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Role Of Ultrasound Technology In Breast Cancer Diagnosis

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Abstract

Breast cancer is one of the scary disease by its high prevalence in mortality and cancer associated morbidity. Accurate diagnosis in the early stage can control the associated complications toa greater extent which also leads to a better provision of early management. Mammography is the widely used technique for the diagnosis and screening of breast cancer and ultrasound appeared to be a better adjunct to mammography, particularly in case of the dense breast. Moreover, the ultrasound technique is very much effective in segregating the mammogram identified lesions to the cyst or a solid mass. This will help the surgeon and other healthcare professionals to call a decision to go for a biopsy and other surgical procedures. Overall, the ultrasound revealed a sensitivity of 80.1% and specify of 88.4% in breast cancer diagnosis with a very good detection rate. However, ultrasound failed to produce a better effect than other techniques in comparative analyses. Hence, with the currently available evidences, ultrasound can't be considered as a single most diagnostic strategy in breast cancer, though it can be a good adjunct to other techniques like mammography. Further high-quality homogenous evidences needs to be explored to confirm its use in breast cancer diagnosis.

Keywords: Breast Cancer, diagnosis, ultrasound, screening

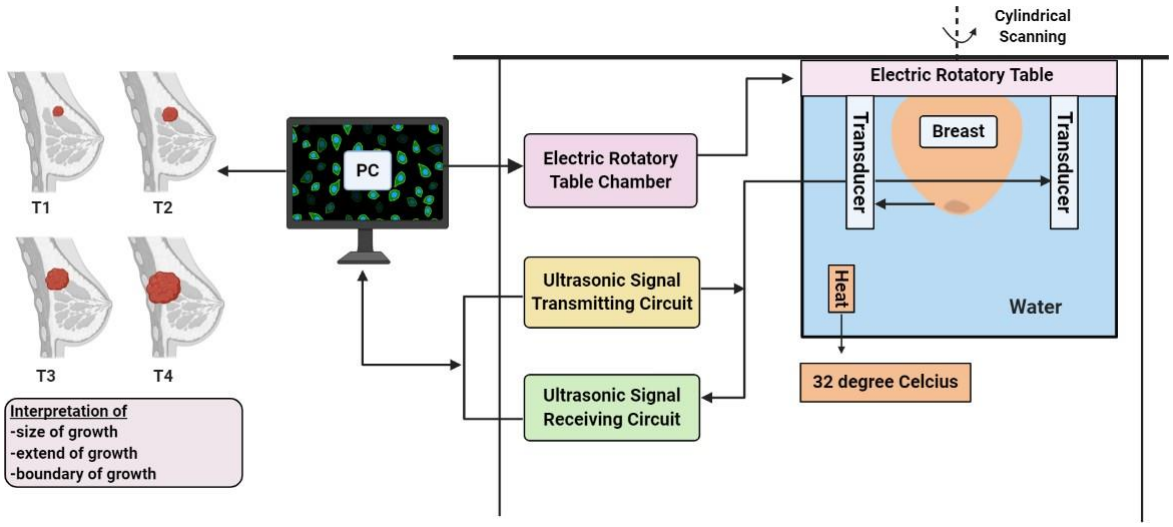
Breast cancer

Breast canceris a multifactorial contributed commonest cancer among the woman with a high level of mortality. Epidemiology, risk factors, outcomes of breast cancer varied across the globe depends on the cultural and environmental diversity such as population factors, lifestyle, genetic characters, and environmental factors with a proportional increment day by day. (1)The metastatic nature of breast cancer to the areas such as bone, lung, brain and liver made it incurable and early diagnosis will give a better survival among the patients. (2) Many factors including the gender, age, hormonal production (estrogen), hereditary factors, genetic mutation; and life and food style can enhance the chances to develop the breast cancer. (2)

Epidemiology of breast cancer

A varying incidence was observed across the world with a higher incidence in developing countries than in other parts. In 2012 itself,1.67 million newbreast cancer cases were identified which equals 25% of all types of cancers. (1)In 2017, one in eight women residing in the United States were estimated to be at the risk of developing breast cancer with a 12.4% lifetime risk with an approximate new case of 252,710 invasive breast cancerand 6,341 cases of breast cancer in situ.(1, 2) A varying incidence of 27 to 92 per 100,000 people was reported across the world which is estimated to be 3.2 million by 2050. (1)China, Japan, and Indonesia appeared to have the highest cases in the Asia-Pacific region with an approximate of 277,054, 107,545,and 223,899 in East Asia, Southeast Asia and in south-central Asia. (1) The 5-year rate for 2005 to 2011 was found to be 89% across the world with a varying 1-year survival rate from 94.1% to 97.1% in European countries. (1)

