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Digital Mammography Imaging: Breast Tomosynthesis and Advanced Applications

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Synopsis

This article discusses recent developments in advanced derivative technologies associated with digital mammography. Digital breast tomosynthesis – its principles, development, and early clinical trials are reviewed. Contrast enhanced digital mammography and combined imaging systems with digital mammography and ultrasound are also discussed. Although all these methods are currently research programs, they hold promise for improving cancer detection and characterization if early results are confirmed by clinical trials.

Keywords

Digital Breast Tomosynthesis; Digital mammography; Computer Aided Detection; Breast Cancer; Breast Imaging; Mammography

Introduction

The Achilles Heel of screening mammography is the detection of cancer in women with radiographic dense breasts. While nearly all cancers will be apparent in fatty breasts, only half will be visible in extremely dense breast [1]. This results, at least in large part, from the masking or camouflaging of noncalcified cancers by surrounding dense tissue. In this chapter, we will discuss several derivative digital technologies being developed to overcome the weakness of conventional mammography (film screen and/or digital mammography). The emphasis will be on digital breast tomosynthesis with secondary discussion of contrast-enhanced digital mammography and combined digital mammographic and ultrasound equipment. It should be emphasized, as of this writing, all the aforementioned technologies are investigational in the United States and none are approved for clinical use by the Food and Drug Administration. The clinical application of these technologies, if any, will be determined by scientific investigation and regulatory approval.

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Digital Breast Tomosynthesis Mammography

Digital breast tomosynthesis mammography (DBT) is one technology being developed to improve detection and characterization of breast lesions especially in women with non-fatty breasts. In this technique, multiple projection images are reconstructed allowing visual review of thin breast sections offering the potential to unmask cancers obscured by normal tissue located above and below the lesion. DBT involves the acquisition of multiple projection exposures by a digital detector from a mammographic X-Ray source which moves over a limited arc angle [2-11]. These projection image data sets are reconstructed using specific algorithms. The clinical reader is presented with a series of images (slices) through the entire breast that are read at a workstation similar to review of a CT or MRI study. Because each reconstructed slice may be as thin as 0.5 mm, masses and mass margins that may otherwise be superimposed with out of plane structures should be more visible in the reconstructed slice. This should allow visualization (detection) and better characterization of non-calcified lesions in particular.

Technique

The advent of digital mammography and computer reconstruction algorithms has allowed derivative technology to be developed including tomosynthesis. In conventional digital mammography, a compressed breast is exposed to ionizing radiation. Energy which passes through the breast is transformed into an electrical signal by a detector which produces the clinical image. The x-ray tube is stationary, the breast is stationary, and the detector is stationary. The image that is produced in any one projection such as a CC or MLO view is a two-dimensional representation of three-dimensional space. Each pixel is therefore an average of the information obtained through the full thickness of the breast. A three-dimensional depiction of the breast would be advantageous similar to three-dimensional depictions allowed by CT, MR, or ultrasound scanning.

In digital breast tomosynthesis, the x-ray tube is moved through a limited arc angle while the breast is compressed and a series of exposures are obtained (Illustration. 1). These individual exposures are only a fraction of the total dose used during conventional digital mammography. The total dose used should be within FDA limits and is expected to be near or slightly above the routine mammographic dose if DBT becomes clinically approved. If there is a 45-degree arc of movement and an exposure is taken every 3 degrees, there will be 15 individual exposures. These raw “projection” data sets require reconstruction using algorithms similar to those used in other three-dimensional image sets. The projection data sets are not usually interpreted by the radiologists, but rather the interpretation is based only on the reconstructed “tomosynthesis” images. Typically, the projection data sets are reconstructed into very thin (eg, 1 mm) slices for radiologist review.

Imaging Technique

Several manufacturers have applied different methods to develop and perform tomosynthesis. There are likely advantages and disadvantages of each technique. However, these differences may produce different clinical results making clinical comparisons between manufacturers difficult. Engineering constraints include total radiation dose, image time, patient motion, detector performance, detector motion, and ability to image the entire breast. There is also the necessity to provide future biopsy capability for those lesions detected only by tomosynthesis.

