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# Sonography as an Adjunct to Digital Mammography in Patients with Dense Breasts

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## ABSTRACT

**Background:** Dense breasts are associated with an increased risk of cancer and also mask lesions on mammograms. In our study, we evaluated the role of sonography as an adjunct to digital mammography in patients with dense breasts.

**Methods:** Sonography of 676 female patients with American College of Radiology category C or D mammographic density was done in this prospective cross-sectional analytical study in the Department of Radiology, Tribhuvan University Teaching Hospital. The final imaging diagnosis was classified as per the American College of Radiology Breast Imaging Reporting and Data System categories. Tissue diagnosis was obtained in patients with sonographic category 3 solid lesions larger than 3 cm, category 4 and 5 lesions. The data were tabulated and analyzed using Statistical Package for Social Service (SPSS) for Windows version 22.

**Results:** Additional sonography confirmed all BIRADS 1 mammograms as normal or benign, 95.7 % (112) of inconclusive, and 82.8% (n=135) of BIRADS 3 ones as benign. It had higher sensitivity and negative predictive value (100%) than mammography with similar accuracy. Most patients (479, 70.9%) had diagnostic indications. There were 540 (79.9%) cases in ACR BIRADS category c. A final diagnosis of benign (316, 46.7%) was most common, followed by normal (293, 43.4%) and malignant (67, 9.9%). The majority of the malignant lesions were Invasive Ductal Carcinoma (59, 88%).

**Conclusions:** Additional sonography confirmed mammography findings as normal, benign, or suspicious for malignancy, definitely described morphology and extent of mass, and also guided biopsy. It had higher sensitivity than mammography in dense breasts.

**Keywords:** Breast density; mammography; ultrasonography mammary.

## INTRODUCTION

According to GLOBOCAN 2020, breast cancer is the second most common cancer in women in Nepal with an incidence of 17.1%.[1] The Population Based Cancer Registry in Nepal which covers about 20.3% of the total population, has reported breast as the second most common site of cancer in either sex, accounting for 13% of all malignancies, and invariably (97%) occurring in females.[2] The early onset breast cancers grow more rapidly and are more aggressive.[3] The efficacy of mammographic screening decreases in dense breasts with a greater amount of fibro-glandular tissue, especially in younger patients with both the lesion and fibro-glandular tissue being hyperdense.[4] In the United States, legislation requires patients to be informed regarding breast density and the benefit of supplemental screening.[5]

Sonography may increase the identification of lesions when added to mammography especially in dense breasts with ominous lesions seen as hypoechoic in a background of hyperechoic fibro glandular tissue. In developing countries like Nepal, mammography is limited by its availability while sonography is much more easily available.

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To the best of our knowledge, there are no similar studies evaluating the additional benefit of sonography in patients with mammographically dense breasts done in the Nepalese population. So, in our study, we evaluated the accuracy of mammography and sonography in patients with dense breasts.

## METHODS

This was a prospective cross-sectional observational study done following ethical clearance from the Institute Review Committee, Institute of Medicine (154/ (6-11) $E^2$ /076-077) and Nepal Health Research Council (Ref no. 1956). The study was conducted in the Department of Radiology, Institute of Medicine, Maharajgunj Medical Campus, Kathmandu. Data were collected over two years from to October 2019- November 2021. Female patients undergoing mammogram with American College of Radiology (ACR) category c or d breast density were included using convenience sampling. Those with previous surgery deforming breasts rendering mammographic interpretation difficult were excluded. Sample size was calculated using the formula: n= z2pq/d2 using p= 71.42, q= 100-p = 28.8, z = 1.96 at 95% confidence level and d= 5% of p = 3.571; n= 606. Adding 10% of n, final sample size derived was 667.

Mammograms were done in digital mammography unit (MAMMOMAT Fusion) in the department and medio-lateral oblique and cranio-caudal views were obtained and evaluated on Syngovia work station YLXRO19095 visually using appropriate magnification tools, for density and findings.[6] Patients with dense mammograms were evaluated further with sonography with high frequency (5-13 MHz) probes done or supervised by experienced radiologist who was not blinded to mammogram findings. Findings and ACR BIRADS category were recorded for both.[6]

The mammogram BIRADS Cat 0 was classified as inconclusive (I). There was no BIRADS 0 category on sonography. BIRADS 1 was normal (N), 2 and 3 benign (B), and 4a, 4b, 4c, 5 and 6- Malignant (M) on both sonography and mammography. New lesions or lesions more clearly demarcated on ultrasound were further categorized as follows:-

Simple cysts or duct ectasia: BIRADS 2

Complicated cysts: BIRADS 3 and aspirated or followed upon.