Breast cancer is the commonest reason for mortality among cancer patients(1, 3) especially in non-developed countries with 324,000 cancer deaths and 197,000 all-cause deaths in 2012. (3) Breast cancer ranked 5th leading cause of cancer death in 2012.(1) Mortality is appeared to be high among the less developed countries than developed countries, though the incidence is vice-versa, (1) which might be due to the unavailability of appropriate screening and management. A variation of 6 to 20 cases per 100,000 people mortality rate was observed across the world with a lesser rate in North America (0.16) and high in Asia (0.48).(1)(Figure 1).



Breast cancer screening

Higher cost of screening techniques is a major barrier, though appropriate breast cancer screening is very much effective in early detection and management which ultimately controls the burden and consequences of the disease with better survival. (1, 2)Access to the adequate facility which enhances the diagnosis of breast cancer is mandatory for efficient management which decreases the burden from the disease. (4)Mammography considered to be a standard technique for breast cancer screening and diagnosis(5, 6), though the sensitivity is less especially among those with radiodense breasts. (6) Widespread early detection of breast cancer helped to reduce the mortality rate though it yielded a higher incidence. (2)

Screening techniques used forbreast cancer

A recent 2018 recommendation for breast cancer screening recorded that,the decision to use mammography in women aged 40 to 49 years should be avoided and can be considered based on

the potential benefit to harm ratio out of the screening. Whereas, the use of a mammogram was recommended in a woman aged 50 to 74 years in every 2 to 3 years interval, though harmful effects need to be considered.(7) Mammography a basic x-ray technique, with a major concern of overdiagnosis of breast cancer. (3) A coherent review of a team of experts recorded that, mammographic screening had a risk reduction of 40% breast cancer development and 23% death from breast cancer among those aged 50-69 years. (8)Other modalities that are using for screening included magnetic resonance imaging, tomosynthesis or ultrasound, clinical breast examinations,and breast self-examination,through this expert's team not recommended these practices unless it is necessary. (7)

Ultrasound technology

Ultrasound is a digital technology or method of detection used in many medical diagnoses. It works on the principle of reflection of high-frequency sound waves. Tissue-dependent boundaries will be generated upon the reflection of sound waves which will be directly proportional to the time intervals of reflection and this will be dependent on the acoustic properties of the tissue. Hence, the application of ultrasound will be an adjunct to other techniques to differentiate the cells or tumor tissues. Also, this will help the surgeon to decide the patients to be selected for biopsy or surgery and to decide the mammogram identified lesion is a cyst or a solid mass.(9)Ultrasound is good enough to understand the size, extent and boundary of breast cancer cell. (10)All these made ultrasound to be used as a diagnostic technique in breast cancer and a recent meta-analysis supported its use particularly in low-resource settings. (4)

Fig: Principle of Ultrasound in breast cancer diagnosis

Ultrasound for the Breast Cancer screening

Ultrasoundis effective in identifying the cases which can't be captured in the mammogram due to many reasons among the women with normal or radiodense breast.(11)Moreover, this technique can be widely applied in the case of small nodules or small sized tumors. (12)Ultrasound is an excellent adjective to the mammographic technique due to its good tolerability, non-ionizable nature, inexpensive and better sensitivity, especially in combination with other techniques. (5, 6)Moreover, it is cheaper compared to the technique like MRI.(5, 6)As a cross-sectional imaging technique and non-overlapping display of tumors, ultrasoundwas a promising one in early reports, though its use is reduced over time due to the requirement of adequately skilled professionals to differentiate small, non-palpable tumors. (6)The expert was not recommending the use of tomosynthesis or ultrasounddue to the lack of pieces of evidence and excess consumption of resources. (7) Many studies also agreed with this evidence that the use of ultrasound is not superior to other methods such as mammography, MRI, and combined techniques for the diagnosis of breast cancer. (13, 14)

Automated whole breast ultrasound techniques have better screening reliability with lesser inter-rater variability. (6) Ultrasoundis appeared to be more effective in case of operable breast cancer to detect the nodes perioperative and consider them for the surgery. (15) Ultrasound was also effective in identifying the cysts, adenocarcinomas, and malignancies in the tissues, especially with radiodense breasts. (11) A receiver operating characteristic analysis of ultrasound combined clinical features and age yielded abetter Az significant value of 0.96 (95%CI: 0.93-0.99), indicating that, ultrasound modulated tissue characterization can significantly reduce the biopsy requirement in case of benign breast lesions. (5)

