Chapter 2

Breast Ultrasound Past, Present, and Future

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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.

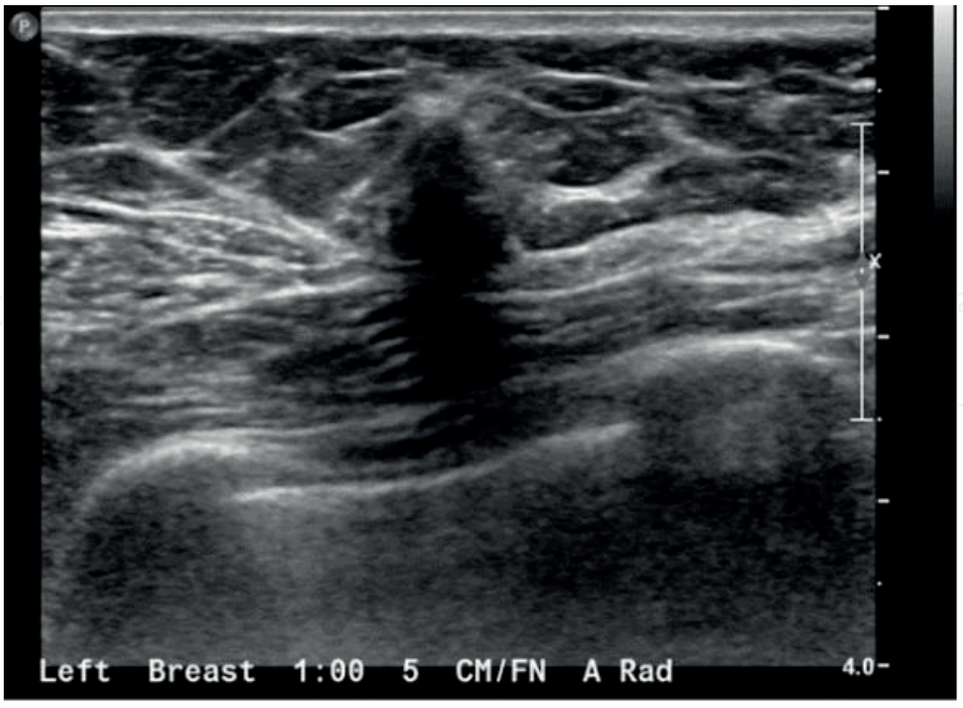

Figure 1. Transverse ultrasound of the left breast demonstrates an irregular, antiparallel mass with posterior acoustic shadowing.

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.

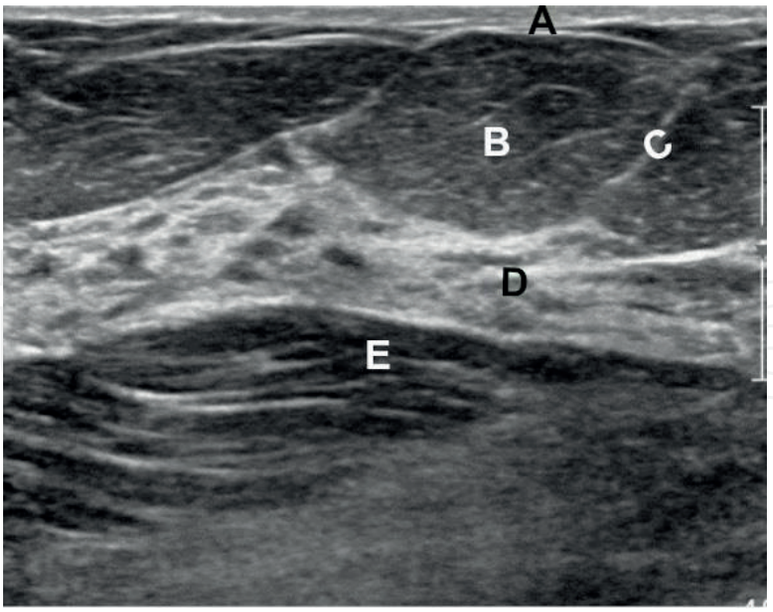

Figure 2. Breast anatomy. Transverse ultrasound shows normal breast anatomy. (A) Skin, (B) fat lobule, (C) Cooper ligament, (D) fibroglandular zone, and (E) muscle.