Solid lesions with benign features: BIRADS 3, biopsy done when larger than 3 cm.

Complex cysts or suspicious lesions: BIRADS 4 or 5 underwent biopsy for pathological diagnosis.

Final Diagnosis was categorized as follows normal (N), benign (B) or malignant (M). All the data from cases were fed in Microsoft (MS) Excel office and then analyzed by Statistical Package for Social Service (SPSS) for window version 22, Inc., Chicago, IL. The Concordance and Discordance of mammogram with sonogram was calculated. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of mammogram and additional sonogram were evaluated respectively. The concordance of mammogram with sonogram was evaluated using Kappa value. P-value less than 0.05 was considered significant.

## RESULTS

The total number of mammograms obtained in this duration was 1524, of which 676 meeting inclusion criteria were included. The mean age of patients undergoing mammograms was 45.5 +/- 8.1 years, ranging from 22 to 80. Of these 676 patients, 479 (70.9%) had diagnostic indications, and 197 (29.1%) were for screening. There were 540 (79.9%) cases in ACR BIRADS category c and 136 (20.1%) in category d. Most of the cases had a final diagnosis of benign (316, 46.7%) followed by normal (293, 43.4%) and malignant (67, 9.9%) (table 1).

**Table 1. Indication, density distribution and final diagnosis in different age groups with percentage in brackets.**

| Age | Indication - Diagnostic (D) / Screening (S) | | Density - ACR cat c / d | | Final Diagnosis | | | Frequency (Percent) |
|---|---|---|---|---|---|---|---|---|
| | D | S | Density c | Density d | Benign | Malignant | N | |
| <35 | 43 (87.8) | 6 (12.2) | 43 (87.8) | 6 (12.2) | 24 (49.0) | 7 (14.3) | 18 (36.7) | 49 (100) |
| 35-44 | 188 (66.9) | 93 (33.1) | 207 (73.7) | 74 (26.3) | 143 (50.9) | 20 (7.1) | 118 (42.0) | 281 (100) |
| 45-54 | 192 (73.0) | 71 (27.0) | 209 (79.8) | 54 (20.5) | 123 (46.8) | 20 (7.6) | 120 (45.6) | 263 (100) |
| >= 55 | 56 (67.5) | 27 (32.5) | 81 (97.6) | 2 (2.4) | 26 (31.1) | 20 (24.1) | 37 (44.6) | 83 (100) |
| Total | 479 (70.9) | 179 (29.1) | 540 (79.9) | 136 (20.1) | 316 (46.7) | 67 (9.9) | 293 (43.3) | 676 |

The most common indication was lump (228/ 676, 33.7%) followed by mastalgia (162/676, 23.9%). Among benign lesions, simple cysts (129, 40.1%) were most common while the majority of the malignant lesions were Invasive Ductal Carcinoma (IDC) (59, 88%). There were 117 (17.3%) inconclusive cases on mammogram, most of which were BIRADS 0 due to very dense breasts, of which 65 (56.4%) were benign, 1 (0.9%) malignant and 51 (43.6%) normal (table 2).

