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FULL PAPER

Digital breast tomosynthesis within a symptomatic “one-stop breast clinic” for characterization of subtle findings

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Objective: The aim of the study was to evaluate the diagnostic accuracy of combination of full-field digital mammography [two dimension (2D)] and digital breast tomosynthesis [DBT, three dimension (3D)] by comparing the combination with 2D imaging in a symptomatic setting.

Methods: A retrospective analysis was conducted involving 103 patients who attended symptomatic breast clinics between March 2012 and September 2012. All had subtle signs on 2D images or ultrasound. Mammographic score distribution was compared between 2D imaging and 2D + 3D imaging, followed by comparison with the gold-standard histopathology. Receiver operative characteristic curves and area under curve (AUC) were calculated for 2D imaging and the combination imaging (2D + 3D). SPSS® v. 21 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for data analysis with $p < 0.05$ as statistically significant.

Results: M3 lesions were reduced from 91 (85.8%) to 18 (16.9%) with the combination imaging. The mean $AUC \pm 95\%$ confidence interval for 2D images alone was 0.721 (0.662–0.905) and for combined 2D and 3D images was 0.901 (0.765–1.00). The difference in AUCs between the two modalities was 0.180.

Conclusion: DBT (3D imaging) increases diagnostic accuracy in a symptomatic breast clinic setting and reduces the number of M3 mammograms, when used as an adjuvant to 2D images. Therefore, DBT has the potential to increase workflow efficiency in a symptomatic setting by reducing benign biopsies.

Advances in knowledge: DBT reduces the number of M3 mammograms when used in the symptomatic breast setting and has the potential to reduce benign biopsies.

INTRODUCTION

Conventional two-dimensional (2D) mammograms have been known to miss between 15% and 30% of cancers in screening programmes.¹ In addition, 2D mammograms are known to have false positives, leading to unnecessary recalls.¹ In extremely dense breasts, sensitivity of conventional 2D mammograms has been reported to be as low as 48%.^{2,3} This low sensitivity may be due to “anatomical noise” consisting of normal dense breast tissue superimposed on a 2D plane.^{4,5}

A tomographic three-dimensional (3D) technique digital breast tomosynthesis (DBT) that reduces the obscuring effect of overlying tissue has the potential to improve sensitivity and specificity compared with 2D full-field digital mammography (FFDM).

A number of studies have been performed^{6–10} to establish the advantages of combination of 3D imaging with 2D, as opposed to only 2D imaging in population-based breast cancer screening. Other studies are test-set observer studies^{11–14} or clinical series^{15–18} comprising a mixture of screening and

symptomatic cases. However, to the best of our knowledge, no study has been conducted in a purely symptomatic setting.

Our study was designed to compare the accuracy of 3D imaging in a setting of symptomatic “one-stop breast clinic.” Hence, the primary objective of the study was to directly compare FFDM (2D) with FFDM + DBT (combination of 2D and 3D imaging) within a purely symptomatic environment.

METHODS AND MATERIALS

Patient population

3D mammography was installed in our department (The Breast Centre, Llandough University Hospital) in March 2012 for routine use within the breast symptomatic services. The proposed study had the prior approval of University Health Board (Innovation and Improvement Services) as a service evaluation project. This retrospective study was an observer study of patients treated in our department and did not involve any additional intervention to patients. A formal ethical approval was deemed unnecessary. All procedures (mammograms, ultrasound and biopsies) were conducted prior to the study, as part of the triple assessment under

standard departmental consent guidelines within a symptomatic “one-stop” clinic. One-stop clinic includes clinical assessment by surgeons, imaging and biopsy (if needed) within a single visit. All patients included in the study had two views of 3D mammograms (craniocaudal and mediolateral oblique view) of the symptomatic side because subtle areas of abnormality had been detected on 2D mammograms or ultrasound. 3D mammograms were performed immediately following routine 2D and ultrasound examinations in the same visit at the one-stop clinic. Standard assessment (workup) of the abnormality was performed irrespective of the 3D option. The result of the diagnostic assessment (ultrasound and needle biopsy when performed) was assumed as the reference standard for the study. The presenting symptoms in all patients included one or more of the following: lumps, tenderness/pain or nipple discharge.