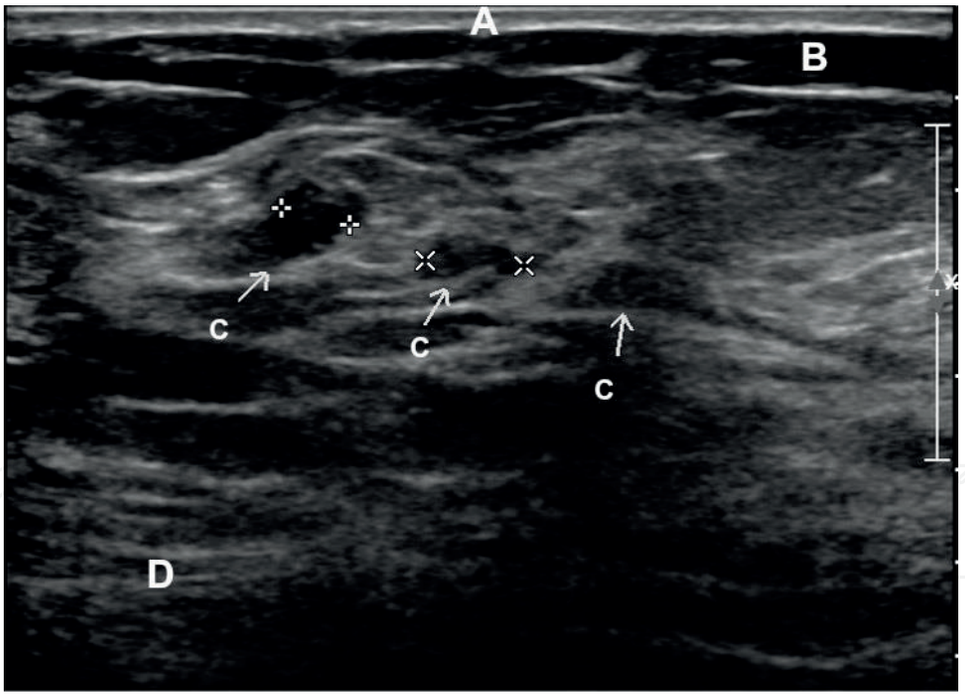

Figure 3. Breast anatomy. Transverse ultrasound shows normal breast anatomy. (A) Skin, (B) subcutaneous fat, (C) terminal duct lobular unit, and (D) muscle.

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].

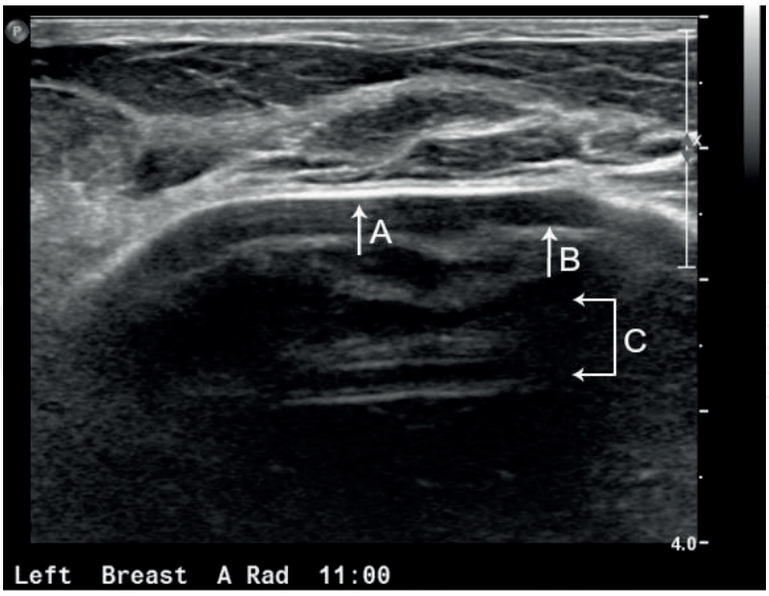

Figure 4. "**Stepladder sign.**" Transverse ultrasound demonstrates an intracapsular silicone implant rupture. (A) Outer capsule, (B) shell of collapsed implant, and (C) "Linguine sign".

