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18.1 Mammography and Tomosynthesis

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Abstract X-ray mammography remains the most effective technique for routine breast cancer screening and plays a key role in imaging the breast in symptomatic patients aged from 40 years. The quality of mammography images has improved significantly during the last decade with the introduction of full-field digital mammography. However, although it is the most acceptable and effective technique used for population-based screening with reported breast cancer mortality reductions of up to 20%, the sensitivity and specificity of mammography are limited particularly in younger women and in those with dense glandular breasts.

In modern practice, mammography is complimented by other imaging modalities to improve lesion detectability and characterisation and establish disease extent. These techniques include ultrasound and contrast-enhanced MRI as well as newer mammographic techniques including digital breast tomosynthesis and contrast mammography.

In this chapter, we discuss the strengths and limitations of mammography in the diagnosis of breast disease and the role of advanced techniques in both diagnosis and screening practice.

18.1.1 Mammographic Technique

Full-field digital mammography is now the standard of care, and the optimisation of technical factors including automatic exposure control, contrast to noise ratio, detail detection, and radiation dose is required for the detection of subtle signs seen with early breast cancer. Breast composition can vary significantly between normal individuals with differing proportions of fat, glandular, and stromal tissue. The correct equipment and technique should allow for the wide variation of patient build, breast size, as well as variations in anatomy.

Careful and skilled positioning of the breast including keeping the patient at ease is essential. Firm and even compression of the breast improves contrast by reducing radiation scatter, improves resolution by reducing tissue overlap; allows for reduced dose, uniform density and minimises both geometric and movement unsharpness. This is essential for the detection of both fine microcalcification and subtle soft tissue signs, for example, distortion.

Standard mammography includes two views of each breast. These are the medio-lateral oblique view and the craniocaudal view (Fig. 18.1). The medio-lateral oblique (MLO) view is performed by angulating the X-ray tube between 30 and 60° depending on patient build, often 45°. The nipple should be in profile, and the anterior surface of the pectoralis major should be visible to the level of the nipple. The inframammary skinfold should be visible with no superimposed skinfolds on the breast. This projection demonstrates more breast tissue than any other projection. The aim of this view is the complete visualisation of breast parenchyma and the retromammary fat as well as low axillary nodes. Review of the area anterior to the pectoralis

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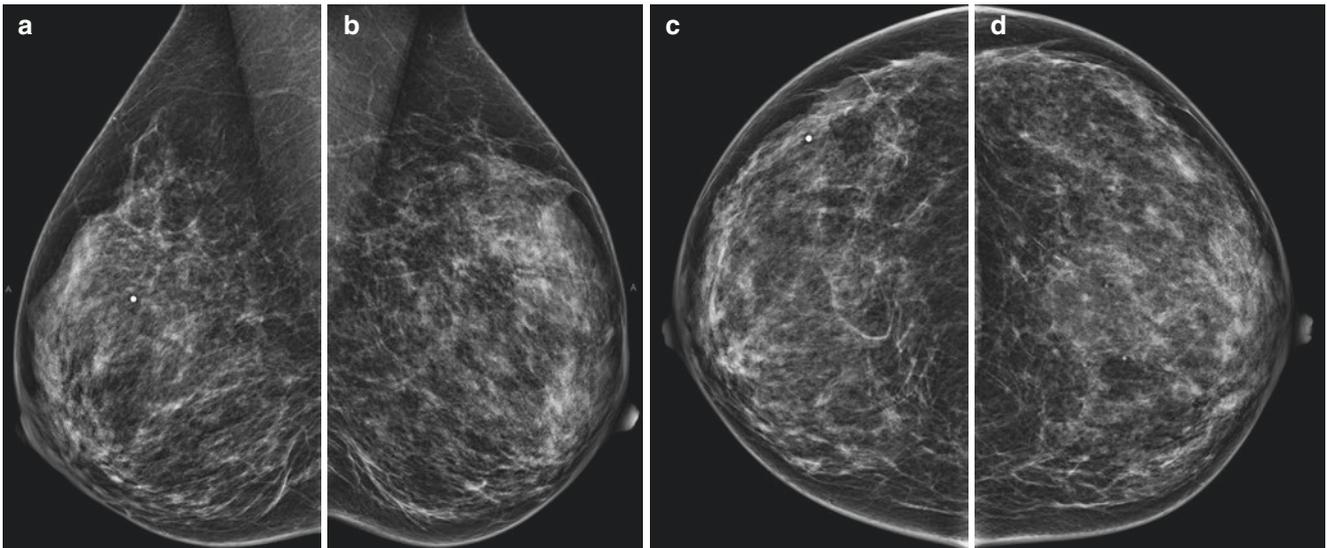


Fig. 18.1 (a–d) Normal two-view mammograms. (a) RMLO, (b) LMLO, (c) RCC, (d) LCC

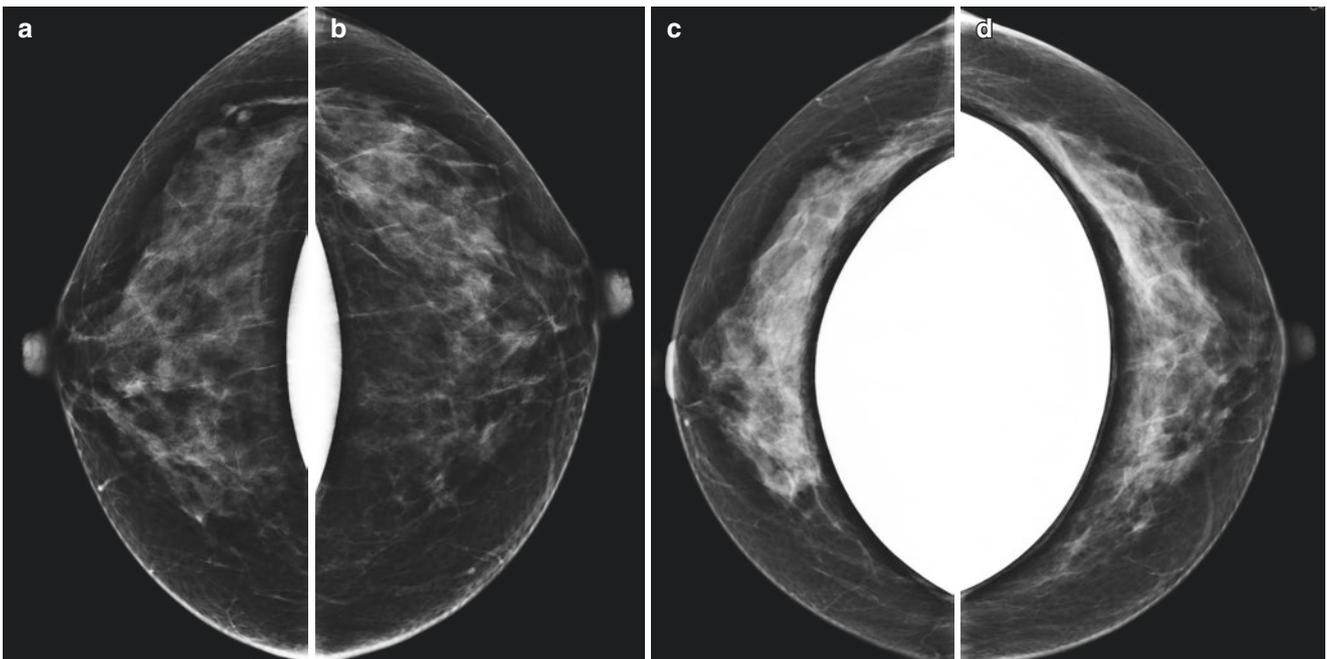


Fig. 18.2 (a) and (b) are Eklund projections which improve the visualisation of breast tissue in women with implants. (c) and (d) are standard cc projection mammograms in a woman with implants

muscle and in the immediate retroareolar region is important for the detection of small breast cancers. An important area of the breast not consistently well demonstrated on the MLO projection is the upper inner quadrant which is better demonstrated on craniocaudal (CC) view. The craniocaudal

view is performed with a vertical X-ray beam. The nipple again should be in profile with as much breast parenchyma as possible visualised, particularly that in the retroareolar, medial and lateral aspects of the breast as well as the retro-mammary fat.

In addition to the standard views, supplementary views can be used to improve the visualisation of abnormalities or areas of the breast. Medially or laterally extended craniocaudal views can be performed by rotation of the patient. Fine-focus magnification views increase resolution and are used for the improved visualisation and characterisation of microcalcification. Focal compression views can be used to improve the characterisation of soft tissue densities, asymmetrical densities as well as distortions by displacing the overlying tissues. The Eklund technique is a modified compression view for patients with breast augmentation (Fig. 18.2). The implant is displaced toward the chest wall with anterior traction of the breast tissue to improve visualisation.

18.1.2 Anatomy

The female breast typically has 12–15 lobes which contain terminal ductal lobular units (TDLU). The TDLU consists of acini and lobules which are constantly changing in size and number according to hormonal status. The lobes are variable in size, and the anatomical boundaries of these lobes are not restricted by the quadrants often used to describe disease location in radiology. The shape and contour of the breast are also influenced by supportive fascia and Cooper's ligaments. The wide spectrum of appearances seen on a normal mammogram is reflective of the heterogeneity in breast composition. The parenchymal subtypes were described in the original classification system by Wolfe [1] to enable the recognition of normal mammographic structures.

Breast density is an important descriptor in the interpretation of mammograms. It has significant effects, both on sensitivity and specificity. The mammographically dense breast is an independent risk factor for breast cancer. Breast density is determined by genetic factors and is influenced by age, weight, pregnancy/lactation, medication including exogenous hormones (inhibitors) and breast disease, for example, inflammation. Breast density can be assessed subjectively by the radiologist, but quantitative systems, for example, Volpara and Qantra, provide more accurate, reproducible data. The most widely used classification system in current practice is the BI-RADS (Breast Imaging-Reporting and Data System).

BI-RADS 1: The breast(s) is almost entirely adipose with <25% glandular tissue (Fig. 18.3).

BI-RADS 2: The breast(s) has scattered fibro-glandular tissue occupying 25–50% of the breast (Fig. 18.4).

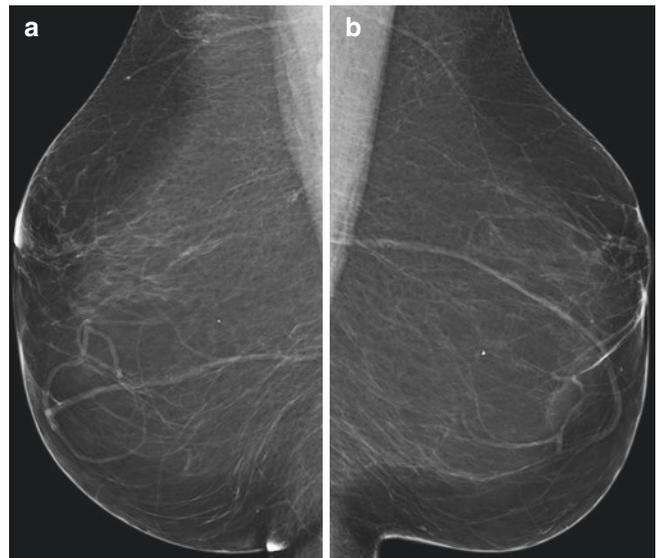


Fig. 18.3 (a–b) MLO projection mammograms demonstrate the BI-RADS classification of mammographic breast density. BI-RADS 1

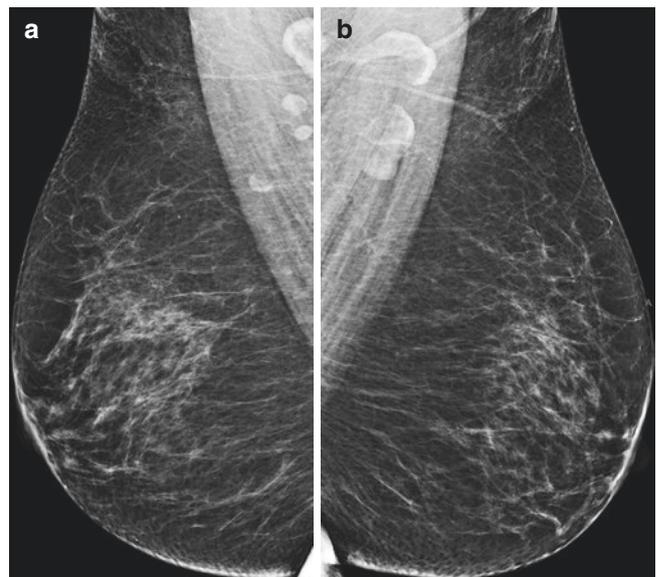


Fig. 18.4 (a–b) MLO projection mammograms demonstrate the BI-RADS classification of mammographic breast density. BI-RADS 2

BI-RADS 3: The breast(s) has heterogeneously dense fibro-glandular tissue ranging between 50 and 75% (Fig. 18.5).

BI-RADS 4: The breast(s) has extremely dense 75–100% glandular tissue (Fig. 18.6).

Fig. 18.5 (a–b) MLO projection mammograms demonstrate the BI-RADS classification of mammographic breast density. BI-RADS 3

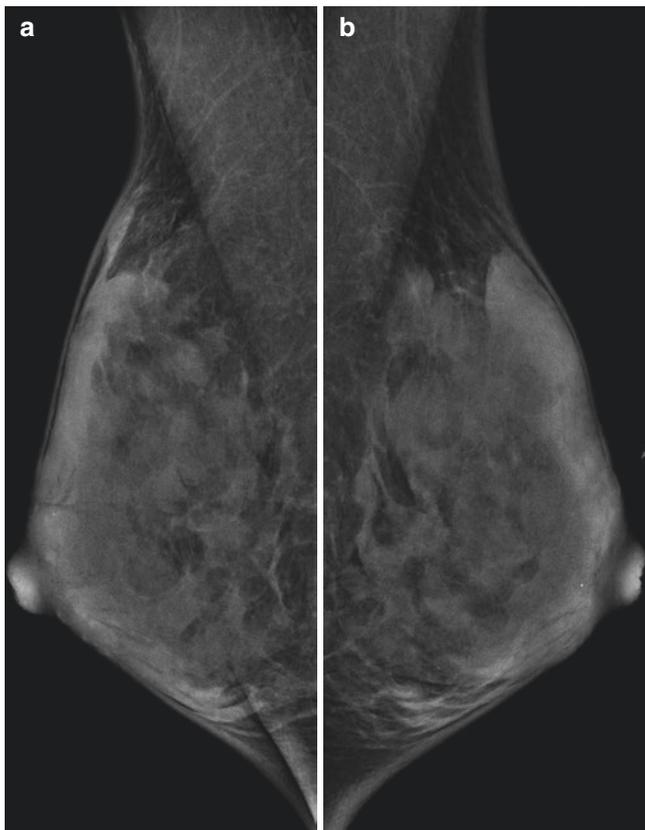
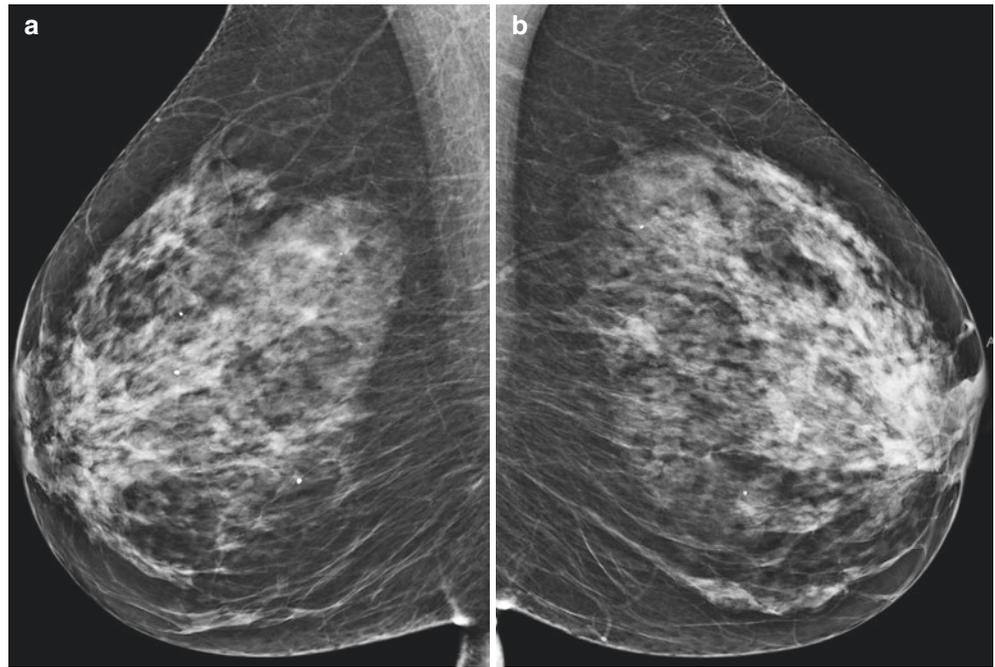


Fig. 18.6 (a–b) MLO projection mammograms demonstrate the BI-RADS classification of mammographic breast density. BI-RADS 4

18.1.3 Indications

18.1.3.1 Symptomatic Patients

The triple assessment approach to patients in diagnostic clinics includes clinical breast examination, imaging and biopsy, if required. This ensures an efficient diagnostic process which results in a definitive diagnosis of normal physiological change, benign or malignant disease. Mammography is routinely used in symptomatic patients who present to the breast clinic and are aged 40 years or over. Mammography should also be considered in those below 40 years presenting with signs and symptoms suspicious for breast cancer and in the investigation of male patients over 50 years with a unilateral firm subareolar mass. Standard two-view mammography in symptomatic patients may be complimented with supplementary mammographic views or digital breast tomosynthesis for further characterisation of mammographic features. Ultrasound should be carried out for any patients with breast lumps, persistent focal lumpiness, change in breast size with signs of oedema, change in breast contour, skin tethering or skin dimpling and women with implant-related symptoms as described by Willet et al. [2].

18.1.3.2 Population Screening

Screening mammography is the modality of choice for routine population screening and has been shown to reduce the mortality rate in those invited to breast screening by approximately 15–20%. A meta-analysis of screening trials by Tabar et al. [3]

demonstrated an overall reduction in breast cancer mortality of 22% with an invitation to breast cancer screening. The paper showed a strong relationship between decreased rates of advanced stage (stage II and higher) tumours and lower breast cancer-specific mortality. The mortality benefit from mammographic screening continues following screening as shown on follow-up data from the Swedish randomised control trials published by Tabar et al. [4].

A screening programme must be underpinned by robust quality assurance and measurements of performance to ensure high quality. Mammographic screening should include MLO and CC projections of each breast. The most common age range for routine screening is 50–70 years. The UK age extension trial is a multicentre trial examining the effect of screening in women aged 47–50 and 70–73 and is to report in 2022–2026. Over 2 million women have been recruited with over 200,000 screens to date. Moser et al. [5] reported the age extension pilot results which showed a 0.5% cancer detection rate in those 47–49 years and 1.1% in those 71–73 years with recall rates 2.5 times higher in those 47–49 years compared with the 71–73 years group. The US Preventive Services Task Force published recommendations in 2009 [6] of biennial screening for women 50–74 years for general population breast screening and no screening for those aged 40–49 years except on an individual case basis. The effectiveness of mammographic screening of women aged 40–49 is less certain than for those over 50 years.

The frequency of mammography is variable dependent on individual risk and the screening programme. Intervals vary from 1 to 3 years. The UK programme invites women triannually. However, Dibden et al. [7] demonstrated 44% of interval cancers in this programme to be in the third year following negative screen, suggesting that 3 years is too long an interval for screening. Biennial screening has been suggested as optimal for normal population screening.

Women of greater than average population risk of breast cancer can be categorised as moderate or high risk. The UK categorises women at high risk if they have a lifetime risk of 30% and moderate risk between 17 and 29%. The European Society of Breast Cancer Specialists recommends high-risk screening for women with a lifetime risk greater than 20–30%, and the American College of Radiology recommends high-risk screening for those with a lifetime risk of >20%. Moderate risk is classified in Europe and the USA as a lifetime risk of >15%. There are a number of risk calculation tools including the Claus model, Gail model and BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm). The BRCAPRO and Manchester scoring system are used specifically for the assessment of BRCA mutations.

Mammographic screening is the mainstay in women with a moderate lifetime risk with annual mammograms. Moderate-risk women may have a family history without known genetic mutations. Other risk factors include women with a personal history of breast cancer; benign conditions like atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS); and dense breasts. Women with a previous personal diagnosis of breast cancer have a 5–10% risk of recurrence in the first 10 years. The mammographic sensitivity is compromised in women who have had breast conservation therapies. Houssami et al. [8] reported sensitivities of 65% vs 76% in those with a personal history of breast cancer vs. those without, with only 25–45% of recurrences detected on mammogram overall. Distortion from surgery and increased density from radiation therapies can affect the detectability of an early breast cancer.

Women of higher risk develop cancers at an earlier age, perhaps in denser breasts with tumours with atypical morphological mammographic features and a faster tumour growth rate. Mammographic screening is often performed annually from a younger age and is enhanced with magnetic resonance imaging in higher-risk women due to the reduced mammographic sensitivity reported in these women. MRI screening studies report sensitivities of 77–100% vs. mammographic sensitivities of 23–50% (Kuhl et al. [9], Kriege et al. [10], Leach et al. [11], Sardanelli et al. [12] and Warner et al. [13]). Women who have a high breast cancer risk due to TP53 mutations or Li-Fraumeni or A-T homozygotes should not undergo routine mammographic surveillance due to increased radiation sensitivity.

18.1.4 Limitations

2D mammography has limitations. The advent of digital mammography and full-field digital mammography has improved the visualisation of breast disease in comparison to film screen, especially in denser breasts; however, there has not been the improvement in cancer detection as had initially been hoped. In the DMIST study, Pisano [14] studied cancer detection in digital vs. film-screen mammography in 49,528 women in a multicentre, multivendor trial and found digital mammography to be more accurate in women <50 years with dense breasts or who were pre-/perimenopausal. The superimposition of structures can lead to the under-detection of breast malignancy. Fifteen to thirty percent of cancers may not be detected by screening mammography and present as interval cancers, between screens.

Interval cancer rates can be used as a measure of the effectiveness of a screening programme. It is not only a key

quality indicator of a screening programme but allows for the surveillance of individual radiologist performance and education. Interval cancers tend to be larger in size at presentation compared to screen-detected tumours and are more likely to have nodal metastasis. They tend to be invasive tumours with less than 5% of interval cancers being due to ductal carcinoma in situ (DCIS) in a study by Bennett et al. [15]. In a review, Housammi et al. [16] report that interval cancers have a prognosis similar to that of other symptomatic cancers. The review found approximately 25–45% of interval cancers were due to a false-negative read, i.e. a perception or misinterpretation error. These errors are usually minimal signs, where perception errors may be improved with double reading or CAD. In those cases clinically assessed, the errors may possibly be reduced by assessment guidelines and improved clinical decision making. True intervals, with no findings on the screening mammogram, account for 18–63% of cases. These cancers are hard to minimise except for the consideration of enhanced screening techniques or shorter screening intervals where feasible. Mammographically occult tumours at diagnosis account for 8–12%.