A systematic review by Nothacker et al., recorded an average detection of 22.5% with a 95% CI of 15% to 34% carcinomas among the asymptomatic women with radiodense mammographic breast tissue and the mean percentage screened out of the whole population was appeared to be 0.32% with a 95% CI of 0.23%to 0.41%. This study also revealed a mean detected carcinoma size of 9.9 mm with a mean percentage of invasive cancer detection of 94% (81%-100%). (16) Moreover, ultrasound appeared to be highly effective in the detection of breast cancer at axillary nodes of the breast. (14) Berg WA et al., reported that the addition of MRI and ultrasound along with mammography was effective in better detection rate, but found to have a high false-positive result. (17)

Zhi H et al. reported that Strain ratio-based elastographic analysis wasa better reliable tool with a higher area under the curve (0.944)than a five-point scoring system (0.885) which found to have a significantly ($P < .05$) better performance. (18) Ultrasound-guided fine-needle aspiration cytology appeared to be effective in patients with lymph node metastasis and this would be helpful to the surgeons and healthcare professionals as a preoperative staging procedure. (19)

A recent meta-analysis of 26 studies by Sood R et al., reported that ultrasound is having an overall sensitivity of 80.1% (95% CI: 72.2% - 86.3%) and specify of 88.4% (95% CI: 79.8% - 93.6%) in breast cancer detection. Moreover, this study identified non-deviating results in the case of subgroup analysis with low- and middle-income countries with a sensitivity and specificity of 89.2% and 99.1%, respectively. However, these findings should be incorporated due to the high level of heterogeneity in studies included.(4)

Sensitivity

A surveillance study by Kuhl CK et al. recorded a sensitivity of 39.5% with ultrasound, which was higher than mammography (32.6%), combined mammography with ultrasound (48.8%), but waslower than MRI (90.7%) and mammography with MRI (93%), respectively among those woman with a familial risk of breast cancer. (13) Another study by Warner et al., reported that the sensitivity of ultrasound(33%) was higher than clinical breast examination (9.1%) but lower than mammography (36%) and magnetic resonance imaging (77%). (20) Damera A et al., recorded a 55% sensitivity among the patients with suspected primary operable breast cancer. (15)

Specificity

A surveillance study by Kuhl CK et al. recorded a specificity of 90.5% with ultrasound, which was higher than combined mammography with ultrasound (89%), but waslower than mammography (96.8%), MRI (97.2%) and mammography with MRI (96.1%), respectively among those woman with a familial risk of breast cancer. (13) Another study by Warner et al., reported that the specificity of ultrasound (96%), was higher than MRI (95.4%), mammography (99.8%), and CBE (99.3%), respectively.(20) Damera A et al., recorded 82% of specificity among the patients with suspected primary operable breast cancer.(15)

Positive and Negative predictive value

A surveillance study by Kuhl CK et al. recorded a Positive predictive value (PPV) of 11.3 with ultrasound, which was lower than all other methods of detection such as mammography, combined mammography with ultrasound, MRI and mammography with MRI with a PPV of23.7, 11.9, 50.0, and 42.1, respectively among those woman with a familial risk of BREAST CANCER. (13) Damera A et al., recorded 74% and 65% of PPV and Negative predictive value (NPV) among the patients with suspected primary operable breast cancer. (15) A systematic review by Nothecker et al., reported an

average PPV of 15% which is ranged from 2% to 28%. A range of 72% to 98% positive classification was observed with ultrasound for those with no carcinoma and this variation may due to the variation in the assessment criteria used.(16)

Table: The diagnostic characters of Ultrasound in Breast cancer

Ultrasoundelastography

Ultrasound elastography is a widely used method to assess the stiffness and strain of tissue which will be helpful differentiate between the hard and soft lesions. Moreover, strain elastography has shown to have better specificity and accuracy than the B-mode imaging for breast cancer diagnosis.(21)Moreover, a combination of B-mode imaging with strain elastography yielded a better sensitivity, specificity, and accuracy than the individual application.(22-24) Though, the application of ultrasound elastography is very easy in clinical practice, it should be considered with caution due to the controversial findings upon its comparison with other techniques. This can be an adjective method to clinical examination or B-mode imaging technique.(21) (Table 1)

