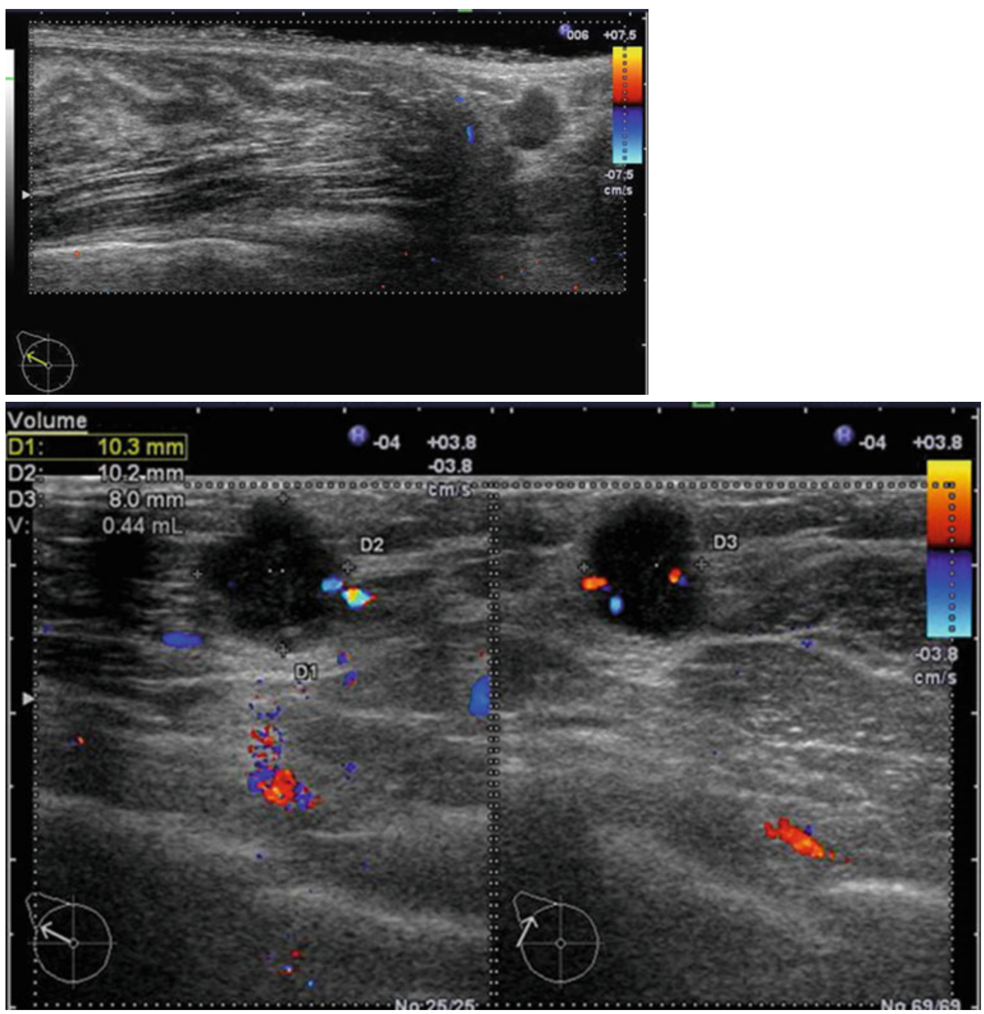
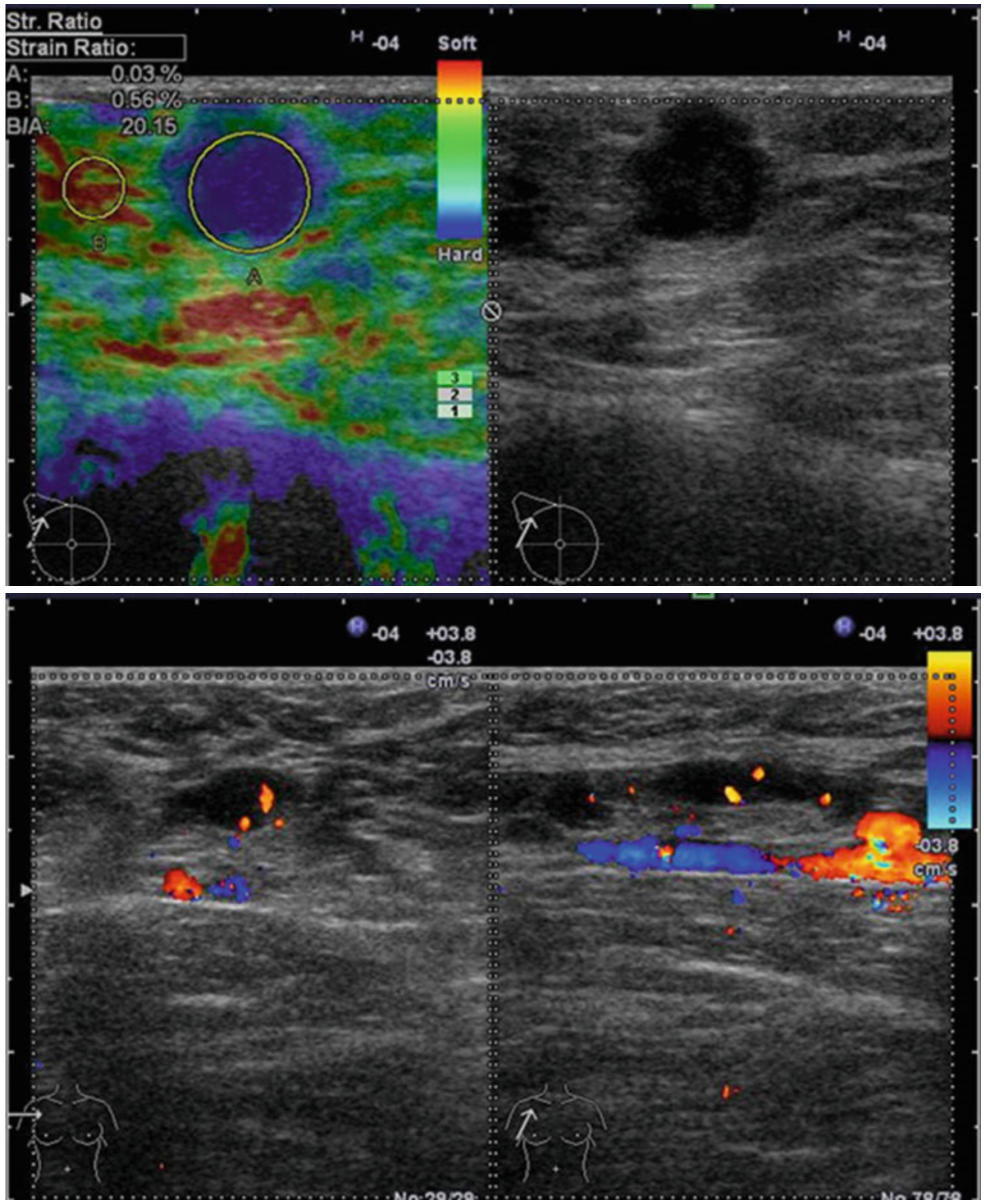


Fig. 8.28 Rare, small 10-mm tumor with both benign and malignant features in a 22-year-old woman. The score 4 Ueno is significant for rapid growth without desmoplastic reaction, concordant with an axillary sentinel node demonstrating thickened node cortex and with salient vasculature (bottom). The highly aggressive tumor is concordant with an undifferentiated cancer

Fig. 8.28 (continued)



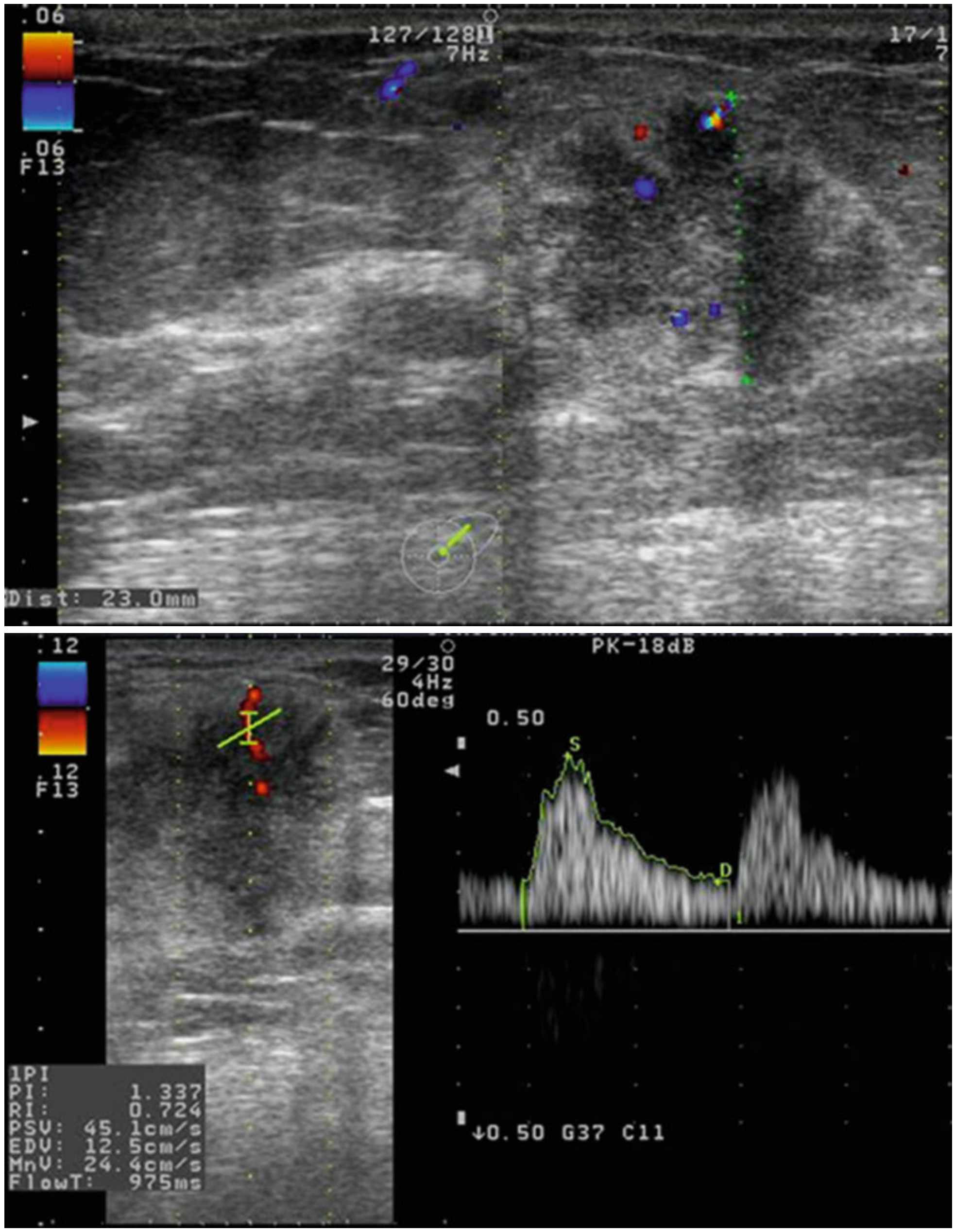


Fig. 8.29 Patient is 54 years old: 4D ultrasound acquisition of a "stellate" cancer with ductal extension. Note the illustration of the pathological architecture, despite the low resolution of the actual 4D transducersD dedicated improvements of the devices are mandatory

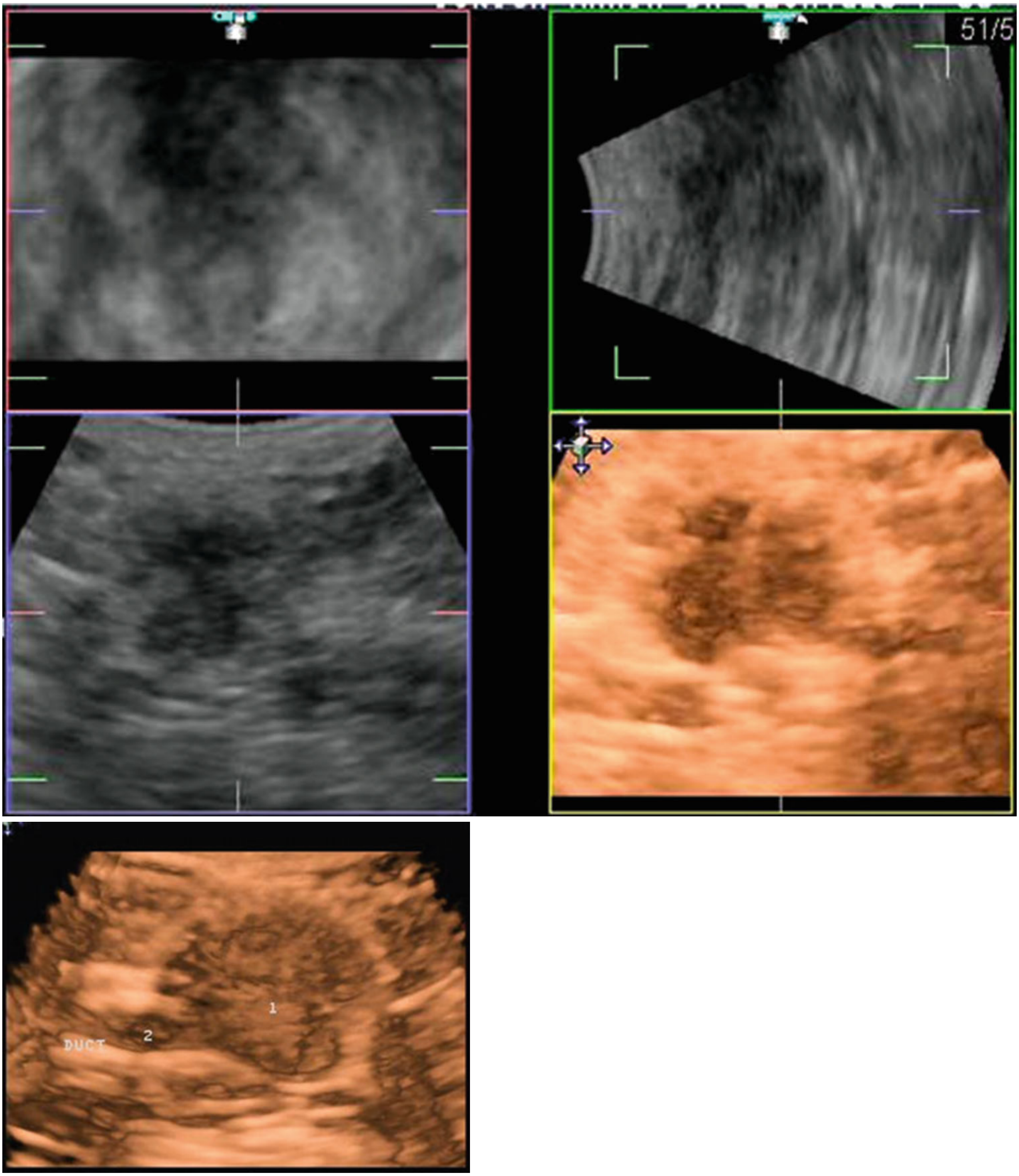


Fig. 8.29 (continued)

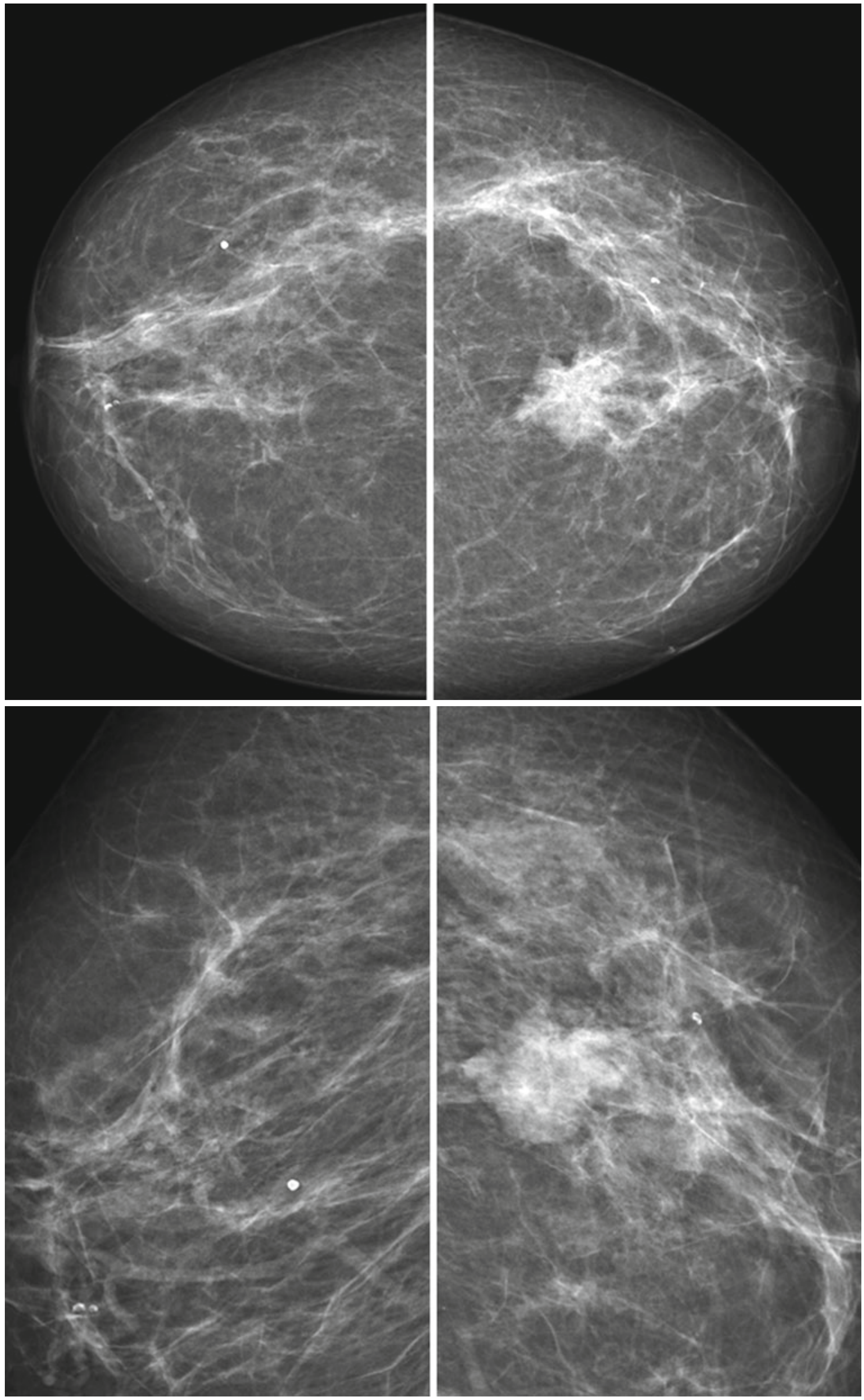


Fig. 8.30 "Stellate" cancer aspect on mammography. The digital mammography finally accepted after the improvement of the resolution cannot pass the limits of an analogue mammography, due to the radiological laws of absorption of the X-rays and the overlapping of the different tissues distributed in multiple layers of the whole breast. Thus, the gray-scale representation cannot distinguish the small associated lesions

