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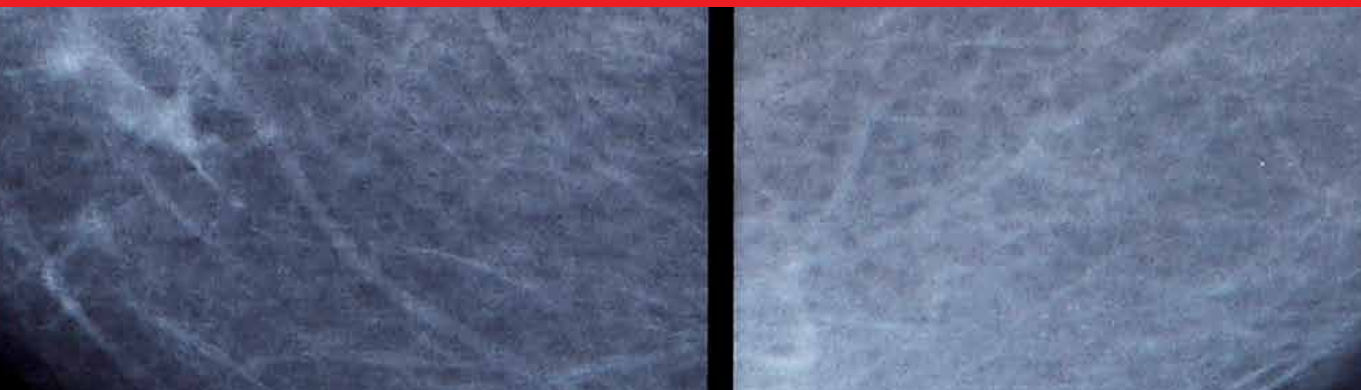
Breast Imaging

Edited by Cherie M. Kuzmiak



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Meet the editor

Cherie M. Kuzmiak, DO, FACR, FSBI, is a breast imaging radiologist who has dedicated her career to the advancement of women's health care. Dr. Kuzmiak has earned numerous accolades as a physician, teacher, and researcher of diseases and imaging of the breast. She has been involved in numerous research and clinical trials in the evaluation of novel breast imaging technologies for the early detection and treatment of breast cancer. In addition, she holds multiple professional leadership roles within her subspecialty. Dr. Kuzmiak is the director of the Breast Imaging Division and an associate professor of Radiology at the University of North Carolina (UNC) School of Medicine. Dr. Kuzmiak has been the director of the Breast Imaging Division and Fellowship Program since 2005. Her current research focus is on radiomics, radiogenomics, breast cancer genomics, digital breast tomosynthesis, dedicated 3D breast computed tomography with positron emission tomography integration, and breast magnetic resonance imaging.

Contents

Preface

Breast cancer is a global disease that does not discriminate in age or ethnicity. Until biomarkers for genomic profiling of risk assessment for all patients are discovered and utilized, early detection of breast cancer with screening mammography is still the best method we have in saving countless women's lives and decreasing the harms of overtreatment.

To overcome the limitations of low-dose screen-film mammography, we have witnessed the transition of mammography to a digital platform. With the development and implementation of full-field digital mammography, and more recently digital breast tomosynthesis, we continue to advance mammographic imaging in order to detect cancers at an earlier stage. In addition, women with dense breast tissue and women who are at a high risk of developing breast cancer continue to benefit from supplemental screening with ultrasound and magnetic resonance imaging, respectively. The concept of finding less advanced cancers and the need for targeting surgical and oncological treatment motivate us.

We have entered into a new era of oncological imaging and care. The goal is precision medicine with personalized screening, prognosis, and treatment. Consequently, this textbook encompasses relevant topics in daily patient care with breast imaging to technical innovations for improving breast cancer detection and treatment.

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Section 1

Clinical Applications

Chapter 1

Detection and Diagnosis of Breast Diseases

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Additional information is available at the end of the chapter

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Abstract

Cancer is a disease that starts in a localized organ or tissue and then grows out of control. Breast cancer is an important health problem as in the Western world; it is the second most frequent cause of cancer death in women (after lung cancer). The incidence rate, however, rises dramatically over the age of 50 years. This is may be due to several risk factors, such as family history, genetics, early menstruation, late menopause, and other factors, that have not yet been identified. The problems of breast diseases have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programs helps improves a woman's chances for successful treatment. It also minimizes pain, suffering, and anxiety that surround patients and their families. The current and the most cost-effective technique used for screening and diagnosis of breast cancer is X-ray mammography. It is the state-of-the-art for earlier detection to improve both prognosis and survival rate. This is may be due to its good availability, high sensitivity, and relatively low cost/patient. The goal of this chapter is to introduce the problems caused by breast cancer. Starting with an overview of the requirement for breast tumor imaging and the diagnostic techniques used for breast cancer assessment are briefly described, highlighting the advantages and disadvantages of each technique. In addition, the problems associated with a relatively new functional breast imaging technique namely scintimammography were introduced and discussed. The intention that the chapter provide the reader with sufficient background on the available diagnostic techniques of breast tumor imaging approach, as well as an overview of the literature.

Keywords: breast cancer detection, molecular imaging, scintimammography

1. Introduction

Most women experience breast changes in their life. This is due to normal growth and changes in hormone levels. However, lumps, bumps, breast pain, nipple discharges, or skin irritation

are examples of breast problems that have similar symptoms. The vast majority of lesions and abnormalities occurs in the breast are not cancer but are far more frequent than malignant ones [1–7]. Benign breast constitutes a heterogeneous group of lesions including various abnormalities, inflammatory lesions, epithelial and stromal proliferations, and neoplasms [3–5]. However, cancer is a disease that starts in a localized organ or tissue and then grows out of control. Breast cancer is an important health problem as it is the most common malignancy in women in Western countries. It is the second most frequent cause of cancer death in women (after lung cancer) [8, 9]. The incidence rate, however, rises dramatically over the age of 50 years. This is may be due to several risk factors such as family history, genetics, early menstruation, late menopause medication, and other factors that have not yet been identified. The above problems have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programs helps improves a woman's chances for successful treatment. It also minimizes pain, suffering, and anxiety that surround patients and their families. The goal of this chapter is to introduce the problems caused by breast cancer, starting with the requirements for breast imaging, an overview of the methods for diagnosing breast abnormalities with the focus on molecular imaging of the breast.

2. Requirements for breast imaging

The goal of breast evaluation is to classify findings as normal physiologic variations, clearly benign, or possibly malignant. The size, shape, and appearance of the female breast are not constant but undergo a number of changes during the lifetime of women. For instance, changes occur with pregnancy, breast feeding, and during the menstrual cycle. In addition, the age of the subject not only influences the shape but also parenchymal density of the breast. That is why young women tend to have dense breasts (more fibro-glandular tissue), creating a rounded appearance. On the other hand, postmenopausal women have breasts containing a large amount of fat. This makes the X-ray mammogram far more effective in older women as the fat content is more radio-translucent (appears darker) compared to glandular tissue (appears under-exposed) in younger women [10]. The above discussion suggests that both the shape and parenchymal density of the breast impose particular constraints on the choice of imaging modality. The imaging technique should be powerful for initial detection and subsequent follow-up of the diseases.

At present, no single technique was used for all cases of breast cancer detection without showing certain clinical or technical limitations. This implies necessity to address the specific needs that can help for breast tumors imaging to overcome these limitations. For instance, breast compression often needed as it holds the breast still and enhances the spatial resolution. It also evens out the breast thickness and reduces scatter in X-ray or γ-ray imaging [11], thus increasing image sharpness. Moreover, it spreads out the tissue so that the overlying breast tissue will not obscure small abnormalities. Since the breast is an external organ and extends to the chest wall, it requires appropriate views to be obtained. For instance, in X-ray mammography, a lateral (from the side) view of the breast allows separation of the chest wall from

lesions deep within the breast. On the other hand, in single photon γ-ray emission imaging, one needs to separate the breast from the heart by employing an appropriate prone (face down) position. However, it has been claimed that with prone imaging view, there is a possibility of missing a small low-intensity medial lesion because of attenuation. This implies that another image is needed but in the lateral view. In addition, shielding the camera from the background cardiac flux is very useful in tumor detection in terms of contrast and resolution.

3. Interpreting imaging test

The usefulness of diagnostic imaging tests, which is their ability to detect a patient or subject with disease or exclude a patient or subject without disease. In other words, the idea in using any diagnostic test is to be able to correctly diagnose the disease and easily interpret the results. The latter is achieved by calculating the probability that a patient has a disease. The diagnostic test performance is usually measured by calculating four important statistical parameters or terms. These are the test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) [12, 13]. **Table 1** illustrates these parameters and their relationship. In breast tumor γ-ray imaging, these parameters are dependent on clinical history, biological factors such as size, site, or location, the type of the lesion, and patient's age. The test parameters may also depend on the physical and the practical aspects as well as on the imaging technology parameters. Sensitivity and specificity are properties of a test that tell us how good the diagnostic test is at predicting the disease and whether it is to be used or not [12]. Sensitivity is the proportion of people with the disease who have a positive test for the disease [12]. Specificity is the proportion of people without the disease who test negative [12]. A high sensitivity test means that the test has a low rate of false-negatives and high specificity means that the test has a low rate of false-positives. In brief, the text here and **Table 1** simply provide a practical application, hence of what these concepts mean in clinical practice and how they can be used in practical settings to aid the diagnostic process.

In clinical practice, the decision to send patients for breast biopsies is arbitrary, i.e., there is no fixed test threshold. Instead, the decision is usually based on the needs of patients and clinicians for the different clinical situations. As a result, for any given image of a breast lesion, there is a kind of trade-off between the sensitivity and specificity, i.e., sensitivity can only

Test outcome	**Condition as determined by "gold" standard**		
	True	**False**	
Positive	True positive	False positive	⇒Positive predictive value
Negative	False negative	True negative	⇒Negative predictive value
	⇓ Sensitivity	⇓ Specificity	

Table 1. The main diagnostic test parameters [12, 13] demonstrating the practical application and the relationship of these four terms.

increase by decreasing the specificity of a test. For instance, if the decision is to only select patients with extremely abnormal images to have breast biopsy, then the test will become extremely specific but not very sensitive. In this case, many patients falsely diagnosed as not having breast diseases or breast cancer. On the other hand, if the decision is to send patients with borderline abnormal images to have biopsy, the test will then become more sensitive but less specific. As a result, many patients who do not have breast cancer sent for an unnecessary biopsy, i.e., the diagnostic tests are useless. This sensitivity specificity trade-off of the diagnostic test is accurately illustrated by the analysis of the receiver operating characteristic (ROC) curve at each test threshold or cut-point. This curve is a plot of the true positive rate against the false positive rate for the different possible thresholds of the diagnostic test. The area under the ROC curve is a measure of test accuracy, i.e., how well the test separates or classifies the patient population into those with the abnormality and those without. An area of 1 represents excellent performance test and an area of 0.5 represents a fail test.

To know the probability that the imaging test is giving the correct diagnosis, the positive and negative predictive values are needed. The PPV of a test is the probability of a patient having the disease following a positive test result [13]. The NPV is the probability of a person not having the disease following a negative test result [13]. These test performance measures are influenced by the probability of disease at any point in time of the total abnormality in the population tested [13]. The predictive values also vary as a function of disease prevalence and patient subpopulation. Thus, a combined measure of diagnostic performance, the likelihood ratio, is a clinically useful diagnostic test performance measure. Negative likelihood ratios measure the ability of the test to accurately rule out disease, and positive likelihood ratios measure the ability of the test to accurately detect disease. In summary, both sensitivity and specificity terms of a diagnostic test suffer from limitations in clinical practice, as they cannot estimate the probability of breast cancer in an individual patient. However, PPV and NPV help to overcome this problem, but they both vary according to disease prevalence and populations.

4. Diagnosis of breast disease

Breast lesion investigations may include self or clinical breast examination, X-ray mammography, and biopsy. In addition, a variety of other efficient complementary imaging modalities provide additional information to achieve a definite breast diagnosis. The following subsections give an overview of the main diagnostic techniques used for breast tumor imaging.

4.1. X-ray mammography and screening

Mammography is a low energy (25–32 keV) X-ray examination of the soft tissues of the breast. It uses the variation in density between normal mammary features and abnormal tissue structures (lesion) to produce the image. The X-ray images are either captured on a film or directly stored on a digital computer. The former is one of the widely used current techniques based on screen-film technology. X-ray mammography considered the gold standard in breast

imaging as it is fast, available, and has a lower cost than other breast imaging techniques. It has two main applications: as a screening method in asymptomatic patients and as a diagnostic method in symptomatic populations. The former application is extremely important and its introduction in the past three decades has significantly reduced the mortality rate of breast cancer in many countries [14, 15]. This is because the screening services accurately detect micro-calcifications and nonpalpable soft tissue masses, which have been beyond other imaging methods, due to the high spatial resolution (~50–100 μm). Normally, screening is achieved by exposing the breast to X-rays after gently compressed between two plates and then taking two views for each breast. A craniocaudal (imaging from above to below) and lateral views are generally taken. A lead grid is used to reduce scattering photons that reach the film. Diagnostic mammography evaluates the entire breast as well as characteristics of the mass. It is used for assessing the size of the lesion, for pre-surgical localization of suspicious areas of breast, and in the guidance of needle biopsies. The reported sensitivity (the fraction of patients actually having the disease and correctly diagnosed as positive) in lesion detection varied between 69 and 90% [16] depending on the breast density. The specificity (the fraction of patients without the disease, correctly diagnosed as negative) is the major drawback of conventional mammography. A variation in specificity between 87 and 97% and a low positive predictive value as low as 15% has also been reported [17]. This 'less than perfect' performance may be due to several confounding factors, e.g., poor mammographic technique, observer error, the lesions are nonpalpable or at a cellular level, and/or the lesions are obscured by the normal breast tissues. The presence of scars or tissue distortion may hide true small tumors on the mammogram. Nevertheless, conventional mammography remains a valuable and cost-effective technique for breast tumor diagnosis. Over the last three decades, considerable efforts are carried out to improve the current screen-film mammographic technique. These improvements include image quality, acquisition techniques, and interpretation protocol in order to reduce some of the mammographic limitations [18].

The use of digital imaging in general radiography has increased rapidly in recent years. This has extended to mammographic imaging. "Digital mammography" (DM) is a possible current direction in breast imaging compared to film-based conventional mammography. This is due to the presence of X-ray detector, which is considered the heart of DM. A number of technologies and several types of integrated digital detector system are in use nowadays. DM has the potential to improve contrast resolution compared with film-screen imaging. This is because DM detectors like other detectors characterized by sensitivity, spatial resolution properties, quantum detection efficiency, noise, and linearity of response.

This has improved diagnostic capability and relatively outweighs the potential reduction in limiting spatial resolution. DM technique offers many inherent advantages over the conventional screen film-based technology [19, 20]. For instance, processing with digital systems increase dynamic range (two to four times the dynamic range of typical film-screen), improved quantum efficiency, signal-to-noise-signal, and storage and display mechanisms.

Moreover, DM detector provides features for automatic control of exposure factors of the image acquisition. This represents the spatial pattern of X-ray transmitted by the breast tissue accurately. The use of computer-assisted image interpretation claimed to be helpful for

the physician. This may enhance different features such as computer-aided diagnosis, which may further improve the visibility of lesions and improve mammographic sensitivity [21]. Therefore, repeated exposures (which are sometimes, needed when using conventional mammography) are not required and this may reduce the radiation dose. The advantage of digital imaging systems compared with film-screen imaging is the ability to manipulate and possibly enhance the displayed image. The breast dose levels required by current digital imaging systems are, in general, similar to those of a modern mammographic film-screen combination. However, developments in detector design and optimization of beam quality may eventually result in a reduction in radiation dose. With the use of DM, a number of image processing operations can be introduced to correct for spatial nonuniformities in detector responses. In addition, it is also possible to improve the effective spatial resolution of the detector. It also overcomes a number of limitations inherent in the screen-film image receptor used in conventional mammography. Consequently, this improved the diagnostic image quality as well as reduced the doses to the breast tissues.

Furthermore, it does not need either cassettes or dark rooms or processors, and thus allegedly saves space and time in archiving and retrieving DM images. However, DM requires large disk space for saving image data. Despite several advantages, DM does not yet reach the level of detail to replace screen film mammography. However, with continuous technical improvements of the digital system, this may be expected to change in the near future. Both conventional and DM systems suffer from substantial technical and clinical limitations. For instance, these systems are unreliable in imaging patients with dense parenchyma tissue especially in the younger female population due to more glandular tissue. Mammographic findings are nonspecific (cannot always differentiate benign from malignant disease) and often underestimate the size of the detected lesion. X-ray-based imaging is also not useful for breast diagnosis following surgery or radiotherapy, as the patient's breasts in these cases have architectural distortion.

Moreover, both the tube spectrum and the peak potential (KVp) are important parameters affecting the image quality in film-screen and digital mammography. Automatic selection of proper target/filter combination in modern mammography systems may be affected by improper KVp. In conventional devices, the user depends on central laboratory calibration and has no easy way to calibrate the instrument during use. It is worth mentioning that X-ray mammography is not always useful for nonpalpable tumors. Another group of women with a known family history of breast cancer was recommended not to repeat X-ray mammography. In other words, those close carrying a mutation in BRCA1 (human gene called breast cancer 1, early onset) or BRCA2 (breast cancer 2) genes. Those groups are at high genetic risk of cancer. Some even have opted for preventative bilateral mastectomy. It is preferred not to repeat scan in this group due to X-ray dose and thus, a more sensitive diagnostic test would be advisable. Once the diagnostic tests particularly X-ray mammography indicates or suspects breast cancer, breast biopsies are then performed. Breast biopsy is an invasive procedure used to remove tissue or cells from the breast for microscopic examination. This technique generally performed under local anesthesia. Several types of biopsy are available depending on location, type, and size of lesion. Fine needle aspiration biopsy is performed by inserting a very thin needle to the lesion for taking a small sample of cells, fluid, or tissue. Core needle biopsy

is used with a large needle to remove a small cylindrical shape of tissue. Surgical biopsy involves removing part (incisional biopsy) or entire (excisional biopsy) lesion tissue.

In addition, a special wire localization technique may be used during surgery for deeply seated lesion. This technique usually performed under X-ray or ultrasound guidance. There are special instruments and techniques that help to guide the needle biopsy. These include stereotactic biopsy with a 3D mammographic technique to find the exact location of breast lesion and vacuum-assisted biopsy using a tube to gently suck the breast lesion and a knife to remove tissue. This technique is much less traumatic than open biopsy. Moreover, a sentinel node (the first lymph node to receive drainage from a breast cancer cell) biopsy may often be used to determine whether cancer cells have spread to other tissue. In summary, invasive breast biopsies play an important role for evaluating breast cancer particularly nonpalpable lesions. These surgical procedures are important for staging (see **Table 2**) and are considered the "gold standard" [17] to determine the presence or absence of breast cancer. However, invasive breast biopsy procedures are expensive, time consuming, and are often associated with emotional stress. It

Stage	Tumor size	Lymph node involvement	Metastasis
0	Carcinoma *in situ*	N0	M0
I	≤2 cm	N0	M0
IIA	No evidence of tumor	N1	M0
	≤2 cm	N1	M0
	2–5 cm	N0	M0
IIB	2–5 cm	N1	M0
	5 cm<	N0	M0
IIIA	No evidence of tumor	N2	M0
	≤2 cm	N2	M0
	2–5 cm	N2	M0
	5 cm<	N1	M0
	5 cm<	N2	M0
IIIB	Of any size	N0	M0
	Of any size	N1	M0
	Of any size	N2	M0
IIIC	Of any size	N3	M0
IV	Of any size	Any N	M1

Note: Beyond stage IIIB, the tumor is usually extended to either the skin or the chest wall and thus can be of any size. The N0 = no regional lymph node, N1 = metastasis in movable ipsilateral axillary lymph node(s), N2 = metastasis in ipsilateral axillary lymph node(s) fixed or matted, and N3 = metastasis in ipsilateral infraclavicular lymph node(s) or clinically apparent.

Table 2. The staging of breast cancer, adapted from Ref. [22].

also causes scar and tissue distortion that complicate the future mammography. As a result, additional imaging tests are being used to reduce the trauma, cost, avoid, or minimize unnecessary invasive breast biopsies, and more importantly to further improve breast cancer diagnosis.

4.2. Complementary diagnostic techniques

From the previous discussion, it is clear that there are some clinical situations where there are significant limitations to use mammography in isolation. In such cases, there is a great need to use sensitive tests to achieve a high confidence and accurate diagnostic decision. The use of breast biopsies is necessary if breast cancer is indicated or suspected in such cases. Of the performed breast biopsies, ≈60–80% [17] are negative of breast cancer or have benign lesions. In these cases, breast biopsies are considered unnecessary. This has led many breast cancer experts to propose complementary imaging modalities to provide additional diagnostic information and reduce unnecessary breast biopsies. Over the last two decades, complementary diagnostic techniques such as ultrasonography (US), magnetic resonance imaging (MRI), and radionuclide breast imaging techniques have emerged as potential investigations for the detection and diagnosis of breast cancer. The radionuclide breast imaging technique, unlike X-ray mammography, is not affected by breast density. This has prompted a number of investigators to evaluate the feasibility of radionuclide breast imaging techniques in a screening context particularly for women with dense breast.

4.2.1. Ultrasonography

US uses high frequency acoustic waves that reflect at boundaries with different acoustic properties. It is a noninvasive technique, easily available, and relatively cheap. Breast US provides unique information in assessing both palpable and nonpalpable breast abnormalities. For instance, it clearly differentiates between solid masses and cystic lesions. It is considered to be useful in cancer staging, measuring tumor sizes, easy accessing lesions located in peripheries, and reducing the number of unnecessary biopsies. It allows accurate needle placement during biopsy and is very useful for aspiration of cysts. The members of the European group for breast cancer screening recommended using US as a complementary method to X-ray mammography. In addition, the use of high frequency transducers has improved spatial resolution and thus claimed to be useful in axillary node evaluation. However, breast US technique is time consuming and operator/observer dependent. It has also a number of other limitations that may be due to the overlapping in sonographic characteristics. For instance, it cannot detect calcifications (micro calcifications or macro calcifications) in ductal carcinoma in situ (DCIS). It could also miss solid lesions especially in a fatty breast and if detected cannot determine whether a solid mass is benign or malignant. For these reasons, US is not used in some institutions as a screening technique for asymptomatic breast cancer as it is difficult to ensure that the entire breast has been scanned.

4.2.2. Magnetic resonance imaging

Magnetic resonance imaging (MRI) images is created by the recording of signals generated after radio-frequency excitation of nuclear particles exposed to strong magnetic field. Breast

MRI is a nonionizing tomographic functional technique that may be used when the diagnosis is uncertain with mammography [23]. The technique is valuable for specific clinical indications such as patients with (1) axillary adenopathy (enlargement or inflammation of lymph gland), (2) possible tumor recurrence after surgery or radiotherapy, (3) lesions overlying implants, or (4) those requiring staging of multi-focal carcinoma (two or more discrete lesions in one breast) [24]. Breast MRI with dedicated breast coil has excellent soft tissue resolution that enhances the ability to both identify the location and in some cases determines the full extent of the lesion. The use of intravenous contrast agent, gadolinium, which accumulates in tissues with a dense blood vessel network, also increases the sensitivity of breast MRI [16]. However, the reported specificity (ability to determine if lesion is benign or malignant) is 56–72% [24]. This technique has a limited application in patients with implanted metal devices or other metallic materials inside the body. In addition, several clinical limitations have been reported in the literature suggested not to use MRI in pre-menopausal women. For example, changes that do occur in the T_1 value of the breast tissue during the menstrual cycle [24] mean that patients should be scanned between the 6th and 16th day of the cycle. In summary, researchers have concluded that breast MRI is very sensitive, but not very specific and thus, cannot be used alone to rule out cancer. MRI is limited by lack of availability and inconsistent quality, and the technique is too expensive for routine use in breast cancer screening in the general patient population.

4.2.3. Radionuclide breast imaging techniques

The need to improve breast cancer detection and to reduce unnecessary invasive breast biopsies has stimulated researchers to investigate functional imaging modalities. These techniques produce a range of different imaging approaches such as positron emission tomography (PET), single photon emission computed tomography (SPECT), planar imaging, and dedicated imaging instrumentation with and without breast compression. These imaging techniques of the breast potentially offer additional information in breast cancer diagnosis. This is because these imaging methods rely on the physiological and biochemical characteristics of a lesion. Thus, it is considered as the best hope to differentiate between benign/normal and malignant diseases. These functional techniques are also used to assess and monitor the effect of cancer prevention drugs. The current radionuclide imaging techniques used for breast tumor imaging are briefly discussed.

4.2.3.1. Positron emission mammography

In PET, a small amount of positron emitter radiotracer, ^{18}F fluorodeoxyglucose (FDG), is administered intravenously to the patient [25]. It is then distributed in the body, and as it decays, the radionuclide emits a positron in any random direction. If the positron while travelling interacts with an electron within the body, the two particles then annihilate and produce two γ-rays of 511 keV each. Either a whole body scanner or a breast-specific positron emission mammography (PEM) camera [26] is used to detect the two γ-rays in coincidence (two events that are detected within ≈12 ns). PEM is increasingly used in North America not only in cancer diagnosis but also in staging, planning, and monitoring anticancer therapy. This information can be helpful in eliminating unnecessary axillary dissection [27], biopsies,

and in determining the appropriate treatment. The diagnosis of viable tumor tissue following chemotherapy is another application of PET [28, 29]. Imaging with ^{18}F-FDG has shown considerable promise in breast cancer imaging, but the exact role is still in evolution. Wahl [30] recommended that it is best applied to solve difficult clinical cases in specific patients rather than routinely. There are at least four reasons that limit the wide use of PEM for routine cancer diagnosis. The first one is the high cost (over £2 million) of PET coincidence imaging equipment, i.e., cyclotron, scanner, and radiochemistry facility [25]. The second one is the difficulty of producing and labeling the short half-life PET radionuclides [21]. The third reason is the lack of medical centers with the required experience to develop more advanced methodology appropriate for breast oncology. In particular, more data is still needed concerning the metabolism of different PET radiopharmaceuticals in breast tumors. The final reason is the lack of oncologists with a high knowledge of PET methodology [30].

4.2.3.2. Scintimammography

Scintimammography (SM) is a promising noninvasive functional imaging technique. It has been proposed to complement X-ray mammography and to improve patient selection for biopsy. This single photon imaging of the breast involves injecting the patient in the arm vein with a small amount (555–740 MBq [31]) of radiopharmaceutical. The most commonly used radiopharmaceutical for SM is ^{99m}Tc labeled sestamibi. After injection, the radiopharmaceutical distributes in the breast tissue as well as in other body organs. It accumulates more in the target object (breast lesion) with uptake ratio nearly 9:1 tumor-to-background-ratio (TBR) [32]. A standard full-size clinical gamma camera is then used to scan the patient and thus measure the 3D distribution of the radioactivity. SM imaging using full size clinical γ-camera includes a range of different imaging approaches such as planar (2D) imaging or SPECT technique. The latter technique gives a 3D image but is not widely used because it is difficult to accurately localize the lesion [33]. In contrast, planar SM is the technique that is more widely used in clinical practice because it provides better lesion localization particularly the prone images with lateral views [33]. In this case, the gamma camera is usually equipped with a low energy high resolution (LEHR) parallel-hole collimator and two views (prone and supine) are taken, to the diagnosed breast. Since the energy imaged is 140 keV representing the photopeak, 20% energy window (symmetric ±10%) is often used and thus, centered over the photopeak. The main clinical applications of planar SM imaging are summarized here and the details are found in literatures [33–39]. In brief, SM with a general purpose γ-camera introduced to evaluate patients with dense breast tissue and prior to breast biopsy [34]. The technique is considered valuable for many clinical applications such as evaluating the axillary lymph nodes, investigating patients with micro calcifications [35], assessing multi-focal and multi-centric breast cancer diseases [36]. It is also useful for imaging patients following surgery, chemotherapy, hormonal replacement therapy, and radiotherapy as well as for patients with breast implants [33]. The technique may also assist in the differentiation of benign and malignant breast abnormalities by measuring the radiotracer uptake in the lesion as compared with surrounding breast tissue. Studies such as Refs. [37, 38] suggested that SM may be used as a second-line diagnostic test in cases where the sensitivity of mammography is decreased or there is a doubt about the presence of a lesion.

In summary, SM using conventional γ-camera is considered as a useful complementary imaging modality to aid the diagnosis and the detection of breast cancer [39]. It may also help to assess patients recommended for biopsy and this may reduce the number of unnecessary or benign breast biopsies. However, the major drawback of the current standard clinical gamma camera SM imaging systems is the use of mechanical collimator. This causes the camera imaging system to utilize a very small fraction, ~0.01%, of the total number of the emitted photons. This limits the statistics and hence the quality and diagnostic value of the observed images. The collimator sensitivity and resolution are a trade-off and the camera is also limited by its intrinsic spatial resolution. As a result, these factors make it difficult to practically image cases of smaller, nonpalpable lesions (<1 cm) that may be deep seated or those close to the chest wall. These have stimulated the development of newly dedicated (breast specific) instrumentations that used for breast tumor imaging applications.

4.2.3.3. Dedicated breast cameras

Recent years have seen considerable interest by scientists in developing new compact medical imaging detectors. These instruments proposed for different clinical applications with the aim to improve image quality by building cameras of suitable size and shape for the part of the body under investigation. Among these designed detectors is the small-dedicated gamma camera for functional breast tumor imaging. The justification for this development is that a standard full size clinical gamma camera designed for whole body imaging and thus, is not been optimized for breast tumor imaging. In other words, there are a number of shortcomings with such general purpose gamma camera such as the limiting sensitivity. On average (50% [40]) for lesions <1 cm such as DCIS particularly, the medially located tumors. In addition, several studies [41–52] have pointed out that due to the large FoV of the camera and the bulky collimators, it is difficult to position the camera close to the breast, and thus, imaging breast tissue adjacent to the chest wall may not be possible. This may, ultimately, decrease the spatial resolution of the camera imaging system and thus affect the diagnostic value of the test in detecting such a small lesion size. To overcome some of the limitations offered by conventional gamma camera on breast imaging, Gupta et al. [41] reported the first preliminary clinical data that performed with breast-specific detectors and then compare it with the data obtained from standard full-size camera. A limited number of patients were investigated in this study but interestingly reported a higher sensitivity for the dedicated camera. Following this and due to the large research activities, new generation of detectors have been designed and developed for breast tumor imaging. For instance, the position-sensitive photo-multiplier tubes (PSPMT), semiconductor arrays, and scintillation crystals are coupled to an array of solid-state photodetectors. **Table 3** summarizes the features and the physical parameters of some of the currently under investigation and the commercially available dedicated breast camera. In general, these small FoV detectors have led to the improvement of the overall spatial resolution of such imaging system.

The commercially available dedicated breast camera has two detectors and is designed and optimized to image only the breasts. It possesses a high intrinsic spatial resolution and the camera is also equipped with ultra-high resolution parallel-hole collimator and thus, optimized

Cameras and study (reference)	Crystal sizes (mm^3)	FoV sizes (cm^2)	Intrinsic resolution (mm)	Spatial resolution (mm)	Energy resolution (%)
CsI(TI) [47]	2 × 2 × 3	10 × 10	2	9	n/a
CsI(Si) [49]	3 ×3 × 6	21 × 21	3	6.5	n/a
NaI(TI) [50]	3 ×3 × 6	15 × 20	3	6.3	10%
LumaGEM Nal(TI) [42, 50]	2 ×2 × 6	12.8 × 12.8	2.2	3.4	10%
LumaGEM 32000S/12K^2 (CZT) [51]	2.5 ×2.5 × 5	16 × 20	1.58	2.5	6%
LumaGEM (CsI) 5600 crystal [52]	3 × 3× 6	10 × 10	1.7	n/a	n/a

All cameras are based on PSPMT(s) principle. The CZT detector array absorbs the γ-rays directly and converts their energy into electrical signal without the conversion to visible light as in the case with a scintillation detector. The spatial resolution is measured with general purpose collimator at 10 cm distance except the LumaGEM cameras that based on ultra-high resolution collimators.

Note: n/a, not available.