**Table 2. Distribution of Final diagnosis in various Mammogram categories (B/I/M/N)**

| S.no. | | Mammogram categories (B/I/M/N) | | | | |
|---|---|---|---|---|---|---|
| | **Diagnosis** | **B** | **I** | **M** | **N** | **Total** |
| 1. | Normal | 91 | 51 | 1 | 150 | 293 |
| 2. | Cyst/ Fibrocystic disease | 74 | 33 | 2 | 20 | 129 |
| 3. | Fibroadenoma | 40 | 8 | 8 | 5 | 61 |
| 4. | Complicated Cyst | 18 | 13 | 1 | 2 | 34 |
| 5. | Duct ectasia | 12 | 2 | 0 | 9 | 23 |
| 6. | Mastitis | 12 | 5 | 4 | 1 | 22 |
| 7. | Lipoma (breast and pectoralis muscle) | 5 | 2 | 0 | 3 | 10 |
| 8. | Intra Mammary Lymph Node | 9 | 0 | 0 | 0 | 9 |
| 9. | Intraductal Papilloma | 5 | 2 | 1 | 0 | 8 |
| 10. | Proliferative/ Non proliferative breast disease | 1 | 0 | 2 | 0 | 3 |
| 11. | Hamartoma | 2 | 0 | 0 | 1 | 3 |
| 12. | Fat necrosis | 2 | 0 | 0 | 0 | 2 |
| 13. | Sclerosing adenosis | 2 | 0 | 0 | 0 | 2 |
| 14. | Post-operative changes | 2 | 0 | 0 | 0 | 2 |
| 15. | Sebaceous Cyst | 0 | 0 | 0 | 2 | 2 |
| 16. | Atypical Ductal Hyperplasia | 0 | 0 | 1 | 0 | 1 |
| 17. | Filariasis | 1 | 0 | 0 | 0 | 1 |
| 18. | Galactocele | 0 | 0 | 1 | 0 | 1 |
| 19. | Keloids | 1 | 0 | 0 | 0 | 1 |
| 20. | Haemangioma | 0 | 0 | 1 | 0 | 1 |
| 21. | Phyllodes | 0 | 0 | 1 | 0 | 1 |
| 22. | IDC | 10 | 1 | 48 | 0 | 59 |
| 23. | Invasive Lobular Carcinoma (ILC) | 1 | 0 | 4 | 0 | 5 |
| 24. | Ductal Carcinoma in Situ (DCIS) | 0 | 0 | 1 | 0 | 1 |
| 25. | Locally Advanced Breast Cancer (LABC) | 0 | 0 | 1 | 0 | 1 |
| 26. | Metaplastic Carcinoma | 0 | 0 | 1 | 0 | 1 |
| **Total** | | **288** | **117** | **78** | **193** | **676** |

On mammogram, most of the cases were either normal (193, 28.5%) or probably benign (BIRADS category 3) (163, 24.1%), while on sonogram majority of the patients were categorized as normal (290, 42.9%) followed by benign (191, 28.3%) (Figure 1). In the diagnostic group, there were 154 (32.2%) normal, 65 (13.6%) malignant and 260 (54.3%) benign, while there were 139 (70.6%) normal, 56 (28.4%) benign and 2 (1.0%) malignant in the screening group.

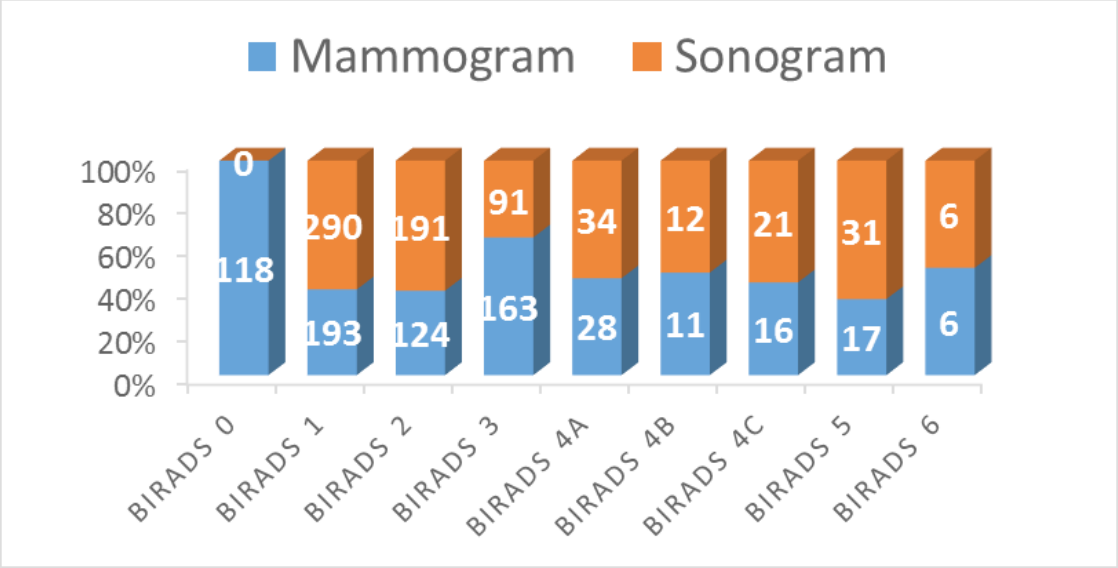



**Figure 1. BIRADS category distribution on Mammogram and Sonogram.**

On mammography, 198 (28.6%) were normal, BIRADS 1 category, 288 (42.6%) benign, belonging to BIRADS categories 2 or 3, and 78 (11.5%) malignant in categories 4, 5, and 6. On sonography, 290 (42.9%) were normal, 282 (41.7%) benign, and 104 (15.4%) malignant. All the normal mammograms were normal or benign on the additional sonography. Of the 117 cases which were inconclusive on mammography, most (95.72%, n=112) were normal or had benign findings on sonography and did not need further intervention, while five were suspicious and underwent pathological correlation, proving one of these was malignant. Likewise, there were 163 BIRADS 3 cases on mammography where additional sonography confirmed 135 (82.82%) as normal or benign and suggested 28 (17.17%) to be malignant, of which 11 (6.7%) were confirmed on pathological examination (Table 3). All the BIRADS 5 mammography studies were also suspicious for malignancy on sonography and confirmed on pathology in all but one case. Sonography was used to guide the biopsy in all the suspicious cases. Fifty-four lesions (77.1%) lesions deemed malignant on mammography were confirmed so on final diagnosis.