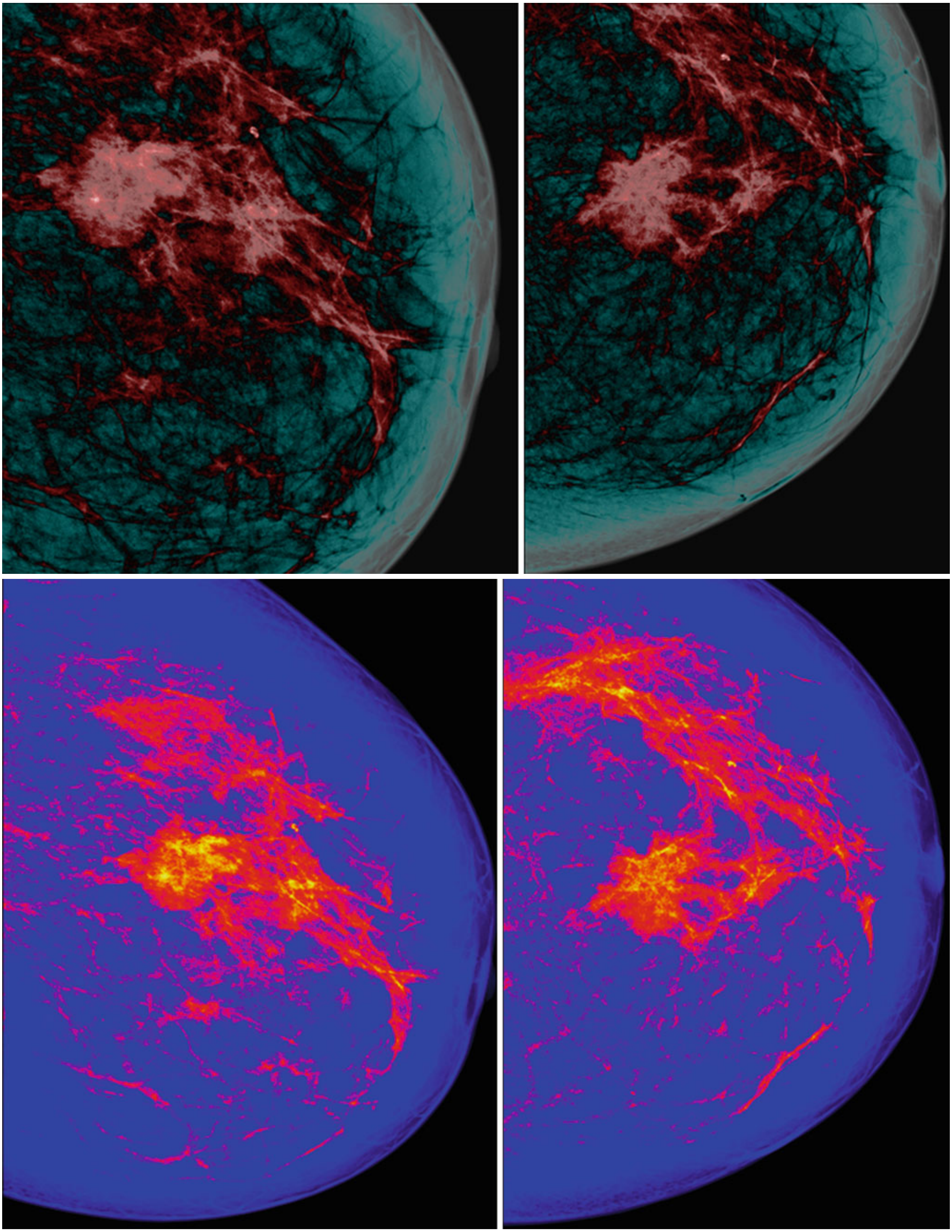


Fig. 8.31 The same case as in Fig. 8.30: by applying the Color Lookup technique, digital mammography allows better differentiation of the tissular densities, thus a multifocal breast cancer may be more easily suspected, changing the estimation of the extension of the malignancy and thus of the staging

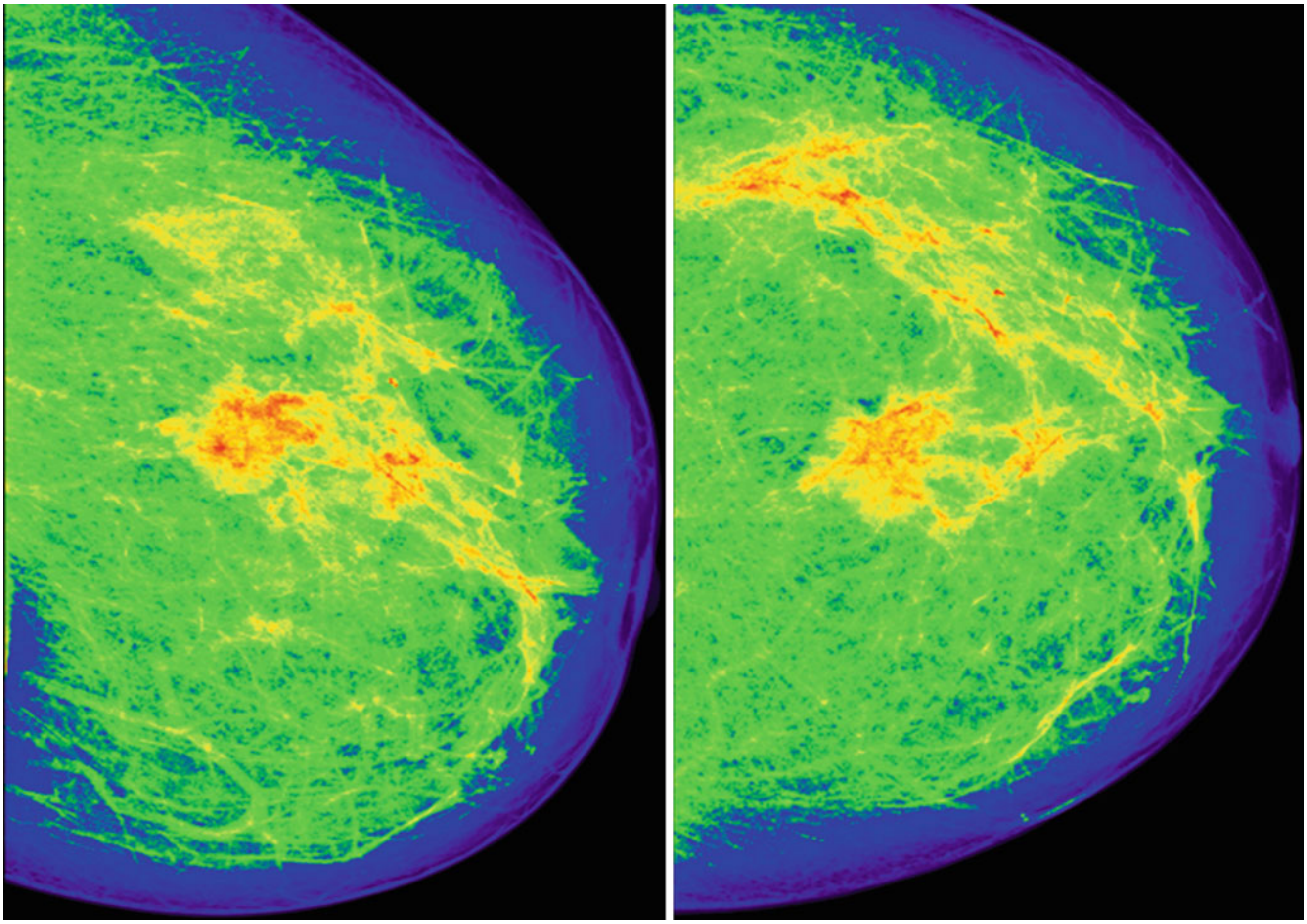


Fig. 8.32 The same case, different Color Lookup application, demonstrates the secondary centripetal lesion with increased density, and the upper-outer quadrant with increased diffuse glandular thickening, with radial orientation; however, the precise anatomy cannot be visualized, nor the precise location of the suspect masses. A more precise location, by eliminating the overlapping of the tissues, could be obtained by tomosynthesis, but the ductal branching anatomy remains unapparent and the differential diagnosis of multifocal from multicentric cancer is based on an arbitrary definition (different quadrants or more than 5 cm distance between the multicentric lesions)

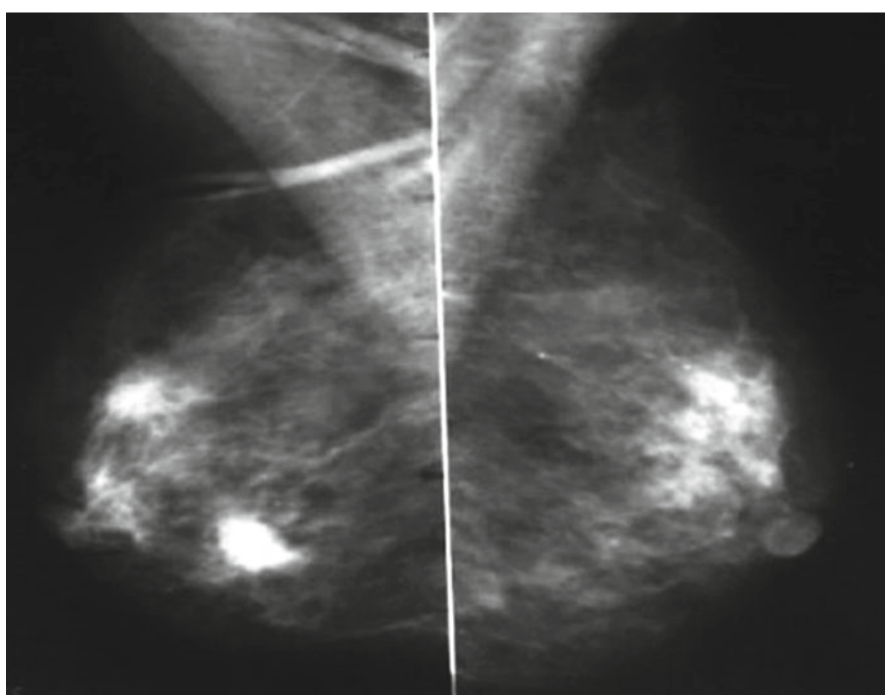


Fig. 8.33 Patient is 88 years old: mammography is first intention examination in the case of a patient with a sister with mucinous carcinoma confirmed 10 years earlier, illustrates in the MLO (mediolateral oblique view) incidence (CC (cranial caudal view) not shown): a mass with irregular borders but well delineated in the right lower (inner) quadrants, classified as BI-RADS category 4 and two spiculated masses in the right upper (outer) quadrants, classified as BI-RADS category 5

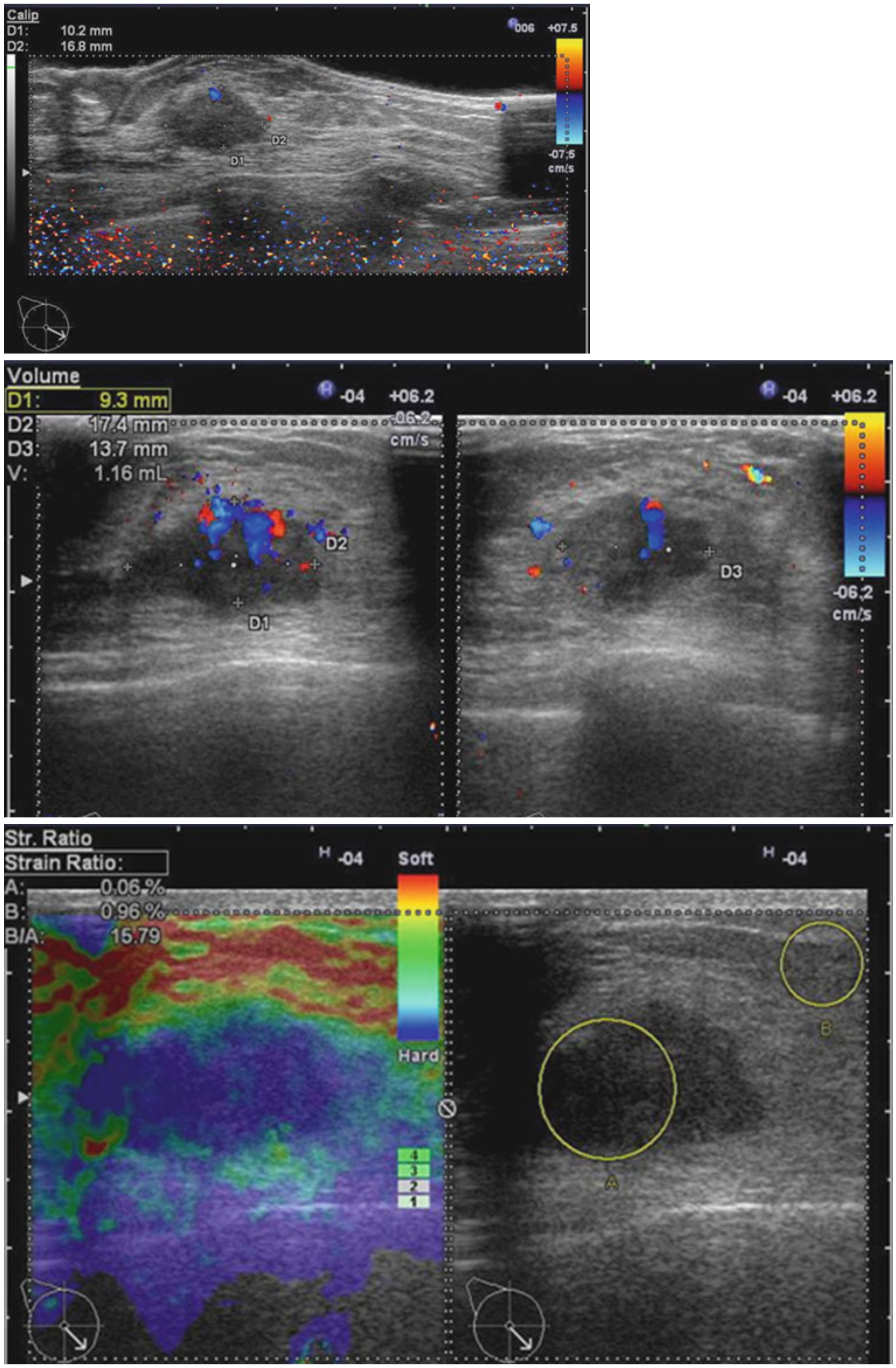


Fig. 8.34 Patient is 88 years old, same case as in Fig. 8.33: the lump in the lower-inner quadrant in FBU presents some benign 2D features (horizontal long axis, posterior acoustic enhancement) associated with malignant characters: hypoechoic, irregular borders, malignant vascular type, sonoelastogram of score 4 Ueno that suggests the absence of the stromal reaction and high FLR of 15.79, concordant with the pathological report of mucinous carcinoma. Ultrasound BI-RADS category 5

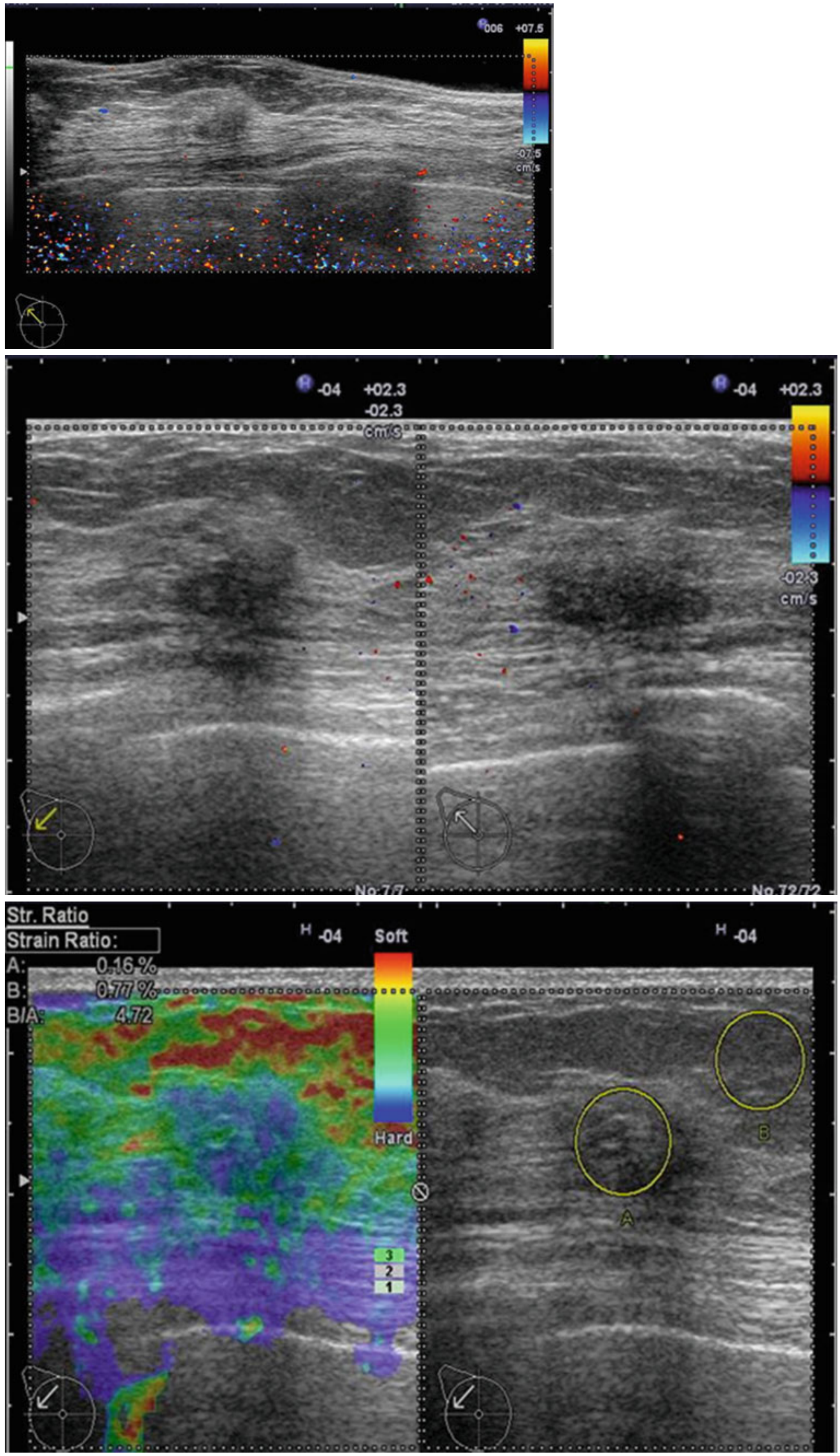
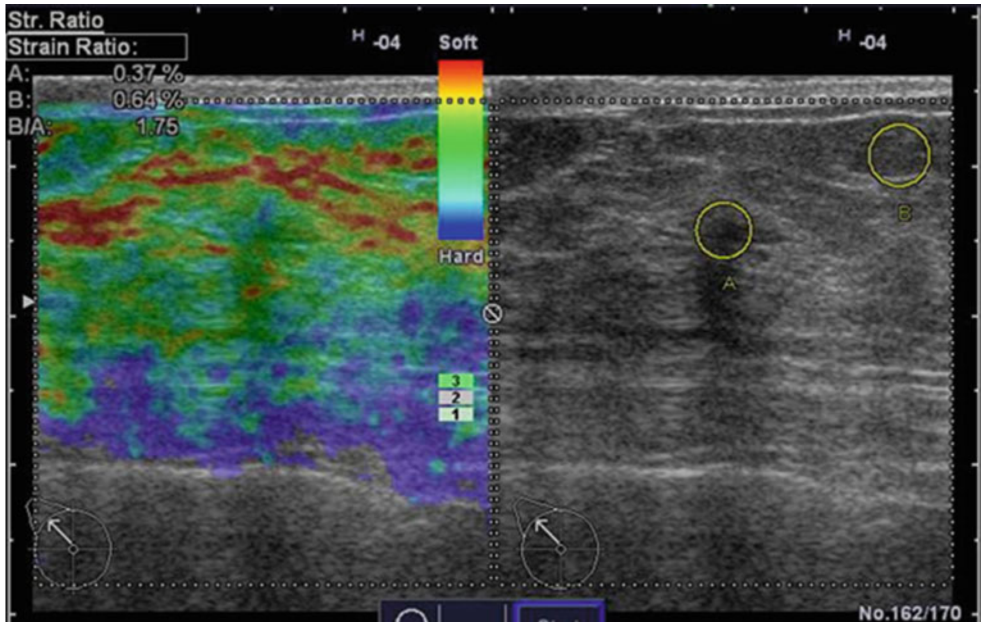


Fig. 8.35 Patient is 88 years old, same case as in Figs. 8.33 and 8.34: the upper-outer mammographic larger mass presented inhomogeneous ultrasound aspect, posterior acoustic shadowing, less vascular signal, and score 3 Ueno with borderline FLR of 4.72. The small mammographic spiculated mass with the same ultrasound features presented the score 2 Ueno with benign FLR of 1.76, despite the acoustic shadowing. These masses represented sclerosing adenosis

Fig. 8.35 (continued)