Table 3. Physical characteristics and specifications of dedicated gamma cameras proposed for scintimammography.

for high-resolution SM. The main advantage of such cameras is the ability to separate the breast from the chest wall by positioning the camera close to the breast. Thus, the camera can be used in areas with limited space (e.g., medial view can be possible), where the use of a full-sized camera is impractical or impossible. The use of moderate breast compression capabilities may improve both the signal-to-noise ratio (SNR) and the spatial resolution [42] and thus increase the sensitivity for detecting smaller lesions. The proposed clinical indications for such dedicated cameras are similar to the full size clinical gamma camera SM. There are some recent clinical studies associated with using these dedicated gamma cameras. For instance, a clinical preliminary study by Brem et al. [43, 44] using dedicated breast camera demonstrated a slight improvement in resolution and tumor sensitivity particularly for lesions ≤1 cm. Rhodes et al. reported [45] on SM, performed on 40 women with small mammographic abnormalities (<2 cm) scheduled to undergo biopsy. The SM examination identified (33/36) malignant lesions confirmed at biopsy. The authors concluded that this preliminary study suggested an important role for the dedicated SM camera in women with dense breasts.

In another study, Brem et al. [46] evaluated 94 women (median age 55 years) who presented with normal mammographic and physical examination results but all subjects were considered at high risk of developing breast cancer. Of these women, 35 had a history of previous breast carcinoma or atypical ductal hyperplasia. The authors concluded that with this camera, they could depict small (8–9 mm) nonpalpable lesions in women at a high risk of breast cancer. In summary, while these studies using breast-specific cameras are promising, all are considered preliminary in nature because they are based on very few cases. Additional studies with a larger sample size are needed to accurately assess and reach scientific conclusions concerning these proposed cameras. They also need to be cost competitive with the general

purpose gamma cameras in order to be widely used in breast tumor imaging applications. In addition, the smallest lesion sizes that can be detected with these cameras claimed to be 3–3.3 mm [47] compared to 4–5 mm [48] with conventional camera. However, the evidence published to date did not demonstrate a statistically significant difference in lesion detection. The spatial resolution of these proposed cameras may further improve by increasing the pixel size but there are practical limitations in the development of cameras with small pixel sizes, including cost and detector design. More importantly, due to the use of collimator, these dedicated cameras suffer from low detection efficiency.

4.3. Summary of the role of different imaging modalities

In many centers, the current evaluation and primary diagnosis of breast are based on combination of physical examination, mammography, and breast biopsy. Mammography represents a significant contribution and remains the gold standard for breast tumor imaging. This is because mammography is relatively simple, cost-effective, and relatively, highly sensitive. However, in many clinical cases, mammography may be nonspecific and lesions may not be detected. This is because the breast lesion can be indistinguishable from normal breast tissue or obscured by the dense parenchyma. Mammography is also not reliable following radiation therapy, surgery, and hormonal replacement therapy. Consequently, breast biopsies are used for many cases as a second-line diagnostic test to evaluate a suspicious lesion. Unfortunately, many breast biopsies are performed on normal patients, which results in high cost and patient's stress. Thus, other noninvasive imaging techniques are needed and can be used as complementary functional methods to minimize unnecessary breast biopsies.

MRI and US are adjunctive imaging techniques to mammography. Breast US is relatively inexpensive and is currently the commonest complementary method. This technique is also useful particularly when there is a cyst in the breast, but has lower accuracy in solid lesions. Breast MRI with contrast is a sensitive and relatively specific technique for some certain indications but are too expensive to be used routinely. Both MRI and US are useful tools in breast diagnosis, in particular for solving problems in selected applications. For the aforementioned reasons, the use of complementary imaging techniques, to aid in the diagnosis, is necessary. Thus, additional imaging methods are needed for investigation, detection, and diagnosis of breast cancer. Functional breast γ-ray imaging techniques have aided breast cancer diagnosis.

Among the currently used techniques are planar SM with ^{99m}Tc labeled sestamibi and PET with ^{18}F-FDG. Both radionuclide techniques have been emerged as potential investigation for the detection and diagnosis of breast cancer. Consequently, it is increasingly used particularly for imaging patients with dense breasts. Having discussed commercial imaging methodologies, various weaknesses in each approach has led to the need for new complimentary imaging methods. Of these approaches, SM is one of the most promising approach. The current research in this area is focusing on dedicated collimator-based cameras. These dedicated cameras also suffer from low detection efficiency. In addition, this is an unattractive option for many health providers, due to limited clinical applications of such an imaging system. This provides the motivation for investigating the application of collimator-less method in breast tumor imaging. A gamma camera, employing a low energy high resolution (LEHR)

parallel-hole collimator is used, to generate an image of the resulting radionuclide distribution. The LEHR collimator geometrically selects γ-photons from a predetermined direction and as a result, a very small fraction of the total emitted photons reaches the detector. Thus, this limits the detection efficiency and spatial resolution of the observed image–collimator are trade-off.

Factors like these have generated massive research aimed to improve the accuracy and efficiency of the current SM imaging systems and reduce the overall costs of breast surgical biopsies procedures but without the need for the new dedicated camera instrumentation development. This is one of the primary motivations to carry out research using a simple coded aperture (CA) mask, instead of a collimator, coupled to a standard clinical gamma camera for breast tumor imaging without the need for a new dedicated camera instrumentation development. This is particularly attractive at general hospital level, where the cost of running an additional dedicated imaging system may be prohibitive. In addition, the smallest lesion sizes that can be detected with dedicated cameras claimed to be 4–5 mm compared to 8–10 mm with conventional camera. The spatial resolution of these proposed cameras may further improve by increasing the pixel size, but there are practical limitations in the development of cameras with small pixel sizes, including cost and detector design. CA imaging as originally developed for astronomical applications is well suited for detecting faint pseudo-point like objects in a nonzero background. Thus, it appears to be well matched to the imaging objectives in SM. While related prior work has also considered, this approach is characterized by gross simplifications in terms of clinical reality [53, 54].

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Chapter 2

Breast Ultrasound Past, Present, and Future

Jocelyn A. Rapelyea and Christina G. Marks

Additional information is available at the end of the chapter

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Abstract

This chapter will review the utilization of breast ultrasound for screening and diagnostic purposes. Currently, ultrasound is primarily used to investigate palpable lesions in women less than 30 years old, to provide further characterization of abnormal mammographic findings, and to guide invasive breast interventions. Innovations in ultrasound technology have improved the detection and diagnosis of breast cancer. Computer-aided detection (CAD), elastography, quantitative breast ultrasound technology, and ultrasound contrast agents (microbubbles) were developed to improve diagnostic accuracy. These advancements have the potential to impact overall survival by detecting cancers that are smaller and less aggressive.

Keywords: screening ultrasound, elastography, CAD, quantitative ultrasound, breast cancer, breast ultrasound, targeted breast ultrasound, automated whole breast ultrasound, breast density, ultrasound guided biopsy

1. Introduction

Breast ultrasound is an integral component of the diagnostic evaluation of breast lesions. It is the primary modality used to examine palpable abnormalities in young women (<30 years old), is routinely employed to further characterize mammographic abnormalities as solid or cystic, and provides direction for image-guided breast interventions [1].

For many years, the primary utility of breast ultrasound was differentiating cysts from solid masses. Cysts can occur at any age, but are most commonly found in pre- and perimenopausal women. To classify a lesion as a simple cyst, it must meet a strict set of criteria; it must be entirely anechoic, sharply marginated, round or oval in shape, and demonstrate posterior acoustic enhancement [2]. Lesions containing low-level echoes, which otherwise meet the criteria for simple cysts, are referred to as complicated cysts. Complicated cysts may also have

fluid-fluid or fluid-debris levels that may shift with changes in a patient's position. Complex cystic masses with discrete solid components are suspicious for malignancy and require further evaluation with biopsy [2].

Today, there is a paradigm shift in the application of breast ultrasound. Its new role as a primary screening tool in women with dense breast tissue is growing. The limitation of mammography in women with dense breast tissue has opened the door to supplemental screening with ultrasound and magnetic resonance imaging (MRI). Ultrasound has become the supplemental screening tool of choice for breast cancer detection in this select group of women given that it is low in cost, is widely available and has no ionizing radiation. Whether breast ultrasound is used for diagnosis or screening, evidence of its utilization over the last 50 years has deemed it an invaluable tool.

2. Background/historical perspective

In the mid to late 1960s, there was a significant amount of research involving breast ultrasound. Issues such as transducer design and manipulation of the ultrasonic beam became the focus of many researchers. Improvement in resolution and the advent of grayscale imaging segued to modern day imaging and an effort to shift from evaluating pathological breast findings toward screening healthy women.

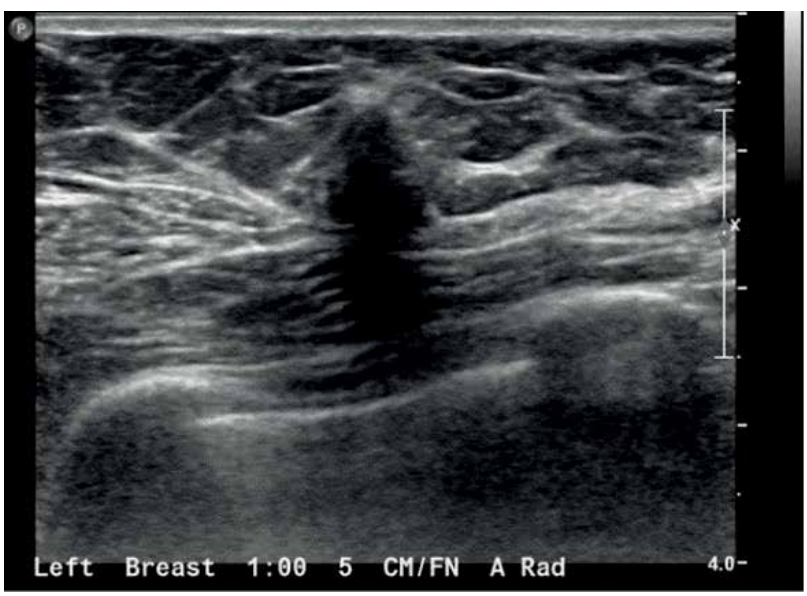

Figure 1. Transverse ultrasound of the left breast demonstrates an irregular, antiparallel mass with posterior acoustic shadowing.

It was not until 1970 that there was regular clinical use of breast ultrasound, mainly in the United States and Asia. During this time, Japanese authors Kobayashi et al. published several papers [3, 4] discussing the various characteristics that could differentiate benign and malignant breast disease. Published work from these authors linked the characteristic descriptor of acoustic shadowing with breast malignancy [5]. Further development in the late 1980s and early 1990s of Doppler ultrasound helped complement B-mode grayscale images, augmenting the ability to differentiate cancerous masses from benign findings (**Figure 1**). In 1995, Stavros and colleagues described a set of criteria to improve specificity in determining benign and malignant features of breast masses [6]. By the late 1990s and early 2000, advancement and application of tissue harmonics and spatial compounding further refined ultrasound images; helping to improve image resolution and reduce noise [7, 8].

Optimization of the ultrasound image is essential, but not the only component needed to properly classify masses as benign vs. malignant. The knowledge of normal breast anatomy, breast scanning technique (artifactual tissue shadowing will resolve with increase in transducer pressure), along with the understanding of common artifacts encountered can improve the overall effectiveness of the examination. Recent publication of the American College of Radiology's (ACR's) Breast Ultrasound Lexicon (++) has helped to standardize the descriptive language of breast lesions, thus improving the positive predictive value (PPV) and confidence in determining the likelihood of malignancy.

3. Basics of breast ultrasound

3.1. Anatomy

The female breast is made up of glandular tissue and fat, held together by a framework of fibers called Cooper's ligaments. The female breast, representing a modified sweat gland, spans the distances between the second and sixth anterior ribs, sternum, and midaxillary line. Normal anatomical structures imaged during breast ultrasound include the skin, nipple, fat, Cooper's ligaments, ducts, breast parenchyma, pectoralis muscles, pleura, and ribs (**Figure 2**). These appear as six distinct layers on ultrasound images as follows (from anterior to posterior): skin, subcutaneous fat, breast parenchyma (including ducts and lobules), retroglandular (retromammary) fat, pectoralis muscles, and chest wall (**Figure 3**). It is the sonographic appearance of the breast fat which gives reference for comparing other structures within the breast [9]. Breast fat appears dark gray on ultrasound images. Ducts and cysts are anechoic. The nipple and blood vessels appear hypoechoic, while breast parenchyma, Cooper's ligaments, and skin appear hyperechoic.

Ultrasound imaging of the skin and nipple can best be imaged using a stand off pad, which can help eliminate the acoustic shadowing commonly seen posterior to the nipple [1]. The skin is usually less than or equal to 2 mm in thickness, except over the areola where the skin is often thicker.

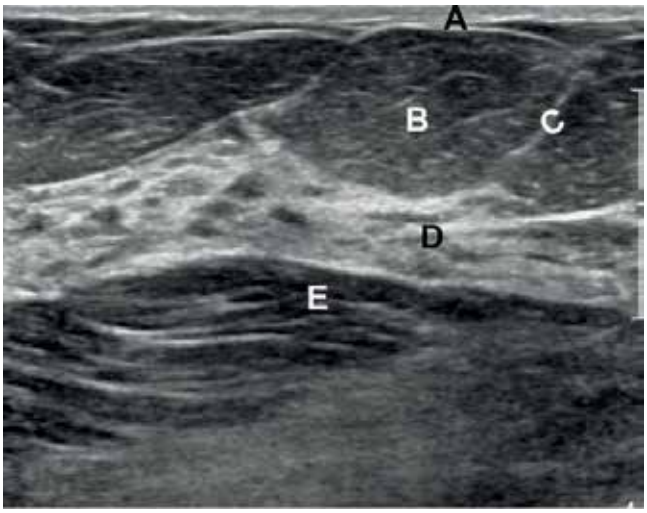

Figure 2. Breast anatomy. Transverse ultrasound shows normal breast anatomy. (A) Skin, (B) fat lobule, (C) Cooper ligament, (D) fibroglandular zone, and (E) muscle.

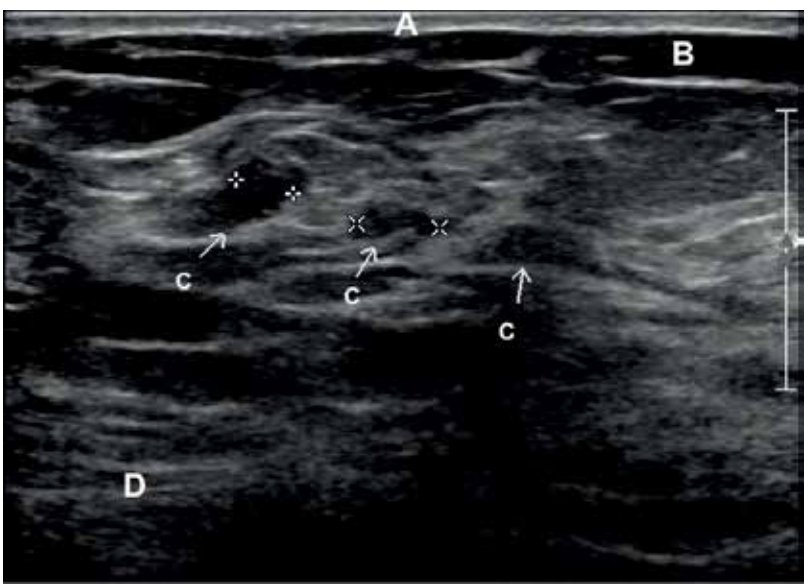

Figure 3. Breast anatomy. Transverse ultrasound shows normal breast anatomy. (A) Skin, (B) subcutaneous fat, (C) terminal duct lobular unit, and (D) muscle.

3.1.1. Male vs. female

In contrast to the female breast in which ducts, stroma, and glandular tissue are found, the male breast contains mostly fatty tissue with a few ducts and stroma. The sparse ductal

and stromal elements within the male breast give rise to the most common disease seen within the male breast, gynecomastia. Gynecomastia is typically bilateral and appears on ultrasound images as subareolar glandular tissue, which may be hypoechoic to hyperechoic. There are no standard protocols for imaging the male breast with many institutions performing a mammogram prior to ultrasound. Male breast cancer is very rare, representing only about 1% of all breast cancers [10].

3.1.2. Maturation phases

Mastogenesis begins around the sixth week of development and by the eighth week, a mammary gland is formed from the thickening located at the epidermic "milk line" [11]. During puberty, both estrogen and progesterone stimulate breast development.

3.1.3. Lactation changes

During pregnancy and lactation, the breast undergoes many hormonal changes resulting in glandular proliferation, ductal distention, and stromal involution. Ultrasound is the modality of choice for evaluating palpable masses, bloody nipple discharge, and focal pain in the lactating breast. Masses unique to the lactating breast include lactating adenomas and galactoceles [12].

3.1.4. The postoperative breast

Patients who have undergone lumpectomy surgery often present with postoperative fluid collections such as seromas, hematomas, and lymphoceles with spontaneous resorption of these fluid collections occurring over time. It is important not to confuse scar formation for recurrent cancer in this patient population, as areas of scarring can appear as areas of acoustic shadowing [1]. In patients who have undergone radiation therapy, skin thickening, and breast edema are frequently identified and eventually decrease over time.

3.1.5. The postimplant breast

Breast implants include both silicone and saline implants which are surgically placed for either breast augmentation or reconstruction. While MRI is the imaging modality of choice to evaluate for silicone implant integrity, there are characteristic sonographic appearances associated with silicone implant rupture. The appearance of an intact breast implant on ultrasound is similar to a large cyst, with presence of an anechoic implant lumen surrounded by a hyperechoic linear shell [13]. The "stepladder sign," which appears as horizontal, hyperechoic, straight, or curvilinear lines across the implant lumen, is characteristic of intracapsular silicone implant rupture (**Figure 4**) [13]. The "snowstorm sign" is reportedly the most significant sonographic finding for extracapsular rupture and appears as hyperechoic nodules with defined anterior margin and posterior acoustic shadowing within the breast parenchyma or axillary lymph nodes [13]. The ability to diagnose extracapsular rupture on sonography approaches accuracy of MRI, with one study finding 100% diagnostic accuracy for extracapsular rupture with ultrasound (**Figure 5**) [13].

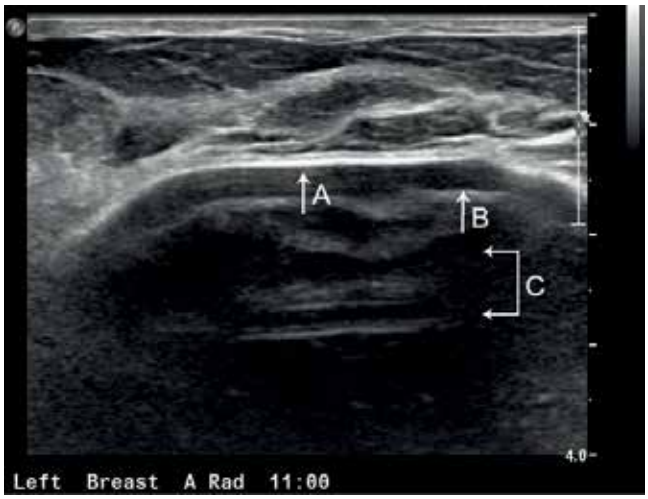

Figure 4. "**Stepladder sign.**" Transverse ultrasound demonstrates an intracapsular silicone implant rupture. (A) Outer capsule, (B) shell of collapsed implant, and (C) "Linguine sign".

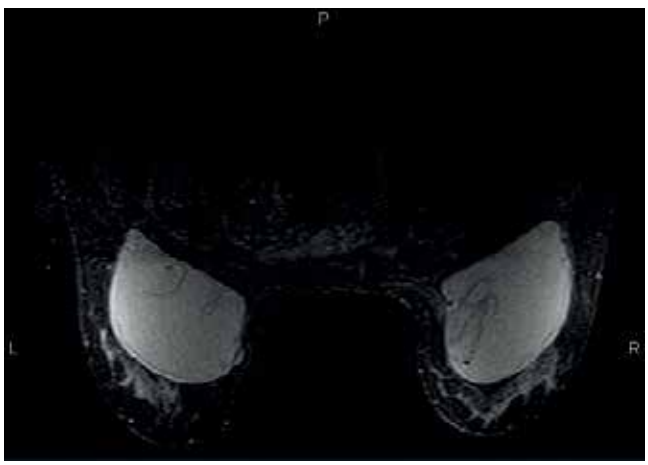

Figure 5. Axial T2W MRI demonstrates bilateral intracapsular silicone implant ruptures.

3.2. B-mode and Doppler

B-mode or brightness mode, ultrasound images are the standard two-dimensional grayscale images routinely obtained during breast ultrasound. The higher the probe frequency, the better the axial resolution, which is the ability to resolve objects within the imaging plane located at different depths [14]. For this reason, high frequency probes (12–18 mHz) are often utilized for breast ultrasound, which requires relatively steep time gain curve to compensate for rapid beam attenuation (**Figure 6**). If a large breast is being imaged, a lower frequency probe may be preferable to image deep lesions close to the pectoralis muscle given that high frequency

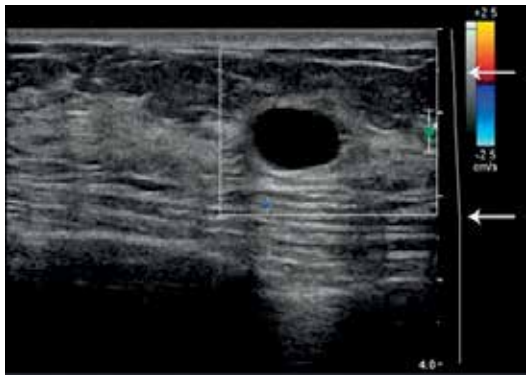

Figure 6. Gain. Transverse ultrasound illustrates gain. Ultrasound waves are absorbed by tissue. The deeper the tissue, the greater the absorption. A gradual increase in the gain with deeper tissues is recommended.

probes often do not penetrate as deeply as lower frequency probes. Alternatively, adjusting the patient's position or compressing the breast can help bring the lesion into the focal zone [1]. Ensuring the focal zone is centered at the depth of interest within the breast is also essential to ensure optimization of lateral resolution (**Figure 7**). Lateral resolution is the ability to resolve objects located side by side at the same depth and is best at the focal zone, where the ultrasound beam is at its narrowest [14]. Doppler ultrasound utilizes the Doppler Effect to analyze the frequency of the returning echo allowing for color Doppler images to be obtained demonstrating both tissue morphologies in grayscale as well as blood flow in color [14]. While the use of color Doppler can help differentiate solid masses from complicated cysts [9], some propose that Doppler ultrasound will further improve ultrasound performance by aiding in the assessment of tumor vascularity and tumor blood flow [15].

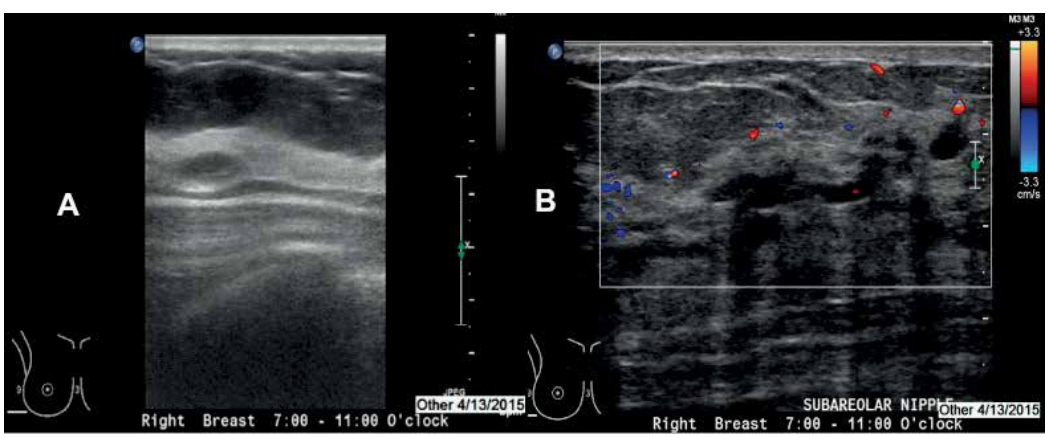

Figure 7. Focal zone. Transverse ultrasound of the right breast illustrating focal zone settings. The focal zone should be set at the anterior to middle third of the region of interest. (A) Partial volume averaging—loss of detail and (B) image with appropriate focal zone setting.

3.3. Artifacts

Ultrasound is a modality with many artifacts. Some artifacts most commonly encountered in breast ultrasound include acoustic shadowing, posterior acoustic enhancement, refraction, speckle, and reverberation. While some artifacts make detection or differentiation of lesions more difficult, other artifacts help identify and characterize lesions in the breast. Acoustic shadowing and posterior acoustic enhancement are both artifacts that routinely aid in characterization of breast lesions. Acoustic shadowing is secondary to a decrease in the energy of transmitted sound either secondary to reflection and/or absorption and appears on ultrasound images as a dark or hypoechoic band beneath an object of high attenuation [14, 16]. Sound is gradually attenuated as it passes through solid structures. Alternatively, sound is less attenuated as it passes through fluid-filled structures, giving the appearance of a brighter signal deep to cystic structures [14, 16]. The presence of posterior acoustic enhancement helps distinguish cystic versus solid breast lesions, although it is important to note that some solid lesions also demonstrate posterior acoustic enhancement. Refraction is often encountered in breast ultrasound when the sound beam is refracted at a curved interface between the higher velocity soft tissues and a lower velocity cyst resulting in narrow refractive bands along the margins [17]. Refractive artifacts should not be confused with acoustic shadowing. Speckle refers to a granular appearance of an otherwise fat homogeneous region of breast tissue. It can affect image contrast and reduce visibility of lesions by masking small differences in the level of gray (**Figure 8**). Reverberation artifact occurs when sound is reflected off strong acoustic interfaces creating a ping-pong of echoes resulting in an image of parallel, linear bright bands or diffuse low-level echoes in the superficial most aspect of a cyst [14, 16, 17]. Decreasing the gain can help reduce reverberation artifact [14].

3.4. Spatial compound imaging

Compound imaging refers to the technique by which images are acquired from multiple angles of isonation and then added together while maintaining a static transducer position. Each image has its own artifact profile and when multiple images are averaged together, the artifacts become less apparent and true structures are better visualized [18]. One benefit of spatial compound imaging is reduced speckle artifact (**Figure 9**). Reduced image speckle has been shown to improve the conspicuity of low contrast lesions, enhance the delineation of tumor margins, and improve the depiction of the internal architecture of solid lesions and microcalcifications. One limitation of spatial compound imaging is the reduced visibility of the posterior echo pattern (acoustic shadowing or enhancement), artifacts often used to aid in characterization of lesions as cystic or solid [19]. Additionally, spatial compound imaging requires frame averaging during compounding, producing motion blurring if the ultrasound probe is moved too quickly [15].

3.5. Clutter

Clutter is a noise artifact caused by either aberration or reverberation of echoes, which causes filling in and loss of contrast [20, 21]. On ultrasound images, clutter appears as a diffuse haze thereby reducing image contrast and is most easily visualized in anechoic or hypoechoic

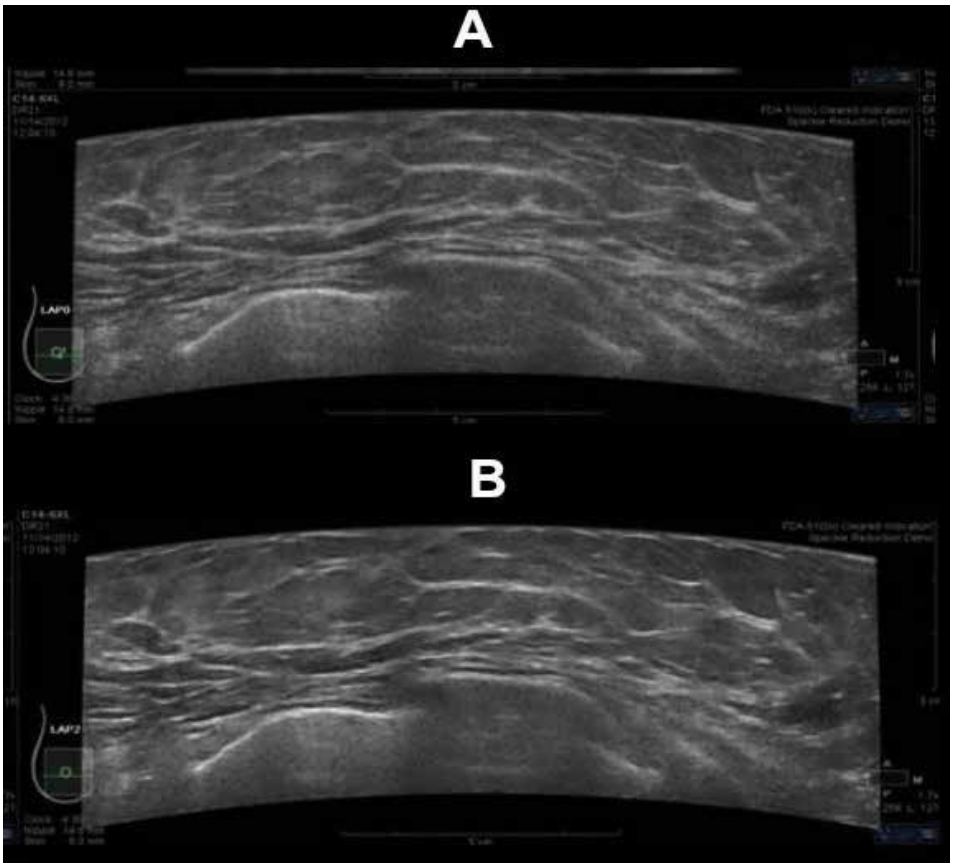

Figure 8. (A) Long axis view of transverse ultrasound demonstrating speckle artifact. Increased noise noted throughout the image and (B) long axis view of transverse ultrasound demonstrating speckle reduction.

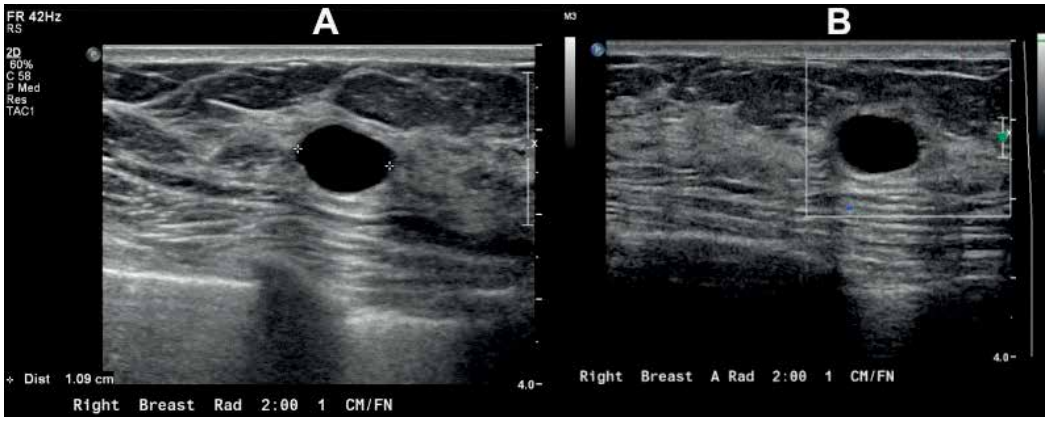

Figure 9. Compound imaging. Transverse ultrasound of the right breast illustrates compound imaging. (A) Utilization of compound imaging and (B) without compound imaging.

structures [21]. Clutter is of particular concern when imaging small, low-contrast lesions [21]. Methods to reduce clutter include second-order ultrasound field imaging, short-lag spatial coherence imaging, filtering techniques, and tissue harmonic imaging [20].