Studies have reviewed the characteristics of undetected and missed cancers (Table 18.1). Birdwell et al. [22] reviewed the data used in the Warren Burhenne et al. [20] study above to demonstrate 30% of the missed cancers were microcalcifications and 70% were masses (28% were spiculate or irregular). They reported breast density to be the second most common cause for missing a breast cancer (34% of cases) following a distracting lesion as the most common cause

(44%). Bird et al. [18] also demonstrated missed cancers were less likely to have microcalcifications and more likely to be an increasing opacity in denser breasts.

Elmore et al. [23] report the overall sensitivity for screening mammography to be 75% with a specificity of 92.3%. The accuracy of mammography is variable, being limited by breast density and symptoms. Sensitivity and specificity in fatty breasts are as high as 87% and 97%, respectively.

The sensitivity of mammography is reduced in situations where the breast tissue may be obscured or distorted including cosmetic techniques as well as following breast-conserving treatments (Fig. 18.7). Heterogeneously and extremely dense breasts are an independent risk factor for breast cancer. Boyd et al. [24] discussed the increased risk of breast cancer in women with dense breasts to be four- to sixfold. The reasons for this are likely multifactorial, not only due to the reduced sensitivity of mammography which is only a “masking effect” but the increased volume of tissue

Table 18.1 Table of interval cancer studies with undetected and missed cancer analysis

Author	Year	Interval cancers reviewed	% with (actionable) signs on previous mammogram
Ikeda et al. [17]	1992	96	32
Bird et al. [18]	1992	320	24
van Dijck et al. [19]	1993	84	38
Warren Burhenne et al. [20]	2000	427	27
Brem et al. [21]	2003	377	32

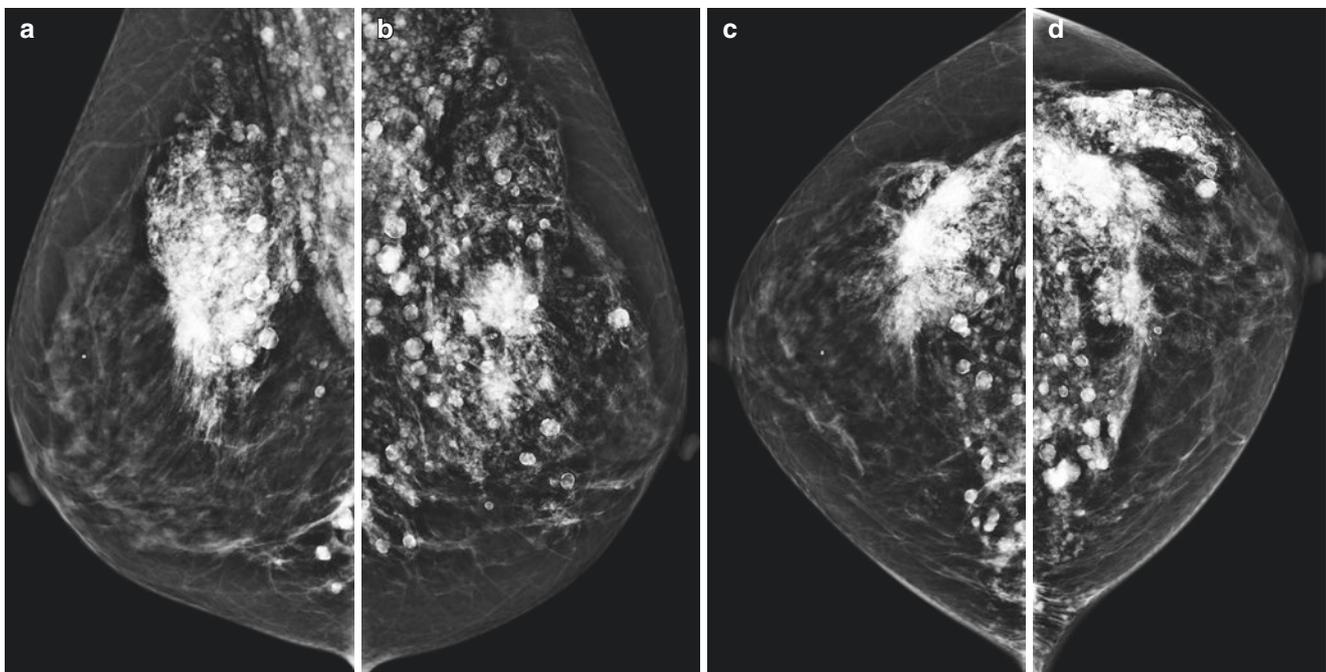


Fig. 18.7 (a–d) Silicone prevents the optimal visualisation of breast tissue reducing the sensitivity of the mammogram in the detection of early breast cancers

that may potentially undergo malignant change and possible underlying genetic predisposition. Dense breasts are associated with epithelial proliferation and stromal fibrosis. The review also looked at the effect of age, family history, diet, alcohol consumption, exercise and race on breast density and suggested age to have the strongest effect. Berg et al. [25] reported a sensitivity of 45% for the detection of malignant lesions in patients with extremely dense breasts. The study also examined cancer detection by tumour type. The sensitivity for invasive ductal cancer was 81% but 34% for invasive lobular cancer.

Mammographic sensitivity can be affected by a number of factors. The mammographic breast density and lifestyle factors affecting this, patient age, and reader experience affect the sensitivity (Banks et al. [26], Britton et al. [27]). Patient age has been shown to be a significant factor in mammographic sensitivity by multiple study groups. Kolb et al. [28] showed the sensitivity in younger women with dense breasts (<49 years) to be significantly lower than in older women with dense breasts. The mammographic accuracy may be affected by the context in which it is performed, as the reader may look for an abnormality on mammography to explain a presenting clinical symptom. Kavanagh et al. [29] reviewed 106,826 women presenting for routine screening and compared asymptomatic women to those with symptoms. The sensitivity in those with breast-specific symptoms was 80.8% vs. 75.6% in those asymptomatic but with significantly lower specificities of 73.7% and 94.9%, respectively.

The sensitivity of mammography is improved by double reading which may be carried out by two readers independently or together. This is common practice in the UK and other European countries. A systematic review by Taylor and Potts [30] has shown a significant increase of approximately 10% in cancer detection rate with double reading. Published data shows a variable effect on recall rate. In most studies specificity is not compromised. In cases where there is discordance between reader 1 and reader 2, the process of arbitration or consensus is used. Arbitration is performed by a single reader and consensus is by a panel. Duijm et al. [31] have shown the process of consensus and arbitration to be effective in recalling the majority of cases with cancer while minimising the recall rate.

Increasing the recall rate reduces the positive predictive value and the cost-effectiveness of mass screening. Schell et al. [32] performed a study of 1,872,687 mammograms in the USA and concluded recall rates between 6.7 and 10% (incident and prevalent screens) were optimal. Europe recall rates are between 3 and 10%. Smith-Bindman et al. [33] reported the average recall rate in the USA to be double that of the UK with no difference in cancer detection rates. This was explained in the study by multiple variations in screening practice between the UK and the USA. The UK national programme has robust radiology quality assurance in place

including a minimum reading volume of 5000 mammograms per year per radiologist. The balance of sensitivity vs. specificity depends on multiple factors. It may be affected by litigation concerns; if the aim is to detect all cancers, i.e. maximise sensitivity, this will increase recall rates and reduce specificity.

The use of computer-aided detection (CAD) may optimise cancer detection by one reader where double reading is not available. The Computer-Aided Detection Evaluation Trial II (CADET II) compared single reader with CAD with double reading to show cancer detection/sensitivity between the two arms was similar, 87.2% and 87.7%, respectively (James et al. [34]). The specificity of double reading was higher at 97.4% in comparison to 96.9% with CAD which also resulted in a higher recall rate. There was no statistical difference between cancer subtypes although the CAD arm detected more in situ disease and smaller, higher-grade invasive disease. Pooled estimates from two meta-analyses of 27 studies with CAD by Taylor and Potts [30] concluded with the same results for cancer detection rates between CAD and double reading but a lower recall rate with double reading. It is reported that radiologist productivity was unaffected by CAD, perhaps due to radiologist experience in the final decision as to whether or not to recall (Brem et al. [21]). In addition to this, Freer and Ullissey [35] reported CAD not to affect the positive predictive value for biopsy.

CAD has been shown to be particularly effective in the detection of microcalcification clusters. The detection of microcalcification does not appear to be affected by breast density (Brem et al. [36], Birdwell et al. [22]). Distortions are the third most common mammographic sign for breast cancer and can be very subtle with appearances often mimicking overlapping tissues. Baker et al. [37] reviewed the performance of CAD on benign and malignant architectural distortions. In this study, CAD was not sensitive to subtle signs, detecting <50% of the cases. Among the cancers not detected by CAD, studies have shown a posterior location is more common; however, quadrants are equal.

CAD is a sensitive system; however, mammographic reading also requires the expertise of an experienced radiologist who is able to distinguish correctly between true-positive and false-positive prompts, ensuring that the correct areas are recalled without compromising specificity (Azavedo et al. [38]).

The positive predictive value (PPV) of mammography for malignancy and that for biopsy varies widely according to the mammographic sign, between 15 and 75%. The mammographic signs with the highest predictive value for malignancy are masses with a spiculated margin or irregular shape and linear microcalcifications in a segmental or linear distribution (Lieberman et al. [39]). Lazarus et al. [40] reviewed the PPV by BI-RADS category with BI-RADS 4 and above recommended for biopsy and reported a PPV between 6% for BI-RADS 4a and 91% for BI-RADS 5 lesions.

The recall rate following screening reflects the specificity of mammography. The UK National Health Service Breast Screening Programme (NHSBSP) screened 2.08 million women in 2013–2014, detecting 8.6 cancers per 1000 screened of which 39.9% were 15 mm or less. The prevalent and incident screen recall rates were 7.9% and 3%, respectively. The false-positive rate in mammographic screening is a limitation which has significant morbidities related to anxiety and biopsy.

Screening is performed in otherwise (breast) healthy women; the harm vs. benefit must therefore be addressed. The Marmot review [41] of the benefits and harms in population mammographic screening reported for every life saved with breast screening, 180 women are screened or 235 women are invited to screening for 20 years. Screen-detected disease that may not otherwise have resulted in harm to the patient in her lifetime is known as overdiagnosis. The review estimated that 19% of screen-detected cancers are due to overdiagnosis or for each breast cancer death prevented, three women are overdiagnosed.

Overdiagnosis may include the detection of small low-grade invasive tumours and DCIS. The detection of DCIS has significantly increased with the advent of screening accounting for approximately 20% of screen-detected malignancy. The benefit of detecting DCIS against harm has been questioned. This is partly related to the very different natural history of low-grade DCIS in comparison to high-grade DCIS within the same disease category and the uncertainty about the progression of disease. A review of over 5.2 million screened women by Duffy et al. [42] provided evidence that the diagnosis and treatment of DCIS in screening are worthwhile and suggested that one less invasive interval cancer occurred for every three cases of DCIS detected.

The recognition of the variable sensitivity and specificity of mammography dependent on patient factors has led to the development of new techniques which enhance lesion detection compared with conventional mammograms. We discuss digital breast tomosynthesis and contrast-enhanced digital mammography.

18.1.5 Digital Breast Tomosynthesis (DBT)

DBT, sometimes called 3D mammography, provides the reader with images of the breast in thin slices and overcomes many of the interpretation problems of 2D DM due to overlapping normal tissue, sometimes referred to as “anatomical noise”. The mammographic signs of breast cancer may be obscured, particularly in women with dense fibro-glandular breast tissue (Al Mousa et al. [43]), resulting in delay in the diagnosis of cancer. The UK national interval cancer data shows that up to 4000 women per annum (2.88 per 1000 screened) are diagnosed with breast cancer in the interval

between screens (Offman and Duffy [44]). Conversely, superimposition of normal tissues may produce features on mammography which are suspicious for cancer and lead to unnecessary recall for further diagnostic tests. UK national screening data for 2012/2013 show that of 2.3 million women screened, 79000 (3.4%) without breast cancer were recalled to specialist diagnostic assessment clinics for further tests (Centre for Cancer Prevention [45]). DBT has been incorporated into the routine for further mammographic investigation of breast lesions in many centres replacing conventional spot compression views. Some centres in North America and Europe are already using DBT in addition to conventional 2D mammography to screen asymptomatic patients.

18.1.5.1 Technique

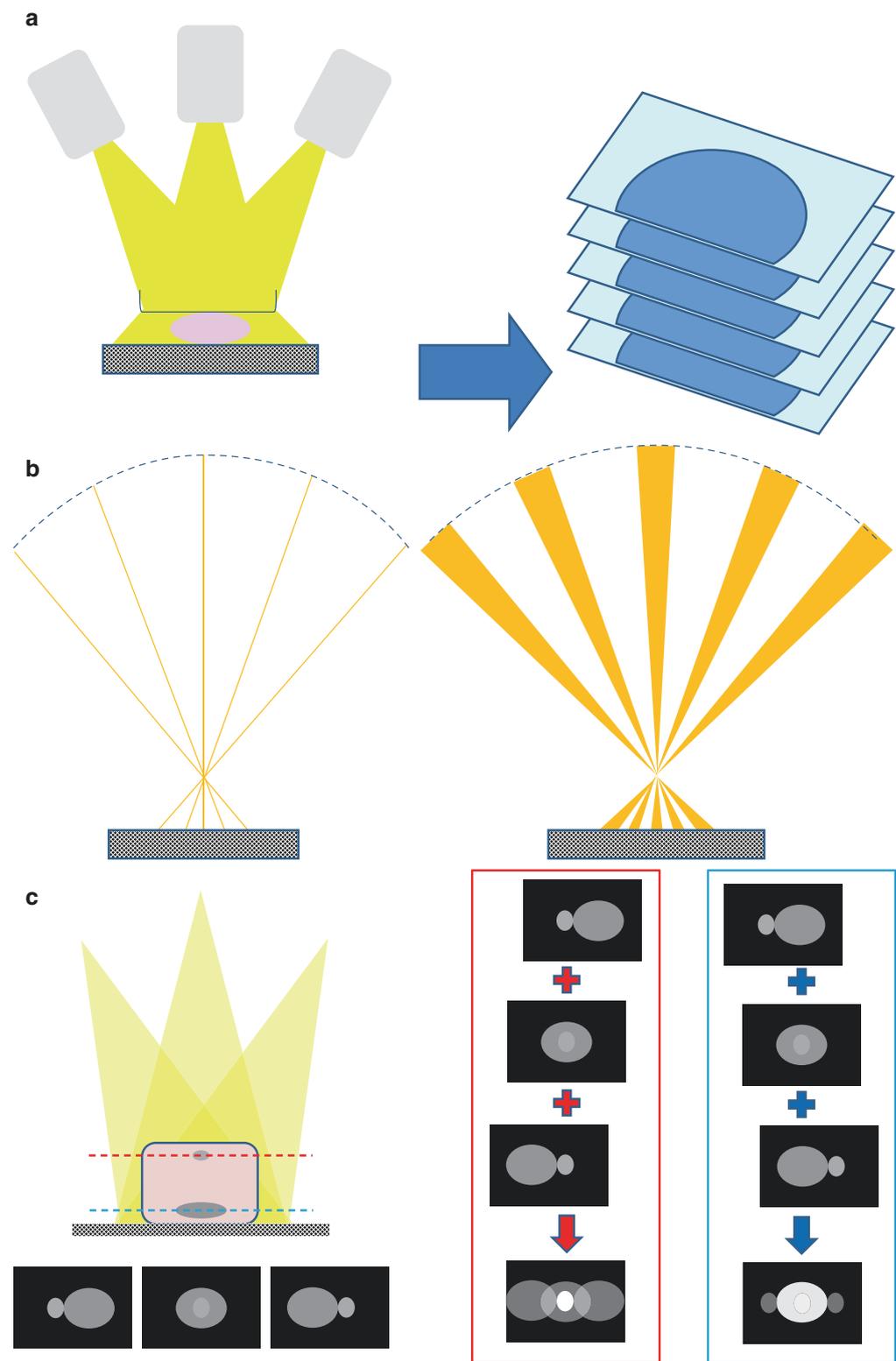
Tomosynthesis involves the movement of the X-ray tube in an arc during which data from multiple low-dose projection images are acquired. Between 9 and 25, low-dose projections are taken over an angular range of 15–50 degrees depending on the manufacturer. Images for viewing are reconstructed using either a filtered back projection or iterative method from the low-dose projection image data and are typically displayed as 1 mm thickness in-focus planes. The images may be viewed singly or as a series, similar to viewing a CT scan. The total dose is comparable to that of conventional full-field 2D digital mammography but depends on the manufacturer. Certain systems can also produce a reconstructed or synthetic 2D image from the tomosynthesis images which can reduce the total dose further by avoiding the need for conventional FFDM (Fig. 18.8).

18.1.5.2 Indications

This technique has been demonstrated to show increased accuracy in comparison to film-screen and full-field digital mammography (FFDM). This is particularly the case in the characterisation of soft tissue abnormalities. There does not, however, appear to be an advantage of DBT in the assessment of microcalcification (Spangler et al. [46]). The TOMMY trial (TOMosynthesis with digital MammographY) reported DBT specificity was highest for distortions and lower for microcalcifications (Gilbert et al. [47]). Michell et al. [48] demonstrated an accuracy of 97% when interpreting using DBT in comparison with 90% with 2D FFDM. Cancer visibility has been shown to be superior with DBT. Studies have shown single-view MLO projection DBT to be more accurate in the detection of tumours than two-view DM (Andersson et al. [49], Svahn et al. [50]).

The improved visibility of the margins of circumscribed soft tissue lesions may enable readers to predict the likelihood of malignancy as presented by Wasan et al. [51]. The addition of DBT improves lesion conspicuity, margin analysis and the detection of additional abnormalities.

Fig. 18.8 (a–c)
 Illustrations courtesy of Dr. Celia Strudley, The Royal Marsden Hospital, London. (a) Illustrates how DBT acquires multiple images through an arc. The focal planes taken from sequential depths are then stacked approximately 1 mm apart. (b) These images demonstrate tube motion. The step and shoot tube movement has a small focal spot and produces sharp images but is slower to acquire images. The continuous tube movement elongates the focal spot causing blurring in the direction of the motion but is faster and has smoother motion. (c) This illustrates the simple back projection reconstruction method used by some DBT systems



The role of DBT in the diagnostic workup of soft tissue masses, distortions and asymmetrical densities is established. The reported advantage is the improved ability to predict malignant lesions without increasing the false-positive rate

(Morel et al. [52] and Zuley et al. [53]). Studies have shown fewer benign biopsies and short-term follow-up are recommended with the use of DBT. This results in a significant improvement in the accuracy of diagnostic assessment. There

are further advantages to using this technique over coned compression views as visualisation of the whole breast improves detection of multifocal disease.

Gur et al. [54] demonstrated an improved performance with DBT including demonstrating lesion location and multifocal lesions; however, this was at the cost of an increased

false-positive rate which was justified by the increased true positives (Figs. 18.9, 18.10, 18.11, 18.12, 18.13).

18.1.5.3 Potential Use in Screening

A topic which is of interest in research at the time of writing this chapter is the possible use of DBT in the routine

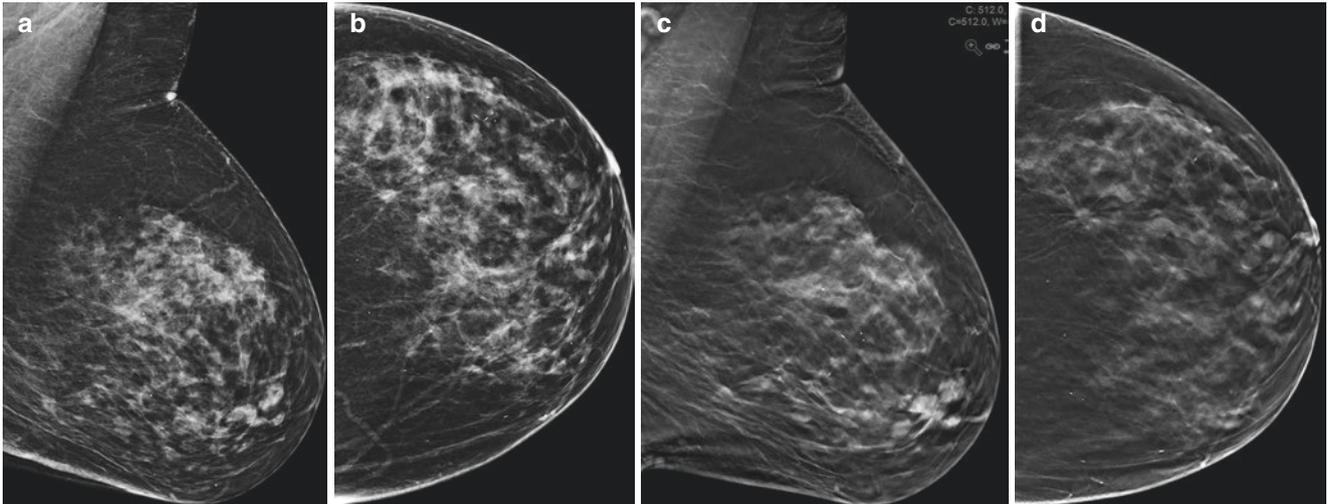


Fig. 18.9 (a–d) DBT increases the conspicuity of a lesion enabling a sign change in this case from a circumscribed mass to a spiculate mass. This case is a screen-detected lymph node negative 12 mm grade 2 invasive lobular carcinoma recalled to assessment on the (a) LMLO and (b)

LCC 2D FFDM, which demonstrated a circumscribed mass in the lower outer breast. (c) LMLO (d) LCC DBT demonstrates a spiculate lesion improving reader confidence and BI-RADS 5 score from the initial BI-RADS 4a based on the 2D images