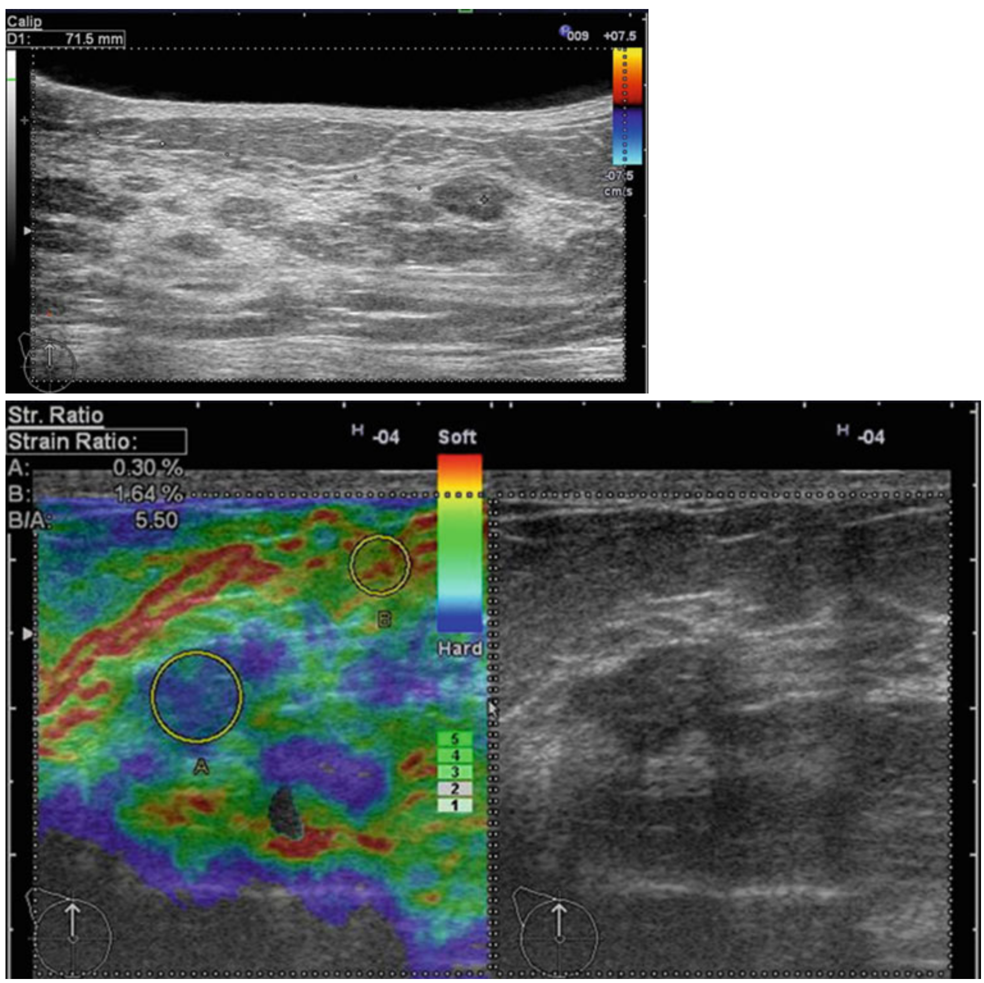
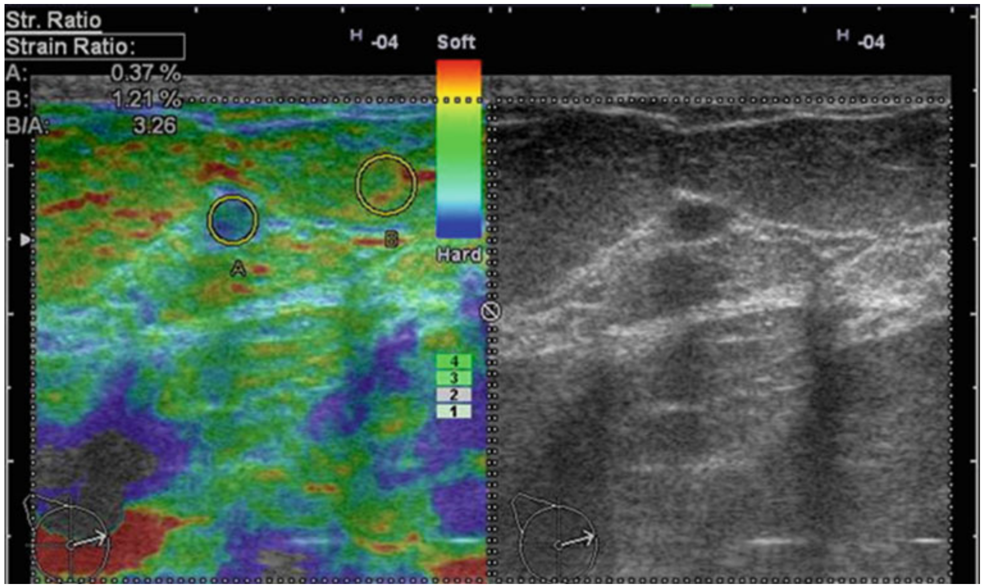
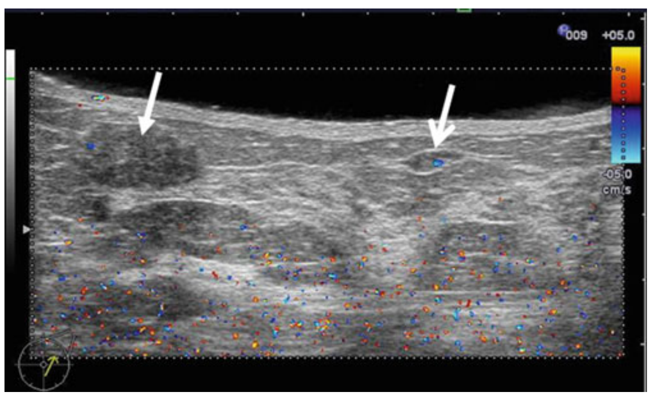


Fig. 8.36 A screening FBU was performed on a 43-year-old patient: bilateral nodular suspect lesions, with polycyclic shape, located in TDLU, with moderate new formation vasculature, scored 3 and 4 Ueno with FLR over 5.00. The connection with some thickened ducts is significant. In the right breast, the more important findings located at 12:00 and 2:30 radiuses are apparent as multicentric lesions

Fig. 8.36 (continued)





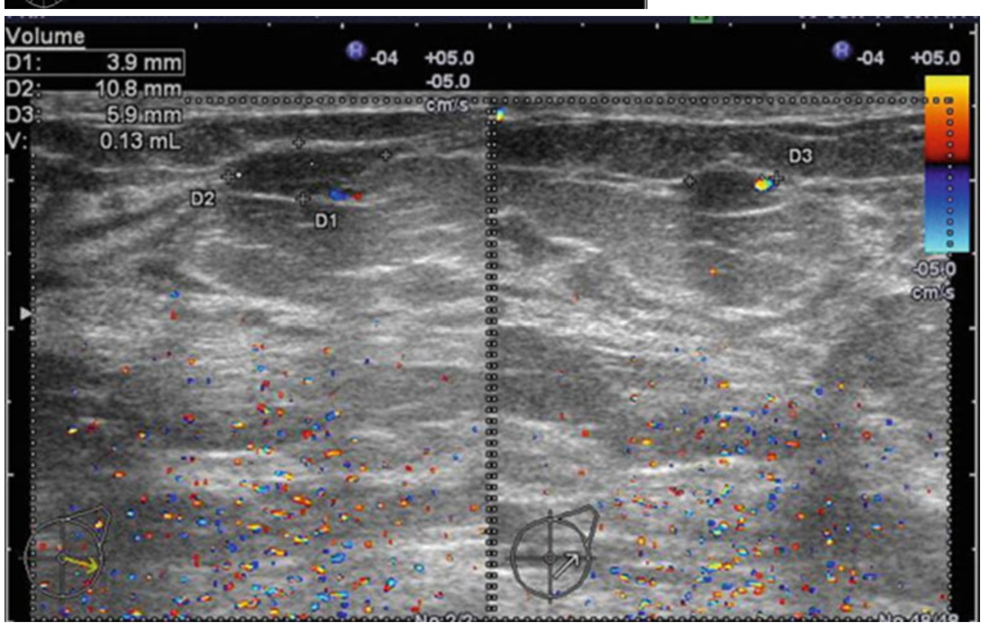
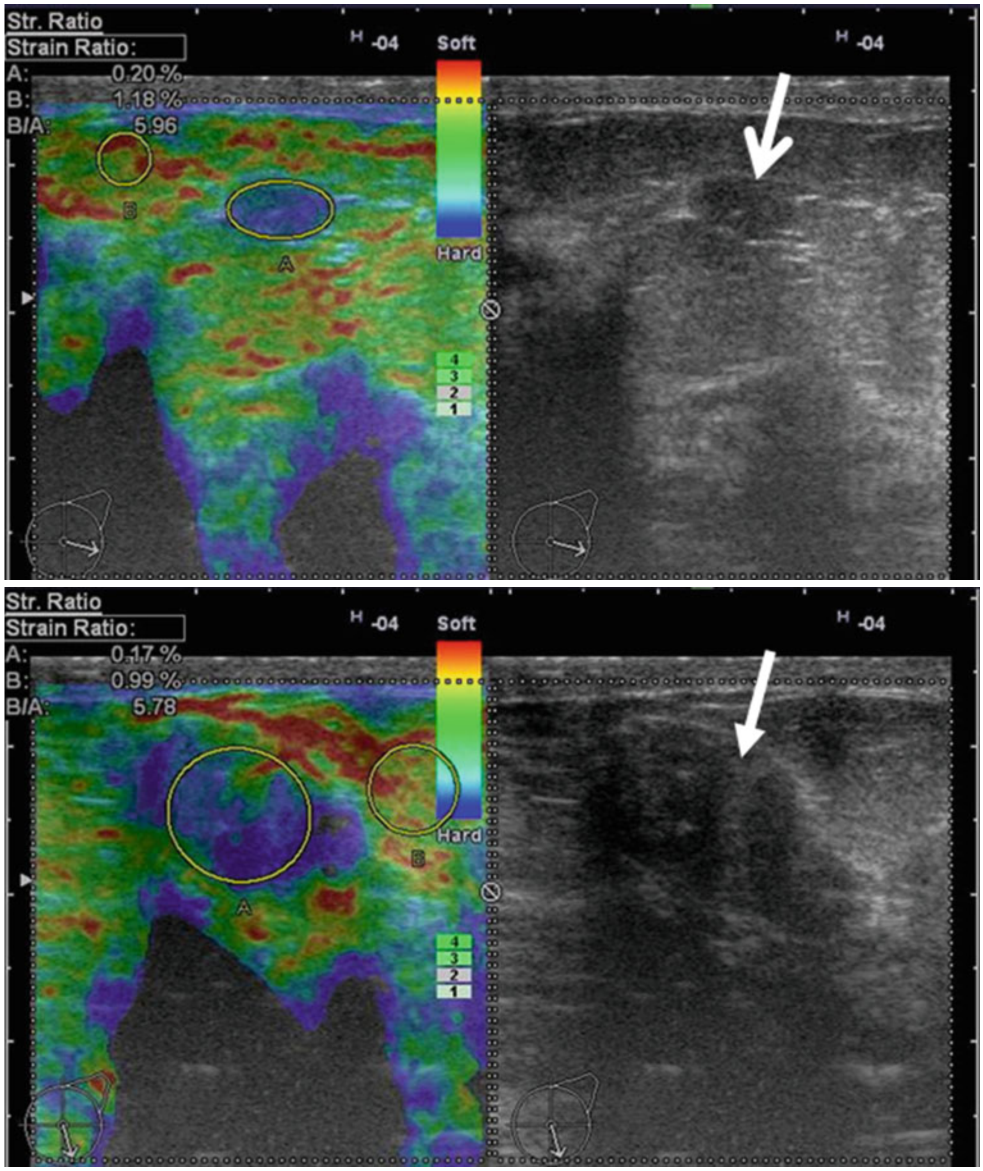


Fig. 8.37 Patient is 43 years old, the same case as in Fig. 8.36: the antiradial scan with the long probe illustrates a few lesions at L4:00 and L5:30 radius, with ductal evident interconnection, thus multifocal cancer (*white arrows*). Because of presence of other small, borderline lesions, a complementary breast MRI was recommended for the full cartography and therapeutical decision making (bilateral multicentric and multifocal cancer)

Fig. 8.37 (continued)



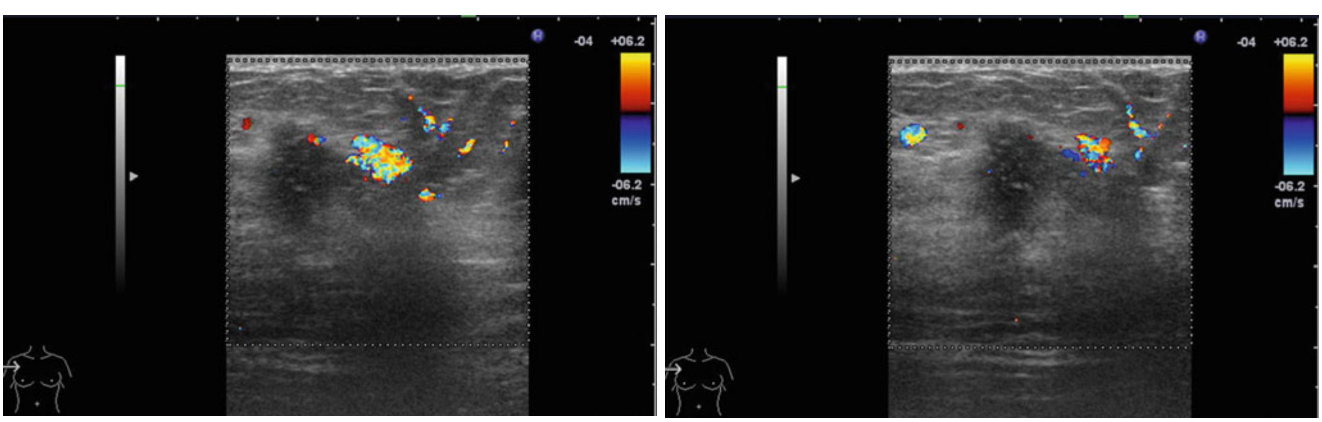


Fig. 8.38 Patient is 53 years old with breast cancer in the axillary prolongation of the R mammary gland (the Spence tail). The tumor architecture, type of vasculature, and extension along Cooper's ligaments differentiate this from the axillary lymphadenopathy

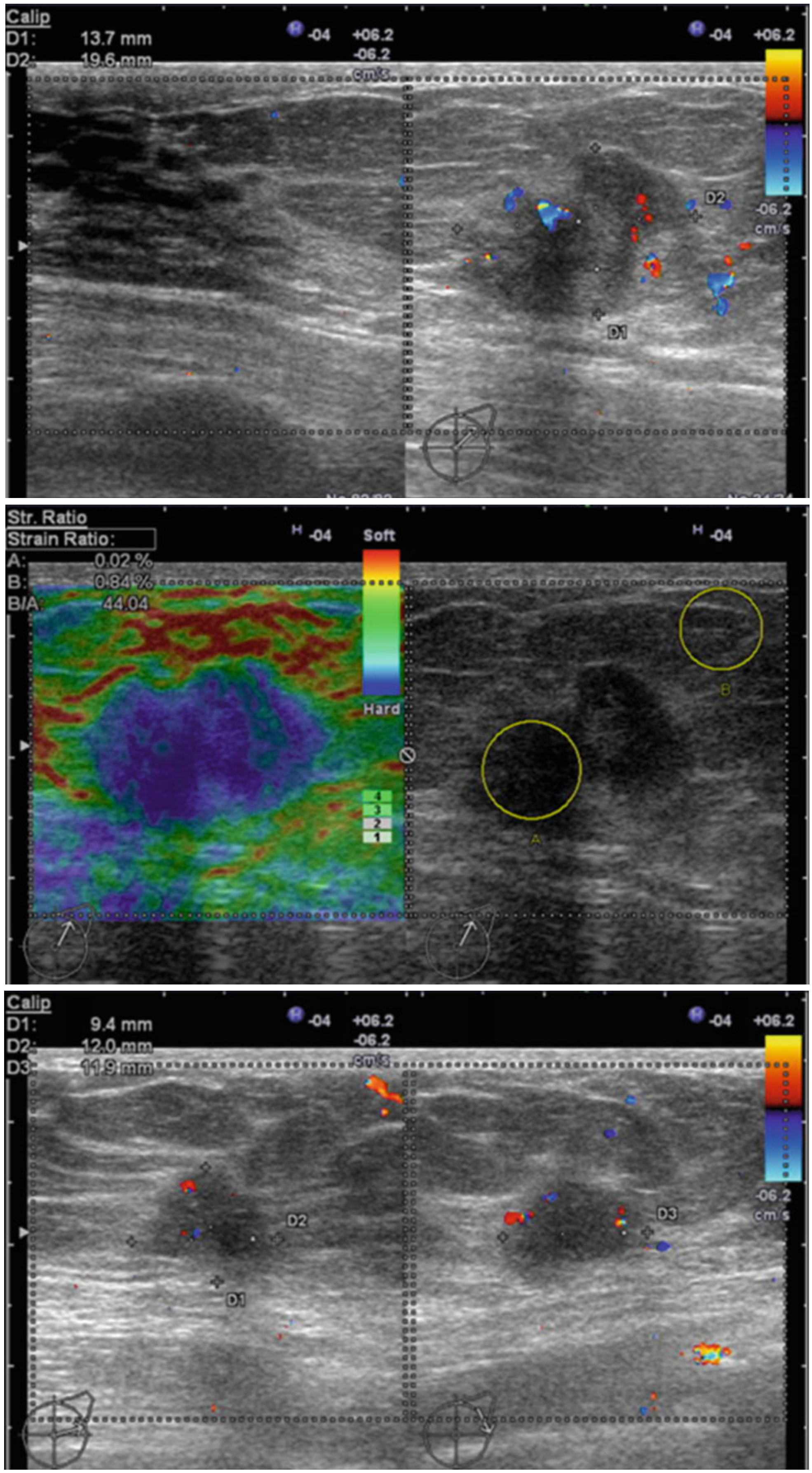
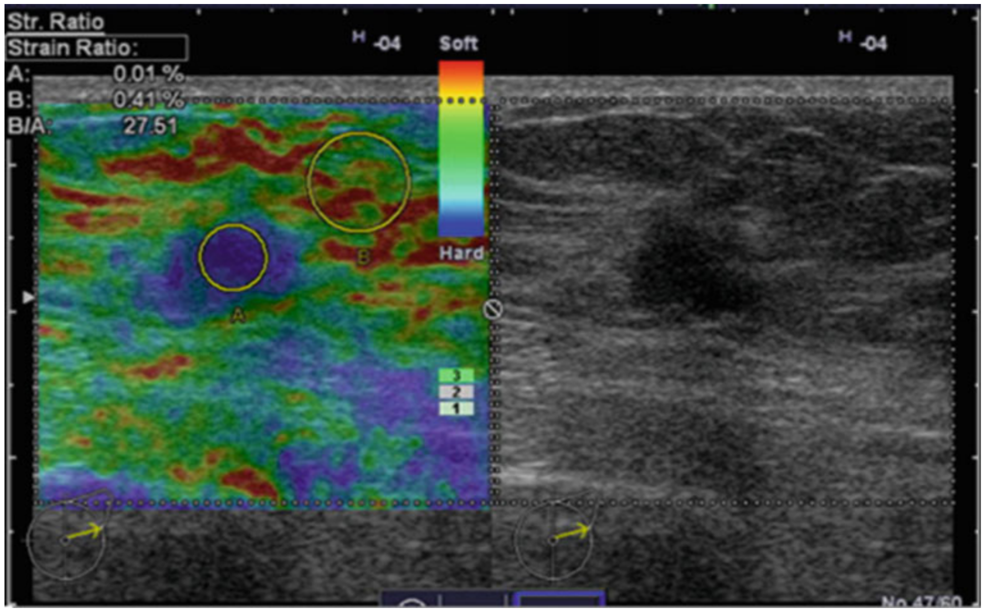


Fig. 8.39 Patient is 55 years old with L1:00 (double lesion) and L2:00 multifocal cancer, score 4 Ueno, ultrasound BI-RADS category 5

Fig. 8.39 (continued)