Manufacturers vary the arc of movement (typically 11-60°), the number of individual exposures (typically 9-25), use of continuous or pulsed exposure, stability or movement of the detector, exposure parameters, total dose, effective size of pixels, X-ray source/filter

source, single or binned pixels, and patient position. These theoretical and engineering decisions may lead to different clinical outcomes and different reading recommendations for the different manufacturers. Of particular importance is the assessment of microcalcifications and whether one attempts to accurately depict microcalcifications by DBT. Because of the limited angle of scanning, the images are only "quasi" 3D. The x-y plane perpendicular to the x-ray beam has the highest resolution. There is less resolution in the parallel plane or z axis. One may reconstruct the data set for the radiologist to read by displaying different thicknesses. For example, if a 60 cm compressed breast is reconstructed at 1 mm thickness, there will be 60 slices for the physician to review. If the images are reconstructed at 0.5 mm thicknesses, there will be 120 images to be reviewed. If the images are reconstructed at 10 mm thick "slabs" using maximum intensity projection (MIP) thick slices, there will be 6 images to review.

Radiation Dose

A major consideration for DBT manufacturers and regulators is the balance between dose and image quality. Because image quality tends to be directly related to dose, compromises are necessary. All manufacturers have produced equipment with dosing parameters less than current FDA limit of 300 millrads per exposure. Common convential mammographic dose per view is 150-250 millirads. However, achieving lower doses is optimal. Variations in target filter, breast thickness, and breast density further complicate this analysis. However, if DBT leads to reduction in recall rate or improvement in sensitivity and specificity, a minimally higher dose may be acceptable.

Tomosynthesis Reconstruction Algorithms

Similar to CT and MR, reconstruction algorithms are a critical element for tomosynthesis [3-8, 12-14]. It is beyond the scope of this discussion to provide more than a cursory explanation. Unlike historic tomography used for intravenous pylograms where the projection images were interpreted as is, tomosynthesis reconstructs raw projection image data sets to produce clinical images. Reconstruction techniques include shift-and-add, tuned aperture computed tomography, matrix inversion, filtered back projection, maximum likelihood reconstruction, and simultaneous algebraic reconstruction technique. Certain reconstruction methods may be better for masses and other methods better for calcifications. Details of specific manufacturer algorithms are not always in the public domain.

Potential Benefits of Clinical Breast Imaging with Tomosynthesis

The potential benefits of DBT include improvement in screening sensitivity, improvement in lesion size at detection, improvement in characterization, and decrease in recall rates. DBT may be useful in both the screening and diagnostic evaluation. Neither has been proven in randomized controlled trials.

In theory DBT, with thin section display, should allow superior detection of lesions that historically have been masked by overlying tissue. The primary benefit of DBT would be expected to be for non calcified mammographic findings such as masses, asymmetries, distortion (Figs 1-4) In the most basic application, DBT would allow visualization of cancers not apparent by conventional mammography thus improving sensitivity. While many regard tomosynthesis as a technique for dense breast tissue, it may also have significant applications for those patients with non-dense breasts by allowing detection of smaller lesions. This is a variant of improved sensitivity as a decrease in size at time of detection may be associated with improvement in clinical outcome. DBT also offers the possibility that characterization or specificity may be increased by better assessment of detected lesions and reduction in false positive recalls. This is because the margin of a mass or character of an asymmetry may be better visualized. Malignant lesions may appear

"more" malignant and benign lesions "more" benign. If these concepts are born out, DBT may allow for improved sensitivity coupled with improved specificity. Recall rates for asymmetries and possible masses may be lowered if DBT better depicts the morphologic characterization of such findings. Diagnostic evaluation of potential masses and asymmetries found by screening mammography could also be a DBT function. It is unlikely that calcification characterization would improve dramatically.

An understated but important aspect of DBT theory is that the basic technology used is mammography. To date, mammography is the only screening imaging technology which has proven itself in randomized controlled trials to show survival benefit [15]. Improvement in mammographic technology with DBT would therefore be closer to the original mammographic methods than other competing technologies such as MR, ultrasound, or CT with the clinical implication of improved screening.

Proving the superiority of a new technology is more difficult than showing non inferiority. Even if the technology proves useful, there are many clinical considerations that will impact on potential use. Given the current cost climate, incremental reimbursement will be challenging. If DBT costs more and takes longer to read, there will be barriers to acceptance. Work flow issues need careful attention as does technologist and physician training. Obviously, there are many questions to answer before these theories are accepted or refuted.