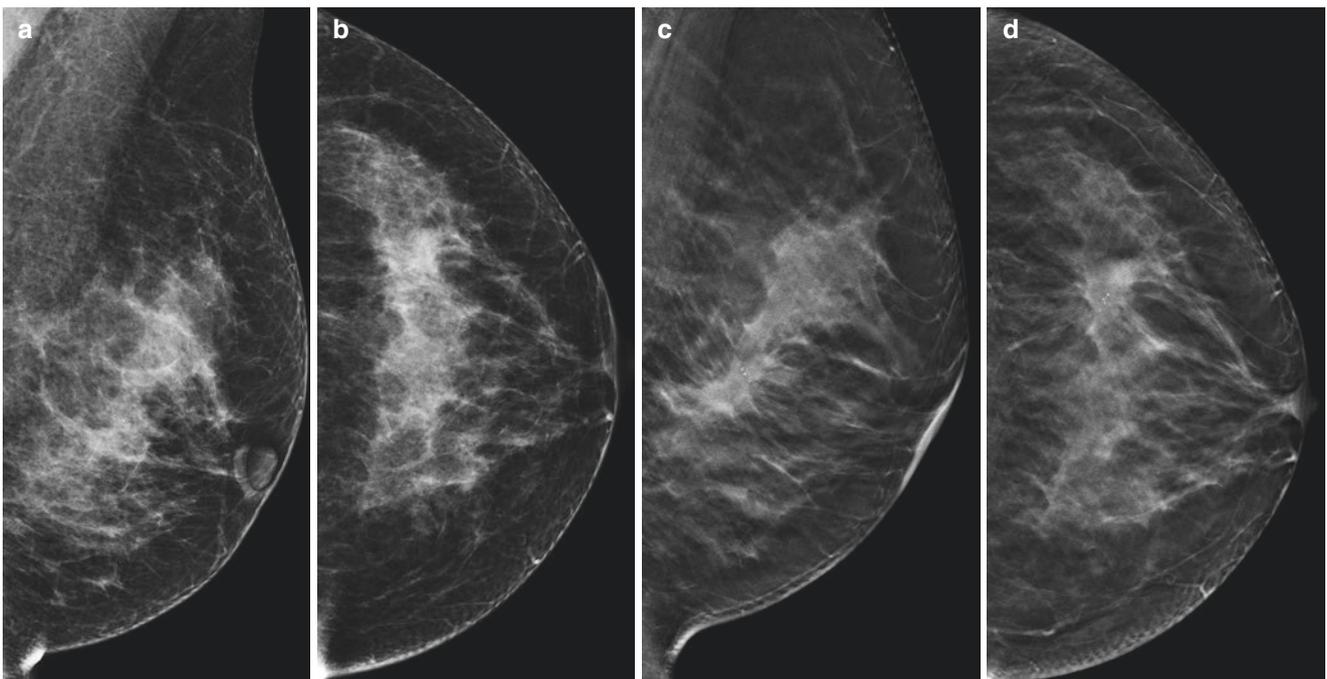


Fig. 18.10 (a) LMLO 2D FFDM, (b) LCC 2D FFDM, (c) LMLO DBT, (d) LCC DBT, (e) left lat magnification view and (f) left CC magnification view. The 2D FFDM screening mammograms (a, b) demonstrate microcalcification which underwent supplementary views. DBT

(c, d) demonstrates a spiculate mass which is occult on the 2D. The magnification views (e, f) demonstrate the microcalcification and subtle increased density. Final pathology demonstrated a grade 2 invasive ductal carcinoma with axillary lymph node involvement

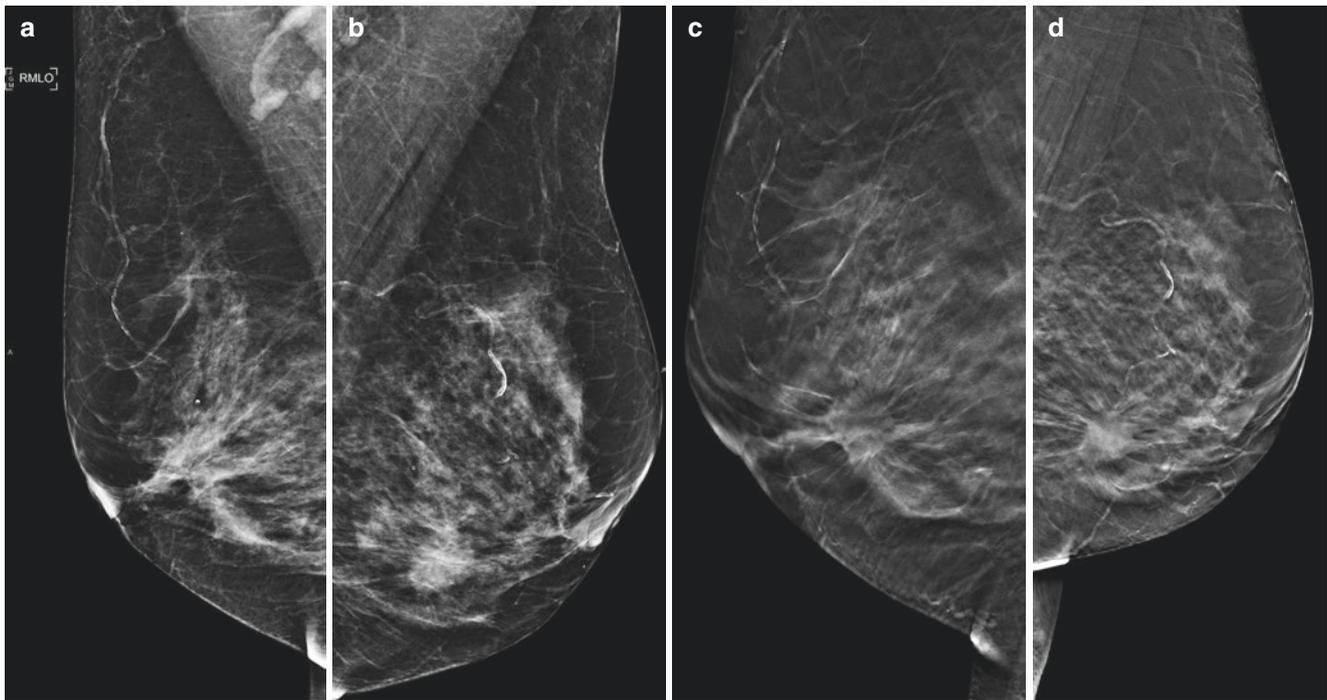
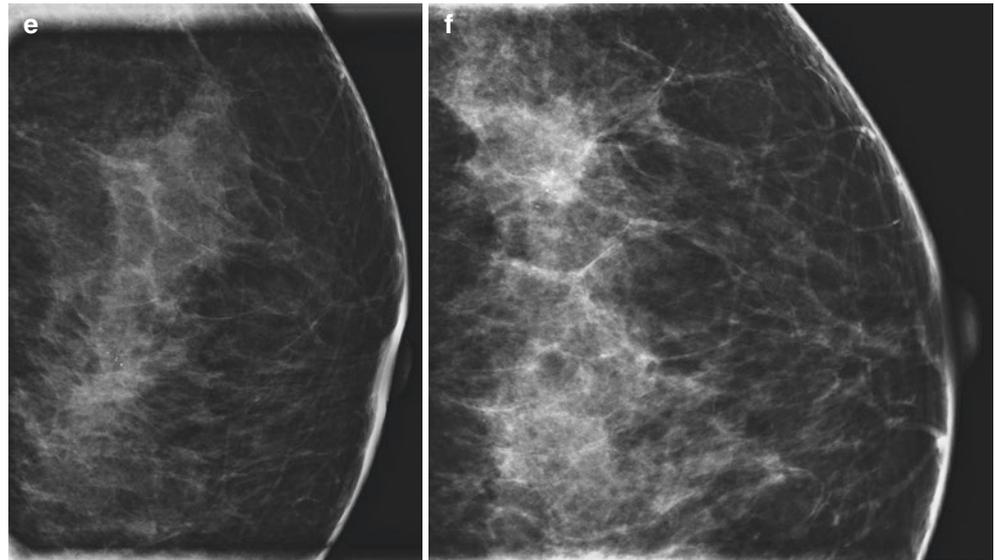
Fig. 18.10 (continued)

Fig. 18.11 (a) RMLO 2D FFDM, (b) LMLO 2D FFDM, (c) LMLO DBT and (d) RMLO DBT. The 2D FFDM demonstrates bilateral breast cancers. The *left breast cancer* was a grade 2 invasive ductal carcinoma with spread into the axillary lymph nodes. The *right breast cancer* was

a grade 2 invasive lobular carcinoma. However, the extent of the breast tumour is more clearly appreciated with the DBT especially the *right breast tumour*

screening of women for breast cancer. The radiation dose of DBT is similar to that of established 2D DM which invites the possibility of this technique being used for population screening. Studies of DBT used in addition to 2D DM have shown a significant increase in invasive cancer detection rates with no significant effect on DCIS. Further prospective

trials are underway in North America (TMIST), Norway (Oslo trial), Italy (Storm trial), Sweden (Malmö trial) and the UK (PROSPECTS).

The Malmö Breast Tomosynthesis Screening Trial (MBTST) showed an increase in sensitivity in cancer detection with single-view DBT vs. two-view mammography. This

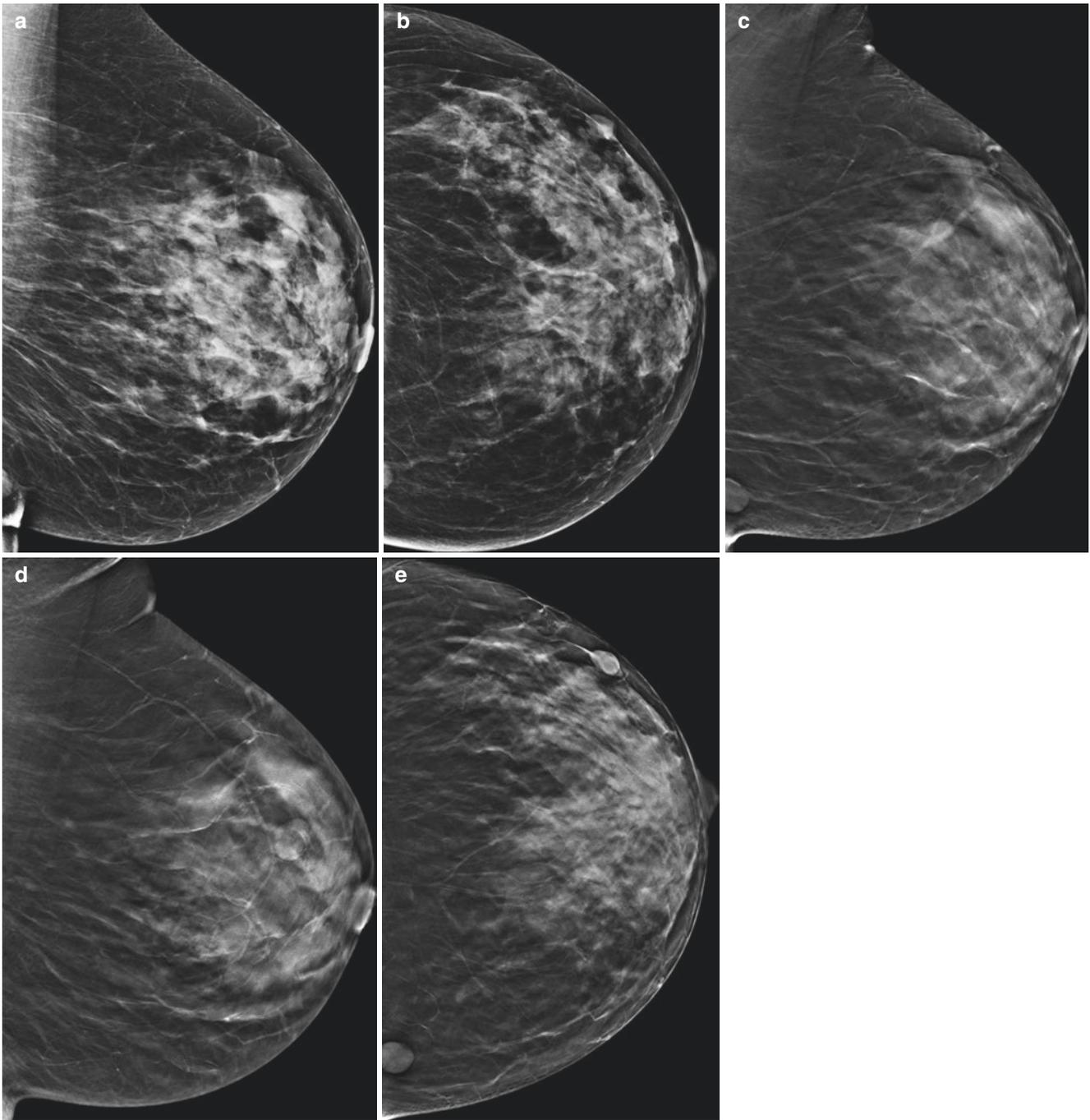


Fig. 18.12 (a) LMLO 2D FFDM, (b) LCC 2D FFDM, (c) LMLO DBT, (d) LMLO DBT and (e) LCC DBT. (a–b) 2D FFDM images of the left breast demonstrate BI-RADS 3 breast density with a nodular parenchymal pattern and multiple densities with partial visualisation of

the margins. (c–e) DBT images enable clear visualisation of 100% of the margins of these multiple lesions which were biopsy-proven fibroadenomas. The DBT images enable confident diagnosis of benign lesions which would require no further investigation

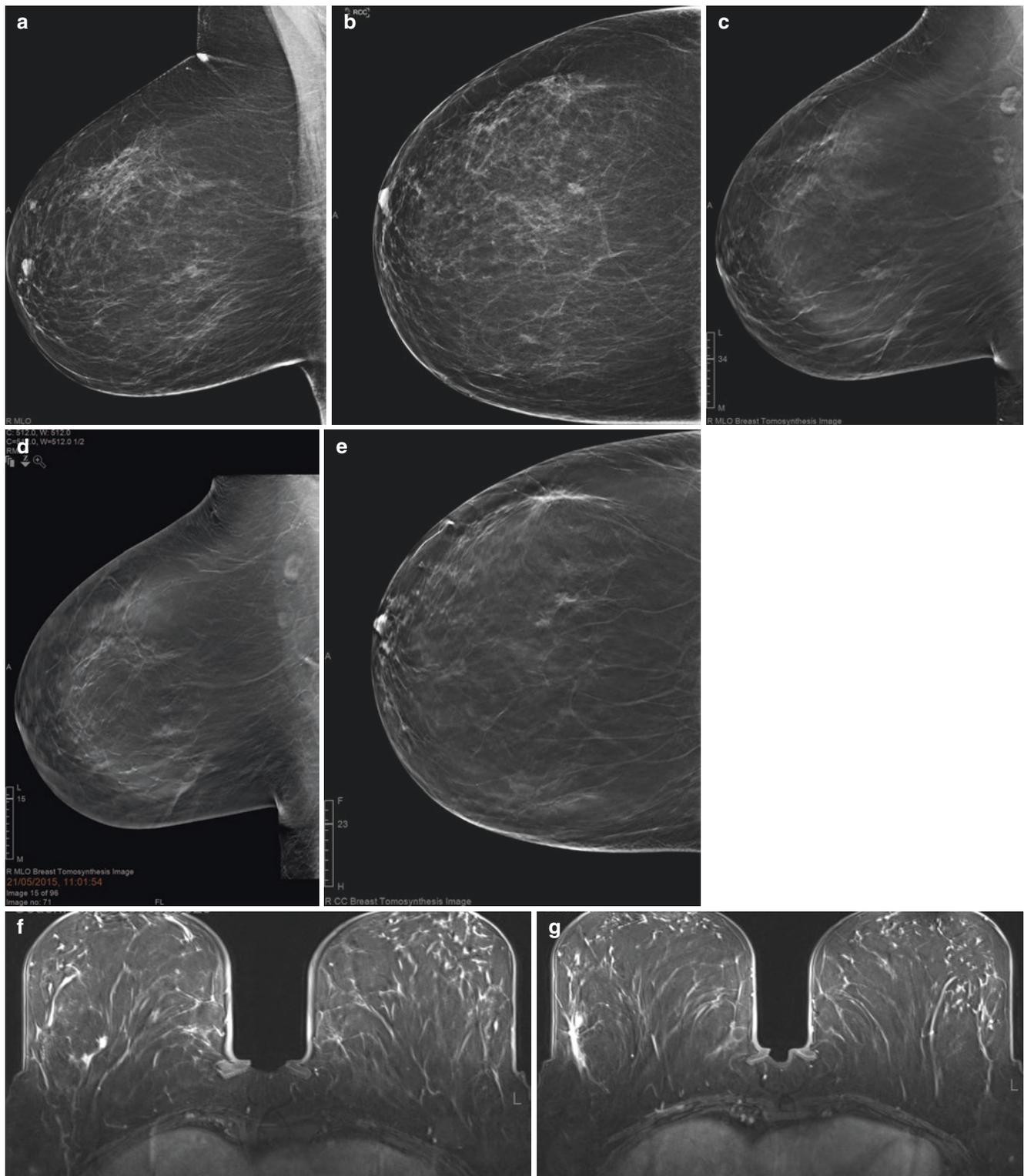


Fig. 18.13 (a) R MLO 2D FFDM, (b) R MLO 2D FFDM, (c) R MLO DBT, (d) R MLO DBT, (e) R CC DBT, (f) axial 1 min post-contrast MRI and (g) axial 1 min post-contrast MRI. This case illustrates the detection of multifocal disease in a screen-detected multifocal grade 2 invasive lobular carcinoma. The asymptomatic woman was recalled for a new central irregular-shaped mass on routine 2D screening mammo-

gram (a–b). DBT at the time of assessment demonstrated the central mass as two spiculate lesions on (c) R MLO DBT and (e) R CC DBT. Further to the recalled lesions is a distortion in the *right upper outer breast* not appreciated on 2D FFDM but detected on the (d) R MLO DBT and (e) R CC DBT. Post-contrast MRI images (f–g) illustrate the three tumours

study design takes into account the practical issues of increased radiation dose and radiologist reading time, increased costs and increased data storage by the use of a single MLO DBT view as opposed to two-view DBT. This may enable DBT to be more feasible in the context of mass screening (Table 18.2).

A further area of interest is the reconstruction of tomosynthesis images into a synthetic 2D mammogram which may be comparable to conventional 2D FFDM (Fig. 18.14). The clear advantage is the dose reduction as a result of not needing to perform conventional 2D digital mammography. Skaane et al. [58] demonstrated cancer detection using conventional 2D FFDM vs. reconstructed synthetic 2D imaging showing no statistical difference when using the most current software. They also reported that a single read of synthetic 2D with DBT detected more cancer than double read FFDM.

DBT may demonstrate subtle lesions which are not visible using conventional 2D mammography or ultrasound. DBT-guided biopsy/intervention is now available. This technique can be used not only for the biopsy of subtle lesions seen on DBT alone but also for the same indications as stereo-guided biopsy or wire insertion.

There are challenges and some uncertainties related to the implementation of DBT in routine screening. There is a continued requirement for 2D or synthetic 2D mammogram images. There is uncertainty about the continued effect of DBT on sensitivity and specificity following the first “prevalent” DBT screen.

There are mixed results from studies for recall rates as well as a possible increase in single reader/discordant cancer detection. This would imply there is a learning curve with the perception and interpretation of tomosynthesis images. It is also possible that DBT may further increase overdiagnosis rates. The Oslo Tomosynthesis Screening Trial showed increased cancer detection with biologically significant disease and no increase in the detection of DCIS. The improved performance of DBT was seen in all breast densities including fatty breasts.

There may be increased costs associated with the technology, image data storage and longer reading time

(Bernardi et al. [59]). The increase in radiologist reading time which may improve with experience; however, this may limit reading volumes possible by a reader as well as have cost implications. The Oslo screening study estimated a reading time of 45 s for 2D and 91 s with DBT. It is possible that reading times are longer than this depending on experience, equipment and hanging protocols. The quality assurance workload for radiographic and physicist staff is increased as is the time to perform studies. This again has implications for a high volume screening workloads and cost. The Oslo study estimated an increase of 10 s per view for an experienced mammographer to perform DBT in combination with the 2D DM. A centre using tomosynthesis will also consider the increase in data storage capacity required (an approximation of 20 MB for 2D vs. 2000 MB for DBT).

CAD may play a role in DBT screen film reading. This is being investigated in an arm of the Oslo trial; however, Kilburn-Toppin and Barter [60] have suggested CAD would remain a supplementary tool only and will not substitute radiologist reading.

18.1.6 Contrast-Enhanced Spectral Mammography

This new technique has been described as a more accessible breast MRI study. Contrast-enhanced spectral mammography (CESM) utilises tumour angiogenesis in a similar way to contrast-enhanced breast MRI (CE-MRI). CE-MRI is currently accepted as the most sensitive imaging technique for detecting and staging breast cancer.

18.1.7 Technique

There are two recognised techniques used in CESM: temporal subtraction and dual energy. Both techniques involve the administration of iodinated contrast at a rate of approximately 3 mL/s.

Table 18.2 Table of prospective DBT Breast cancer screening studies with double reading

Study	No. of patients	Design	Recall	False-positive rate	Cancer detection rate	No. of cancers/1000 2D vs. 3D(+2D)
Oslo (Interim results: Skaane et al. [55])	12,621	2 view (V) 2D vs. 2 V 2D + 2 V 3D	Increase 32%	Decrease 13%	Increase 31%	6.1 vs. 8.0
Malmö Lang et al. [56]	7500	2 V 2D vs. 1 V 3D	Increase 43%		Increase 43%	6.3 vs. 8.9
STORM (Interim results: Ciatto et al. [57])	7292	2 V 2D vs. 2 V 2D + 2 V 3D		Decrease 17.2%	Increase 51%	5.3 vs. 8.1

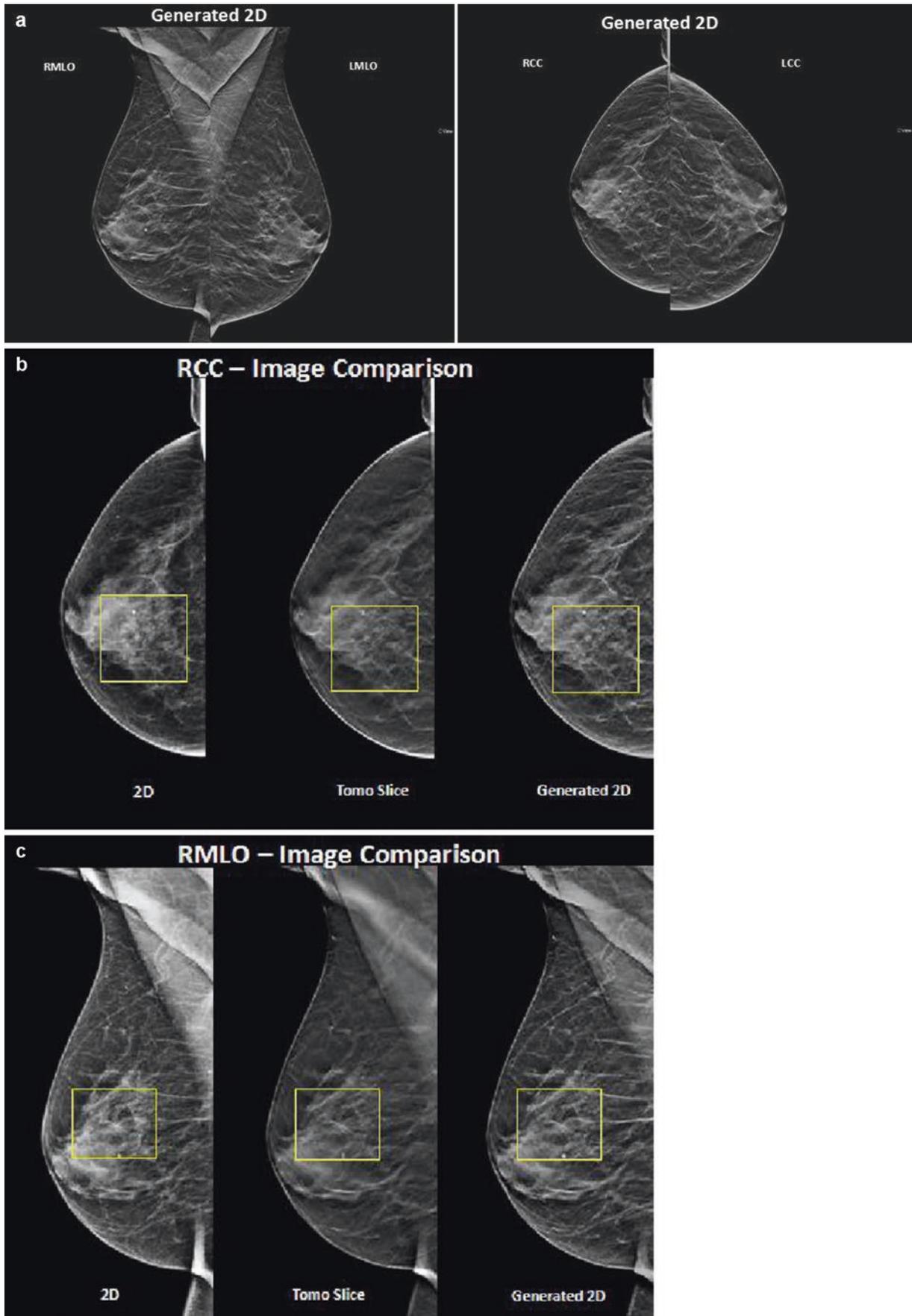


Fig. 18.14 (a–c) Images courtesy of Hologic, Inc. This is a case of invasive ductal carcinoma seen as an architectural distortion with associated microcalcification seen on the 2D, DBT and reconstructed 2D

Temporal subtraction acquires images with the patient's breast held in a single light compression which limits movement and minimises compression of the blood vessels. A pre-contrast image is taken and contrast is administered via power injector. Multiple high-energy images are taken over several minutes. The pre-contrast image is subtracted from the post-contrast images. Software enables the kinetic analysis of a lesion as with CE-MRI. A single contrast dose is required for each analysis with one breast in one projection.