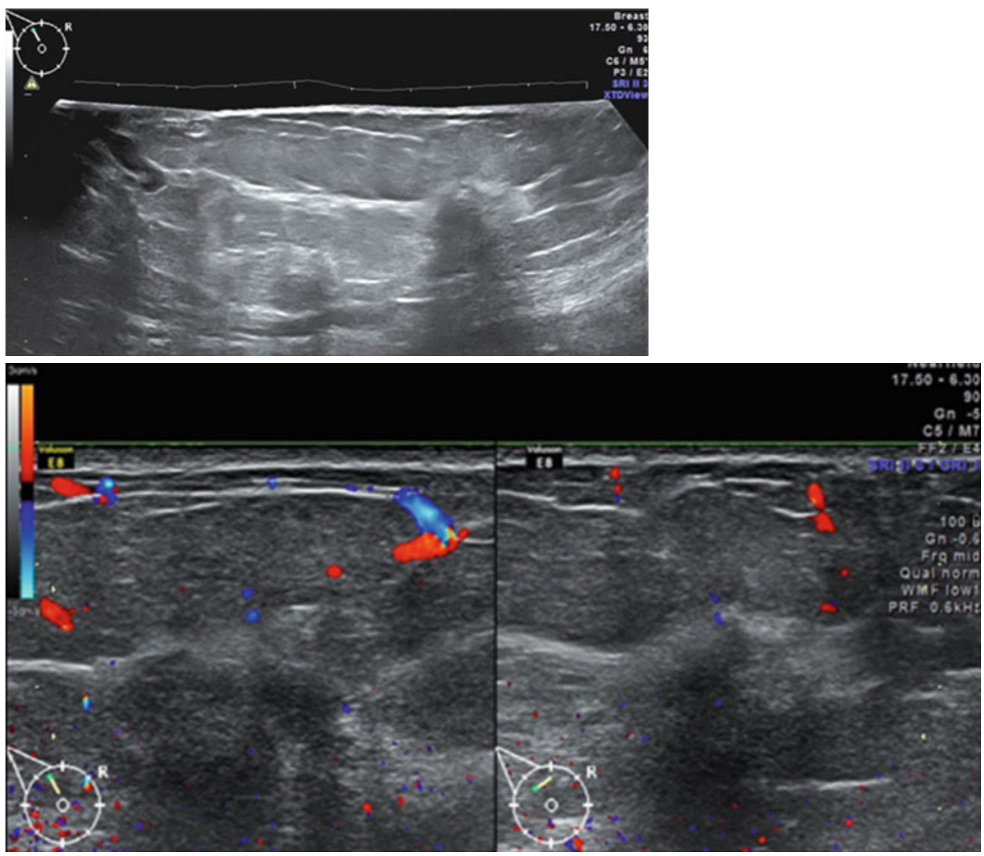


Fig. 8.40 Patient is 64 years old with fatty breasts and glandular atrophy, however, the lobar anatomy is recognizable. Multifocal breast cancer in R11:00 with new formation vasculature and score 5 Ueno. Note the central ductal-ampullary ectasia

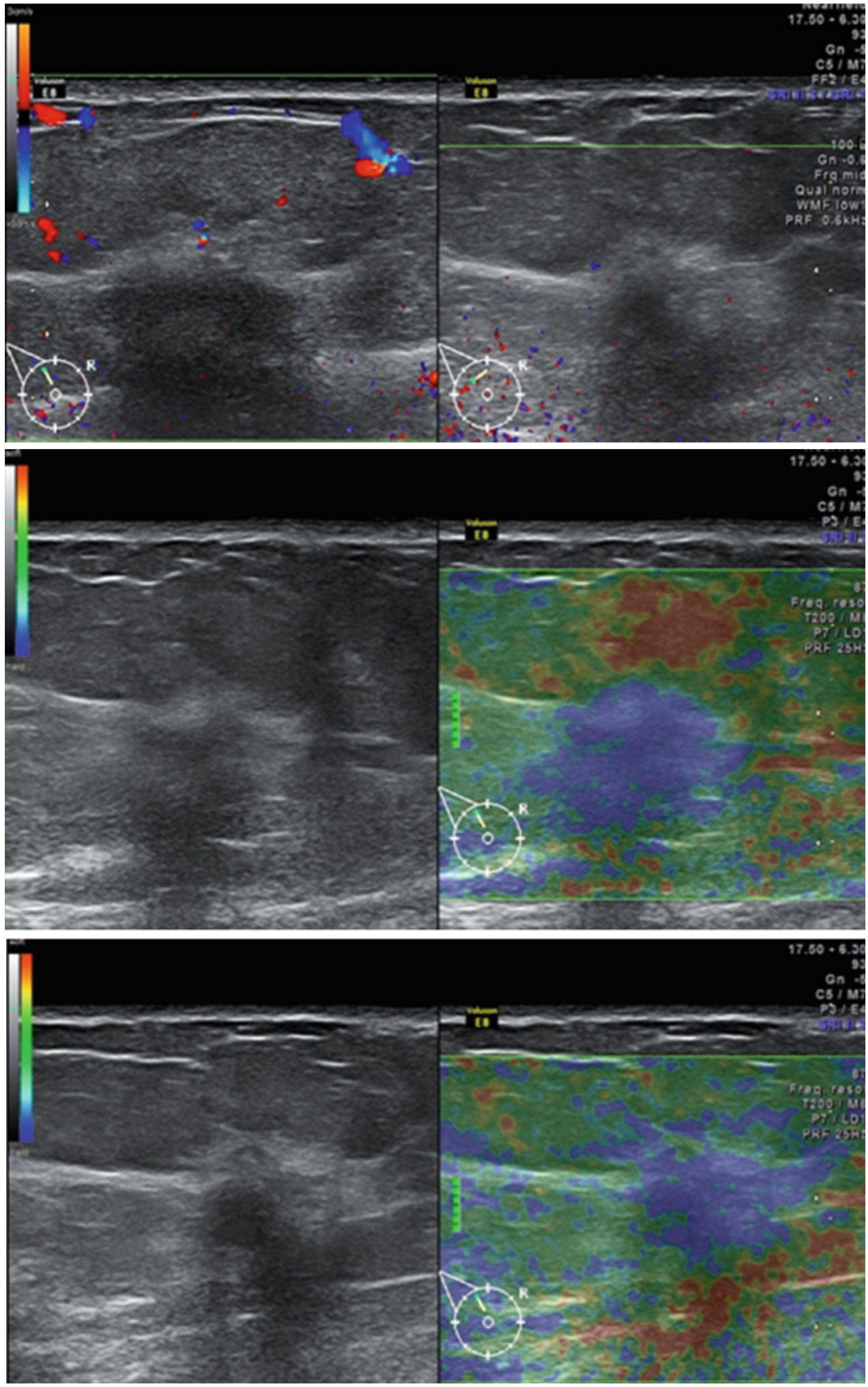
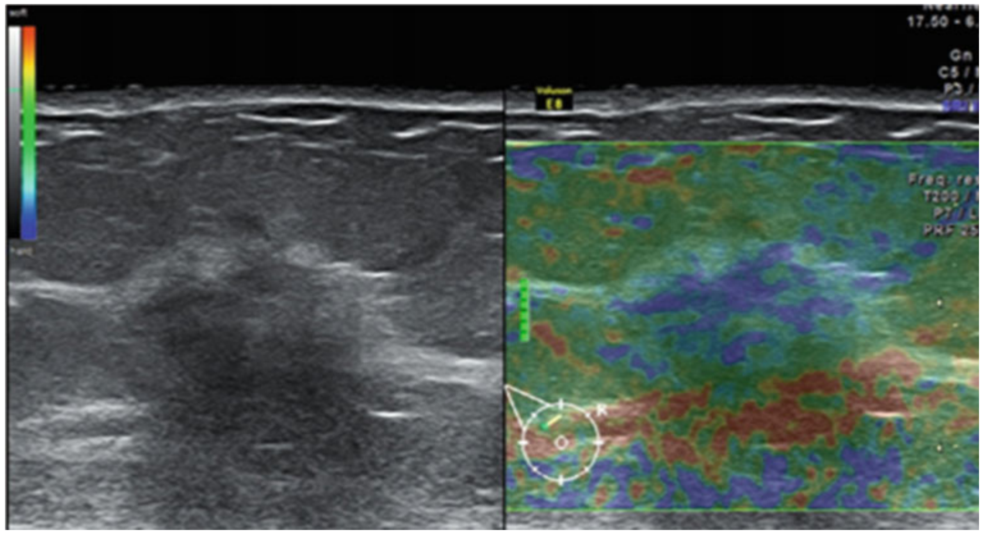


Fig. 8.40 (continued)

Fig. 8.40 (continued)



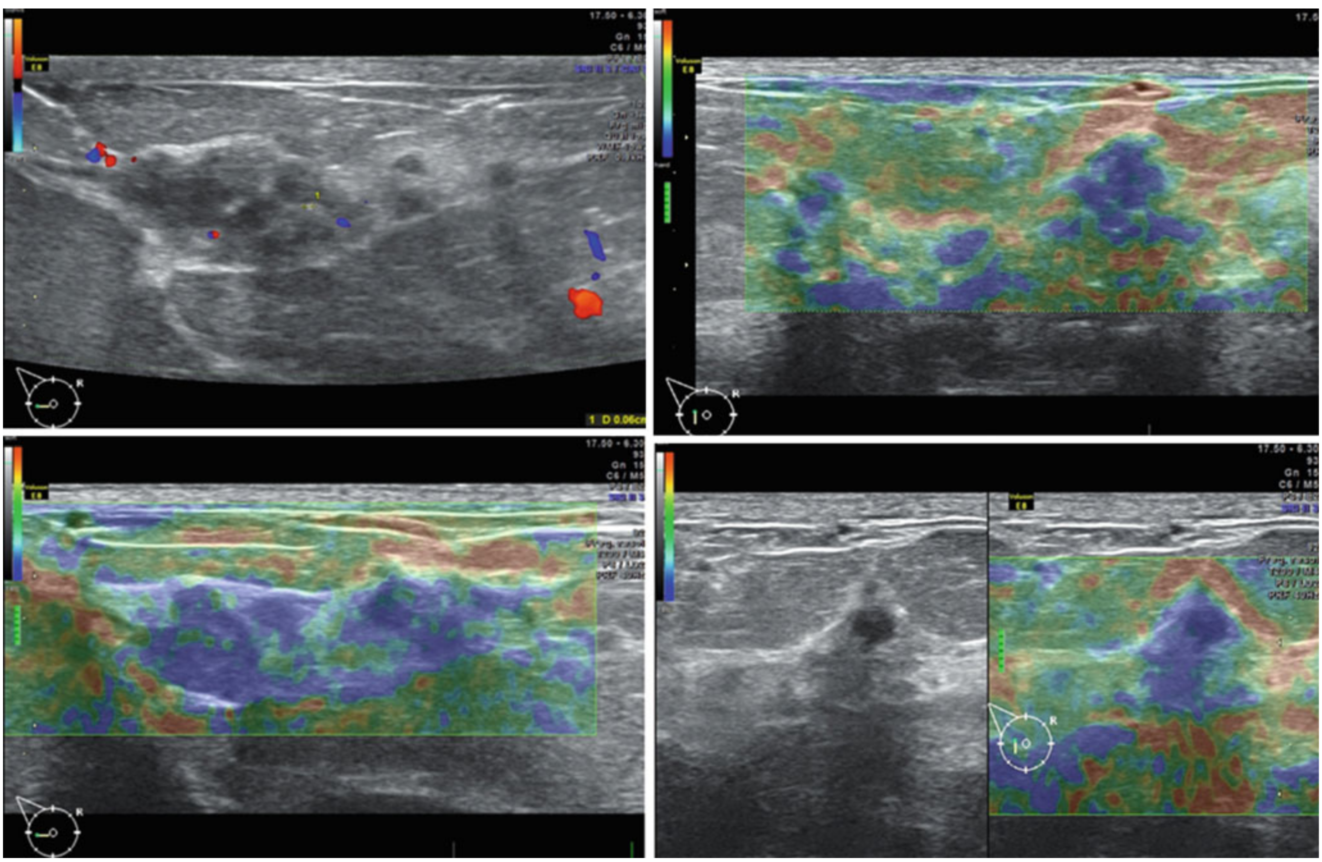


Fig. 8.41 FBU in a 42-year-old patient, after many miscarriages; lobar-type breast cancer, or diffuse, with typical shape of the lobe in the radial scan and with salient multifocal lesions in the anti-radial scans. Sonoelastography is mandatory, with scoring 4 and 5 Ueno, but the new vasculature just moderate. The axillary lymph nodes of benign-type, in the illustration with normal or hypoechoic hilum (*arrows*) and normal cortex, vasculature, and strain, are arguments for large, lobar extension of the malignancy but with reduced distant invasiveness

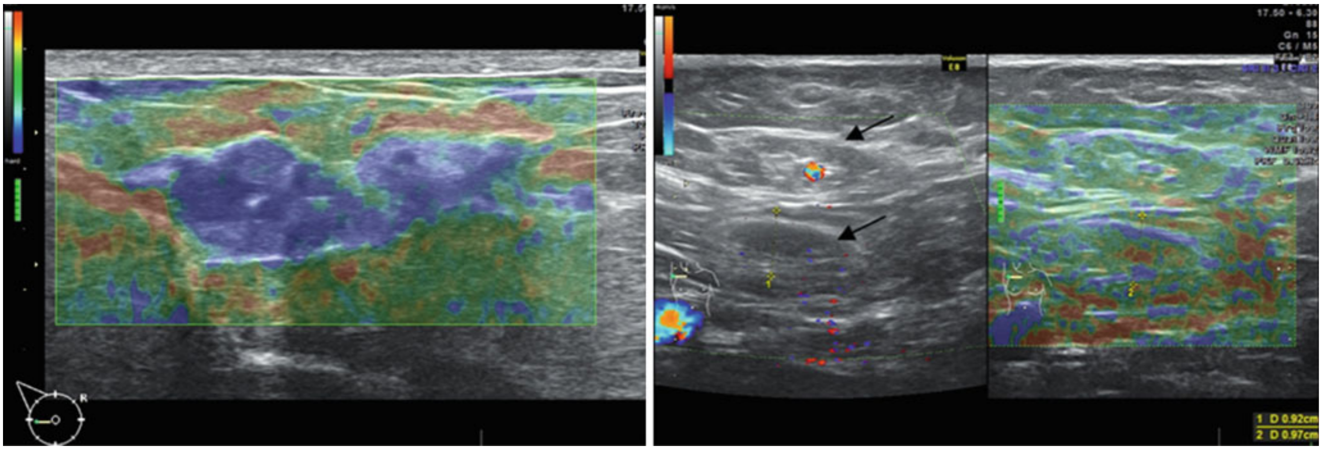


Fig. 8.41 (continued)

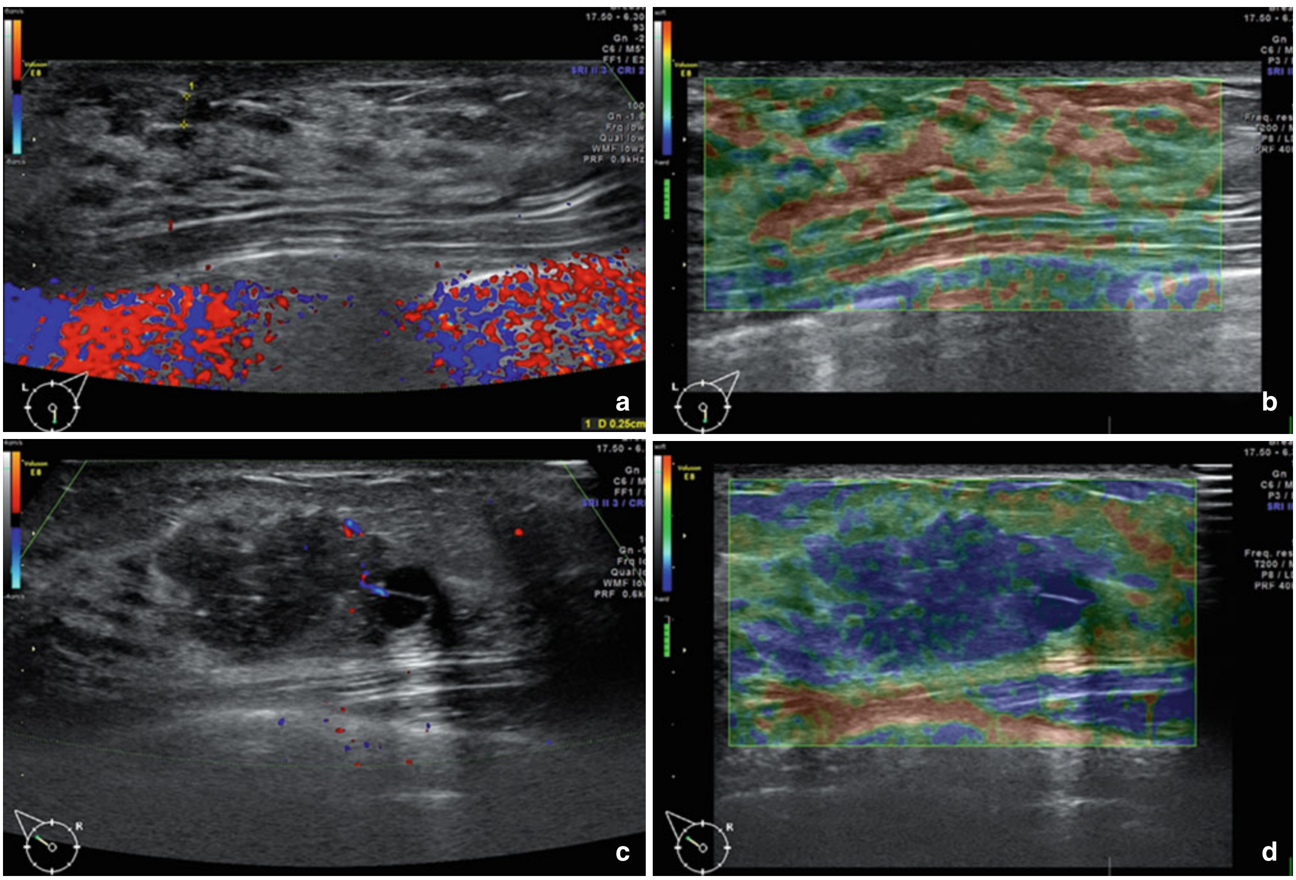


Fig. 8.42 FBU in a 31-year-old patient with dense breasts and “simple dysplasia” with focal ductal-lobular thickening, no abnormal vasculature, and benign-type sonoelastography illustrated at L6:00 (**a**, **b**). Diffuse malignancy with ill-defined palpable mass in the right upper-outer quadrant illustrates the breast parenchyma diffuse thickening with confluence in a mass strictly delimited by the Cooper’s ligaments to the glandular volume, without extension to the fatty tissue. The pathological mass demonstrates salient new formation vasculature (**c**), increased stiffness with type 4 Ueno sonoelastogram both in the radial and antiradial scans (**d**–**f**). Note the abnormal score 4 Ueno of the cystic component (**d**), unusual in the nodular fibro-micro-cystic dysplasia. The malignancy is spreading ductally to the surrounding parenchyma, probably to the neighboring mammary lobes, such as demonstrated in the antiradial view (**f**)

Fig. 8.42 (continued)