3.6. Tissue harmonic imaging

Tissue harmonic imaging is an ultrasonographic technique that can potentially provide images of higher quality than those obtained with conventional ultrasound techniques. Tissue harmonic imaging involves the use of harmonic frequencies that originate within the tissue

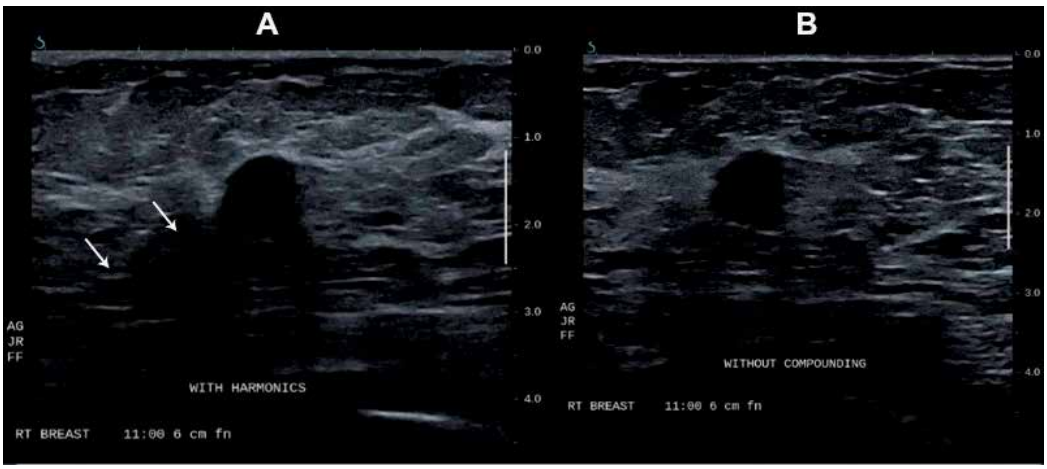

Figure 10. Harmonics increase real echoes. Transverse ultrasound of the right breast shows harmonics increasing real echoes. (A) With harmonics and (B) without harmonics.

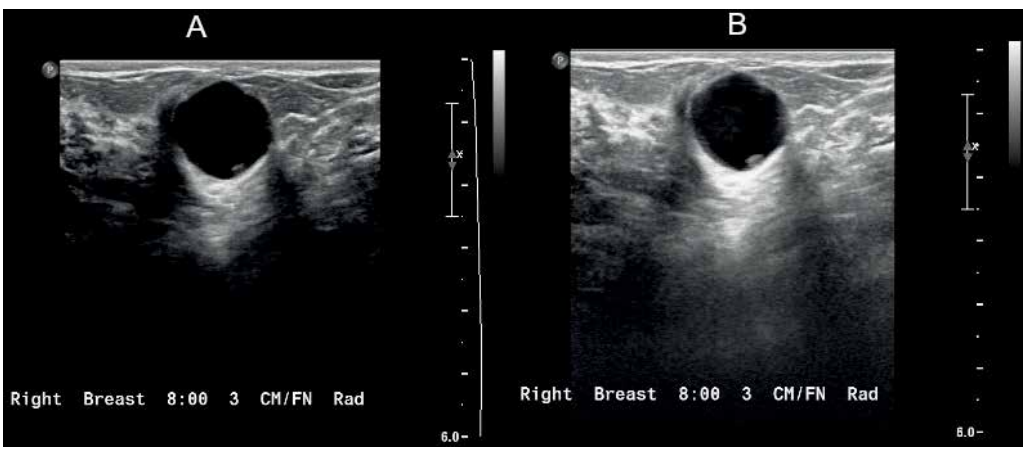

Figure 11. Harmonics reduce artefactual echoes. Transverse ultrasound of the right breast shows harmonics reducing artefactual echoes. (A) With harmonics and (B) without harmonics.

as a result of nonlinear wave front propagation and are not present in the incident beam (**Figure 10**). These harmonic signals are generated differently at anatomic sites with similar impedances and thus lead to a higher contrast resolution. In addition, use of tissue harmonic imaging helps reduce many of the artifacts that occur with conventional ultrasound, such as side-lobe, near-field, reverberation, and clutter artifacts, and improves the signal to noise ratio (**Figure 11**) [22, 23, 20].

4. Lesion characterization with BI-RADS Lexicon

4.1. Correlative BI-RADS classifications and positive predictive value (PPV)

Similar to the BI-RADS system used to standardize the language of mammography reporting, the American College of Radiology (ACR) also developed a BI-RADS lexicon for breast sonography for the characterization of the sonographic lesions. This lexicon includes descriptors of masses such as shape, orientation, margin, echo pattern, and posterior features as well as associated features such as architectural distortion, duct changes, breast edema, skin changes, vascularity, and elastography. Special cases delineated by BI-RADS lexicon include simple cyst, clustered microcysts, complicated cyst, skin masses, foreign bodies (including implants), intramammary and axillary lymph nodes, vascular abnormalities, and postsurgical fluid collections. BI-RADS lexicon defines a simple cyst as oval or round in shape, anechoic, circumscribed margin, and with posterior acoustic enhancement (BI-RADS) (**Figures 12–14**). BI-RADS descriptors showing a high predictive value for malignancy include spiculated margin, irregular shape, and nonparallel orientation (**Figure 15**). Circumscribed margin, oval shape, and parallel orientation are characteristics predictive of a benign lesion [24, 25].

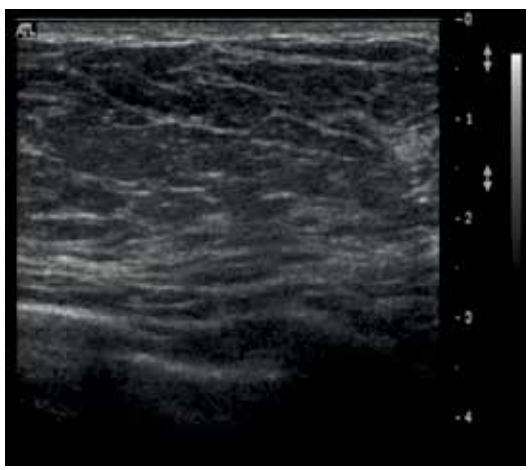

Figure 12. Homogenous background echotexture—fat. Transverse ultrasound demonstrates fat lobules, with uniform echogenic bands of supporting structures making up the bulk of the breast tissue.

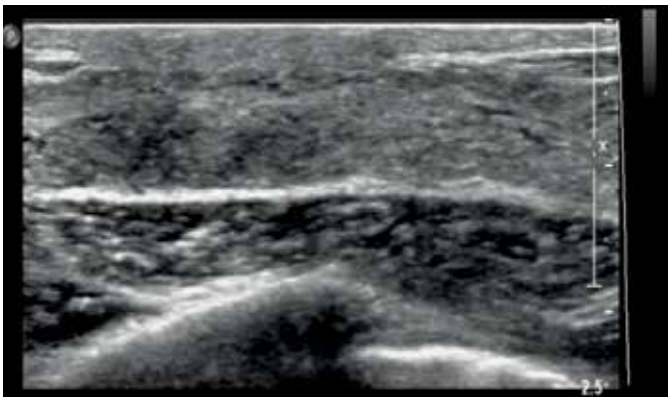

Figure 13. Homogenous background echotexture—fibroglandular. Transverse ultrasound shows a thick zone of homogenously echogenic fibroglandular tissue present beneath a thin hypoechoic layer of fat lobules.

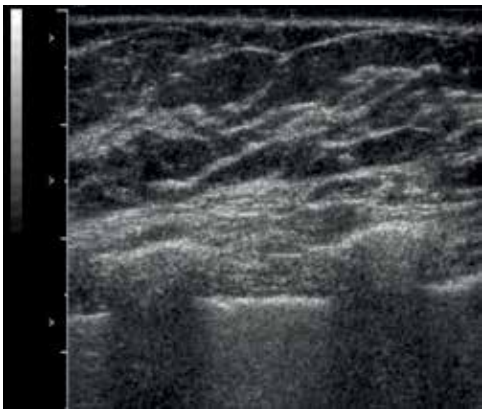

Figure 14. Heterogeneous background echotexture. Transverse ultrasound depicts multiple areas of increased and decreased echogenicity. Heterogeneity can be either focal or diffuse.

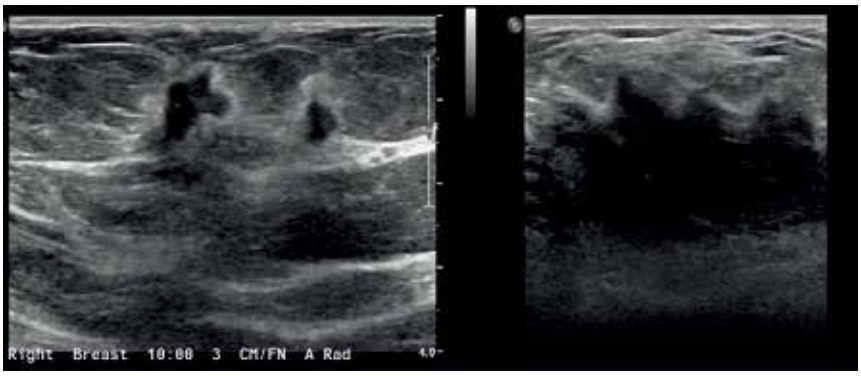

Figure 15. Margin assessment. Transverse ultrasound of the right breast demonstrates an irregular mass with angular margins. Some or all of the margins has sharp corners, often forming acute angles.

5. Indications for targeted breast ultrasound

5.1. Characterization of a mammographic mass

Ultrasound is an adjunct to mammography for mass characterization and is the next examination to perform for characterization of a mammographic mass, per ACR appropriateness criteria [26]. It is critical to establish the location and depth of the mass identified on mammography to ensure that the same area is imaged during breast ultrasound. If a mass is identified on breast ultrasound and is thought to correlate with the mammographic mass, the size, shape, location, and surrounding tissue composition should correlate between the two modalities [27]. If no sonographic correlate is found for a mass identified on mammogram, then revaluation of the mammogram should be performed. If mammographic findings remain suspicious for a sonographically occult mass, then further evaluation with a different imaging modality and/or biopsy can be pursued (**Figure 16**).

5.2. Evaluation of a palpable mass in a patient with negative mammogram

Fifty years ago, women who presented with a palpable mass eventually underwent surgical excision to exclude malignancy [28]. With advances in ultrasound imaging, many women now who present with a palpable mass and no mammographic correlate undergo diagnostic targeted ultrasound, often on the same day as diagnostic mammogram, to evaluate the region of palpable concern. If no mammographic or sonographic abnormality is identified, women can be safely reassured that there is no abnormality instead of undergoing

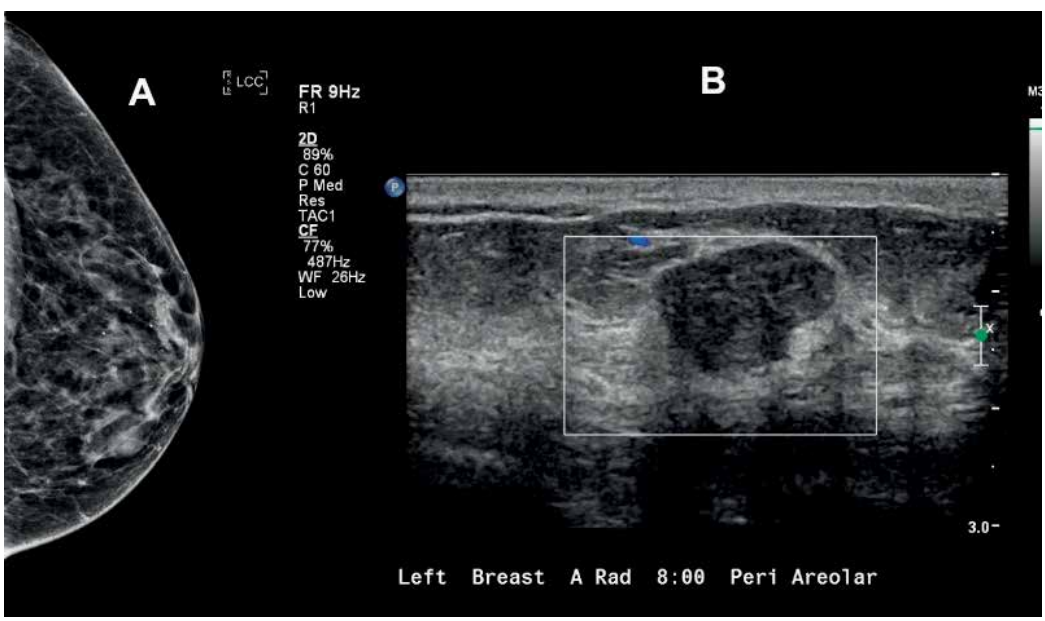

Figure 16. Lesion visibility. (A) CC mammogram of the left breast and (B) transverse ultrasound of the left breast.

unnecessary surgery or biopsy [29]. However, if a patient presents with a palpable mass with negative mammogram, ultrasound has been shown to be effective in identifying an abnormality in about 50% of cases, with the majority of these abnormalities characterized as benign (mostly cysts) or likely benign [30]. Recent studies also question whether a repeat mammogram is even necessary when a woman presents with a new palpable mass within 12 months of prior negative mammogram, given that ultrasound has been shown to yield the most diagnostic information [30].

5.3. Evaluation of a palpable mass in young patients (<30 years old)

Ultrasound is the initial imaging modality used to evaluate a palpable mass in a patient less than 30 years old [26]. After an abnormality is detected with ultrasound, it is debatable as to whether the next examination to perform is a unilateral mammogram imaging the breast with the sonographic abnormality, a bilateral mammogram, or an ultrasound guided biopsy of the abnormality. Per ACR appropriateness criteria, either mammography or a biopsy is appropriate and the determination of the next examination is likely patient dependent [26]. Masses often found in this patient population include cysts, fibroadenomas, and very infrequently breast cancer.

5.4. Ultrasound guided interventional breast procedures

Historically, the most important role of breast ultrasound was differentiating a solid from a cystic mass [1], for which ultrasound has a reported accuracy of 96–100% [27]. However, as ultrasound imaging has improved, the indications for utilization of ultrasound have expanded from lesion characterization to real-time sampling of the lesion using ultrasound guidance. Some are now also using ultrasound guidance for treatment of breast lesions with percutaneous ablation. The real-time nature of ultrasound imaging, lack of radiation, cost effectiveness, and relative patient comfort make ultrasound an ideal modality with which to perform biopsies and treat breast lesions.

Ultrasound guided interventional breast procedures include fine needle aspiration, ultrasound guided core biopsy, ultrasound guided vacuum assisted biopsy, and ultrasound guided presurgical localization. Indications for ultrasound guided fine needle aspiration include symptomatic relief of a painful cyst and confirmation of cystic nature of an indeterminate mass [1]. Varying needle sizes are used for ultrasound guided fine needle aspirations ranging from 25 up to 18 gauge. Percutaneous image guided core-needle biopsies have almost completely replaced surgical needle-localization biopsy of breast lesions as they are faster, less invasive, less expensive, safe, and accurate, with specificity and positive predictive value for detection of malignancy nearing 100% [31]. Not only does a negative core needle biopsy prevent a patient from undergoing unnecessary surgery, but ultrasound guided core needle biopsy for malignancy reduces the incidence of positive margins after local excision and decreases the number of surgeries for definitive breast cancer treatment [31]. Ultrasound guided 14-gauge automated core biopsy was described almost 25 years ago with 100% concordance between ultrasound guided core biopsy results and surgery [32]. While many practices still perform ultrasound guided core biopsies with an automated 14-gauge biopsy needle, there are now a wide array

of gauges and needles available for breast biopsy. Automated biopsy needles range from 20 to 14 gauge and vacuum assisted biopsy needles range from 13 to 9 gauge. The needle chosen to perform an ultrasound guided core biopsy is physician and patient dependent. While the risks of severe complications from ultrasound guided breast biopsy are very rare, occurring in less than 1% of procedures, there has been slightly more severe bleeding events associated with vacuum-assisted biopsies than with automated gun biopsies [33]. Perhaps this can be attributed in part to the needle size as most vacuum-assisted biopsy needles are larger in size than automated biopsy guns and other studies also support increased risk of hematoma formation after biopsy with a larger gauge needle (9-gauge) compared to a smaller gauge needle (12- or 14-gauge) [34]. Historically, percutaneous breast biopsies performed on patients on antithrombotic therapies, including clopidogrel, daily non-steroidal anti-inflammatory drugs, aspirin, and warfarin, have been performed with caution given concern for increased risk of bleeding and hematoma formation with many breast imagers requiring patients to cease antithrombotic therapy prior to biopsy. Recent data suggest that patients may be able to safely undergo percutaneous breast biopsy without stopping antithrombotic therapy, with one prospective studying showing no clinically significant hematomas in women taking antithrombotics [34].

Ultrasound-guided percutaneous ablation procedures, including cryoablation, irreversible electroporation, laser therapy, microwave ablation, radiofrequency ablation, and high-intensity focused ultrasound, of benign and malignant breast lesions that are 2 cm or less in size are also being performed [35]. These ultrasound-guided ablation techniques are particularly appealing for patients who are not surgical candidates; however, identifying the group of patients best suited for percutaneous ablation procedures is evolving [35]. While many of these percutaneous ablation techniques can be performed with local anesthesia alone, both radiofrequency ablation and high-intensity focused ultrasound must be performed with sedation and may be performed with MRI guidance instead of ultrasound guidance [35].

5.5. Targeted breast ultrasound secondary to abnormal MRI or molecular breast imaging

The use of breast magnetic resonance imaging (MRI) and molecular breast imaging (MBI) has increased over the past several years, with breast MRI offering the highest sensitivity of all modalities. A "second-look ultrasound" is a targeted reevaluation of the breast with ultrasound after an abnormality, which is not characteristically benign, is identified on either MRI or MBI [36]. Similar to mammographic-sonographic correlation of masses, it is critical to establish the location and depth of the abnormality identified on MRI or MBI to ensure that the same area is imaged during breast ultrasound. Studies suggest identification of MRI-detected abnormalities on ultrasound imaging range between 23 and 89%, with lesion type being the most important predictor [37]. If a sonographic correlate for the MRI or MBI detected abnormality is discovered, then most breast imagers will proceed with an ultrasound guided biopsy of the abnormality. This is advantageous to the patient who can undergo biopsy without breast compression in a relatively comfortable reclined position and the ability to often use a smaller gauge needle for biopsy. In contrast, MRI guided biopsies are performed with the breast in compression with the patient in a prone position and utilize large gauge vacuum assisted needles. Additionally, ultrasound guided biopsies are less expensive and less time consuming. However, if there is concern that the abnormality biopsied under ultrasound did

not correspond to the MRI detected abnormality, then confirmatory MRI images could be obtained with attention to susceptibility artifact from the metallic clip placed at the time of ultrasound guided core biopsy [38]. Some recommend a T1-weighted, axial, noncontrast, gradient-echo sequence MRI to verify metallic marker placement [36]. If no ultrasound correlate is identified for the MRI or MBI abnormality, revaluation of the MRI or MBI is required with possible recommendations for MRI or MBI guided biopsy of the abnormality.

6. Screening breast ultrasound

Although mammography is the only screening modality proven to reduce mortality [39, 40], its performance is diminished in women with dense breast tissue. Dense tissue refers to the mammographic appearance and the amount of stromal, epithelial, and connective tissue elements of the breast – all of which are radiodense on the mammographic image [41]. All of which are radiodense on the mammographic image. Breast density can change based on hormonal activity, BMI, and age. Mammographic sensitivity may be as low as 30–48% in women with dense breasts [42]. The association of breast density identified on mammography, using the American College of Radiology BI-RADS classification [43], C and D (heterogeneous or extremely dense) is coupled with a reduction in the effectiveness of the examination. This is in large part due to the masking effect observed when dense fibroglandular tissue is superimposed over breast cancer, limiting visualization of the known cancer. In a recent study, 78% of tumors were found to be mammographically occult secondary to overlapping tissue [44]. Furthermore, the inherent four- to sixfold increased risk of developing breast cancer in women with dense tissue compared to women with predominantly fatty breast composition [45] is associated with a higher occurrence rate of interval breast cancers [5, 46–48]. For these reasons, supplemental screening with other modalities is considered.

Breast ultrasound is not limited by breast density, and its use as an adjunct screening tool can improve the diagnostic accuracy of the screening examination. The use of ultrasound can detect early, node negative invasive cancers and interval breast cancers, thus improving the prognosis and morbidity in women diagnosed with the disease [48]. Based on earlier studies published by Kolb et al. 42% more invasive cancers were identified using adjunct screening with ultrasound [49]. Results from other single institutional studies validate these findings, demonstrating a range between 0.4 and 5.7 additional cancers detected per 1000 women screened (see tables). The ACRIN 6666 trial, a multi-center observational study, confirmed that cancer detection could improve with the addition of ultrasound, by approximately 4.2 additional cancers per 1,000 women screened [42]. In both Kolb's analysis and the ACRIN study, nearly 1/3 to 1/2 of all women undergoing supplemental screening with breast ultrasound were considered at increased risk for developing breast cancer.

Thus, the incremental increase in cancer detection may in part be due to the higher prevalence of disease detected in the cohort of women [49]. Subsequent studies focusing on evaluating women at average risk with mammographically dense breast tissue, demonstrate an additional 3.2 cancers detected per 1000 women screened with breast ultrasound [50, 51]. The advantage of supplemental screening ultrasound, regardless of the population screened

or the variation in study design, demonstrates an incremental increase in cancer detection. Whether this translates to a decrease in breast cancer mortality is unknown, as there are no randomized control trials assessing this outcome.

While optimizing breast cancer screening is of utmost importance, establishing a balance between improving sensitivity while maintaining specificity proves to be difficult. Of main concern, is the possibility of increasing the number of false positive findings which can lead to unnecessary tests and biopsies. Many studies have demonstrated that screening breast ultrasound does have a higher false positive rate than mammography alone [52]. This includes the Japan Strategic Anti-cancer randomized Trial (J-START), where the sensitivity was significantly higher in the intervention group (mammography plus ultrasound screening) than in the control group but the specificity was significantly lower (87.7% decreased from 91.4%) [53]. Alternatively, in another multiinstitutional trial including 12,519 Chinese women, the authors found comparable PPVs between mammography and ultrasound screening (72.7 vs. 70.0%), which did not reach statistical significance [54]. The lack of decline in the PPV from one modality to the next in this study may be secondary to emphasis on consistency. Radiologists participating in the study had to undergo additional training in interpretation in order to keep consistency among all study centers.

Another major concern is the time needed to perform the screening ultrasound examination. Depending on the number of pathological findings and the patient's breast size, the time to perform screening with handheld ultrasound can range from 3 minutes and 59 seconds [55] to 4 minutes and 39 seconds [49]. In both studies, the screening ultrasound was performed by an experienced radiologist, alleviating operator variability. Ultrasound, which relies on the examiner's experience and acquisition and interpretation of the exam, is operator dependent. In the ACRIN 6666 trial, in order to keep consistency among all study centers, ultrasound scans were performed by the physician per strict protocol. The time it took to perform a bilateral handheld screening ultrasound was on average 19 minutes. Given the long acquisition times and the limited number of trained personnel, real world implementation would be impractical. Thus in recent years, there have been a number of manufacturers that have developed automated whole breast ultrasound systems that may minimizing the aforementioned time constraints and improving the through-put of the patient.

Automated whole breast ultrasound systems were approved on the premise that they could improve efficiency in the diagnostic and screening setting. Some manufacturers have attached a computer-guided articulating arm to the existing 4 cm transducer, while others have distinguished themselves with a larger 15 cm transducer (Invenia, GE healthcare; Acuson S2000, Siemens healthcare) that can methodically map and image the breast in a reproducible way. The use of automation allows for images to be obtained of the entire breast in under 5 minutes. Images obtained with the larger transducer can be reconstructed in multiple planes with the potential to decrease false positive findings and improve diagnostic accuracy. All systems have software to generate a cine loop of the images to be reviewed by the radiologist which can be read at time of completion or at a later time and date. Authors of the Somo-Insight multicenter study, assessed outcome measures using automated whole breast ultrasound and found an overall improvement in cancer detection rate of 1.9 per 1000 women screened, similar to prior single institution studies yet PPV was significantly reduced [56] (**Figure 17**, **Tables 1** and **2**).

Figure 17. Handheld (left) vs. automated whole breast ultrasound (right).

Study	No. of Cancers	No. of Women	Incremental Cancer Detection Rate (per 1000)	PPV_3 (%)	Comments	Country and Year
Single Institution						
Girardi et al [70]	41	22131	1.9	–	Women were at average risk. CDR for dense breasts – 2.2, nondense breasts – 1.6, AVG RISK	Italy, 2013
Parris et al [71]	10	5519	1.8	5.5	Women were at average risk.	US, 2013
Hooley et al [50]	3	935	3.2	6.5	Women were at average risk.	US, 2012
Leong et al [72]	2	141	1.4%	14.3	Reported CDR. Included women at increased risk.	Singapore, 2012
De Felice et al [73]	12	1754	6.8	6.4	Women were at average risk.	Italy, 2007
Brancato et al [74]	2	5227	0.4	3.2	Women were at average risk.	Italy, 2007
Leconte et al [75]	16	4236	3.8	–	Included nondense breasts, palpable lesions, diagnostic exams, and women at increased risk.	Belgium, 2003

Study	No. of Cancers	No. of Women	Incremental Cancer Detection Rate (per 1000)	PPV_3 (%)	Comments	Country and Year
Crystal et al [76]	7	1517	4.6	18.4	Included women at increased risk.	Israel, 2003
Kolb et al [49]	33	4897; 12193 exams	2.7	10.3	CDR based on patients with normal mammogram and dense breasts. Included scattered fibroglandular tissue and women at increased risk.	US, 2002
Kaplan [77]	6	1862	3.2	11.8	Included women with focal abnormal mammographic findings or palpable lesions	US, 2001
Buchberger et al [78]	32	8103	3.9	8.8	Included scattered fibroglandular tissue, CDR based on patients with normal mammogram and nonpalpable lesions	Austria, 2000
Maestro et al [79]	2	350	5.7	13.3	Included women at increased risk. Solid mass incidentally detected in 14% of patients.	France, 1999
Multi-Institution						
Ohuchi et al [53]	67	36752	1.8	–	Women were at average risk.	Japan, 2016
Weigert and Steenbergen [51]	28	8647	3.2	6.7	Women were at average risk.	US, 2012
Berg et al [42]	32	7473	4.3	5.9	1st year US screen – 2659 women, 2nd year US screen – 2493 women, 3rd year US screen – 2321 women, 612 women had MR screen after 3rd US screen. Included women at increased risk.	US, 2012
Corsetti et al [48]	21	8865; 19728 exams	1.1	–	CDR based on negative screening exams. Women were at average risk.	Italy, 2011
	37	9157	4.0	5.9	Women were at average risk. 13/50 cancers found were excluded due to symptoms/ palpable lesion	Italy, 2008
Schaefer et al [80]	116	59514; 62006 exams	1.9	5.2	Included nondense breasts and women at increased risk.	Germany, 2010

Table 1. Incremental cancer detection rate of handheld ultrasound.

Study	No. of Cancers	No. of Women	Incremental Cancer Detection Rate (per 1000)	PPV_3 (%)	Comments	Country and Year
Single Institution						
Wilczek et al [81]	4	1668	2.4	33.3	Decreased PPV3 for mammography + ultrasound. Included women at increased risk.	Sweden, 2016
Giuliano et al [82]	42	3418	12.3 (Mammography + ABUS)	–	CDR for mammography alone – 4.6. Women were at average risk in the test group.	US, 2012
Multi-Institution						
Brem et al [56]	30	15318	1.9	–	SomoInsight Study – Increased sensitivity and recall rate associated with a decreased specificity and PPV3. Included women at increased risk.	US, 2015
Kelly et al [83]	23	4419; 6425 exams	3.6	38.4	Included women at increased risk	US, 2010

Table 2. Incremental cancer detection rate of automated breast ultrasound.

7. Future directions in breast ultrasound

Innovations in ultrasound technology have improved our ability to detect and diagnose breast cancer. Computer-aided detection (CAD), elastography, quantitative breast ultrasound technology, and ultrasound contrast agents (microbubbles) were developed to improve diagnostic accuracy. These advancements have the potential to impact overall survival by detecting cancers that are smaller and less aggressive.

7.1. Computer-aided detection

To date, there are a limited number of computer-aided detection (CAD) systems approved by the Food and Drug Administration (FDA) for ultrasound. CAD for ultrasound is analogous to CAD for mammography in that it can improve the overall diagnostic performance of the interpreting radiologist. The software will interpret regions of interests marked by the radiologist for further characterization—providing anatomical shape and potential for malignancy based on the ACR BI-RADS Lexicon. Similar to other modalities, the radiologist can accept or reject the analysis based on his or her interpretation. Interpreting automated whole breast ultrasound images has also demonstrated an improvement in overall specificity and differentiation of true and false positive findings with the use of computer-aided detection [57].

7.2. Elastography

Elastography can help differentiate normal tissue from adjacent tumors improving specificity and diagnostic performance, and is routinely incorporated into the ultrasound equipment. The two most frequently used elastography techniques in the breast are strain elastography and shear-wave elastography [58]. Shear-wave technology is reported to be highly reproducible [59] unlike strain elastography which can have a significant amount of interobserver variability [60]. Both techniques are used in conjunction with B-mode ultrasound, but differ in how they measure tissue stiffness. Shear-wave technology uses an impulse produced by a focused ultrasound beam to measure propagation of speed within the tumor and surrounding tissue, quantifying the stiffness in kilopascals. The quantitative estimates in stiffness are independent of the morphologic features of a mass. In contrast, strain elastography determines the underlying elasticity of the lesion by repeated manual compression of the transducer (strain) over a lesion. Both techniques can improve specificity of ultrasonography (US) breast masses without a reduction in sensitivity. However, the sensitivity and specificity of strain and shear-wave elastography can differ based on the underlying pathology and grade of a tumor [58, 61].

7.3. Quantitative breast ultrasound

Quantitative breast ultrasound measures the transmission and speed of sound through the breast. Images are obtained using a ring transducer that emits acoustic transmissions through the breast, receiving information on the attenuation and transmission of sound through the breast. In addition, the reflective (analogous to b-mode images) properties of the fibrous stroma of the breast is evaluated. The transmission data that is acquired is used to construct a cross-sectional tomographic image. Dense tissue tends to have high transmission and attenuation of sound (characterized as white on the tomographic image), while fatty tissue demonstrates low-sound speed and low attenuation (appears as dark on the tomographic image). Given these parameters some authors have suggested that it can provide a surrogate measure of breast density [62]. Others suggest that it can improve specificity by determining solid masses from complicated cysts [63].

7.4. Contrast enhanced ultrasound of the breast

Early published work documents the improved visibility and visual intensity of Doppler signals with the use of ultrasound contrast agents (microbubbles) at the size of 100 um or less [64]. This work has led to more recent developments that can quantify tumor neovascularity using contrast agents (microbubbles) at the size of 1–8 um. Contrast-enhanced ultrasound imaging is based on the principle of acoustic excitation of the microbubbles which produces nonlinear frequency components that can be received at the transducer. The differences in the received signal relative to the transmitted signal produces what is called harmonic imaging. Signals identified below transmission are called subharmonic emissions which can be differentiated from the inherent tissue signals allowing for improved visualization of tumor angiogenesis [65]. Additional studies have investigated the use of certain algorithms using ultrasound contrast agents to quantify breast vasculature, density, and perfusion patterns [66–68]. This novel approaches to differentiating between benign and malignant lesions and promises to improve overall diagnostic accuracy.

8. Summary

The role of breast ultrasound has evolved over the last 50 years, progressively gaining recognition as a diagnostic tool. Current and future applications of this modality can assist the radiologist in improving sensitivity, specificity, and differentiation between benign and malignant findings. The prospect of ultrasound-guided minimally invasive therapy to target breast cancer tumor angiogenesis with therapy-bound microbubbles is an exciting prospect, and one that may be on the horizon for future clinical implementation [69]. Ultrasound provides a significant contribution in the management of breast cancer and will continue to be considered as an indispensable diagnostic and screening tool.

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Chapter 3

High-Risk Breast Lesions

Azlena Ali Beegan and Gozie Offiah

Additional information is available at the end of the chapter

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Abstract

It is well known that certain types of pre-malignant lesions can predispose some women to increased risk of breast cancer. These certain types of pre-malignant lesions are generally classified as high-risk breast lesions. These lesions become invasive cancers in about 15% of patients and hence the management and treatment of these lesions warrant a significant discussion. There are several categories of these lesions, to include atypical hyperplasia of the breast (atypical ductal hyperplasia and atypical lobular hyperplasia); carcinoma in situ (ductal carcinoma in situ and lobular carcinoma in situ); columnar cell pre-malignant lesions; lobular intraepithelial neoplasia (LIN III); radial scar/complex sclerosing lesion; sclerosing adenosis and papillary lesions of the breast. These lesions are morphologically, radiologically, histologically and clinically heterogeneous and early identification can help to prevent progression to invasive cancers. The management of these lesions has been debated internationally for years by experts as to the best treatment modality with surgical excision of the lesion often not considered necessary. It is thus important to evaluate each patient on an individual case-by-case basis. The characteristics of these high-risk breast lesions are further discussed in this chapter.