As no tomosynthetic system is currently clinically approved by the Food and Drug administration for use in the United States, there are differences of opinion regarding what the "best" clinical practice acquisition and display methods will be. Of particular interest is whether DBT would replace conventional mammographic views or would be an adjunct to current mammographic views or some combination of the two. The number of DBT views and number of conventional views that would constitute a "routine mammogram" have not been determined. From a physician's standpoint, one may consider two extremes and then postulate multiple hybrid reading scenarios. If tomosynthesis is extremely sensitive for masses and calcifications, it may be theoretically possible that a single tomographic view such as the MLO would constitute a routine "mammogram". A reader would be presented with a MLO DBT image set for assessment. Masses, calcifications, distortions, etc. would all be detected. At the other extreme of clinical options would be the obtaining of tomosynthesis images in both the CC and MLO projections and two conventional digital images in both the CC and MLO projection (4 views each breast). In this scenario, a physician would read the two conventional digital images (CC and MLO) as well as two tomosynthetic images. A reader may concentrate on mass detection on the tomosynthesis views and calcifications on the conventional mammograms. In between are hybrid reading scenarios that would have various combinations of these two extremes. For example, mammographic study could include a MLO DBT image and conventional CC view. To date, the best or likely method of acquisition has not been scientifically determined. This determination may be manufacturer dependent, technology dependent, and likely will be a compromise among sensitivity, dose, and practice guidelines. Different manufacturers may seek to solve the same problem with different theories and methods to achieve the same end point result.

Early Clinical Tomosynthesis Evaluations

We are now able to review several early experimental clinical DBT studies. These DBT studies for masses have generally shown good patient acceptance, physician preference for DBT images, improvement in sensitivity, improvement in characterization, and often longer physician reading times [16-27]. The findings with calcifications have been mixed. The test is neither 100% sensitive nor 100% specific. The real world performance of DBT may be

different than these experimental clinical studies because actual decisions regarding clinical care are not made in these studies. We will review some of the early studies undertaken.

Reader Preference Studies

Poplack, et al, in 2007 evaluated 99 cases with DBT that were recalled for further evaluation from a screening trial [16]. Only 14% of the recalls were for calcifications. One of two readers was asked to determine his/her preference regarding image quality. For 51% of cases, readers determined the DBT image quality was equal, 37% considered it superior, and 11% considered it inferior. Calcification assessment was problematic. Of those cases deemed of inferior image quality, 72% of cases were for calcifications. In this select population, the authors concluded that the recall rate could have been diminished by 40% if tomosynthesis images had been obtained at time of screening examination. This decrease in recall rate, however, is likely an overstatement of clinical practice as they did not study the potential increase in recall rate if tomosynthesis had been initially applied to a larger group of patients.

Good et al assessed nine physicians' opinion on image quality with DBT [17]. They evaluated 30 mixed diagnostic cases consisting of 2/3 masses and 1/3 calcifications. The readers determined that DBT image quality was somewhat better (44%) or significantly better (23%), in 67% of cases. 31% were comparable and only 1.9% DBT images were worse than conventional images. These results were very similar to Poplack's results. This study also measured reading time which was longer for DBT than conventional reading, with a mean time for conventional reading of 1.6 minutes and for DBT, 2.7 minutes, a difference of 69%.

Andersson et al, using several expert readers and 40 cases that were considered extremely subtle or occult, assessed visibility of cancers by DBT [18]. In this series, only 12% of cases were calcifications. The readers rated DBT image quality higher in 55%, equal in 32%, and inferior in 2%. Of note, 10% of cases were false negative by both DBT and digital mammography. The differences in perceived image quality were significant to a statistical value of $p = .01$

Clinical Trials of DBT

Helvie et al, using 4 readers and a diagnostic set of mass cases scheduled for biopsy, determined that more masses were detected by DBT (49.5) than conventional mammography (36.5), an increase of 35.6% which was significant for each reader [19]. Only 7 malignant cases were included in the initial study. However, DBT detected 100% of cancers by all readers while only 71% were detected by conventional mammography, an incremental cancer detection increase of 40%. Lo et al, in a similar study of diagnostic cases and lesion detection, also noted a 40% incremental detection rate for DBT (91% vs. 65%) although no difference in cancer detection was noted in 4 cancer cases [20].