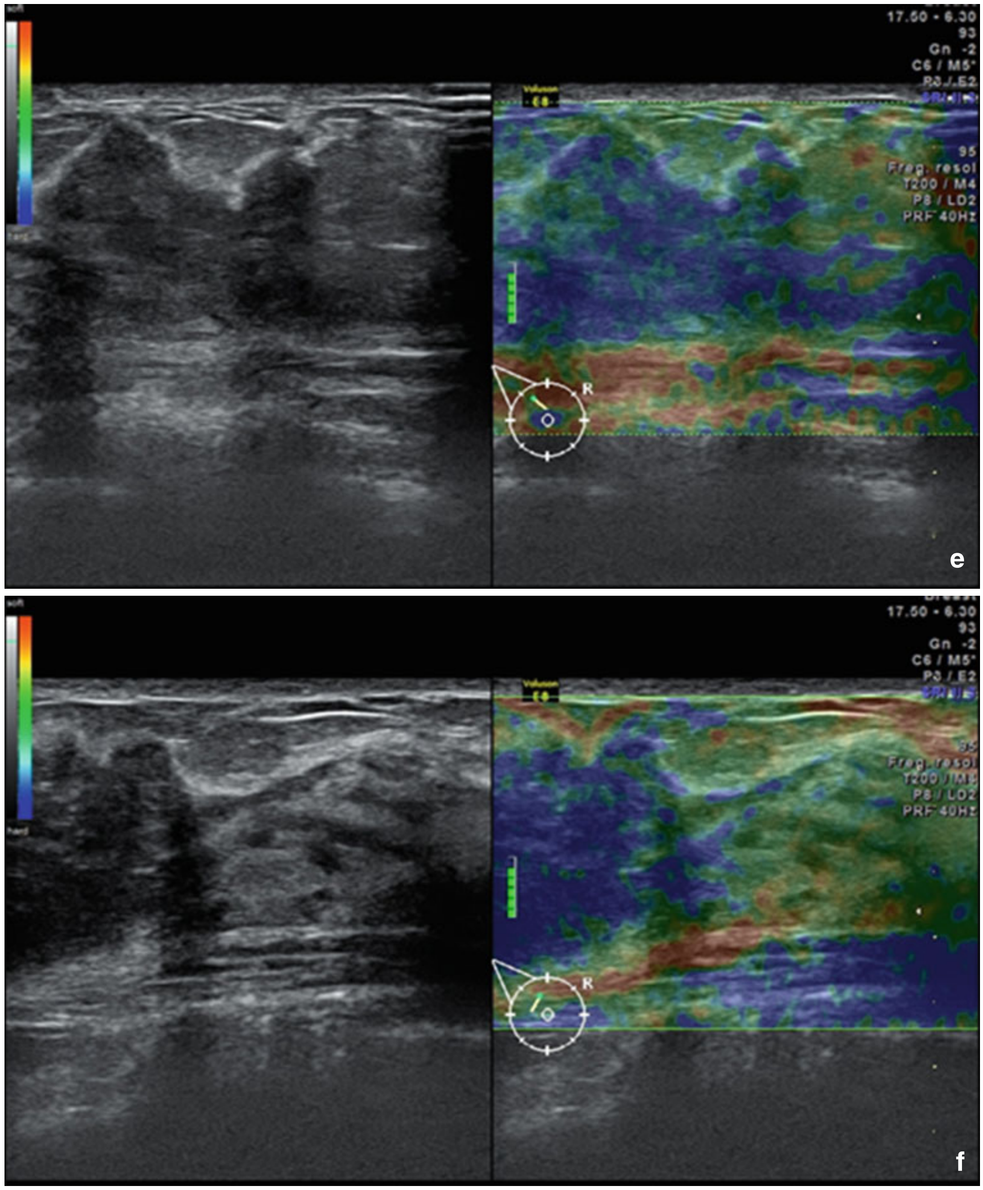


Fig. 8.43 Retroareolar malignancy; the mass has benign posterior effects after Kobayashi, but the new formation vasculature is significant; note the ductal-lobular segmental-associated hyperplasias

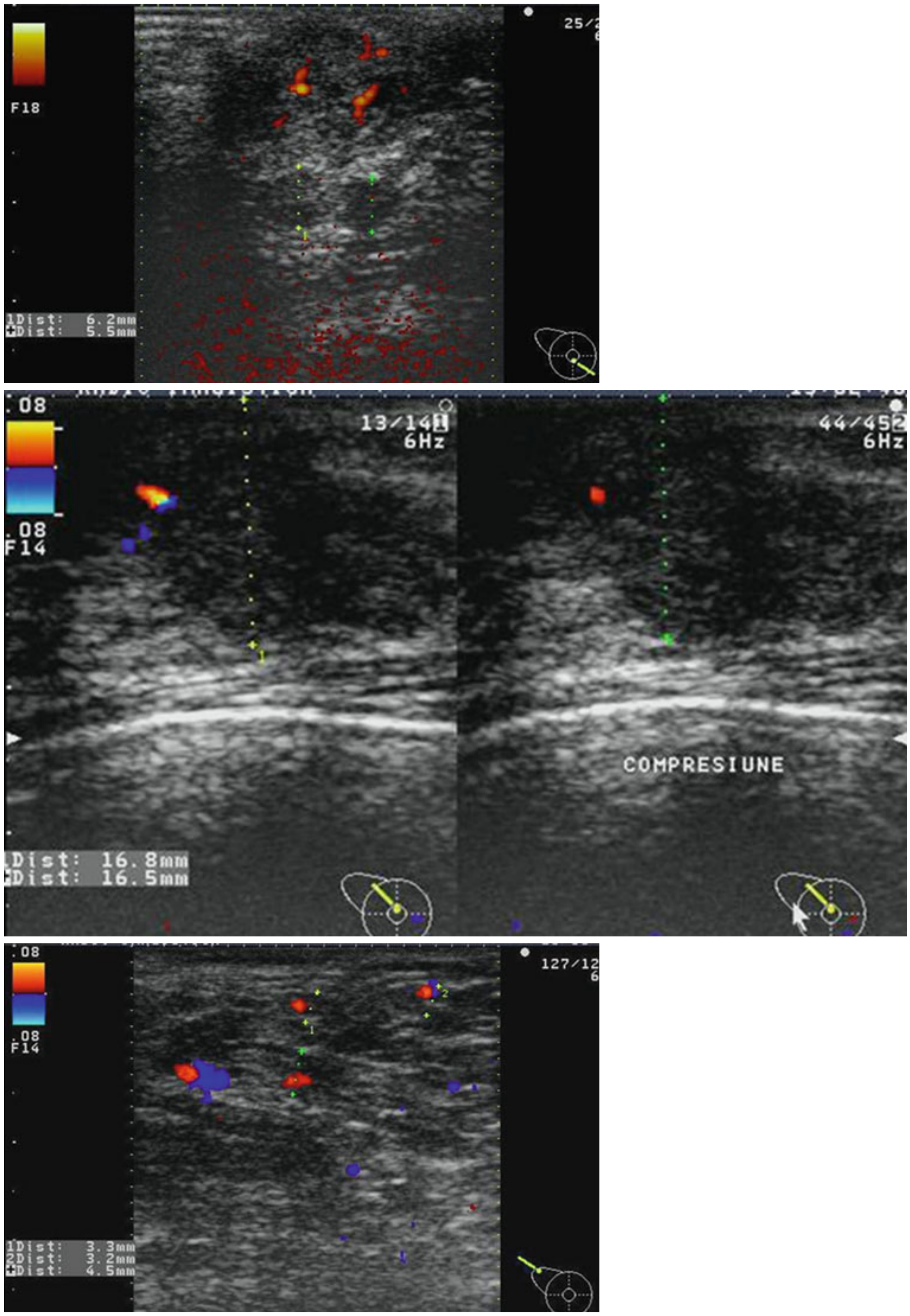
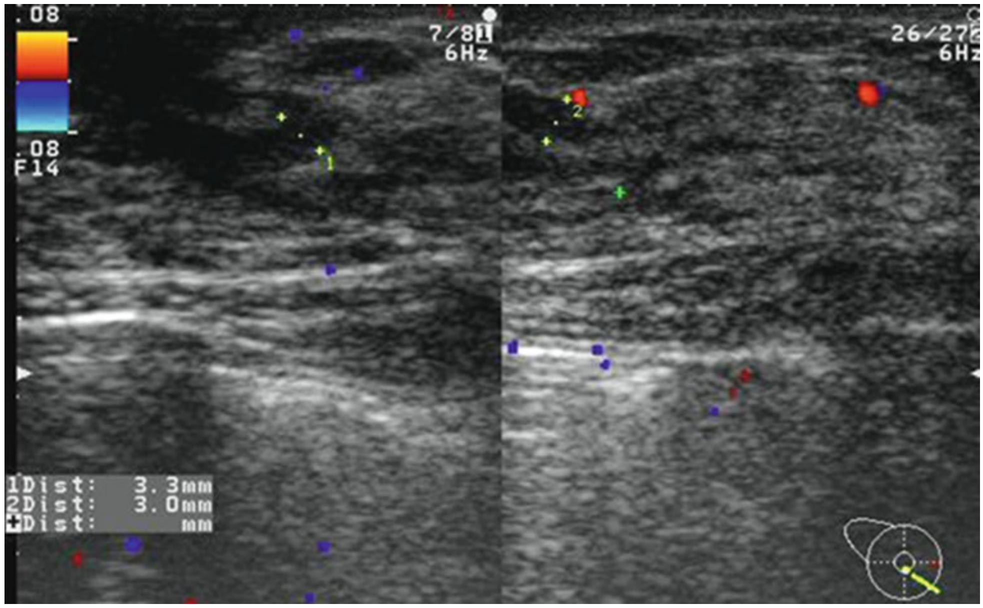


Fig. 8.43 (continued)



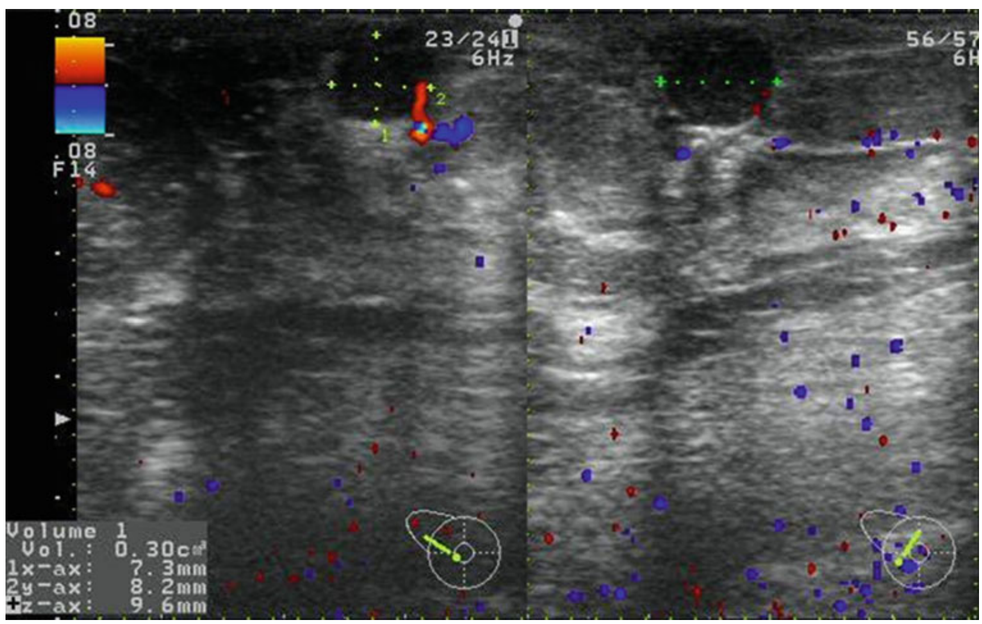


Fig. 8.44 Paget's disease with a retroareolar lesion less than 10 mm, suspect due its salient vasculature and its close relation with the nipple

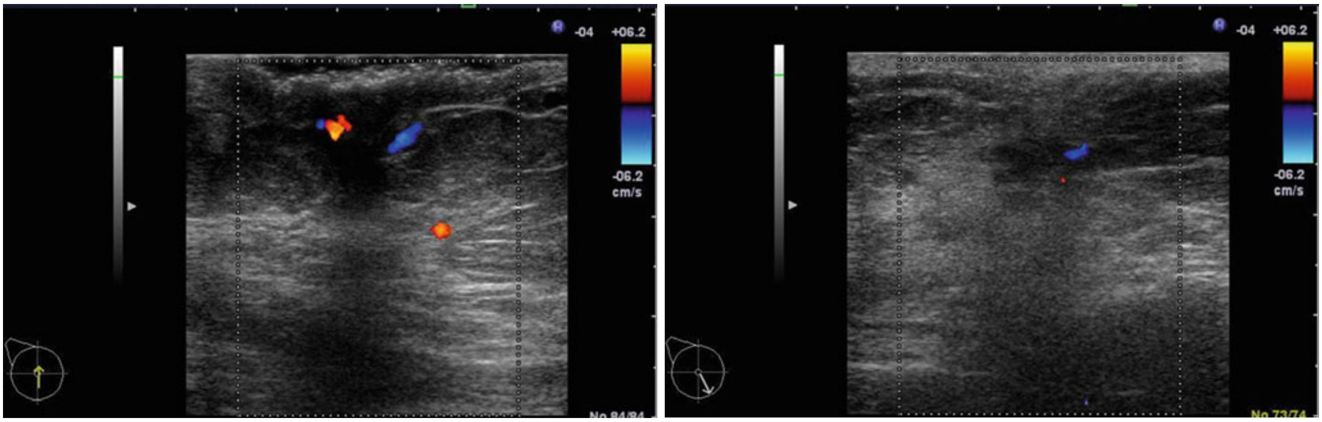


Fig. 8.45 Paget's disease with nipple and areola presenting a hypoechoic thickened aspect and salient vasculature (*upper image*); peripheral L5:00 infracentimetric mass with malignant descriptors: spiculated, with hallo, hypoechoic, acoustic shadowing, incident plunging artery (*below*)

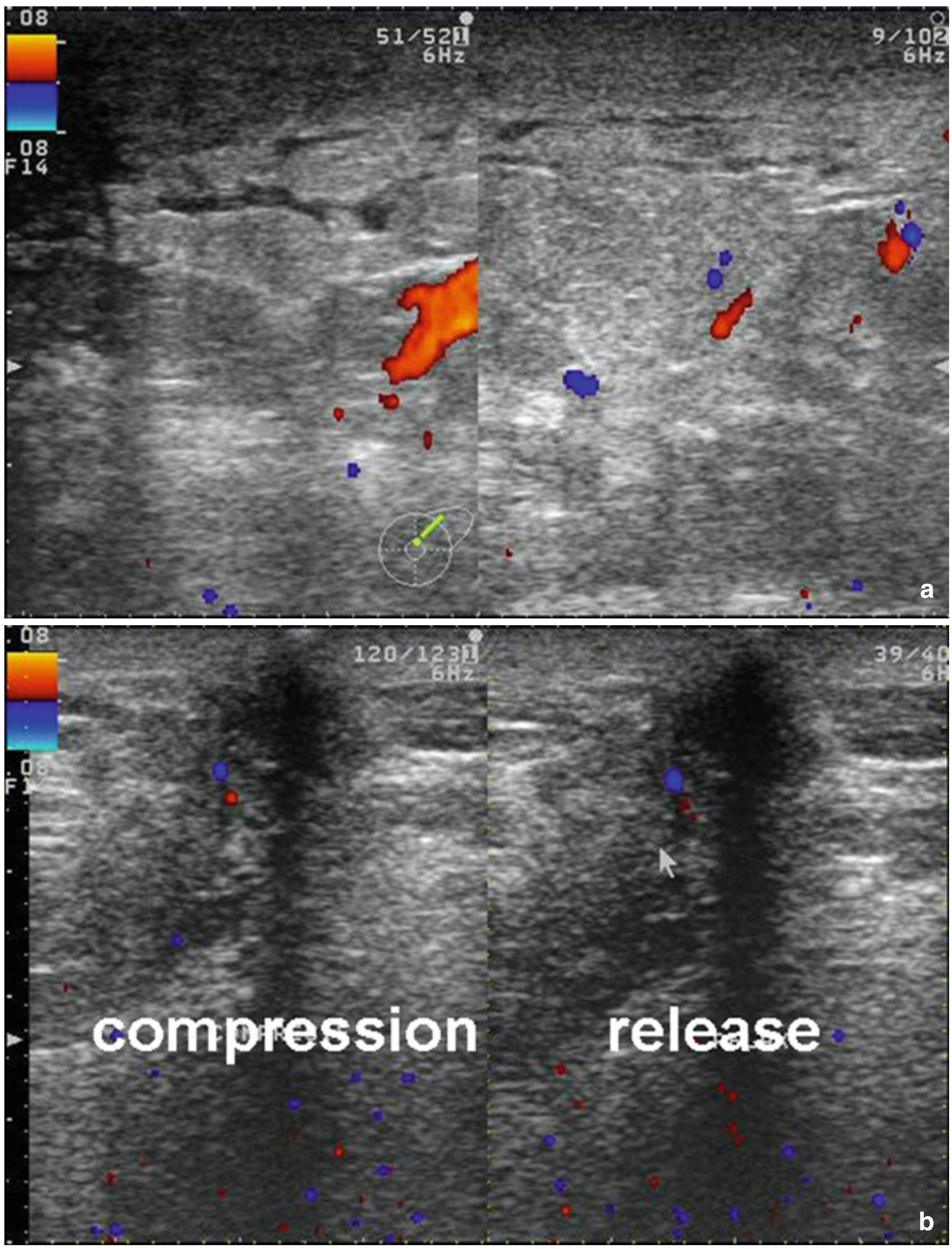
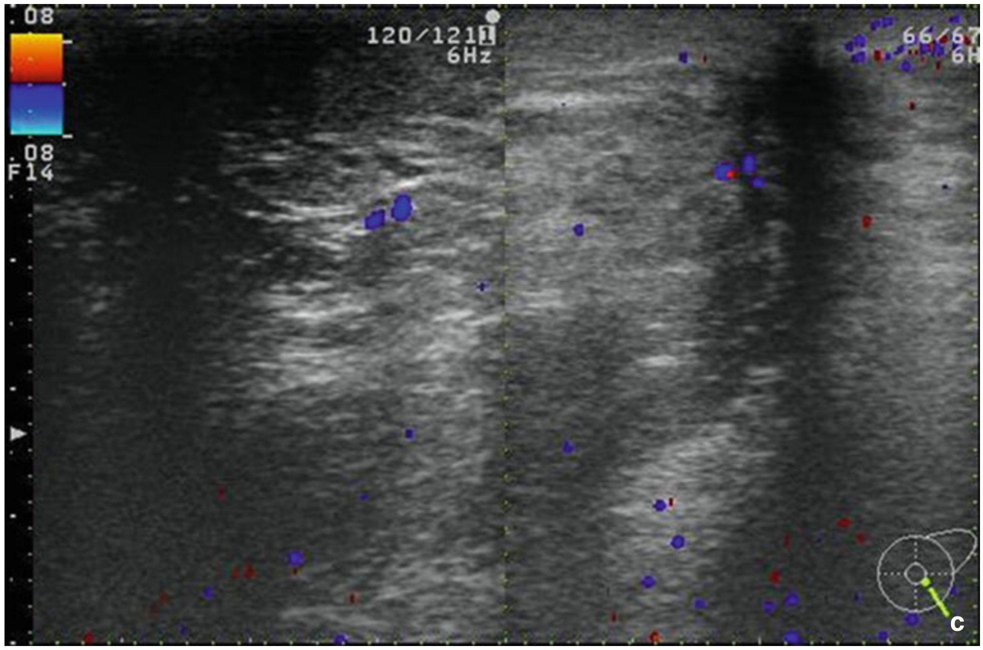


Fig. 8.46 Patient is 46 years old with left breast carcinomatous mastitis, dense breast in mammography without focal abnormality. Doppler DE illustrates lymphedema with superficial lymphatic spaces (**a**), increased vasculature in the glandular areas and a centimetric mass at L5:00, with malignant features after Stavros (**b**, **c**). In the absence of sonoelastography, a direct compression with the transducer may demonstrate low elasticity with persistent acoustic shadowing and no/small change in the vasculature. For ultrasound machines without a long linear probe, the double-screen option may help to realize a composed radial scan, suggestive of the anatomic relation between lesion and nipple (**c**)

Fig. 8.46 (continued)