Keywords: breast cancer, in-situ carcinoma, atypical hyperplasia, pre-malignant, breast lesions, mammogram, breast ultrasound

1. Introduction

Breast cancer is the most common cancer diagnosed in women worldwide [1]. It is the fifth most common cause of death from cancer worldwide but is the second most common cause of death in developed countries [1]. The mortality rates up to 5 years after diagnosis is higher in the less developed countries compared to more developed countries specifically in Europe and North America [1]. Breast lesions can be divided into benign or non-proliferative, high risk or pre-malignant and invasive or infiltrating breast lesions [2]. Benign or non-proliferative

breast lesions are non-cancerous breast lesions that can occur in any anatomical structure of the breast and can present symptomatically or as an incidental finding on imaging or histological findings [3]. Types of benign breast lesions include mammary duct ectasia, mastitis, fat necrosis, benign cysts, breast abscess, epithelial-related calcifications, non-sclerosing adenosis, benign intraductal papilloma, breast haematoma, lipoma, fibroadenoma, periductal fibrosis and gynaecomastia (in men) [3]. Invasive breast cancers are a group of heterogeneous malignant breast lesions that originate from breast epithelial cells and invade surrounding breast tissue as well as having the potential to metastasise via lymphatics and blood to distant sites [4]. Invasive or infiltrating breast cancers tend to commonly involve the ducts and lobules of the breast [4]. These include the invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), which comprise of around 80 and 10% of the total invasive carcinoma types respectively [2]. The other less common types of invasive breast carcinomas (~10% of all breast cancers) include medullary, mucinous, tubular, inflammatory, papillary, adenoid cystic, apocrine, lymphoma, sarcoma, phyllodes and Paget's disease of the nipple [2].

This chapter will primarily focus on high-risk or pre-malignant breast lesions. High-risk or pre-malignant breast lesions are breast lesions that have the potential to become malignant but the risk and time to progression is variable in each lesion [5]. These lesions are usually asymptomatic and are detected incidentally on breast imaging in the majority of cases [6]. Some of the more proliferative lesions (e.g. DCIS) may present with symptoms [6]. Types of high-risk breast lesions include atypical ductal hyperplasia (ADH), atypical columnar cell hyperplasia/columnar alteration with prominent apical snouts and secretions (CAPSS), ductal carcinoma in situ (DCIS), atypical lobular hyperplasia (ALH), lobular intraepithelial neoplasia (LIN III), lobular carcinoma in situ (LCIS), radial scar/complex sclerosing lesion, sclerosing adenosis, papillary lesions of the breast and flat epithelial atypia [5, 7].

In an attempt to classify breast lesions to determine the lesions that have a high relative risk of becoming malignant, Page categorised breast lesions based on morphological features into four categories [20]. The first category included non-proliferative lesions (no increased risk) such as florid adenosis, apocrine change, mild epithelial hyperplasia of usual type and duct ectasia [20]. The second category included epithelial proliferative lesions without atypia (1.5–2 times increased risk) such as moderate/florid hyperplasia of usual type or papillomatosis [20]. The third category consists of atypical hyperplastic lesions (4–5 times increased risk) such as ADH and ALH [20]. Finally the fourth category is lesions considered to be carcinoma in situ and high-risk lesions (8–10 times increased risk), which include DCIS and LCIS [20]. This criterion is still referred to by pathologists to classify breast lesions based on their histology.

2. Types of high-risk breast lesions

2.1. Atypical hyperplasia of the breast (ADH and ALH)

2.1.1. Atypical ductal hyperplasia (ADH)

Atypical ductal hyperplasia (ADH) is a pre-malignant lesion of the breast that carries a four to five times increased risk of developing carcinoma of the breast in the general population [8].

Several previous studies showed that the cumulative risk for developing invasive breast cancer is approximately 13% over a duration of up to 25 years post diagnosis of ADH [9–11]. This risk is doubled in women with a family history of breast cancer in a first-degree relative [8]. Over half of the breast cancers that develop from ADH are moderate or high grade and usually involve the ducts on histology [11]. Of the invasive breast cancers, 25% tend to be node-positive and over 80% being oestrogen receptor (ER) positive [11]. These cancers are also more likely to develop on the same breast that had ADH as opposed to the contralateral side [11]. Menopausal status of patients with ADH was also considered in determining the risk of developing invasive cancer. Some authors report that the risk is greater in premenopausal women with atypical hyperplasia [12]; while others suggested that this may only be relevant in ALH but not in ADH and that this risk was modified once the patient approaches menopause [13]. A more recent study done in 2017 showed a reduction of the cumulative risk to two times the risk of developing invasive breast cancer 10 years after the diagnosis of ADH [14]. This study was performed on a cohort of 955,331 women of which 2785 were diagnosed with ADH following either a core needle biopsy (CNB) or excisional breast biopsy (EBB) [14]. The results from this study showed a reduction in the risk of developing invasive breast cancer at 10 years following an ADH diagnosis to 5.7–6.7% [14].

It has been shown that ADH and DCIS have very similar characteristics histologically. Often it has been difficult to distinguish between ADH and DCIS especially on smaller tissue samples such as those obtained from fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) [15]. Hence, the most accurate method for diagnosis is by excisional biopsy of the entire lesion [15]. ADH is described histologically as lesions with structurally complex patterns formed from the expansion and filling of breast ducts with the proliferation of monotonous epithelial cells and the presence of secondary lumens [16]. Its features are very similar to DCIS on radiological investigation and can be difficult to distinguish using imaging and CNB only [16]. On mammography, a cluster of calcifications may represent ADH [17]. Atypical hyperplasia diagnosis is confirmed in up to 10% of all the CNB performed on these calcifications [17]. Its features are similar to DCIS on ultrasonography and appears as a mildly hypoechoic microlobulated mass with normal acoustic transmission [18]. There is also a higher rate for an inaccurate diagnosis by using only an ultrasound-guided CNB instead of an excisional biopsy [19]. Studies have shown that more than half of the ADH diagnosed using this technique yielded a malignant pathology on surgical excision [19].

Page had previously categorised breast lesions based on morphological features into four categories based on the risk of developing malignancy [20]. To assess if these categories of diagnosing pre-malignant breast lesions are reproducible, a study was performed evaluating the inter-observer variation in the diagnosis of various pre-malignant ductal breast lesions including non-atypical ductal hyperplasia, ADH and DCIS [21]. Pathologists in the study followed strictly to Page's standardised criteria [20]. The study concluded that there were no significant inter-observer differences in forming the diagnosis of these lesions and if adhered to, the standardised diagnosis criteria can be a useful tool [20, 21]. However, despite these classifications, some pathologists argue that the interpretation of ADH and DCIS lesions are still subjective as histologically these lesion are very similar despite being quantitatively different as ADH involve less than two ducts in the breast [22].

ADH is usually diagnosed with a CNB; however, due to the small quantity of samples obtained, a DCIS or invasive carcinoma are unable to be excluded as previous studies have shown that ADH may exist alongside DCIS and invasive cancer [23]. A study done by Gadzala et al. confirmed this notion as they found in 36 patients that had a diagnosis of ADH on stereotactic CNB, 17 patients (47%) were confirmed to have DCIS or IDC after EBB was performed [23]. Therefore, excisional breast biopsy (EBB) was found to be the best option to confirm the ADH diagnosis and outrule ductal carcinoma [23]. In contrary, some researchers believed that it was unwarranted to perform EBB when the more improved techniques of CNB used larger gauge needles (9-, 11- or 14-gauge) and has the potential to diagnose as well as treat ADH without the need for EBB [24]. They suggested that ADH with fewer than three foci and the complete removal of calcifications on biopsy was adequate and prevented the need for EBB in some patients, which has some cosmetic deformity consequences as well as the unnecessary risk of undergoing a surgical procedure [24]. Nevertheless, the clinical recommendation for the definitive management of ADH still remains as EBB despite the improved CNB techniques as the percentage of underestimation of cancer after an ADH diagnosis can carry a risk of over 10% [11, 15].

2.1.2. Atypical lobular hyperplasia (ALH)

Another type of atypia that can be found in the breast is atypical lobular hyperplasia (ALH). Similar to ADH, its risk of developing future breast cancer is high (4–5 increased risk compared to women with no atypia), hence ALH is also categorised as a pre-malignant breast cancer [8]. Page et al. had previously reported that the high risk may be due to the involvement of ducts in some ALH lesions; however, if there is no ductal involvement, the risk is reduced to 2.7 [25]. The risk of developing breast cancer with a prior ALH lesion is higher in pre and perimenopausal women (aged 46–55) and reduced in the postmenopausal cohort, conversely, menopausal status has no bearing on ADH risk of breast cancer as both pre and post menopausal women have similar risk scores [13]. The cumulative risk for developing invasive breast cancer is approximately 18% over a duration of up to 25 years post the diagnosis of ALH, which is higher than the risk seen with ADH [9–11]. Previous studies have also shown that ALH tend to develop into moderate or high grade breast cancers and has an increased risk when associated with a strong positive family history of breast cancer as similarly observed in patients with ADH diagnosis [11]. ALH has not only been associated with the occurrence of future ipsilateral breast cancer but also with contralateral breast cancers [26].

ALH is usually asymptomatic and may be found incidentally using breast imaging; however, the majority of ALH are found as an association to mass lesions like fibroadenomas, radial scars, ADH, intraductal papillomas, pleomorphic LCIS or DCIS following a CNB [26]. If seen solitarily, these lesions appear as clustered calcifications and can be difficult to diagnose using the imaging modality alone as its characteristics on a mammogram are similar to other pre-malignant breast conditions [26].

ALH and LCIS have morphologically similar findings and have been termed collectively as lobular neoplasia (LN); however, they differ primarily based on the filling of the lobular unit and the degree of proliferation [27]. The histology of ALH obtained from either a CNB

or EBB (if associated to another mass lesion) shows the filling of the acini in the lobular unit with monotonous, small, round, cuboidal or polygonal cells with a loss of acinar lumens [16]. The diagnosis of ALH can be obtained following Page's criteria based on the morphology of breast lesions [20]. ALH falls into the third category, which also consists of ADH [20].

Multiple studies have been carried out to determine the most suitable management option for ALH. The diagnosis of ALH was made using stereotactic CNB or EBB if another pre-malignant lesion was present [16]. The perplexing issue with ALH is whether the need for management via a surgical excision is justified when it presents on its own in a CNB specimen or if it presents alongside a benign lesion on an EBB sample. The management of ALH diagnosed on CNB has remained controversial as there are conflicting opinions. A study performed by Bauer et al. divided the diagnosis of LN observed into three groups coexisting with other breast pathologies, which comprised of DCIS or invasive cancer (Group 1), ADH, phyllodes tumour, radial scar or intraductal papilloma (Group 2) and benign fibrocystic changes (Group 3) [28]. They concluded that LN in the absence of breast cancer or pre-malignant conditions (Group 1 and 2) do not need EBB [28]. Other authors had similar recommendations as patients with ALH alone or in association with benign breast disease were not associated with breast carcinoma (<8% associated with cancer) and were not deemed high risk; hence, the residual microcalcifications did not require a further EBB [29]. In addition to this, it was suggested that if strict radiographic-pathologic correlation and histologic criteria are adhered to, then the patients who do not require EBB, should be closely monitored with regular clinical follow-up and breast imaging (mammogram, ultrasound, MRI breast) [26, 30]. Another study contradicted this recommendation as they found that 17% of the patients with LN developed either DCIS or invasive carcinoma [31]. Of the ALH cohort of 20 patients, 2 developed DCIS, hence only the LCIS cohort developed invasive carcinoma [31]. Nevertheless, the group suggested that due to the high percentage of patients with cancer after the diagnosis of LN, an EBB is warranted [31]. Supporting this recommendation, other studies performed using CNB also found that LN lesions had a higher risk for developing breast cancer and an underestimation of 8–19% if CNB alone was performed without a completion EBB [32, 33]. To further stratify the exact criteria of ALH or LCIS (LN lesions) that warranted surgical excision, histologic findings of these lesions with more than 1 lobule per core involvement were considered to be diffuse lobular neoplasia while those with 1 or less lobules affected in each core (focal lobular neoplasia) did not require full excision [34]. In summary, ADH and ALH are radiologically difficult to diagnose as they have features similar to DCIS and LCIS respectively and thus are best diagnosed and managed by excisional breast biopsy (EBB).

2.2. Carcinoma in situ of the breast (DCIS and LCIS)

2.2.1. Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ (DCIS) are pre-malignant breast lesions that can present both symptomatically and asymptomatically as an incidental finding on breast imaging. It accounts for up to 30% of breast cancer lesions detected on mammography [35]. These numbers have risen significantly following the introduction of screening mammography as compared to previous diagnosis of DCIS, which comprised of only 0.8–5% of all breast cancers primarily diagnosed

clinically due to symptomatic DCIS [6, 35]. It represents a premalignant proliferation of malignant epithelial cells in the lumen of the breast ducts that have not invaded the basement membrane and retains its myoepithelium layer [36]. DCIS may present with symptoms of a palpable breast lump, nipple changes and discharge or asymptomatically for smaller sized lesions seen on mammography, which has been associated with a higher risk for the development of invasive carcinoma and treatment failure [6, 37]. The risk of invasive cancer in patients diagnosed with DCIS on CNB is 11-fold and vary from 17 to 50% depending on the type of DCIS lesion as the invasive cancers tends to occur in the same location as the DCIS lesion [38, 39]. DCIS is associated with similar risk factors to that of invasive breast cancer such as increasing age (peak at postmenopausal age), family history of breast cancer, nulliparity or late first pregnancy after the age of 30 and the use of hormone replacement therapy [40].

Radiologic findings account for the majority of DCIS detection. The majority of DCIS lesions appear as microcalcifications on mammography [41]. However, they can also present as circumscribed masses or focal nodular patterns [41]. Screening mammography has led to the early diagnosis and investigation of breast cancer lesions. The early implementation of the appropriate management of breast cancer has reduced mortality rates by 30% [42]. This is relevant in the case of DCIS lesions as a large percentage of the higher grade lesions have potential to become invasive and early diagnosis and management is key to reduce this risk [42]. A focused ultrasound can also be carried out once a lesion is detected on mammography to further evaluate the characteristics of the lesion and can aid in the CNB of the lesion [43]. Typical findings representing DCIS on ultrasound include features of a microlobulated irregular mass with no acoustic shadowing [43].

As mentioned previously, DCIS and ADH have similar morphology [15]. However, DCIS lesions are more proliferative and can be diagnosed based on CNB [44]. DCIS are localised lesions that usually present in one quadrant of the breast and can be as larger as 5 cm in size [44]. It can be classified based on its size, nuclear grade, architectural subtype and the presence of necrosis following the 2009 College of American Pathologists/American Society of Clinical Oncology protocol [45]. The nuclear grades are subdivided into low (Grade I), intermediate (Grade II) or high grade (Grade III) [45]. High grade DCIS is comprised of proliferative large pleomorphic cells with abundant normal and abnormal mitoses [36]. Intermediate grade DCIS have similar characteristics of both high and low grade DCIS with an intermediate degree of pleomorphism [36]. They tend to present more commonly as a solid cribiform pattern [36]. Low grade DCIS has small cells that are in a uniform pattern [36]. Architectural subtypes include comedo, Paget's disease of the nipple, cribriform, micropapillary, papillary and solid patterns (listed in increasing order towards a higher grade subtype of DCIS) [45]. DCIS lesions was also found to have varying risk of developing invasive breast cancer based on genetic alterations and receptor status of the lesion with a majority of lesions exhibiting ER positivity on immunohistochemistry staining [37, 44]. Palpable DCIS lesions were more commonly associated with negative ER and PR status, which confirms its association to a higher grade DCIS and leading to more aggressive phenotype compared to DCIS found incidentally on screening [37].

As with other pre-malignant disease of the breast, the diagnosis of DCIS warrants further management with either surgery and/or other adjuvant treatments due to its nature to progress to

invasive malignancy [46]. Multiple trials have been carried out to determine the effectiveness of these treatments in the prevention of recurrence after DCIS diagnosis [46]. The options for the surgical management of DCIS consist of mastectomy of the affected breast or breast conserving surgery such as wide local excision (WLE) [46]. Suitability for either type of surgery is based on the grade of the lesion and presence of microinvasion, the patient's age at diagnosis and pre-existing co-morbidities (life expectancy) as these may influence the decision to perform a more definitive surgery like mastectomy instead of WLE due to the risk of having to re-excise the margins and the chance of local recurrence [46]. Rutter et al. reported on the increasing use of mastectomy as a treatment of DCIS especially in patients with higher grade DCIS and younger age [47]. This was due to the increased risk of recurrence and development of invasive breast cancer. Other authors have reported the effectiveness of nipple-sparing mastectomy in comparison with mastectomy whereby the probability of local recurrence was similar and low in the case of DCIS treatment [48]. However, these results were not similarly replicated favourably when the breast conserving treatment of DCIS was used as a solitary treatment modality. The RTOG 9804 trial was conducted to evaluate the effectiveness of breast conserving surgery (BCS) with or without adjuvant radiotherapy in patients diagnosed with low or intermediate risk DCIS on CNB [49]. Results showed a low risk for recurrence with BCS alone at 6.7%; however, this was significantly lower in the adjuvant radiotherapy arm at 0.9% recurrence risk [49]. This opened up the possibility of DCIS subtype with good prognosis to be considered for BCS treatment alone without further adjuvant therapy; however, the authors concluded that a longer follow-up time of more than 7 years was required to give more reproducible results as the BCS and adjuvant radiotherapy cohort had much better response [49]. In contrary to this, other studies have not yielded promising results as patients treated with BCS alone had recurrence rates of approximately 14–16%, despite the stratification of patients into the low risk DCIS category [50, 51]. Conflicting evidence has been reported regarding the need for sentinel lymph node biopsy (SLNB) in the treatment of DCIS. Some studies suggest that SLNB should not be part of the standard surgical treatment of all subtypes of DCIS as the percentage of positive SLNB range from 1 to 22% with majority of the studies reporting a lower percentage of positive findings, hence rendering it unnecessary [52]. Furthermore, some authors argue that performing a SLNB in these patients could disrupt the diagnosis of future lymphatic spread in the case where invasive carcinoma occurs [53]. The general consensus surrounding the addition of SLNB as part of the surgical treatment of DCIS is to be only reserved for those lesions with high grade of DCIS exhibiting microinvasion, large lesions of more than 5 cm in size, lesions treated with mastectomy and DCIS subtypes with high risk of developing invasive cancer [52, 53].

2.2.2. Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ (LCIS) is similar in histology to ALH; however, it is more extensive and proliferative compared to ALH [27]. It is on the higher spectrum of lobular neoplasia (LN) [27]. LCIS lesions are usually diagnosed incidentally via breast imaging such as through mammographic screening or are detected incidentally as part of a CNB or an EBB for another breast lesion diagnosis [54]. LCIS is a pre-malignant lesion that has a 15% risk of developing subsequent invasive carcinoma (IDC and ILC) on the ipsilateral breast, as well as a 9% risk

of developing invasive carcinoma on the contralateral breast (mostly ILC) [27, 55, 56]. Its estimated incidence is varied between 0.5 and 3.8% as it is most often overlapped with other premalignant or invasive lesions in the breast [57–59]. The risk of DCIS or invasive carcinoma after the diagnosis of LCIS is 17% at 15 years post diagnosis of LCIS with a relative risk of 8–10 [59]. Similarly to ALH, LCIS may be affected by menopausal status. Its incidence was observed to be higher in premenopausal women with only 10% incidence in postmenopausal women, suggesting it may be affected by reproductive history such as age at the birth of first child and ovarian function status [8, 60].

Due to the majority of LCIS being detected incidentally on CNB, it is difficult to characterise its possible findings on breast imaging. A retrospective study evaluated the appearance of LCIS on breast imaging after the diagnosis was confirmed on CNB in an attempt to define the characteristics of LCIS [61]. They described the mammographic findings of LCIS as micro calcifications [61]. Choi et al. used ultrasound imaging to characterise the feature of LCIS and described it as ill-defined, asymmetrical, elongated or round lesions with hypoechogenicity [62].

Histological findings of LCIS are well defined on CNB. LCIS morphology consists of type A and B cells [27]. The type A cells have a smaller sized nuclei compared to the larger and more pleomorphic type B cells that are usually polygonal, cuboidal or round shaped [27]. These cells fill and expand more than half of the acini in the lobular unit with loss of central lumina, which differentiates it from the features of ALH [27, 61]. There has been an ongoing debate whether CNB is sufficient to diagnose LCIS without further EBB. Murray et al. performed a prospective study that investigated the underdiagnoses rate of LN (LCIS and ALH) in samples obtained from their institution over 5 years [63]. When there was radiologic and histologic discordance, 50% of samples diagnosed as LCIS by CNB turned out to be DCIS on EBB [63]. However, when there is radiologic and histologic concordance, there were no underdiagnosed LCIS lesions by CNB [63]. They compared their results with previous studies and discovered that the underdiagnoses risk of DCIS or invasive carcinoma in samples that had radiologic and histologic disconcordance is significant in ~38–67% of CNB samples diagnosed as LCIS [63].

The management of LCIS is another controversial issue due to its low incidence and lack of distinguishing mammographic findings, as well as its incidental co-diagnosis with other breast lesions such as DCIS and IDC [58, 59]. Conflicting opinions have risen with some indicating that surgical excision is unnecessary, while others disagree and recommend the excision of LCIS is crucial to prevent future development of invasive carcinoma. Nagi et al. agreed with the recommendation that type A cell LCIS lesions should be treated conservatively. The reasoning is that the cohort of patients with this type of lesion, who did not have surgical excision, did not develop progressive disease up to 8 years of follow-up [26]. The authors rationale was that as long as strict criteria were followed histologically and close monitoring were performed radiologically, surgical excision did not provide further benefit in these type A lesions [26]. The type B cell LCIS lesions have poorer prognosis compared to type A, hence will require surgical excision [26]. Similar to the management of ALH, lesions diagnosed, as LCIS also did not require surgical excision unless associated or is adjacent to other co-existing more aggressive premalignant or malignant breast lesions or in the case where there is discordance between radiologic and histologic diagnosis [28]. In more aggressive forms of LCIS

that can present in the contralateral breast, some studies have recommended the option to manage LCIS by bilateral prophylactic mastectomies as part of a risk reduction surgery [64]. However, the decision to follow through with these surgeries required meticulous discussion with a multidisciplinary team (MDT) to assess the patient's risk of future carcinoma and the best management plan for the patient [64].

2.3. Columnar cell pre-malignant lesions of the breast

Types of columnar cell pre-malignant lesions of the breast include columnar alteration with prominent apical snouts and secretions (CAPSS; also known as columnar cell lesions: CCL) and flat epithelial atypia (FEA; also known as CCL with atypia) [65]. Fraser et al. described a type of breast lesion that had similar features on imaging to ADH and DCIS [66]. Although the lesion on imaging did not appear benign, it could not be classified specifically as either ADH or DCIS on histology as it lacked some features that can confirm these diagnoses [66]. These spectra of lesions were described as architecturally complex lesions that exhibited columnar epithelial cells with prominent apical cytoplasmic snouts and intraluminal secretions, which may or may not have nuclear atypia lining the terminal duct lobular unit (TDLU) [66]. This group of lesions were therefore named as columnar alteration with prominent apical snouts and secretions (CAPSS) [66]. CAPSS lesions lie on a spectrum depending on the atypia of the cells and were routinely diagnosed on ultrasound-guided CNB [67]. Studies have shown that CAPSS lesions with atypia closely resembled DCIS and had a higher risk of association with invasive cancer when compared to CAPSS lesions without atypia [67]. CAPSS and FEA lesions are described as clustered microcalcifications that may have amorphous or fine pleomorphic features located in the TDLU on mammography [68]. Again, these features are similar to other pre-malignant disease such as ADH and DCIS, hence it is difficult to diagnose without a CNB [68]. FEAs are observed histologically as dilated basophilic acini, which consists of layers of cuboidal to columnar epithelial cells with low-grade atypia on cytology and distended TDLUs [65, 69].

The presence of CAPSS in the breast was found to increase the risk of breast cancer due to its co-occurrence with other proliferative breast lesions such as DCIS [70]. However, these lesions independently did not confer a high risk of developing breast cancer [71]. FEAs have also been associated with an approximately 20% risk of developing breast cancer and a high underestimation rate for malignancy when diagnosed on CNB due to its similar co-existence with other pre-malignant lesions such as ADH and DCIS [72].

The suggested clinical recommendation for the management of columnar cell pre-malignant lesions of the breast is EBB for both CAPSS and FEA based on radiographic and histologic correlations [67, 72, 73].

2.4. Papillary lesions of the breast

Papillary lesions of the breast are composed of benign and malignant types. The papillomatosis of the breast and atypical papilloma lesions may be considered premalignant due to its association to the development of breast cancer [74]. Pre-malignant papilloma lesions can be

associated with calcifications on mammogram and appear as a homogeneous solid or intracystic lesion that is complex on ultrasound [74]. Clinically, patients with this disease may present with symptomatic findings such as a breast mass or nipple discharge [74]. Histologically, breast papilloma is described as clusters of epithelium in the ducts that develop into branching papillae, which protrude into the lumen [75]. Due to the varying spectrum of pathological findings seen in the papilloma disease of the breast, it is difficult to distinguish between true benign and malignant or premalignant lesions. Multiple studies have shown that the diagnostic technique using either FNA or CNB may be inaccurate as benign findings were often either co-existing with premalignant lesions or were underestimated [75, 76]. The suggested management of breast papillomas diagnosed on FNA or CNB is for active surveillance if there is no atypia and no discordance between imaging and histologic findings [74]. When there is doubt on biopsy or the presence of high-risk papilloma lesions then an EBB is warranted [74].

2.5. Radial scar/complex sclerosing lesion

A radial scar or complex sclerosing lesions of the breast are considered to be pre-malignant breast lesions due to its common association with other more proliferative lesions leading to its increase in breast cancer risk [77]. On mammography, a radial scar/complex sclerosing lesion is described as the presence of radiolucency in the centre of the lesion with spicules that are longer compared to malignant lesions. There is also the presence of radiating radiolucent linear structures and the absence of macrocalcifications [77]. Histologically, radial scars have a fibroelastic core with entrapped ducts and variable surrounding benign epithelial features; however, it can also be associated with atypia usually at the edges of the lesion [78]. The term radial scars was given to lesions smaller than or equal to 1 cm while the term complex sclerosing lesions is larger than 1 cm [78]. There have been various opinions among pathologists and surgeons regarding the most appropriate management of radial scars. Some suggest that a large gauge CNB was adequate to sample radial scars and there was no need for EBB as long as there is no atypia and the radiology and histology correlate [79]. However, other authors still classify radial lesions as high-risk lesions and EBB is the recommend management [79].

3. Adjuvant therapies for the treatment of high-risk breast disease

Adjuvant therapies have been considered in an attempt to reduce the risk of breast cancer following the diagnosis of a pre-malignant breast lesion via CNB or EBB. Several trials have been conducted to determine if adjuvant radiotherapy and/or endocrine therapy may be useful as a measure to reduce this risk [80].

Trials involving the use of adjuvant radiotherapy were performed on pre-malignant carcinoma in situ lesions, predominantly, DCIS. Adjuvant radiotherapy used in a study involving patients with BCS following a DCIS diagnosis, yielded promising results as there was a significant risk reduction compared to the control group especially in the postmenopausal patient cohort [81]. A meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluating the results from four randomised clinical trials

involving adjuvant radiotherapy in the management of DCIS showed that radiotherapy after BCS was successful in reducing the absolute risk of developing ipsilateral DCIS recurrence and invasive breast cancer development by 15% in the 10 year follow-up duration [80]. As similarly seen in the previous study, a greater risk reduction was seen in postmenopausal women and that radiotherapy did not have a significant effect on the contralateral breast or on distant metastatic occurrence [80]. This led to the suggestion that the patients receiving adjuvant radiotherapy as part of the BCS treatment of DCIS should be further stratified to avoid unnecessary exposure to radiotherapy, which carries its own risks [80]. The EORTC 10853 Randomised Phase III Trial further confirmed the benefit of adjuvant radiotherapy as it reduced the risk of any local recurrences after an EBB of DCIS by almost half (48%) after a 15 year follow-up [82]. The treatment of LCIS with adjuvant radiotherapy has not been explored to the same extent as DCIS lesions. A small study carried out with 25 patients treated for LCIS lesions with lumpectomy and radiotherapy reported promising findings as only 1 patient had a local recurrence after a median follow-up of 153 months [83].

Apart from radiotherapy, multiple studies have been performed to explore the effects of oral selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) as part of a preventative measure to reduce the risk of developing breast carcinoma as well as an adjuvant treatment following EBB or BCS of DCIS lesions [84–86]. The randomised International Breast Cancer Intervention Study (IBIS-I) trial was not aimed specifically at women with a known diagnosis of DCIS but was targeted for women with an increased risk for the development of DCIS and invasive breast cancer [85]. The trial reported the benefit of prophylactic tamoxifen in high-risk women leading to a 34% reduced risk of developing invasive cancer [85]. The benefit of tamoxifen was also found to outweigh the risk in this subset of high-risk patients [85]. Although this study was not investigating the adjuvant treatment of DCIS, however, the rationale of this study can still apply to the management of this disease. Most patients have a high risk of developing invasive cancer after a DCIS diagnosis and may benefit from adjuvant treatment with selective oestrogen receptor modulators because of the ER positive nature of DCIS. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and B-24 randomised clinical trials were performed to determine the effectiveness of lumpectomy alone as a surgical treatment of DCIS compared to lumpectomy with adjuvant radiotherapy or tamoxifen therapy [86]. The trial focussed on the long-term prognosis of DCIS with these various treatment combinations and the risk of ipsilateral invasive breast cancer recurrence [86]. The trial reported that the cumulative incidence of ipsilateral invasive breast cancer recurrence (15 year follow-up) was 19.4% for lumpectomy only compared to 8.9% for lumpectomy plus adjuvant radiotherapy while the incidence was 10.0% in the lumpectomy plus radiotherapy combination treatment group compared to 8.5% for the combination treatment of lumpectomy plus adjuvant radiotherapy and tamoxifen [86]. Radiotherapy and tamoxifen therapy were concluded to be effective as adjuvant treatments to lumpectomy to reduce the risk of tumour recurrence [86]. Another prospective cohort study carried out by Thompson et al. over a follow-up period of 62 months reported similar findings to Wapnir et al. with a reduction of risk in developing DCIS recurrence or ipsilateral breast cancer in patients given adjuvant therapy combination with radiotherapy and tamoxifen after BCS [87].

4. Conclusion

High-risk breast lesions vary in the degree of risk of developing either in situ carcinoma or invasive carcinoma. Multi-observer disparities in histology reporting had previously been a concern; however, standardised criteria have been developed to overcome this issue. There is a general consensus that radiologic and histologic concordance is important to formulate an accurate diagnosis to help direct the appropriate treatment regime. The management of high-risk breast lesions is rather confusing and needs to be determined by the risk of developing invasive breast cancer. Risk reduction strategies for these high-risk breast lesions described in this chapter vary from active surveillance to surgical excision in form of an excisional biopsy or a mastectomy with or without adjuvant therapies. These strategies are largely influenced by the patient and the clinicians' decisions.

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Chapter 4

Breast Imaging and Translation into Targeted Oncoplastic Breast Surgery

Michael Friedrich and Stefan Kraemer

Additional information is available at the end of the chapter

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Abstract

Preoperative staging of breast cancer based on breast imaging is mandatory. Breast imaging encompasses mammography, breast sonography and MR-mammography. Earlier diagnosis of breast cancer results in a favourable oncological outcome. Limitations and influences on operative procedures of MR-mammography in diagnosis and staging of breast cancer have to be discussed. Different interventional procedures have been developed. The histological results of interventional procedures guided by ultrasound, stereotactic mammography or magnetic resonance have to be integrated in planning surgical resection margins in oncoplastic breast-conserving surgery. Image-guided wire markings are an important tool for planning these surgical resection margins. This chapter summarises the results of breast imaging, interventional procedures and wire markings for the breast-conserving therapy of breast cancer. Breast imaging and interventional procedures are the basis for a concept of targeted oncoplastic breast surgery.