Rafferty et al, analyzed 310 DBT and DM cases using ROC methods and 15 readers. They compared three reading methods, DM alone vs DM and MLO DBT and finally DM compared to DM and both CC DBT and MLO DBT [21]. This reading method was different in that DBT was used as an adjunct to conventional DM. They found significant improvement in ROC AUC values when DBT views were combined with DM as compared to DM alone. For fatty breasts, the AUC was .880 for DM alone, .898 for DM and MLO DBT, and .915 for DM plus CC DBT with MLO DBT. The incremental advantage of using DBT with DM for dense breasts using the same study methods were proportionally greater, AUC of .786, .832, and .877 respectively. Still, the best DBT AUC was highest for women with fatty breasts (.915) compared to dense (.877) suggesting that while DBT may improve

test performance for cancer in women with dense breast proportionally more than fatty, maximum performance is still for women with fatty breasts. (Robyn – is this better?)

Moore et al compared the recall data on 1957 patients screened with MLO DBT and standard 2 view DM [22]. In this study, 10 readers read the conventional digital mammograms and 2 readers read the DBT studies. The standard DM screening mammography recall rate was 7.5% and the single view DBT recall rate was 4.3%. The decline in recall rate by 43% is similar to the decline noted by Poplack and Rafferty. These studies suggest the potential for DBT to improve recall rates while maintaining sensitivity, at least in experimental reading situations.

Gur et al, reported a retrospective reader study comparing DM with DBT alone and combined DM and DBT using an enriched population of 125 cases which included 35 known cancers [23]. Of 90 benign study cases, 49% had either benign findings or had been recalled from screening. Eight radiologists, in an organized reader study, reviewed images in several reading situations including two view (CC,MLO) DM alone, two view (CC,MLO) DBT images alone, and combined DM and DBT images of a single breast. The authors noted a non significant improvement in sensitivity when reading DBT alone (93%) was compared to digital mammography alone (88%). The combination of DM and DBT did not improve sensitivity compared to DBT alone. Specificity was greatest with DBT combined with DM, compared to DBT alone or to DM alone (0.72 vs 0.64 vs 0.60). Of interest was a corresponding 10% relative decrease in unnecessary recall rate for benign findings by DBT, vs. DM alone There was a significant 30% reduction in recall rate for cancer free cases if DBT was used as an adjunct in combination with DM compared to DM alone. In this experimental situation, the mean time to read DBT was greater than DM (2.05 minutes vs. 1.22 minutes) for a single breast. DBT plus DM reading time was even longer, 2.39 minutes. While encouraging, the authors cautioned further evaluation in a more realistic clinical situation was warranted.

Not all DBT studies have yielded positive results. Teertstra, in the Netherlands compared 513 diagnostic digital mammograms with tomosynthesis [24]. The diagnostic patients included abnormal screen examinations (26%), women with palpable findings (44%), and those seeking a second opinion (30%). There were 344 cases that had histologic proof of diagnosis with 112 newly detected cancers. While a single observer assessed the DBT examination alone 1-3 months after the clinical study, one of 7 different observers reported the initial clinically performed digital mammography study at the time of the clinic visit. Using a positive threshold of BIRAD Category 0, 3, 4, and 5, the authors reported similar sensitivity of 92.9% for both DBT and digital mammography. Specificity was 86.1% with digital mammography and 84.4% for DBT, a non-significant difference. There were 8 cancers that were false negative to DBT. These results suggested no improvement for diagnostic DBT. However, if the more commonly used positive threshold for cancer was Category 0, 4, or 5, then, the sensitivity of DBT was greater than DM (80% vs.73%) with specificity of 96% and 97%,. This was due to the large number of cancers (21%) classified as probably benign by mammography in the study. These assessments for category 3, probably benign, may vary from US practice. The authors noted all clusters of malignant calcifications detected by digital mammography were also detected at breast DBT.

Characterization of masses

One of the touted advantages of DBT has been for characterization and margin assessment of masses. Helvie reported results of 4 readers who assessed the margins of masses scheduled for biopsy [25]. When masses were visible by both DBT and conventional mammography, readers were able to visualize 77% of the perimeter of a mass with DBT vs. 53% of the perimeter of a mass by conventional mammography. The increase in incremental

visible margin was significant for all readers. A weakness of this study was that the conventional mammograms consisted of a mixed population of film screen and digital studies. In another study of 382 DBT views of biopsy proven masses, BIRADS margin characterization of benign masses versus malignant masses showed that circumscribed masses were much more common with benign than cancer (70 vs. 5%) [26]. Conversely, spiculated or indistinct margins were much more common with cancer than benign (81% vs. 11%). Thus most benign masses appeared circumscribed and most malignant masses were spiculated. Using a threshold of cancer probability of 2% for Category 3, in this experimental situation, it was estimated that 39% of masses recommended for biopsy would have been classified as BIRADS 1, 2 or 3, theoretically decreasing the biopsy rate. The real world clinical performance would likely be less.