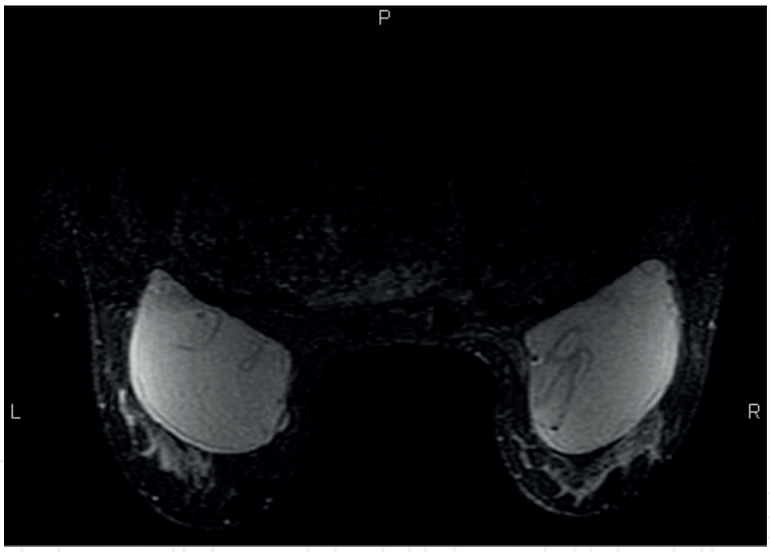

Figure 5. Axial T2W MRI demonstrates bilateral intracapsular silicone implant ruptures.

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

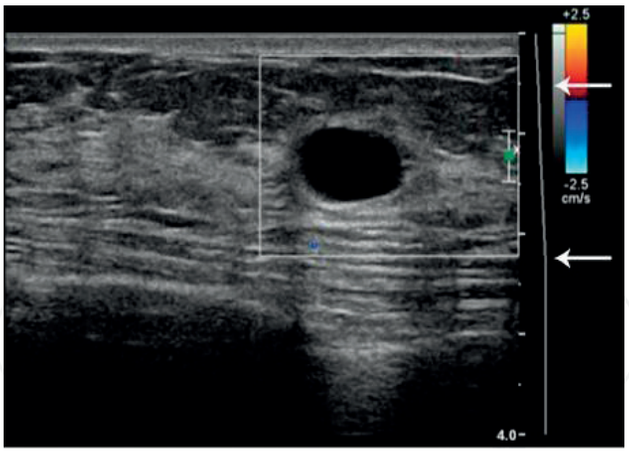

Figure 6. Gain. Transverse ultrasound illustrates gain. Ultrasound waves are absorbed by tissue. The deeper the tissue, the greater the absorption. A gradual increase in the gain with deeper tissues is recommended.

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].

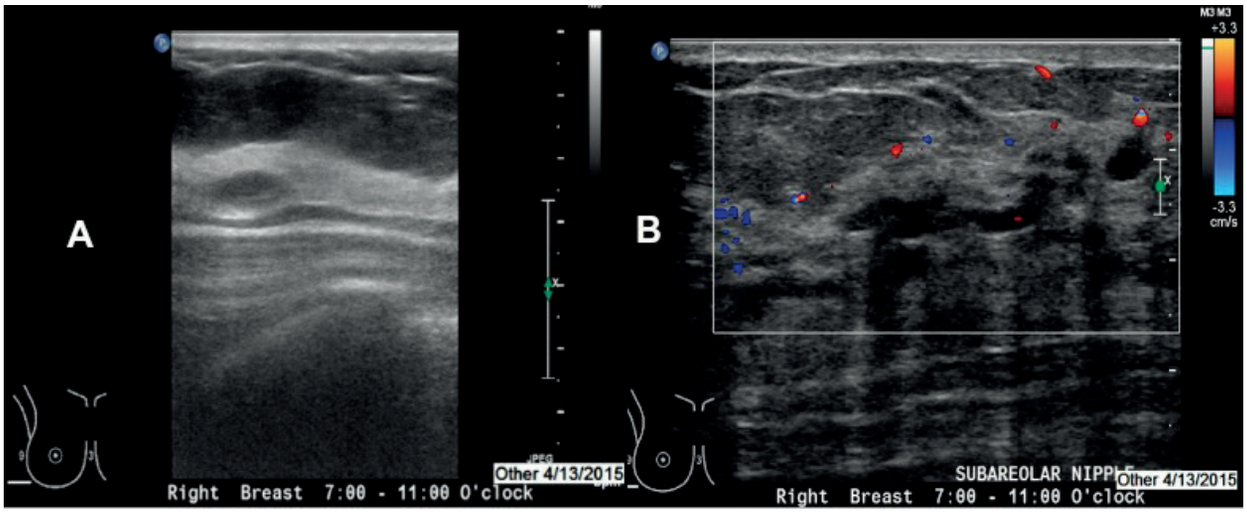

Figure 7. Focal zone. Transverse ultrasound of the right breast illustrating focal zone settings. The focal zone should be set at the anterior to middle third of the region of interest. (A) Partial volume averaging—loss of detail and (B) image with appropriate focal zone setting.