Keywords: breast cancer, breast imaging, mammography, breast ultrasound, magnetic resonance mammography, oncoplastic surgery, interventional breast diagnostics

1. Breast imaging

Earlier diagnosis of breast cancer results in a favourable outcome. Tumour size at diagnosis and the lymph node stage are the best predictive factors of outcome. As a result, the current strategy for reducing breast cancer mortality is to diagnose the disease as early as possible. Breast imaging is fundamental for the early diagnosis of breast cancer when symptoms occur or during screening programs.

Breast imaging is a general term that encompasses mammography, breast sonography, breast magnetic resonance imaging (MRI) and other technologies. To provide uniformity in the

assessment of breast imaging findings, the American College of Radiologists (ACR) established final assessment classifications [Breast Imaging Reporting and Data System (BI-RADS)] [1–3]. The final assessment categories are as follows: BI-RADS 1, negative; BI-RADS 2, benign; BI-RADS 3, probably benign (risk of malignancy <2%); BI-RADS 4, suspicious abnormality (biopsy should be considered); BI-RADS 5, highly suggestive of malignancy.

BI-RADS 4 and 5 assessments indicate abnormalities that require tissue biopsy for diagnosis. These categories represent a wide range (3–100%) of breast cancer risk.

2. Mammography

Mammography has been the basis of breast imaging for more than 30 years. The sensitivity of mammography for breast cancer is age dependent. The denser the breast, the less effective this method is for detecting early signs of breast cancer. In younger women, breast density tends to be higher, and increased density inhibits the detection of early signs of breast cancer [4]. The sensitivity of mammography for breast cancer in women over 60 years of age is about 95%, while mammography can be expected to detect less than 50% of breast cancers in women under 40 years of age [5]. Mammography is based on X-rays. Consensus is that the benefits of mammography in women over the age of 40 years are likely to far outweigh any oncogenic effects of repeated exposure. Screening of women over the age of 50 by mammography is accepted practice. However, in symptomatic patients with a palpable nodule in the breast, there is even an indication for performing mammography in women under the age of 35 when there is a strong clinical suspicion of malignancy. Practice is changing, and ultrasound is being increasingly used for the assessment of women with focal breast symptoms in this age range. Mammography is performed every 2 years in all women in the screening age group (50 years of age – 69 years of age) attending symptomatic patients who have not had a screening mammogram in the past year. Film/screen mammography has been refined over the years and has now reached the limits of this technology [6]. Film/screen mammography is a difficult technique to maintain at the quality levels required for optimal diagnosis because labour-intensive quality control measures are necessary to maintain the diagnostic standards. Today, digital mammography is the new standard. Major benefits have been predicted from acquiring mammograms in a direct digital format [7]. Compared with conventional mammography, the predicted benefits of full-field digital mammography include better imaging of the dense breast, the application of computer-aided detection and a number of logistical advantages providing potential for more efficient mammography services. The much wider dynamic range of digital mammography means that visualization of the entire breast density range on a single image is easily achievable. In the clinical setting, comparative studies have shown that digital mammography performs as well as film/screen mammography [8–11].

Recent preoperative mammographic evaluation is necessary to determine patient's eligibility for breast-conserving therapy. Mammography defines the extent of a patient's disease, the presence or absence of multicentricity and other factors (extent of microcalcifications) that might influence the treatment decision, and evaluates the contralateral breast. If the mass is associated with microcalcifications, an assessment of the extent of the calcifications

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is performed. Magnification mammography is important for further characterisation of microcalcifications.

Mammography is the basis for stereotactic-guided breast biopsy. Stereotactic biopsy can be carried out using a prone biopsy table or by using an add-on device to a conventional upright mammography unit. This technique is used for biopsy of clinically occult lesions that are not detectable by ultrasound (e.g. microcalcifications) [12].

3. Ultrasound

High-frequency (≥7.5 MHz) ultrasound is a very effective diagnostic tool for the investigation of focal breast symptoms. It has a high sensitivity for breast lesions and also a very high negative predictive value. High-resolution ultrasound easily distinguishes between most solid and cystic lesions and can differentiate benign from malignant lesions with a high accuracy. Ultrasound is the technique of choice for the further investigation of focal symptomatic breast lesions at all ages. Under 35 years of age, when the risk of breast cancer is very low, it is usually the preferred imaging technique. Over 35 years of age, when the risk of breast cancer begins to increase, it is often used in conjunction with mammography. Ultrasound is less sensitive than mammography for the early signs of breast cancer and is therefore not used for population-based screening. However, ultrasound increases the detection of small breast cancer in women with a dense background tissue on mammography [13–15]. In the screening setting, there is currently insufficient evidence of any mortality benefit even in women with dense mammograms. Ultrasound is the preferred technique to guide biopsy of both palpable and impalpable breast lesions visible on scanning [16]. Ultrasound is being increasingly used to assess the axilla in women with breast cancer. Axillary nodes that show abnormal morphology can be accurately sampled by needle core biopsy.

Doppler ultrasound adds additional accuracy to breast diagnosis and is widely used. Three-dimensional ultrasound of the breast also increases the accuracy of biopsy and the detection of multifocal disease but is not widely available [17, 18]. Elastography is a new application of ultrasound technology that allows the accurate assessment of the stiffness of the breast tissue. It is being evaluated at present and may prove to be a useful tool in excluding significant abnormalities, for instance, in assessment of asymptomatic abnormalities detected by ultrasound.

4. Magnetic resonance mammography

Magnetic resonance imaging (MRI) is widely available and used in breast cancer diagnosis. Magnetic resonance mammography (MRM) requires dedicated breast coils. In order to image the breast, the patient is scanned prone, and injection of intravenous contrast (Gd-DTPA) is required. A variety of possible clinical indications for contrast-enhanced MRM have been reported. These include screening for breast cancer, determining the local extent of malignant

disease, identifying an occult primary, assessing response to neoadjuvant chemotherapy, identifying local recurrences after breast-conserving therapy, breast imaging after implant reconstruction or breast augmentation, and the detection of ipsilateral breast cancer in patients presented with axillary lymph node metastases (CUP-syndrome) [19–23].

MRM is the most sensitive technique for detection of breast cancer, approaching 100% for invasive cancer and 60–70% for ductal carcinoma in situ (DCIS), but it has a high false-positive rate [24–28]. Rapid acquisition of images facilitates assessment of signal enhancement curves that can be helpful in distinguishing benign and malignant disease. Breast lesions seen on MRM that are larger than 10 mm can be seen on ultrasound if they are clinically significant (second-look ultrasound). MRM is likely to prove the best method for screening younger women (under 40 years) at increased risk of breast cancer but it is unlikely to be used for general population screening. MRM is the best technique for imaging women with breast implants. It is also of benefit in identifying recurrent breast cancer after breast-conserving therapy where conventional imaging has failed to exclude recurrence. Performed more than 12 months after surgery, MRM will accurately distinguish between tumour recurrence and scars [29, 30]. MRM is being increasingly used to examine women for multifocal or multicentric disease prior to conservation surgery, especially in patients with invasive lobular breast cancer. MRI of the axilla will demonstrate axillary metastatic disease but its sensitivity is not sufficient for it to replace surgical staging of the axilla.

Many questions surrounding the use of MRM of the breast in patients with breast cancer remain unanswered. Just because MRM can detect additional areas of cancer, does it really matter clinically? Should surgical treatment be altered because MRM detects additional foci of cancer, especially in those cases when these areas represent foci of DCIS? Would these additional areas of cancer identified on MRM be successfully treated with postoperative radiation therapy? The rate of MRM-detected multifocal disease, which ranges from 16–37%, is clearly much higher than the rate of in-breast recurrence after breast-conserving therapy, with reported rates in two studies with a 20-year follow-up of 8.8% and 14.3%, respectively [31, 32]. This strongly suggests that in some, and perhaps many cases, the additional foci of cancer identified only on MRM, especially those that prove to be in situ disease, would likely be successfully treated with postoperative radiation. Which MRM-detected multifocal or multicentric cancer would be successfully treated with postoperative radiation and which would not, later presenting as a local "recurrence"? In those cases when MRM detects an invasive cancer that is clearly separate from the primary cancer, either in the same or a different quadrant, should mastectomy be recommended, based on the historical treatment of clinically or mammographically detected multifocal or multicentric cancer, or is the patient still eligible for breast-conserving therapy if the lesion can be successfully excised with negative margins [33]? There are additional questions concerning patient selection. Which are the patients at the highest risk for having multifocal or multicentric cancer who would benefit most from MRM (young patients, patients with dense breasts, patients with lobular cancer)? Based on the current success of breast-conserving surgery, it is unlikely that MRM of the breast is warranted in all patients with newly diagnosed breast cancer [20, 34]. Clinical investigation continues in an effort to find answers to these questions (**Figure 1**).

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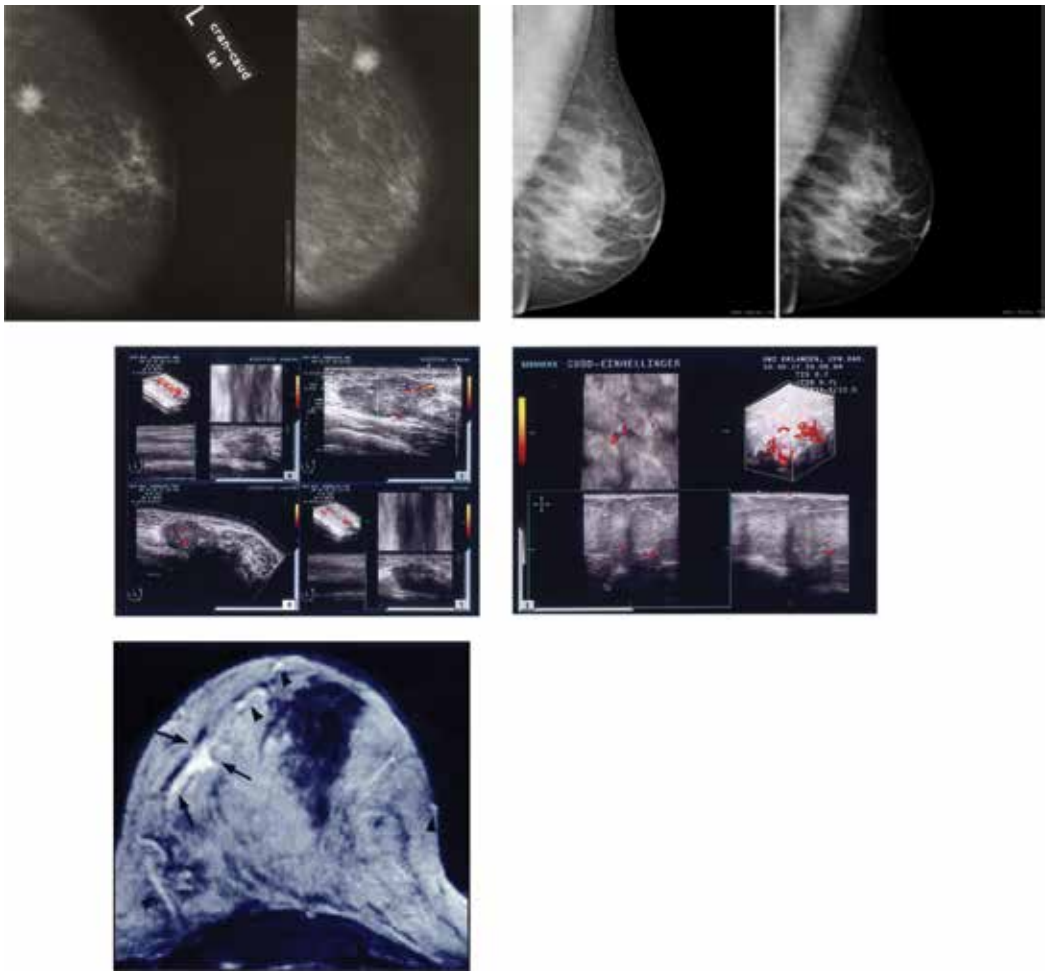

Figure 1. Complementary breast imaging.

5. Breast cancer screening

The aim of breast cancer screening is to reduce mortality through early detection. Randomised controlled trials and case–control studies demonstrated that population screening by mammography can be expected to reduce overall breast cancer mortality by around 25%. [35, 36]. The validity of these trials was questioned, but subsequent reviews have reaffirmed the mortality benefit of mammographic screening and determined that criticisms of the mammographic screening trials were unjustified [37, 38]. The mortality benefit of screening is greatest in women aged 50–70 years. Screening of women under the age of 40 has not been shown to provide any mortality benefit [39–41].

The screening method is two-view mammography. Clinical examination of the breast and breast self-examination have not been shown to contribute to mortality reduction through early detection.

Women at increased risk of developing breast cancer due to a proven inherited predisposing genetic mutation, family history, previous radiotherapy or benign risk lesions may be selected for screening at young age [42, 43]. There is evidence that MRM is the most sensitive method of imaging young women [44]. The specificity of MRM is low and the rate of false-positive results is high—these circumstances have been extensively discussed. Second-look and targeted ultrasound and preoperative MRI-guided biopsy can increase the low specificity of MRM.

6. Image-guided breast biopsy

Needle biopsy is highly accurate in determining the nature of most breast lesions classified as BI-RADS 4 or 5. Patients with benign conditions avoid unnecessary surgery. Carrying out open surgical biopsy for diagnosis should be regarded as a failure of the diagnostic process. For patients who prove to have breast cancer, needle biopsy provides accurate understanding of the type and extent of disease, so ensuring that patients and the doctors treating them are able to make informed treatment choice. Needle biopsy not only provides information on the nature of malignant disease, such as histological type and grade, but also enables pretreatment analyses of prognostic and predictive factors to characterise the immunohistochemical phenotype and the tumour biology (hormone-receptors, HER-2 receptor, genetic profiling, etc.) [45, 46].

Breast needle biopsies of nonpalpable lesions require imaging to guide needle placement. Imaging guidance can be performed with ultrasonography, stereotactic mammography or MRM. Ultrasound guidance is the technique of choice; it is less costly and easy to perform. Ultrasound provides real-time visualisation of the biopsy procedure and visual confirmation of adequate sampling. Between 80 and 90% of breast abnormalities will be clearly visible on ultrasound [47]. For impalpable abnormalities not visible on ultrasound, stereotactic-guided biopsy is required. A few lesions are only visible on MRM and require magnetic resonance-guided biopsy.

Most lesions selected for ultrasound-guided biopsy are solid masses that can be sampled with 14-gauge core needles. The technical aspects involved in performing ultrasound-guided procedures with a free-hand approach have been described previously [48]. The technique used consists of the following steps: imaging the lesion, finding the needle in the longitudinal plane through the breast, maximally visualising the needle tip and placing the needle in the lesion. Development of good hand-eye coordination is crucial to a successful lesion sampling (**Figure 2**) [49].

Using the 14-gauge needle, multiple core biopsy samples are necessary to ensure accurate sampling of different areas of the lesion. In most cases, accurate lesion sampling can be achieved by obtaining 3–5 core samples for masses and 5–10 core samples for microcalcifications [50, 51].

To improve sampling of microcalcifications using digital, stereotactic mammography guidance, the vacuum-assisted biopsy instrument with probes coming in 11-gauge size has been developed [12]. In contrast to the automated biopsy gun devices, the directional, vacuum-assisted biopsy instrument is inserted once and rotated while in the breast to obtain samples from different areas of the lesion. A vacuum is used to pull tissue samples into the sample notch, where it is cut and transported back through the needle and out to the collection chamber. Multiple tissue samples are collected without removing the needle from the breast (**Figure 3**).

Studies have shown improved sampling of microcalcifications with the vacuum-assisted biopsy instrument [52, 53]. For calcifications, it is imperative that there is a proof of representative

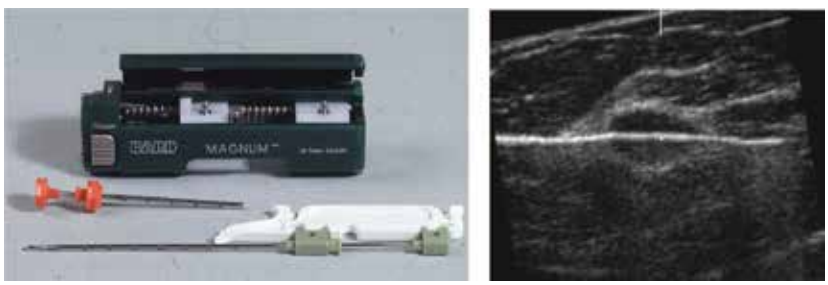

Figure 2. US-guided breast core biopsy (14-gauge).

Figure 3. Vacuum-assisted core biopsy (11-gauge).

sampling with specimen radiography. If calcification is not demonstrated on the specimen radiography and the histology is benign, then management cannot be based on this result as there is a high risk of sampling error; the procedure must either be repeated or open surgical biopsy carried out [54–60].

An 8-gauge vacuum-assisted biopsy probe is preferred for therapeutic removal of breast lesions such as fibroadenomas [61–64].

The low specificity of MRM requires the ability to perform MRI-guided biopsies, which require an additional specialised MRI biopsy coil and MRI-compatible wires and needles for localisation and core biopsies [65–67]. Centres that cannot perform MRI-guided localisation and biopsy lack the ability to manage lesions visible only with MRI and are at a clear disadvantage.

The technical aspects of MRI-guided localisation and biopsy are similar to those for stereotactic biopsies in that the patient is prone during the procedure, the breast is held in compression, and the needle plane is guided into the tissue parallel to the chest wall. Needle placement is performed with the patient outside the bore of the magnet using an MRI-compatible needle, often made of titanium. The patient is then returned to the magnet, and confirmation of adequate needle placement is obtained. After sufficient core samples are obtained outside of the bore of the magnet, a clip is placed marking the biopsy cavity. In our practice, patients with MRM-detected indeterminate or suspect lesions are first scheduled for targeted second-look ultrasonography because often these lesions can be visualised after discovery on MRM.

In cases of complete radiological removal of small occult breast lesions with needle biopsies, clip marking with the possibility for re-localisation in cases of necessary therapeutic open surgical resection is mandatory. Core needle and vacuum-assisted biopsy is extremely useful in the evaluation of patients with multiple suspect lesions.

It is important that the result of needle breast biopsy is always correlated with the clinical and imaging findings before clinical management is discussed with the patient. This is best achieved by reviewing each case at prospective multidisciplinary meetings. The results of image-guided breast biopsies are translated in the planning process of targeted oncoplastic breast surgery when malignancy is diagnosed. Breast surgery is directly based on breast imaging and interventional diagnosis. Multidisciplinary coworking between radiology, pathology and breast surgery is mandatory.

7. Wire-guided surgical excision

The number of impalpable, clinically occult breast lesions is increasing. Accurate localisation techniques are required to facilitate their surgical excision as the therapeutic part of a planned oncoplastic breast-conserving procedure [68]. The hooked wire is the most commonly employed technique and has proved very reliable. There are various designs of localisation wire in common use. All have some form of anchoring device such as a hook with a splayed

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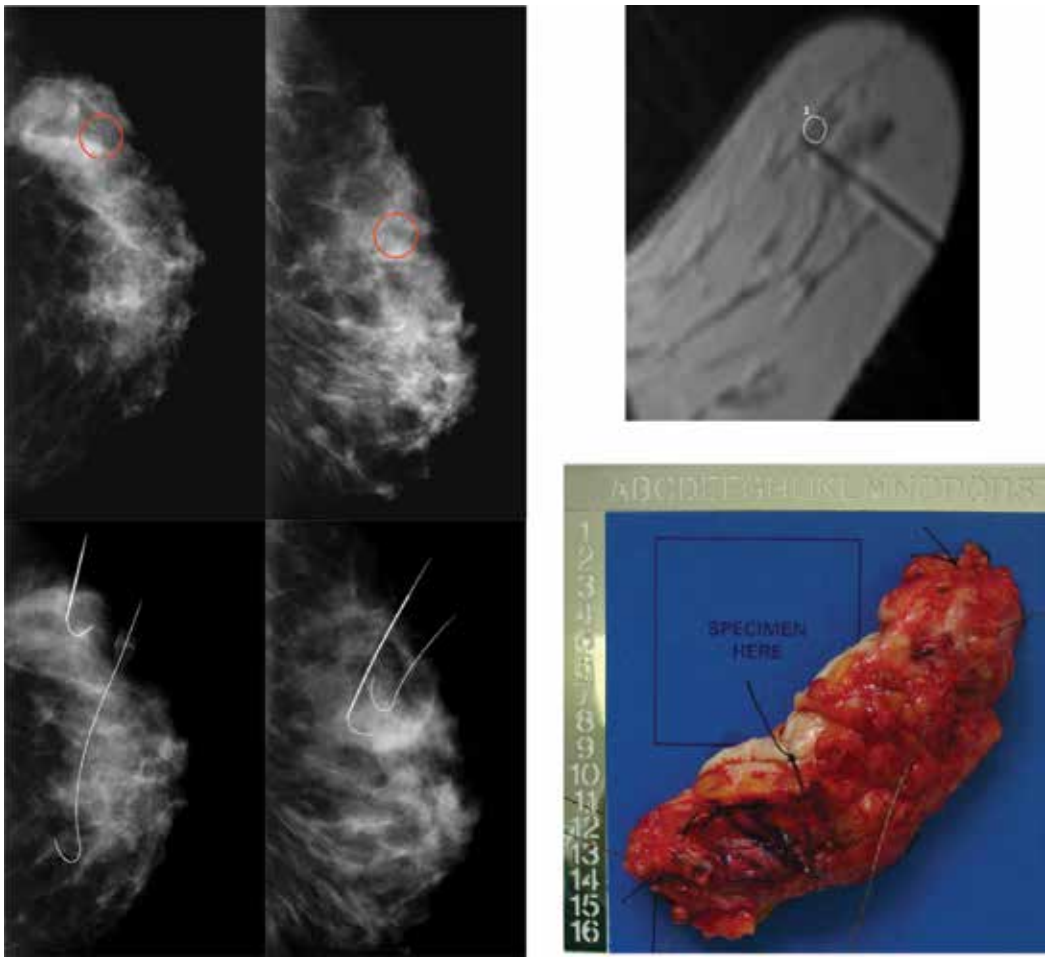

Figure 4. Wire-guided (mammography and MRI) segmental excision.

or barbed tip. The wire is placed under ultrasound, stereotactic or MRI guidance (for MRM lesions only) within a rigid over-sheath cannula, which is then removed once positioning is satisfactory. Most wires are very flexible, and when the cannula is removed, the wire may assume a quite circuitous course. Care must be taken to avoid displacing the wire.

Procedures that can be surgically more challenging are wide local excisions (segmental resection) for DCIS with no mass lesion. In such cases, where the distribution of disease is often more eccentric, careful three-dimensional excision planning especially in oncoplastic procedures is necessary. Inserting more than one wire and even bracketing and framing the lesion with two or three can occasionally be useful (**Figure 4**).

If the procedure is being performed to establish a diagnosis (diagnostic segmentectomy), a representative portion of the lesion is excised through a small incision, thus leaving a satisfactory

cosmetic result if the lesion proves to be benign. In the therapeutic situation, the marked lesion should be completely excised. Intraoperative specimen radiography is essential, both to check that the lesion has been removed and, if cancer has been diagnosed, to ensure that adequate radiological resection margins have been achieved. We have to consider that especially in DCIS, the proved radiological resection margin (specimen radiography) sometimes differs from the histological resection margin [68–71].

8. Translation of breast imaging into targeted breast surgery

Advances in breast imaging have led some to question whether whole-breast ultrasound or MRM should be part of the standard preoperative evaluation of a patient with breast cancer. Golshan et al. [72] reviewed the impact of ipsilateral whole-breast ultrasound on the surgical management of 426 patients with clinical stage I and II cancer. Seventy-five of the 426 patients (18%) had additional lesions identified by ultrasound, but only 12 were malignant. The role of ultrasound as a diagnostic tool for the evaluation of breast masses is well established (as is its role in defining lesions that are poorly seen on mammogram or are mammographically occult), and the available data support its use as a routine tool when evaluating patients for breast-conserving therapy.

Tillmann et al. [73] reported the results of a similar study of the impact of MRM on the management of 207 women with DCIS and stage I and II breast cancer. The MRM findings affected clinical management in 20% of cases. In 6%, MRM had an unfavourable effect due to false-positive findings that resulted in unnecessary mastectomy or additional breast biopsies.

The work of Holland et al. [33] indicated that microscopic foci of invasive and non-invasive cancer are present at a distance from apparently localised primary tumours in a significant number of patients. Only 39% of specimens showed no evidence of cancer beyond the reference tumour, while in 20%, additional cancer was found within 2 cm of the reference tumour. Forty-one per cent of patients had residual cancer more than 2 cm from the reference tumour. The percentage of patients with residual cancer more than 2 cm from the reference tumour corresponds well to the rate of local recurrences reported in patients treated with breast-conserving surgery alone without postoperative radiotherapy. Radiotherapy is effective in controlling the majority of these occult foci of carcinoma.

The ability of MRM and ultrasound to identify these tumour foci raises the possibility that significant numbers of women who could be treated with breast-conserving therapy will be subject to unnecessary mastectomy. Histologic subtype other than invasive ductal carcinoma does not appear to be associated with an increased risk of recurrence. If the tumour is not diffuse in the breast and can be completely excised with negative margins, patients with invasive lobular carcinoma are candidates for breast-conserving therapy. However, because of the increased incidence of multicentricity, invasive lobular cancer associated with increased mammographic density is an accepted indication for preoperative MRM before breast-conserving therapy.

9. Conclusion

The translation of breast imaging, interventional procedures and wire-guided surgical excision into a concept of targeted oncoplastic breast-conserving surgery is mandatory, and an interdisciplinary task for the breast radiologist and the breast surgeon to achieve the best oncological and aesthetic outcomes for patients with breast cancer is also mandatory.

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Innovative Imaging

Chapter 5

Computer Aided Diagnosis - Medical Image Analysis Techniques

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Additional information is available at the end of the chapter

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Abstract

Breast cancer is the second leading cause of death among women worldwide. Mammography is the basic tool available for screening to find the abnormality at the earliest. It is shown to be effective in reducing mortality rates caused by breast cancer. Mammograms produced by low radiation X-ray are difficult to interpret, especially in screening context. The sensitivity of screening depends on image quality and unclear evidence available in the image. The radiologists find it difficult to interpret the digital mammography; hence, computer-aided diagnosis (CAD) technology helps to improve the performance of radiologists by increasing sensitivity rate in a cost-effective way. Current research is focused toward the designing and development of medical imaging and analysis system by using digital image processing tools and the techniques of artificial intelligence, which can detect the abnormality features, classify them, and provide visual proofs to the radiologists. The computer-based techniques are more suitable for detection of mass in mammography, feature extraction, and classification. The proposed CAD system addresses the several steps such as preprocessing, segmentation, feature extraction, and classification. Though commercial CAD systems are available, identification of subtle signs for breast cancer detection and classification remains difficult. The proposed system presents some advanced techniques in medical imaging to overcome these difficulties.

Keywords: breast cancer, computer-aided diagnosis, segmentation, feature extraction, classification

1. Introduction

In medical imaging field, computer-aided detection (CADe) or computer-aided diagnosis (CADx) is the computer-based system that helps doctors to take decisions swiftly [1, 2]. Medical imaging deals with information in image that the medical practitioner and doctors has to

evaluate and analyze abnormality in short time. Analysis of imaging in medical field is very crucial task because imaging is basic modality to diagnose any diseases at the earliest but acquisition of image is not to harm the human body. Imaging techniques like MRI, X-ray, endoscopy, ultrasound, etc. if acquired with high energy will provide good quality image but they will harm the human body; hence, images are taken in less energy and therefore, the images will be bad in quality and low contrast. CAD systems are used to improve the quality of the image, which helps to interpret the medical images correctly and process the images for highlighting the conspicuous parts [3].

CAD is a technology which includes multiple elements like concepts of artificial intelligence (AI), computer vision, and medical image processing. The main application of CAD system is finding abnormality in human body. Among all these, detection of tumor is the typical application because if it misses in basic screening, it leads to cancer [4].

1.1. Objectives of the CAD system

The main goal of CAD systems is to identify abnormal signs at an earliest that a human professional fails to find. In mammography, identification of small lumps in dense tissue, finding architectural distortion and prediction of mass type as benign or malignant by its shape, size, etc.

1.2. Significance of the CAD system

CADe usually restricted to marking the visible parts or structures in image, whereas CADx helps to evaluate the structures identified in CADe. Both together the CAD models are more significant in identifying the abnormality at an earliest. For example, it highlights microcalcification clusters, marginal structure of mass, and highly dense structure of tissue in mammography. This helps the radiologist to draw the conclusion. Though the CAD has been used for over 40 years, still it does not reach the expected outcomes. We agree that CAD cannot substitute the doctor but definitely it makes radiologists as better decision makers. It plays a supporting and final interpretative role in medical diagnosis.

1.3. Applications of CAD system

CAD is used in the diagnosis of breast cancer, lung cancer, colon cancer, prostate cancer, bone metastases, coronary artery disease, congenital heart defect, pathological brain detection, Alzheimer's disease, and diabetic retinopathy.

1.4. CAD for breast cancer

Breast cancer ranks as second leading cause of death in women worldwide. According to American Cancer Society, about one in eight women will have breast cancer in her lifetime and only 5–10% of breast cancers occur in women with clearly defined genetic link [5]. Hence, the early detection will help to have better quality of life, economical treatment, and mental peace of patient and family. With a low dose of X-ray imaging, mammography is a most basic screening test for breast cancer and also records better visualized internal details of the

breast [6]. Usually, mammography images consist of many artifacts and noises and makes medical images too difficult to detect and understand the cancer at the primary stages [7]. Therefore, standardization of image quality and extraction of Region of Interest (ROI) are essential to limit the hunt for abnormalities.

CAD systems fundamentally work on highly complex patterns found in image. For breast cancer, it is used in screening mammography. Mammography is a basic screening test for breast cancer. It is low level X-ray imaging of the female breast. It helps for early detection of breast cancer [8, 9] and it is mainly, established in the Netherlands and United States in addition with human evaluation conducted every year. The first CAD for mammography was developed in University of Chicago as research project. Today, commercially offered by iCAD, R2 image checker (version 3.8.17), and Hologic. Some of the non-commercial systems were developed such as Alan Hshieh gradient-based software and Ashita project. Some studies of CAD in mammography have positive impact, but some show no improvement [10, 11]. A systematic review on CAD in screening mammography conveyed that it does not have any significant impact, but it undesirably increases false-positive rates. A CAD system helps in achieving high accuracy, sensitivity which benefits for diagnosing mammography and also the patients. Normally, CAD systems are optimized by number of images. These images are analyzed in many steps as shown in **Figure 1**.

1.4.1. Preprocessing

- Reduction of background artifacts (bugs in images)
- Removal of noise
- Filtering
- Enhancing the quality of the image by leveling and increased contrast for clearing the image's

1.4.2. Segmentation

- Disparity of different structures in the image, e.g., mass, microcalcification, and tissue
- Finding the ground truth from anatomic databank

1.4.2.1. Feature extraction

Detected region of interest is analyzed individually for special features (characteristics):

- Size, location, and border
- Gray levels analyzed in ROI
- Texture of the ROI
- Patterns found in ROI
- Architectural distortion of the ROI

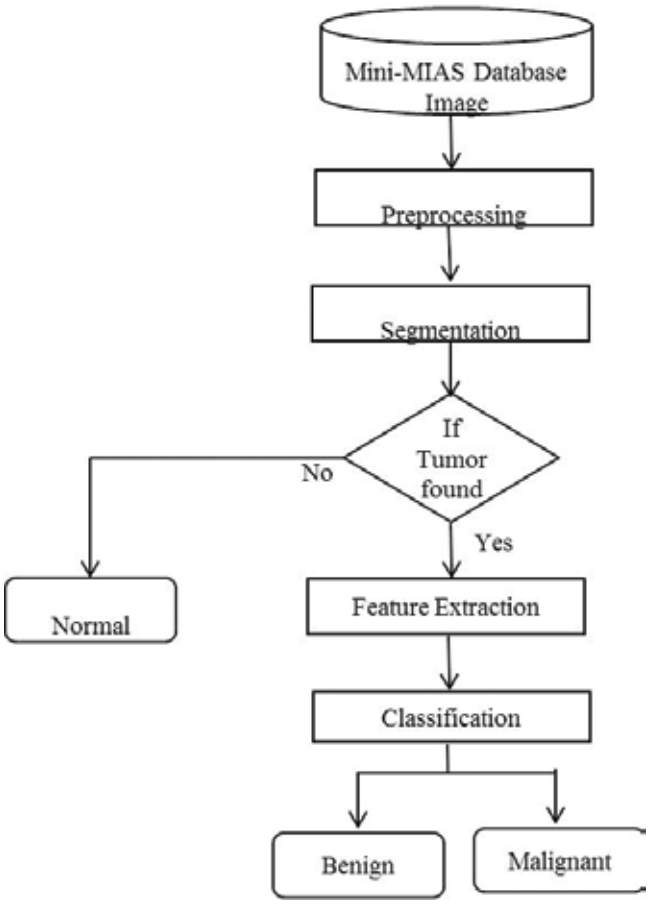

Figure 1. Block diagram of CAD model for breast cancer.