**Table 3. BIRADS on additional sonography and final diagnosis of inconclusive, BIRADS 3 and 4 cases on mammography.**

| Mammogram | USG BIRADS | Number | Final diagnosis | | |
|---|---|---|---|---|---|
| Inconclusive | | | Normal | Benign | Malignant |
| | 1 | 51 | 51 | 0 | 0 |
| | 2 | 38 | 0 | 38 | 0 |
| | 3 | 23 | 0 | 23 | 0 |
| | 4a | 3 | 0 | 3 | 0 |
| | 4b | 1 | 0 | 1 | 0 |
| | 5 | 1 | 0 | 0 | 1 |
| Total | | 117 | 117 | | |
| BIRADS 3 | USG BIRADS | Number | Final diagnosis | | |
| | | | Normal | Benign | Malignant |
| | 1 | 27 | 27 | 0 | 0 |
| | 2 | 60 | 0 | 120 | 0 |
| | 3 | 48 | 0 | 48 | 0 |

**Table 3. BIRADS on additional sonography and final diagnosis of inconclusive, BIRADS 3 and 4 cases on mammography.**

| Mammogram | USG BIRADS | Number | Final diagnosis | | |
|---|---|---|---|---|---|
| | 4a | 19 | 0 | 16 | 3 |
| | 4b | 2 | 0 | 1 | 1 |
| | 4c | 6 | 0 | 0 | 6 |
| | 5 | 1 | 0 | 0 | 1 |
| Total | | 163 | 163 | | |
| BIRADS 4 | USG BIRADS | Number | Final diagnosis | | |
| | | | Normal | Benign | Malignant |
| | 1 | 1 | 1 | 0 | 0 |
| | 3 | 7 | 0 | 7 | 0 |
| | 4a | 9 | 0 | 9 | 0 |
| | 4b | 6 | 0 | 3 | 3 |
| | 4c | 4 | 0 | 0 | 4 |
| | 5 | 1 | 0 | 0 | 1 |
| Total | | 28 | 28 | | |

Concurrent sonography findings were seen for 92.8% malignant and 85.2% benign mammograms, suggesting moderate agreement between the two modalities with Kappa value of 0.663. All sonographically benign lesions had consistent final diagnosis and 67 (64.4%) of the malignant lesions were confirmed so on pathological diagnosis. The sensitivity and negative predictive value of additional USG was higher than MG (table 4).

**Table 4. Sensitivity, Specificity, PPV, PVN, and accuracy of mammogram and sonogram.**

| | Sensitivity | specificity | PPV | PVN | Accuracy |
|---|---|---|---|---|---|
| MG | 81.8 | 92.8 | 78.3 | 94.1 | 90.1 |
| USG | 100 | 88.2 | 64.4 | 100 | 90.3 |

## DISCUSSION

Mammography is the only investigation that has a proven role in reducing mortality by about 20% when women in the 50-70 years age group are screened once in three years and by 40% in 40-74 years age group screened once every 1-2 years.[7,8] In Nepal, screening remains opportunistic in the absence of any guidelines with primarily NGO-based activities of awareness and hospital-based research.[9]

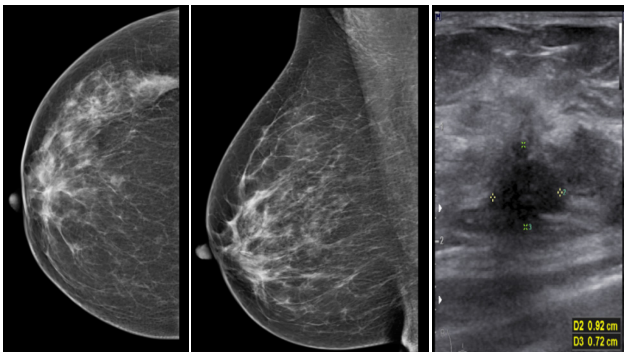
According to the ACR recommendations, women with a lifetime risk of greater than 20–25% of developing breast cancer should undergo annual surveillance with magnetic resonance imaging (MRI) in addition to MG, in the absence of which ultrasound should be done.[10] It is necessary to include breast density in the report as higher density is a double-edged sword, increasing patients' risk for malignancy on one hand and obscuring small lesions on the other. There are various systems of classifying the breast density as well which include Tabar and Wolfe's.[11, 12] Chiu et al, have suggested additional imaging modalities in patients with dense mammograms.[13] Additional imaging modalities includes sonography, digital breast tomosynthesis and MRI. Of these, sonography which is easily available at low cost, has a proven role in breast imaging in younger patients with similar detection rates when done after mammography or tomosynthesis.[12]