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

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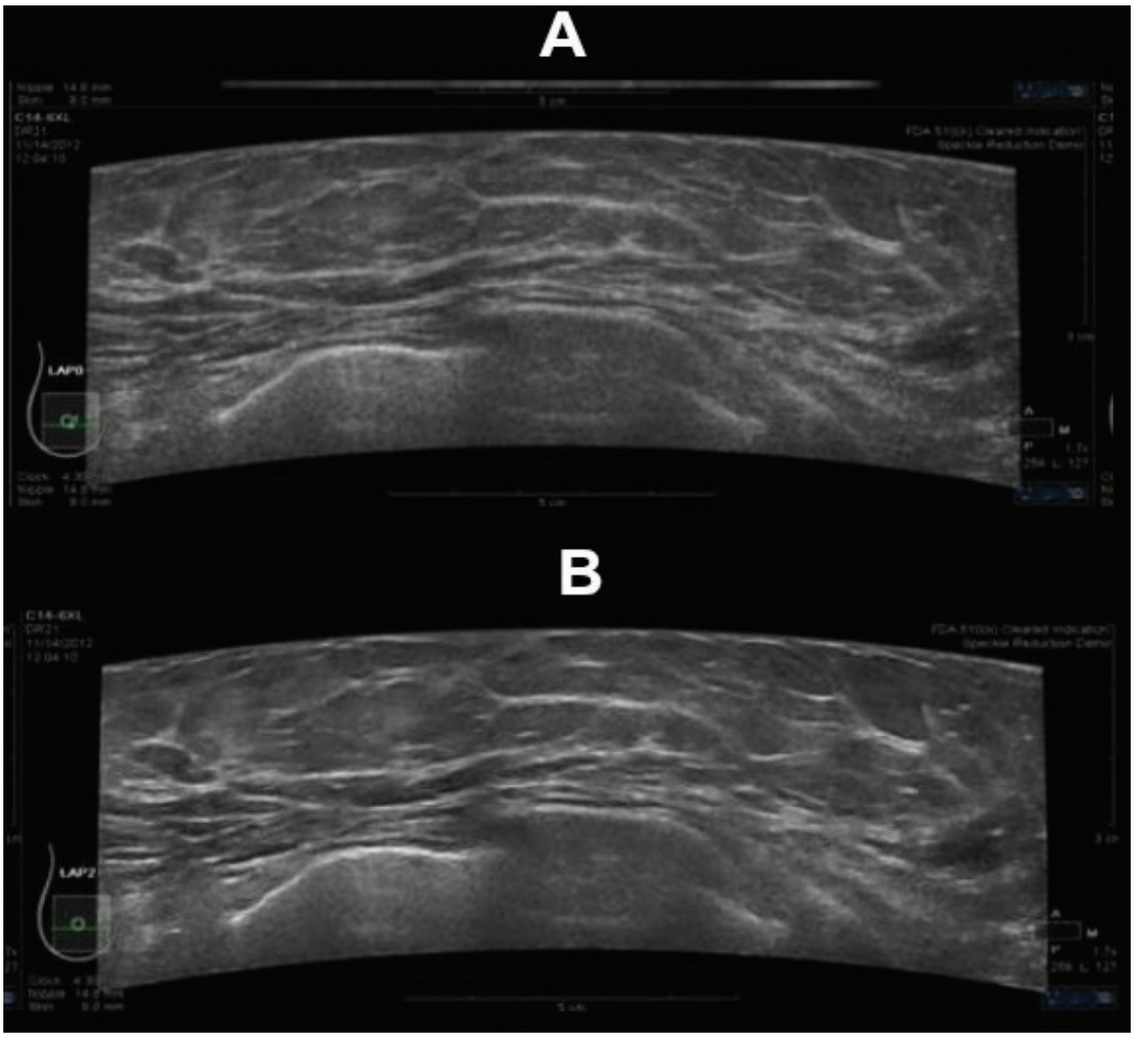

Figure 8. (A) Long axis view of transverse ultrasound demonstrating speckle artifact. Increased noise noted throughout the image and (B) long axis view of transverse ultrasound demonstrating speckle reduction.