In the dual-energy technique, images are acquired using high- and low-energy exposures following contrast administration via a power injector. A subtraction technique is then used to suppress the background of fibro-glandular tissue and fat, enabling clear demonstration of enhancing tissue. The light compression used is to avoid motion but enable blood flow. The shorter time to acquire the images in this technique limits motion artefact compared with the temporal subtraction technique. Images in MLO and CC projections of both breasts can be taken with a single contrast injection over 5–10 min. The dose is between 20 and 50% higher than that of a single mammographic view. Kinetic analysis is not possible with this technique (Fig. 18.15).

18.1.8 Possible Indications

This technique is predominately used in the research setting at the time of writing this chapter, although some centres have begun using this technique in diagnostic clinics and possibly in the screening of high-risk patients. It is proposed this technique can be used with similar clinical indications as CE-MRI, although this has yet to be established. These include:

- The staging of diagnosed breast cancer particularly in women with dense breasts or distracting benign lesions. This includes evaluating disease extent as well as multifocal disease and contralateral disease which may be mammographically occult.
- The investigation for equivocal breast lesions.
- An alternative to CE-MRI for the screening of high-risk family history screening.
- The detection of a primary tumour in patients with positive axillary lymph nodes and negative standard mammography and ultrasound.
- The potential evaluation of treatment response for breast tumours undergoing neoadjuvant chemotherapy or primary hormonal therapy.
- The investigation of recurrent disease where posttreatment changes may make mammographic interpretation challenging.

The sensitivity of CESM has been proven to be comparable to that of CE-MRI in the detection of index tumours. Jochelson et al. [61] demonstrated CESM and CE-MRI to both exhibit a sensitivity of 96% in detecting the index tumour (81% with conventional mammography) using the dual-energy technique. However, CE-MRI was significantly more sensitive in the detection of multifocal and multicentric additional ipsilateral disease than CESM (56% vs. 88%, respectively). CESM has been shown to give an accurate size measurement/disease extent compared with the final histology (Dromain et al. [62] and Jochelson et al. [61]).

The improved sensitivity of CESM in comparison to non-enhanced mammography is seen in all breast types (Diekmann et al. [63]). The higher spatial resolution of mammography to MRI enables a more critical analysis of lesion morphology as well as the visualisation of microcalcification, not visible with CE-MRI. This is evident by the high rates of specificity reported with CESM than with CE-MRI. Jochelson et al. [61] reported a PPV of 97% for malignancy with CESM compared with 85% for CE-MRI. The improved specificity with CESM may reduce the false-positive findings and benign biopsies secondary to CE-MRI as well as avoiding the practical limitations of scheduling the study by the woman's menstrual cycle, which does not affect CESM. Studies using the temporal subtraction technique have shown very variable kinetic analysis curves for malignant lesions that do not reflect those seen with CE-MRI. However, the enhancement patterns and distribution seen with CESM may mimic those seen with CE-MRI. Jong et al. [64] describe rim-like enhancement, irregular masses and inhomogeneous and linear enhancement of malignancies using a temporal subtraction technique.

CESM would be more cost-effective and time efficient in the diagnostic clinic setting where it may be performed along with standard mammography and ultrasound. CESM may also enable a more accessible means to biopsy and localise disease occult by conventional imaging methods.

The limitations of CESM include the contraindications for contrast administration which are documented contrast allergy, renal insufficiency and the relative contraindications of pregnancy and lactation. Similarly, potential complications include those of intravenous access and contrast reactions. Tumour conspicuity may be affected by the possible reduced blood flow and hence subsequent enhancement from compression of the breast, the reduced contrast resolution and the effect of enhancing overlying fibro-glandular tissue. The limitations of this technique in enhanced high-risk screening instead of CE-MRI would be secondary to the ionising radiation dose.

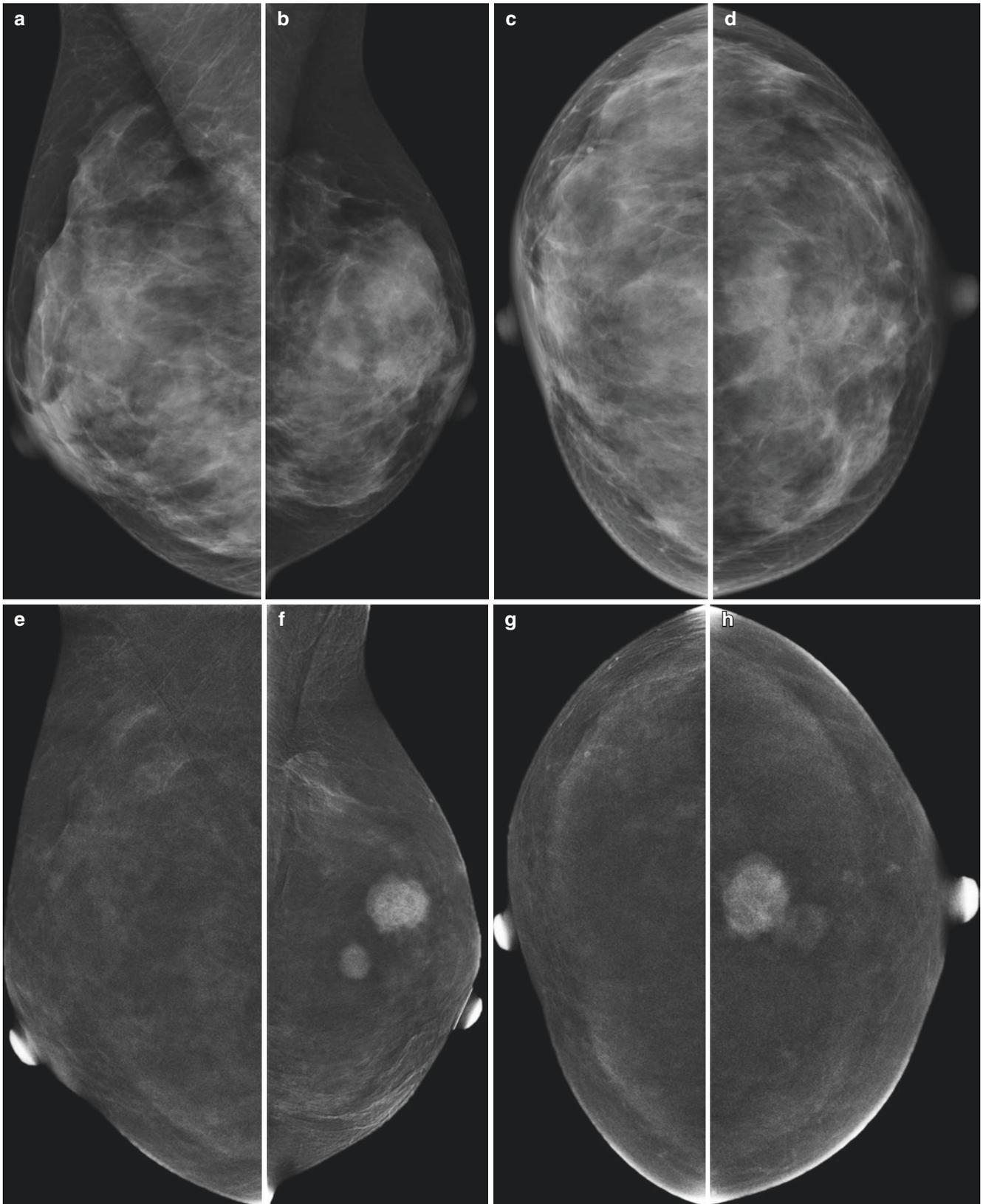


Fig. 18.15 (a–h) Images courtesy of Dr. Sarah Tennant, Nottingham University NHS Hospital and the Nottingham Breast Institute. (a–d) are the low-energy images of BI-RADS 4 dense breasts. The smaller tumour is seen on the (b) LMLO 2D FFDM with only a subtle increased density seen within the upper breast representing the larger tumour.

This area of increased density may easily be overlooked on 2D DM. The post-contrast subtracted images (e–h) clearly demonstrate two grade 3 invasive ductal cancers measuring 19 and 13 mm on final histology without overlapping breast tissue or distracting lesions

18.2 Ultrasound

Viviana Londero, Chiara Zuiani, Martina Zanotel, and Massimo Bazzocchi

Abstract Breast ultrasound (US) is an indispensable tool in breast imaging, and, thanks to advances in US technology, its role is currently not limited to distinguish cystic from solid masses. In fact, a variety of new technical developments, the use of high-resolution probes and the application of a standardised BI-RADS US lexicon have improved characterisation of solid breast masses.

The authors provide an overview of recent advances in US technology, highlighting the applications of breast US in clinical practice. A description of BI-RADS US lexicon and the semiotic of cystic and solid breast lesions will also be presented.

Keywords Breast ultrasound • BI-RADS US • Breast disease • Colour Doppler • Elastography • 3D US • ABUS

18.2.1 Introduction

Breast ultrasound (US) has become an indispensable tool in breast imaging, usually complementary to mammography and magnetic resonance (MR) imaging. Although is under discussion the use of whole-breast US as supplement screening tool in women with dense breasts, its primary and routinely role is the characterisation of lesions detected at mammography, MR imaging or clinical breast examination [65].

The first clinical applications of breast US in the 1960s exploited the ability of US to distinguish cystic from solid masses, with the result that cystic benign lesions did not require further workup [66]. However, the poor image contrast and fair resolution of the first US machines did not allow further differentiation among solid breast masses [65]. Over the next decades, the advances in US technology, the development of high-frequency US transducers and the application of a standardised BI-RADS US lexicon allowed to obtain more detailed information about shape, orientation, margins, lesion boundary, echo pattern and posterior acoustic features of breast lesions, with the result to improve lesion conspicuity in the background of surrounding parenchyma and to improve characterisation of solid breast masses.

The US semiotic was subsequently ameliorated after the publication of Stavros' landmark study in 1995 [67], demonstrating that high-resolution greyscale US imaging could accurately distinguish benign from malignant lesions. In particular, Stavros et al. [67] developed a classification system for solid breast masses that achieved a 98.4% sensitivity and

a 99.5% negative predictive value for malignancy. Among benign US features, the author included ellipsoid shape, gentle bi- or tri-lobulations, a thin echogenic capsule and a homogeneously echogenic echotexture [67]. Malignant US features included spiculated or angular margins, "taller-than-wider" orientation, marked hypoechogenicity, posterior acoustic shadowing and microcalcifications [67].

These important results were confirmed by other authors [68, 69], and the "Stavros' sonographic features" or "Stavros' criteria" are currently considered the cornerstones in the US assessment of breast solid lesions. Nowadays, these US signs ("descriptors") are widely illustrated and validated by the ACR BI-RADS US (Breast Imaging-Reporting and Data System) [70].

18.2.2 Conventional 2D Ultrasound, Compound Imaging and Harmonic Imaging

In addition to traditional greyscale US examination (B-mode), complementary tools now available in almost US units include compound imaging and harmonic imaging that can be used to ameliorate image contrast and resolution. Colour Doppler and power Doppler (more sensible to low-flow vessels) analysis allows to assess vascular architecture of the lesion and of surrounding breast tissue.

18.2.3 Compound Imaging and Harmonic Imaging

High-quality 2D US in combination with a precise examination technique, including radial and anti-radial scanner movements and a moderate tissue compression, is the basis for improving lesion conspicuity and for detecting small breast lesions and early-stage breast cancers.

Compound imaging and harmonic imaging represent 2D US technical advances introduced to ameliorate the image contrast and resolution, and these tools should be routinely used during US examination in order to optimise image quality. Compound imaging, with the use of an electronic beam steering, allows to acquire multiple US images from different angles, providing in real time a single final image that represents the average of these multiple images [71, 72]. The main advantage of compound imaging is that returning echoes from real structures are enhanced, with improved contrast resolution, resulting in a better definition of lesion margins, echogenic halos, posterior and lateral borders and better visualisation of microcalcifications and subtle architectural distortions [72]. Therefore, compound imaging is

able to reduce some advantageous artefacts such as artefacts behind Cooper's ligaments, but, at the same time, some helpful artefacts typically used as semiotic signs to differentiate cystic from solid nodules (such as posterior acoustic enhancement or shadowing) can be eliminated. Therefore, caution is necessary when applying this technique to lesion analysis.

Another modern algorithm, called "speckle reduction imaging" (SRI), that can be used simultaneously with compound imaging can help to enhance contrast and to optimise image quality during US examination.

To explain harmonic imaging, we have to consider that when US pulses travel along breast tissue, they can be

distorted, creating harmonic frequencies [72]. The returning US signals may therefore contain both the original fundamental frequency and its multiples or harmonics. In harmonic imaging, the higher harmonic frequencies are filtered and used to create the greyscale US image with improved contrast, whereas lower-frequency artefactual internal echoes (typical of fluid components) are eliminated. As a consequence, the harmonic technology provides a better characterisation of simple cysts (especially if small) (Fig. 18.16) and a better definition of subtle lesions. Harmonic imaging also improves lateral resolution and assessment of lesion margins (Fig. 18.17).

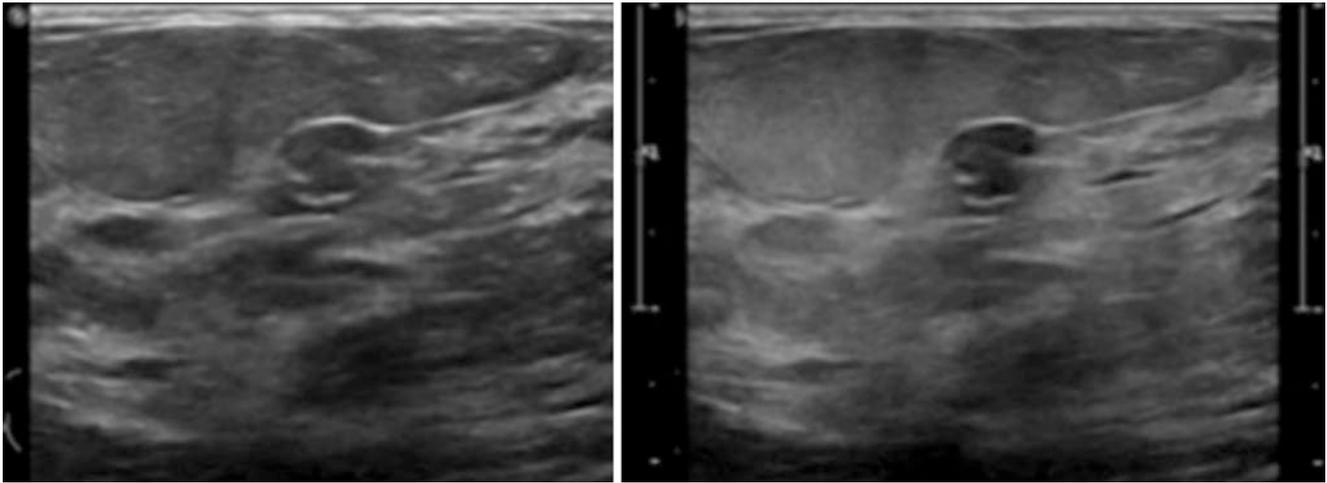


Fig. 18.16 Harmonic imaging. Solid hypoechoic lesion (fibroadenoma). Harmonic imaging (*right figure*) shows more accurately lesion margins and allows a significant increase of signal to noise ratio

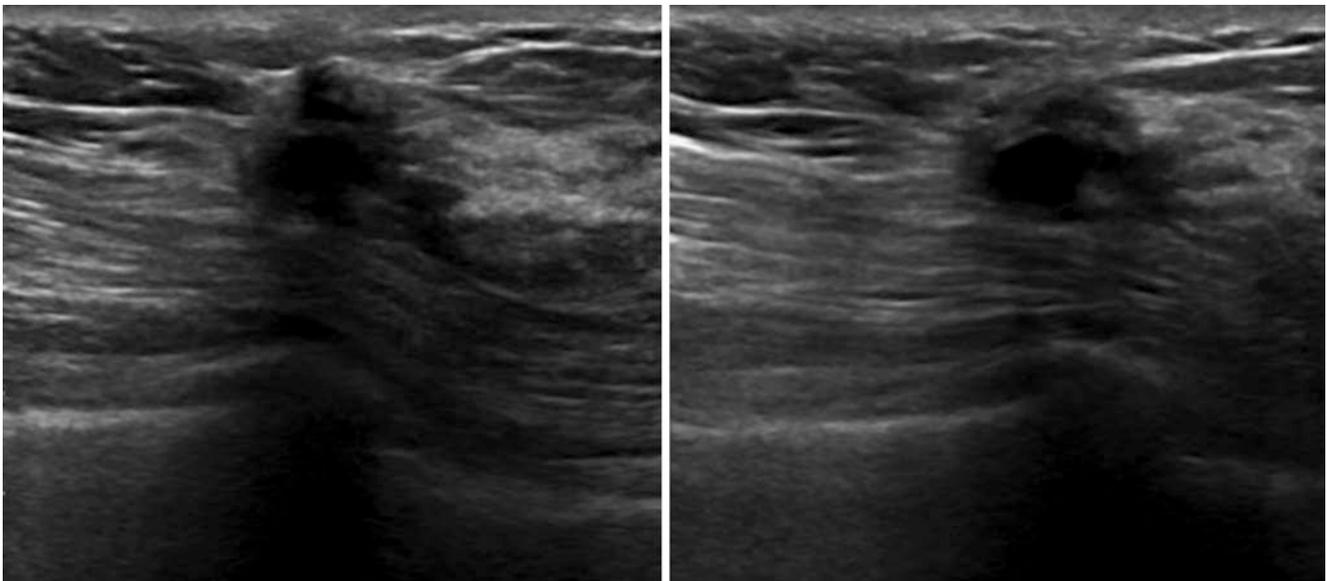


Fig. 18.17 Harmonic imaging. Hypo-anechoic lesion in woman with previous quadrantectomy; harmonic imaging (*right figure*) highlights with greater accuracy the oval morphology and partially circumscribed margins defining the cystic nature of the lesion (liponecrosis)

18.2.4 Colour Doppler and Power Doppler

With improvements in breast US technology, colour Doppler and power Doppler have become complementary tools to greyscale breast ultrasound, giving information about vascularity of solid lesion and of surrounding breast tissue. Power Doppler has been seen to be more sensible to low-flow vessels typical of breast lesions that, generally, require a moderate tissue compression in order to prevent occlusion of vessel lumen.

First applications of colour Doppler in the mid-1990s and early 2000s demonstrated that the presence of increased vascularisation within a solid breast mass could raise the suspicion of malignancy. In fact, Cosgrove et al. [73] in 1993 found that 99% of malignant lesions exhibited significant vascularisation at colour Doppler compared to only 4% of benign lesions. Sehgal et al. [74] found that benign lesions were two times more vascular than the surrounding tissue, compared to five times higher vascularity of malignant lesions.

Further studies in subsequent years did not confirm these initial promising results and concluded that colour Doppler should not be considered a reliable tool in the assessment of breast disease, because it could not accurately differentiate benign from malignant lesions [75, 76]. Although consensus has not been reached on usefulness of Doppler analysis, nowadays these vascular tools should be an integral part in every breast ultrasound practice.

In Gokalp's study [76], power Doppler criteria predictive of malignancy included hypervascularity, penetrating vessels within a solid mass and neovessels with branching-disordered course; however, the authors did not find any contribution to BI-RADS US, with the addition of power Doppler ultrasonography and spectral analysis.

Thanks to higher sensitivity to low-flow vessels, power Doppler may be useful in distinguishing a "centripetal" vascular pattern, generated by anomalous neovessels in malignant lesions, from the "centrifugal" vascularity (with a parallel artery and vein in the periphery or inside a lesion), predominantly associated with benign lesions (such as fibroadenomas) or with anatomic structures (such as lymph nodes). In particular, lymph nodes can be easily recognised because they exhibit a rich hilar vascularisation, also if small sized. Therefore, power Doppler, when used in addition to B-mode US, may reinforce the benign or malignant suspicion of a solid mass and can help to improve BI-RADS assessment category.

Assessment of lesion vascularity is recommended but is not considered mandatory in the BI-RADS US lexicon [70] that includes three descriptor choices ((a) absent, (b) internal vascularity, (c) vessels in rim). In the US section of the new BI-RADS fifth edition [70], the special category has been expanded with the additional terms of arteriovenous malformations and Mondor disease.

In addition to all potential uses above described, the application of colour Doppler may be helpful during breast

interventional procedures, in order to avoid hitting great vascular structures with the risk of bleeding and obscuring the target lesion (particularly frequent in lesions of small dimensions or located deep in the breast). Besides, a biopsy marker clip may create a twinkle artefact, best appreciable with colour Doppler.

