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Two-dimensional or three-dimensional imaging for breast cancer screening? An evaluation study of sensitivity and specificity from Northern Kerala, India

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SUMMARY

Breast cancer is considered the most serious lesion among different breast lesions. Mammography is the corner stone for screening for detection of breast cancer. It has been modified to Digital Mammography (DM) and then to Digital Breast Tomosynthesis (DBT). Tomosynthesis is an emerging technique for diagnosis and screening of breast lesions. Breast cancer is the second most common type of cancer globally and a most frequent cancer in females, with 1.67 million new cases diagnosed in 2012 alone. Database of Population Based Cancer Registries (PBCRs) (2009-2011) from India denote breast cancer as the most common type of cancer followed by cancer of cervix and gall bladder. Mammography is a modality of early diagnosis, which is affordable, reliable and reproducible with proven reduction of mortality from breast cancer. This may be more helpful in early detection of cancers, especially in case of non-palpable lesions. However, technology has undergone drastic changes from analogue mammography to digital mammography which is reported to have significantly higher cancer detection rate in women aged 40-49 years (82.4% vs 75.6%). Digital system has improved contrast resolution because of higher detective quantum efficiency and dynamic range.

Key words: cancer registries, digital breast tomosynthesis, escalating

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INTRODUCTION

Breast cancer is the second most common type of cancer globally and a most frequent cancer in females, with 1.67 million new cases diagnosed in 2012 alone [1]. Database of Population Based Cancer Registries (PBCRs) (2009-2011) from India denote breast cancer as the most common type of cancer followed by cancer of cervix and gall bladder [2]. There are 0.3 million deaths reported annually, constituting 14.3 % of the total cancer deaths [1]. Breast cancer contributes to the highest mortality among cancer patients in underdeveloped countries.

If detected at an early stage, breast cancer is one of the few cancers with high cure rate. Mammography is a modality of early diagnosis, which is affordable, reliable and reproducible with proven reduction of mortality from breast cancer [3]. This may be more helpful in early detection of cancers, especially in case of non-palpable lesions [4]. However, technology has undergone drastic changes from analogue mammography to digital mammography which is reported to have significantly higher cancer detection rate in women aged 40-49 years (82.4% *vs* 75.6%) [5]. Digital system has improved contrast resolution because of higher detective quantum efficiency and dynamic range [6].

Digital Breast Tomosynthesis (DBT) or three dimensional tomography is a new advancement in the field of mammography which uses multiple low dose radiographic exposure over an arc to generate a projection image dataset and to reconstruct thin images in standard mammographic view [7]. This is particularly useful in dense breast (which obscures as well as mimics malignancy) as it deals with tissue overlapping. DBT can eiter be used in one view or both view along with standard mammographic views. Trials including interim analysis of Screening with Tomosynthesis or Mammography (STORM) l as well as the Oslo and Malmo breast tomosynthesis Screening Trials have shown superior cancer detection rate by DBT [8].

Empirical evidence suggests that sensitivity of mammogram decreases with increase in breast parenchymal density leading to increased incidence of interval malignancy in screened women [9]. After its introduction in 1997, there was widespread acceptance of DBT and lot of observational studies have shown high sensitivity for cancer detection even in dense breast and reduced recall rate [10]. On the other hand, due to absence of adequate randomized controlled trials, US Preventive Services

Task Force in its 2016 systematic review has concluded that there is insufficient evidence to suggest DBT as a screening tool for breast cancer [11]. As there is a huge cost difference between digital mammogram and DBT, such recommendation may have a huge impact in resource limited countries like India where escalating the cost of screening tool may reduce the patient acceptance rate. In this study we have attempted comparison of sensitivity and specificity of these newer modalities.

METHODOLOGY

Study design

A cross sectional study to evaluate screening tool.

Study population

The study included mammography images of women having mammography reading by all three technologies (2D, standalone 3D and Integrated 2D-3D) with non palpable lesions between 1st January 2015 and 31st September 2016. Images of those patients, whose diagnosis was confirmed by histopathology were included in the study. Those women with age less than 30 years and those with palpable lesions were excluded from this study.

Study setting

Tertiary level rural cancer institute under the Department of Health, Government of Kerala, catering majorly to the population in northern Kerala, and adjacent parts of Karnataka and Tamil Nadu. Screening is done in women who are referred for mammogram, who have completed cancer treatment and are on follow up, and in recently diagnosed case of breast cancers to look for lesions in contra-lateral breast.