Table: The diagnostic characters of Ultrasound in Breast cancer

Reference, Country	Study design; Follow-up	Participants; Sample size	Comparator with US	Diagnostic characters of US in BC			Key Outcome of the study
				Sensitivity (%)	Specificity (%)	PPV/ NPV (%)	
Wang Y et al., 2019; China (25)	Population based cohort; 4 years	Women those at high-risk for breast cancer; l72,250	-	-	-	-	• The overall detection rate of BI-RADS categories of III, IV, and V was found to be 11.75%, 1.67%, and 0.09%, respectively among the participants • A modest prediction accuracy was observed with an area under the curve of 0.55.
Berg WA et al., 2012; United states (17)	Surveillance cohort study;; 2 years	Women at elevated risk for breast cancer; 2809	MRI and mammography	-	-	-	• Mammography plus ultrasound group had a better sensitivity (0.76 vs 0.52) than the mammography alone, whereas, specificity (0.84 vs 0.91) and PPV (0.16 vs 0.38) lesser in combination group than the mammography alone. • A better sensitivity (1.00 vs 0.44) and PPV (0.19 vs 0.18) was observed for MRI and mammography plus ultrasound than the mammography and ultrasound only. Whereas,specificity was lesser in MRI added group (0.65 vs 0.84) than mammography and ultrasound only.
Kelly KM et al., 2010 (6)	Surveillance cohort study; 1-year	Women with dense breasts and/or at elevated risk of breast cancer; 4419	mammography	BC: 67; Invasive: 81	89.9	38.4/-	• The sensitivity (67%) was appeared to be higher with AWBU than mammography (40%), which was further increased to 81% in combination of AWBU with mammography for BC detection • The sensitivity of AWBU for invasive cancer detection was appeared to be81% which was higher

							than mammography (33%) • A significantly (p=0.02) better detection rate was found in AWBU (65%) than mammography (39%) in dense/extremely dense breast women • Specificity based on recalls for AWBU was 89.9%, which was lower than mammography (95.15%) and combination technique (98.7%)
Zhi H et al., 2010; China(18)	Prospective cohort study; 1-year	Patients benign and malignant breast lesions; 437	-	92.4	91.1	78.2/ 97.2	• Strain ratio-based elastographic analysis was better reliable tool with a higher area under the curve (0.944), than five-point scoring system (0.885) which found to have a significantly (P < .05) better performance
Kuhl CK et al., 2005; Germany(13)	Surveillance cohort study; 5.3 years	Surveillance of women at increased familial risk for breast cancer (lifetimerisk of 20% or more); 529	Mammography, MRI	39.5	90.5	11.3/-	• Sensitivity for BC diagnosis by US (40%) was higher than mammography (33%), but lower than the combination of US with mammography (49%). • Specificity for BC diagnosis by US (90.5%) was higher than combination of US with mammography (89%), but lower than mammography (96.8%)
Dillon et al., 2005;Ireland(26)	Retrospective study; 5 years	Patients undergoing core biopsy for breast abnormalities; 2427	clinical-, and stereotactic-guided cores biopsy	-	-	-/1.7	• There was a lesser rate of false-negative with ultrasound guided (1.7%) core than the clinical (13%), and stereotactic-guided (8.9%) cores with an overall rate of 6.1%.
Warner E et al., 2004; Canada(20)	Surveillance cohort study; 5.4 years	Women with hereditary susceptibility to breast cancer due to a BRCA1 or BRCA2 mutation; 236	mammography, MRI, and CBE	33	96	-	• The sensitivity of US (33%) was higher than CBE (9.1%), but lower than mammography (36%) and MRI (77%) • The specificity of US (96%), was higher than MRI (95.4%), mammography (99.8%) and CBE (99.3%), respectively.