The scoring system for evaluating mammograms and ultrasound was the Royal College of Radiologists classification system:¹⁹ Five grades were assigned as follows: 1—normal breast tissue, 2—benign changes, 3—probably benign changes, 4—suspicious for malignancy and 5—definitely malignant. The prefixes M and U refer to mammographic and ultrasound scores, respectively.

Patients with microcalcification on 2D mammograms were excluded from this review as these patients had further magnification views and not 3D mammograms. Patients with definite malignant mammographic findings (M5) were also excluded. Other exclusion criteria included breast implants, pregnancy and history of radiotherapy or ongoing chemotherapy/radiotherapy.

Following these exclusions, we had 103 consecutive patients who underwent both 2D and 3D mammography at our “symptomatic one-stop clinic” between March 2012 and September 2012, which were included in this evaluation. The mean age of 103 patients included in this study was 52.5 years (range 35–81 years).

These 103 patients had subtle signs (subtle distortion/density or indeterminate mass lesion with no definitive sign to suggest malignancy or benign lesion) on 2D mammograms (M3, M4) or normal mammograms but abnormal ultrasound (M1, M2 with U3, U4 or U5). The choice to have 3D mammograms was based on the subtle signs on 2D imaging or ultrasound findings, and this was decided by any one of the readers (GJB/Karene Lim/PY/Zebby Rees).

Four patients were found to have multifocal lesions. In total, there were 103 symptomatic patients with 106 lesions.

Image acquisition

The images were acquired using a FFDM unit with tomosynthesis capability (Hologic® Selenia® Dimensions®; Hologic Inc., Bedford, MA). The X-ray tube moved through a 15° arc and acquired 11 low-dose projection images, which were then reconstructed at 1-mm sections for viewing. Routine quality control measurements were made throughout the study, following the methods and protocols suggested by National Health Service—Breast screening programme and Institute of Physics and Engineering.²⁰

Image reading

Each case was read by one of the four readers (GJB, Karene Lim, PY and Zebby Rees). All readers had between 3 to 20 years’

experience of reading 2D images, in a department in which more than 4000 2D mammograms are reported every year. All had more than 1-year experience of evaluating 3D mammograms and had received formal training in reading 3D images by attending an approved course.

A standard mammogram evaluation *pro forma* was designed along with an instruction sheet indicating the method to be followed for reporting mammograms. Readers filled the *pro forma* for each patient individually and independently. They were free to review previous films for comparison to mirror the reporting in a symptomatic clinic.

Readers did not have access to the histopathology, ultrasound findings or clinical history of these cases at the time of review and were therefore blinded to the final result.

2D mammograms of each patient were read first and mammographic scores were recorded, followed by review and scoring of combination of 2D and 3D images of the same patient in each sitting. Images were read in batches of 10–15 patients to avoid fatigue.

In addition to the scoring, lesion conspicuity and exact site were also recorded on the data sheet. If there were multiple lesions, they were all scored independently. This evaluation was performed using a SecurView® Mammographic workstation (Hologic Inc.), which had two 5-megapixel liquid crystal display displays with a mammography workflow keypad. The system included tools for contrast adjustment and magnification, which the readers were free to use.

The radiological finding was recorded for both 2D and 2D + 3D imaging as one or more of the following: subtle asymmetric density, mass, distortion or normal glandular breast. Breast density was classified onto one of the four categories as defined by the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS®) (fifth edition) categories:²¹ Category A: the breasts are almost entirely fatty; Category B: there are scattered areas of fibroglandular density; Category C: the breasts are heterogeneously dense, which may obscure small masses; and Category D: the breasts are extremely dense, which lowers the sensitivity of mammography.

Statistical analysis

Statistical analysis was performed using receiver operative characteristics curve, and area under the curve (AUC) was calculated and compared between 2D imaging and 2D + 3D imaging. Mammographic scores for the two imaging modalities were compared with histopathology. SPSS® v. 20.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for data analysis with $p < 0.05$ taken as statistically significant.