Study sample

All breasts subject to screening were assigned a breast composition category based on subjective analysis of fibro-glandular tissue within the breast [9]

Breast categories included

- The breasts are almost entirely fatty
- There are scattered areas of fibro glandular density
- The breasts are heterogeneously dense, which may obscure small masses
- The breasts are extremely dense, which lowers the sensitivity of mammography

BI-RADS is an acronym for Breast Imaging Reporting and Data System which is published by American College of Radiology (ACR) [9]. It was designed to standardize mammogram reporting and to monitor the outcome. We have used the latest ACR BI-RADS 2013 Atlas for mammogram [9] and ultrasound reporting [10]. We have used latest BI-RADS lexicon to describe all mammographic and ultrasound detected lesions. Based on the findings, a mammography report was generated with incorporation of assessment categories, which has been explained in [Table.1].

Data collection and data quality

Image archives stored and secured in the system of department of imageology were used to collect the study data. Histopathology reports were collected from oncopathology department after obtaining permission from concerned authority.

All the possible and available 2D and 3D images were collected from the concerned department described above and were given serial numbers to avoid identification. The investigator studied the 2D and 3D images separately, at one-week interval (wash-over period) to identify the BIRADS STAGING, which were noted and sealed. For reading of 3D images, 2D images were blinded from the radiologist with the help of a technologist

Tab. 1. Assessment categories for BI-RADS grading[12]

	Assessment	Management	Likelihood of cancer
Category 0	Incomplete – needs further imaging or comparison with previous mammogram	Recall the patient	Not available
Category 1	Negative	Routine mammography screening	0% likelihood of malignancy
Category 2	Benign	Routine mammography screening	0% likelihood of malignancy
Category 3	Probably Benign	Short-interval follow up – clinically or by surveillance mammography	>0% but ≤ 2% likelihood of malignancy
Category 4	Suspicious	Tissue diagnosis	>2% but<95% likelihood of malignancy
Category 4A	Low suspicion for malignancy	Tissue diagnosis	>2% to ≤ 10% likelihood of malignancy
Category 4B	Moderate suspicion for malignancy	Tissue diagnosis	>10% to ≤ 50% likelihood of malignancy
Category 4C	High suspicion for malignancy	Tissue diagnosis	>50% to <95% likelihood of malignancy
Category 5	Highly Suggestive of Malignancy	Tissue diagnosis	≥ 95% likelihood of malignancy
Category 6	Category 6 Known Biopsy-Proven Malignancy	Surgical excision when clinically appropriate	Not available

who provided only 3D images for reporting. For the integrated 2D/3D reporting, the investigator saw both the images combined and concluded the BIRADS staging. Histopathology results for these corresponding serial numbers were collected and entered.

Data entry and analysis

All the sequential data thus collected were double entered into Epidata and validated. Duplicate version of the database was used for statistical analysis using Epidata software (version 3.1, Odense, Denmark). Data analysis were done to compare the sensitivity and specificity of the 2D, 3D and integrated imaging. Statistical significance was considered at 95% CI ($p<0.05$).

Ethics approval

Ethics approval were obtained from the Institutional Review Board of the Institute and The Ethical Advisory Committee of the International Union Against Tuberculosis and Lung Diseases, Paris. As the study was carried out using images already available in the hospital console and the histopathology reports available in the pathology department without involvement of patients or active interventions, written consent was not deemed necessary. Approval to use the hospital data were obtained from the concerned authorities.

RESULTS

Images were obtained for the 2142 women who underwent screening mammogram during study period. Histopathology results were available for 70 of the women whose images were available. Of these, images of 30 women were excluded for missing 3D images and remaining 40 patients were included in the study. The socio-demographic, radiological and histopathological characteristics of the patients enrolled in the study are summarised in Table 2. The median age of women whose images were included in the study was 51 years (IQR: 37-69 years). Majority of the patients were aged between 40-59 years. Most of the women (73%) had breast density category b. Majority of them had BI-RADS> 4 in mammograms and histopathologically confirmed benign breast tumours.