1.4.3. Classification

After analysis of structure, every ROI is evaluated individually for scoring of the probability value for true positive (TP), false positive (FP), false negative (FN) and true negative (TN). The following procedures are examples of classification algorithms:

- Nearest-neighbor rule (e.g., k-nearest neighbors')
- Minimum distance classifier
- Cascade classifier
- Naive Bayesian classifier
- Artificial neural network
- Radial basis function network (RBF)

- Support vector machine (SVM)
- Principal component analysis (PCA)

For classification of mass type in mammography, SVM classifier is used. If the detected structure reached to certain threshold level then they are marked by the radiologist, in some CAD systems abnormality marked automatically and saved for later examinations.

1.5. Evaluation of CAD systems

Evaluation of CAD systems measured by two major factors, such as sensitivity and specificity, they seek for suspicious structure. CAD systems may not be 100% but their hit rate means sensitivity can be up to 98% these days. But accuracy of the CAD depends on the conditions of the images used for training the system and factors like retrospective design. Image quality, conditions of mammography examination, radiologists marks, type of lesion, and size and location of mass are highly influences.

2. Materials and methods

2.1. Dataset used

There are many standard datasets that are recommended by researchers to test CAD algorithms for mammography. Most of the datasets are not freely available. The most easily available datasets are mammographic image analysis society (MIAS) and the digital database for screening mammography (DDSM). Besides with these mini-MIAS database, B-SCREEN—Bayesian decision support in medical screening, AMDI—indexed atlas of digital mammograms, image retrieval in medical applications (IRMA), MammoGrid—European federated mammogram database implemented on a grid structure, and grid platform for computer-aided library in mammography (GPCALMA) datasets are available [12]. To test and analyze the CAD model, MIAS mini-mammographic database (i.e., mini-MIAS database of mammograms) [13] dataset is used. MIAS dataset is organized by research group of UK, films taken for National Breast Screening Programme and digitized to 50-μm pixels. A dataset consists of 322 images of 1024×1024 sizes with radiologist mark if abnormality exists.

2.2. Methodology

Breast cancer diagnosis requires systematic image analysis and characterization and integration of numerous clinical and mammographic variables, which are difficult and error-prone tasks for physicians [14, 15]. This leads to low positive predictive value of imaging interpretation. The integration of computer models into the radiological imaging interpretation process can increase the accuracy of image interpretation. Hence, the CAD models help in early detection and accurate analysis of breast cancer. This CAD model aims to detect abnormality and identification of type of abnormality. The detailed diagram describes the steps carried out in CAD system for breast cancer detection and classification as shown in **Figure 2**.

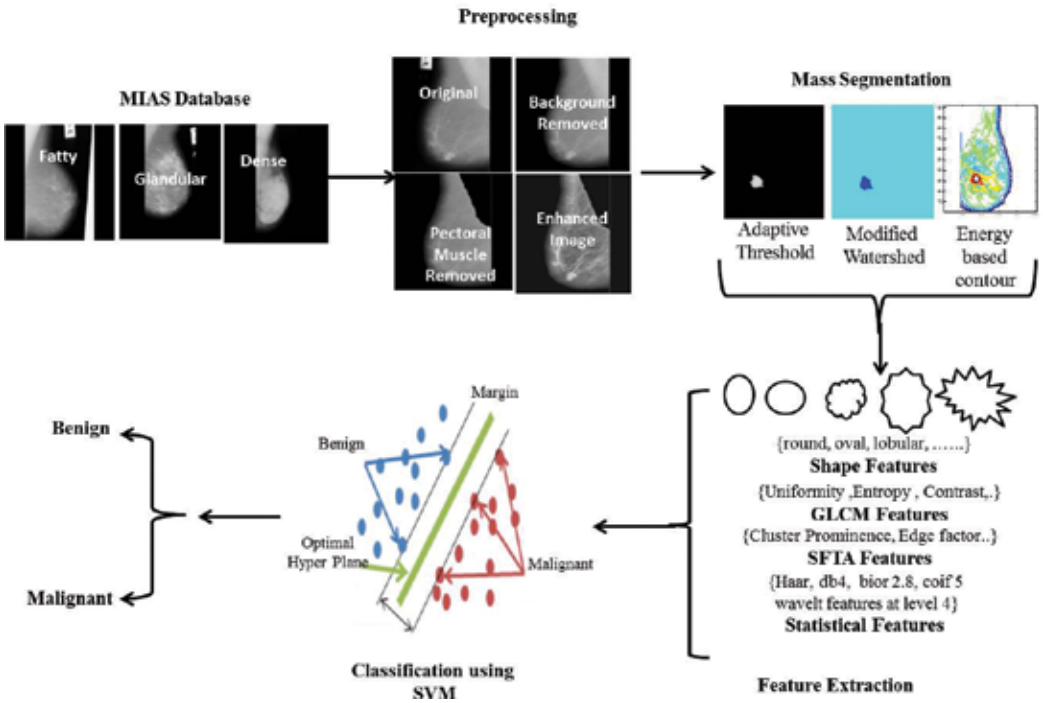

Figure 2. Detailed diagram of CAD model for breast cancer.

2.2.1. Preprocessing

Preprocessing is the foremost task in medical imaging, it helps to identify the abnormal part, which cannot be recognized by visualizing the image but can be detected through CAD systems. Here in preprocessing, image quality enhanced by removing unwanted artifacts marked in **Figure 3** from mammography.

Several methods have been reported for preprocessing mammography images since 1980 because of its influences in detection of cancer. The techniques like adaptive median filter, mean filter, adaptive mean filter, histogram equalization, histogram modified local contrast enhancement, breast region and pectoral muscle extraction, Contrast Limited Adaptive Histogram Equalization (CLAHE) technique, and morphological have been discussed earlier [16–18]. Preprocessing of mammography [19] explored that the selection of significant parameters for quality improvement influences in the efficiency of CAD system [20]. **Figure 4** shows the steps carried out in preprocessing.

2.2.1.1. Removal of background

Histogram is the traditional method to remove the background. By identifying the threshold value from histogram, background of mammography removed. Using identified threshold value, image binarized and ordered with connected components, the largest component indicated the breast profile [21].

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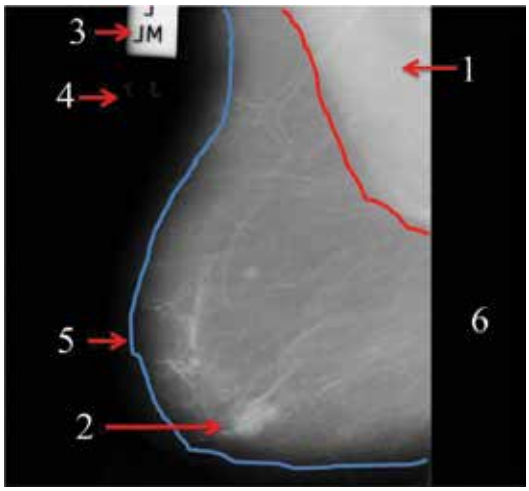

Figure 3. Types of noises observed in original image and marked with numbers as 1. pictorial muscle, 2. tumor, 3. high intensity, 4. low intensity, 5. breast part, and 6. background.

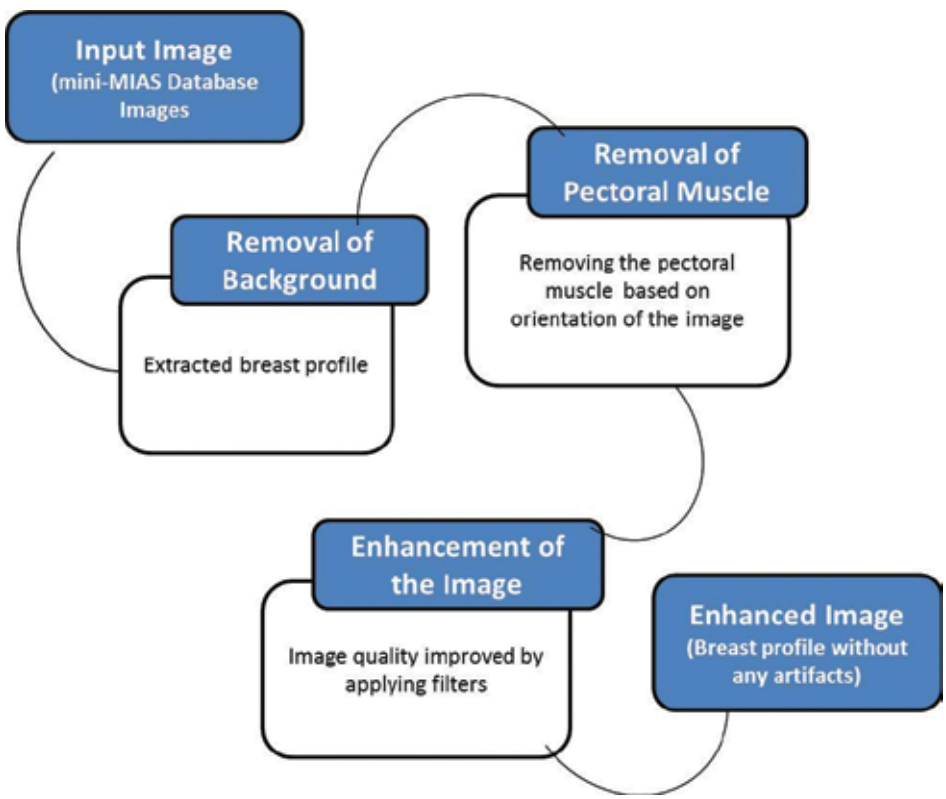

Figure 4. Steps carried out in preprocessing of mammography.

2.2.1.2. Removal of pectoral muscle

Another challenging task in preprocessing of mammography is removal of pectoral muscle [21]. The modified region growing method used to remove the pectoral muscle by identifying the origin of the image either left oriented or right oriented. Once origin is identified, then it selects first top corner pixel as seed point and segments the pectoral muscle. This process carries until the complete muscle part is marked.

2.2.1.3. Image enhancement

The visual effect of the mammography uplifted by median filter followed by CLAHE [22]. As stated, earlier dataset consist of fatty tissue, glandular tissue and dense tissue and the preprocessing was more helpful in dense tissue.

The evaluation of quality measure by the traditional image quality measuring parameters like root mean square error (RMSE), Peak signal to noise ratio (PSNR), and image quality index (IQI). RMSE and PSNR values are calculated by using Eqs. (1)–(3), respectively.

$$RMSE = \sqrt{\frac{1}{MN}\sum_{i=1}^{M}\sum_{j=1}^{N}\Big(x(i,j) - y(i,j)\Big)^2} \tag{1}$$

$$PSNR = 10\log\frac{(2^n - 1)^2}{RMSE} \tag{2}$$

IQI is measured if $x = \{xi \mid i = 1, 2 \ldots M\}$ and $y = \{yi \mid i = 1, 2 \ldots N\}$ are original and test image signals, respectively. The IQI is measured as Eq. (3)

$$Q = \frac{4\sigma_{xy}\, x'y'}{(\sigma_x^2 + \sigma_y^2)[x'^2 + y'^2]} \tag{3}$$

where

$$x' = \frac{1}{M}\sum_{i=1}^{M} xi \quad \text{and;} \quad y' = \frac{1}{N}\sum_{j=1}^{N} yi;$$

$$\sigma_{xy} = \frac{1}{N-1}\sum_{i=1}^{N}(xi - x')(yi - y');$$

$$\sigma_x^2 = \frac{1}{M}\sum_{i=1}^{M}(xi - x')^2;$$

$$\sigma_y^2 = \frac{1}{N}\sum_{i=1}^{N}(yi - y')^2.$$

There is a strong reason for using Wiener filter and CLAHE for image enhancement. Comparing the median filter, adaptive min-max and Wiener filter, we obtained high PSNR for all the images tested, as shown in **Figure 5**.

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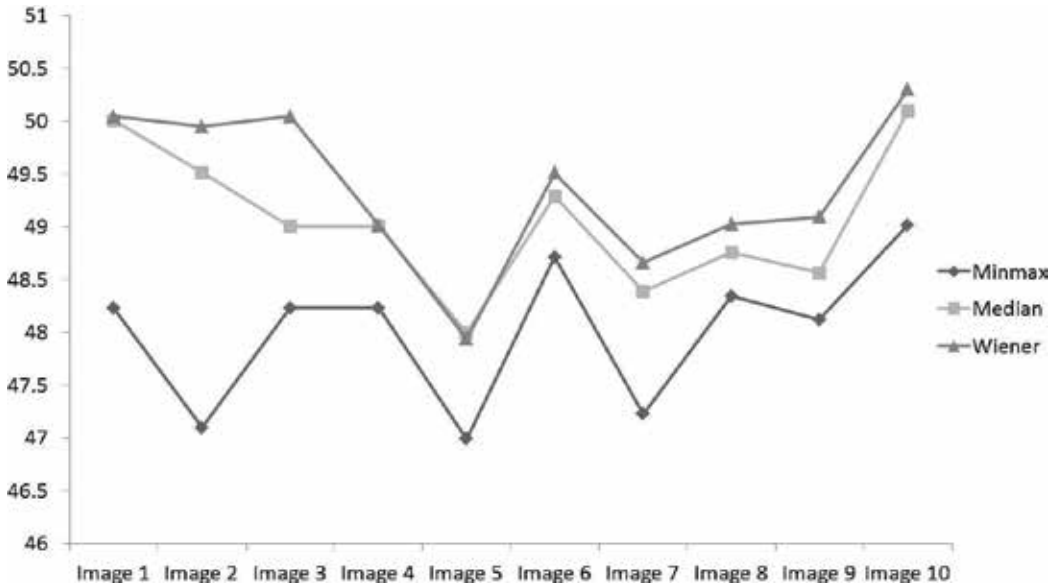

Figure 5. Comparison of different filters.

It is clear from this figure that Wiener filter is suitable for noise removal of mammography image because it has high PSNR compared to min-max and median filter. It was tested with different filtering mask from [1 1] to [8 8] to select significant filter mask for Wiener filter as shown in **Figure 6**.

As mask of Wiener filter increased the PSNR value for mask [1 1], [2 2], and [3 3], whereas the RMSE, IQI values were reduced. Hence, [3 3] mask selected as significant filter mask for Wiener filter. However, mask increased beyond significant, PSNR increased but image gets blurred. Similarly, for the contrast index (CI) values, the default CI is suitable as compared with different CI values. For CI = 0.2, PSNR increased and continued with slight increase RMSE and IQI reduced from the CI = 0.2. Hence, contrast index 0.2 selected as significant value. The stepwise results acquire in preprocessing stage are shown in **Figure 7**.

Timely screening is the main aim of reducing death rates in breast cancer but traditional screening system may miss the abnormality because of low radiation. Hence, preprocessing is one of the essential components to detect abnormality at earliest.

2.3. Segmentation of mass

Segmentation is the process of partitioning the abnormal part from the normal part. Each identified regions represents the information that it belongs to and structuring elements to differentiate the abnormality [23, 24]. The main aim of segmentation in this CAD model is mass segmented from the breast tissue as shown in **Figure 8**. Mass in mammography is one of the subjects to identify the abnormality. Usually, abnormality of mass is identified by its shape, margin, and intensity. Sometimes, the high intensity with circular objects is likely to be ill-

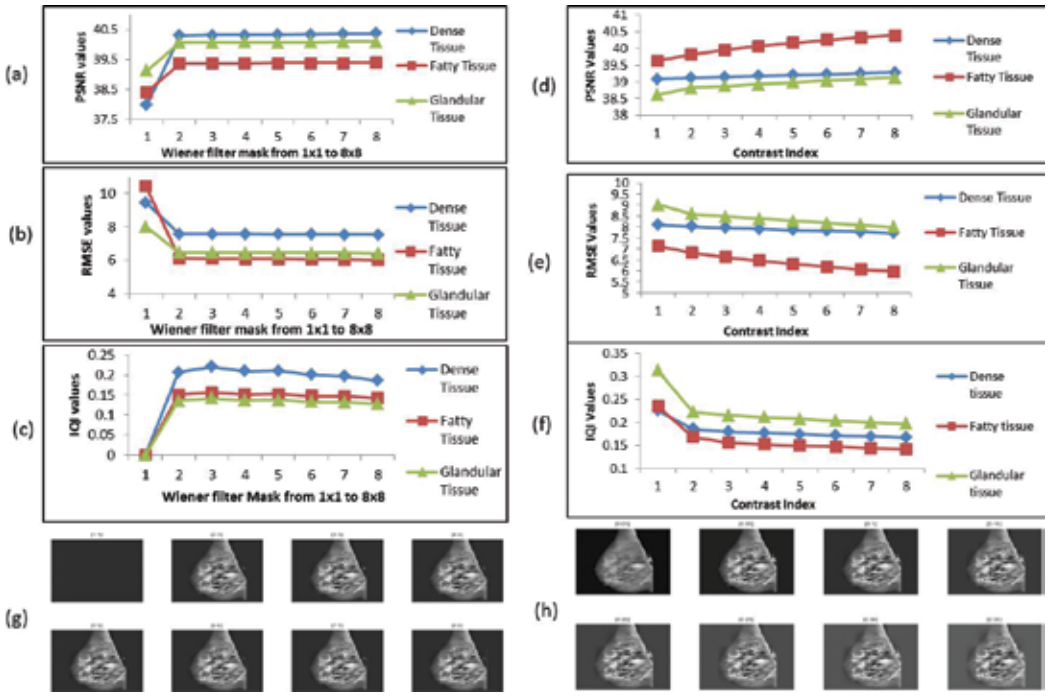

Figure 6. Selection of significant filter mask for Wiener filter (a) PSNR, (b) RMSE, and (c) IQI values of different filter masks from [1 1] to [8 8] for dense, fatty, and fatty glandular tissues. Selection of significant CI for CLAHE (d) PSNR, (e) RMSE, and (f) IQI values of different CI from 0.1 to 0.8 for dense, fatty, and fatty glandular tissues, (g) is results of different filter mask in Wiener filter (h) is results of different CI in CLAHE.

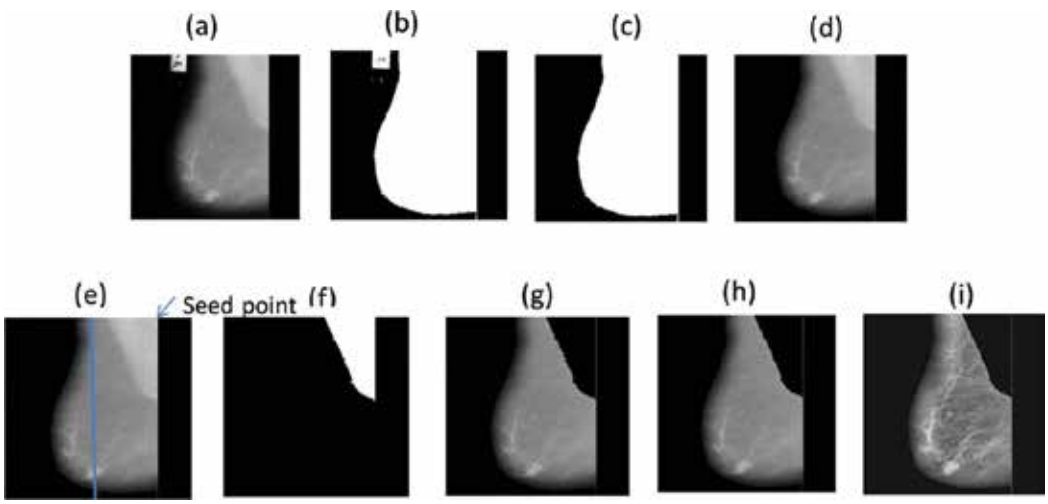

Figure 7. Experimental results proposed method (a) original image, (b) binary image with threshold value 0.1, (c) breast part extracted, (d) multiplication of (a) and (c) which consist only breast part without background, (e) seed point marked for region growing, (f) pectoral muscle segmented, (g) suppressed from original image, (h) Wiener filter, and (i) result of CLAHE.

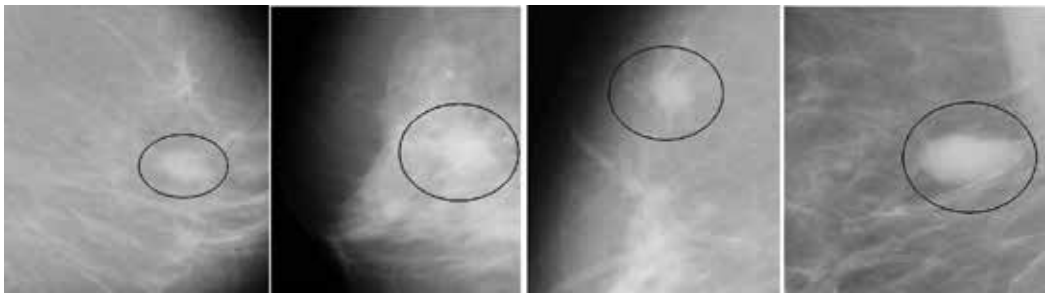

Figure 8. Mass in mammography.

defined [25]. To train the system is too difficult in such cases hence CAD models cannot reach 100% of accuracy till today.

Many mass detection techniques have been developed for CAD systems earlier [26–28]. More recently used mass segmentation approaches are region growing, watershed, threshold based, contour based, and clustering methods.

In the proposed system, we have identified three different segmentation techniques such as adaptive thresholding segmentation techniques, modified marker controlled watershed segmentation technique, and energy-based contour segmentation technique are applied to extract ROI.

2.3.1. Adaptive thresholding segmentation techniques

Thresholding is yet effective and simple method of segmenting the image into different regions. In proposed algorithm, before applying thresholding to the image it transformed with watershed and morphological operations [29]. Watershed was originally proposed by Digabel and Lantuejoul [30, 31]. It is one of the useful concepts in image segmentation. Many modifications have been carried out on the watershed algorithm, because it gets oversegmented on the gray scale image. The concept of the watershed could be illustrated by geography as the representation of a topographical representation of the image. If the image is of the landscape it start filling with the water from the minimum gray value in the region of interest [18]. When water fills up two or more regions it start merging, so we have to prevent merging by increasing the margins of basins till the high intensity. To control this more commonly creates a dam at points where water of two different regions meets. These regions are considered as catchment basins and the dams or the watershed lines which divide two different regions based on similarity satisfy the region. Most of the time, it over segments the image; to control oversegmentation, mathematical, morphological, and logical operations are used. The proposed work is a threshold-based segmentation and it is modified to extract the ROI with watershed transform and morphological operation. Threshold of the image is measured by the adaptive method, and ROI is extracted by iteratively selecting the threshold as shown in **Figure 9**.

2.3.2. Mathematical morphological operations

Mathematical morphological operations help to structure elements and measure the shape of the image. It also helps to refine the characteristics of the image in order to maintain the image

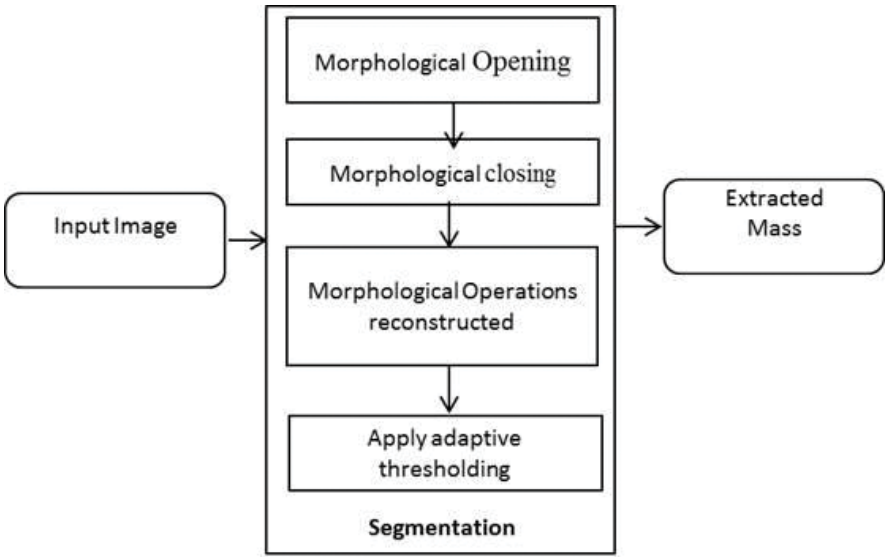

Figure 9. Steps in adaptive thresholding segmentation techniques.

data and characters [32]. This work considered two morphological operations are opening and closing. Opening and closing are most commonly used operators in morphology [33]. They have implemented by the basic operations such as erosion and dilation. The morphological opening is denoted by Eq. (4) and it is achieved by erosion followed by dilation.

$$A \circ B = (A \ominus B) \oplus \ominus \tag{4}$$

Morphological opening helps to smoothen the edges and breaks the weak connections. Also it helps to remove the unwanted regions that do not contain structuring elements.

The morphological closing operation is denoted by Eq. (5) and it is achieved by dilation followed by erosion. It is union of all translations of B without overlap on A.

$$A \cdot B = (A \oplus B) \ominus B \tag{5}$$

It helps to join the weak edges and fill the breaks in the edges. Also it helps to fill gaps and small holes in the structuring elements.

After calculation of gradient, the proposed method finds the regional minima, on which watershed transformation is applied. The watershed lines are obtained by "ORing" with minimum values to get mask. Then the mask is imposed on the gradient image. But it results in oversegmentation. Then the morphological operations, such as opening and closing, are applied to minimize the regions and fill the gap between the edges. Then the level-wise thresholding is applied to select appropriate threshold point [34] as shown in **Figure 10**.

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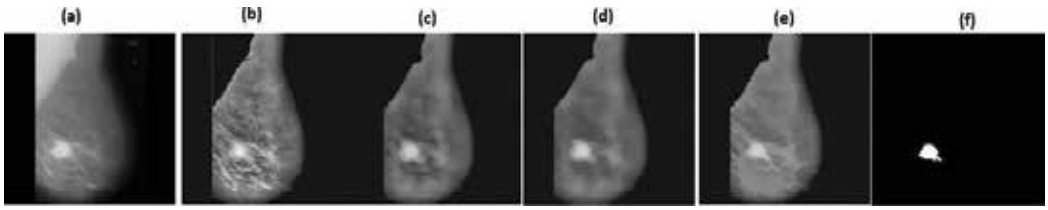

Figure 10. Experimental results of threshold-based segmentation (a) original image from the mini-MIAS database, (b) preprocessed image, (c) opening, (d) closing, (e) reconstructed from opening-closing, and (f) mass identified fourth level of thresholding.

Comparing with the Otsu thresholding method [35], at fourth levels of thresholding successfully extracted ROI as shown in **Figure 11**.

2.3.3. Modified watershed segmentation

The traditional watershed method has the disadvantage of oversegmentation; hence, marker controlled watershed segmentation is used to extract the mass part from breast profile. The modified watershed method works systematically as shown in **Figure 12**. The preprocessed image passed to the gradient of the image with *sobel* operator to smoothen the edges. Then traditional watershed is applied to oversegments. Applying morphological operation opening followed by closing helped to find regional maximum and minimum values to apply watershed segmentation.

Stepwise results of watershed segmentation techniques are as shown in **Figure 13**. This method does not work well on dense and low contrast images, either it over segments or it miss the mass part in segmentation.

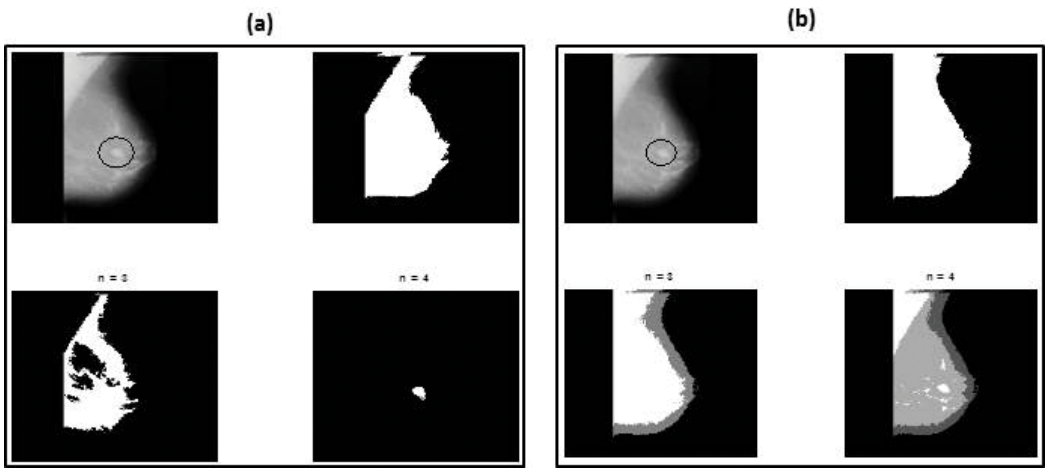

Figure 11. Comparison of (a) threshold-based segmentation method with (b) Otsu thresholding method.

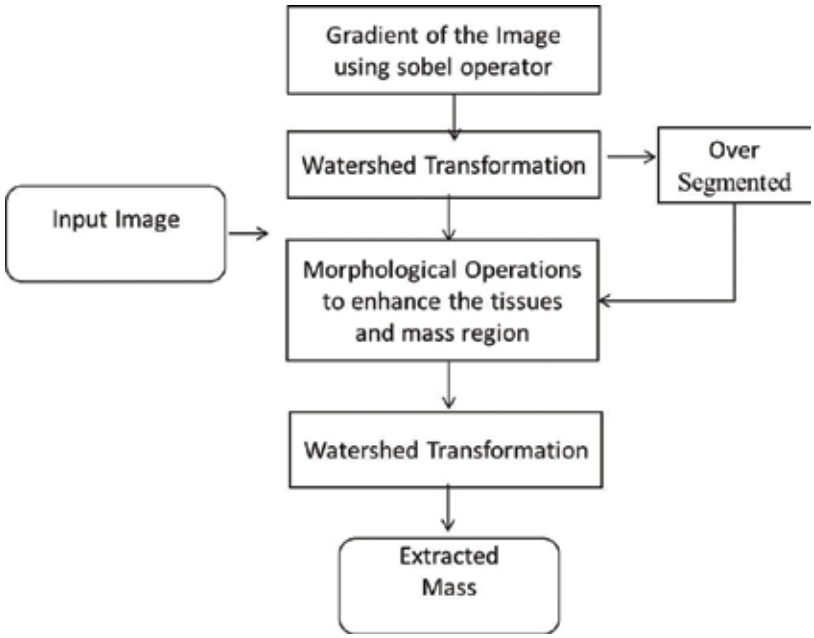

Figure 12. Steps of modified watershed segmentation technique.