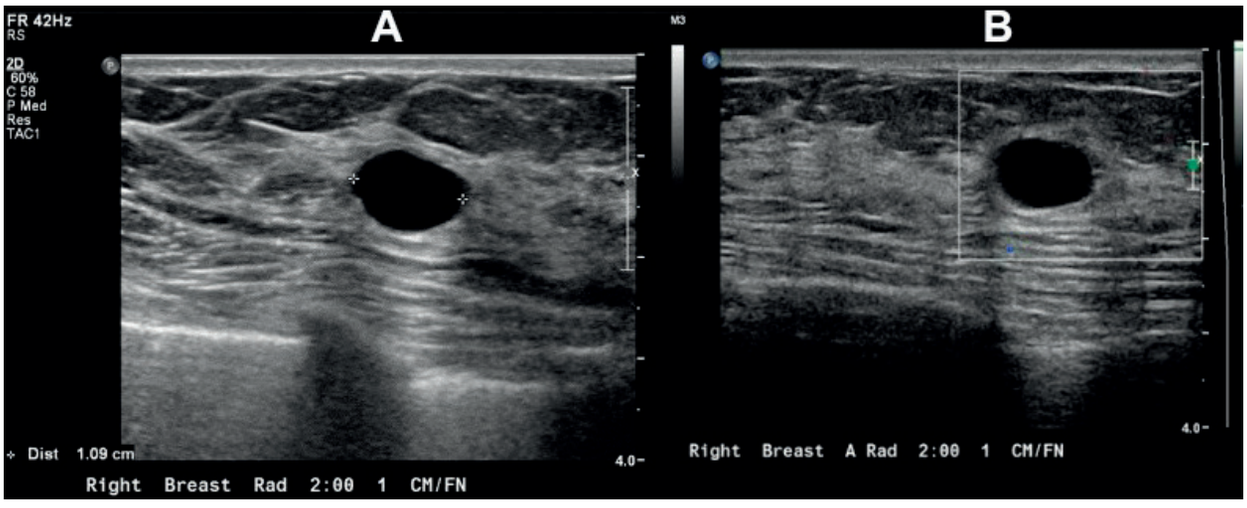

Figure 9. Compound imaging. Transverse ultrasound of the right breast illustrates compound imaging. (A) Utilization of compound imaging and (B) without compound imaging.

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

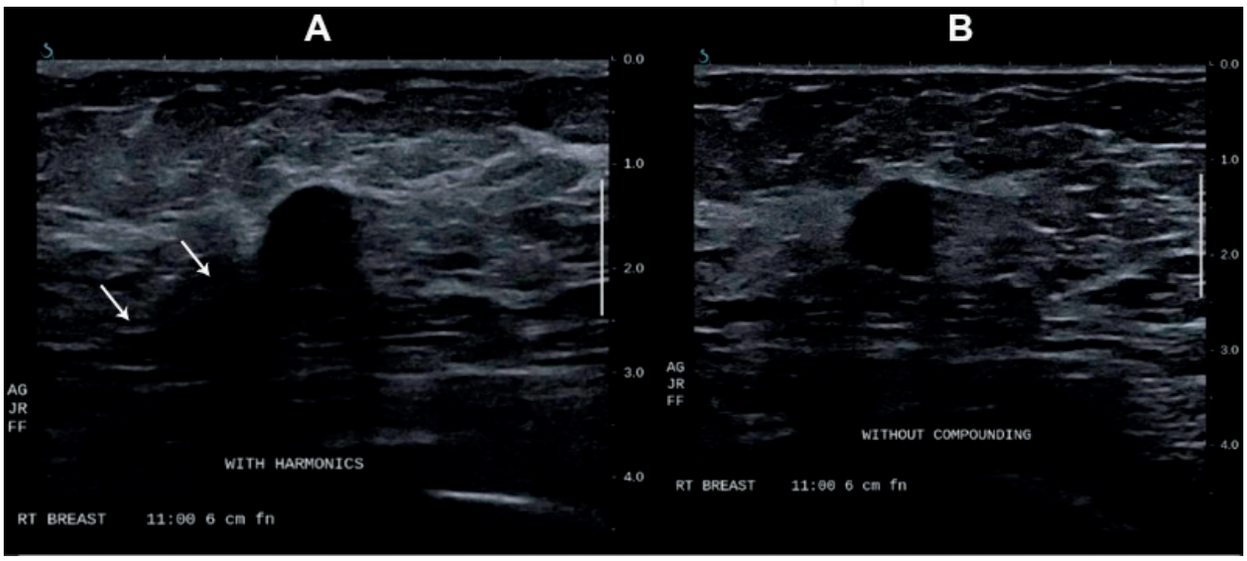

Figure 10. Harmonics increase real echoes. Transverse ultrasound of the right breast shows harmonics increasing real echoes. (A) With harmonics and (B) without harmonics.