18.2.5 US Elastography

US elastography has the ability to measure tissue stiffness, in a similar manner of palpation during physical examination. Two types of elastography are available today: strain and shear wave.

Strain elastography requires gentle compression with US probes that results in a tissue displacement (or strain), usually inversely correlated with tissue stiffness [77]. This technique provides qualitative information, in a colour-scale image, although the strain ratio, comparing the strain of lesion to the surrounding breast tissue, can be calculated [78, 79]. Stiff malignant masses usually exhibit higher strain ratio in comparison with benign lesions.

In shear-wave elastography, the US probe generates transient, automatic pulses that induce transverse waves in the tissue. The US system measures the speed of these waves, which travel faster in hard tissue compared with soft tissue [80]. A quantitative information, represented by the tissue elasticity and measured in KPa or m/s, can be calculated.

Therefore, some parameters obtained with elastographic analysis such as strain ratio, shape, homogeneity and maximum lesion stiffness (Fig. 18.18) can enrich the conventional sonographic features, improving specificity in the diagnosis of breast lesions.

On elastography, malignant lesions typically appear more irregular, heterogeneous and larger compared with greyscale B-mode examination [81, 82]. Moreover, although malignant lesions exhibit maximum stiffness greater than 80–100 KPa [82, 83], a variability among lesions and among elastography techniques may exist [82].

Some papers found that high stiffness, measured at shear-wave elastography, is highly correlated with more aggressive behaviour tumours, including high-nuclear-grade, large-sized lesions and early lymphatic and vascular invasion [84].

Despite these initial promising results about usefulness of elastography in clinical practice, some limitations exist such as differences between the two methods (strain and shear wave) and among different US machines and the presence of inter- and intra-observer variability, affected by degree and method of compression, although shear-wave technique seems to be less operator dependent [85]. In addition, one must be aware that elastographic assessment is less accurate in lesions deeper than 2 cm and that soft cancers or hard benign lesions may exist.

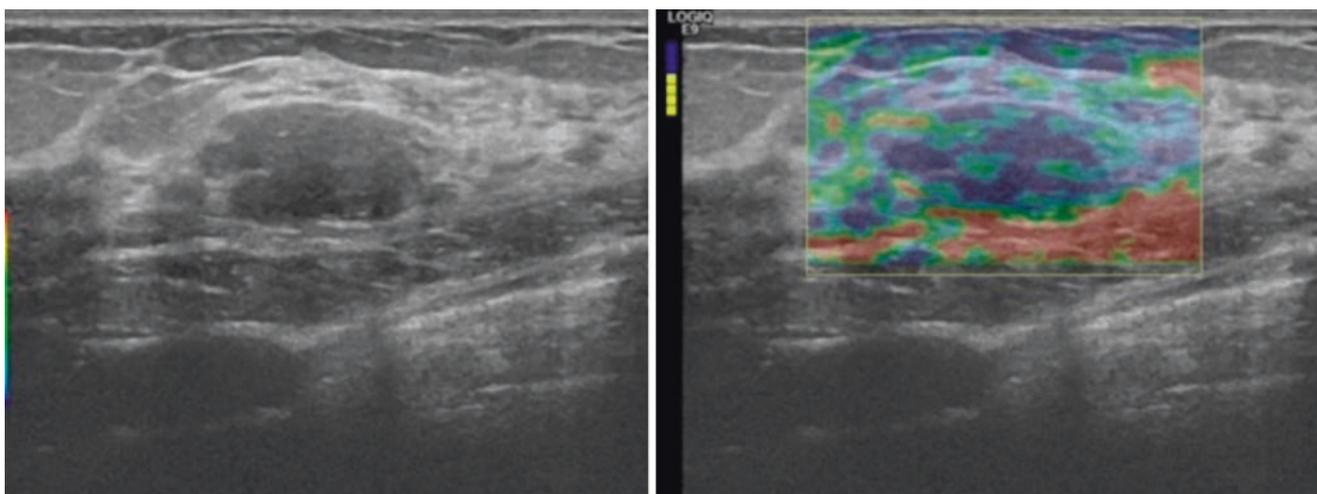
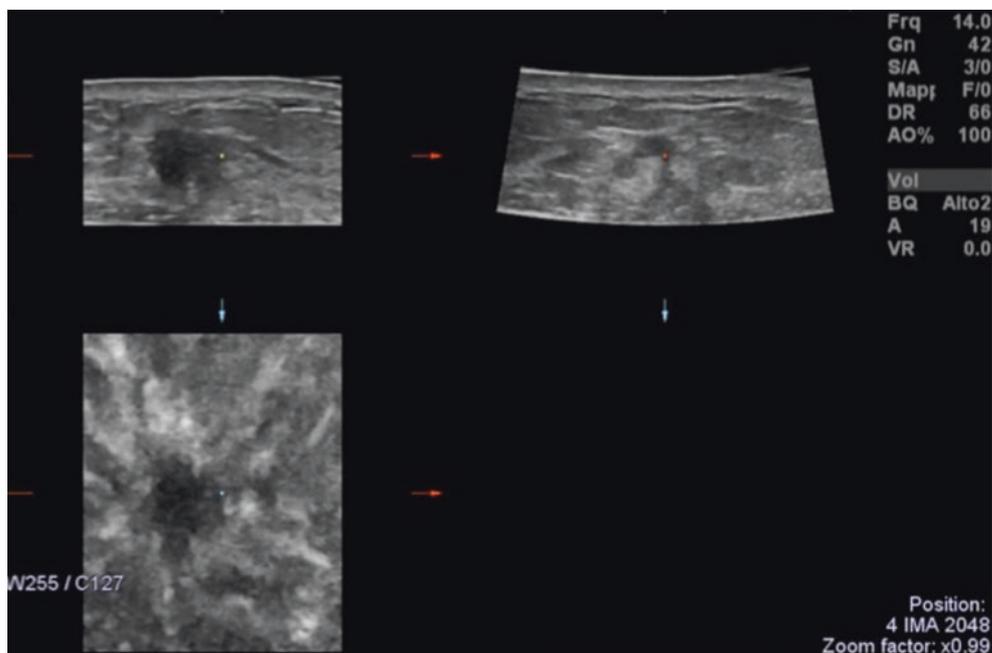


Fig. 18.18 Elastography. Hypoechoic circumscribed lesion (fibroadenoma) that is predominantly elastic, depicting the typical mosaic pattern of green and blue (BI-RADS US 2) on elastography (right image)

Fig. 18.19 3D ultrasound. Invasive ductal carcinoma grade 1. Images of 3D US are presented in three planes (“multiplanar display mode”). The coronal plane allows a better evaluation of tumour margins and distortion type of growth pattern, typically associated with malignant lesions



18.2.6 Advances in US Technology

New technical developments such as 3D ultrasound, dedicated CAD (computer-aided diagnosis) and automated whole-breast ultrasound (ABUS) are promising methods suitable for the future clinical practice [65, 72, 86].

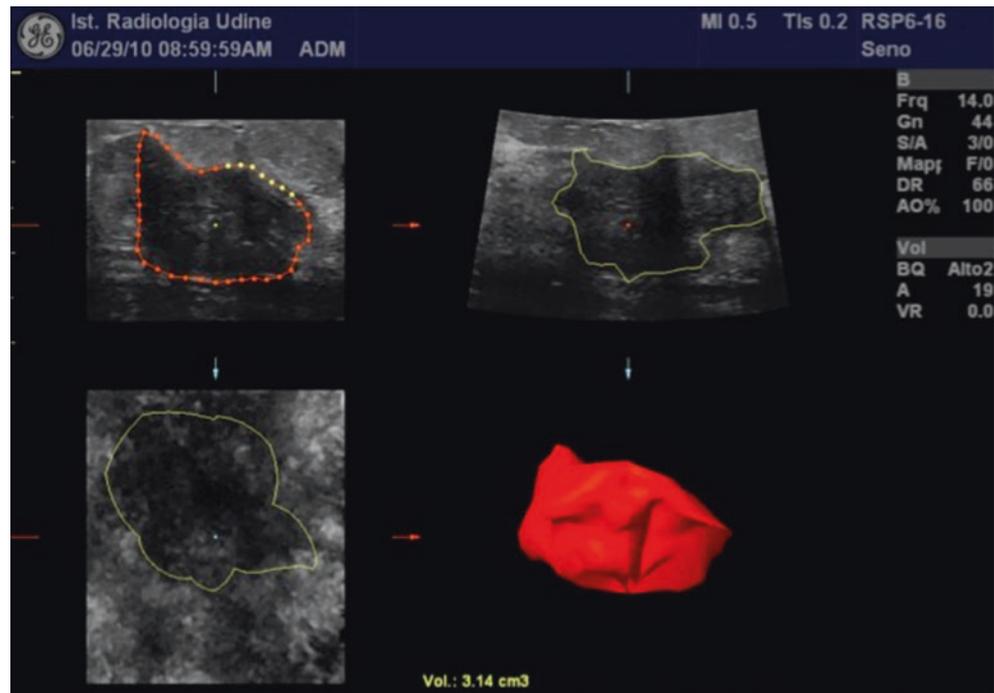
18.2.7 Three-Dimensional (3D) Ultrasound

3D ultrasound has been recently developed, and high-resolution linear 3D transducers are available in new US machines for a new multidimensional breast imaging. 3D US technology, with

a single pass of the ultrasound beam, allows the acquisition of a volume data set, from which the static 3D information will be reconstructed. In 3D US, reconstructed 3D sonographic images are displayed in a “multiplanar display mode” allowing the representation of breast lesions and of surrounding breast tissue in three spatial planes (coronal, sagittal, and transverse plane) [86, 87] (Fig. 18.19). The system allows to navigate through the entire volume, performing parallel movements through the image slices in the three orthogonal planes.

Compared to standard 2D US, 3D images provide a more accurate assessment of tumoural margins and of surrounding breast tissue; moreover, the multiplanar representation is available for a double reading.

Fig. 18.20 3D Ultrasound. Invasive ductal carcinoma grade 2 with intraductal component, with lesion's volume calculation. 3D US can easily obtain calculation of tumour volume (cm^3) by the VOCAL software ("virtual organ computer-aided analysis")



In particular, Rotten [87], by using 3D US, described two main peritumoural tissue patterns, particularly visible in the coronal plane, corresponding to “compressive pattern”, typically associated with benign lesions, and “converging or stellate pattern”, associated with malignant lesions. By using these criteria of peritumoural tissue pattern, the authors [87] achieved a 91.4% sensitivity, a 93.8% specificity, an 86.9% positive predictive value and a 96% negative predictive value in the differentiation between malignant and benign lesions.

Moreover, 3D US has a potential role in the assessment of tumoural response to neoadjuvant chemotherapy, offering a precise and reliable volume calculation with VOCAL software (“virtual organ computer-aided analysis”) [86] (Fig. 18.20). 3D US can also be used for the volumetric assessment in the preoperative evaluation of breast lesions [88].

A future application of 3D technology should include 3D ultrasound guidance during breast needle biopsies, with the goal of reducing sampling errors due to “partial volume effect”, especially with small-sized breast lesions.

18.2.8 Automated Whole-Breast Ultrasound (ABUS)

ABUS is a new technological advance in which breast scanning is performed automatically by using a curved transducer that is larger compared to traditional handheld (HHUS) probe

and is similar, in size and shape, to a mammography compression paddle. This automated transducer is placed over the breast using a moderate tissue compression, with patient lying supine on the table, and allows to scan the whole breast automatically. Usually, three acquisitions (AP, lateral and medial) for each breast are needed, which may increase to four or five acquisitions in women with larger breasts. On average, total acquisition time is 15 min, with medium-sized breasts [89].

All imaging data obtained during scanner acquisition are processed and stored on a computer hard drive and finally can be visualised on a standard workstation during reporting and interpretation session. On workstation screen, ABUS images can be displayed in the transverse, coronal or sagittal plane (Fig. 18.21), typically not available with traditional 2D US imaging. In particular, the coronal view is particularly helpful in detecting areas of architectural distortions, which may be difficult to appreciate on standard axial images [90] (Fig. 18.22). ABUS offers also the possibility to visualise real-time images at the time US examination is performed, in a similar manner of HHUS examination.

Automated US offers several advantages over traditional HHUS scanning, such as higher reproducibility, less operator dependence and less physician time for image acquisition. In fact, the physician time required by ABUS includes only time for interpretation, approximately 3 min to read a negative examination, whereas time for image acquisition has been now eliminated [89].

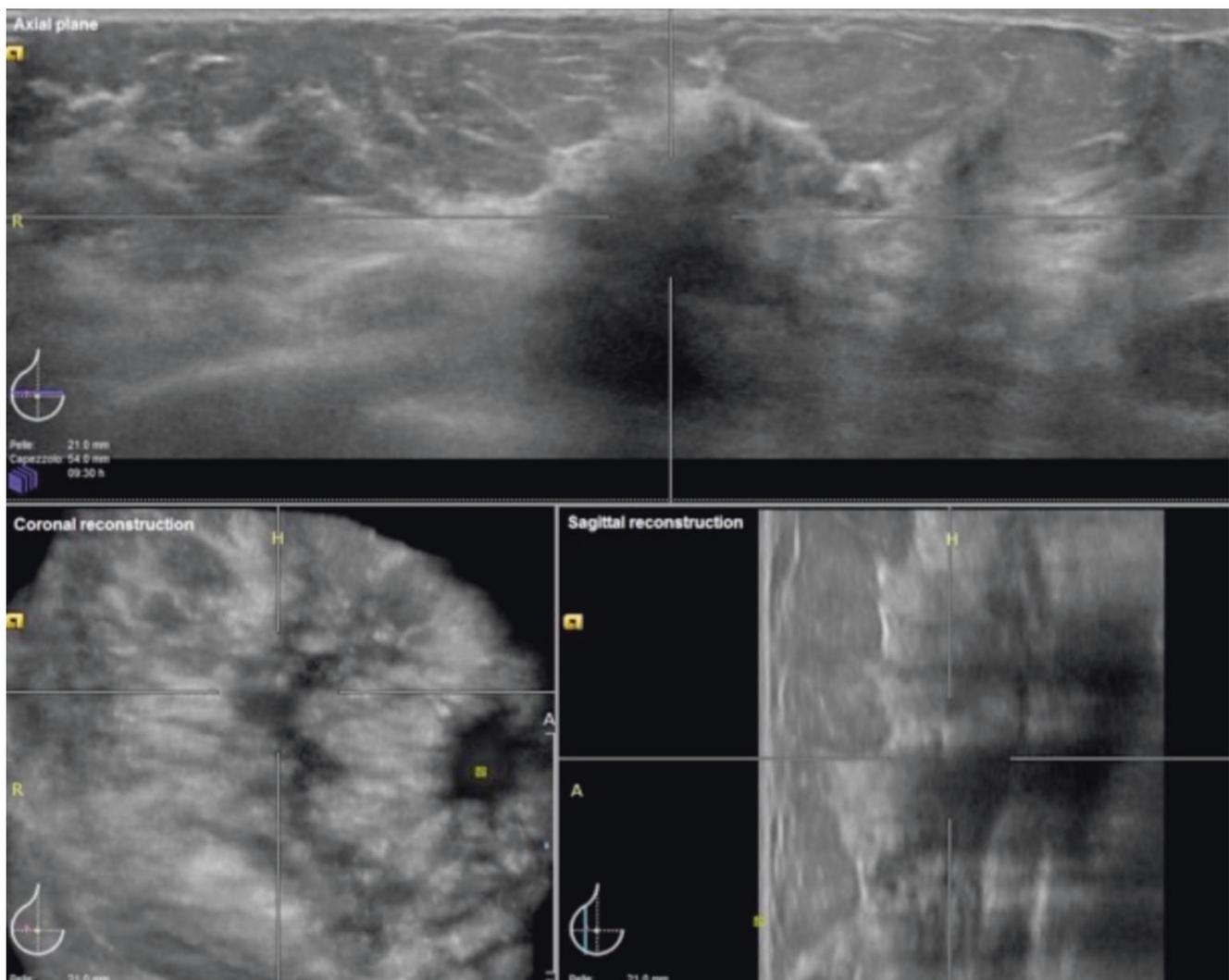


Fig. 18.21 ABUS. Invasive lobular carcinoma. Hypoechoic lesion with indistinct margins and posterior shadowing artefacts (BI-RADS US 5) shown in axial, sagittal and coronal planes

There are some limitations in automated US technology, which are the presence of shadowing artefacts in the sub-areolar region (that may obscure actual lesions or create unreal findings) and the incomplete assessment of breast tissue, being the axillary region not included in the automatic scanning [89]. Some authors [91] report that ABUS is a promising diagnostic tool with a good interobserver agreement, comparable to that of HHUS, on lesion characterisation and on final category assessment.

One topic of interest is the potential application of ABUS, as a promising screening tool in adjunct to mammography, for examining radiologically dense breasts [89]. In the large observational study of Brem [92], the addition of ABUS to

screening mammography in women with dense breast tissue has resulted in an increase of cancer detection rate (1.9 additional cancers per 1000 screened women) but also in an increase of false-positive results. In fact, 552 additional needle biopsies were performed to identify 30 cancers detected with ABUS alone (most of these were invasive clinically important cancers). This high false-positive rate inducing to perform unnecessary biopsies should be however overtaken with higher operator experience and higher diagnostic confidence. Some recent works have demonstrated an equivalence in lesion detection [93] and an equivalence or, in some cases, a superiority in lesion characterisation in the comparison between ABUS and HHUS [94, 95].

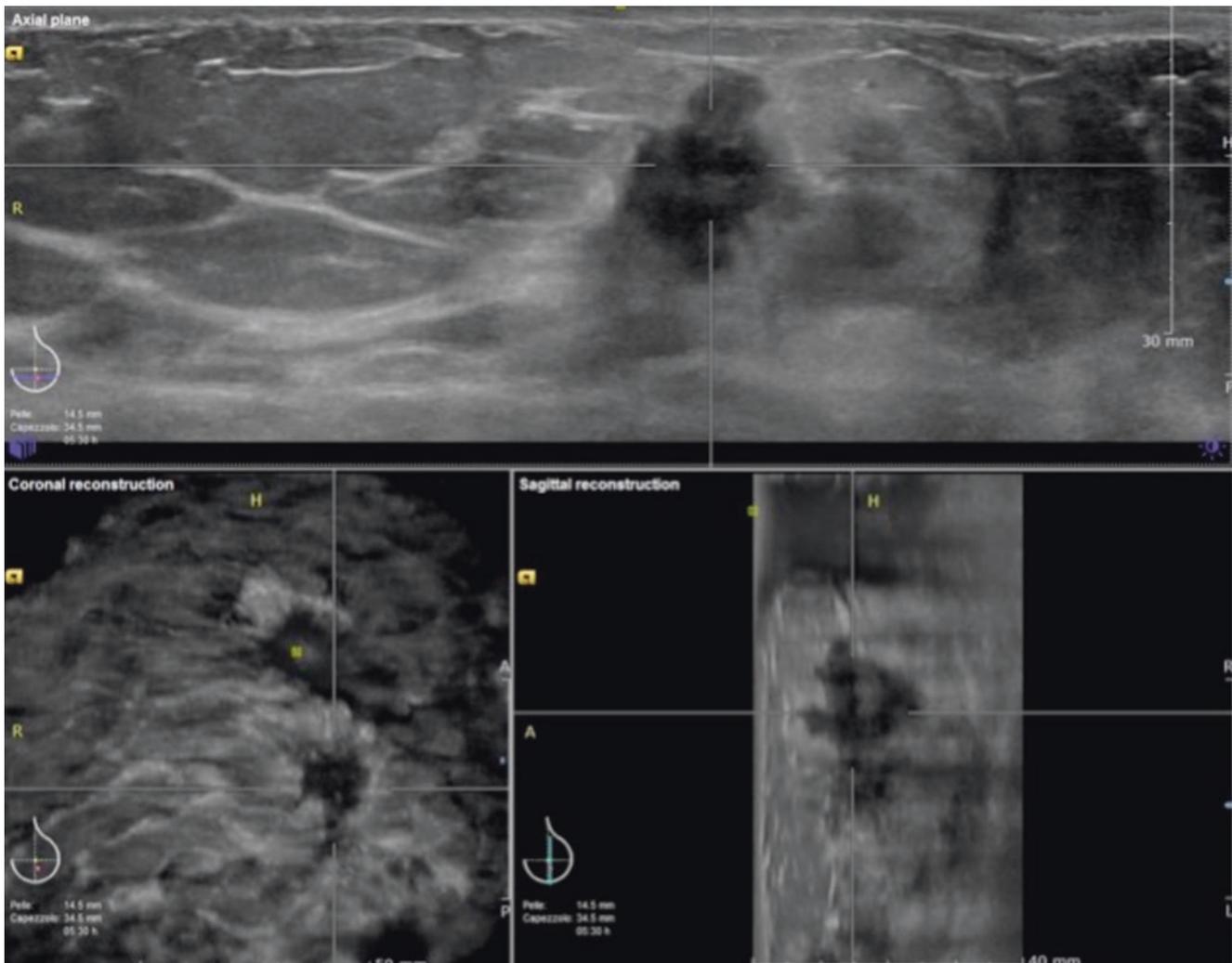


Fig. 18.22 ABUS. Invasive ductal carcinoma. Hypoechoic lesion with vertical growth and irregular margins (BI-RADS US 5) shown in axial, sagittal and coronal planes

18.2.9 Breast Ultrasound in Clinical Practice

Breast ultrasound (US) is the modality of choice for differentiating cystic from solid breast masses, and its primary role is the characterisation of lesions detected at mammography, at MR imaging, or at clinical breast examination [96].

Current indications for breast ultrasound, as recommended by the ACR Practice Guidelines [96], include the evaluation and characterisation of palpable masses or other breast symptoms and the evaluation of abnormalities detected with other imaging modalities, including the role of targeted US after a contrast-enhanced breast MR examination to find an ultrasound correlate. US can also be used as first-line imaging modality for palpable masses in women under 30 years and in lactating and pregnant women and for evaluation of breast implants. In addition, US can

be used as guidance for breast biopsy or other interventional procedures, including biopsy guidance of abnormal axillary lymph nodes [96]. The use of bilateral whole-breast US, in women with dense breast tissue, as an adjunct to screening mammography, is a topic of discussion and debate [89, 96].

18.2.10 ACR BI-RADS US

In light of the widespread use and implementation of breast US in clinical practice, a standard lexicon for sonography was initially developed in 2003 by the ACR in order to provide a standardised lexicon for sonographic reporting, to facilitate final category assessment and to validate management recommendations. The correct adherence to BI-RADS

US lexicon can improve differentiation between benign and malignant lesions and potentially reduce the number of unnecessary biopsies [97].

