Breast Calcifications in Full Breast Ultrasonography

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7.1 Breast Calcifications in US: Technical Aspects

Because the mammography still represents the main imaging method to visualize the breast (micro-)calcifications and the US BI-RADS assessment was created upon the first radiological one, the extension of the terms and the intention to interpret the sonographic images using the same descriptors added disillusion for the overall classical US accuracy. Results of both mammography and classical US have limitations that reduce their clinical usefulness, and alternative breast imaging modalities are being sought.

Indeed, the main important findings in detecting breast cancer by mammography are microcalcifications, architectural distortions, and asymmetric breast densities eventually with peripheral spiculations. Contrarily, FBU can visualize the main normal breast tissues, represented by breast parenchyma (mammary ductal tree ended by lobules) and the glandular stroma, surrounded by the pre-, retro-, or interlobar fatty tissue, delimited by the fibrous tissue represented by the network of Cooper ligaments; in addition, there are identified the main vessels and the satellite lymph nodes, and thus any abnormal benign or malignant structures issued in the breast become salient.

The typical size of breast microcalcifications ranges from 50 to 500 μm, but the size measurable using usual high-frequency transducers of up to 14 MHz is over 400 μm, usually in the domain of benign calcifications. Current ultrasound scanners do not reliably detect microcalcifications in the size range of clinical interest for breast cancer diagnosis. However, some theoretic, simulation, and experimental studies focused on the improvement of the ultrasonic visualization of microcalcifications were presented [1]. But the results are still unsatisfactory, because the use of the US as an adjuvant or complementary method for mammography (which has low sensibility in dense breasts) is wrong and confusing; otherwise, US has other descriptors, more accurate and more specific than mammography, especially when combining the results of all the developments in US, achieving the concept of FBU.

The research of the tissues' elasticity was based on clinical experience, but the best imaging method was not easy to define. Many methods have been proposed to measure the mechanical response of the tissues to the impact of a force. The method named *vibro-acoustography* uses the ultrasound radiation force to harmonically vibrate tissue and measure the resulting acoustic emission field with a nearby hydrophone. Another method, *vibrometry*, uses the ultrasound radiation force accompanied with a measurement of the resulting velocity or displacement of the vibrating tissue or object. An extension of the vibro-acoustography method using a multifrequency stress field to vibrate an object was described [2]. Resulting images of the vibro-acoustography show soft tissue structures and calcifications within breast with high contrast, high resolution, and no speckles [3]. These methods are not popular, and there are few manufacturers that implemented them in their ultrasonographic machines. Contrarily, sonoelastography was more successful, and its technique and applications were standardized and implemented by many manufacturers, becoming a technique as available and useful as is the Doppler in the US practice; however, sonoelastography can diagnose the malignancy without correlation with the presence of the microcalcifications; even admitting the strain is influenced by the presence of undetectable malignant microcalcifications.

The best characterization of the microcalcifications is realized of course by mammography. The radiologist can visualize all the microcalcifications and their shape, size, and distribution. A classification of the calcifications in benign (not cancerous), probably benign, indeterminate (not sure), and suspicious (might be cancer) was adopted. Benign calcifications tend to be round or oval, uniform in density, and scattered in the breast tissue. Suspicious microcalcifications, on the other hand, vary in shape, size, form, and density and are usually clustered in a linear or segmental pattern.

Mammography cannot diagnose small breast invasive cancer or DCIS that do not present microcalcifications; nevertheless, it is useful in detecting DCIS because 90 % of cases present microcalcifications with suggesting distribution

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(branching calcifications in DCIS) [4]. Any areas of microcalcifications should be evaluated with magnification views to accurately define their morphological features as well as their number and distribution. However, there are limitations of the mammography that are due to the image blur on magnification views that may compromise image quality. Digital mammography was finally accepted as screening method, and some advantages such as good magnification without repeated exposure made quickly its success. In addition, tomosynthesis is proposed as a better technique of detection of breast cancer, microcalcifications included, but it is far the era of using it for breast cancer screening.

It is assumed microcalcifications often cannot be localized with US; however, some authors consider microcalcifications in malignant lesions that are reliably recognized by US (100 %), but they are difficult to detect in fibrocystic breast changes because of their spreading without correlation with a sonographic mass [5].

The classical US used especially as a complementary examination may be helpful in:

- The determination of the presence of a solid mass that corresponds to an area of distortion.
- Further evaluation of a palpable mass in any patient with dense breast parenchyma and negative mammographic findings.
- The evaluation of asymmetric densities seen at mammography because US can precise the differential diagnosis of the density as either a breast tissue or a true mass. Soo et al. [6] and Skaane [7] found the NPV of US with mammography for a palpable lesion to be 99.8 % and 100 %, respectively. Moy et al. [8] affirm a negative mammographic and US finding of a palpable abnormality does not exclude breast cancer, but the likelihood of breast cancer is low, approximately 2.6–2.7 %. However, the classical practice considers a palpable mass that appears solid at US which warrants further evaluation with biopsy, in the absence of the full analysis by Doppler and sonoelastography.
- The detection of the thickened ducts that are associated with malignancy: a unilateral solitary dilated duct [9] and dilated ducts associated with microcalcifications or in a non-subareolar location.

Limitations of breast US that are recognized in the classical examination (as a complementary method, with the main scans in the transversal and sagittal planes) include:

- The inability to visualize some solid masses owing to small size (particularly intraductal carcinomas) or to izoechogenicity.
- Overlap in ultrasonographic appearance of some benign and malignant lesions.
- Difficulty in identifying intraductal microcalcifications that are readily depicted on mammography in the absence of a mass. However, the noncalcified DCIS that is commonly occult or shows subtle findings of malignancy on mammography may be visible on US as a variable figured mass or nonspecific ductal changes sometimes with suspicious findings [10].

In US, microcalcifications of malignant type could not be positively identified because of the limiting factor of the low frequency of the transducers. However, microcalcifications larger than 0.5 mm could be differentiated as strong echogenic foci in hypoechoic masses. The main value of the US was the ability to demonstrate masses in the area of mammographic microcalcifications, which were associated with invasive carcinoma. Reports in literature affirm the introduction of higher-frequency 7.5 MHz transducers with automatic scanners that improved visualization of microcalcifications up to 57 % of cases but only when associated with masses; they appear as echogenic foci in hypoechoic areas and do not attenuate. Using 7.5–10 MHz real-time ultrasound equipment, ultrasound abnormalities corresponding to clustered microcalcifications were identified in 59.6–76 % cases with specificity for malignancy of 82–93 %. There is, however, lower accuracy in the positive identification of benign microcalcifications, and not all malignant microcalcifications could be positively identified on ultrasound. There is no clear distinction in whether the malignant lesions identified sonographically were invasive carcinomas, which were usually associated with a sonographic mass or pure in situ disease. Other investigators using similar equipment to localize impalpable lesions presenting solely as microcalcifications have not been able to achieve this level of detection. The use of higher-frequency ultrasound probes with operating frequencies above 7.5 MHz and claimed axial and lateral resolution of 0.1–0.5 mm improved the ability of detecting microcalcifications greater than 0.6 mm in size. Moreover, the detection of microcalcifications of 0.15 mm in size is possible using a 13 MHz transducer with an axial resolution of 0.118 mm. However, the results are mixed with sensitivities ranging from 52 to 88 % patients in the literature, but almost all authors used US as a complementary method [11].

In conclusion, the ability to visualize microcalcifications is likely to be multifactorial, depending not only on the presence of any associated sonographic abnormalities but also on operator experience.

Nevertheless, the definitive identification of benign microcalcification is comparatively lower from that of malignant disease and ranges from 33.5 to 85.7 % in prospective studies where histological correlation is available, the main size being larger than of the malignant type of up to 2–4 mm. Malignant lesions are usually more readily identified even in

the absence of a mammographic detectable mass, because the breast cancerous cells are not dense and do not form a mammographic opacity in the absence of the desmoplastic reaction, while the proliferative lesion is always salient in US.

Classical US describes morphological features in DCIS with vague relationship with the breast anatomy; the presence of dilated ducts that contain flecks of microcalcifications, which may be associated to sonographic parenchymal changes or hypoechoic lesions, is included. Adjacent strongly echogenic foci representing microcalcifications are also described, but without specific location related to the breast anatomy. Masses or irregular attenuating areas may also be present particularly with high-grade or comedo DCIS, which have the appearances of the typical spiculated or irregular borders. Where invasive carcinoma is present, the positive identification of a sonographic abnormality approaches that of 100 %; the ability to visualize a sonographic abnormality is particularly high where the mammogram shows a suspicious appearance or where there is clustering of more than 10 mm in extent. In fact, the increased detection rate of malignant calcifications using ultrasound was due to the use as a complementary method, but it was not proved US can visualize with good accuracy any calcification as the first technique of diagnosis; moreover, US was exploited by investigators as a means of performing guided needle biopsy or preoperatory localizations of the mammographic abnormalities.

The mammographic classification of the breast calcifications was correlated with the risk of malignancy; this classification cannot be superposed on the sonographic findings, because the resolution is less performing and the geometrical aspect is different; indeed, if the microcalcifications are too small, under 200 μm, they may be not visualized as distinct sonographic foci, and if they are larger, usually in the benign lesions over 500 μm, they may present acoustic shadowing and their shape cannot be precise. This is the reason the usefulness in US diagnosis of the microcalcifications is poor, because the main characters used in mammography are not interpretable: the morphology, the distribution, and the change over time.

Therefore, the US examination must be correlated with the mammographic findings, and the radiological classification of the breast calcifications must be considered as the gold standard.

Breast calcifications in mammography may be:

Benign Calcifications
- Skin calcifications—tattoo sign
- Vascular calcifications
- Coarse or "popcorn-like"
- Large rodlike, plasma cell mastitis
- Round and punctate calcifications
- Lucent centered
- Eggshell or rim calcifications
- Milk of calcium
- Suture calcifications
- Dystrophic calcifications

Suspicious Calcifications
- Amorphous calcifications
- Coarse heterogeneous

High Probability of Malignancy
- Fine pleomorphic
- Fine linear or fine linear branching

ACR BI-RADS 2013 had reunified the suspicious and high probability of malignancy calcifications, because of biopsy recommended in both cases.