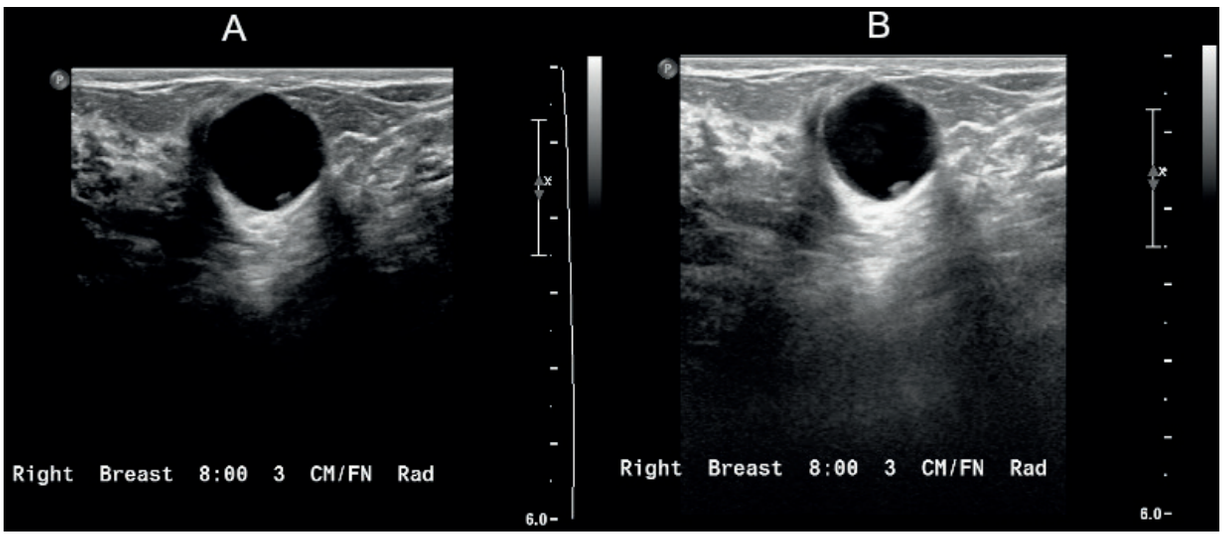

Figure 11. Harmonics reduce artefactual echoes. Transverse ultrasound of the right breast shows harmonics reducing artefactual echoes. (A) With harmonics and (B) without harmonics.

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].

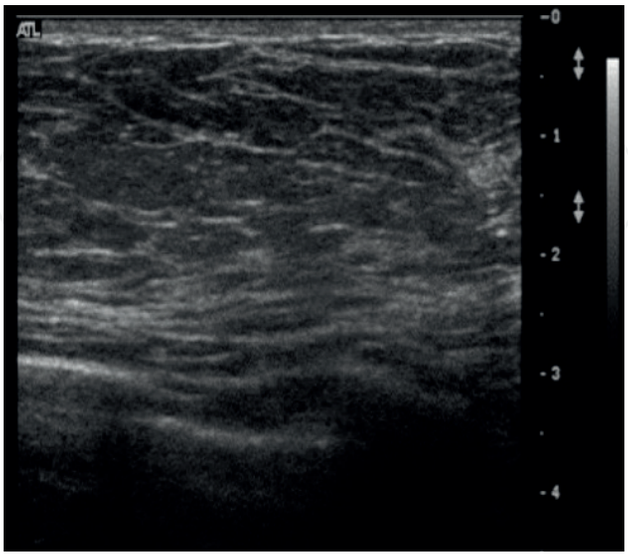

Figure 12. Homogenous background echotexture—fat. Transverse ultrasound demonstrates fat lobules, with uniform echogenic bands of supporting structures making up the bulk of the breast tissue.

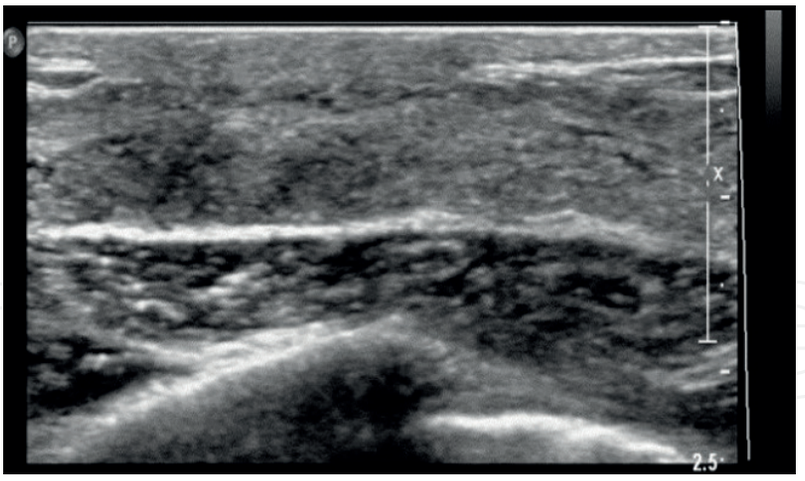

Figure 13. Homogenous background echotexture—fibroglandular. Transverse ultrasound shows a thick zone of homogenously echogenic fibroglandular tissue present beneath a thin hypoechoic layer of fat lobules.