Anderson explored the theoretical incremental characterization assessment change when reviewing DBT with a single view DM mammography vs. a two-view conventional mammography for subtle breast cancers [18]. They noted a 25% incremental upgrade rate (from Category 1, 2, or 3 to Category 4 or 5) when DBT was compared to a single view conventional DM image. That is, lesions that were considered benign by conventional imaging were deemed more suspicious by DBT and a biopsy recommendation was made. This upgrade rate decreased to 20% when DBT image was compared to a two-view digital mammography. This study suggests a very small incremental yield even for subtle cancers when a two view (single DBT and single DM) study is compared to a three view study (single DBT plus CC DM and MLO DM).

Microcalcifications by DBT

There is limited literature regarding clinical microcalcification assessment by DBT for detection and characterization. The engineering, physics, and reconstruction of different manufacturer equipment may lead to different results and completely different conclusions even though all are “tomosynthesis.” X-Ray source, motion, pixel size, and reconstruction algorithms are of particular concern. Although the in plane resolution of DBT is very good, out of plane resolution is poor. Because calcifications may be dispersed in 3-D space, viewing thin DBT images may make perception of calcification clusters difficult as only one or two may be seen on a slice. To overcome this issue, manufacturers have developed maximum intensity projection (MIP) images consisting of thick slices such as 1-2 cm for reviewing calcifications (Fig 4). In a feasibility study, we showed that for cases which were subjected to biopsy based on conventional imaging, calcifications were visible by DBT in either CC or MLO view in 100% (93 of 93) of cases [27]. However, the per view visualization was less. By view, 96% of benign lesions and 97% of malignant lesions were apparent by DBT. This study merely assessed if calcifications were visible by DBT, not reader preference or performance between DBT and conventional mammograms. Poplack et al DBT study of image quality showed a disproportionate number of calcification cases to be inferior [16]. When image quality was considered inferior, 72% of lesions were calcifications. Yet in the study population, only 14% of cases were for calcifications. Teertstra showed all malignant calcification cases which were visualized by DM were also visualized by DBT [24]. Much more work is necessary before conclusions can be drawn regarding microcalcifications and DBT.

Computer-aided detection (CAD) Tomosynthesis

Due to the marked increase in number of images for physician review, with potential increased time necessary for interpretation, DBT may impose clinical workflow challenges. Further, it can be postulated that secondary to increased workload and the increased number of images to review, physician oversight of findings could increase. CAD may be very important for clinical DBT and have a more significant clinical role than with conventional

DM mammography in improving work performance. It is possible that CAD will also perform better with tomosynthesis images compared to DM images because of better margin visibility of masses. Several researchers have developed CAD systems for DBT. Chan, et al, reported on CAD for masses with DBT (28, 29]. Mass detection sensitivity of 90% has been achieved at 2.0 false positive cases per breast volume. At 80% sensitivity, 1.2 false positives per case has been achieved. Singh, et al, also has developed a CAD program for mass detection [30]. Their reported optimal performance was 85% sensitivity for masses at 2.4 false positives per breast. Reiser, et al, developed mass and calcification detection programs for DBT [31,32,]. In a small series of calcifications, performance sensitivity of 86% was achieved at 1.3 false positives per volume. This performance was noted to be better than CAD performance for DM systems. The development of these CAD systems was based upon a limited enriched DBT data sets but show encouraging results. Like digital mammography, CAD will be a supplemental adjunct to human observation and characterizations and act as a second, not primary reader.

Important Considerations for Assessment of New Technology such as DBT

While preliminary experimental clinical studies have generally been favorable for tomosynthesis, more rigorous scientific investigation is underway to establish the true nature of tomosynthesis and potential application for clinical breast imaging. There are several biases to be considered when reviewing preliminary clinical investigations. Experimental clinical trials do not exactly replicate real world clinical realities. Readers may have heightened awareness for cancer detection given enriched cancer populations which may overstate sensitivity and specificity compared to normal lower cancer incidence encountered in clinical practice. Another important but overlooked positive bias relates to the initial performance vs subsequent test performance on a screened population. “Prevalent” detection bias occurs when a new screening technology is applied to a population that has not been previously exposed to that technology. In general, cancer detection rates and outcomes are higher at prevalent detection than subsequent annual incident screening. The magnitude of this bias is often under appreciated. For conventional mammography, prevalent detection rate is 6-10/1000 and annual incident detection rate is 2-4/1000 [33]. A study of MRI of high risk women showed the prevalent detection of MRI of 13.2 per 1,000 which decreased to 5.3 per 1,000 at incident detection [34]. In the same study, mammography prevalence detection was 16.5 per 1,000 which decreased to 2.1 per 1,000 at incident screening. Therefore, when analyzing new technology, one must be aware of potential positive bias induced by the prevalent (first) testing situation. In almost all reported cases, DBT has been tested as a prevalent test. Simply increasing the number of views for a radiologist to interpret may by itself increase sensitivity even without the addition of new a technology which may have impact when assessing trials using DBT as an adjunct to mammography.