The lobular calcifications fill the acini, which are often dilated. This results in mammography to uniform, homogeneous, and sharply outlined calcifications, which are often punctate or round, sometimes visible accidently in US; when the acini become very large, as in cystic dysplasia, "milk of calcium" may fill these cavities, and fluid/fluid level can be demonstrated in US. However, when there is more fibrosis, as in sclerosing adenosis, the calcifications are usually smaller and less uniform, usually unapparent in US, but the pseudotumoral aspect with increasing acoustic shadowing may be demonstrated. In these cases, it can be difficult to differentiate them from intraductal calcifications in the classical US. Lobular calcifications usually have a diffuse or scattered distribution and are almost always benign.

The intraductal calcifications represent calcified cellular debris or secretions within the intraductal lumen; the uneven calcification of the cellular debris explains the fragmentation and irregular contours of the calcifications in mammography. These calcifications are extremely variable in size, density, and form, from pleomorphic to a complete cast of the ductal lumen. This explains the fine linear or branching form and distribution, specific in the radiological examination, but rarely detected by US as the first technique of examination, because different ducts are scanned in the transverse, variant-oblique, and longitudinal short plans in the same time, without anatomical relationship. Intraductal calcifications are suspicious of malignancy and are classified as BI-RADS 4 or 5.

The differential diagnosis in US is more important and more difficult as in the radiological examination. There are no sufficient studies about the sensibility and specificity of the US microcalcifications when using as the first method of diagnosis, but the overall accuracy is less 30 %, insufficient for the validating of the method. In fact, the most cases present *false-negative diagnosis* for microcalcifications, especially for the malignant ones, which are too small and are masked in the acoustic shadowing of the mass; moreover, there are microcalcifications in the glandular stroma that is

hyperechoic and has no sufficient contrast toward the tinny foci. Small benign calcifications of the glandular acini are isolated and usually are underdiagnosed in US, already being without clinical significance.

The most cases of *false-positive diagnosis* are microcysts, in the nodular form of the fibro-micro-cystic dysplasia, or ductal micropapillomas associated with ectasias. In other cases, the vascular calcifications may appear as ductal or lobular lesions if the non-anatomical/random scans are performed. The Cooper ligaments are easily differentiated, but abnormal fibrous changes may be confused with breast calcifications presenting hyperechoic foci. Because of their small size, the malignant microcalcifications have no acoustic shadowing, which is more conclusive for US; thus, we cannot make the differential diagnosis of the hyperechoic foci, resulting to false-positive diagnosis.

7.2 Breast Calcifications in FBU: Improvements and Limits in Detection and Interpreting

FBU has the same limits as the classical US in the detection of the tinny microcalcifications, due to the limits of the US length wave and to their unspecific aspect: small hyperechoic foci without acoustic shadowing. As consequence, microcalcifications are not essential findings in the FBU diagnosis. However, when visible, they must be interpreted and integrated in the diagnosis.

The localization of the visible microcalcifications is more precise in FBU than in the classical US or mammography: intraductal, in the surrounding stroma, and intratumoral; the site is specified according to the clockwise notation, useful in the follow-up examination. Moreover, the salient pathological vasculature and the increased FLR are high suggestive for malignancy in the site with mammographic microcalcifications that are not visible in US.

The benign calcifications are usually larger than 1 mm, well identified as hyperechoic lesions sometimes with an eggshell aspect and with acoustic shadowing effect; the new vasculature is either absent, or the Doppler signal may present the twinkling artifact, while the FLR may be increased, mimicking malignant lesions.

FBU is useful in the managing of cases after surgical conservative therapy of the DCIS, usually diagnosed by mammography based on the suggestive microcalcifications, with/without preoperatory biopsy; recidivate in the local area after lumpectomy or segmentectomy can be demonstrated in FBU by segmental thickening of the ductal tree with loss of the central line sign; the eventual remnant axillary lymph nodes are observed during adjuvant therapy. In rare cases, in DCIS with extended microcalcifications, they are visualized by the DE of Teboul, using transducers with high resolution.

The IDC or ILC may develop in the same or in the contralateral breast after breast-conserving surgery, and 6-month interval follow-up FBU for the next 5 years should be preferred in the asymptomatic cases, instead of mammographic follow-up or of unrepeatable biopsy as the clinical practice still recommends [12, 13]. In fact, the clinical practice uses the FNAB in verifying a malignancy and the core-needle biopsy in establishing definitive preoperatory diagnosis; despite the preoperative diagnostic algorithm in case of round/oval densities, stellate lesions, or microcalcifications found on the mammogram which are usually based on the guided biopsies [14], there is no consensus about the interval between negative biopsies or histologically proved benign/premalignant breast proliferation [15].

As a conclusion, FBU and US in general are not useful in detecting and characterizing the *microcalcifications as indirect signs* of breast malignancy, as does the mammography, which is still missing up to 30 % of breast cancers because of various types of pitfalls [16]; however, FBU can detect any *proliferative abnormality of the ductal tree*, from the ductal/lobular hyperplasia to the DCIS or IDC/ILC, based on the *direct* anatomical findings (Figs. 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, 7.14, 7.15, 7.16, 7.17, and 7.18).

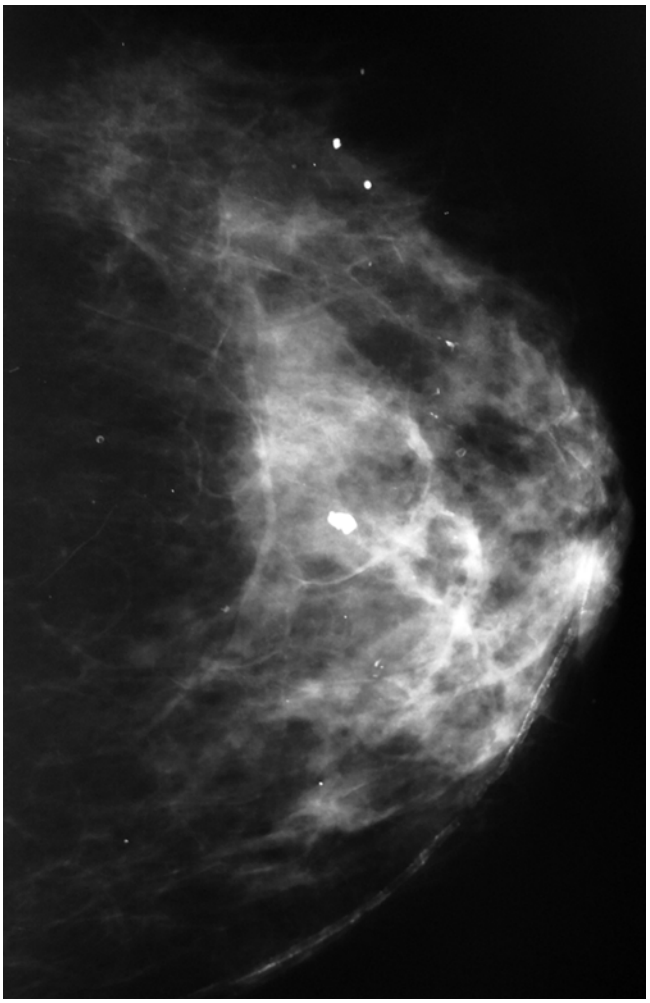

Fig. 7.1 Analogue mammography (zoomed plain-film mammography) illustrating benign calcifications

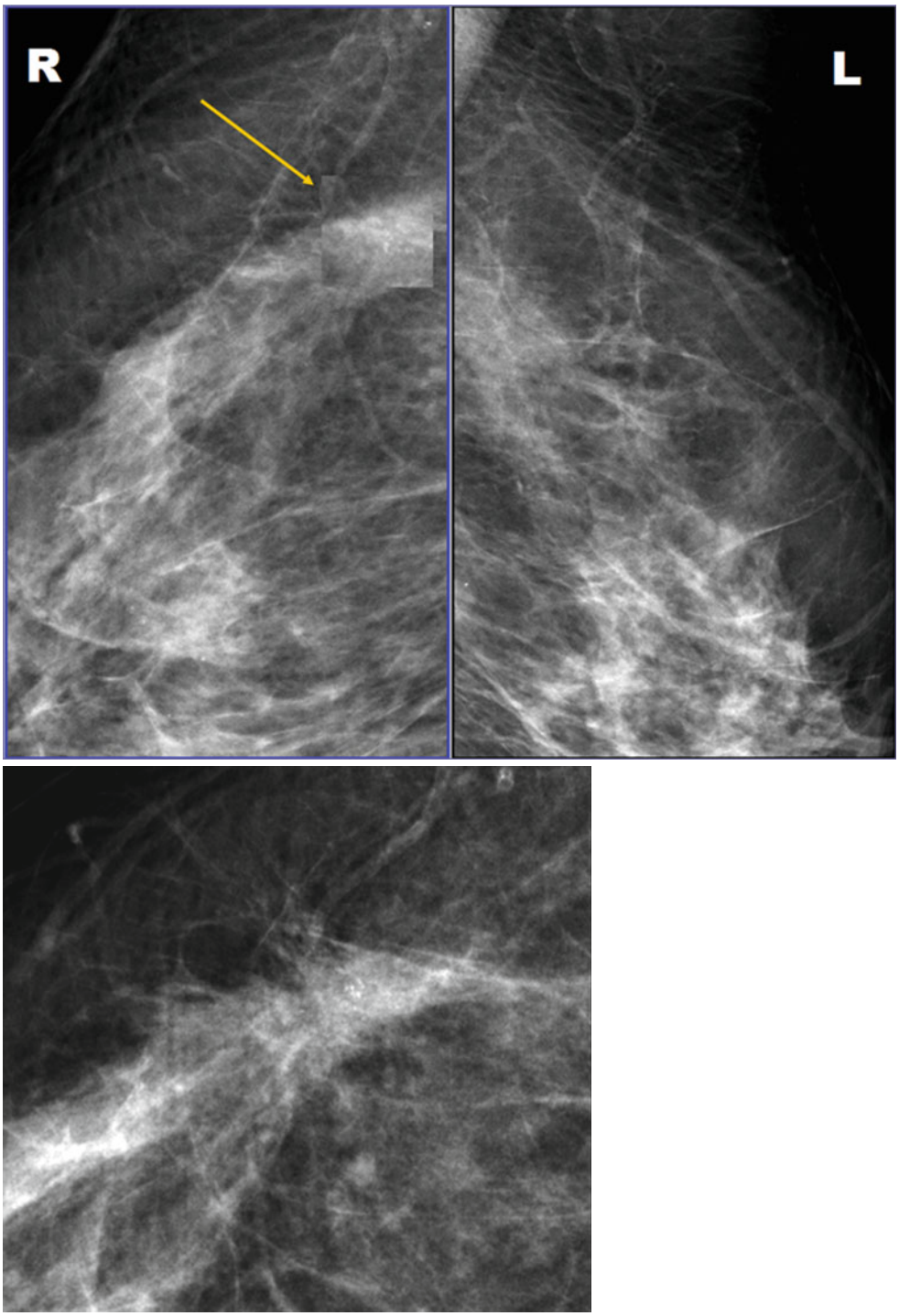

Fig. 7.2 IDC with mammographic tinny microcalcifications in the R-UOQ, visible with electronic magnification in this case; the focal surrounding increased breast density is difficult to delimitate from the rest of glandular structures and represents the stromal reaction, the tumor itself being invisible radiologically