Sensitivity and specificity of 2D, standalone 3D and integrated 2D-3D mammogram are summarised in Table 3. While sensitivity (2D=90%, 3D=95% and 2D/3D=100%) and negative predictive value (NPV) (2D=92.3%, 3D=92% and 2D/3D=100%) are high across all three technologies for malignancy, the same were low (sensitivity: 2D=42, 3D=16, 2D/3D=23; NPV: 2D=67%, 3D=62%, 2D/3D=64%) for benign tumours. Specificity varied from 18% to 40% for malignancy and 73% to 86% for benign tumours. Positive Predictive Values were low for all technologies below the benchmark of 50%. Breast density was not found to be statistically significant with 2D mammogram($p=0.18$), 3D mammogram ($p=0.68$) and integrated 2D-3D (0.322). Quadrant wise lump detection using 2D, 3D and integrated 2D and 3D mammograms are summarised in Figure 1. Overall, the detection of lump was more in Upper Outer Quadrant (UOQ) of the breast with over half of all lumps detected in UOQ across all technologies (2D=53%, 3D=51% and 2D-3D=65%).

The inter-rater variability between imaging techniques used in mammography are summarised in Table 4. While Kappa statistic for agreement between 2D versus 3D and 2D versus Integrated

Tab.2. Socio demographic, radiological and histopathological characteristics of patients who underwent screening mammography in the Institute from January 2015 to September 2016

Variable	Category	Number	(%)
Age group	30-39	3	-8
	40-49	15	-38
	50-59	13	-33
	60-69	9	-23
Breast Density#	Category a	2	-5
	Category b	29	-73
	Category c	9	-23
	Category d	0	0
Mammogram 2D¢	BIRADS § <4	13	-33
	BIRADS § ≥ 4	27	-68
Mammogram 3D€	BIRADS § <4	6	-15
	BIRADS § ≥ 4	34	-85
Integrated 2D & 3D	BIRADS § <4	7	-18
	BIRADS § ≥ 4	33	-83
Side of involvement as per HPR¶ Right	Benign	17	-43
	Malignant	11	-28
	Not involved	12	-30
Side of involvement as per HPR¶ Left	Benign	14	-35
	Malignant	9	-23
	Not involved	17	-43

Breast Density are classified according to American College of Radiology classification
§ BIRADS: Breast Image Reporting and Data System
¶ HPR: Histopathology Report;
¢ 2D: 2 Dimensional Imaging
€ 3D: 3 Dimensional Imaging

Tab.3. Sensitivity and specificity of 2D, 3D and integrated 2D and 3D mammogram in detecting malignant and benign breast lesions in patients who underwent screening mammography in the Institute from January 2015 to September 2016

MAMMOGRAM	BIRADS§	SENSI-TIVITY	95 CI#		SPECI-FICITY	95 CI#		PPV^	95 CI#		NPV¶	95 CI#	
			Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
2D¢	MALIGNANT	90	68.3	98.8	40	27.6	53.5	33.3	28	39.2	92.3	75.7	97.9
	BENIGN	42	24.6	60.9	73	58.9	85.1	50	34.9	65.1	67	58.7	73.8
3D€	MALIGNANT	95	75.1	99.9	18	9.5	30.4	28	24.9	31.2	92	60.2	98.8
	BENIGN	16	5.5	33.7	86	72.8	94.1	42	19.9	67.3	62	57.1	66.2
INTEGRATED 2D & 3D	MALIGNANT	100	83.2	100	23	13.4	36	30	27.4	33.3	100	0	0
	BENIGN	23	9.6	41.1	86	72.8	94.1	50	28	72	64	58.4	68.6

(All values are in percentages)
CI: Confidence Interval
§ BIRADS: Breast Image Reporting and Data System
^ PPV: Positive Predictive Value
¶ NPV: Negative Predictive Value
¢ 2D: 2 Dimensional Imaging
€ 3D: 3 Dimensional Imaging

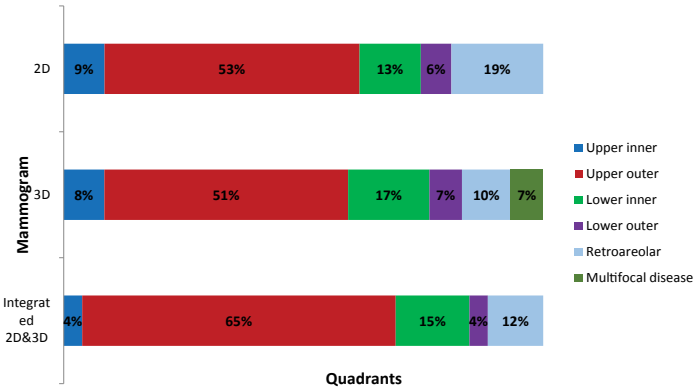

Fig. 1. Quadrant wise breast lump detection using 2D, 3D and integrated 2D and 3D mammogram in patients who underwent screening mammography in the Institute from January 2015 to September 2016