Extensive physician training will be necessary if DBT proves efficacious in clinical trials. Radiologist mammographic interpretation and performance variability remains a major weak link in the assessment of mammographic images. Technologist training with a new modality will also be important for proper image acquisition. Training regarding appropriate reading time, methods, and thresholds for recall and biopsy will all be necessary. In particular, determining which t structures are “normal” and which require intervention will be an ongoing educational process. It is quite possible that further refinements of what constitutes a BIRADS Category 3, probably benign lesion, and what constitutes a Category 2 benign lesion will be necessary. Completely circumscribed masses such as cysts may be able to be classified as Category 2 by DBT. Conversely, some lesions such as fibroadenomas which may currently be classified as Category 3 due to circumscribed margins by DM may show more margin variability by DBT which could change their classification to Category 4A. Lesions that are considered suspicious but only visualized on DBT will require

manufacturers to develop biopsy capability which will further increase the training need for physicians utilizing DBT.

Other New Digital Mammography Systems

Contrast Enhanced DM (Robyn, I flipped paragraphs back to original way)

Combining high resolution digital mammography with the functional attributes obtained with contrast enhancement offers another potential derivative application for digital mammography. The advantage of contrast enhanced digital mammography (CEDM) would be to obtain functional contrast information attributed to malignant neovascularity directly linked to high quality anatomic information. Breast MRI has utilized this principle for years. The potential advantages postulated for using CEDM would be the widespread installation of mammography units, superior resolution, patient acceptance of mammography, and potential lower cost. The disadvantage of such a technique for screening is the necessity for an intravenous contrast administration, adverse consequences of contrast, increased cost, increased time, and patient acceptance compared to standard DM. Competing against contrast-enhanced digital mammography is a body of work utilizing contrast-enhanced MRI. Potential applications could be similar to MRI including screening, diagnostic, staging, and treatment monitoring. Currently, screening for MR has been stratified based upon high risk for breast cancer. If CEDM proves efficacious, its application may follow a pattern of high risk or special situation application.

There are two main methods described for contrast-enhanced digital mammography; serial exams over time and dual energy imaging [35-41]. Both employ iodinated contrast material, and modified digital mammography units for imaging. Higher kV, often 45 -49, is used to take advantage of the K-edge of iodine. Serial imaging can be obtained for a single projection only. Although this may have application for diagnostic or staging reasons, it would be less applicable to screening situations. For this reason, dual energy methods have been developed to allow imaging of both breasts with a single contrast administration. Early work has shown technical and clinical feasibility. The actual number of patients studied to date has been very limited so the application if any for future potential clinical use is uncertain.

Serial CEDM

Serial or temporal contrast-enhanced digital mammography is similar to contrast-enhanced breast MRI. The patient’s breast is placed in compression in a single view such as the MLO. Prior to contrast injection, a non-contrast image is obtained. Next, following contrast administration, a series of images are obtained. Each image is a fractional dose of conventional mammography. There is insufficient visible enhancement to allow primary interpretation, and for this reason the enhanced images are subtracted from the baseline image leaving areas of enhancement visible. Using this methodology, enhancement curves can be obtained. Weaknesses of this type of study include the ability to only image the breast in a single projection at a time significantly limiting application to a routine screening situation. Technically, motion may cause mis-registration errors limiting sensitivity, visualization of enhancing lesions, and overall confidence in interpretation.