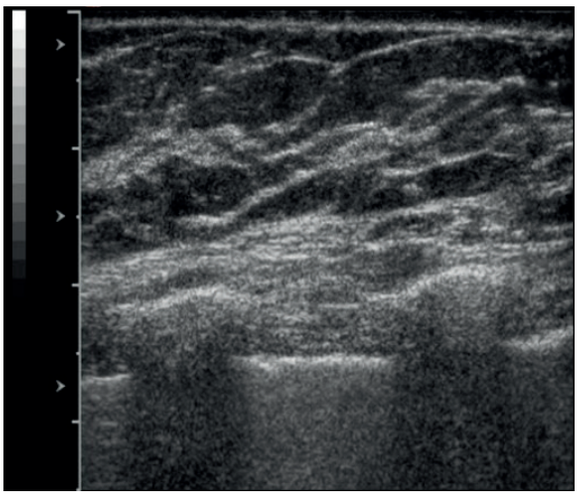

Figure 14. Heterogeneous background echotexture. Transverse ultrasound depicts multiple areas of increased and decreased echogenicity. Heterogeneity can be either focal or diffuse.

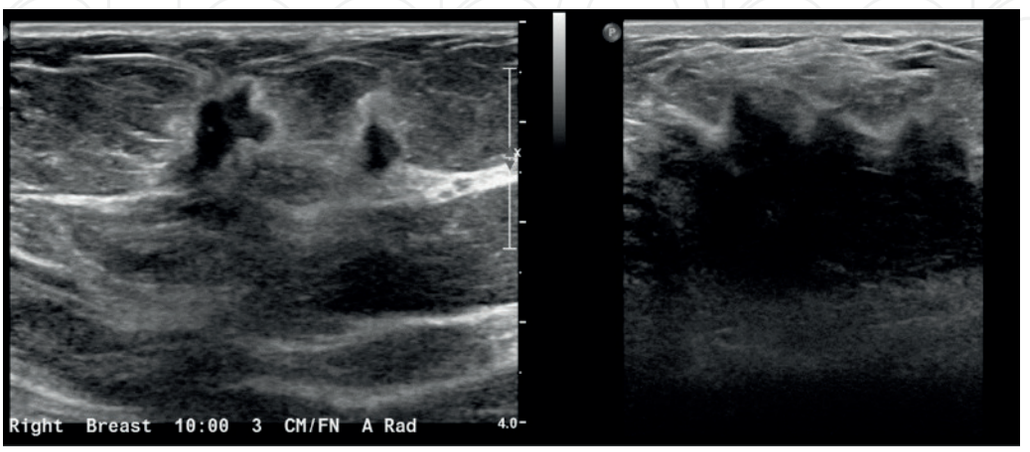

Figure 15. Margin assessment. Transverse ultrasound of the right breast demonstrates an irregular mass with angular margins. Some or all of the margins has sharp corners, often forming acute angles.