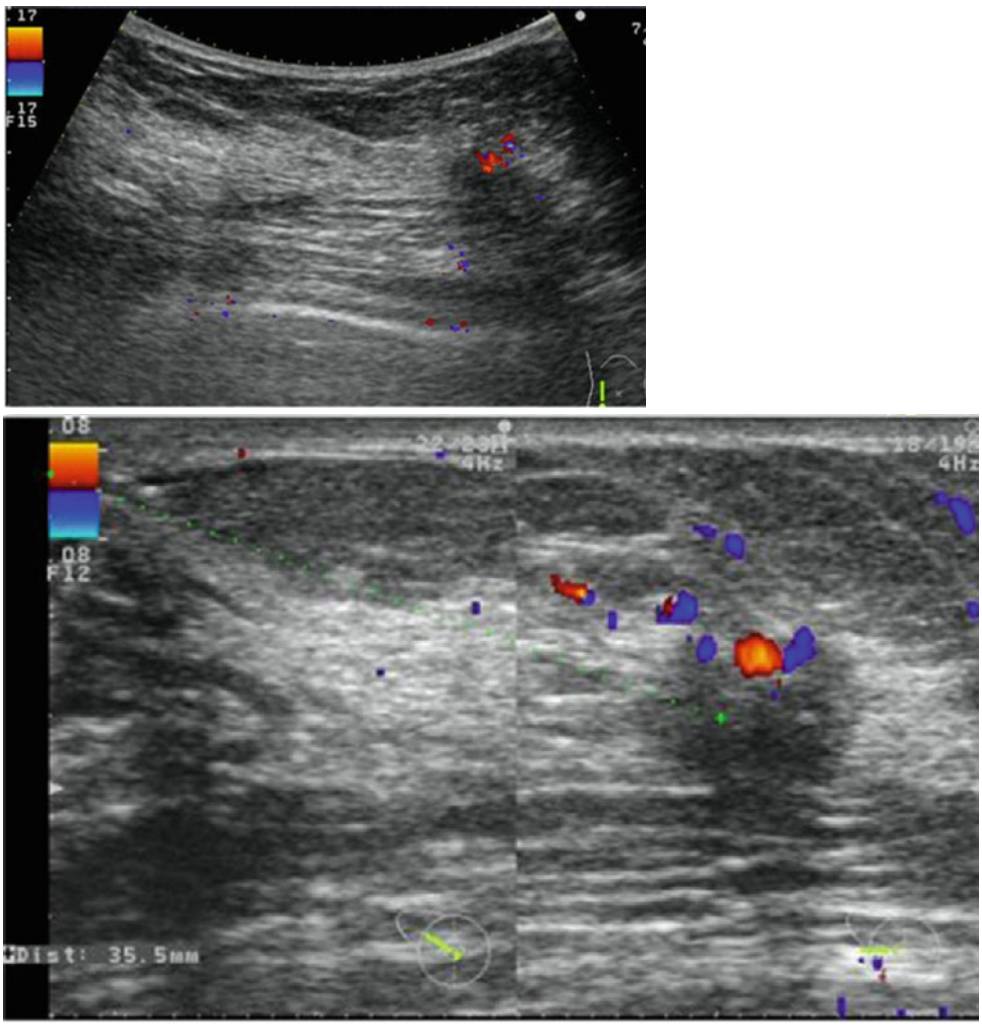

Fig. 7.3 The same case: R: 10:00 peripheral mass less 12 mm size, with ductal connection, malignant characters upon Stavros and salient new vasculature with incident plunging angle, tortuous and enlarged vessels with high velocity determining aliasing; the hyperechoic foci cannot be interpreted as microcalcifications without previous radiological information

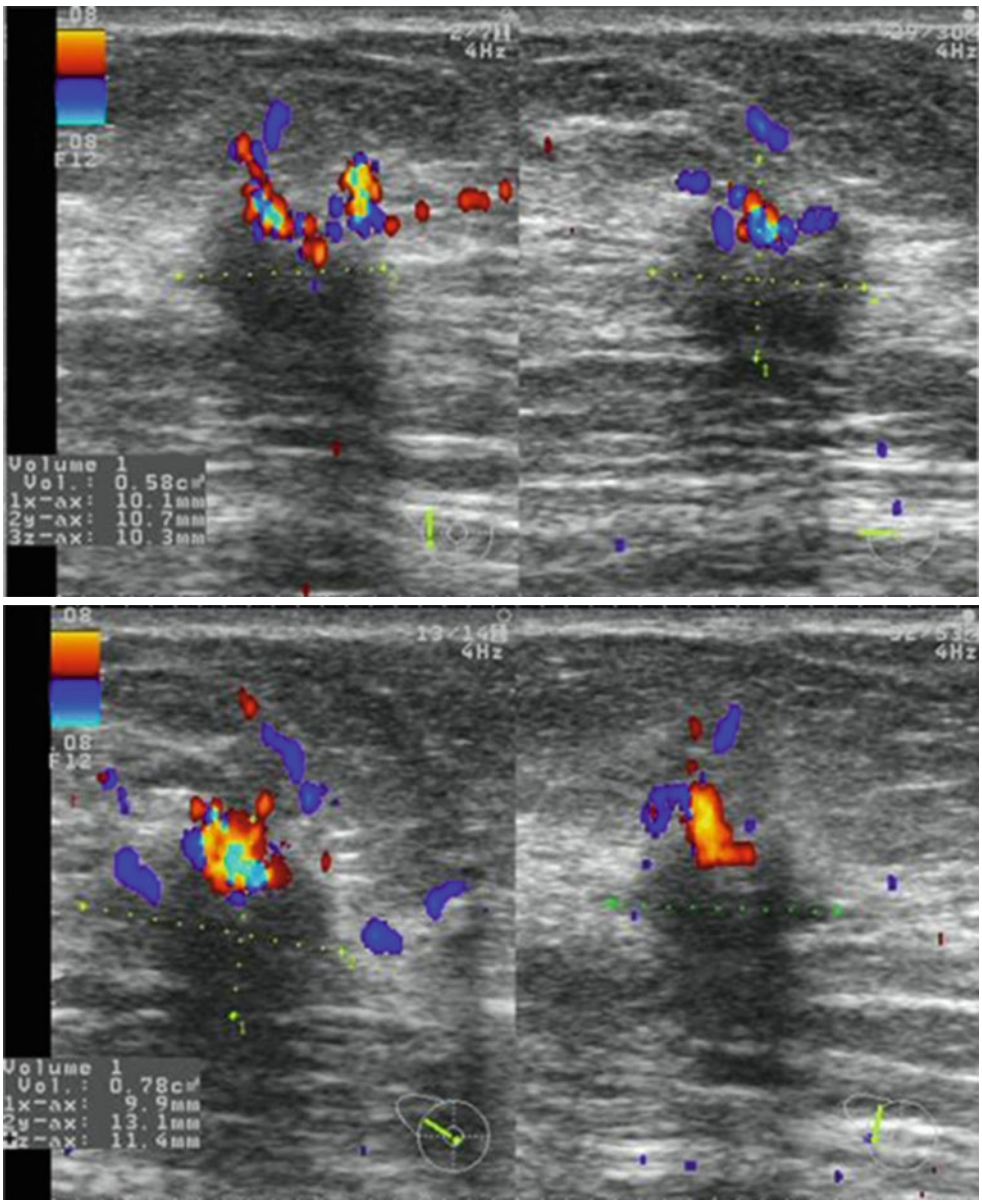

Fig. 7.3 (continued)