RESULTS

The final diagnosis was recorded as normal/benign or malignant based on histological or ultrasound findings. Cases recorded as normal/benign included all cases in which either needle biopsy or fine-needle aspiration (FNA) had confirmed benign results or further imaging showed no features of malignancy. None of the

normal/benign cases returned back to our clinic with any change for 24 months. We have assumed lack of presentation at our centre in 24 months as indicating normal or benign status and were not aware of any cancers in this subcohort. Malignant results were based on final surgical histology, all cases being discussed at weekly multidisciplinary team meetings, as per protocol in our department. Overall, 13 patients (12.6%) had invasive malignancy, and 90 patients (87.3%) were reported to have benign/normal findings either on the basis of imaging (75; 72.8%) or FNA/core biopsy (15; 14.5%).

24 of 103 patients (23%) had dense breasts (Category C or D), and the rest of the patients with mixed density [Category B (79; 76%)]. There were no fatty breasts (Category A) in our cohort of patients.

The addition of 3D images to 2D images resulted in reallocation of majority of M3 mammograms into M2 or M5, as illustrated in Figure 1. M3 lesions were reduced from 91 (85.8%) to 18 (16.9%) with the combination imaging (Figures 2–4).

There was a false-positive (M4 with normal/benign histology) rate of 0.93% with 2D images, which remained at 0.93% with 2D + 3D mode. This was a case of subtle distortion in a mixed density (Category B) breast, which on subsequent ultrasound was shown to be normal glandular tissue (Figure 5a,b). There were no false negatives (M1/2 with malignant histology) with 2D imaging. There was a false-negative (M1/2 with malignant histology) rate of 1.87% with the combination of 2D and 3D images. In this case, a score of M3 was given with 2D. This was a case of invasive lobular cancer involving an extensive area of breast in dense (Category D) breasts. The diagnosis in this instance was established with ultrasound guided core biopsy (Figure 6).

The mean AUC $\pm$ 95% confidence interval (CI) for 2D images alone was 0.721 (0.662–0.905) and for combined 2D and 3D

images was 0.901 (0.765–1.00). The difference in AUC between the two modalities was 0.180 (Figure 7). However, the CIs were overlapping, suggesting that the results were not statistically significant.

12 cancers (out of a total of 13 cancers) were classified as malignant (M4/M5) when read in 2D and 3D combination mode, as elucidated above (Table 1).

In our series, with the combination mode, we could have potentially reduced benign biopsies from 15 (14.1%) to 10 (9.4%) lesions (M3/U3 and M2/U3 on 2D imaging vs M3/U3 and M2/U3 on 2D + 3D imaging) (Figures 3 and 4).

DISCUSSION

3D mammography was installed in our department for use in symptomatic services as part of the routine diagnostics in March 2012, following which we evaluated a subgroup of patients, who might benefit most from 3D imaging, *i.e.* those with subtle signs on 2D or mammogram occult cancers. Patients with microcalcifications were excluded from our evaluation, as previous studies^{6,22} have found 3D mammograms unhelpful in patients with microcalcifications. We believe that 3D imaging could have the potential to improve workflow efficiency of a symptomatic clinic. The improvement in the evaluation of subtle signs using 3D imaging would enable the reader to classify indeterminate lesions found on 2D imaging (M3) as either benign or malignant (M2/M5). There are potentially important implications for diagnostic practice from this study, as it has been conducted in a purely symptomatic setting. This was possible in our centre as symptomatic and screening services are at separate sites.

Previous studies have demonstrated that 3D mammograms when used as an adjunct to 2D mammograms can improve the accuracy of the classification of mammographic features, as measured using BI-RADS or similar classification systems.^{2,6,13,23} Earlier studies

Figure 1. Distribution of mammographic scores between two-dimensional (2D) and combined two-dimensional and three-dimensional (2D + 3D) imaging.