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

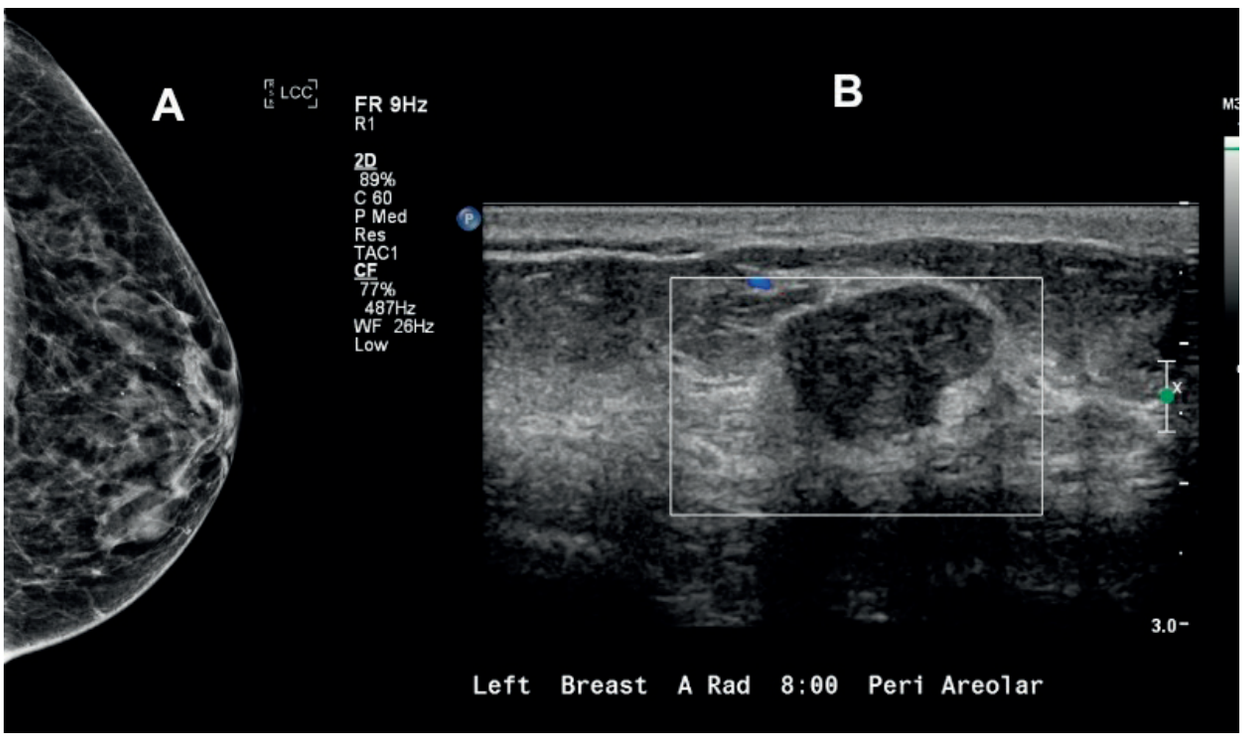

Figure 16. Lesion visibility. (A) CC mammogram of the left breast and (B) transverse ultrasound of the left breast.

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**).

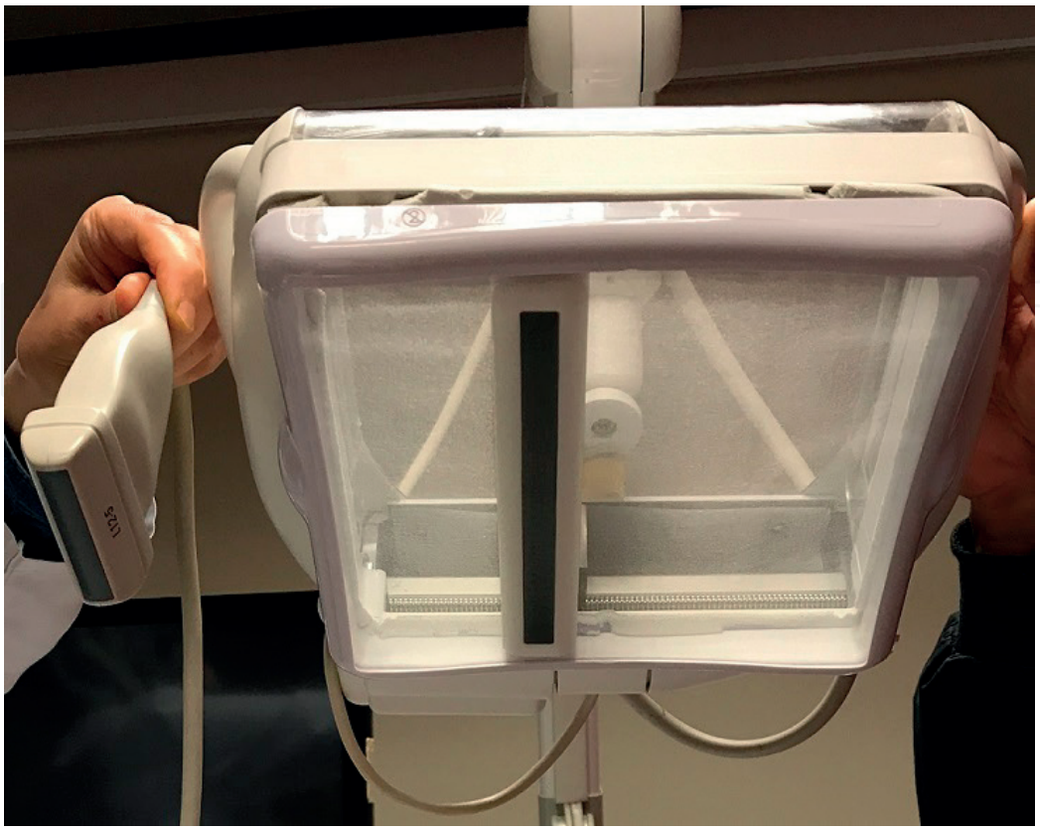

Figure 17. Handheld (left) vs. automated whole breast ultrasound (right).

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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