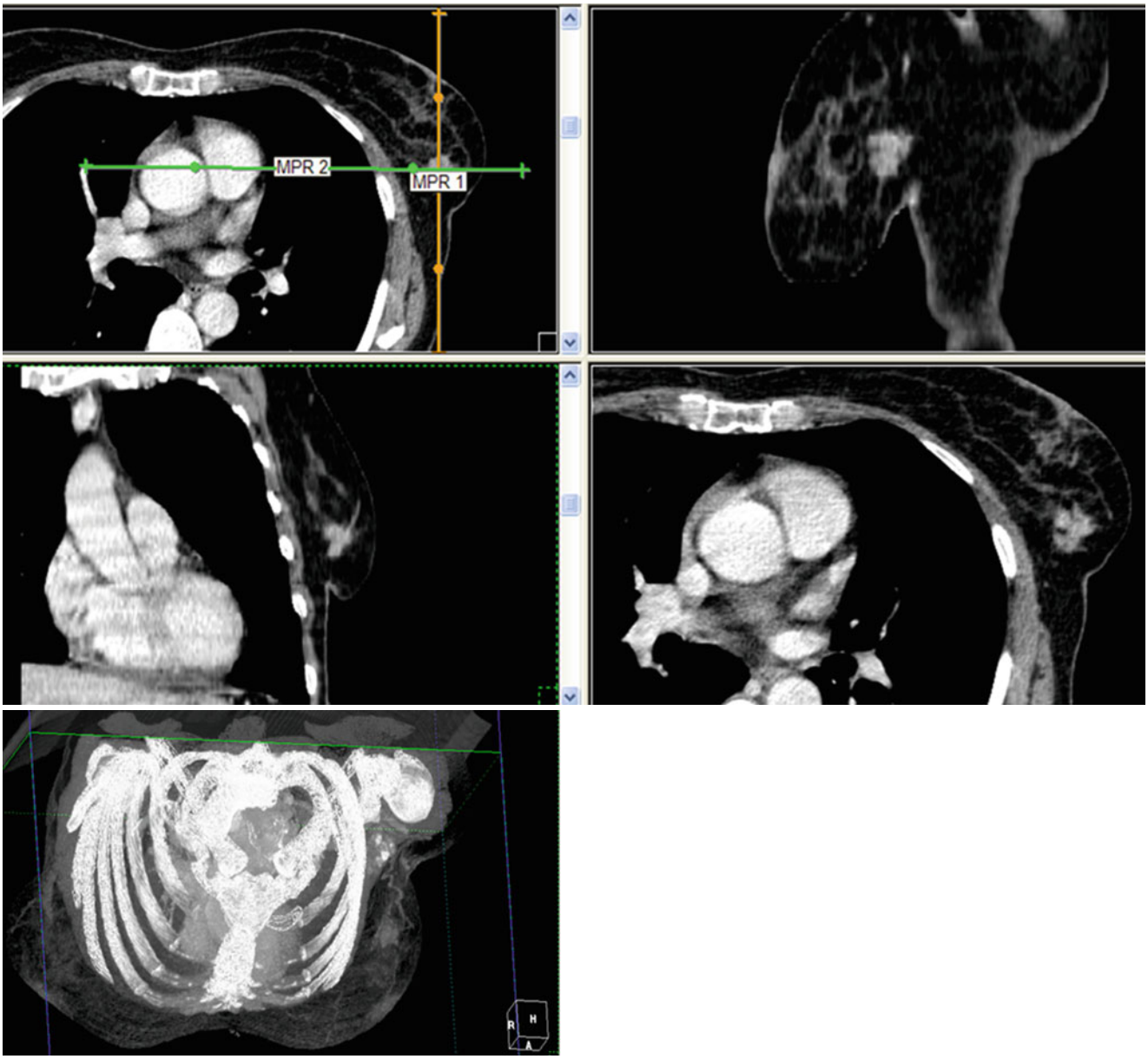

Fig. 7.4 Breast cancer with axillary lymph nodes metastasis: the multidetector CT examination with multiplanar reconstructions illustrates the breast tumor, with microcalcifications detectable at mammography, confirmed as IDC; the tumor connection with the armpit is demonstrated by the nourishing vessel and the axillary lymph nodes that present calcifications detectable by 3D reforming with bony density

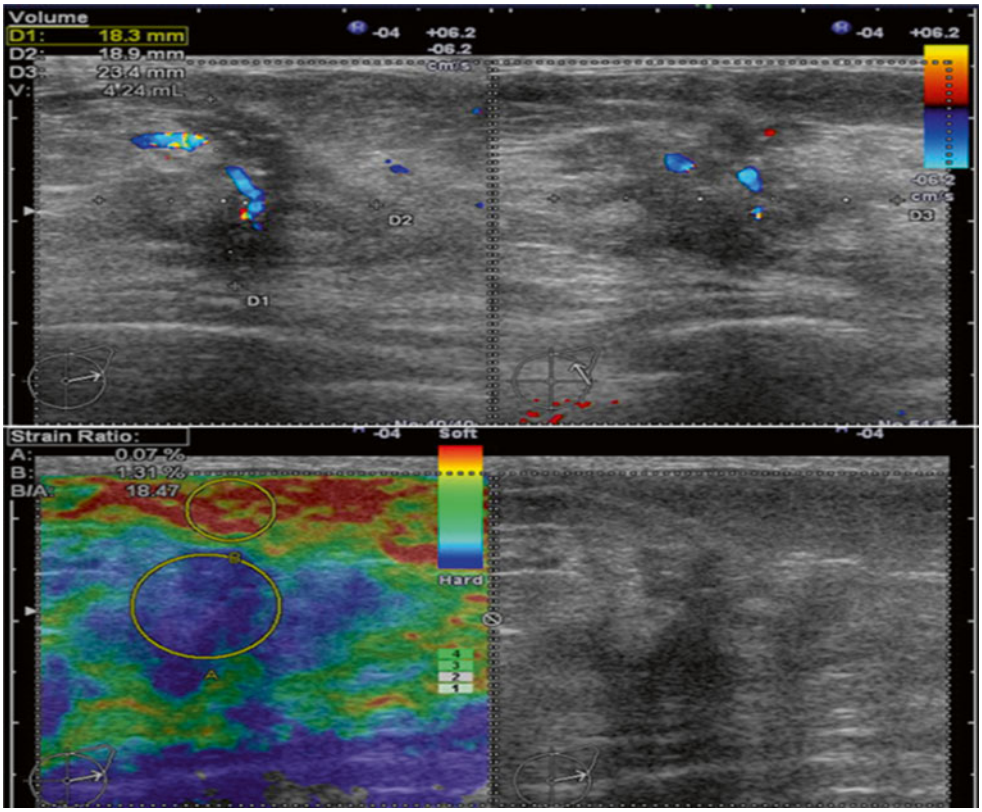

Fig. 7.5 The same case: IDC with FBU characteristic findings in L: 2:00 with irregular shape, acoustic shadowing, new vasculature with incident plunging angle, and score 5 Ueno with high FLR of 18.47. The presence of many hyperechoic foci inside the pathological mass may suggest microcalcifications in association with the other findings, but the sensibility of the method does not exceed 60 %, while other illustrated descriptors for malignity acquire an overall accuracy superior to 95 %

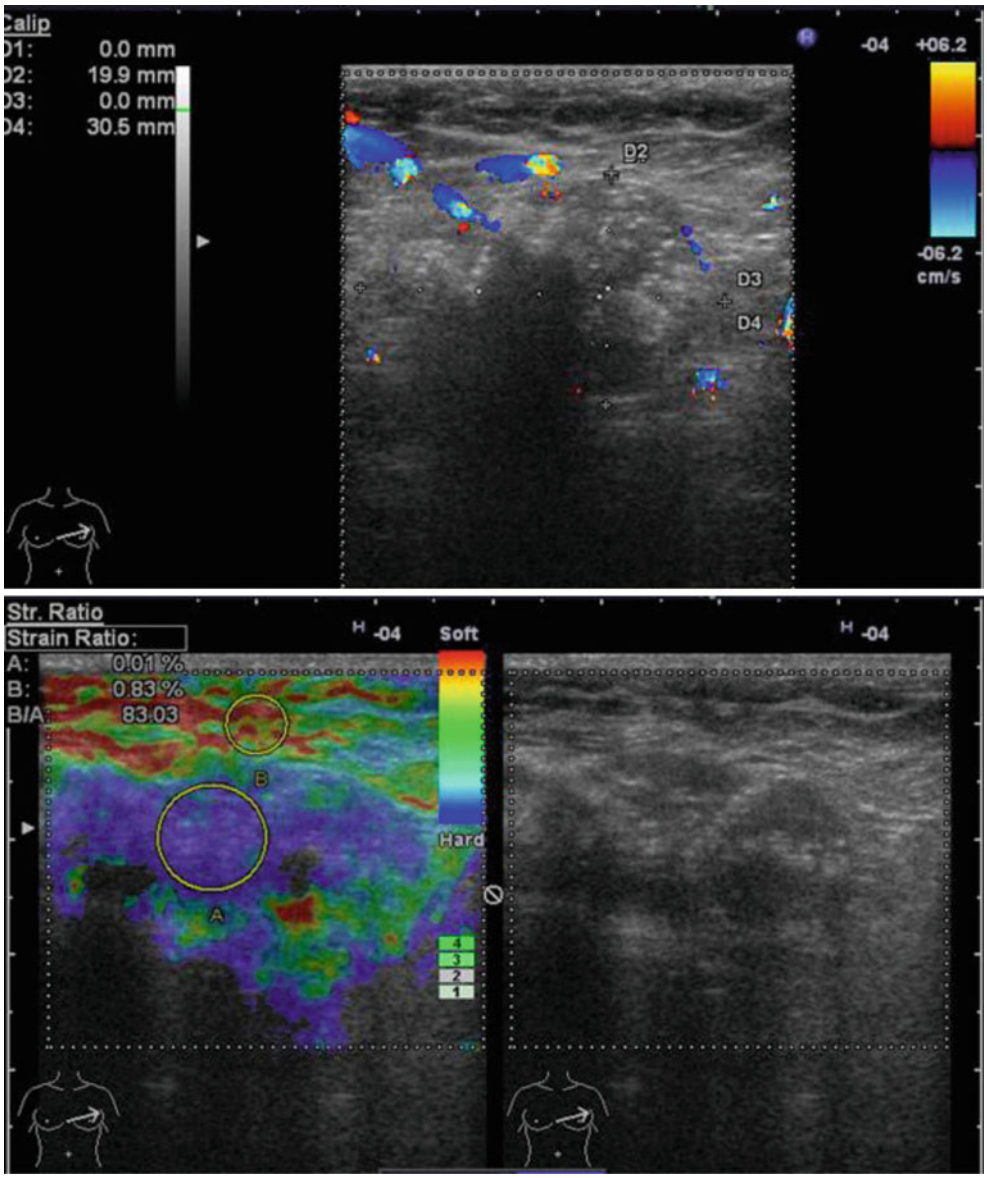

Fig. 7.6 The same case, with peripheral new vasculature of the axillary lymph nodes, small hyperechoic foci and macrocalcifications with irregular shape, hypoechoic aspect, and acoustic shadowing; the high strain is confirmed by sonoelastography with score 4 Ueno and FLR over 80.00