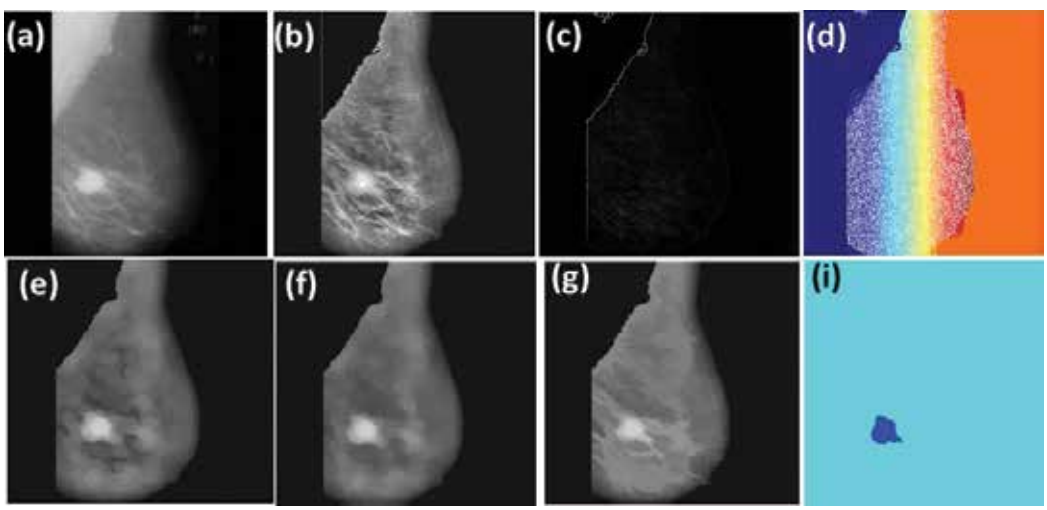

Figure 13. Step-wise results of modified watershed segmentation method. (a) original image, (b) preprocessed image, (c) gradient with *sobel* operator, (d) watershed transformation, (e) opening, (f) closing, (g) reconstructed from opening and closing, and (h) watershed transformation with mass identified.

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2.3.4. Contour-based segmentation technique

The contour-based segmentation algorithm works in five steps as follows:

Step 1: Read the preprocessed image as input image.

Step 2: By performing the morphological operations, the abnormality is super imposed on original image.

Step 3: Apply active contour technique to identify the suspicious lesions; the suspicious lesions are peaks of the contour.

Step 4: Extract peak of the contour by calculating the energy of each contour.

Step 5: Mark extracted contour as ROI.

The stepwise results are shown in **Figure 14**. Energy of the contour is calculated by adding the intensity of pixels from each contour and finding average. Average of each contour is compared to select the mass region.

The contour-based technique works well on all kinds of tissues like fatty, glandular, and dense as shown in **Figure 15**. Also it works with high-intensity and low-intensity images.

2.4. Feature extraction of mass ROI

Radiologists depict masses by their shape, gray levels, and texture properties. The properties of mass surroundings are important discriminators from the background tissue. The shape of the mass changing from early benign to malignant as round, oval, lobular, or irregular circumscribed, micro-lobulated, obscured, indistinct, or peculated [36–39]. **Figure 16** shows a schematic diagram of mass shapes and boundary characteristics differ from benign to malignant. We also note that masses with speculated and indistinct boundaries have a greater probability of malignancy than circumscribed masses.

It also notes that masses with speculated and indistinct boundaries have a greater probability of malignancy than circumscribed masses. Along with the mass margin and shape, intensity of gray level is one of major feature to classify the mass. Hence, in this CAD system, different

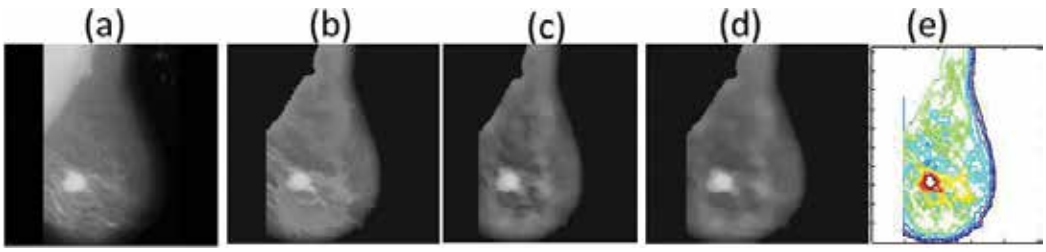

Figure 14. Experimental results of contour-based segmentation technique (a) original image, (b) preprocessed image, (c) opening, (d) closing, (e) reconstructed from opening and closing, (f) active contour.

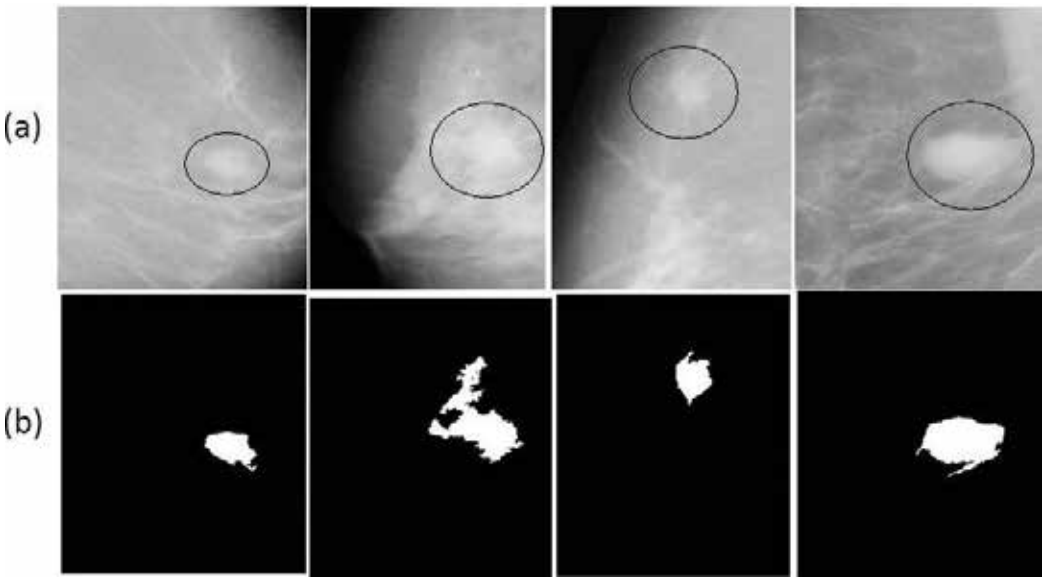

Figure 15. Mass segmented on different tissues using contour-based segmentation. (a) Ground truth (b) results of proposed work.

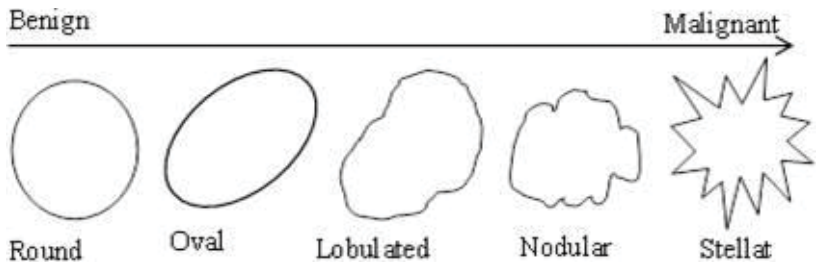

Figure 16. Morphological changes of mass in image from benign to malignant.

features have extracted by wavelet features, Gray Level Co-Occurrence Matrix (GLCM) features, and Segmentation-based Fractal Texture Analysis (SFTA) features calculated.

2.4.1. Discrete wavelet transform (DWT)

The DWT is wavelet transform using discrete set of scales and translations followed by some rules. To use a wavelet, it is necessary to discretize with respective to scale parameters, i.e., sampling. The scale and translation parameters are given by, $S = 2 -$ m and $T = n2 - m$, where m and n are the subset of all integers. Thus, the family of wavelet is defined in Eq. (6).

$$\psi_{m,n} = 2^{\frac{m}{2}}\psi(2^m t - n) \tag{6}$$

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The wavelet transform decomposes a signal $\chi(t)$ into a family of wavelets as given in Eq. (7).

$$\chi(t) = \sum_m \sum_n c_{m,n} \psi_{m,n}(t) \tag{7}$$

where

$$C_{m,n} = \{x(t), \psi_{m,n}(t)$$

For a discrete time signal $x[n]$, the decomposition is given by Eq. (8):

$$x[n] = \sum_{i=1 \text{ to } l} \sum_{k \epsilon Z} C_{i,k} g[n - 2^i k] + \sum_{k \epsilon Z} d_{1,k} h_1[n - 2^i k] \tag{8}$$

In case of images, the DWT is applied to each dimensionality, separately. The resulting image X is decomposed in first level is xA, xH,xV, and xD as approximation, horizontal, vertical, and diagonal, respectively. The xA component contains low frequency components and remaining contains high frequency component. Hence, X= xA + {xH + xV + xD}. Then, DWT applied to xA for second level decomposition. Hence, the wavelet provides hierarchical framework to interpret the image information [40, 41]. The basis of wavelet transform is localized on mother wavelet. Hence, in the proposed work, Haar, Daubechies (db2,db4 and db8), coiflet and bi-orthogonal wavelets at decomposition of level 4 used for the dataset and passed feature vector for the classification.

2.4.2. GLCM features

In texture analysis, widely used features are GLCM features. The GLCM is representation of frequently occurred gray levels combinations [42]. It is second order statistics that can be used to analyzing the texture features based on number of pixels in different combinations as shown in **Figure 17**. The matrices are constructed at different gray levels, such as 1, 2, 3, 4, and so on, for the different directions, such as 0, 45, 90, 180° and so on. Depends on the number of combinations the statistics are measured as features in first order, second order, and in higher

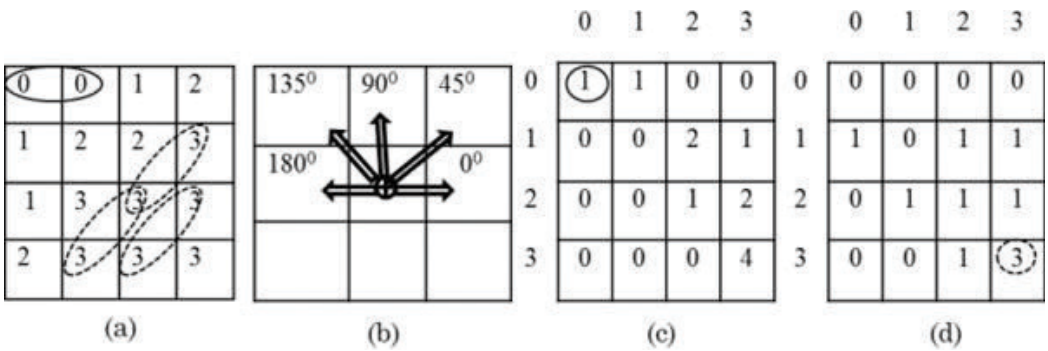

Figure 17. Example of GLCM (a) four-level gray image, (b) direction of combination with single pixel distance, (c) covariance matrix of four levels with direction 00 with single pixel distance, and (d) co-variance matrix of four levels with direction 450 with single pixel distance.

orders. Initially Haralick et al. [43] has defined 13 GLCM features then Soh and Tsatsoulis [44], and Clausi [45] have increased them to 21 features. In most of the CAD systems, these gray level features are used to interpret the symptoms. In the proposed work, we have extracted 21 GLCM features which are contributing to the discrimination of mass type.

2.4.3. SFTA features

Texture feature extraction is time-consuming process with basic filters because of scale and time invariant. This time consuming problem overcome by applying SFTA algorithm proposed by Costa [46]. SFTA works on multilevel thresholding on gray image. In purpose of using SFTA is to get the clear structure for mass boundaries. The 21 texture feature vector corresponds to texture information like dimension, different gray levels, and area of ROI. The region-based 21 shape features extracted from the ROI such as area, orientation, bounding box, extent, perimeter, centroid, extrema, pixel_idx_list, convex area, filled area, pixel list, convex hull, filled image, solidity, convex image, sub_array_idx, eccentricity, major_axis_length, equi_diameter, minor_axis_length, and Euler number. All together there are 73 features extracted from mass to train the CAD system to discriminate the mass type as benign and malignant [48].

2.5. Classification

Support vector machine (SVM) is a supervised learning technique that seeks an optimal hyperplane to separate two classes of samples. Mapping the input data into a higher dimensional space is done by using Kernel functions with the aim of obtaining a better distribution of the data. Then, an optimal separating hyperplane in the high-dimensional feature space can be easily found as shown in Ref. [47]. An example of an optimal hyperplane is shown in **Figure 18**.

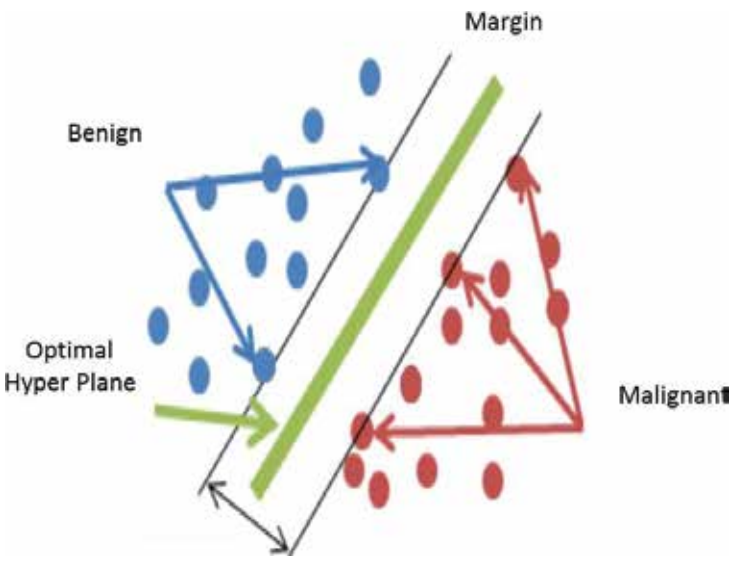

Figure 18. Optimum hyperplane for support vector machine.

3. Experimental results

The proposed algorithm implemented in MATLAB13a, classification accuracy measured with confusion matrix shown in **Table 1** and tested on MIAS dataset. MIAS contains a total of 322 mammograms of both breasts (left and right) of 161 patients.

According to above definitions of true positive, true negative, false positive and false negative. The equations related to specificity (the accuracy of negative class), sensitivity (accuracy of positive class and accuracy), and accuracy of recognize both negative and positive classes are defined as in Eqs. (9)–(11), respectively.

$$\text{Specificity} = \left(\frac{\text{TN}}{\text{TN} + \text{FP}}\right) * 100 \tag{9}$$

$$\text{Sensitivity} = \left(\frac{\text{TP}}{\text{TP} + \text{FN}}\right) * 100 \tag{10}$$

$$\text{Accuracy} = \left(\frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}\right) * 100 \tag{11}$$

Classification measured based on different feature extraction techniques with contour-based segmentation and SVM classifier as shown in **Table 2**, the number of images used to test the system is 50, and among them, 37 are malignant cases and 13 are benign cases. The accuracy is high using wavelet db4 features [50].

Though wavelet db4 gives high accuracy, it is important to consider texture based and gray level features to discriminate the mass type as benign and malignant. Hence, for the proposed CAD model all features together passed to measure the performance of algorithm with different segmentation techniques such as adaptive threshold-based technique, modified segmentation technique, and energy-based contour segmentation shown in **Table 3**.

Actual/predicted classes	Benign	Malignant
Benign	TP	FP
Malignant	FN	TN

Table 1. Confusion matrix.

Parameters	GLCM	Wavelet dB4	SFTA	Stats from region props
Total number of images	50	50	50	50
Number of benign images	13	13	13	13
Number of malignant Images	37	37	37	37
Number of misclassification	04	02	03	05
Accuracy (%)	92	96	94	90

Table 2. Samples used for performance evaluation.

Segmentation techniques	Accuracy	Specificity	Sensitivity
Adaptive threshold based	97.32143	98.03922	96.72131
Modified watershed segmentation	96.46018	100	93.75
Energy-based contour segmentation	98.26087	100	96.8254

Table 3. The performance measures of the SVM classifier with different similarity matrices.

Comparing with all the three techniques, energy-based technique gives more accurate results as shown in **Figure 19**.

The performance of the classifier compared with previous work shown in **Table 4**, the combination of different features achieved more accuracy comparing with existing work.

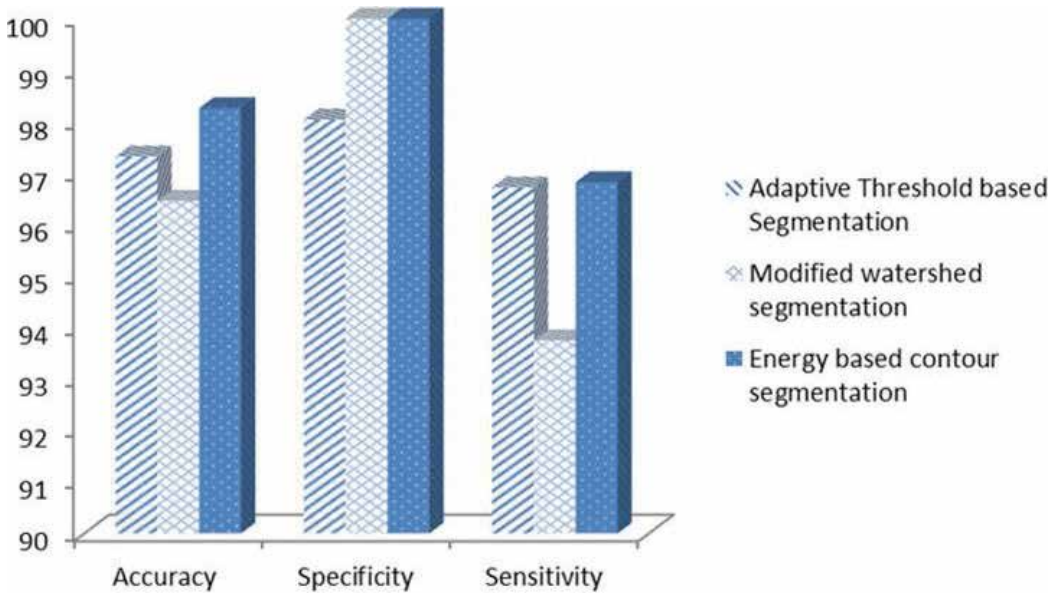

Figure 19. Comparative analysis of accuracy rate for adaptive threshold, modified watershed, and energy-based contour segmentation techniques.

Features	Classifier	Accuracy (%)	Reference
Fractal features	SVM	85.7	S. D. Tzikopoulos et al. (2011) [48]
SIFT, LBP, texton histogram	SVM	93.54	G. Liasis et al. (2011) [49]
GLCM, statistical, histogram (ROI)	K-NN	82.5	M. Mario et al. (2012) [50]
Statistical moments (ROI)	Combined K-NN	91.72	K. Vaidehi and T. S. Subashini (2015)[51]
Db4 wavelet, GLCM, SFTA features	SVM	98.26	Proposed method

Table 4. Comparison of preset algorithm with previous works reported.

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4. Discussion

Early detection of breast cancer may reduce the death rate. The advancement in technology is needed in the detection of all types of masses in terms of increasing sensitivity and reducing false positive rate. Masses can be varying in size and shape and thus, the proposed segmentation and feature extraction techniques are more suitable to measure in terms. As the experimental results reported based on individual feature sets such as GLCM, wavelet, SFTA, and region-based statistical features, the accuracy was 92, 96, 94, and 90%, respectively as observed in **Table 2**. With same segmentation technique accuracy is increased by passing combined set of features to SVM classifier as shown in **Table 3**. The CAD system is compared with different set of features with different classifiers as shown in **Table 4**. It proved that with less number of features and simple classifier, it improved the accuracy of detection and classification with less complexity.

5. Conclusion

The CAD system is used to help the radiologists to interpret the medical images like mammography, X-ray, ultrasound, MRI, etc. It used as a second opinion by the radiologists. Improving CAD accuracy increases the treatment option and a cure is more likely. There are some commercial CAD systems that have been reported, which are R2 technology Inc, intelligent system software Inc. (ISSI), CADx medical systems, and iCAD. All of these commercial CAD systems perform better at detecting calcifications than the masses. Architectural distortions become the challenging task to all the commercial CAD system. One cannot make a direct comparison between these systems and their work because there is no same clinical dataset to study and compare the performances. The proposed CAD model is more suitable for mass detection and classification. The obtained result show that selection of suitable approaches to design an algorithm for CAD is subject to the accuracy, sensitivity, and false positive identifications. To remove background noise and pectoral muscle, region growing and thresholding methods are proved to be good. The quality of the mammography was enhanced by using CLAHE and Wiener. Mass in mammography is extracted with proper marking use of contour-based segmentation. The set relevant features are provided to SVM classifier to discriminate mass type as benign or malignant. Finally, the outcomes from this study predict that the selection of appropriate technique at each stage of medical image analysis is subjective to relevant and significant to design a CAD model.

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Chapter 6

Breast Ultrasound Tomography

Nebojsa Duric and Peter Littrup

Additional information is available at the end of the chapter

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Abstract

Both mammography and standard ultrasound (US) rely upon subjective criteria within the breast imaging reporting and data system (BI-RADS) to provide more uniform interpretation outcomes, as well as differentiation and risk stratification of associated abnormalities. In addition, the technical performance and professional interpretation of both tests suffer from machine and operator dependence. We have been developing a new technique for breast imaging that is based on ultrasound tomography which quantifies tissue characteristics while also producing 3-D images of breast anatomy. Results are presented from clinical studies that utilize this method. In the first phase of the study, ultrasound tomography (UST) images were compared to multi-modal imaging to determine the appearance of lesions and breast parenchyma. In the second phase, correlative comparisons with MR breast imaging were used to establish basic operational capabilities of the UST system. The third phase of the study focused on lesion characterization. Region of interest (ROI) analysis was used to characterize masses. Our study demonstrated a high degree of correlation of breast tissue structures relative to fat subtracted contrast-enhanced MRI and the ability to scan ~90% of the volume of the breast at a resolution of 0.7 mm in the coronal plane.

Keywords: breast, ultrasound, 3-D imaging, tomography, cancer

1. Introduction

Breast cancer is the most common cancer among women, accounting for one-third of cancers diagnosed. Statistically, ~230,000 new cases of invasive breast cancer and ~63,000 in situ breast carcinomas are diagnosed in the US annually; breast cancer is the third leading cause of cancer death among women, causing ~40,000 deaths in the US every year [1]. According to SEER statistics, approximately 61% of women are found to have localized breast cancers at the time of diagnosis; about 31% are found to be regional disease; another 5% are diagnosed with distant metastases while about 3% are unstaged [2]. The 5-year survival rate for women with localized

cancer is 98%; for those with regional disease, it drops to 84%; for those diagnosed with distant stage, the survival rate drops dramatically to 23%; while for unstaged cancers the 5-year survival rate is about 58%. **Figure 1** illustrates the dependence of survival on cancer stage.

There are many reasons why cancers are not detected early but some of the major factors relate to limited participation in breast screening and the performance of screening mammography.

1.1. Limited participation in screening

National cancer screening statistics indicate that only 51% of eligible women undergo annual mammograms [4]. That rate is even lower for African American women and/or those of lower socioeconomic groups. Access, fear of radiation and discomfort are some of the factors that contribute to the low participation rate. Greater participation would lead to detection of breast cancer at an earlier stage leading to longer survival. Increased participation and improved breast cancer detection would have the greatest effect on the statistic of nearly 1 in 3 women who are diagnosed each year with later stage (regional or greater) breast cancer, totaling approximately 60,000 women per year in the USA. The net effect would be an increase in survival time and a corresponding decrease in mortality rates. This is also suggested in a recent meta-analysis, whereby increased participation and sensitivity lead to additional invasive cancer detection and greater mortality reduction [4].

1.2. Limited performance of mammography

For women with dense breast tissue, who are at the highest risk for developing breast cancer [5–8], the performance of mammography is at its worst [9]. Consequently, many cancers are

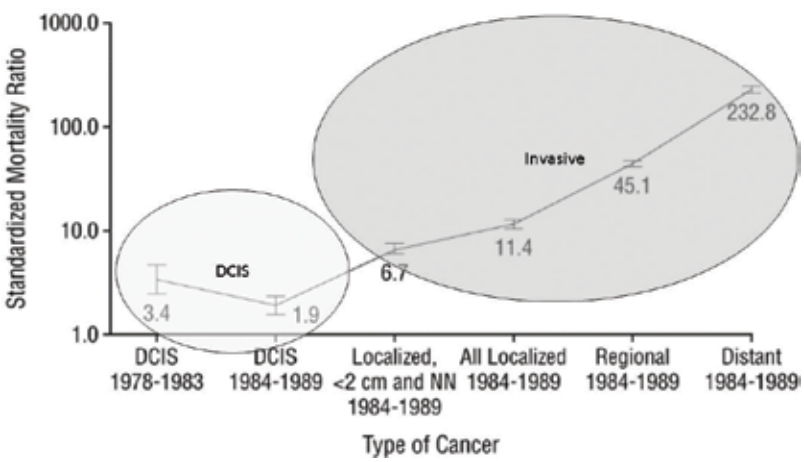

Figure 1. The dependence of mortality rates on cancer type and stage. From Kerlikowske et al. [3].

missed at their earliest stages when they are the most treatable. Improved cancer detection for women with denser breasts would decrease the proportion of breast cancers diagnosed at later stages, which would significantly lower the mortality rate.

1.3. The breast screening challenge

X-ray mammography detects about 5 cancers per 1000 screens [10]. However, its positive predictive value (PPV) is low and its sensitivity is greatly reduced in women with dense breast tissue [10]. Although digital breast tomosynthesis (DBT) may improve upon some of the limitations of standard mammography, it is unlikely to create a paradigm shift in performance [11] while generating even higher levels of ionizing radiation [12]. MRI can significantly improve on these limitations by virtue of its volumetric, radiation-free imaging capability. Studies have shown that MRI can have a positive impact in the breast management continuum ranging from risk assessment to diagnosis and treatment monitoring [12, 13]. However, MRI can have a high false positive rate, requires contrast injection and the exams can be both long and costly [14]. Furthermore, MR has long been prohibitively expensive for routine use and there is a need for a low-cost equivalent alternative. Yet, for high-risk women, MRI is now viewed as the gold standard for breast cancer detection and screening [15–23]. Positron emission tomography is also limited by cost and radiation concerns.

Recent studies have demonstrated the effectiveness of hand held ultrasound imaging in detecting breast cancer, particularly for women with dense breasts (**Table 1**). These studies have shown that up to 4.5 extra cancers were detected per 1000 screens [24–34]. A striking aspect of the added detections is that they are predominantly node negative invasive cancers which would have potentially progressed to a later stage before possible mammographic detection. Moreover, there is little risk of over detection of ductal carcinoma in situ (DCIS). The sensitivity of mammography is greater for DCIS than it is for invasive cancer, with DCIS making up approximately 25% of mammographic screen-detected breast cancers [35].

We have examined the data from these studies to extract the statistics of cancer detection by imaging mode (**Table 1**). The results are summarized in **Figure 2**. It is striking to note that ultrasound (US) almost doubles the cancer detection rate in dense breasts. However, despite these successful study outcomes, handheld ultrasound is unlikely to be adopted for screening because it is operator dependent, and its imaging aperture is small, which hinders whole breast imaging. Furthermore, ultrasound's increased sensitivity to invasive cancer is offset by lowered sensitivity to DCIS by virtue of mammography's greater ability to detect microcalcifications. Although such a trade-off may be justified by the fact that mortality from invasive cancers is much higher than that from DCIS, a combined screening [mammography plus automated breast ultrasound (ABUS)] would provide a comprehensive screen. It has therefore been proposed that ABUS be used for screening, supplemental to mammography.

Author (Year)	Center	Type	Exams	US only cancers	Yield per 1000
Brem et al. (2014)	Multi	ABUS	15,318	30	1.96
Berg et al. (2012)	Multi	HHUS	7473	32	4.28
Hooley et al. (2012)	Single	HHUS	935	3	3.21
Kelly et al. (2010)	Multi	AWBU	6425	23	3.58
Corsetti et al. (2008)	Multi	HHUS	9157	37	4.04
Crystal et al. (2003)	Single	HHUS	1517	7	4.61
Leconte et al. (2003)	Single	HHUS	4236	16	3.78
Kolb et al. (2002)	Single	HHUS	13,547	37	2.73
Kaplan (2001)	Single	HHUS	1862	6	3.22
Buchberger et al. (2000)	Single	HHUS	8103	32	3.95
Gordon et al. (1995)	Single	HHUS	12,706	44	3.46

Table 1. Summary of studies used in the analysis.

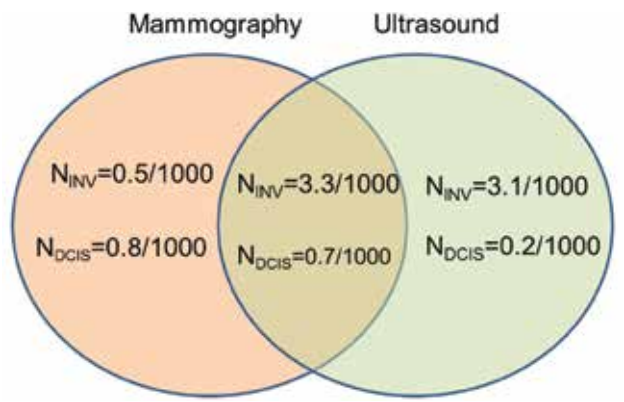

Figure 2. Venn diagram summarizing comparative cancer detection rates for screening mammography and ultrasound.

To that end, automated breast ultrasound (ABUS) has been introduced as a way of overcoming these issues, mainly by reducing operator dependence and increasing the field of view. For example, the GE Invenia ABUS ultrasound system for breast cancer screening, originally developed by U-Systems., recently received screening approval, adjunctive to mammography, from the FDA, because it demonstrated an ability to detect cancers missed by mammography in dense breasts. The SomoInsight screening study [24], indeed showed that ABUS plus mammography outperformed mammography alone, leading to the first FDA approval for ultrasound screening for breast cancer.

The fundamental quandary of breast screening today is the knowledge that (i) mammography misses cancers in dense breasts, (ii) that Automated Breast ultrasound (ABUS) detects cancers that mammography misses and yet (iii) screening continues largely with mammography only. This paradox

is amplified even further by the proliferation of state breast density notification laws in the USA which mandate that this information be available to women undergoing breast cancer screening. The primary reason this paradox exists today is that ABUS screening increases call back rates (up to a factor of two in case of the SomoInsight study [23]). The improvement in classification performance, measured by the area under the ROC curve, is modest because the increase in sensitivity is partially offset by an increase in false positives thus slowing its adoption. Technically, with its basic B-mode capability, ABUS has the same issue with false positives as hand held ultrasound. It is therefore unlikely that ABUS will be widely adopted for screening in the foreseeable future without more tissue-specific imaging capability. Improved lesion characterization would help lower the barriers to adoption of screening ultrasound.

1.4. Potential role of UST

Ultrasound tomography (UST) is an emerging technique that has the potential for tissue-specific imaging and characterization, by virtue of its transmission imaging capability [36–61]. Improved specificity would lower call back rates and lower the barriers to adoption. An adjunctive use of UST would have the potential to improve specificity relative to current ABUS and provide a comprehensive screen that would uncover invasive cancers otherwise missed by mammography. Detection of such early stage invasive cancers would provide women with curative treatment, the opportunity for which might be otherwise lost.

Conventional reflection ultrasound exploits differences in acoustic impedance between tissue types to provide anatomical images of breast tumors [62, 63]. However, reflection is just one aspect of a multi-faceted set of acoustic signatures associated with the biomechanical properties of tissue. UST is a technique that moves beyond B-mode imaging by virtue of its transmission capabilities. The latter provides additional characterization by measuring tissue parameters such as sound speed and attenuation (ATT) [64–68]. These parameters can be used to characterize lesions in a quantitative manner, a capability not available in current whole breast ultrasound systems. By merging reflection images with images of the bio-acoustic parameters of sound speed and attenuation, UST offers the possibility of exploiting differences in anatomical and physical properties of tissue to accurately differentiate cancer from normal tissue or benign disease. UST parameters are also quantitative, which allows new consideration of second and third-order statistical image analyses, or radiomics. Ultrasound has previously not been suitable for the burgeoning applications of radiomics due to its lack of true quantitative parameters such as sound speed (m/s) and attenuation (dB/cm/MHz). Initial assessments of UST performance was carried out, as described below.