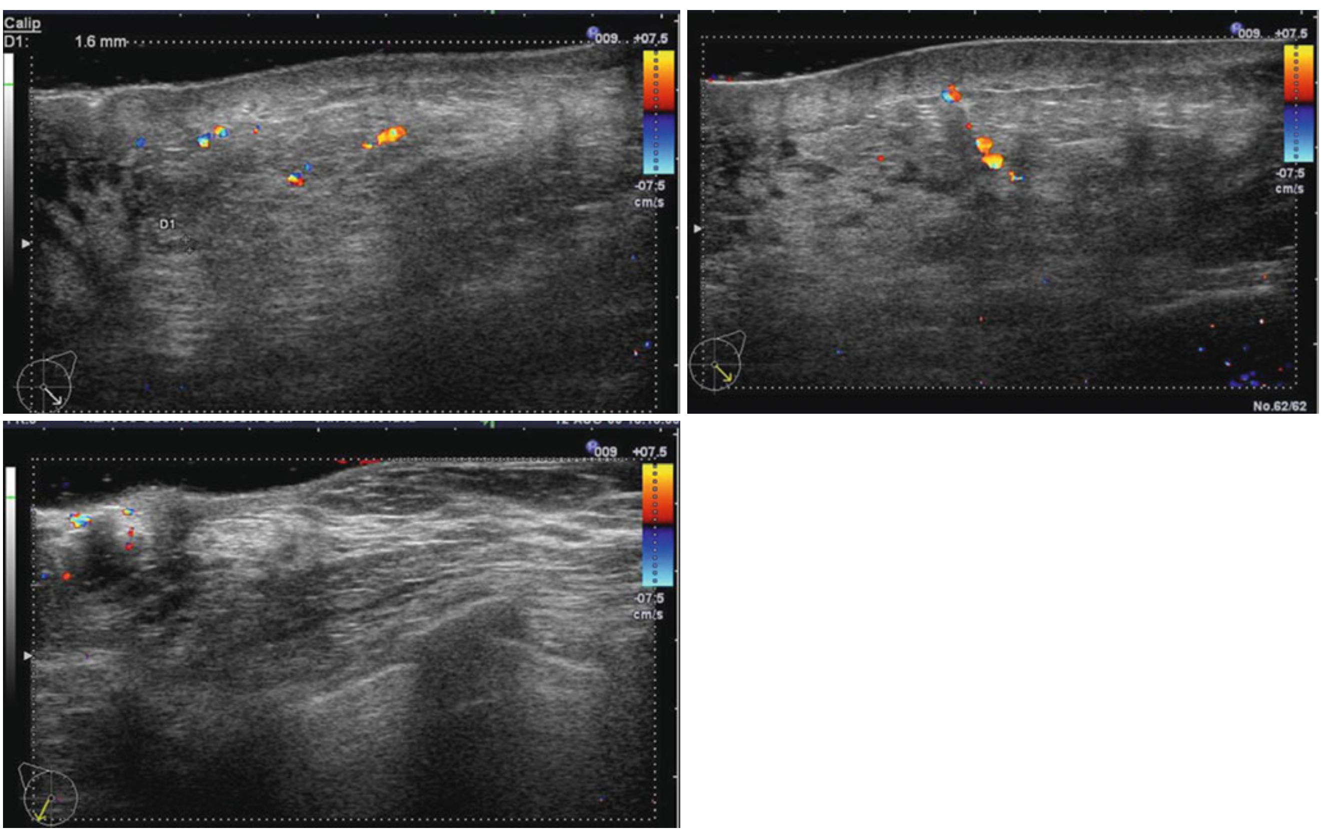


Fig. 8.47 Patient is 62 years old with left breast suspect carcinomatous mastitis, with skin thickening, loss of parenchymal differentiation, deep glandular hypoechogeneicity, and diffuse hyperemia. Comparative slices with the contralateral breast at the same radius scanning

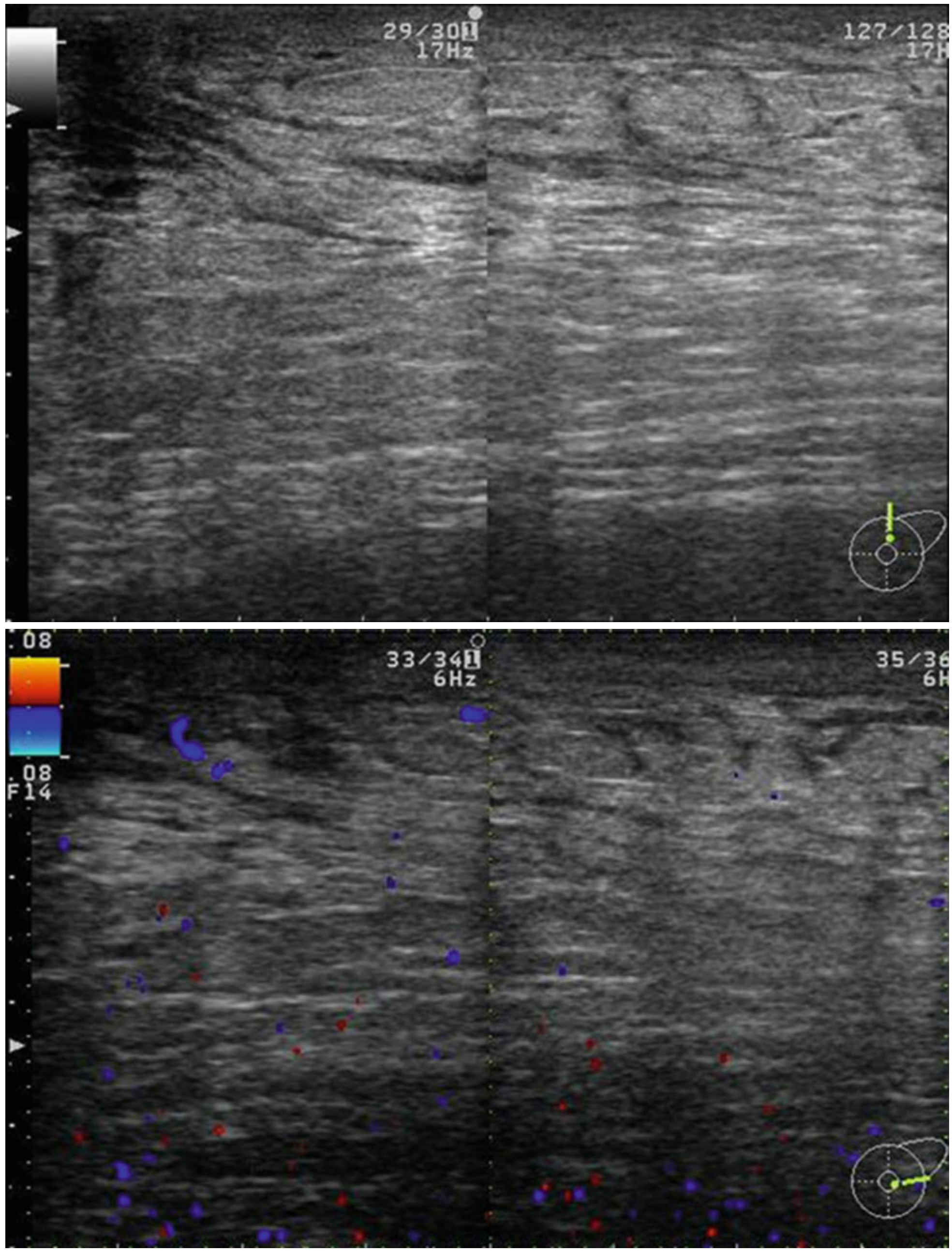
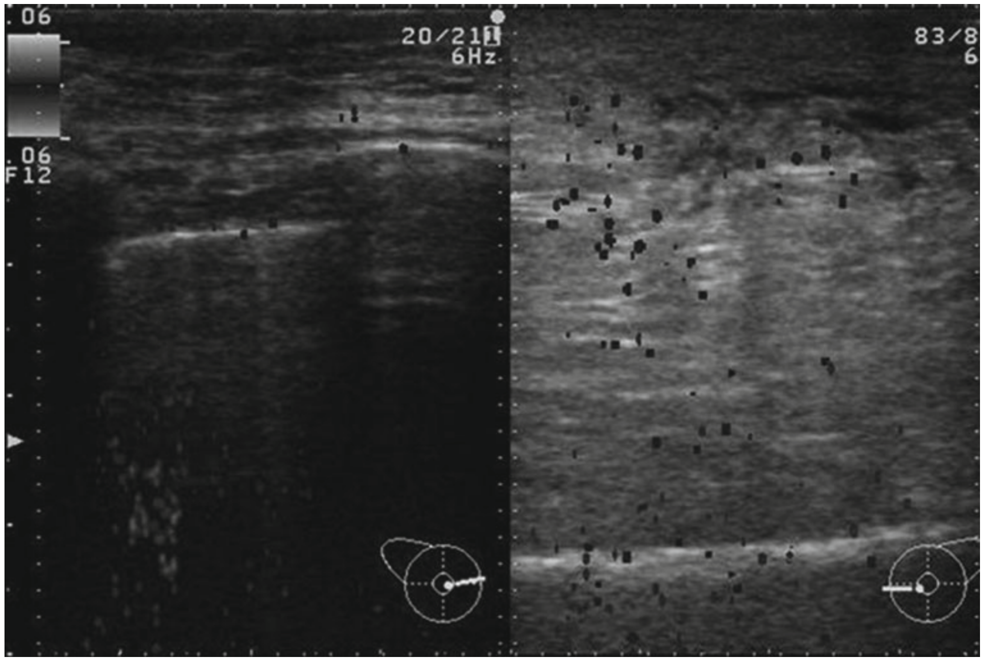


Fig. 8.48 Patient is 72 years old: left breast edema with normal vasculature of a patient with right shoulder fracture and cardiac insufficiency with bradycardia, arrhythmia, and pericardial effusion. No breast etiology was found for the breast edema, considered as secondary to the cardiac failure and the selective dorsal and left decubitus

Fig. 8.48 (continued)



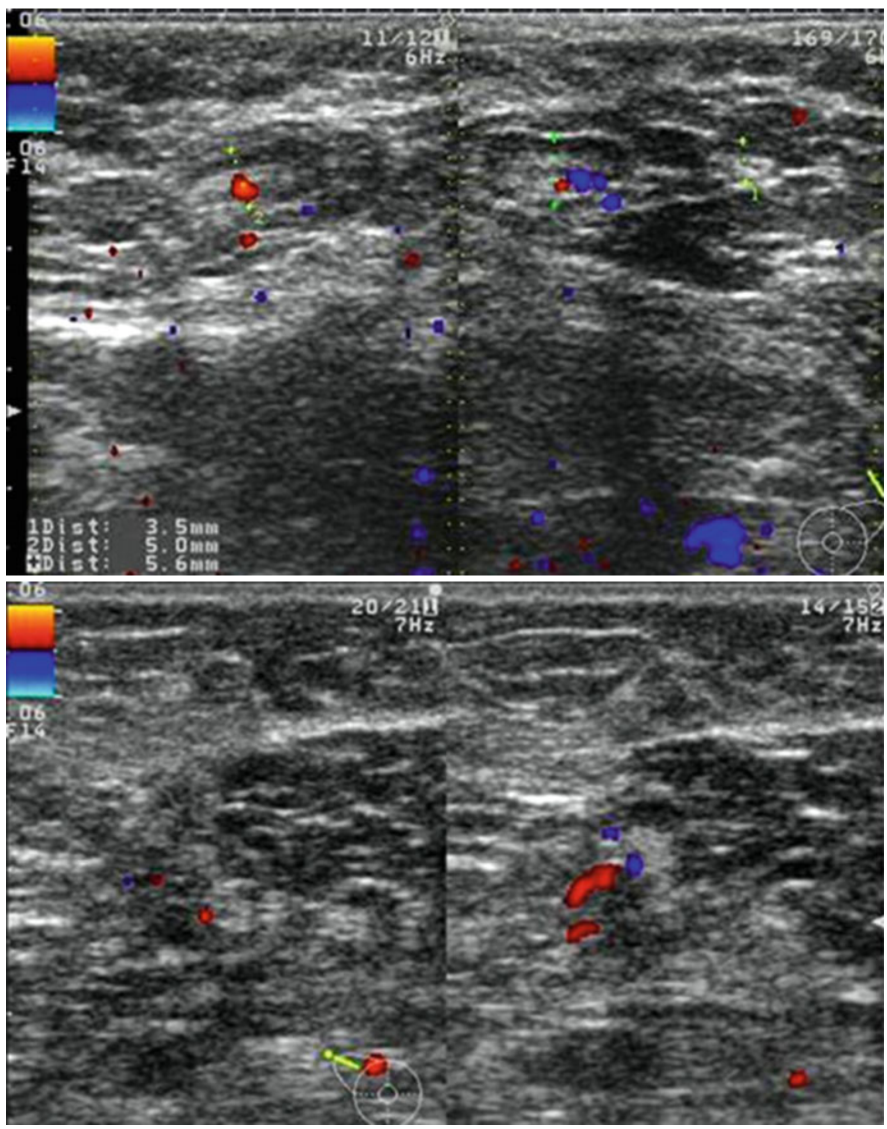
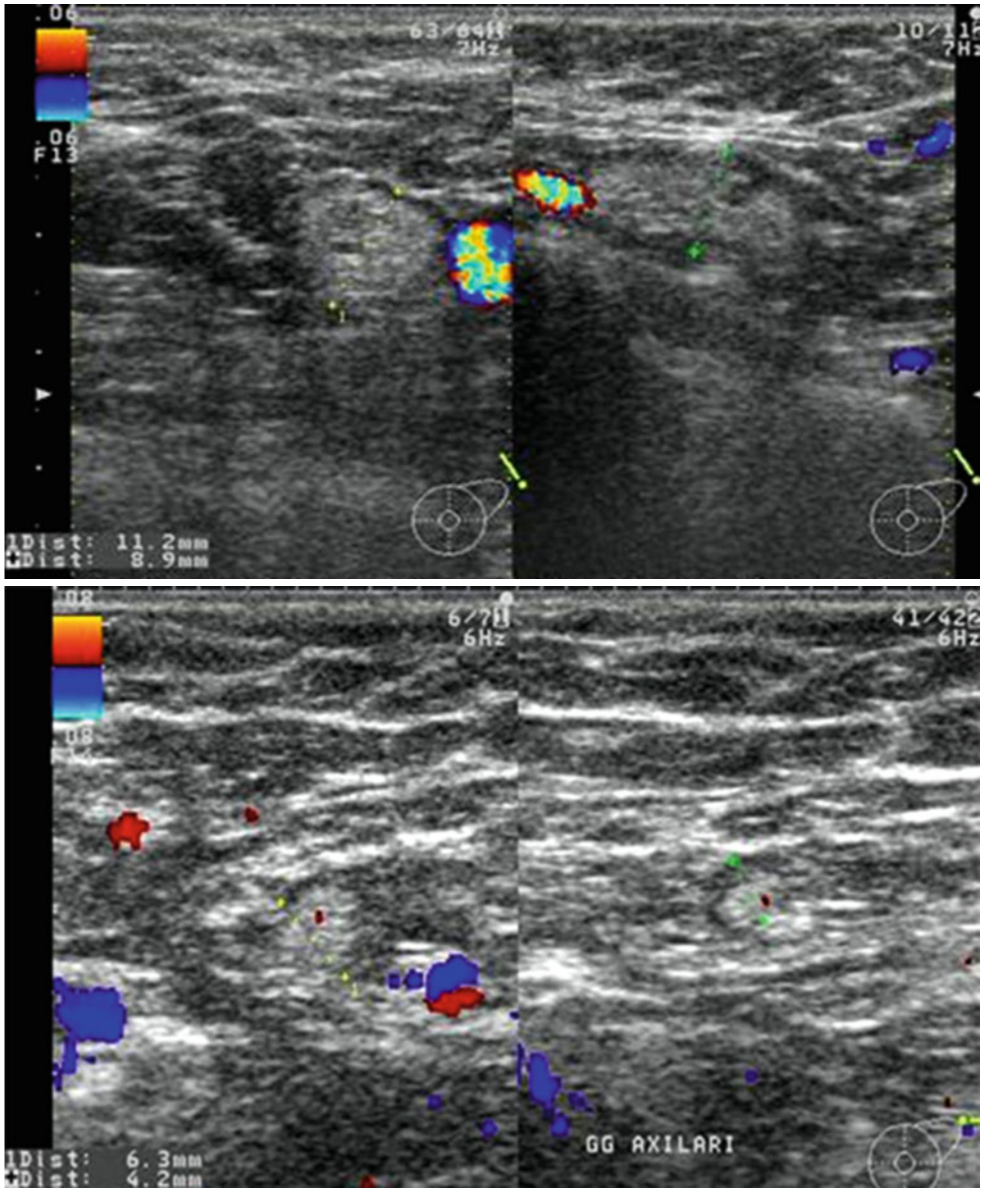


Fig. 8.49 Normal shapes of axillary lymph nodes. Their recognition is easier when using color Doppler acquisition, otherwise they are difficult to differentiate from the surrounding fatty tissue

Fig. 8.49 (continued)



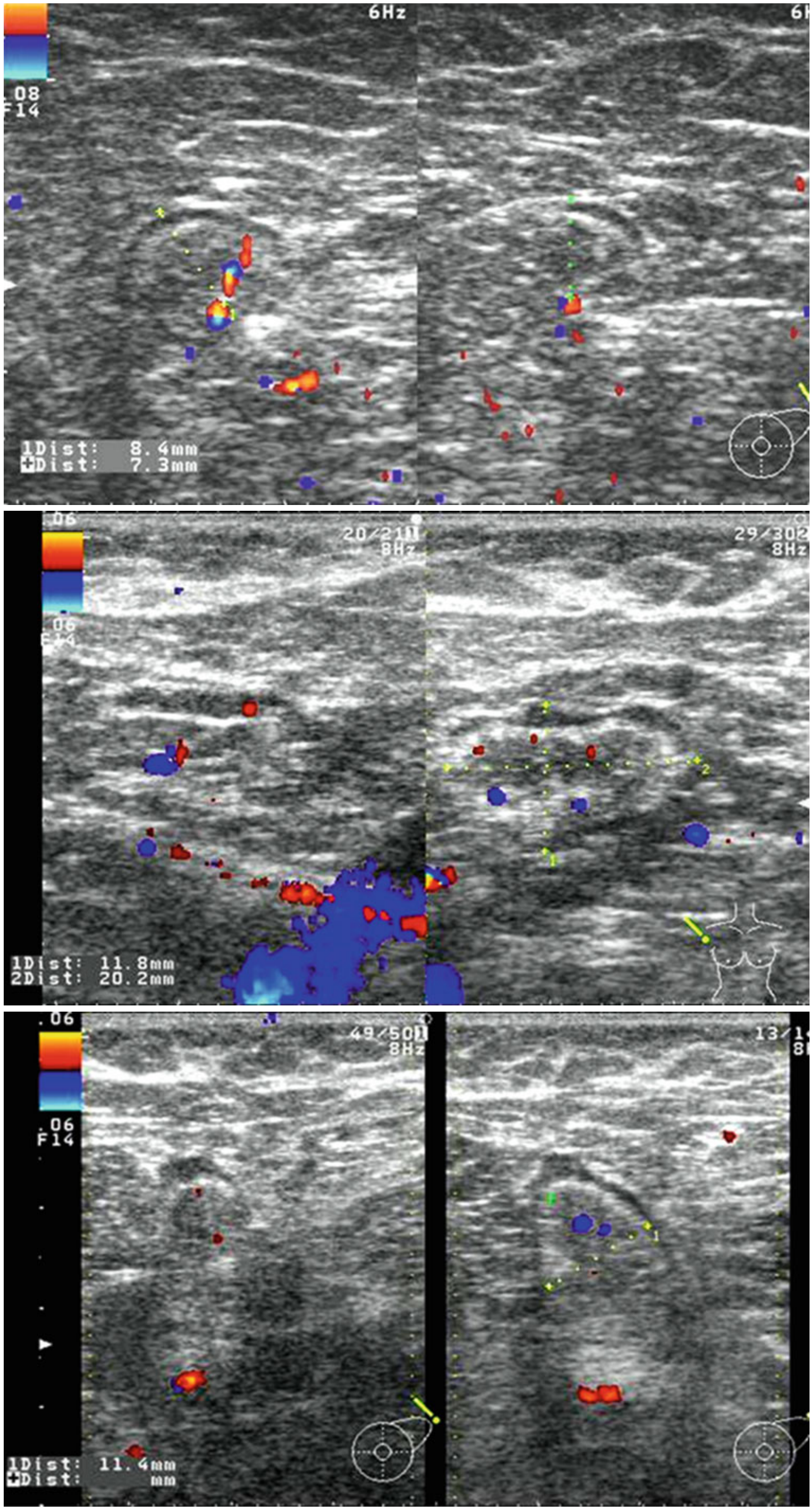


Fig. 8.50 Orthogonal slices of different axillary lymph nodes presenting ovoid shape, thin cortical zone, and peripheral hyperechoic medullary rim with central hypoechoic heterogeneous area. This aspect is suggestive of chronic inflammation and/or possible benign histiocytosis. The vascular aspect is of the benign type, with relative few and thin vessels arising from the hilum