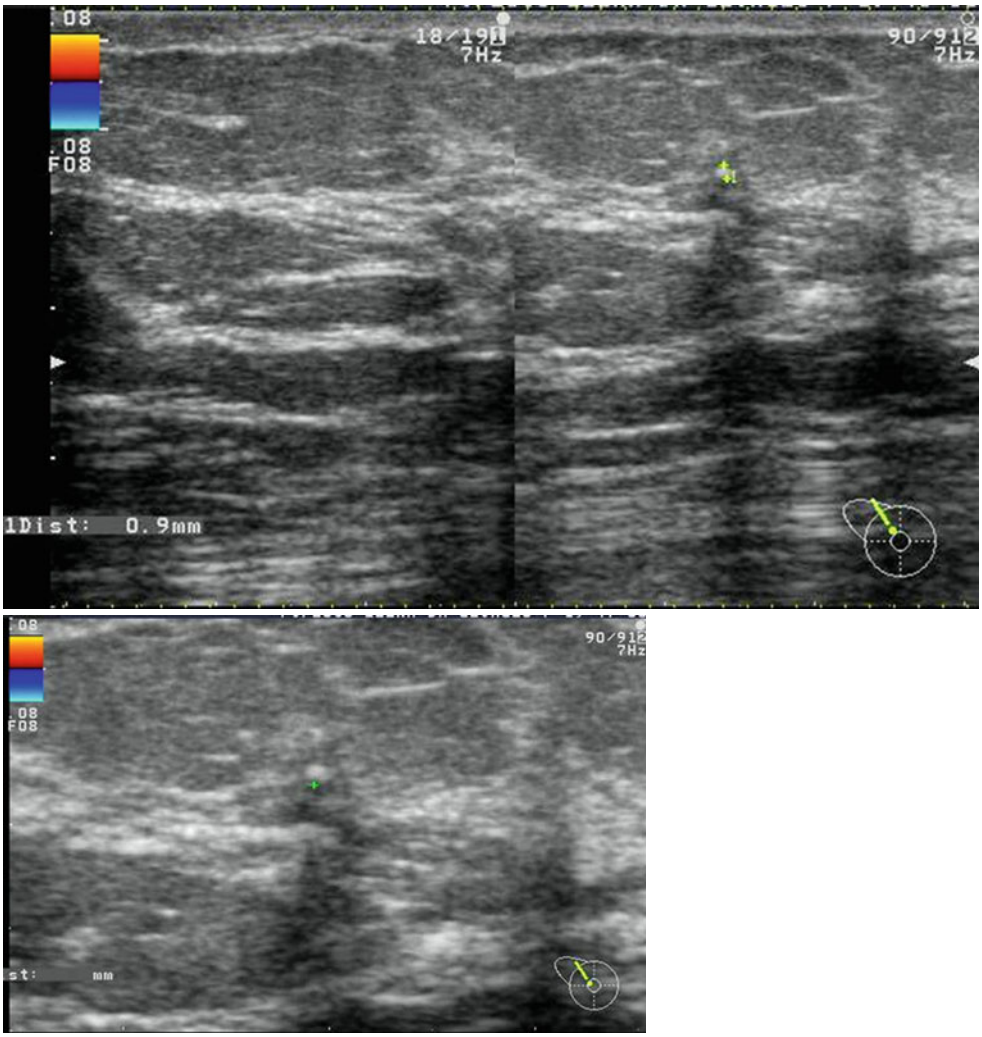

Fig. 7.7 Benign calcification of 0.9 mm, in a TDLU location, typically for a calcified lactiferous cyst; Doppler DE confirms beside the dimension, shape, location, and the absence of the new formation vessels, conclusive for the benign lesions; the acoustic shadowing is due to the Cooper ligament, these calcifications being too small for producing posterior effects

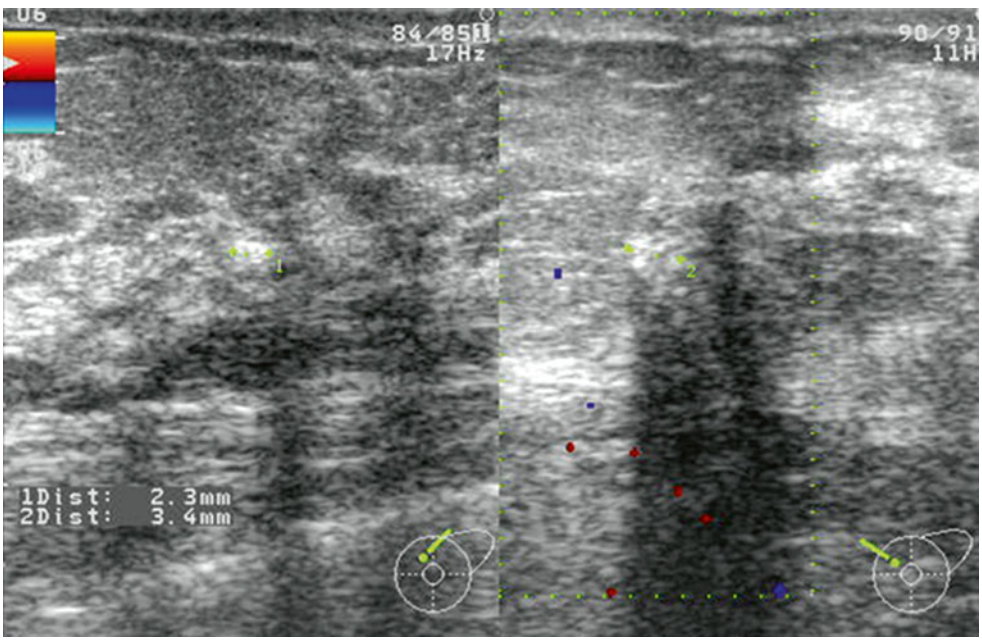

Fig. 7.8 Microcalcifications visualized on US with a size over 1 mm diameter present the characteristic posterior acoustic shadowing; these dimensions correspond to the benign mammographic microcalcifications. The finest malignant ones mammographic detectable are either not visualized or have not specific aspect on US, which has low PPV and NPV

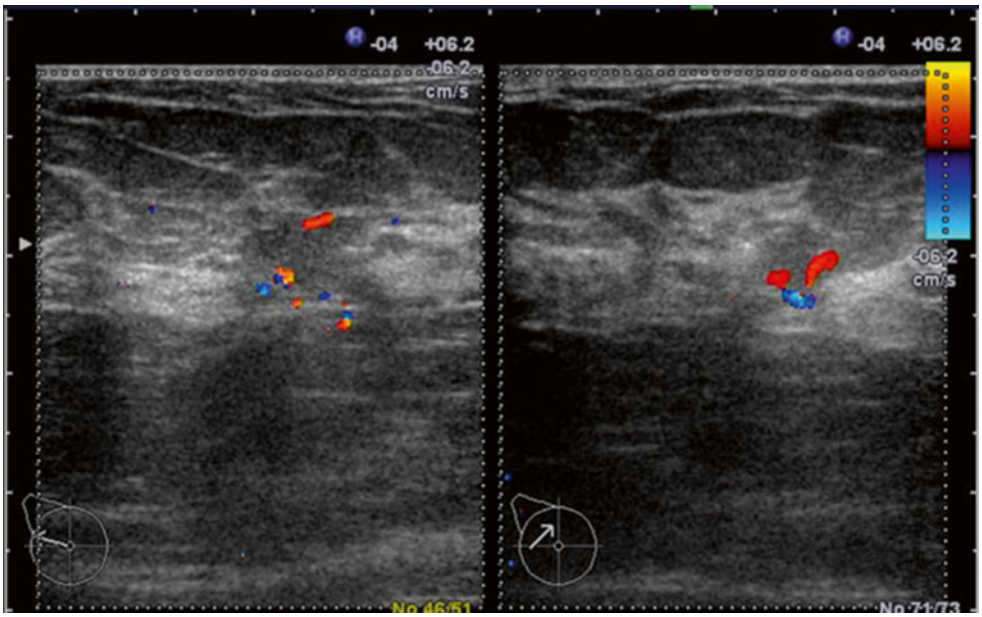

Fig. 7.9 DCIS with segmental thickening of the ducts and new formation vasculature with incident plunging angle artery; no microcalcifications detectable by US, but mammographically, they were visible as cluster of amorphous less than 0.3 mm in diameter that assessed suspect microcalcifications