The BI-RADS sonographic categories include size, shape, orientation, margins, echogenicity, lesion boundary, attenuation features, special cases, vascularity, and surrounding tissue [70]. In the last BI-RADS fifth edition [70], new terms have been added to the US lexicon to simplify reporting and to reflect technologic advances (such as the addition of elastography). In particular, a new section, including “elasticity assessment” with three descriptor choices ((a) soft, (b) intermediate, (c) hard), has been added. The ACR recommends the use of these elasticity descriptors instead of the colour scale, not yet standardised.

Some authors report an interobserver variability with the use of BI-RADS US lexicon comparable to that for mammography. Abdullah et al. [98] found a fair interobserver agreement ($k = 0.30$) in the final BI-RADS category, in particular in final BI-RADS 4 a, b, and c subcategories ($k = 0.33, 0.32$ and 0.17 , respectively), reflecting difficulties of radiologists to indicate a degree of suspicion. Promising results were obtained by Heinig et al. [99] that reported malignancy rates in BI-RADS US category 3, 4 and 5 similar to those of mammography (1.2%, 17% and 94%, respectively), underlying the usefulness of BI-RADS US descriptors to obtain a final degree of suspicion.

18.2.11 Sonographic Findings of Cystic and Solid Breast Masses

Thanks to its ability to differentiate cystic from solid masses and to state a suspicion degree among solid masses, breast US is usually complementary to mammography in the characterisation of breast lesions, characterisation that sometimes may appear difficult if lesion is small (<5 mm) or located deep in the breast [100, 101].

The traditional sonographic signs used in breast US reporting refer both to the “Stavros’ sonographic criteria” [67], which represent a landmark in this context, and to the US descriptors illustrated and validated by the ACR BI-RADS US [70].

1. Cysts

Simple cysts are defined as well-circumscribed, anechoic masses, with posterior acoustic enhancement. Complicated cysts are hypoechoic masses, not vascularised at colour Doppler analysis, that may contain internal echoes or exhibit indistinct margins. Complicated cysts are benign findings, typically associated with low malignancy rate (0–0.08%) [102]; however, when associated with a mammographic correlate or with a palpable mass, they should be classified as BI-RADS 3, and a short follow-up or an US-guided aspiration should be recommended.

“Complex masses” present a heterogeneous echo pattern with an anechoic (liquid) component and a hypoechoic (solid) vascularised component; sometimes mural nodules, thick walls or irregular internal septations may coexist. In relation to their high malignancy rate (23–31%), these complex masses should be assessed as BI-RADS 4 and should require further characterisation with US-guided needle core biopsy.

The application of harmonic imaging can improve characterisation of simple cysts (particularly if small sized), allowing the elimination of artefactual internal echoes, whereas the application of elastography is useful in improving the specificity of lesions assessed as BI-RADS 3 or BI-RADS 4a, including complicated cysts, with the result of reducing the need of unnecessary biopsies [82].

2. Solid Breast Masses

(a) Sonographic criteria of benignity

The benign sonographic features described by Stavros [67] and later confirmed by Hong [103], typically associated with a low risk of malignancy, include ellipsoid or oval shape (negative predictive value, 84%), circumscribed margins with gentle bi- or tri-lobulations (90%), the “wider-than-taller” appearance with parallel orientation (78%), as well as the absence of any malignant features.

Lesions with these sonographic benign findings are typically fibroadenomas that may be managed with a short-term imaging follow-up, even if the mass is palpable [97, 104].

However, considerable overlap between benign and malignant US features exists; therefore, a careful correlation with mammography is essential, keeping in mind that an US benign-appearing solid mass requires biopsy if it exhibits any suspicious mammographic features.

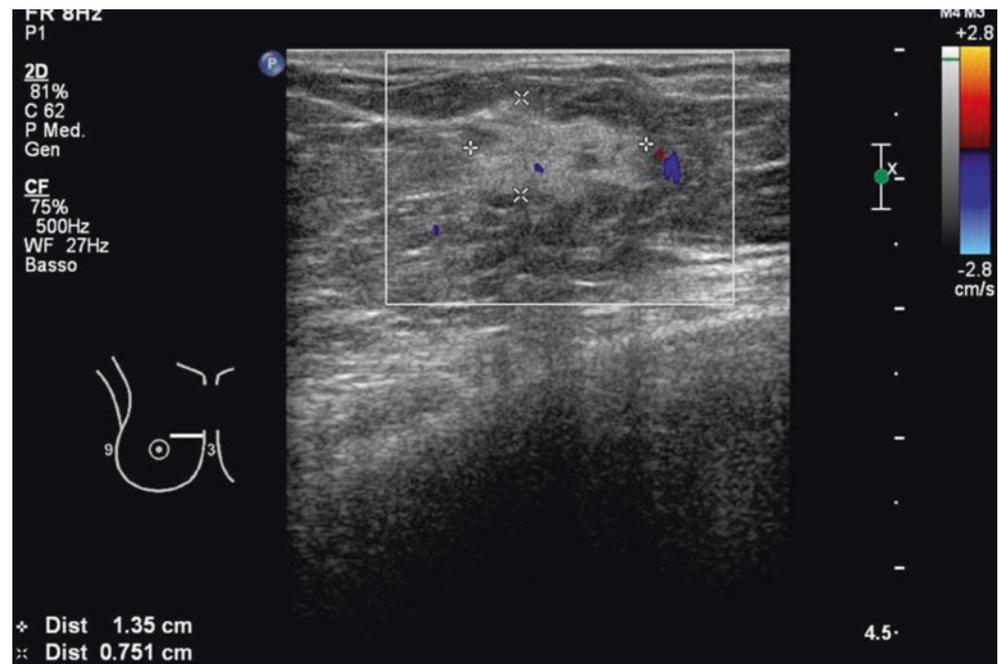
(b) Sonographic criteria of malignancy

Sonographic findings predictive of malignancy include spiculated (positive predictive value, 86%) or angular (60%) margins, irregular shape (62%), the “taller-than-wider” appearance with antiparallel orientation (69%), posterior acoustic shadowing (52%) and echogenic halo (70%), expression of peritumoural desmoplastic reaction [67, 103]. Other sonographic Stavros’ criteria predictive of malignancy include marked hypoechoicity, microcalcifications, duct extension, branch pattern and the presence of microlobulated margins [67].

Among US descriptors, Lazarus [40] found a good agreement for lesion orientation, shape and boundary ($k = 0.61, 0.66$ and 0.69 , respectively), a moderate agreement for margins and posterior acoustic shadowing ($k = 0.40$, for both) and a fair agreement for lesion echo pattern ($k = 0.29$) and final assessment category ($k = 0.28$).

In addition to sonographic signs, the value of these criteria in distinguishing benign from malignant solid

Fig. 18.23 Invasive ductal carcinoma grade 2. Hyperechoic lesion, with irregular morphology and indistinct margins (US signs suspicious for malignancy)—BI-RADS US 4b



lesions is affected also by lesion size, with improving accuracy of breast US when evaluating lesions greater than 7 mm [105].

3. Hyperechoic Breast Masses

Although lesion hyperechogenicity is considered the benign feature with the highest (100%) negative predictive value for malignancy [67, 103, 105], hyperechogenicity at US alone does not exclude malignancy, and uncommon hyperechoic malignancies may exist [106, 107].

When evaluating a hyperechoic lesion, suspicious sonographic features that should help to avoid misdiagnosis include the presence of focal hypoechoic areas within the hyperechoic lesion, non-parallel orientation, non-circumscribed margins, posterior acoustic shadowing and rich internal vascularisation at colour Doppler examination (Fig. 18.23). In addition, correlation with clinical history and with mammographic appearance should be recommended.

4. Ductal Carcinoma In Situ and Microcalcifications

Ultrasound is considered to have a marginal role in the evaluation of ductal carcinoma in situ (DCIS), in relation to the poor demonstration of microcalcifications, particularly when located in a dense breast parenchyma.

The advances in US technology with the use of high-frequency transducers (high-resolution sonography) and with improved spatial and contrast resolution allow a better depiction of microcalcifications, particularly when they form large (>10 mm) clusters or when they are located in solid hypoechoic masses, highly suspicious for malignancy.

US features associated with DCIS usually include hypoechoic masses, intracystic masses, and architectural

distortions [108, 109]. In Moon's study [108, 110], a microlobulated mass, with mild hypoechogenicity, ductal extension and normal acoustic transmission, was the most common US finding of DCIS.

Some studies [108–110] have investigated the potential roles of US in the evaluation of DCIS, including those without calcifications; in particular, (1) US can be used to visualised large (>10 mm) clusters of microcalcifications, suspicious for malignancy; (2) US may be helpful in detecting DCIS without calcifications and in evaluating disease extent; and (3) US may reveal mammographically occult DCIS in dense breasts.

Another main benefit of US detection of DCIS is to identify the invasive component and to guide interventional procedures that are usually more comfortable and less time-consuming compared with stereotactic breast biopsies.

18.2.12 Conclusions

Breast ultrasound has become an indispensable tool in breast imaging, and, thanks to technological advances, its role is currently not limited to distinguish cystic from solid masses and to characterise solid breast masses but also to identify small malignancies in mammographically dense breasts or to detect abnormalities in patients with breast implants or breast reconstruction.

Re-evaluation of the breast with US targeted upon the site of a suspicious MRI-detected lesion (“second-look US” or “targeted sonography”) offers the possibility to identify a correlative lesion on ultrasound so that needle core biopsy

may be obtained using sonographic guidance (as an alternative to MR-guided biopsy).

Finally, US can be used to guide interventional breast procedures (such as needle core biopsies or preoperative needle localisations), with several advantages compared with stereotactic guidance.

18.3 MRI

Christiane K. Kuhl

Abstract Magnetic resonance imaging (MRI) is one of the fastest developing fields in contemporary diagnostic radiology. Within the field of breast MRI, there are currently two major research directions. One direction is to increase the complexity of image acquisition methods in order to further improve our ability to characterise disease, i.e. to distinguish nonproliferative changes, changes with atypias, preinvasive and invasive cancer as well as for improved prognostication, prediction and response assessment, according to the concept of “multiparametric breast MRI”. The other direction is to reduce the complexity and facilitate image acquisition as well as interpretation, according to the concept of “abbreviated breast MRI”. These two research directions are complemented by the development of new methods for MR-guided biopsy and MR-guided surgery. This chapter reviews the current status of the three development directions.

18.3.1 More Technology for Better Answers: Why We Strive to Improve Breast Cancer Imaging Methods

Today, breast cancer is understood as an entire group of diseases that exhibit significant biological differences in terms of their clinical course and outcome [111]. Former breast cancer classification systems that relied mainly on morphological features have been refined or replaced by classification systems that are determined by the cancer’s variable molecular features. Improved knowledge of these features and their role in cancer progression is not only useful for prognostication, but opens up the possibility to exploit these features for targeted therapies. However, heterogeneity is not only observed between cancers but also within a given cancer [112]. Based on current oestrogen receptor, progesterone receptor or human epidermal growth factor receptor 2 (HER2) and Ki-67 classification systems, it is possible that the majority of individual cells within a given cancer exhibit features that are inconsistent with the assigned overall classification. Such intra-tumoural variations are even more important on a genomic or proteomic level.

Yet the more targeted breast cancer therapies become, the more important will be the issue of intra-tumoural heteroge-

neity as a source of tumour resistance. The overall clinical course of a given patient may be driven by a relatively small subset of primary tumour cells—the primary cancer and its metastases may thus exhibit different types of receptor status. Accordingly, during the course of disease, targeted therapies may need adjustment to account for secondary mutations and/or compensatory pathways that may yield resistant tumours. This, in turn, has sparked interest in the development of advanced imaging methods that help demonstrate intra-tumoural heterogeneity, depict and quantify response or depict resistance to treatment.

Currently, information on a cancer’s biological potential is mainly obtained from histologic, immunohistochemical and molecular biological/genomic processing of cancer tissue that needs to be retrieved from invasive methods, i.e. image-guided biopsy. In patients undergoing novel adaptive neoadjuvant therapies, such biopsies may have to be done even repetitively over the course of treatment in order to monitor treatment-related changes. Research on risk stratification of breast cancer relies on such tissue-based markers that provide information on molecular biology, i.e. genomic and proteomic alterations found in cancer. These techniques have been readily integrated into clinical decision making. A possible shortcoming of this focus on tumour genomics and proteomics is the fact that successful tumour growth does not only depend on a tumour’s genomic toolbox but also on its microenvironment, i.e. features of the tissues that host the cancer [113].

Noninvasive, “functional” *in vivo* imaging tests such as multiparametric MRI refer to the acquisition of information on tissue microstructure and tissue metabolic homeostasis through the use of advanced and increasingly complex MR imaging methods such as higher magnetic fields (3.0–7.0 T systems), improved surface coil technology, improved digitisation of signal transduction, new pulse sequence approaches or hybrid imaging, i.e. a combination of MRI with positron-emission tomography, among many other approaches. Functional imaging helps assess the interaction between a cancer and its microenvironment and the degree to which a cancer is successful in shaping its environment to sustain its growth. Growth pattern, cellular turnover, cellularity, degree and type of vasculature and immune cell infiltrate have an impact not only on clinical behaviour but also on presentation in imaging, i.e. yield the “imaging phenotype” of cancers. Accordingly, functional MR imaging methods provide *in vivo* imaging biomarkers that correlate with, and, thus, provide surrogate markers of, cancer biology. Such imaging methods therefore promise to provide further independent diagnostic and prognostic information that will add to our understanding of a cancer’s ability to grow and metastasize.

Established and new “functional” MRI pulse sequence approaches discussed in the following are diffusion-weighted imaging and its derivatives: diffusion tensor and diffusion kurtosis imaging (DTI and DKI) and “intravoxel incoherent

motion imaging” (IVIM); dynamic contrast-enhanced (DCE) MR imaging including its many varieties and kinetic analyses; blood oxygenation level-dependent imaging (BOLD); and MR spectroscopy (MRS) and spectroscopic imaging (MRSI) of proton (^1H) or phosphorus (^{31}P) nuclei—all of which can, in principle, be combined into so-called “multiparametric” breast MRI protocols (mp breast MRI). Moreover, there are completely new pulse sequence approaches such as MRI fingerprinting and chemical saturation transfer or CEST imaging which will probably be used for advanced non-invasive breast cancer phenotyping in the foreseeable future.

Currently, the commonest way to use MRI for breast cancer detection, staging, and classification is by exploiting the angiogenic activity of breast cancers. We identify enhancement, i.e. a signal intensity increase, in images obtained early after intravenous injection of an intravenously administered contrast agent [114, 115]. Tissues that accumulate the injected

contrast agent appear bright on so-called T1-weighted post-contrast MR images. To track the enhancement of lesions, clinical breast MRI protocols always consist of a so-called dynamic series. This means that a stack of cross-sectional images is obtained before and then repetitively after the i.v. bolus injection of the contrast agent. Cancers are characterised by fast and strong enhancement that is observable already on early post-contrast images, usually followed by a washout of signal intensity. Benign changes and the normal fibro-glandular tissue exhibit less and usually only slowly progressive enhancement over time. Since angiogenic activity is the main driver of enhancement, all regular clinical breast MR protocols will reflect this activity (Figs. 18.24 and 18.25). Accordingly, even the most basic breast MRI study will contain “functional” information on pathophysiological changes that are implicated in carcinogenesis and metastatic growth [116]. Moreover, MRI depicts these changes by true 3D

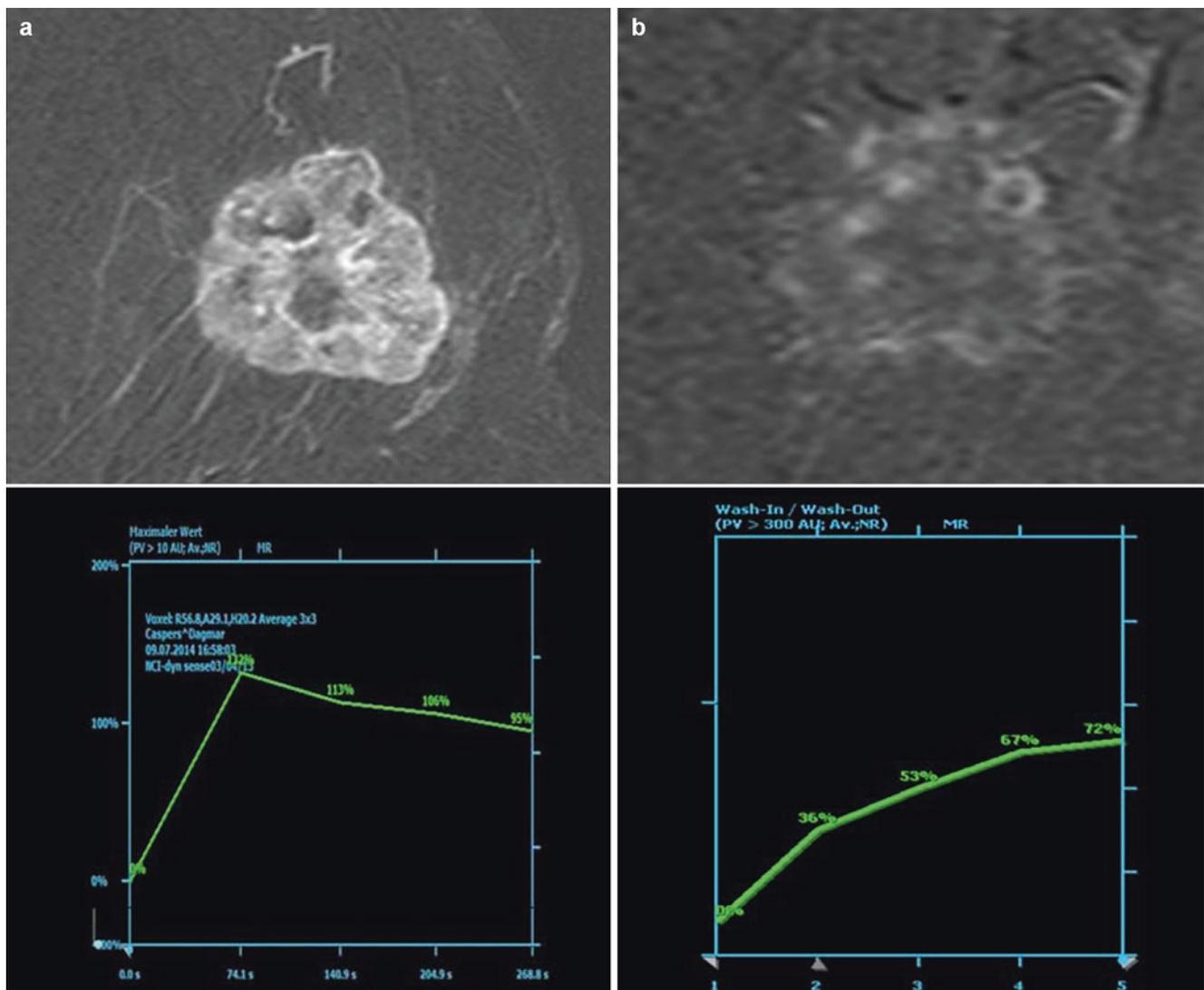


Fig. 18.24 DCE-MRI for response assessment: Note strong and early enhancement with washout time course at baseline and slow enhancement

with flattened enhancement curve after the first cycle. Tumour size is still unchanged. **(a)** Before chemotherapy, **(b)** after first cycle of chemotherapy

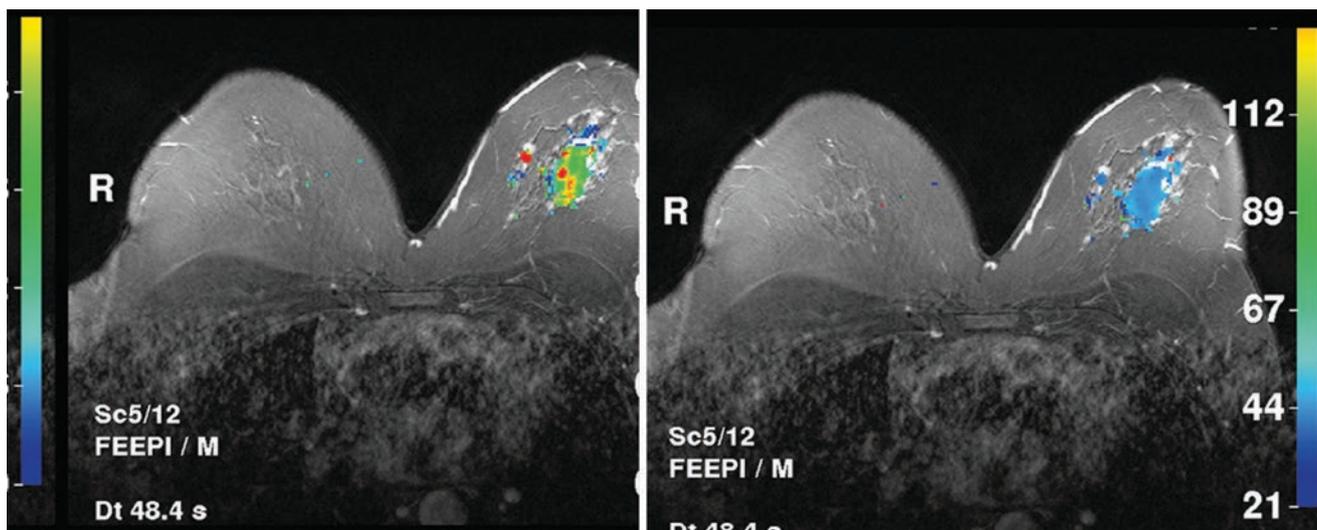


Fig. 18.25 Colour coding can be used to depict within-tumour heterogeneity of enhancement kinetics and the change of enhancement after neoadjuvant chemotherapy. *Left image*, enhancement map of the cancer at baseline, before treatment. *Right image*, enhancement map of the

cancer after the first cycle of neoadjuvant chemotherapy. Note that the size of the cancer is unchanged, but the enhancement pattern has changed towards slowly-progressive enhancement

cross-sectional imaging—unlike, e.g. breast tomosynthesis that provides planigraphic images that are not true, but only “quasi” cross-sections—similar to conventional tomography used before the advent of CT. In contrast, breast MRI allows the depiction of tumour margins and internal architecture with very high spatial and contrast resolution. The assessment of such morphological details is usually best possible in images obtained early after contrast injection, i.e. at a time when the signal intensity difference (i.e. the contrast) between the enhancing cancer and the progressively enhancing adjacent fibro-glandular tissue is maximal.

Diffusion weighted imaging (DWI) is based on the Brownian molecular motion of free (interstitial) water. The distance over which an interstitial water molecule can travel depends on its microenvironment. The smaller the interstitial space, and/or the more cell membranes build barriers against free diffusion, the slower will water diffuse, and the shorter is the distance water can travel within a given period of time. The concept of diffusion-weighted imaging is to “label” water molecules and, after a specific waiting time, sample their response. The more diffusion is restricted, the more molecules will stay in place and be able to contribute to the MR signal [117]. Diffusion is restricted in tissues with increased intracellular, and thus, reduced interstitial space, either due to cell swelling, e.g. in the context of hypoxia, or due to increased cellularity of tissue, e.g. in the context of cancer. DWI can thus be used as a noninvasive measure of the cellularity, to serve as surrogate marker of the proliferation fraction of cancer [118]. Tumours with high Ki-67 levels are hypercellular compared with surrounding normal breast tissue, which translates into restricted diffusion of free water molecules on DWI. It has been shown that tissue apparent

diffusion coefficient or ADC values correlate with proliferation rates in luminal-B cancers [119, 120]. Another important clinical application of diffusion-weighted imaging is assessing response of breast cancer to neoadjuvant chemotherapy (Fig. 18.26).