2D: 2 Dimensional Imaging; 3D: 3 Dimensional Imaging

Tab.4. Inter-rater variability between imaging techniques used in mammography of women evaluated for Breast Cancer in the Institute from January 2015 to September 2016.

a. Inter-variability between 2D and 3D standalone imaging

2D¢ Imaging	3D€ Imaging					Kappa Co-efficent
BI-RADS#0		BI-RADS#2	BI-RADS#3	BI-RADS#4	BI-RADS#S5	
BI-RADS#0	0	0	0	0	0	NA
BI-RADS#2	0	1	1	0	0	0.42
BI-RADS#3	0	1	2	1	0	95%CI
BI-RADS#4	2	3	3	9	2	0.24-0.61
BI-RADS#5	0	0	0	5	10	NA

b. Inter-variability between 2D and Integrated 2/3D imaging

2D¢ Imaging		3D€ Imaging				Kappa Co-efficent
BI-RADS#0		BI-RADS#2	BI-RADS#3	BI-RADS#4	BI-RADS#S5	
BI-RADS#0	0	0	0	0	0	NA
BI-RADS#2	0	1	0	0	0	0.5
BI-RADS#3	1	1	3	1	0	95%CI
BI-RADS#4	1	2	3	12	2	0.31-0.70
BI-RADS#5	0	1	0	2	10	NA

c. Inter-variability between 3D and Integrated 2/3D imaging

2D¢ Imaging		3D€ Imaging			Kappa Co-efficent
BI-RADS#2		BI-RADS#3	BI-RADS#4	BI-RADS#S5	
BI-RADS#2	1	0	0	0	NA
BI-RADS#3	1	3	2	0	0.75
BI-RADS#4	0	1	16	3	95%CI
BI-RADS#5	0	0	1	12	0.59-0.90

¢ 2D: 2 Dimensional Imaging
€ 3D: 3 Dimensional Imaging
BI-RADS: Breast Image Reporting and Data System

2D-3D are moderate (0.4 and 0.5 respectively), Kappa statistic agreement between 3D and Integrated 2D-3D is good (0.75).

DISCUSSION

To our knowledge, our study comparing sensitivity and specificity of digital 2D, standalone 3D and integrated 2D-3D mammogram is the first of its kind from India. There were few important findings. First, considering the role of mammography as a screening tool for breast tumors, 2D is not inferior to 3D in both sensitivity and negative predictive value. Though 3D alone without 2D is not used for clinical purpose, it was separately evaluated in our study and was found to be more sensitive than 2D for non-palpable malignancy [12]. Non palpable lesions included both soft tissue lesions and clustered pleomorphic micro-calcifications which are not palpable to both the patient and the clinician. Second, specificity for malignancy and sensitivity for benign lesion was more with 2D mammogram compared with standalone 3D and integrated 2D-3D mammogram, which had better sensitivity for non-palpable malignancy than 2D mammogram alone. Third, except multifocal and retro-areolar tumors, the detection of tumors by 2D and 3D imaging are perfectly comparable both in sensitivity and NPV and there is not much advantage with 3D imaging. Fourth, though the specificity of these techniques is above 73%, they cannot be used as diagnostic tools as the PPV is low (just about 50%).

Though there is lot of debate and controversies on potential benefit and harm of undergoing screening mammogram, it is the only strategy which has shown 20% reduction in mortality in different randomised controlled trials [13]. With technological advancement in mammography equipment, there are claims of increased cancer detection rate and hence an inclination to include these in population screening.

Though screen film mammography was not included in our study as this modality of diagnosis was not existent at the study site, evidence from Oslo II study have demonstrated increased cancer detection rate of digital mammogram compared to screen film mammogram [14]. Digital mammogram is increasingly being used in breast cancer screening not only due to increased cancer detection rate, but also due to the advantages of digitalization of images aiding easy cross referral and archiving. Though 3D alone without 2D is not used for clinical purpose, it was separately evaluated in our study and was found to be more sensitive than 2D for non palpable malignancy. This option can be further explored on larger samples to implement 3D alone as a cost-effective approach for screening technology. Non palpable lesions included both soft tissue lesions and clustered pleomorphic micro-calcifications which are not palpable to both the patient and the clinician.