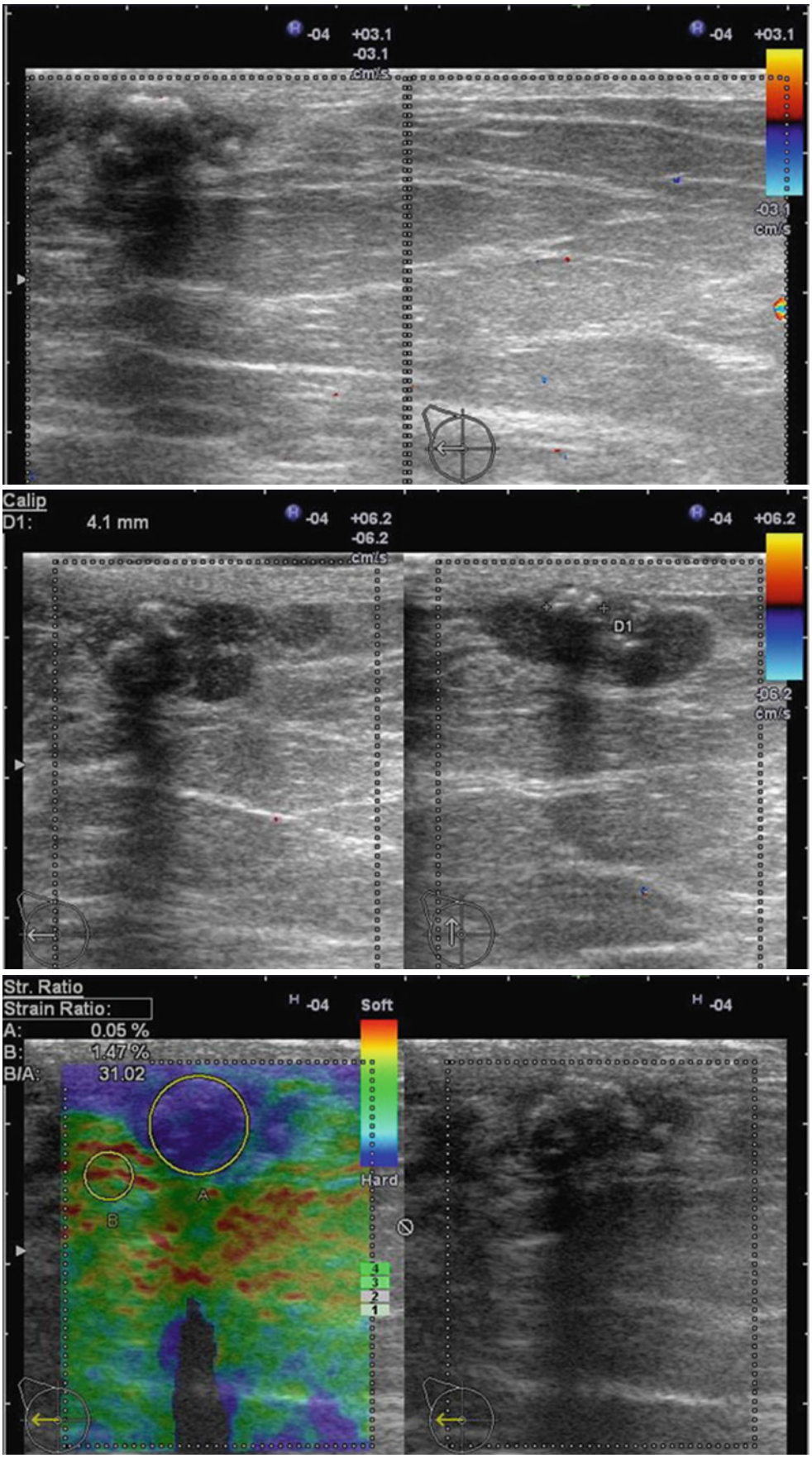

Fig. 7.10 Superficial periareolary lump in a fatty breast, with polycyclic contour, heterogeneous structure with hypoechoic aspect, and macrocalcifications in popcorn, scored 4 upon Ueno classification and with high FLR; therefore, the absence of Doppler signal argues the FBU diagnosis of benign lesion, assessed US BI-RADS 2 category, while the sonoelastographic score for this case is just estimative

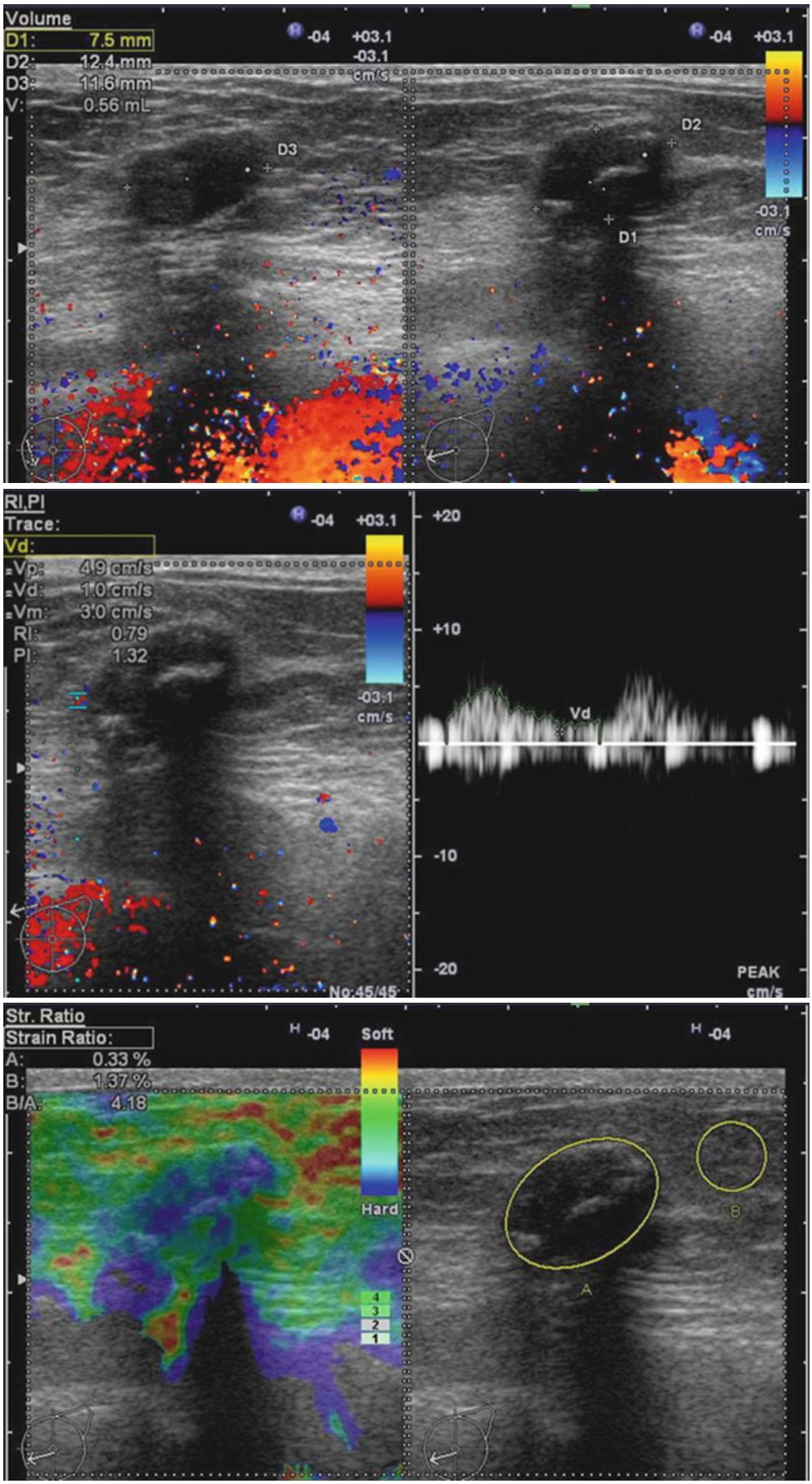

Fig. 7.11 Macrocalcifications in a cystic lesion, with peripheral vasculature and score 3 Ueno; despite the well-delineated contour, the complex aspect and the correlation between Doppler and sonoelastography can be assessed as US BI-RADS 3 category

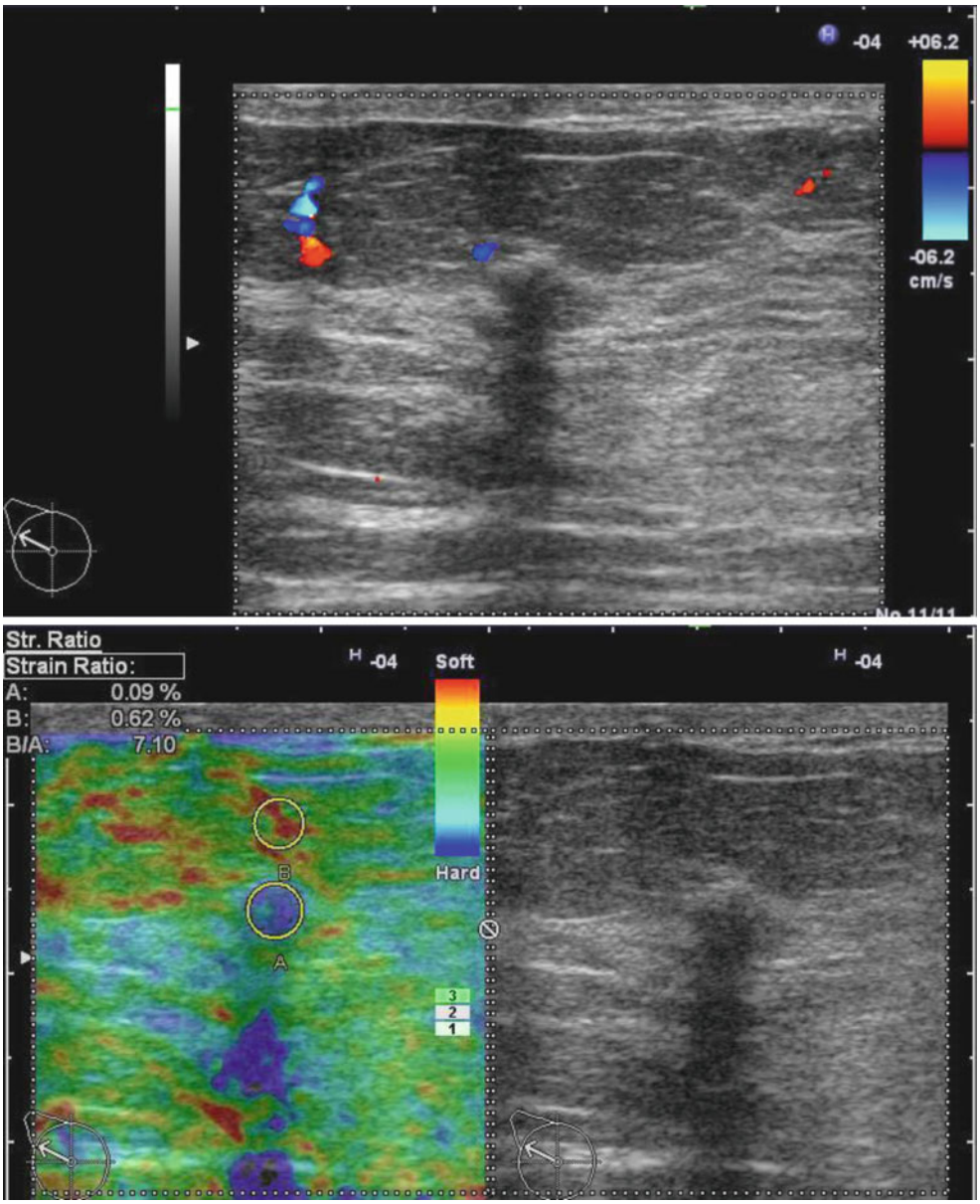

Fig. 7.12 Macrocalcifications grouped in TDLUs, with overall benign characters, despite the score 4 Ueno with high FLR (7.10); the calcifications have over 1 mm size, hyperechoic round-oval shape, and salient acoustic shadowing reinforced by the adjacent Cooper ligament's own shadow