A Damera et al., 2003; United Kingdom(15)	Surveillance cohort study; 9-month	Patients with suspected primary operablebreast cancer; 187	-	55	82	74/65	• 103 of 166confirmed invasive carcinoma were identified on US • 64 of 166 (39%) had axillary metastases identified through US • 46 (72%) of 64, identified nodes at surgery, of which 35 (55%) met thecriteria for biopsy and 27 (42%) of these were diagnosed preoperatively by US-guided biopsy • US was effective identifying the operable breast cancer
Kuenen-Boumeester et al., 2003;Netherlands(19)	Surveillance cohort study; 2.5 years	Patients with non-palpable lymph node metastases in primary breast cancer; 183	-	57	96	92/70	• US guided fine needle aspiration cytology was useful as a pre-operative procedure in axillary lymph nodes in breast cancer patients • It found to have a sensitivity, specificity, PPV and NPV of 57%,96%, 92% and 70%, respectively.
Crystal P et al., 2003; Israel(12)	Surveillance cohort study; 2 years	Asymptomatic women with dense breastused US as an adjunct to physical examination and mammography;1517	-	100	94.4	-	• A total of 7 (0.46%) cancer cases were diagnosed out of 1517 woman screened • Three and four carcinoma were detected in baseline risk and higher risk participants, respectively. • A significantly ($p < 0.04$) higher rate cancer was detected in high-risk women (1.3%), than the baseline risk group (0.25%).
Leconte I et al., 2003; Belgium(27)	P	patients who had completed mammography and whole-breast sonography; 4236		88	-	-	• The sensitivity of sonography was 88% in all grades of non-palpable BC was higher, compared to the mammography for grades 1-4 (69%); grades 1 and 2 (80%); and grades 3 and 4 (56%), respectively. • There was a higher chances of cancer detection in US than mammography, in which grades 1–4

							(relative risk,1.29; p = 0.024); and grades 3 and 4 (relative risk, 1.57; p = 0.013) was significant, whereas, and in but grades 1 and 2(relative risk, 1.1; p = 0.445) breasts was not significant.
Kolb TM et al., 2000;United States(28)	Surveillance cohort study; 5 years	Asymptomatic women underwent mammography and subsequent PE screening; 11130	Mammography, and PE	75.3	96.8	20.5/ 99.7	• Sensitivity of US (75.3%), was better than PE, (27.6%), but not than mammography were (77.6%) • Specificity of US (96.8%) was lesser than both mammography (98.8%) and PE (99.4%) • Negative predictive value for US (96.8%) was lesser than mammography (99.8%) and PE (99.4%) • Positive predictive value for US (20.5%) was lesser than mammography (35.8%) and PE (28.9%) • Accuracy in US (96.6%) was lesser than mammography (98.6%) and PE (98.8%)
Buchberger et al., 2000;Austria(29)	Surveillance cohort study; 4 years	Women used US as an adjunct to physical examination and mammography; 8,970	-	100	31	13.7/100	• The US observed to have a 100% sensitivity with 31% specificity for the prospective sonographic classification for malignancy • An overall prevalence of 0.41% cancers detected US and 22% of total non-palpable cancers was detected among all cancers
Bonnema J et al., 1997; Netherlands(14)	Surveillance cohort study; 15-month	Breast cancer patient; 148	US in combination with fine-needle aspiration biopsy	87	56	58/86	• Sensitivity was higher in US (87%) than combination with FNAB (80%) • Specificity appeared to be lesser with US (56%) than combination with FNAB (100%) • Overall accuracy appeared to be lesser with US (68%) than combination with FNAB (88%) • Positive predictive value appeared to be lesser with

							US (58%) than combination with FNAB (100%) • Negative predictive value was higher in US(86) than the combination with FNAB (76%)
De Freitas et al., 1991; Brazil(30)	Retrospective study; NR	Cases of breast cancer; 115	Clinical examination	56	89	92/49	• A better specificity and (89% vs 68%) and positive predictive values (82% vs 92%) were observed with US than clinical examination • A lesser sensitivity (56% vs 68%) and negative predictive values (49% vs 50%) was observed with US compared to the Clinical examination • A similar accuracy was observed for the clinical examination (68%) and US (67%).
Rothschild P et al., 1988; United Stes (11)	Cohort study; 3 years	asymptomatic, had no masses on their mammograms, because theirbreasts were radio dense on mammography	Mammography	-	-	-	• US was effective in identifying the cyst and solid masses among the 23.5 % (187) and 4.3%(40) of 796 examinations, though 71.5%(569) appeared to be normal. • One malignancy, two fibroadenomas and one normal breast tissue were yielded out of 4 biopsied masses.

AWBU: Automated whole breast ultrasound; BC: Breast cancer; CBE: Clinical Breast Examination; FNAB: Fine-needle aspiration biopsy;MRI: magnetic resonance imaging; NPV: Negative predictive value;PE: Physical examination; PPV: Positive Predictive Value;US: Ultrasound;

Conclusion

Ultrasound is of an effective technique to identify and distinguish breast cancer which can be more effective when it is in combination with the ultrasound elastography. Though ultrasound is appeared to have a better sensitivity and detection rate in breast cancer, current evidence not supporting its use over other methods. However, ultrasound can be considered as an adjuvant method for a better differentiation along with other methods such as clinical examination or normal mammography.

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