Standalone 3D and integrated 2D-3D mammogram had better sensitivity for non-palpable malignancy than 2D mammogram alone. However, specificity for malignancy and sensitivity for benign lesion was less compared with 2D mammogram. Both the Oslo study [15] and STORM study [16] has shown increase in the cancer detection rate (CDR) when integrated 2D-3D mammogram is used. In Oslo study, there was 31% increase in CDR and 13% decrease in false positivity rate with integrated 2D-3D mammogram [15]. In STORM study [16], there was 33.9% increase in CDR and 17.2% reduction in false positivity rate. B. Haas et al in their study showed insignificant (9.5%) increase in cancer detection rate and significant reduction in recall rate [17]. There was only moderate kappa statistics of agreement (0.4 and 0.5 respectively) between 2D and standalone 3D and 2D and integrated 2D-3D mammogram in our study signifying that there is only minimal increase in sensitivity with integrated 2D-3D mammogram.

A total of 20 non-palpable malignant lesions were detected in 19 patients. One patient had malignancy in both breast. Of the 19 patients with malignancy, 13 (68.4%) patients had breast category b. Further research could be undertaken to see association between the type of malignancy and the breast density.

The study has many strengths. Our study strictly followed the STARD (Standards for Reporting Diagnostic accuracy studies) 2015 guidelines [18].It also followed the Strengthening Reporting of Observational studies in Epidemiology (STROBE) guidelines and adhered to sound ethical principles [19]. All the patients whose images were available for all three technologies and the histopathology reports were included in the study. All the variables in the study were doubly entered in EpiData entry software and the data entry errors were corrected using hard copies to ensure clean dataset. Nevertheless, the study has certain limitations. The study has small sample size and effect of different modalities on recall rate and detection of different grades of tumour were not studied.

The study has three important policy implications. First, mammogram with above 98% sensitivity for detection of malignancy with any of the technology (2D, 3D and integrated 2D-3D), should be used as a screening tool for early identification of breast malignancies. Combined with presence of lump in the breast, the BIRADS grading can be used for early detection in district level hospitals where a radiologist is available. This will prevent the out of pocket expenditure by the patients with suspected breast cancer, as only the screened positive patients at the peripheral health institutes can be referred to tertiary care cancer hospitals which will be at times distant from the patients resident place costing them commutation charges and loss of daily wages. This will also reduce the patient load at the tertiary hospital, which will aid the specialists to give more precious time to the much needy patients.

Second, 2D mammography is equally sensitive to detect malignancies compared to 3D and integrated 2D-3D. So when using mammography as a screening tool it will be cost effective to go for 2D technology. This will be especially helpful in choosing technology for screening at the district level hospitals, as the initial and the recurrent cost difference is huge (2-3 times) with 3D costing much higher than 2D. However, it will be advisable to have all the technologies at the tertiary hospitals, to detect the presence of multi-focal and retro-alveolar tumors, which may differ in its treatment modalities.

Third, though the specificity of these techniques are high for detection of benign breast tumor with over 73% in all three techniques, these imaging cannot be used as a diagnostic tools as the PPV is low (just about 50%). This means even if the imaging shows the presence of benign tumor a second imaging

modality should be used for characterization. This is important in establishing the hub and spoke model, where feasible, the peripheral institutes should screen the breast tumors using the mammogram and send the BIRADS 4 and 5 lesions to the tertiary cancer care hospitals for confirmation and treatment.

CONCLUSION

The study shows the sensitivity and specificity of the 2D, 3D and integrated 2D-3D mammography imaging techniques compared with gold standard histopathology. While sensitivity of all three techniques is above 98% for detection of breast malignancy, it varied from 16%-23% for detection of benign tumors. Though specificity of these techniques is above 73% for benign tumors, these technologies cannot be used as diagnostic tools as the PPV is low. As there is not much advantage with 3D over 2D for screening for breast malignancies, 2D techniques can be used effectively in the peripheral level with much cost advantage which is no way inferior to 3D imaging.

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