Diffusion tensor imaging and diffusion kurtosis imaging investigate not only the mobility of water but also its directionality [121]. Diffusion might be directed, i.e. facilitated in specific directions, and impeded along other directions of tissue, depending on the microstructure of tissue. Accordingly, DTI as well as DKI can be used to demonstrate tumour ultrastructure and infiltrative growth way beyond the resolution of regular structural MR imaging [118, 122]. IVIM is increasingly used as a non-contrast means to depict perfusion of tissue, again on a microstructural, i.e. capillary level [123, 124].

MR spectroscopy is a well-established technology that has been in use for decades for analytical tests in biochemistry. It interrogates noninvasively the (quantitative) distribution of specific metabolites in a given probe. The underlying principle is the fact that the Larmor (resonance) frequency of a given nuclide, usually proton or phosphorus, depends on (a) the respective type of nuclide and on (b) the individual magnetic field in which the nuclide resides. The magnetic field experienced by a given water or phosphorus nucleus will depend on the individual molecular environment of that nuclide, because there will be shielding of the magnetic field by different neighbouring atoms. The individual, specific structure of molecules will thus modulate the magnetic field experienced by a proton or phosphorus nuclide. Thus, nuclei bound in different molecules will be exposed to a slightly different magnetic field. Since there is a direct correlation

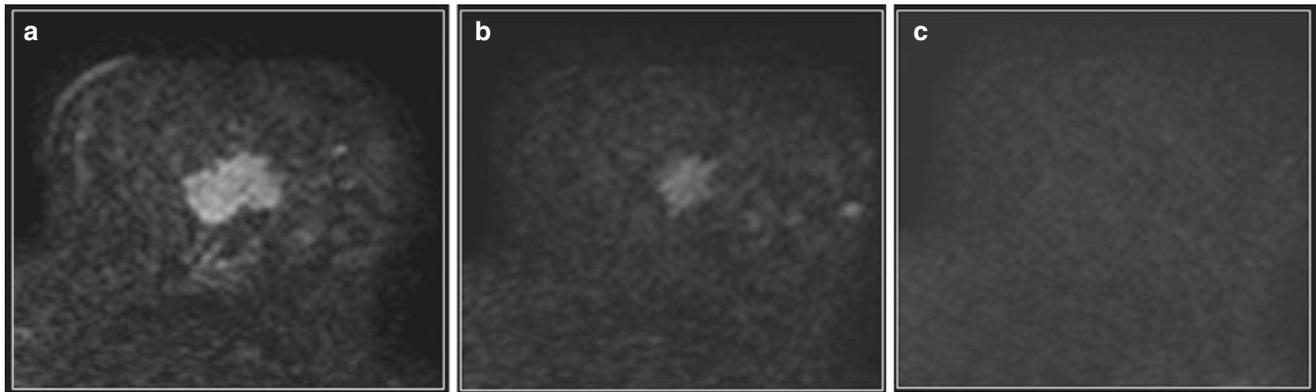


Fig. 18.26 Use of diffusion-weighted imaging for response assessment. (a) Baseline, (b) Mid-treatment and (c) After treatment. Note on (a) the bright signal on DWI at baseline, due to diffusion restriction secondary to the high cellularity of cancer. At mid-treatment (b), the cytotoxic effects lead to reduced cellularity of the tumor, such that

diffusion of free water is improved, and the DWI signal drops. At conclusion of treatment, the diffusion of free water is back to normal; the DWI signal is isointense to normal tissue. Histology confirmed complete pathological response (pCR)

between the magnetic field and a proton's resonance frequency, protons or nuclei located in different molecules will exhibit slightly different resonance frequencies. Magnetic resonance spectroscopy displays the distribution of resonance frequencies and, thus, of different metabolites or molecules in a given probe. For *in vivo* MR spectroscopy of the breast, most experiences exist with proton MRS. Compared with *ex vivo* biochemistry measurements, many effects such as field inhomogeneity and low SNR lead to the fact that the spectral resolution that is attainable in patients is not as high as in *ex vivo* MRS of biochemical probes. Thus, the individual resonances of individual molecules are broadened; the observable spectral peaks usually comprise several different resonances (and, thus, metabolites). For ^1H MR spectroscopy of the breast [125], detection of protons bound in choline compounds has been found to be clinically useful [126]. The detectable choline peak represents proton bound in free choline, in phosphocholine and in glycerophosphocholine. Other constituents will be phosphoethanolamine and myo-inositol. Cellular turnover, either anabolic or catabolic, may increase the contribution of phosphocholine to the observable choline [127, 128]. ^1H MRS has been shown to help discriminate breast cancer from benign enhancing lesions and as a prognostic marker to assess cellular (i.e. membrane) turnover. Especially rapidly growing tumours will lead to a detectable choline peak (tCho). Moreover, MR spectroscopy is useful to demonstrate early response to neoadjuvant chemotherapy. Reduction of total choline helps distinguish between responders and nonresponders after two treatment cycles (PPV and NPV of 89% and 100%); with current technology, it is, however, limited to the analysis of larger tumours, i.e. locally advanced breast cancer [127–130].

Tumours need to maintain growth by increasing their local supply with oxygen and nutrients. This is achieved by releasing peptides like VEGF that induce local angiogenesis. Angiogenesis

leads to a fundamental change of a tumour's microvascular architecture, with sprouting of existing vessels as well as development of *de novo* formed vessels, usually with fenestrated vessel wall linings that go along with increased vessel permeability. The increased metabolic turnover leads to an increased amount of toxic waste products that are removed through dilated drainage veins. The increased perfusion leads to the well-known strong and early enhancement in DCE-MRI, and the increased permeability, together with the efficient venous drainage, causes the washout time course that is characteristic for breast cancer [131]. It has been shown that DCE-derived enhancement kinetics correlate with estrogen receptor status, HER2 status, nuclear grade/Ki-67 and EGFR expression.

The increased permeability leads to leakage of larger molecules such as proteins from the intravascular to the interstitial space, which will increase the oncotic (colloid osmotic) pressure within the cancer—a fact that drags water from the intravascular into the interstitial space and thus increases the interstitial water volume fraction. This, in turn, will correlate with a cancer's signal in T2-weighted imaging. If angiogenesis fails, or is insufficient to reach the innermost cell layers of a cancer, then hypoxia will occur, again detectable through the tumour's internal architecture of enhancement in DCE-MRI (rim enhancement) or through BOLD contrast MRI [132].

The abovementioned functional MR imaging methods are thus used to depict tissue features on a microstructural level. The respective pulse sequences are usually associated with borderline signal to noise ratio (SNR). To improve SNR, the use of higher magnetic fields such as 3.0 T or, more recently, even 7.0 T promises an even more accurate and extensive assessment of tumour biology [127, 133, 134].

Functional imaging methods can be used for classification of enhancing lesions seen in breast MRI, i.e. for the further differentiation of benign, high-risk and malignant lesions in breast MRI. The combination of high-resolution cross-sectional

morphological information, enhancement kinetics and lesion's signal in T2-weighted images and in diffusion-weighted images yields a high specificity and positive predictive value of contemporary breast MRI protocols. Even the most basic, 1.5 T dynamic contrast-enhanced breast MRI protocols are inherently "multiparametric" compared with, e.g. mammography or DBT. The diagnostic accuracy achieved with such protocol is sufficient to be used for so-called problem-solving.

Accordingly, and in contrast to currently held beliefs, we have recently shown that breast MRI can indeed be used definitely to settle screen-detected mammographic or ultrasound findings and thus help avoid unnecessary biopsies [135].

More importantly, functional imaging methods provide additional, independent diagnostic information that adds to our understanding of a cancer's ability to sustain its

growth and/or its propensity to metastasise. Multiparametric MRI techniques can therefore be used to investigate a tumour's aggressiveness and its biologic and prognostic importance or its response to systemic treatment [120, 123, 136–140].

In the neoadjuvant situation, the local breast cancer serves as an *in vivo* marker to rate the efficacy of systemic treatment protocols. Since even regular, clinical breast MRI studies provide functional information on tissue perfusion, it is possible to depict response to treatment earlier than what is achievable by imaging methods that rely on tumour size estimates only such as radiographic imaging methods (digital mammography, digital breast tomosynthesis) or ultrasound-based methods (Figs. 18.24, 18.25, 18.26, 18.27, 18.28, 18.29 and 18.30; Table 18.3) [141–146]. Results on the use

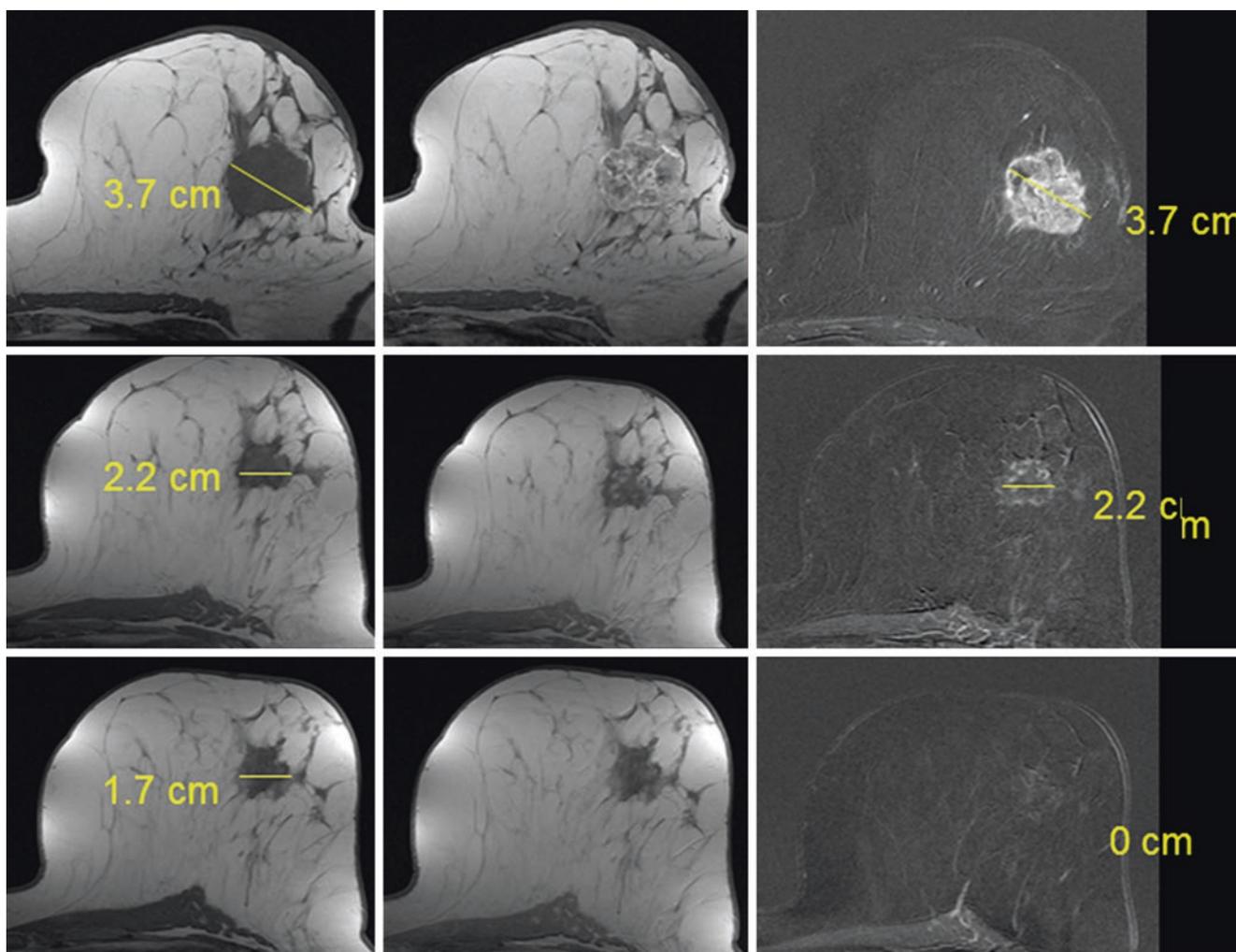


Fig. 18.27 Utility of DCE-MRI vs. structural breast imaging. Patient with triple-negative breast cancer. Incomplete response was suggested based on breast ultrasound and mammography, with residual diameter of 1.7 cm. This residual mass is also visible on pre-contrast T1-weighted imaging of her breast MRI study (*right column*). However, after con-

trast injection, DCE-MRI (*middle column*, post-contrast source images; *left column*, corresponding subtracted images) reveals absence of enhancement in the remaining tumour, suggesting presence of scar formation. Complete pathologic response with fibrotic tumour remnants without vital tumour cells was found at histology

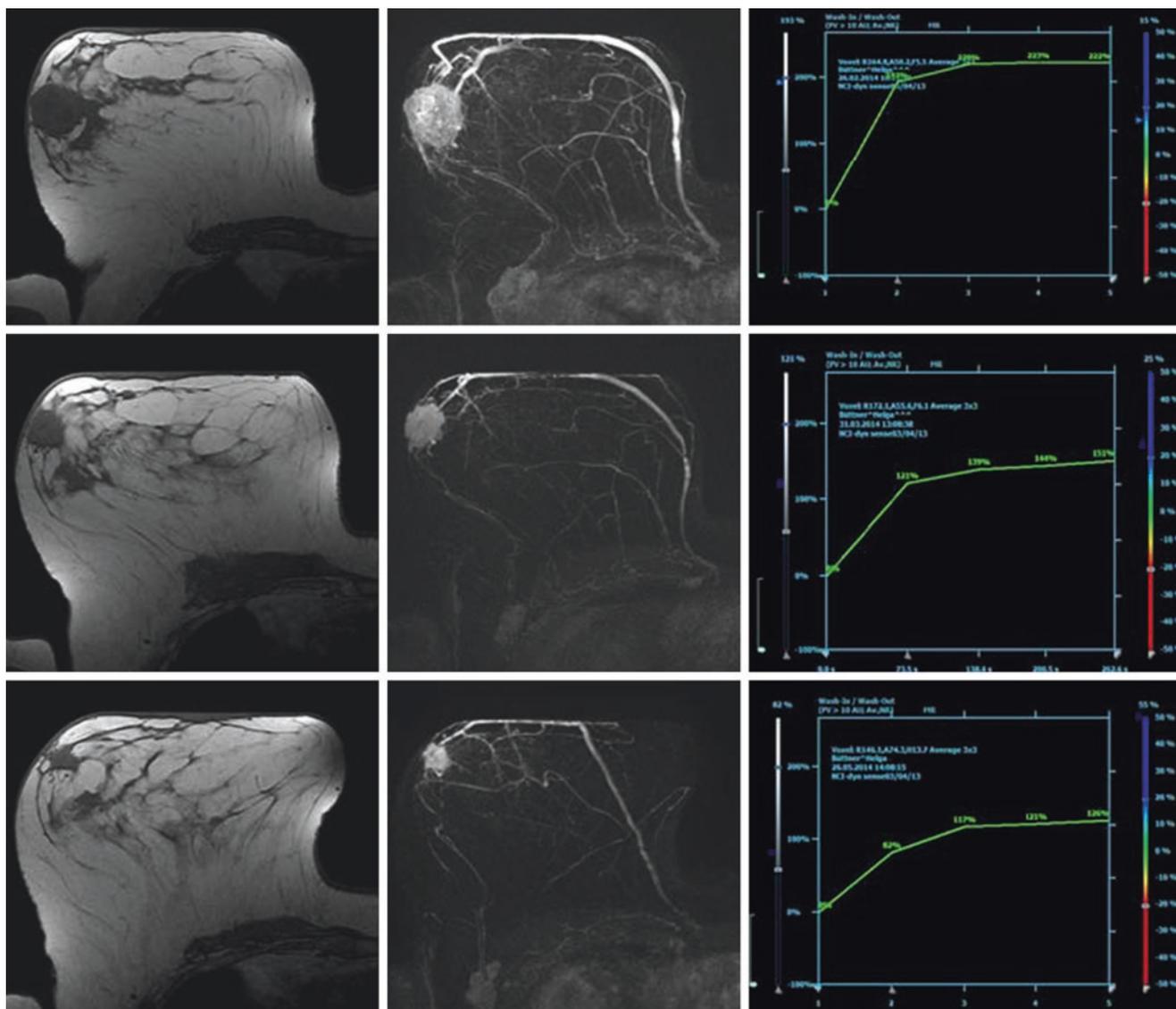


Fig. 18.28 Patient with residual disease after neoadjuvant chemotherapy. Minimal residual mass visible but with strong enhancement. Histology confirmed presence of a 9 mm residual vital tumour. *Upper*

row, MRI before chemotherapy. *Middle row*, MRI at mid-treatment. *Bottom row*, MRI after conclusion of neoadjuvant chemotherapy

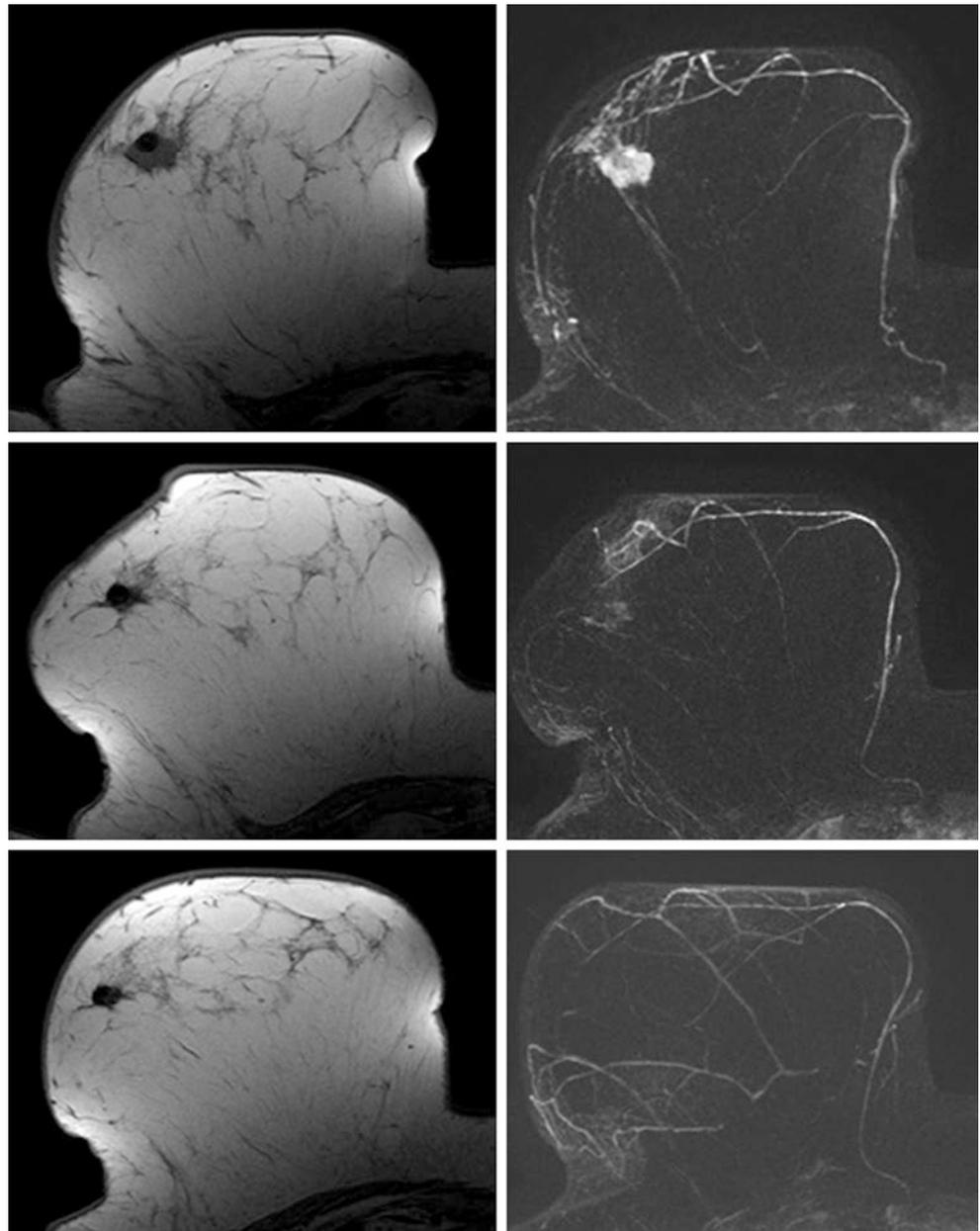
of more advanced functional imaging methods or “multiparametric MRI” for this purpose are emerging [141]. For instance, diffusion-weighted imaging and DKI are candidate methods to further improve assessment of response; an increase in mean tumour ADC (apparent diffusion coefficient) of over 20% from baseline is predictive of response in triple-negative and HER2-enriched cancers (Fig. 18.30) [143, 146, 147]. Similar results have been obtained for the detection of changes as early as a couple of days after even a single administration of chemotherapy by proton spectroscopy [128, 140, 146–151].

Another task in the neoadjuvant setting is to identify residual disease. Since there can be scar tissue formation at the site of the previous tumour, this is a difficult task with imaging methods that rely on depiction of structure alone. Since regu-

lar DCE-MRI, but even more so advanced multiparametric MRI provides information beyond structure, it is much more accurate than, e.g. mammography or ultrasound for this purpose. Marinovich et al. provided an excellent review on the evidence of using regular clinical breast MRI for predicting response to neoadjuvant chemotherapy. They reported on 13 different studies, comprising 2549 patients who underwent DCE-MRI before and after one to two cycles of neoadjuvant treatment. They found that the accuracy for prediction of response is highest in studies that evaluated enhancement kinetics and found a mean accuracy of 88% [142].

The next step now is to use the plethora of imaging features provided by multiparametric breast MRI to describe “MR imaging phenotypes” of breast cancers. Modern methods of machine learning (“deep learning”) can then be used

Fig. 18.29 Prediction of pCR based on DCE-MRI. Pre-contrast images (*right column*) to provide structural information and post-contrast subtracted images (*left column*) to demonstrate enhancement. Already at mid-treatment (*middle row*), there is almost complete loss of enhancement at the site of the cancer. Absence of enhancement was noted at completion of neoadjuvant treatment (*lower row*). Pathological complete response was found. The focal black spot at the site of the cancer corresponds to the clip inserted after US-guided biopsy



to correlate different MR imaging phenotypes with patient outcomes, similar to the way genomic typing has been correlated with outcomes to establish their prognostic utility. It is to be expected that such “radiomics” will be helpful to amend the predictive and prognostic information derived from genomic and proteomic studies.