In an initial attempt to assess the potential of UST in breast imaging, studies were carried out at the Karmanos Cancer Institute, Detroit, MI, USA. Informed consent was obtained from all patients, prospectively recruited in an IRB-approved protocol following HIPAA guidelines. Patients were scanned at the Alexander J Walt Comprehensive Breast Center. Standard multi-modality imaging was available for all patients. The Walt Breast Center houses SoftVue, a UST system manufactured by Delphinus Medical Technologies, Inc (Novi, MI). SoftVue embodies a number of attributes that differentiate it from conventional imaging modalities:

- *Water-based pulse coupling*: SoftVue utilizes a water filled imaging chamber that is kept at body temperature. Its primary purpose is to couple the sound energy between the transducer and the breast tissue.
- *Closed geometry probe*: A circular ring transducer surrounds the breast while both are immersed in water. There is no compression of the breast since the transducer is offset from the breast with water acting as the pulse coupling agent. The closed transducer geometry allows collection of signals that pass through the entire width of the breast, a requirement for transmission imaging and the reconstruction of sound speed and attenuation images. These parameters provide quantitative information in absolute units that are tied to externals standards (km/s and dB/cm, respectively).
- *Operator independence*: Unlike mammography and other ABUS systems, multiple positionings are not required for larger breasts. Once the patient is positioned on the table, the operator simply presses the button and the exam is performed automatically without further intervention from the operator.
- *Scan time*: SoftVue scan time is 1–2 min per breast (depending on breast size). This scan duration minimizes intra-slice and inter-slice motion artifacts.
- *Image reconstruction time*. In this study, reconstruction time for a bilateral breast exam was ~30 min for the average patient and current hardware/software processing ability.

SoftVue was used to scan the recruited patients for this study. Coronal image series were produced by tomographic algorithms for reflection, sound speed and attenuation. All images were reviewed by a board-certified radiologist who has more than 20 years of experience in breast imaging and US-technology development. Symptomatic study participants were scanned with a SoftVue UST system. Pathological correlation was based on biopsy results and standard imaging (e.g. US definitive cyst).

Tomographic algorithms were used to generate images stacks of reflectivity, sound speed and attenuation for each patient. Lesions were identified based on correlation with standard imaging so that the tumor sound speed (SS) and attenuation (ATT) could be assessed. An example each type of image is shown in **Figure 3**.

In the first phase of the study, correlative comparisons with multi-modal imaging were carried out to assess lesion properties relative to mammography, US and MR. In the second

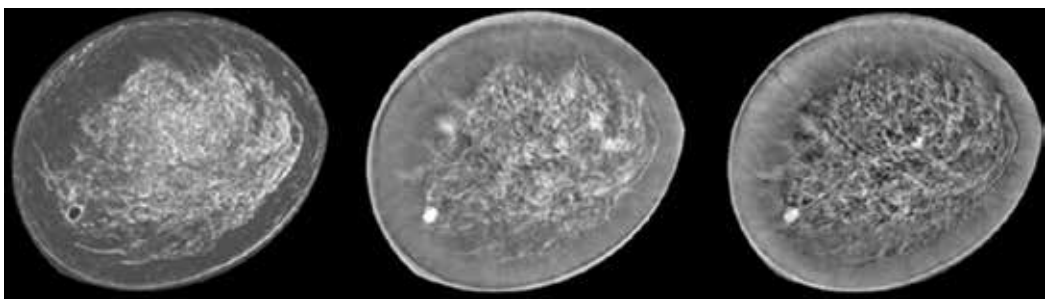

Figure 3. From left to right, reflection, sound speed and attenuation image slices depicting breast parenchyma and a fibroadenoma at 7 o'clock.

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phase, MR breast imaging was used to establish basic operational capabilities of the UST system including the identification and characterization of parenchymal patterns, determination of the spatial resolution of UST and an estimate the breast volume that can imaged with UST. The third phase of the study focused on lesion characterization. Region of interest (ROI) analyses were performed on all identified lesions using all three UST image types. Combinations of the ROI generated quantitative values were used to characterize all masses, particularly in relation to relative differences with surrounding peritumoral regions.

2. Multi-modal comparisons

Since the patients were recruited at KCI on the basis of having a suspicious finding, standard imaging such as mammography, US and sometimes MRI were available, as well as the radiology and pathology reports. These images and the associated reports were used to retroactively locate the lesions in the UST image stacks for visual comparison. **Figures 4–7** show examples of UST images in relation to the other modalities. When MRI was available, the images were projected into the coronal plane for easier comparison with the UST whose native format is coronal.

Figure 4 shows a 9mm IDC at 3 o'clock. CC and MLO mammographic views of the affected breast are shown on the left with the lesion identified by arrows. The UST views corresponding

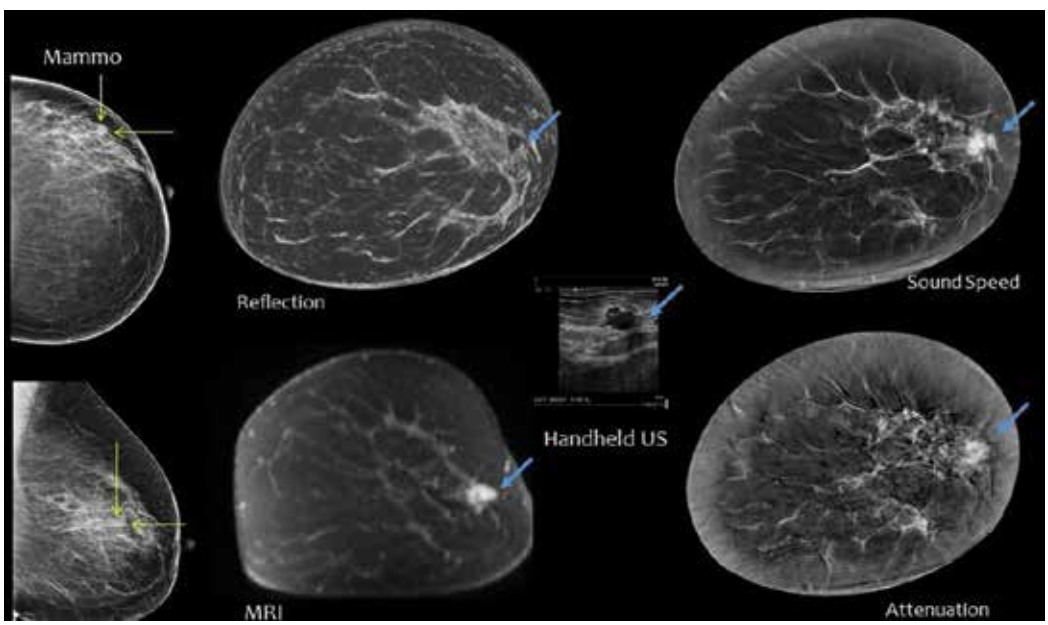

Figure 4. A 9 mm IDC at 3 o'clock. CC and MLO mammographic views of the affected breast are shown on the left with the lesion identified by arrows. The coronal UST views are shown in the form of reflection, sound speed and attenuation images. The corresponding ultrasound and MR images are also shown.

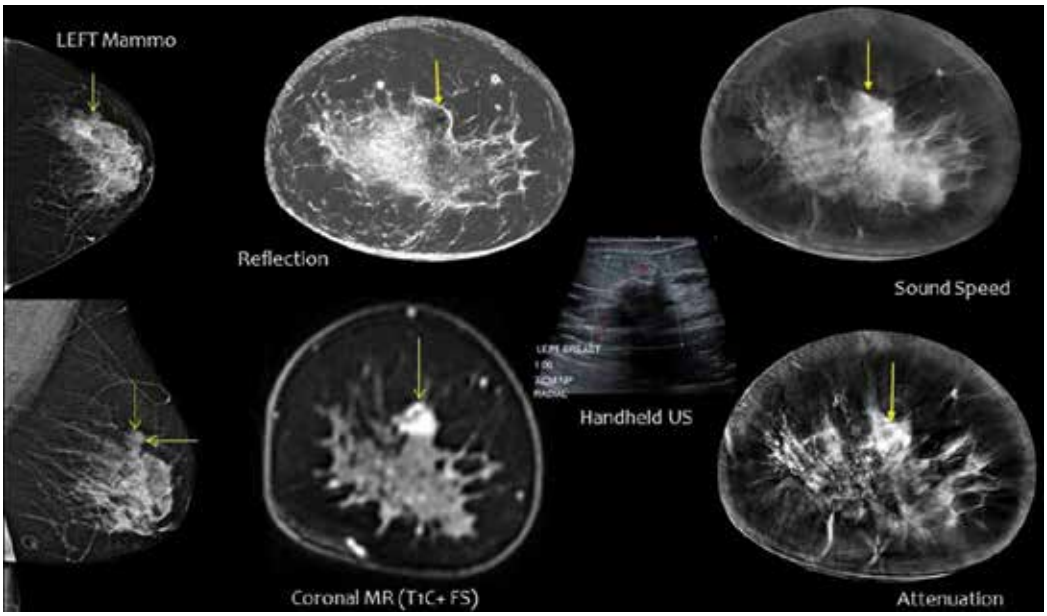

Figure 5. Multimodality images compared to UST reflection, sound speed and attenuation. An IDC is shown at 12 o'clock.

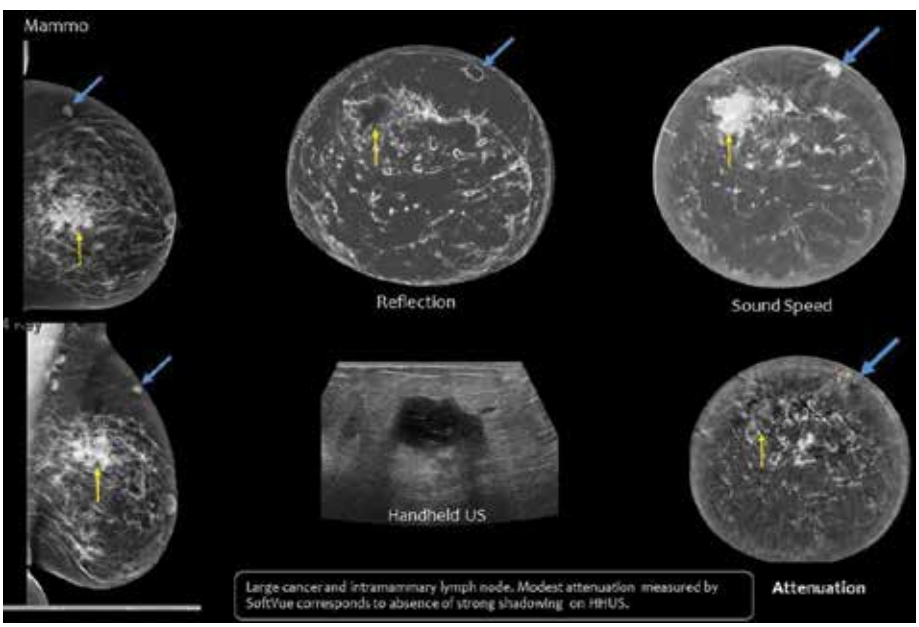

Figure 6. Multimodality images vs UST reflection, sound speed and attenuation showing an IDC and intramammary lymph node.

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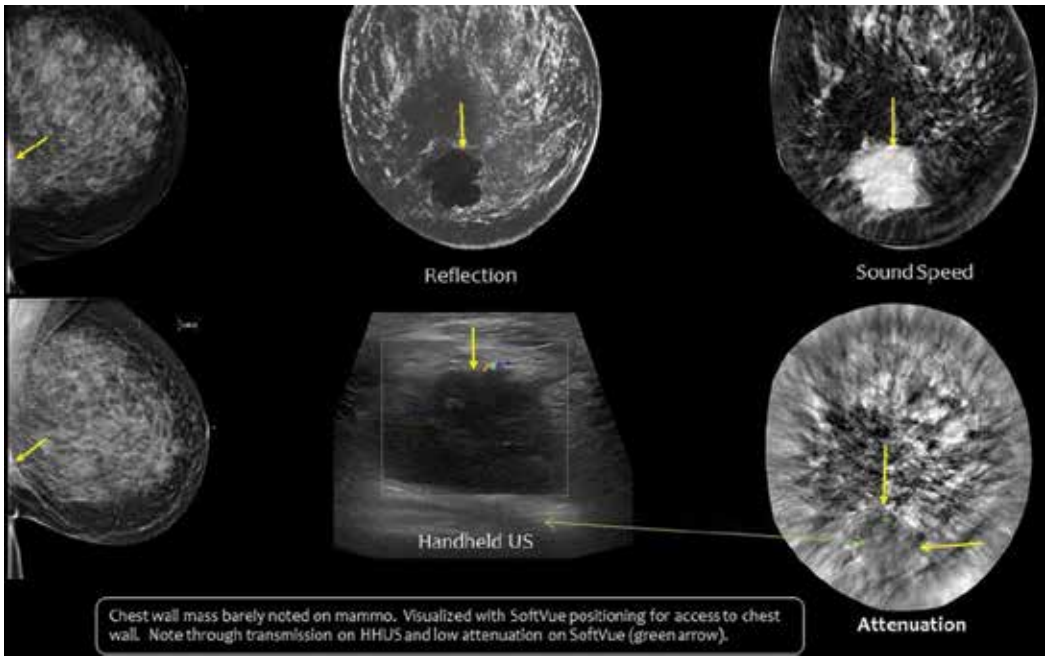

Figure 7. Illustrating the chest wall access achievable by UST relative to mammography.

to the coronal planes that contain the lesions are across the top with reflection, sound speed and attenuation images laid out from left to right. The corresponding ultrasound and MR images are shown along the bottom. Inspection of the images shows good correspondence in shape and location of the lesion. The greatest similarity is between the UST images and MRI. The IDC is seen to be hypoechoic in reflection and has high sound speed and attenuation contrast. An IDC in a heterogeneously dense breast is shown in **Figure 5** This IDC was initially missed by mammography. A large IDC and an intramammary lymph node are shown in **Figure 6**. Note the concordance between the UST images and mammography. **Figure 7** illustrates the chest wall access achievable by UST relative to mammography. Although UST does not access the entire axilla it does visualize the cancer that has invaded the chest wall.

3. MR concordance

UST and MR imaging was performed within weeks of each other. UST imaging was carried out with the SoftVue system (Delphinus Medical Technologies) and the MR exams with a Philips Achieva 3T system. The resulting image sequences were qualitatively and quantitatively to assess imaging performance of UST. As discussed above, UST images correlate best with MR images. Further inspection shows that of the three UST image types, the sound speed image correlates best with MR. **Figure 8** shows a coronal view comparison between UST speed of sound and MR contrast-enhanced fat subtracted images of representative breast parenchyma.

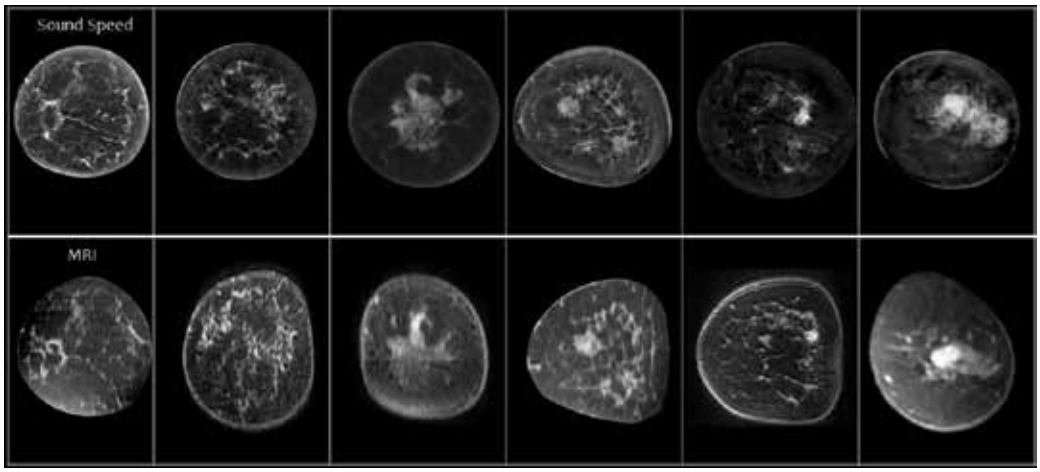

Figure 8. Top: Coronal UST sound speed images for six different patients. Bottom: Corresponding fat subtracted contrast-enhanced MR images.

The parenchymal patterns are very similar with the only major difference relating to the shape of the breast. This difference can be explained by the fact that the SoftVue system utilizes water so that buoyancy foreshortens the breast while with MR, gravity lengthens the breast in the AP dimension (i.e. prone).

As discussed above, UST images correlate best with MR images. Further inspection shows that of the three UST image types, the sound speed image correlates best with MR, as illustrated in **Figure 8**. The parenchymal patterns are very similar with the only major difference relating to the shape of the breast. This difference can be explained by the fact that the SoftVue system utilizes water so that the buoyancy force helps shape the breast while with MR, gravity shapes the breast.

4. Breast volume comparisons

MRI was used as the gold standard for defining the extent of the breast tissue. MRI and UST breast volumes were compared using a paired t-test. In the first step, a k-means segmentation algorithm was applied to T1 breast MR images to automatically separate out the non-tissue background. In the second step, the boundary between the breast tissue and the chest wall was drawn manually and the chest wall removed, leaving behind only breast tissue (**Figure 9**).

In the UST images a semi-automated tool was used to draw a boundary around the breast tissue in each coronal slice and everything outside the boundary removed (water signal). Any slices containing chest wall signal were also removed. The resulting stack of slices then represented the pure breast volume scanned by UST.

The two sets of volumes were plotted against each other as shown in **Figure 10**. The average breast volumes for MRI and UST were compared and the result shown in **Table 2**. As expected, the UST

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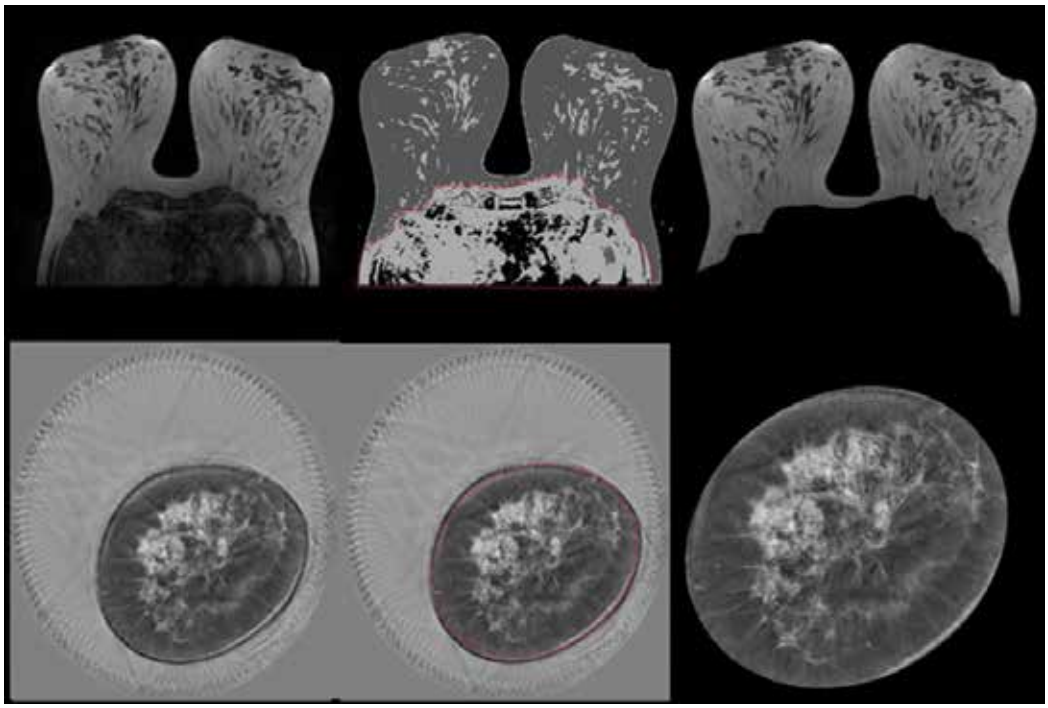

Figure 9. The segmentation process for MR images (top) and UST images (bottom). From left to right, original image, segmentation boundary and the final segmented image.

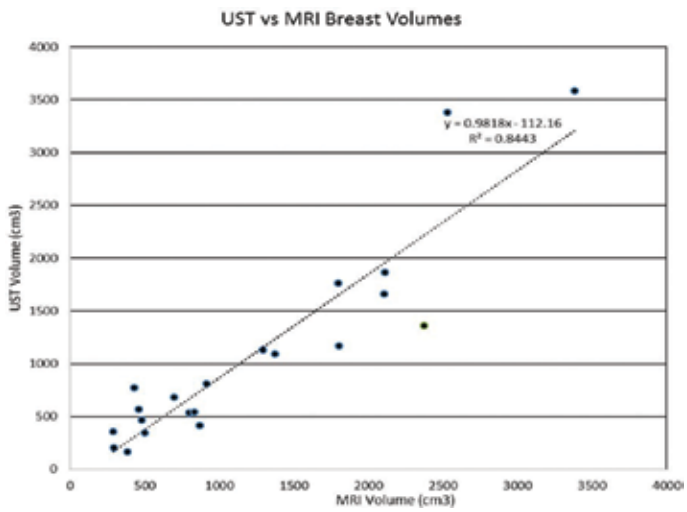

Figure 10. Correlation between UST and MR measured breast volumes.

Mean MRI volume (cm^3)	Mean UST volume (cm^3)	*p* Value
1224	1089	0.113

Table 2. Volume comparison.

scanned volume was less than that of MRI and was found to be about 89% of the MRI volume on average. However, a student's paired t-test indicates that this difference is not significant. Since UST cannot fully access the axilla, it is likely that the UST scanned volume is somewhat lower than that of MRI, even though UST generally reaches the pectoralis muscle at the chest wall.

5. Spatial resolution assessment

The spatial resolution of each modality was estimated using profile cuts of thin features using, the full-width, half-maximum criterion as shown in **Figure 11**. The results of the spatial resolution analysis are shown in **Table 3**. The spatial resolution was found to be dependent on the reprojection type for both MRI and with UST outperforming MRI in the coronal plane and MRI outperforming UST in the other projections. (However, MR acquisitions with isotropic voxels would show comparable resolution to UST in the coronal plane). The UST image voxels are not isotropic and data acquisition cannot be readily adjusted like MR, such that UST reconstructed in axial and sagittal planes have resolution that approach the 2.5 mm slice thickness at this time.

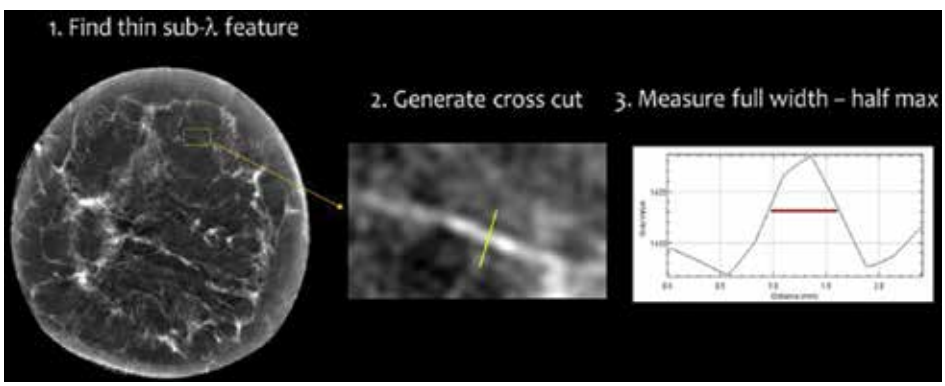

Figure 11. The spatial resolution of each modality was estimated using profile cuts of thin features using, the full-width, half-maximum criterion, as illustrated.

Resolution	UST	MRI
Coronal	0.7 ± 0.1 mm	1.6 ± 0.3 mm
Axial/sagittal	2.5 ± 0.5 mm	0.8 ± 0.1 mm

Table 3. Spatial resolution comparison.

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6. Lesion characterization

Ultrasound breast imaging reporting and data system (US-BI-RADS) criteria are predominantly devoted to assessment of tumor shape, margins and interaction with adjacent tissue. However, criteria such as shadowing or enhanced through transmission are not applicable to UST's circular geometry. In addition, UST, operating at 3 MHz, appears more sensitive to the specular reflectors of benign mass capsules, or the spiculations and/or architectural distortions of many cancers. Therefore, we developed a 5-point scale that combined US-BI-RADS criteria for tumor margins, as well as possibilities for peritumoral tissue interaction (**Figure 12**).

Masses were characterized by a (i) Margin Boundary score, (ii) reflectivity, (iii) quantitative SS evaluation and (iv) ATT evaluations. A semi-automatic region-of-interest (ROI) tool was used to determine the quantitative properties of each mass. After identifying the mass of interest, a simple elliptical ROI is drawn around the mass. The ROI algorithm then generates 20 radial ellipsoids – 10 inside and 10 outside the mass. Quantitative information was then measured for each of the 20 annuli for subsequent analysis. The region of interest (ROI) analysis was performed on all identified lesions using all three UST image types. Combinations of the ROI generated values were used to characterize all masses in the study.

Ongoing analyses of the ROI tool have not yet led to full evaluation of second and third-order statistics of textural analyses, as well as their impacts upon decision analysis and predictive values. However, our recent RSNA presentation highlighted the significant impacts of first-order statistics such as standard deviation, within the tumoral ROI and comparisons with the surrounding peritumoral region [69]. Scatterplots and box plots of the optimal methods were used to illustrate the characterization potential. The box plot in **Figure 13** shows the differentiation achieved when using the boundary score (**Figure 6**) combined with the first-order statistic of standard deviation, a more crude measure of heterogeneity, based upon tumoral ROI extracted from ATT images, which had only slightly higher significance than SS [69]. These ROIs were again obtained by simply drawing an elliptical ROI around the mass and determining the standard deviation with in the ROI. The box plot was based on taking the average values for 107 benign lesions and 31 cancers [69].

Upon further investigation, it was found that the SS of the peritumoral mass region (defined by an annular area just outside the mass boundary ROI) further separated the benign masses from cancer. A scatter plot based on all of these parameters is shown in **Figure 14**. The scatter plot shows separately the cancers, fibroadenomas and cancers. The cancers are tightly

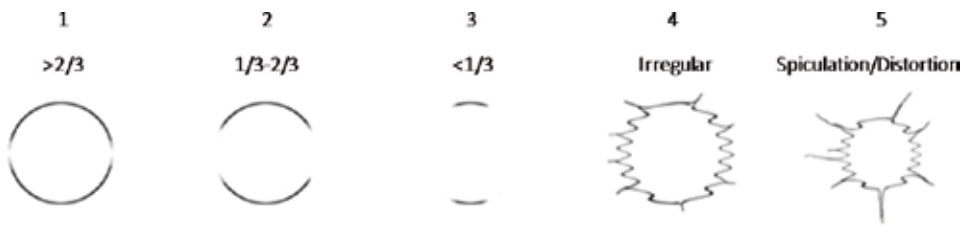

Figure 12. Schematic of shape and margin analysis and associated grading scheme.

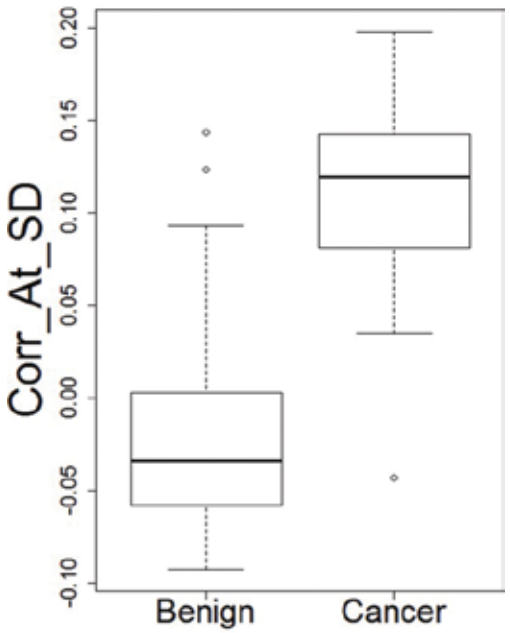

Figure 13. Separation of cancer from benign when using boundary score and hetrogeneity score.

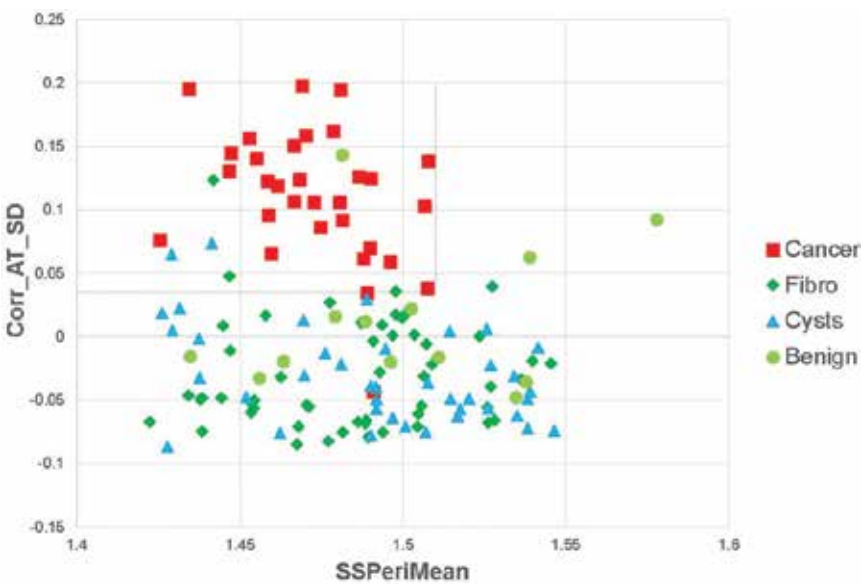

Figure 14. Scatter plot showing the distribution of cancers (squares), Fibroadenomas (diamonds), cysts (triangles) and other benign (circles).

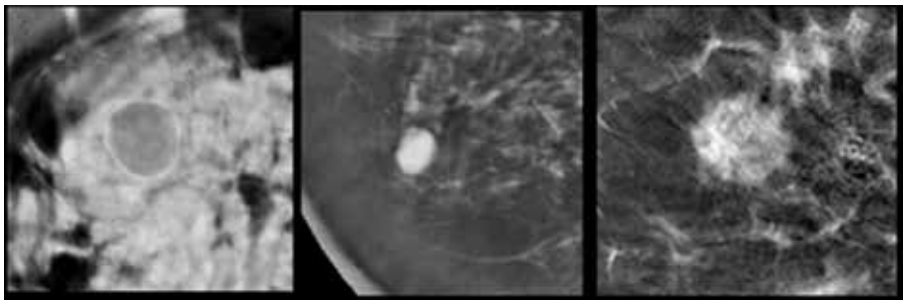

Figure 15. Cyst, fibroadenoma, cancer: Waveform SS images showing well circumscribed margins and smooth internal textures for both the 1.5 cm cyst in dense white breast tissue (left) and the 0.7 cm fibroadenoma (middle) in darker fat. The 1.8 cm cancer (right) has irregular margins, heterogeneous content and subtle peritumoral spiculations.

grouped in the top left corner of the plot indicating high boundary scores, high heterogeneity and lower peritumoral sound speed. By these measures, there was not much separation between cysts and fibroadenomas but significant separation between them and cancer. ROC analysis of the data represented in the scatter plot indicates a PPV of 91% when the sensitivity is 97%. However, this is a subset of data relative to an expanded ongoing study that includes more quantitative margin analyses. The ultimate goal is to generate textural analyses that will be less operator dependent and serve as appropriate diagnostic aids for a detected mass by simply requiring the radiologist to draw an ellipsoidal ROI. This method can also serve as a teaching tool for identifying grossly apparent textural differences within the tumor and surrounding peritumoral region. **Figure 15** shows the basic differences in sound speed texture noted for many cysts, fibroadenomas and cancer.

7. Conclusions

In this study we reviewed the status of breast cancer screening and the potential role that ultrasound tomography (UST) could play in breast imaging. Several results from recent ongoing UST studies were used in this review. The main conclusions from those studies are:

(i) UST sound speed demonstrated a high degree of correlation of breast tissue structures relative to fat subtracted contrast-enhanced MRI. This correlation of structures was most evident in the coronal plane comparisons.

(ii) UST can scan ~90% of the volume of the breast compared to MRI. With proper positioning UST can image the pectoralis muscle and a portion of the axillary tissue.

(iii) UST demonstrated a spatial resolution of 0.7mm in the coronal plane, similar to MRI.

(iv) Initial clinical results suggest an ability to characterize lesions using margin boundary scores in combination with sound speed and attenuation parameters. These parameters leverage all three imaging modes of UST (reflection, sound speed and attenuation).

UST is a promising new modality that has the potential to complement existing breast imaging methods to aid in lesion detection and characterization. Future larger scale studies will assess UST's role in diagnostic and screening settings.

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