Dual Energy CEDM

A conceptually different approach utilizes dual energy technology. The technology makes use of different iodine k-edge x-ray absorption at low and high energies. Dual energy mammography requires a modified mammographic machine which is capable of producing both normal mammographic images and images obtained at higher energy (45-50kV) acquired in rapid succession after contrast administration. The patient is injected with

contrast and placed in compression. Two paired exposures are obtained, one at low kV and the other at high kV. A subtraction image is produced which highlights areas of iodine concentration or enhancement. The mammographic image at low energy can be used as a routine gray scale mammographic interpretation. With efficient technologists, 4 views (2 views of each breast) can be obtained during a single administration of contrast. This technique does not allow for kinetic assessment of enhancement curves.

Early studies have shown the clinical feasibility of CEDM with test sensitivity ranging from 80-91%. Jong et al reported enhancement by serial CEDM in eight of 10 (80%) cancers in a 22 patient study [37]. Lewin et al, using dual energy CEDM, showed strong enhancement in 11/13 (85%) malignancies and moderate or weak enhancement in the remaining two cases [38]. A similar 80% sensitivity was noted by Dromain et al for 20 malignant cases undergoing single CC view serial CEDM [35]. Chen, et al [41] combined CEDM with DBT in a feasibility study with 13 patients where ten of 11 (91%) patients with malignancies had abnormal enhancement visible by CEDM. Most recently, a multicenter 5 reader retrospective study of 85 lesions (68 cancers) compared DM alone with DM plus CEDM [40]. The authors demonstrated sensitivity improvement for readers from 0.81 to 0.86 with the addition of CEDMand the area under the ROC curve was greater for all readers although significant for only 2 readers.

While CEDM appears technically feasible in small series, the clinical utility has yet to be established. Both types of CEDM compete against a large body of breast MR knowledge and clinical experience. It is possible that CEDM techniques would be less expensive that current MRI examinations, while possibly generating similar information. However, some of the issues limiting breast MR would apply to CEDM including the necessity of intravenous contrast administration which is a barrier to routine screening of a general population compared to routine DM, breast ultrasound or potentially DBT. Patient motion is a problem with repetitive time sampling leading to misregistration and potential diagnostic problems. There are many patients who are unable to tolerate MR scanning so this technology could be used for such individuals. Unlike MR, compression is applied for CEDM to limit motion. However, excessive compression may inhibit blood circulation within the breast which could limit enhancement.

Combining Digital Mammography with other Imaging Technology

Digital imaging allows the potential to co-register systems' different technologies to produce fused images. Screening breast ultrasound detects mammographically occult cancers in women with dense breasts. ACRIN 6666 trial showed a 4.2/1000 improvement in cancer detection with the addition of physician-performed hand-held ultrasound screening of high risk women with dense breasts [42]. However, there are potential limitations of whole breast ultrasound screening by physician due to the time necessary to perform the examination and resources available. In Berg's study, the mean scanning time was approximately 20 minutes. Automated ultrasound scanning methods have appeal. Methods to combine simultaneous mammography and automated ultrasound would have the theoretical advantage of the improved sensitivity of ultrasound with an automated approach and the ability to simultaneously correlate the sonographic findings with the mammographic findings. Screening and diagnostic scanning could occur simultaneously.

Equipment and methods have been developed which allow automated digital mammography (with or without tomosynthesis) and automated ultrasound at the same patient sitting [43-45]. Using prototypes, the patient's breast is compressed as with a typical mammographic image. A conventional mammographic image is obtained. Subsequently, while still under compression, the breast is scanned mechanically by ultrasound. The

mammograms and ultrasound images can be reviewed independently. In addition, a direct 3-D registration is possible which allows correlation of a lesion found by one technology with the other technology (Fig5). For example, a circumscribed mass detected by mammography could be correlated with a simple cyst found at sonographic scanning and no recall would be necessary. Conversely, if a sonographic suspicious finding is detected and the mammogram is normal, the improved sensitivity of ultrasound screening could be realized. There are other potential combined systems under early investigation including combining DM with nuclear medicine functional imaging or optical scanning.

Summary

Advanced digital mammographic technology such as digital breast tomosnythesis is an exciting new development for breast cancer screening and diagnostic applications. Favorable preliminary experimental clinical trial results especially for masses must be confirmed with larger more representative clinical trials. The assessment of microcalcifications awaits further study. Major advantages of DBT as a new imaging technology include the linkage to the scientific basis for screening mammography, the existent extensive installed mammographic base, familiarity with existing digital equipment, and decades old medical and radiologic experience with mammography. Patient acceptance would be expected to be good. If successful, and born out by rigorous clinical trials, this technology has the potential to change conventional mammographic screening and diagnostic imaging with possible improvements in cancer detection, decreased call backs, and fewer false positive biopsies.