18.3.2 Keep It Simple and Short: Abbreviated Breast MRI for Cancer Screening

Although there has been a decline in breast cancer mortality over the last two decades, breast cancer continues to represent the first (Europe) or second (USA) leading cause of cancer death in the female population. Notably, several decades

of mammographic screening programmes have not changed this situation. Since there is a close correlation between disease stage (i.e. the size and stage distribution of cancer) at the time of diagnosis and ultimate survival of an individual woman, the persistently high mortality rates indicate that there is room and need for improved methods of early diagnosis of breast cancer. Interval cancer rate, i.e. the number of cancers that occurs in women who did participate in mammographic screening, but are not diagnosed by mammography, compared to the number of cancers that are mammography detected, ranges between 30% and 50%. These interval cancers are associated with adverse biologic profiles and poor prognosis compared to screen-detected cancers. Accordingly, the current scientific evidence suggests that mammographic screening is associated with a

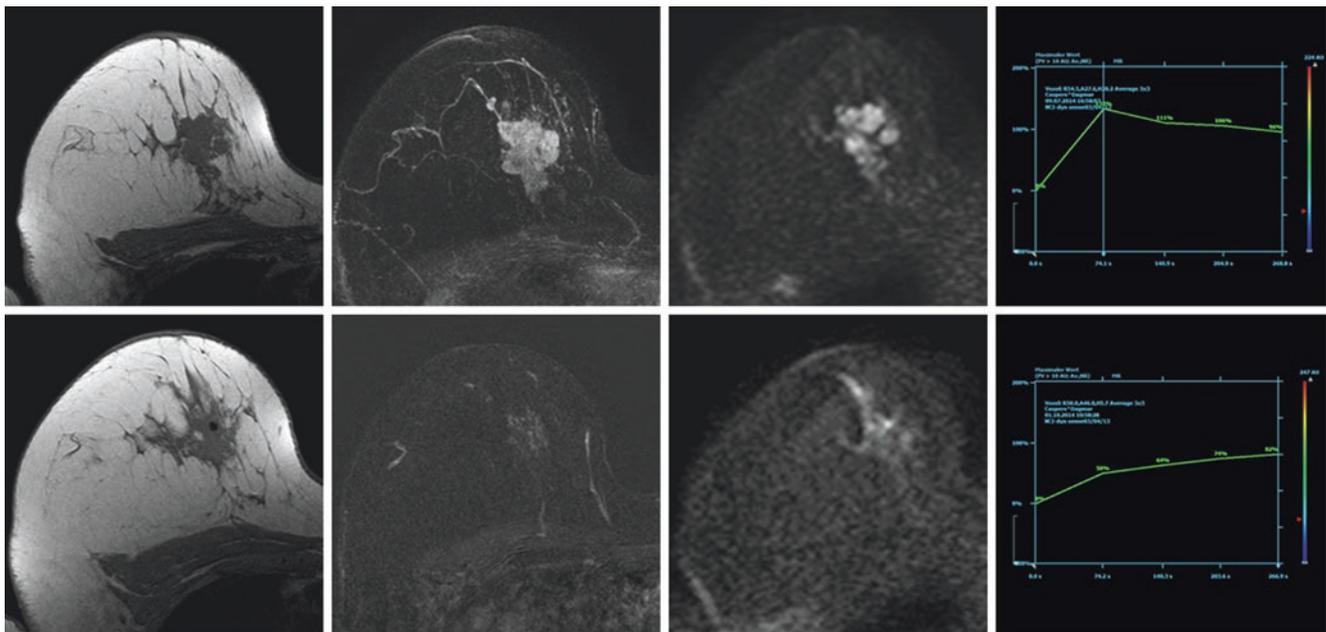


Fig. 18.30 Utility of diffusion-weighted imaging to complement DCE-MRI for response assessment. *Upper row*, baseline study. *Lower row*, study after completion of neoadjuvant treatment. *Left column*, pre-contrast T1-weighted images. *Middle left column*, contrast-enhanced subtracted images. *Middle right column*, corresponding DWI at $b = 800$.

Right column, corresponding time/signal intensity curves. Note that there is still questionable enhancement at the site of the index cancer. DWI supports the diagnosis of incomplete response or presence of residual disease, with still visible diffusion restriction. Note the clip that marks the centre of the index cancer in the images after treatment

Table 18.3 Published meta-analyses on using breast MRI for predicting pCR after neoadjuvant chemotherapy

Author	Journal	No. of studies	No. of patients	Sensitivity for pCR	Specificity for pCR
Yuan et al. [144]	Am J Radiology 2010	25	1213	DCE-MRI: 63% (55–70%)	DCE-MRI: 91% (91–92%)
Wu et al. [3]	Breast Cancer Res Treat 2012	34	1932	DCE-MRI: 68% (57–77%) DWI: 93% (82–97%)	DCE-MRI: 91% (87–94%) DWI: 82% (70–90%)
Marinovich et al. [142]	J Nat Cancer Institute 2013	44	2549	DCE-MRI: 89–92%	DCE-MRI: 83%
Lobbes et al.	Insights Imaging 2014	35	2359	Correlation between residual disease on pathology and MRI: 0.698	Overall accuracy: 88%

significant underdiagnosis of breast cancer, that is to say, mammography fails to pick up cancers that are prognostically relevant [152, 153].

In addition, mammographic screening has been associated with overdiagnosis of breast cancer. Overdiagnosis relates to the fact that cancers that are picked up by mammography may be biologically unimportant. Some breast cancers can exhibit rapid growth and become life-threatening and difficult to treat; others are relatively slowly growing. Some cancers, especially many screen-detected DCIS, may indeed prove self-limiting and will not progress to a life-threatening disease, even if left undiagnosed and thus left untreated [154, 155].

An important reason for overdiagnosis is a well-established effect referred to as “length-time bias”. Women whose cancers were screen detected, i.e. women whose cancers were mammography detectable, enjoy a better prognosis than women whose cancers were not screen detected, i.e. mammographically occult. In short, mammography-detectable cancers are associated with a better prognosis than cancers that are occult on mammography. This, in turn, is attributable to the fact that for diagnosis of breast cancer, radiographic breast imaging methods (mammography or also tomosynthesis) rely on the depiction of regressive changes such as calcifications, architectural distortions and fibrosis, i.e. pathophysiological processes that are associated

with slowed growth, with tissue hypoxia or with frank tissue necrosis. Overdiagnosis is length-time bias put to an extreme. Overdiagnosis causes a huge financial burden to the society; most importantly, however, it leads to unnecessary anxieties and morbidity in women who are stigmatised as “cancer patient” and treated as such, without benefit for the involved women.

In summary, mammographic screening is associated with both significant underdiagnosis of prognostically important breast cancer and overdiagnosis of prognostically unimportant, i.e. self-limiting breast cancer, or rather pseudo-disease.

Magnetic resonance imaging (MRI) has been used to diagnose breast cancer over the last three decades; it is in use for screening for 15 years. Over and over again, it has been shown that contrast-enhanced MRI is by far the most accurate imaging method to diagnose invasive as well as intraductal breast cancer and primary as well as recurrent cancer, irrespective of breast density [9–13, 156–162]. In view of the important discussion around overdiagnosis, the most important feature that makes breast MRI an attractive screening tool is its sensitivity profile. The sensitivity of breast MRI increases in parallel with the prognostic importance of breast cancer. It is exceedingly high in rapidly growing, heavily perfused disease, and it is desirably lower than that of mammography for low-grade DCIS. Thus, MRI is associated with a “reverse length-time bias”. This, together with the fact that MRI works without ionising radiation, makes MRI the most promising screening tool that is currently available.

A screening trial completed in our department suggests that MRI screening is not only beneficial in high-risk women but also in average-risk women. The gradient between the diagnostic sensitivities of MRI, compared to that of mammography or even the combined use of mammography and ultrasound, appears similar, more or less independent of the

respective lifetime risk of women [163]. We found that if MRI is used in women at average risk, the interval cancer rate drops down to zero—which compares to an interval cancer rate, i.e. missed cancer rate, of around 30–50% for quality-assured European mammographic screening programmes. Since interval cancer rates are the single most important driver of mortality rates, there is good reason to assume that using MRI instead of mammography for breast cancer screening would allow a substantial further reduction of breast cancer mortality. Also the positive predictive value—a major driver of costs associated with screening—is similar for mammographic and MRI screening, suggesting that the previously held belief of the low specificity of MRI has been overcome with growing clinical experience with screening breast MRI.

The single main reason why MRI is not used on a broader scale is the cost associated with this method. Therefore, in 2014, our group inaugurated the concept of “abbreviated breast MRI” (AB-MRI) [164]. We were able to demonstrate that MRI, due to its high-contrast images, can be completed within a magnet, i.e. examination time of only 3 min, and, most importantly, can be read by radiologists within a few seconds. The superior diagnostic accuracy and cancer yield that is afforded by MRI was preserved also for these abbreviated protocols. A group of 443 women with mildly increased risk of breast cancer and with normal screening mammograms and normal screening ultrasound underwent 606 screening MRI studies with abbreviated and full protocol. Abbreviated MRI detected a total of 11 cancers that had been occult on the respective digital mammograms and screening ultrasound studies, for an additional cancer yield of 18.2 per 1000 (Fig. 18.31a). The examination time of the abbreviated protocol had been 3 min, and the average radiologist reading time to establish absence of breast cancer had been 2.8 s. For comparison, even batch reading of a screening mammogram

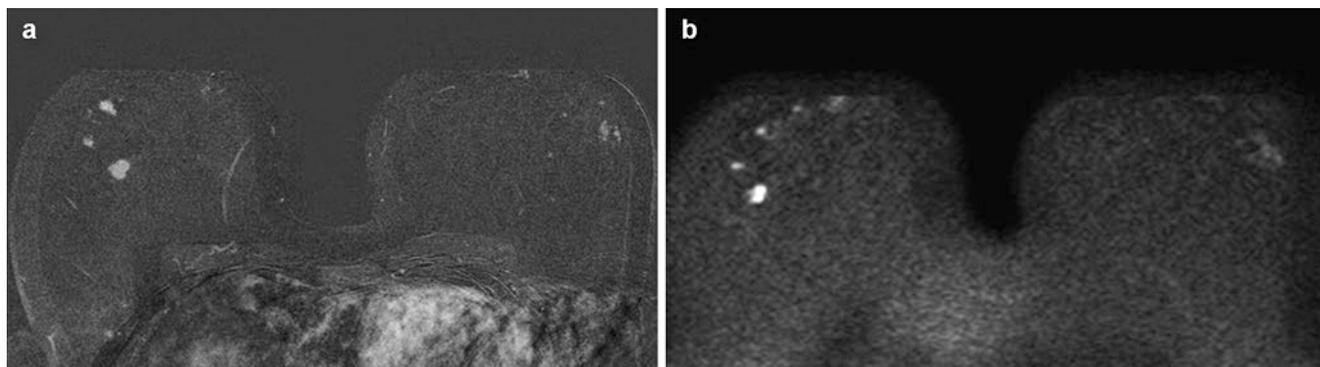


Fig. 18.31 Utility of abbreviated breast MRI, and un-enhanced diffusion-weighted imaging in a 52-year old woman at average risk undergoing MRI screening; her mammogram was normal. (a) First post-contrast subtracted or FAST image, generated by subtracting the image obtained within 60 s after contrast injection from the pre-contrast

image, for a total acquisition time of 2 minutes. Note the multifocal breast cancer visible in the right breast and absence of cancer in the left breast. Note that similar information is provided by the diffusion-weighted image, which was obtained prior to contrast injection

usually takes over 60 s, and the acquisition of the four views that constitute a screening mammogram takes well over 4 min. For screening ultrasound, the reading and/or scanning time takes about 20 min on average, i.e. takes far more radiologist time and is thus far more expensive—and far less sensitive or specific than breast MRI. Abbreviated breast MRI has sparked great interest in the broader use of breast MRI for breast cancer screening. Several studies have meanwhile been published that confirm the high accuracy of abbreviated protocols. The ECOG/ACRIN (Eastern Cooperative Oncology Group/American College of Radiology Imaging Network) has launched a multicentre prospective randomised trial (EA1141) that will investigate not only the cancer yield but also the type of cancers detected by abbreviated breast MRI compared with contemporary, digital breast tomosynthesis [165]. Several countries have started their own abbreviated breast MRI screening studies.

Moreover, there is evidence to suggest that abbreviated protocols could even work without injection of contrast agents. By using diffusion-weighted imaging with background suppression (DWIBS), cancers are detectable and correctly classifiable with an image acquisition time of only a couple of minutes and very short radiologist reading times (Fig. 18.31b) [166–168].

To fully exploit this for improved breast cancer screening, it would be important to develop dedicated breast MRI systems that are optimised for imaging the breast and optimised to support the fast throughput that is required for broader screening applications. Very similar to the development of dedicated X-ray machines for imaging the breast (i.e. mammography systems) back in the 1940s, this could be done for MRI scanners.

18.3.3 Advances in MR-Guided Interventions

Breast MRI studies are done to obtain information on presence and extent of breast cancer beyond what is available through radiographic or ultrasound imaging. If this is achieved and breast cancer is identified or suspected on MR imaging, it is important to offer noninvasive means to retrieve tissue from the suspected area. No breast radiologist would ever offer a breast imaging service without being able to also offer mammography and ultrasound-guided needle localisation and (vacuum) biopsy—but it seems to be quite popular to run a breast MRI service without such interventional capacities. This is increasingly unacceptable, regarding the fact that equipment for MR-guided vacuum biopsy and MR-guided needle localisation and bracketing is commercially available and has been commercially available for almost two decades now. Accordingly, the American College of Radiology requires availability of

such equipment or proof of an established collaboration with sites that offer these interventions in order to receive an accreditation for breast [169].

Recently, we inaugurated the concept of MR-guided vacuum-assisted large-volume biopsy (VALB). For this intervention, we collect larger amounts of tissue than what is usually retrieved during mammography or MR-guided vacuum biopsy procedures, i.e. between 24 and 60 samples with a 9G needle. Such MR-guided VALB was done on a cohort of 1414 consecutive MR-only visible lesions with a false-negative rate, i.e. a rate of missed lesions, of 0.3% (4/1414), all four discovered immediately after the procedure due to an obvious radiologic-pathologic mismatch. The cohort consisted of target lesions with an average size of 9 mm for mass enhancement, and 23 mm for non-mass enhancement, found in small to very large breasts and located in all locations, including far dorsal, far medial, far lateral or immediate retroareolar locations. The results suggest that MR-guided VALB helps avoid previously reported causes of technical failures of MR-guided biopsies. Moreover, we could show that MR-guided VALB procedures are very well tolerated, with a complication rate (major complications) of 0/1414 (Fig. 18.32) [170].

Reoperation rates tend to be high for breast cancer surgery, especially if a high rate of breast conservation is attempted. A recent editorial published in the *New England Journal of Medicine* was entitled *Re-excision—The Other Breast Cancer Epidemic* [171]. There are numerous reports that consistently show that MRI is more accurate than mammography or ultrasound for demonstrating the extent of a given cancer. If MRI is done for this purpose, however, it is of utmost importance to help the surgeon translate the imaging information into the operating theatre. Only if this is achieved, it is possible to actually exploit the diagnostic advantage afforded by MRI compared with mammography or ultrasound. If one strives to reduce the number of surgical procedures, it is of course important to use nonoperative, nonsurgical biopsy methods to obtain histologic proof of presumed additional disease components prior to surgery. We have used MRI, followed by MR-guided vacuum biopsy, and MR-guided bracketing of the disease extent if needed (Fig. 18.33), in a cohort of 600 women with biopsy-proven breast cancer. We found that this led to a positive margin rates below 4%, which was achieved at a very high breast conservation rate of close to 90%. These data suggest that, if MRI is combined with contemporary methods of MR-guided biopsy, as well as methods to guide surgery, the improved diagnostic information provided by MRI do indeed translate into improved surgical results, low reoperation rates and very low mastectomy rates [172].

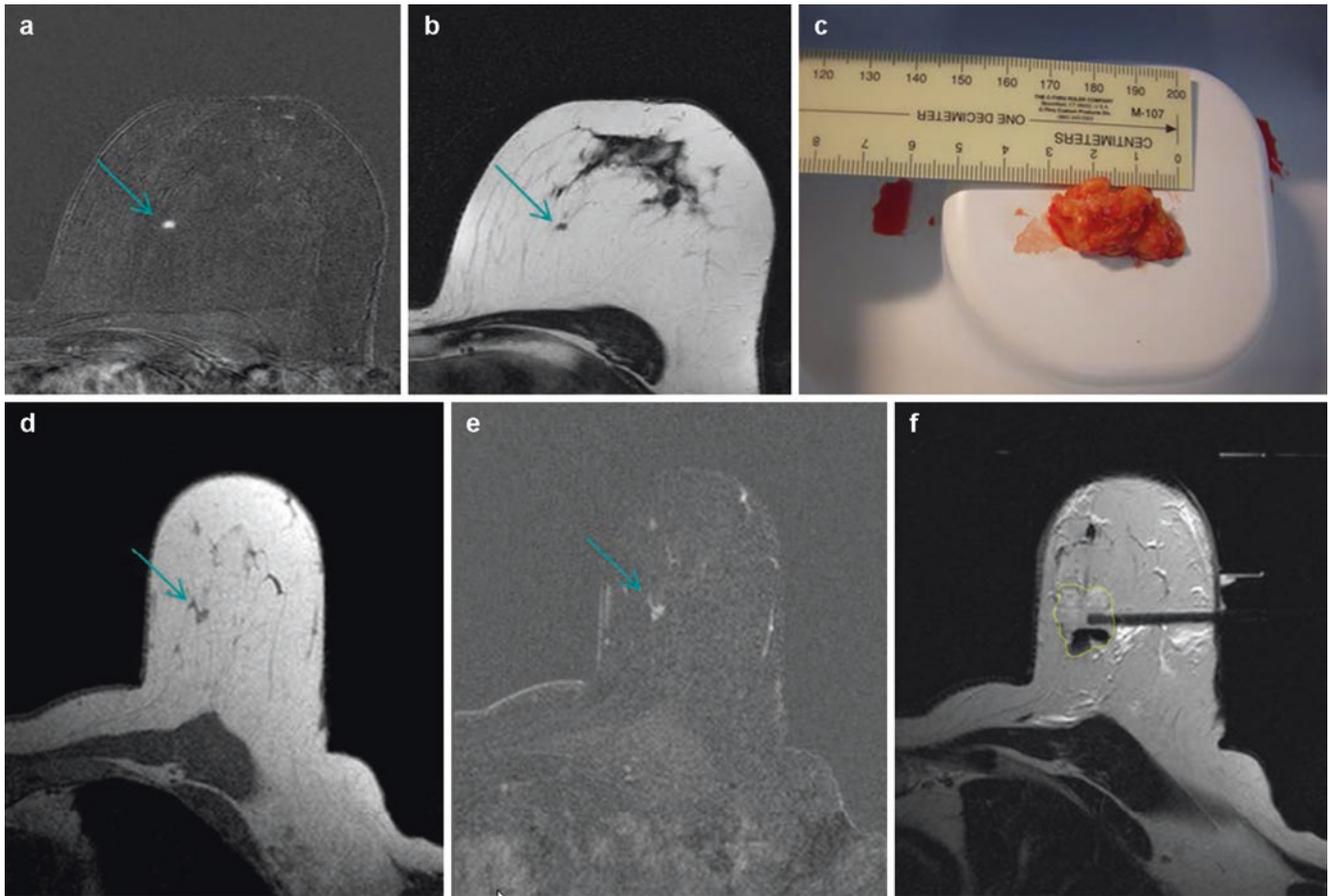


Fig. 18.32 MR-guided vacuum-assisted large-volume breast biopsy (VALB). (a) FAST image that highlights a small enhancing lesion in the upper inner quadrant, 4 mm in longest diameter. (b) Corresponding T2-weighted structural image. (c) T1-weighted image prior to contrast injection during the intervention. (d) Corresponding post-contrast subtracted image reveals the target lesion. (e) T2-weighted image after

completion of vacuum-assisted large-volume breast biopsy, with the biopsy needle still in place. The *yellow line* encircles the biopsy cavity that includes an *air bubble* (black signal inside the cavity). Note that the biopsy cavity includes the entire lesion, plus safety margin. (f) Removed tissue volume during MR-guided VALB. Histology confirmed pT1a; subsequent surgery proved absence of residual tumor

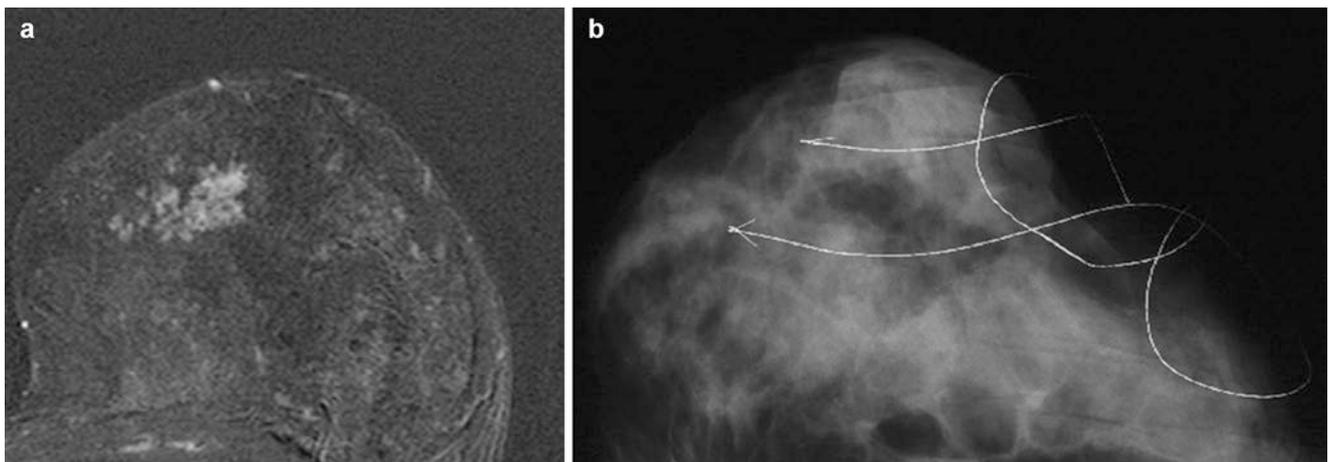


Fig. 18.33 MR-guided surgery. (a) Patient with MRI screening detected non-mass enhancement suggestive of DCIS. MR-guided biopsy (not shown) confirmed presence of high-grade DCIS. Patient underwent MR-guided bracketing of the two poles of the enhancing

segment. (b) Mammogram obtained after MR-guided bracketing displays the guide wire position in the breast and absence of any correlate of the DCIS on mammography. MR-guided surgery was done and revealed a 3 cm high-grade DCIS, resected with free margins (R0)

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