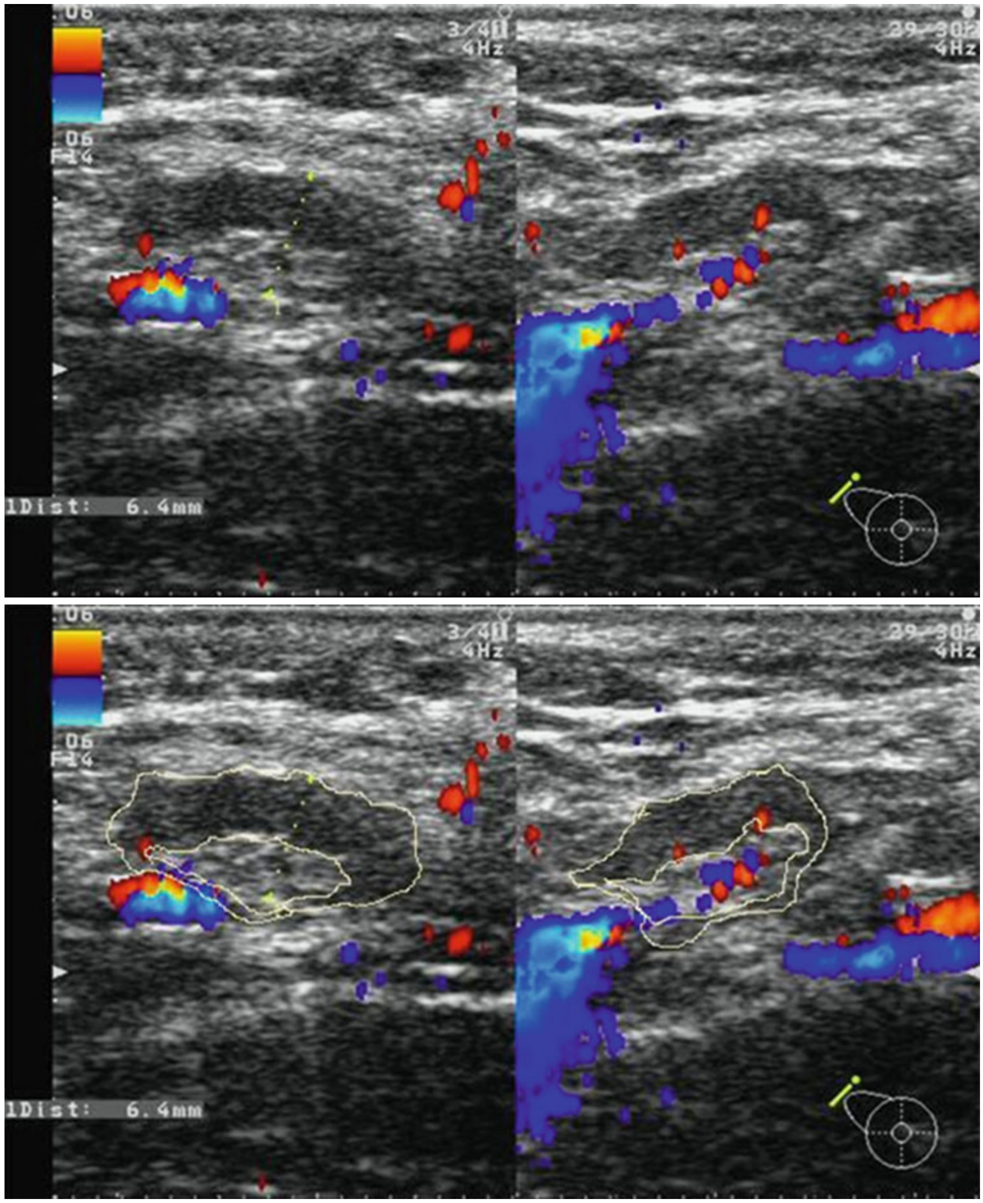


Fig. 8.51 Axillary enlarged lymph nodes with thickening of the cortex and moderate vasculature. This aspect is at least suspect and the biopsy is recommended

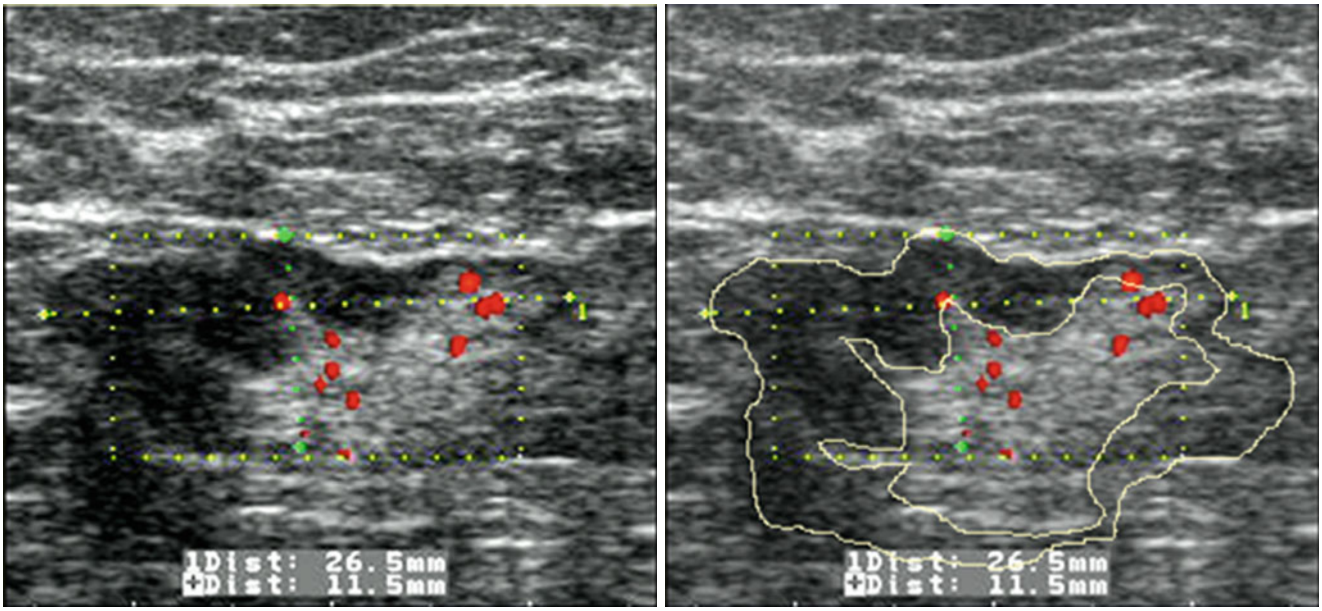


Fig. 8.52 Enlarged axillary lymph node with eccentrically thickened cortical region, more hypoechoic and moderately increased vasculature in power Doppler, in a patient with ultrasound BI-RADS category 4 breast lesion. This aspect, highly suspect for sentinel node, was confirmed by surgical biopsy

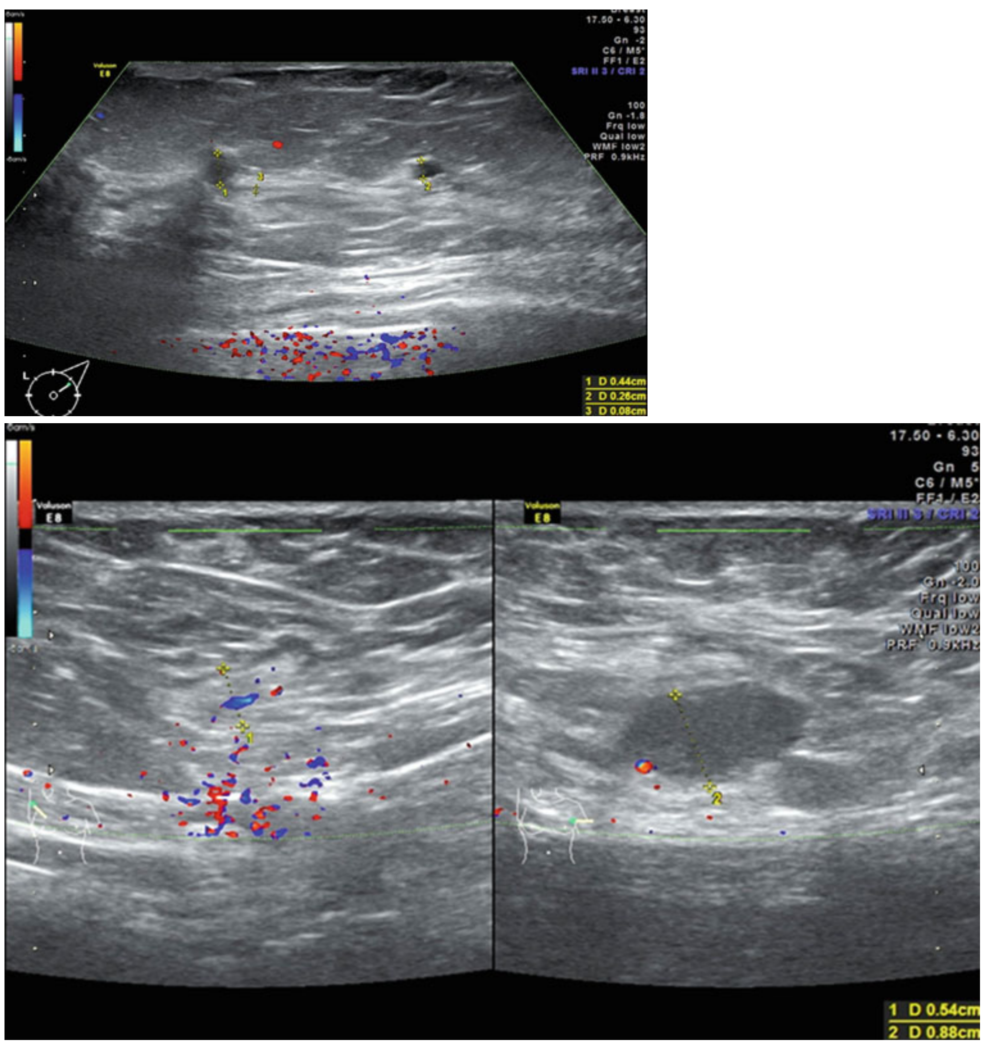
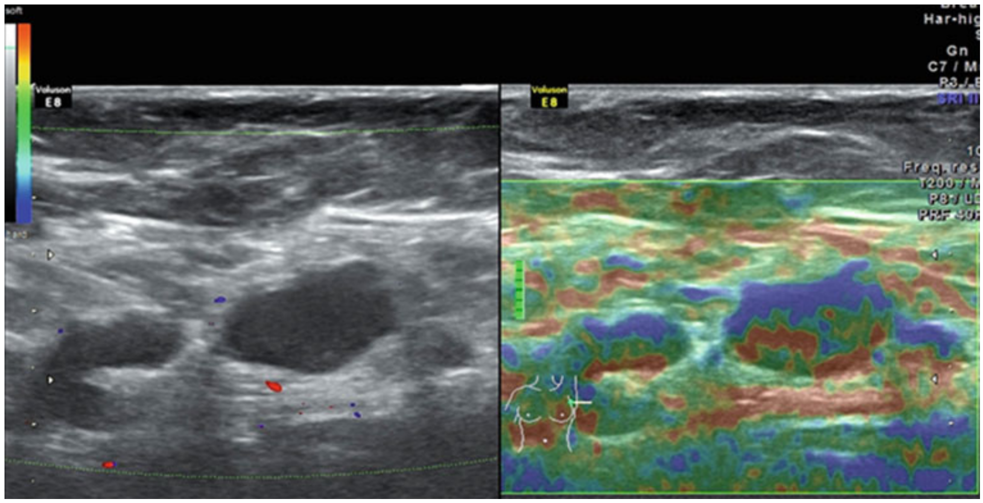


Fig. 8.53 Thirty-seven-year-old patient presents left enlargement of the axillary lymph nodes as compared with the opposite axilla, with cortical thickening and necrotic aspect with less vasculature in Doppler and BGR (Blue-Green-Red) score. The breast ultrasound detected only pseudonodular fibro-micro-cystic lesions in the upper-outer quadrant. Despite a possible etiology outside the breast area, the ultrasound BI-RADS assessment category 0 is mandatory

Fig. 8.53 (continued)



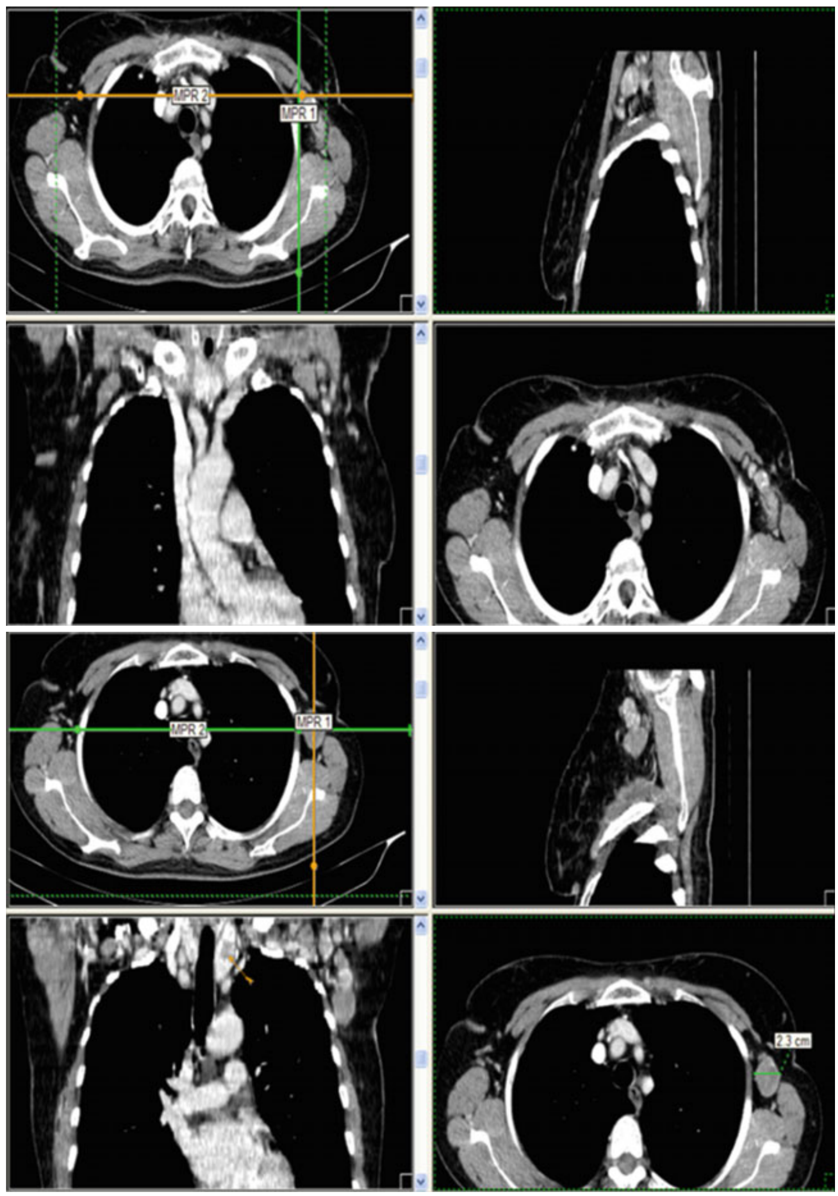


Fig. 8.54 The same case as in Figs. 8.4, 8.5, and 8.6 (Chap. 7): contrast multidetector CT illustrates left axillary adenopathy with and without calcifications in a patient with breast cancer. The MR (Multiplanar Reconstruction) illustrates the extent of the pathological lymph nodes under the lateral margin of the great pectoral muscle

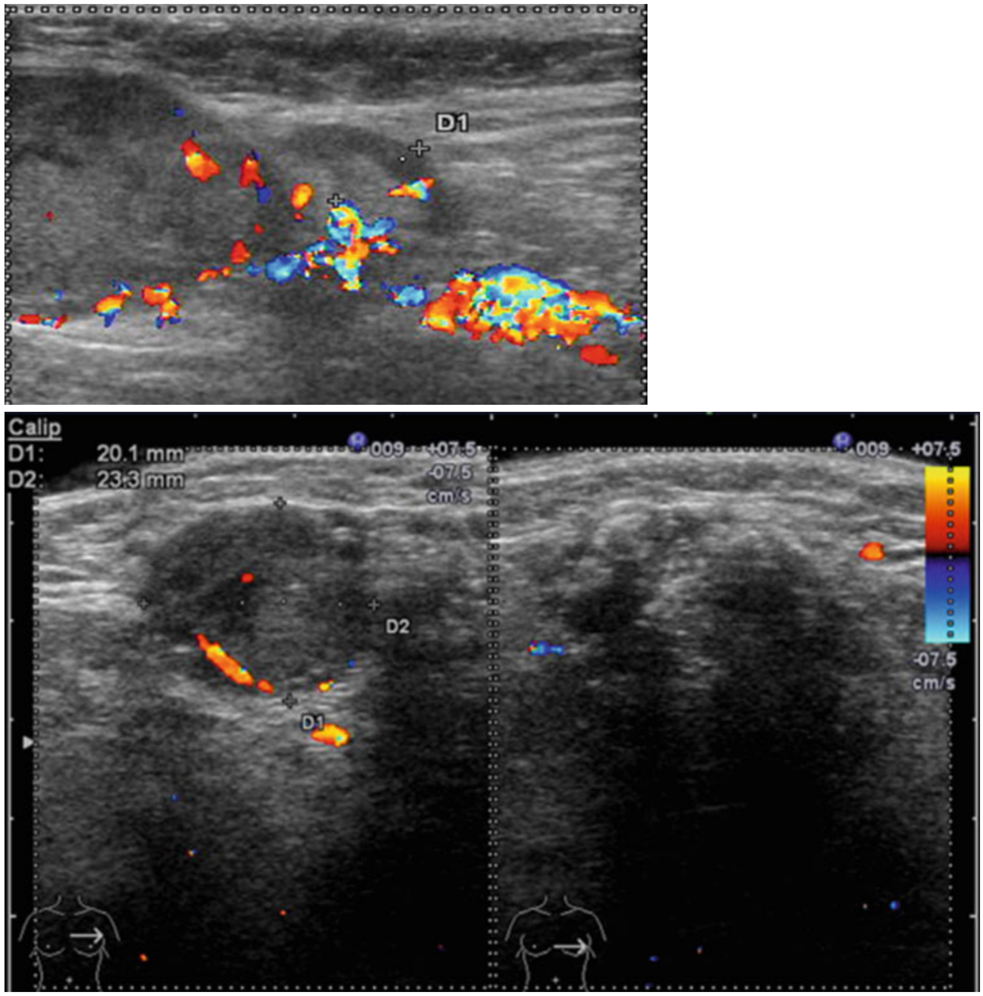


Fig. 8.55 The same case as in Fig. 8.54: Doppler ultrasound illustrates with better resolution and without contrast agent injection the left axillary adenopathy, with huge lymph node with structural changes and peripheral new formation vasculature near an almost normal node (*upper*); other pathological smaller nodes have various amount of microcalcifications (*below*)