Figure 2. (a) Left breast craniocaudal (LCC) view with subtle density in the upper outer quadrant (M3) was changed to M2 after three-dimensional (3D) views. (b) Left mediolateral oblique (LMLO) view of the same patient with subtle density on the upper outer quadrant (M3) was changed to M2 after 3D views. Arrows indicate the site of mammographic abnormality.

have been performed in a screening environment,^{6,10} on enriched samples in an artificial environment^{11–14,24} or included clinical series that comprised symptomatic and screen recalled cases.^{15–18} However, the higher prevalence of abnormality in an enriched sample can introduce biased responses and lead to questionable external validity of the results relative to the real clinical setting.

Our study comprised consecutive patients who attended our breast clinic and had tomosynthesis at the time of their symptomatic evaluation. Our evaluation did not involve an enriched sample. Cancer prevalence in our sample was 11%, which,

although more than the prevalence of cancer of 6.3%^{24,25} in symptomatic females, was still much less than the enriched samples comprising mostly cancers in previous studies.²⁴ The median cancer prevalence of subjects with breast cancer across all previous studies was 28% (interquartile range 17–42%),²⁶ which may have limited the potential to quantify the true detection capability of 3D imaging in previous studies.

Another limiting factor of previous studies is that often responses are oversimplified so that the experiment is streamlined in terms of cost and results interpretation. Our readers

Figure 3. Flow chart showing breakdown of imaging scores with two-dimensional (2D) imaging (numbers in parentheses represent actual patient numbers). FA, fibroadenoma.

Figure 4. Flow chart showing breakdown of patient's imaging scores with combined two-dimensional and three-dimensional (2D + 3D) imaging (numbers in parentheses represent actual patient numbers). FA, fibroadenoma.

were encouraged to respond in the same manner and format they would have performed in a clinic setting in terms of mammographic scoring. Moreover, they were asked to review previous images and compare with the contralateral breast, as they would have performed in a clinical setting.

In this way, we reduced artificiality of environment, which has adversely affected many previous studies and which can limit the clinical relevance of results. Physical aspects of the viewing environment, such as lighting, physical setting of room and noise, can also influence readers' behaviour. In our evaluation, the physical environment was the same as the usual clinic setting and was properly controlled.

In our study, the false-positive rate for both 2D and 2D + 3D imaging remained at <1%. Better visualization of benign and normal features can improve the diagnostic capability of radiologists and thereby reduce false positives and unnecessary biopsies/anxiety to the patients. In our series, with the combination mode, we could have potentially avoided benign biopsies in 5 (4.7%) lesions (M3/U3 and M2/U3 on 2D imaging vs M3/U3 and M2/U3 on 2D + 3D imaging). Similarly, improved visualization of subtle signs of cancer can decrease the false-negative rate. In our study, false-negative rate was <2% with the combination of 2D and 3D imaging. This was owing to a patient who was given a mammographic score of M2 with the combination mode. In this patient, a large section of the breast was

Figure 5. (a) Right craniocaudal (RCC) subtle distortion (M3), normal on ultrasound and stereo biopsy (false positive on both 2D and 2D + 3D imaging). (b) Right mediolateral oblique (RML) of the same patient as above. Arrow indicates the site of mammographic abnormality.

Figure 6. (a) Right breast craniocaudal (RCC)-lobular cancer involving extensive area of the breast [scored as M3 on two dimensional (2D) and M2 on two dimensional and three dimensional (2D + 3D) imaging] (false negative on 2D + 3D imaging). (b) Right breast mediolateral oblique (LMLLO) of the same patient as above. (c) Ultrasound showing cancer as subtle attenuation. Arrows indicate the site of mammographic abnormality.

abnormal with lobular cancer. We found that 3D imaging has a tendency to falsely reassure in cases of lobular cancer, owing to its infiltrating pattern of spread, which is difficult to diagnose on individual slices of 3D. This cancer was visible as subtle attenuation on ultrasound. Hence, currently, the role of 2D + 3D imaging is only as an adjunct to ultrasound and cannot replace it altogether. However, we replaced spot compression views with 2D + 3D imaging combination for non-calcified soft-tissue abnormalities. Radiographers find doing 3D views easier than spot views as it does not require precise positioning, saving time for both radiologist and radiographers.