Lehman CD et al, reporting higher sensitivity and NPV of ultrasound than mammography in patients aged 30-39 years and have recommended sonography as initial modality of choice for this age group.[5] In our study, the sensitivity and negative predictive value of sonography was 100%, higher than mammography which had greater specificity and positive predictive value with nearly equal accuracy. This is similar to other studies, though we found relatively greater sensitivity and specificity of MG than a few others.[4,5]

Most of our patients were in the 35- 44 years age group with about a quarter having extremely dense breasts which is due to greater number of younger women, like another study evaluating mammography trends where 22.8% of extremely dense breasts were younger than 40 years.[14] Majority of the patients had a diagnostic indication which is also similar to that reported previously in Nepal and highlights the lack of awareness about breast cancer screening.[15] The most common presenting complaints was lump followed by mastalgia in our study unlike other studies where pain was most common.[16-18] Nearly 40 % of the final malignant cases were younger than 45 years which is consistent with the increasing number of malignancies in younger age shown in many studies.[19]

Our study showed moderate agreement between MG, USG and final diagnosis. Mammographic BI-RADS 0 category was mostly normal on sonography or had benign findings like cysts. The benign diagnosis on MG was mostly normal or had benign findings like cysts, complicated cysts, mastitis and fibroadenoma. Sonography helped clinch these diagnoses as well as a rare diagnosis of breast filariasis in a patient with demonstration of the typical filarial dance.[20] There were a greater number of malignant diagnoses on sonography, most in the BIRADS 3 and one in inconclusive group on mammography. Overall, the majority of the lesions that were benign on mammography were confirmed to be either benign or normal on the additional sonography, with 12 (4%) cases being malignant on pathology. Of the suspicious masses, five were mastitis, two intraductal papilloma and one invasive ductal carcinoma on pathological diagnosis. Though this increased the number of biopsies, it also helped to confirm the diagnosis, thus, alleviating patient anxiety and enabling appropriate management.[21]

Among malignancies, IDC was most frequent with only one case of metaplastic carcinoma and LABC.[22,23] All but two of the patients with malignancies were symptomatic, the most common being a lump. Two malignancies diagnosed on screening included a 38-year-old lady for follow-up post-right mastectomy with left breast IDC and another 50-year-old lady with mammographic asymmetry seen more clearly as poorly defined mass on sonography and final diagnosis of ILC (Figure 2). Consistent with this, Gordon et al., concluded that sonography can detect mammographically occult cancers in dense breasts, which may alter treatment plans.[24] Though we did not find satellite lesions in our study, assessment of satellite lesions and locoregional lymph nodes is limited on MG and better on sonography.[25] Hlawatsch et al. determined no additional benefit in pre-operative MRI assessment in most cases if a combination of mammography and whole breast sonography is used.[26]




a. b. c.

Figure 2. Screening mammogram (a and b) and sonogram (c) of a 50 year old lady with invasive lobular carcinoma asymmetry on CC view of MG. An ill defined hypoechoic mass is seen on sonogram (c). US guided biopsy was used for sampling. Final diagnosis: Invasive Lobular Carcinoma.

A limitation of the study is a small increase in expenditure for additional sonography, which was covered by the UGC grant during this study. Sonography on the other hand may provide a definitive diagnosis, thus alleviating anxiety and avoiding 6 monthly follow up with mammograms.

## CONCLUSIONS

Adding sonography was helpful in further evaluating dense mammograms, confirming normal or benign studies without the need for tissue sampling especially in inconclusive BIRADS 0 and BIRADS 3 studies. In mammographically suspicious studies, sonography could more definitely delineate tumor size, extent, satellite lesions, and guide biopsy. Additional sonography had high sensitivity and negative predictive value compared to mammography. We recommend that supplemental sonography can be performed on patients with dense mammograms and combined reports provided.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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