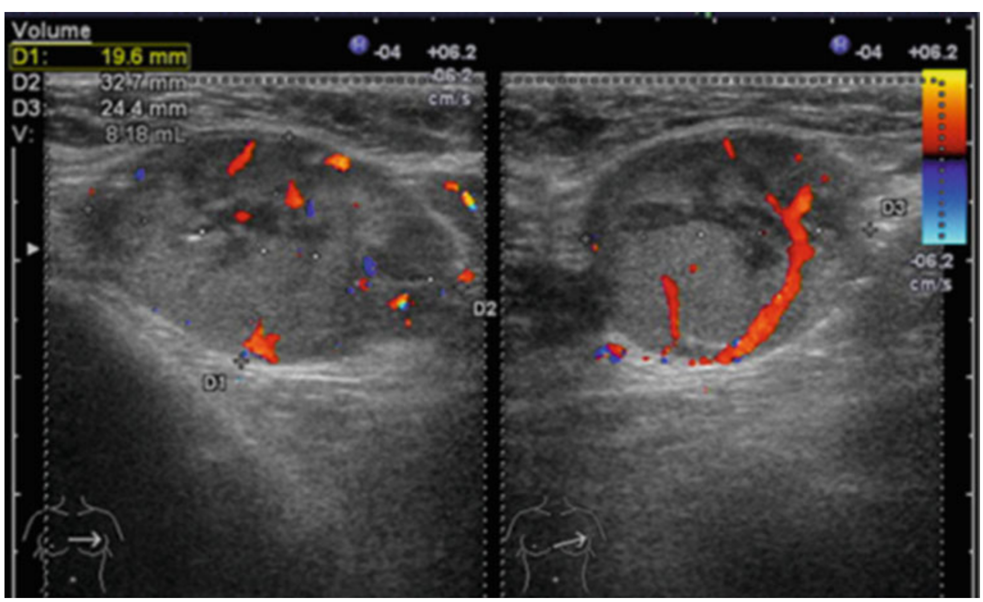
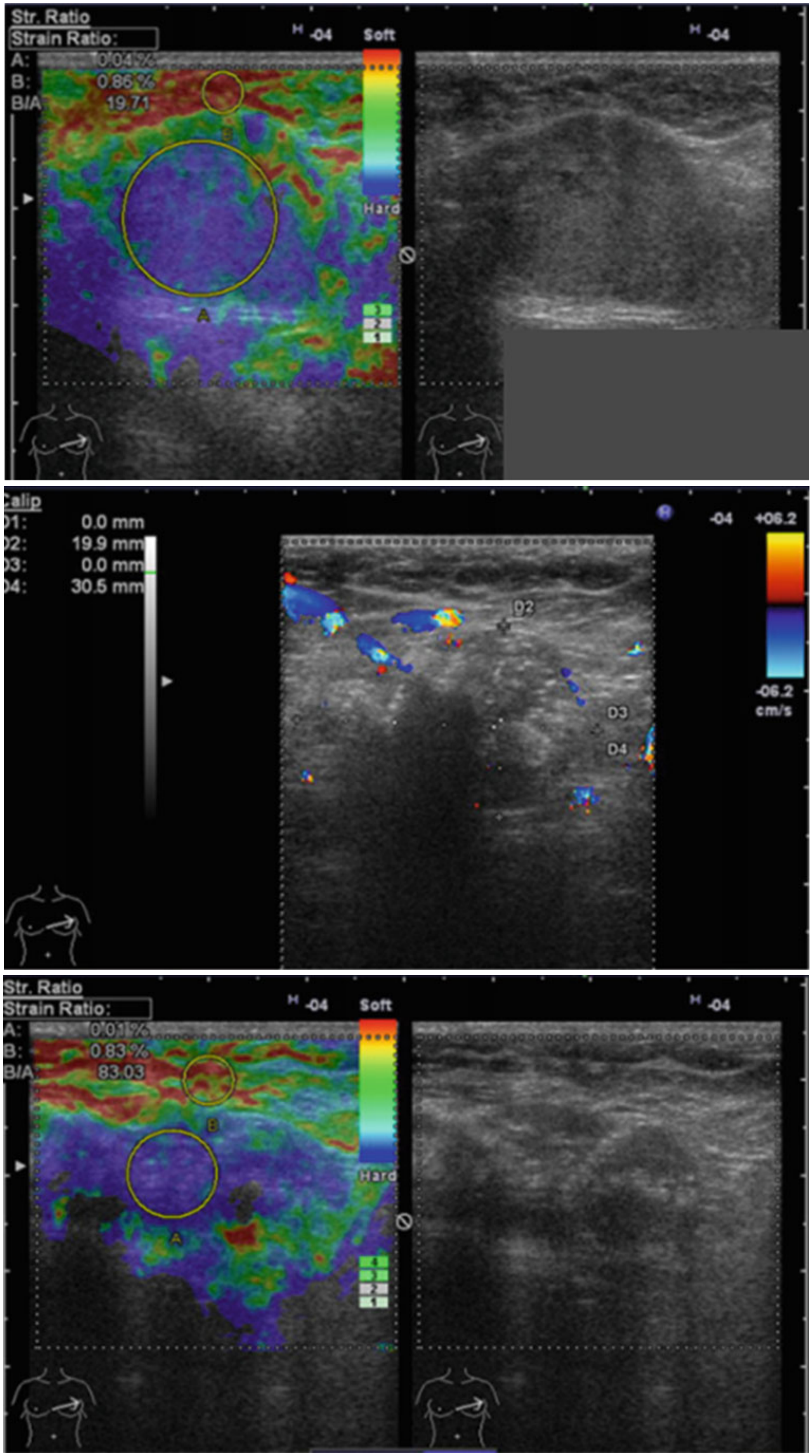


Fig. 8.56 The same case as in Figs. 8.54 and 8.55: FBU illustrates left axillary adenopathy, with and without calcifications. The main findings suggestive of malignancy are the new formation vasculature and increased strain. The sensibility and specificity are better than in classical ultrasound, but the limited field of view is inconvenient compared with computed tomography or MRI

Fig. 8.56 (continued)



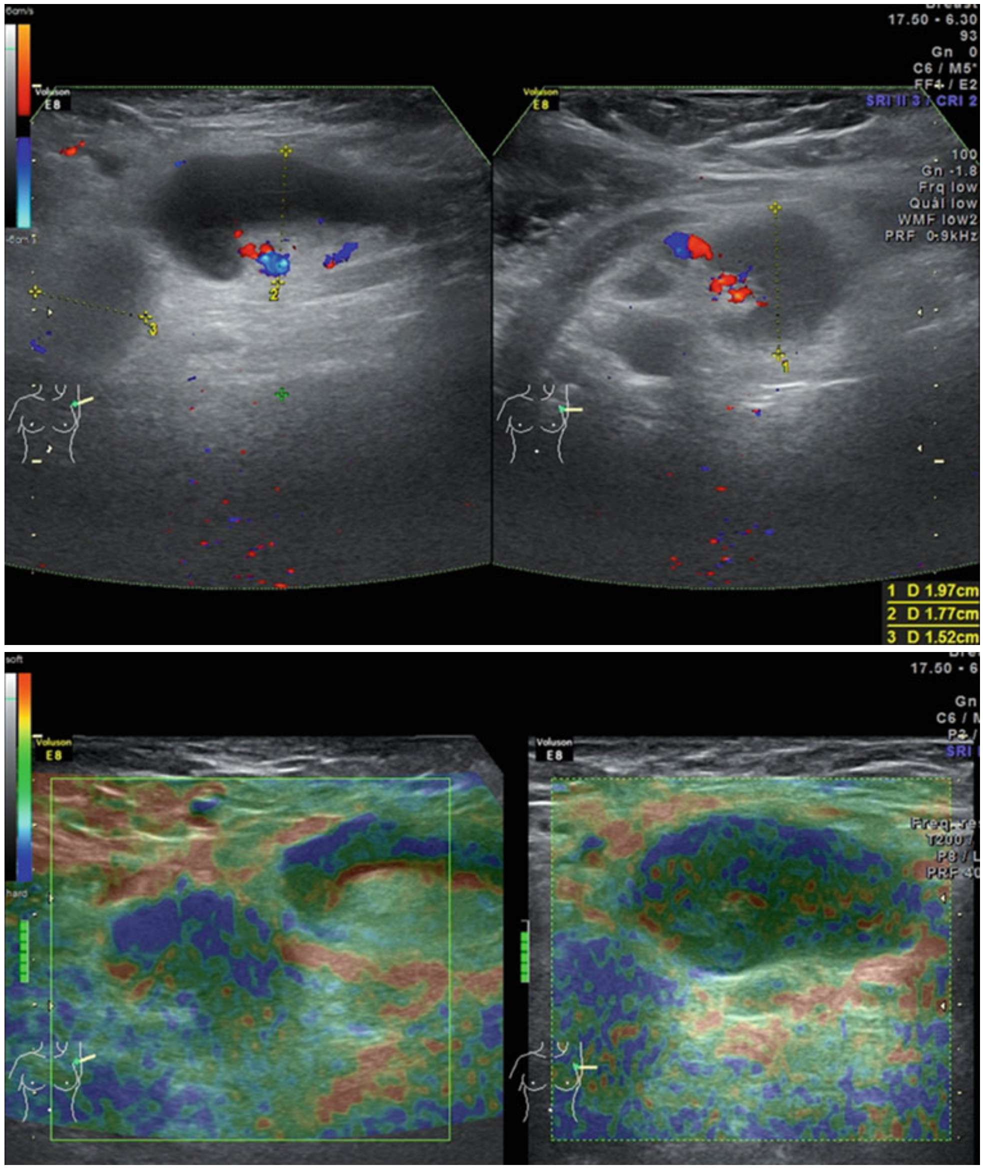


Fig. 8.57 Axillary adenopathy with increased transverse diameter and thickening of the cortical regions but normal vasculature in hilum. The BGR score, significant for either lymph nodes edema or necrosis, cannot eliminate the risk of malignancy, especially in qualitative SE. In this case, quantitative SE with FLR would be useful, but it is not yet implemented by all manufacturers

References

1. Tot T (2007) The theory of the sick breast lobe and the possible consequences. Int J Surg Pathol 1:68–71
2. Georgescu AC, Andrei EM, Enachescu V, Bondari S (2013) New horizons in breast Doppler ductal echography: the positive and differential diagnosis of ductal ectasia, with etiopathological correlations. ECR, Vienna, EPOS™. doi:10.1594/ecr2013/C-0667
3. Grio R, Cellura A, Germao R et al (1998) Clinical efficacy of tamoxifen in the treatment of premenstrual mastodynia. Minerva Ginecol 50(3):101–103
4. Fujimoto Y, Hatama M, Tezuka K, Otani H et al (2005) Ultrasonic screening of the thyroid in the patients with breast complaints. In: Research and development in breast ultrasound. Springer, Tokyo, pp 167–169
5. Fujimoto Y, Kato Y, Maekawa H et al (1988) Ultrasonic screening of thyroid in the patients with breast complaints. J Ultrasound Med 7:39–S283
6. Georgescu AC, Andrei ME, Manda A, Bondari S, Sendroiu I (2015) Contributions of imaging examinations in the diagnosis of the von Recklinghausen disease. ECR, Vienna, EPOS™. doi:10.1594/ecr2015/C-1014
7. Szymanowski K, Niepsuj-Biniaś J, Dera-Szymanowska A et al (2013) An influence of immunomodulation on Th1 and Th2 immune response in endometriosis in an animal model. Biomed Res Int 2013, Article ID 849492:7. doi:10.1155/2013/849492
8. Szymanowski K, Chmaj-Wierzchowska K, Yantczenko A et al (2009) Endometriosis prophylaxis and treatment with the newly developed xenogenic immunomodulator RESAN in an animal model. Eur J Obstet Gynecol Reprod Biol 142(2):145–148
9. Foschini MP, Baldovini C, Ishikawa Y, Eusebi V (2012) The value of large sections in surgical pathology. Int J Breast Cancer 2012, Article ID 785947:7. doi:10.1155/2012/785947
10. Cheatle GL (1906) Early recognition of cancer of the breast. Br Med J 1:1205–1210
11. Cheatle GL (1914) The relation between ducts and acini to cysts and cancer of the breast. J R Soc Med 7:241–244
12. Wellings SR, Jensen HM (1973) On the origin and progression of ductal carcinoma in the human breast. J Natl Cancer Inst 50(5):1111–1116
13. Foschini MP, Flamminio F, Miglio R et al (2007) The impact of large sections on the study of in situ and invasive duct carcinoma of the breast. Hum Pathol 38(12):1736–1743
14. Tot T (2010) Cost-benefit analysis of using large-format histology sections in routine diagnostic breast care. Breast 19(4):284–288
15. Tot T (2007) Clinical relevance of the distribution of the lesions in 500 consecutive breast cancer cases documented in large–format histologic sections. Cancer 110:2551–2560
16. Egan RL (1982) Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. Cancer 49(6):1123–1130
17. Tot T, Gere M, Pekár G et al (2011) Breast cancer multifocality, disease extent, and survival. Hum Pathol 42(11):1761–1769
18. Martin JE (1988) Atlas of mammography. Histologic and mammographic correlations, 2nd edn. Williams & Wilkins, Baltimore, pp 69–268
19. Gallager HS, Martin JE (1969) The study of breast carcinoma by correlated mammography and subserial whole organ sectioning. Early observations. Cancer 23:855–873
20. Gallager HS, Martin JE (1969) Early phases in the development of breast cancer. Cancer 24:1170–1178
21. Teboul M (2010) Advantages of ductal echography (DE) over conventional breast investigation in the diagnosis of breast malignancies. Med Ultrason 12(1):32–42
22. Baldovini C, Foschini MP (2012) Multifocality of breast cancer. In: Proceedings of the 27th congress of the Adriatic Society of Pathology, June 2012
23. Cooper AP (1840) On the anatomy of the breast. London, Longman, Orme, Green, Brown, and Longmans. (special collections, Scott Memorial Library, Thomas Jefferson University, http://jdc.jefferson.edu/cooper/)
24. Sobin LH, Gospodarowicz MK, Wittekind C (eds) (2009) TNM classification of malignant tumors. 7th edn. Wiley Blackwell
25. Saslow D, Solomon D, Lawson H et al (2012) American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 62(30):147–172, Epub, Mar 14
26. American Cancer Society Guidelines for the Early Detection of Cancer (2014) www.cancer.org
27. Amy D (2010) Lobar Ultrasound of the Breast. In: Breast Cancer, 1.T. Tot (ed). © Springer-Verlag London Limited. doi: 10.1007/978-1-84996-314-5_8
28. Amy D (2003) Sub-centimetric breast carcinoma. Echographic diagnosis. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
29. Stavros AT, Rapp LC, Parker HS (2004) Breast ultrasound. Lippincott Williams & Wilkins, Philadelphia
30. Mendelson EB, Baum JK, Berg WA et al (2003) Breast imaging reporting and data system BI-RADS: ultrasound, 1st edn. American College of Radiology, Reston
31. JSUM guidelines for mass image-forming lesions (2005) In: Ueno E, Shiina M, Kuboto K (eds) Research and development in breast ultrasound. Springer, Tokyo. pp 78–84
32. Japan Society of Ultrasonics in Medicine and JABTS- (Draft) (2003) Diagnostic guideline for mass image forming lesions. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
33. Chang R-F, Huang SF, Chen D-R, Moon WK (2003) Detection of spiculation in three-dimensional breast ultrasound. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
34. Kujiraoka Y, Ueno E, Yohno E, Morishima I, Tsunoda-Shimizu H (2005) Incident angle of the plunging artery of breast tumors. In: Research and development in breast ultrasound. Springer, Tokyo, pp 72–75
35. LeCarpentier G (2008) 3D Doppler evaluation helps identify malignant breast lesions. Reuters Health. Radiology 249
36. Chou H-I (2003) Evaluation of periductal angiogenesis using contrast-enhanced ultrasound. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
37. Ricci P, Cantisani V, Ballesio L et al (2007) Benign and malignant breast lesions: efficacy of real time contrast-enhanced ultrasound vs. magnetic resonance imaging. Ultraschall Med 28(1):57–62, PMID: 17304413 [PubMed – indexed for MEDLINE]
38. Drudi FM, Cantisani V, Gnecchi M (2012) Contrast-enhanced ultrasound examination of the breast: a literature review. Ultraschall Med 33(7):E1–E7. doi:10.1055/s-0031-1299408, Epub 2012 May
39. Watermann DO, Foldi M, Hanjalic-Beck A et al (2005) Three-dimensional ultrasound for the assessment of breast lesions. Ultrasound Obstet Gynecol 25:592–598
40. Vallone P, D'Angelo R, Filice S, Petrosino T, Rinaldo M, De Chiara A, Gallipoloi A (2005) Color-doppler using contrast medium in evaluating the response to neoadjuvant treatment in patients with locally advanced breast carcinoma. Anticancer Res 25:595–599, PubMed
41. Singh S, Pradhan S, Shukla RC, Ansari MA, Kumar A (2005) Color doppler ultrasound as an objective assessment tool for chemotherapeutic response in advanced breast cancer. Breast Cancer 12:45–51

42. Kumar A, Singh S, Pradhan S et al (2007) Doppler ultrasound scoring to predict chemotherapeutic response in advanced breast cancer. World J Surg Oncol 5:99. doi:10.1186/1477-7819-5-99
43. Chung SY, Yang I, Kim D, Shin SJ, Bae SH (2003) Characteristic US findings of inflammatory breast carcinoma: comparison with MR imaging. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
44. Lee KW, Chung SY, Yang I, Kim HD et al (2005) Inflammatory breast cancer. Clin Imaging 29(1):22–25. doi:10.1016/j.clinimag.2004.03.006
45. Papotti M, Gugliotta P, Ghiringhello B, Busolati G (1984) Association of breast carcinoma and multiple intraductal papillomas: an histological and immunohistochemical investigation. Histopathology 8(6):963–975
46. Saad RS, Kanbour-Shakir A, Syed A, Kanbour A (2006) Sclerosing papillary lesion of the breast: a diagnosting pitfall for malignancy in fine needle aspiration biopsy. Diagn Cytopathol 34(2):114–118
47. Lefkowitz M, Lefkowitz W, Wargotz ES (1994) Intraductal (intracystic) papillary carcinoma of the breast and its variants: a clinicopathological study of 77 cases. Hum Pathol 25(8):802–809
48. Ueng S-H, Mezzetti T, Tavassoli AF (2009) Papillary neoplasms of the breast: a review. Arch Pathol Lab Med 133(6):893–907
49. Svane G (2005) Ductal Carcinoma in Situ (DCIS): incidence, prognosis, and diagnostic aspects on mammography, galactography, and needle biopsies. In: Research and development in breast ultrasound. Springer, Tokyo, pp 114–118
50. Takebe K, Izumori A (2005) The ultrasonographic diagnosis of nonpalpable DCIS without calcification on mammography and nipple discharge: advocacy of a new term, 3 non-DCIS. In: Research and development in breast ultrasound. Springer, Tokyo, pp 119–126
51. Tanaka K, Sakuma H, Sakamoto G et al (2005) Characteristic mammography and ultrasonography findings of ductal carcinoma in situ of the breast arising in sclerosing adenosis. In: Research and development in breast ultrasound. Springer, Tokyo, pp 135–140
52. Silverstein MJ, Recht A, Lagios M (eds) (2002) Ductal carcinoma in situ of the breast, 2nd edn. Silverstein/Lippincott Williams & Wilkins, Philadelphia
53. Kim EK, Oh KK, Shin HC (1996) Paget's disease of the breast: significance of mammographic findings. J Korean Radiol Soc 34(4):551–555
54. Choi SH, Chung SY, Lee KW et al (2001) Ultrasonography in Paget's disease of the breast: comparison with mammographic findings. J Korean Soc Med Ultrasound 20(20):137–142
55. Bacchetta J, Juillard L, Cochat P et al (2009) Paraneoplastic glomerular diseases and malignancies. Crit Rev Oncol Hematol 70:39–58
56. Kijima Y, Yoshinaka H, Owaki T et al (2004) Breast cancer with nephrotic syndrome: report of two cases. Surg Today 34(9):755–759
57. Valcamonico F, Ferrari V, Simoncini E et al (2004) Paraneoplastic nephrotic syndrome in advanced breast cancer patient. A case report. Tumori 90(1):154–156
58. Yoshizawa H, Akimoto T, Nishino K et al (2011) Nephrotic syndrome and renal failure in a patient with metastatic breast cancer. Clin Exp Nephrol 15(4):567–571. doi:10.007/s10157-011-0425-1, Epub 2011Mar 18
59. Oh KK (2003) The Paget's disease and pagetoid extension of the breast cancers: 3-D sonographic and pathologic correlation. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
60. Sakita I, Yoshida T, Sohma I, Fukuchi N, Izawa H, Ebisui C, Hasuike Y, Ishizawa H, Kobayashi Y, Kotera I, Fujimoto T (2003) Determination of indication for sentinel lymph node biopsy using Doppler imaging. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
61. Wisner ER, Ferrara KW, Short RE, Ottoboni TB, Gabe JD, Patel D (2003) Sentinel node detection using contrast-enhanced power doppler ultrasound lymphography. Invest Radiol 38(60):358–365
62. Britton PD, Goud A, Godward S, Barter S et al (2009) Use of ultrasound-guided axillary node core biopsy in staging of early breast cancer. Eur Radiol 19(3):561–569
63. Chung SY, Kim E-K, Oh KK (2003) Imaging findings of axillary abnormalities.13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
64. Okamoto T, Horiuchi K, Kodama H et al (2005) Probability of axillary lymph node metastasis when sentinel lymph node biopsy is negative in women with clinically node negative breast cancer: a Bayesian approach. Breast Cancer 02/12(3):203–210. doi:10.2325/jbcs.12.203
65. Kusama M, Kawamoto A, Kaise H et al (2003) Ultrasound with tissue harmonic imaging in detection of axillary lymph node metastases in breast cancer patients. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology
66. Esen G, Gurses B, Ylmaz MH et al (2005) Gray scale and power doppler US in the preoperative evaluation of axillary metastases in breast cancer patients with no palpable lymph nodes. Eur Radiol 15(6):1215–1223
67. Rashmi S, Govardhan HB, Satyajt P et al (2014) Colour doppler – an evaluation tool for assessment of breast tumor size, axillary lymph node size and chemotherapeutic response. J Cancer Treat Res 2(2):9–15. doi:10.11648/j.jctr.20140202.11
68. Han SY, Kim HH (2003) Parasternal sonography of the internal mammary lymphatics in breast cancer. 13th International congress on the ultrasonic examination of the breast. International Breast Ultrasound School. The 10th meeting of Japan Association of Breast and Thyroid Sonology