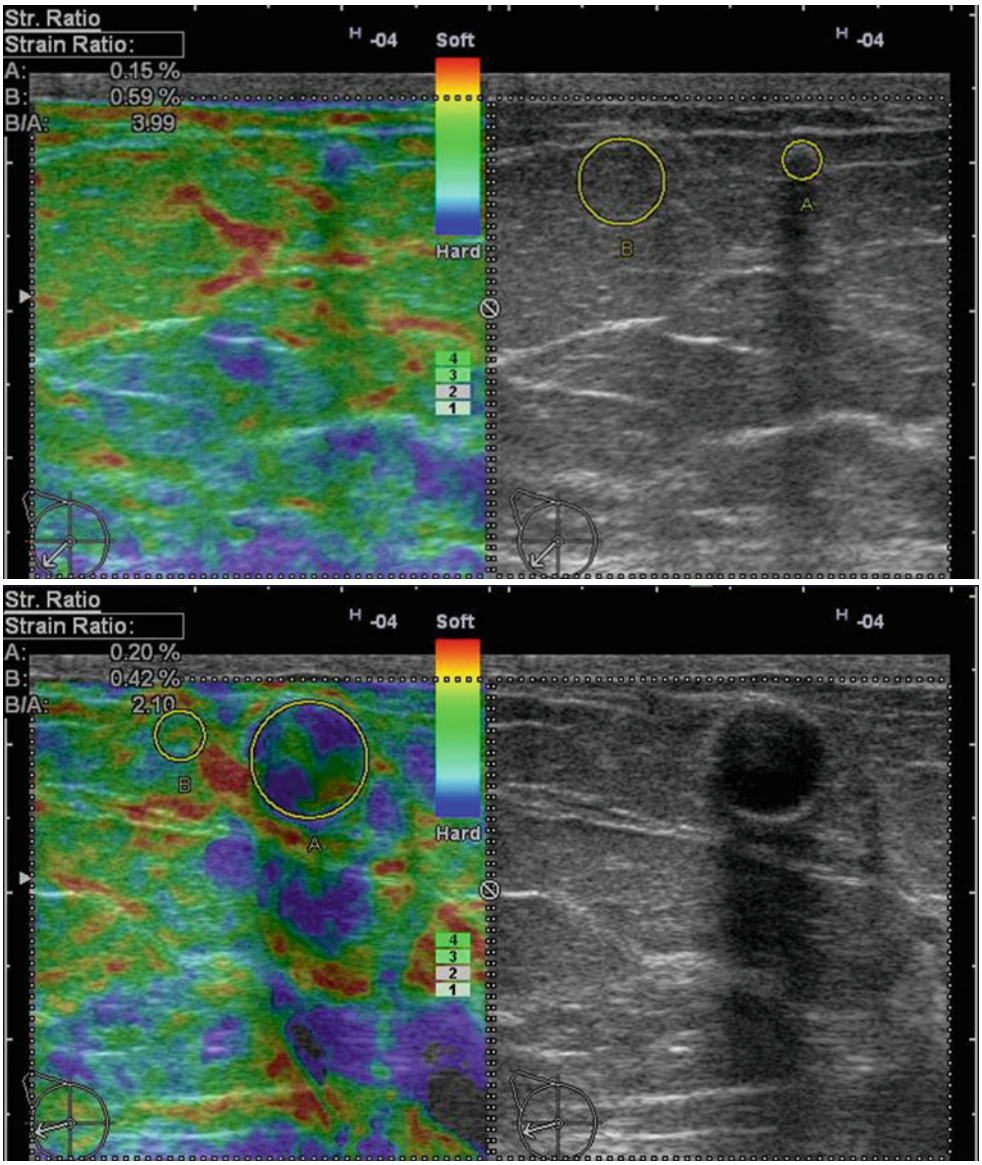

Fig. 7.13 Macrocystic calcifications presenting the eggshell sign, the absence of Doppler signal, and BGR complex score; in this case, the calcified cysts are located in the premammary fatty tissue, without connection with the remnant ductal tree, usually secondary findings after cytosteatonecrosis

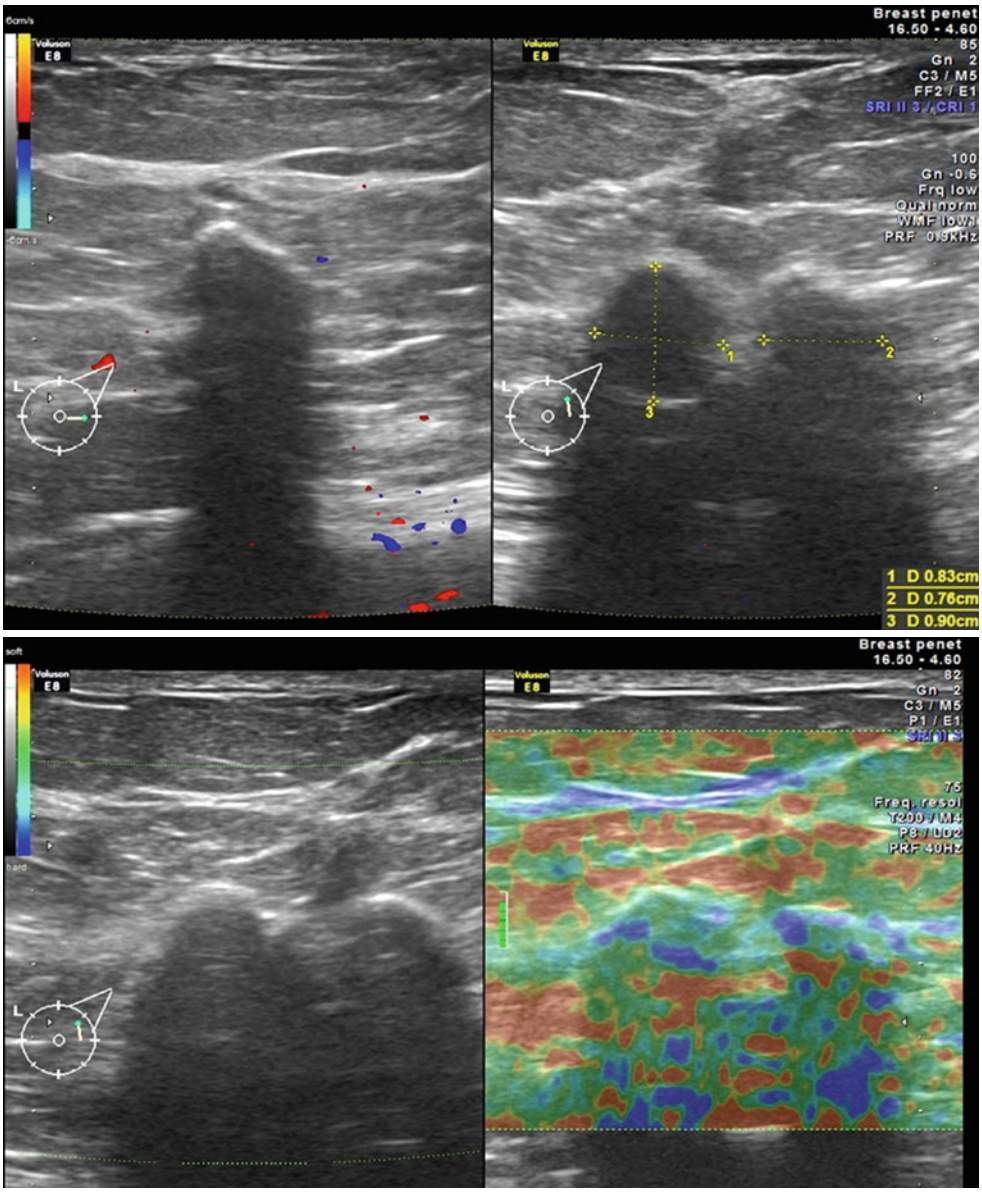

Fig. 7.14 Macrocystic calcifications in a fatty breast presenting the eggshell sign, increased acoustic shadowing, the absence of Doppler signal, and BGR complex score-type reverberation; the cysts have connection with the ductal tree, representing a form of the fibrocystic dysplasia