One potential limitation is that we did not directly compare 3D images with spot views. Performing spot views and 3D mammograms in a single patient would have increased radiation dose. Previous studies^{13,27} have mentioned that 3D imaging can replace spot compression views. We managed to replace these extra views with 3D images in our patients and therefore made dose and time saving in the process. Dose to the patient varies depending on the number of extra spot views, which can be as high as three views in some patients. 2D + spots views combination gives more radiation dose to the patient than 2D + 3D images (2.5 mSv).²⁸ Moreover,

Figure 7. Receiver operative characteristic curves comparing two-dimensional (2D) vs combined two-dimensional and three-dimensional (2D + 3D) imaging. AUC, area under the curve.

Table 1. Distribution of mammographic scores of all cancers

2D score	2D + 3D score	Type of cancer
4	5	Mucinous
4	5	Ductal
3	4	Ductal
4	5	Ductolobular
3	3	Lobular
3	5	Ductal
3	2	Lobular
3	5	Ductal
4	5	Lobular
4	5	Ductolobular
3	5	Ductolobular
4	5	Tubular
4	4	Ductal

2D, two-dimensional imaging; 2D + 3D, combined two-dimensional and three-dimensional imaging.

The missed lobular cancer with 2D + 3D imaging is depicted in bold.

3D imaging helps evaluate the whole breast, can often be performed in the same compression as 2D images and is not dependent on accurate positioning over the target area. Reading time may go up slightly, but this is justified in symptomatic patients, if benign biopsies can be avoided in 5 (4.7%) of lesions.

A direct comparison with ultrasound was also beyond the scope of this service evaluation. All symptomatic patients had traditional workup with ultrasound in our study. Based on our findings, it is proposed that further studies are needed to directly compare 3D imaging with ultrasound and spot compression mammography.

Another limitation of this evaluation is that a majority of our cases were scored as M3 on the 2D images in the clinic and therefore had subtle findings on mammograms. Hence, this subset will not be a representative of the entire spectrum of diagnostic cases that come to our clinic. However, by selecting this specific subset of patients with subtle features, we have chosen a subgroup that will most benefit from 3D imaging, and this subset of patients is most likely to have 3D images in a symptomatic setting.

The readers in our study were blinded to the final results of the cases when reading the mammograms. However, they were

unblinded to the 2D image findings, which were read and scored immediately preceding the 2D and 3D combination. However, we do not feel this to be a limitation as this procedure is typical within a symptomatic clinic setting. Practically, 2D images would always be available, when reading the 3D images. In future, 2D images can be synthesized from DBT images and thus eliminate the need for double acquisitions.

Readers in this evaluation were also part of the initial assessment. However, we do not feel memory bias can contribute to the findings of our study, as there was at least 6 months of time interval between the actual patient attendance in clinic and the study. It has been shown memory washout happens within 10 days.²⁹

Our findings are valid for mixed density and dense breasts, as there were no fatty breasts in our cohort of patients. Both false-negative (lobular cancer) and false-positive lesions were in dense or mixed density breasts, respectively, in our cohort.

Similar results to our study have been found in many previous studies,^{6,11,13,17,24,30–32} although these did not involve purely symptomatic patients. A large study by Michell et al⁶ analysed 738 females within a screening environment. He found that the addition of 3D imaging increased the accuracy in assessment of screen-detected soft-tissue abnormalities with increase in both sensitivity and specificity.

The radiation dose of the combination is approximately double that of 2D mammograms alone.³³ However, this is still below the dose that constitutes an acceptable risk and is less than the Mammography Quality Standard Act limit for a two-view screening mammographic study.²⁸ Moreover, considerable dose saving was made by avoiding spot views, as suggested by Morel et al.³⁴ With the development of synthesized 2D images from the 3D data set, dose issue will be further diluted.

In summary, 3D imaging led to improvement in visualization of subtle signs, which enabled the readers to classify indeterminate lesions found on 2D more accurately as either more suspicious of malignancy or benign. This evaluation has therefore demonstrated that 3D images when added to 2D images in the interpretation of subtle findings in a symptomatic setting have the potential to reduce benign biopsies and replace spot views. Currently, we believe that the role of 2D + 3D imaging is only as an adjunct to ultrasound.

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