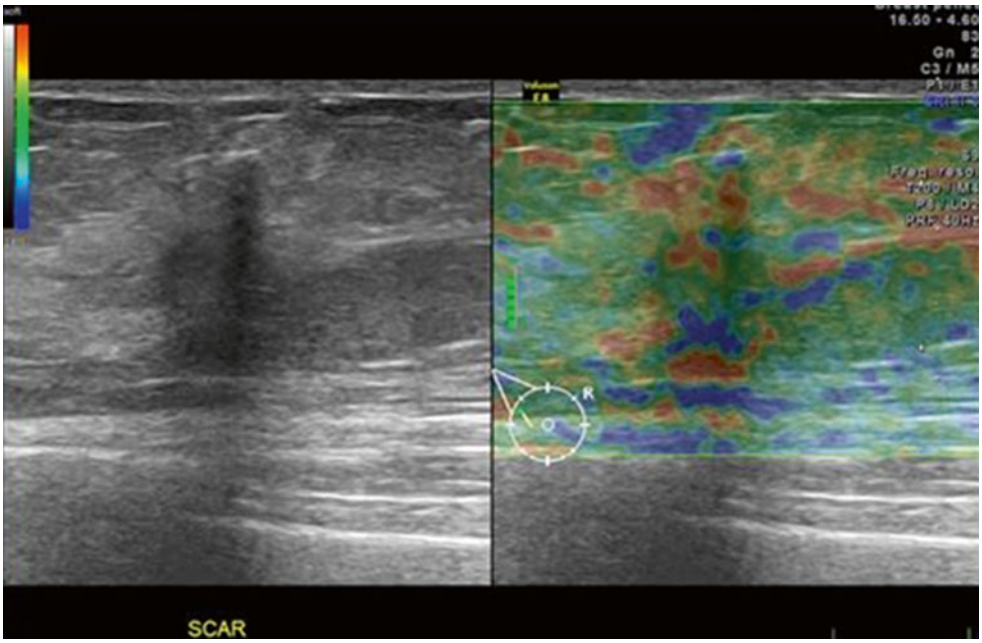

Fig. 7.15 Suture granuloma mimicking breast calcification

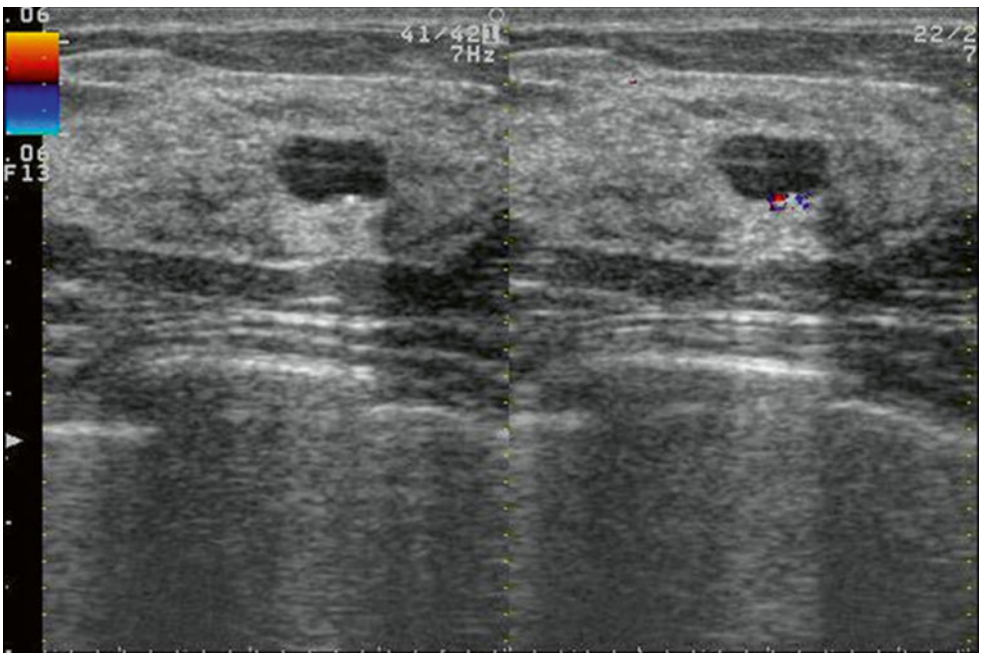

Fig. 7.16 Cystic sedimentary calcifications with hyperechoic debris presenting small Doppler twinkling artifact

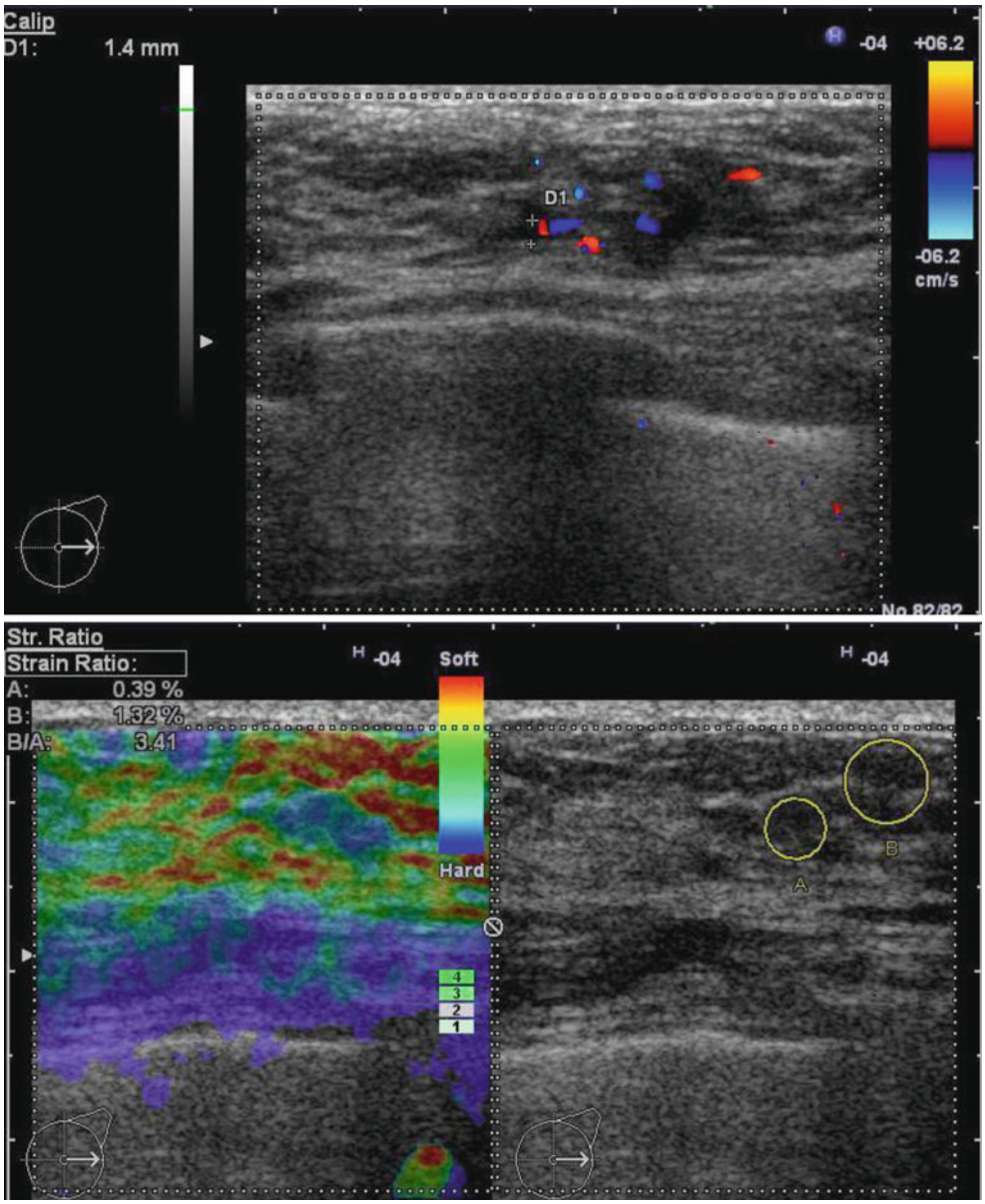

Fig. 7.17 DCIS with mammographic branching microcalcifications, unapparent in 2D US, but with suspect hyperplasias in FBU

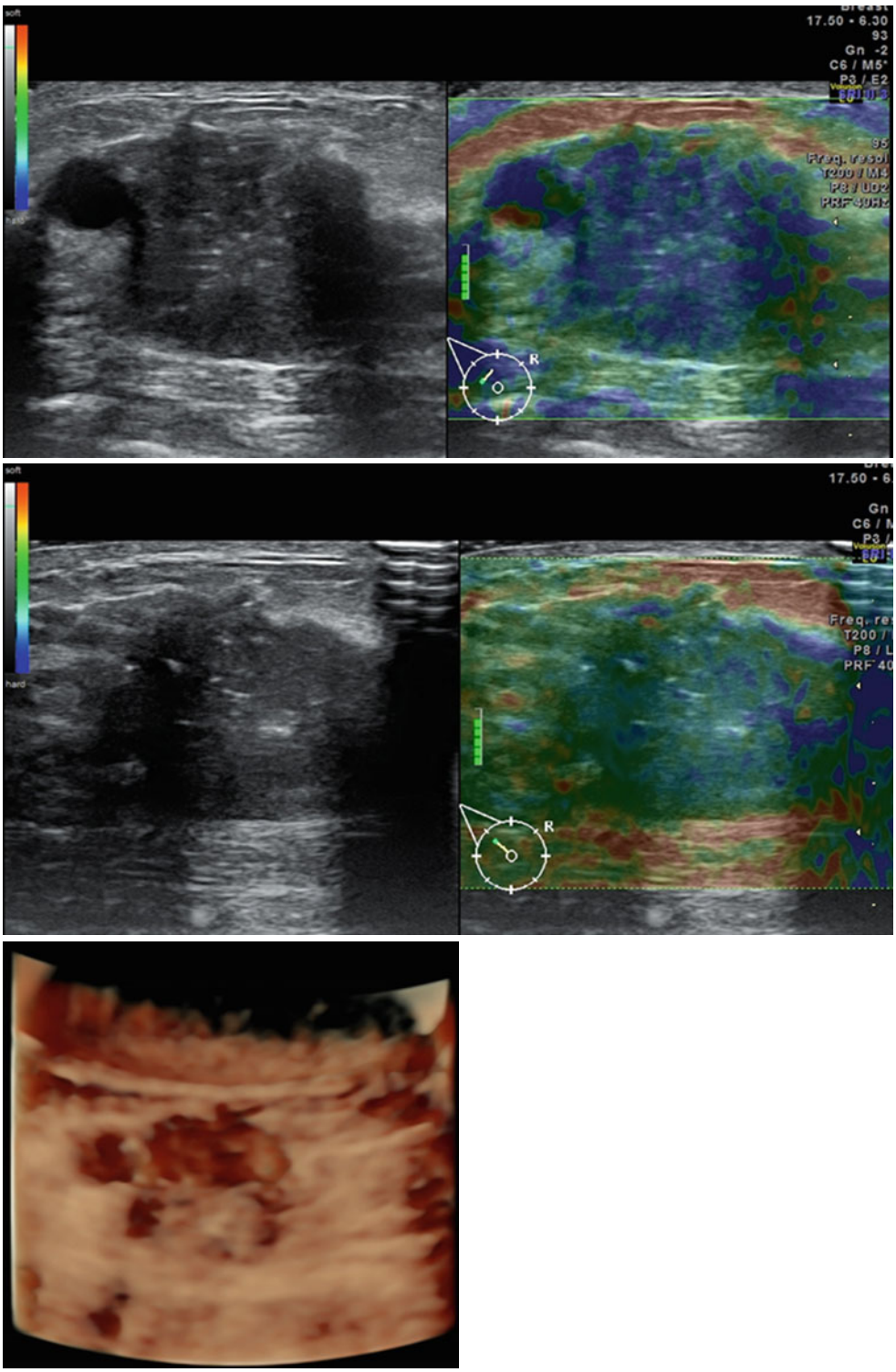

Fig. 7.18 Fibro-micro-cystic nodular dysplasia: there are tinny lesions inside the nodular dysplasia, mimicking microcalcifications with hyperechoic foci representing the posterior acoustic effect behind the almost equal hypoechoic/transonic findings, which represent the microcystic lesions. In the nodular fibro-micro-cystic lesions, usually there is a peripheral larger cyst, and the overall elasticity is of benign score; the 4D US, despite the actual insufficient developed technique, is high suggesting for dysplasia

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