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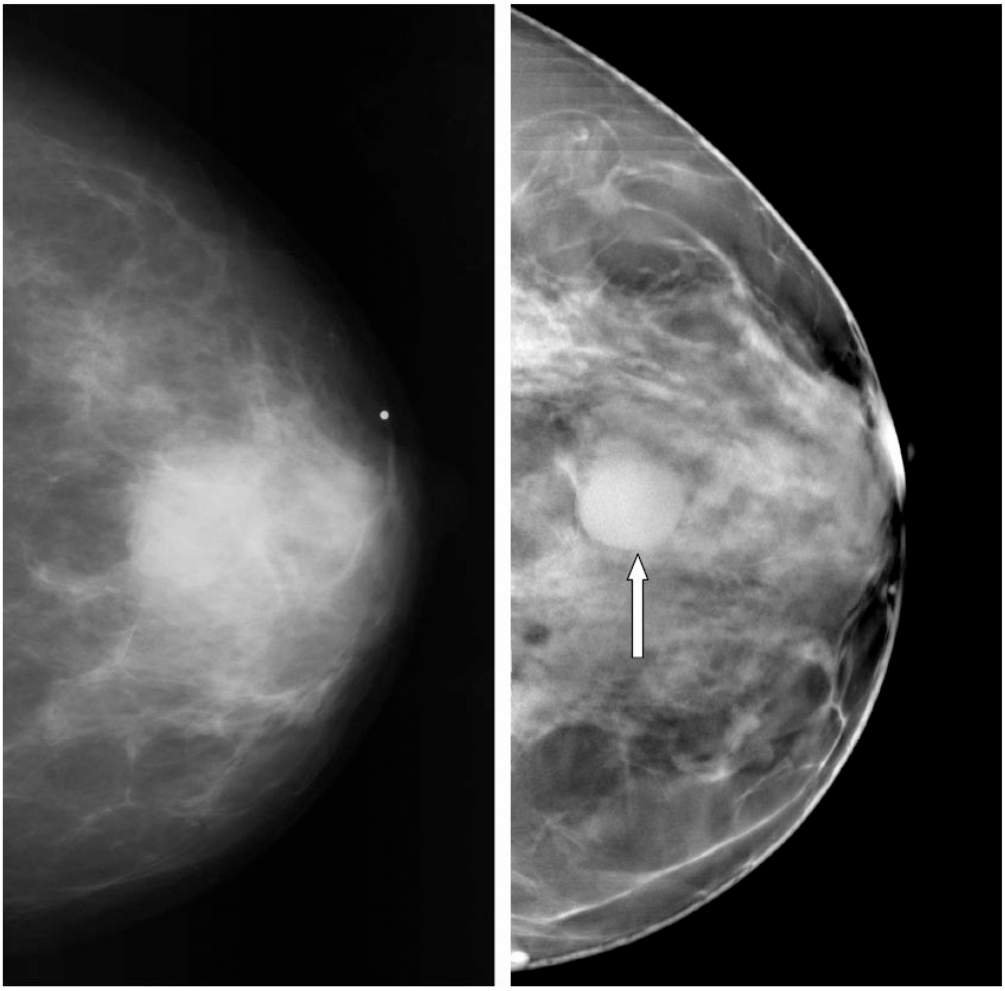


Figure 1.
A, B – Cranial-caudal conventional mammography view (A) of a middle-aged woman presenting with a palpable mass indicated by a metallic BB marker. Tomosynthesis 1 mm thick image (B) depicts a circumscribed mass (arrow). Five such masses were noted by DBT at other levels, all proven to be cysts by ultrasound.

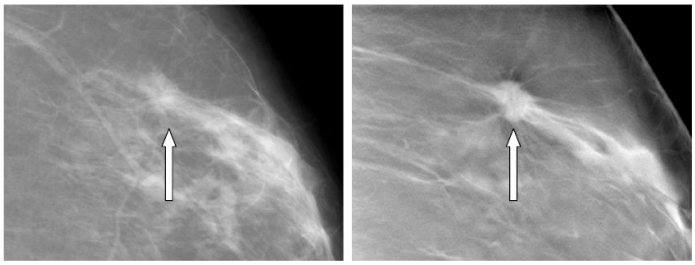


Figure 2.
A, B – Conventional film screen mediolateral oblique mammography view (A) of a patient with invasive ductal cancer. The cancer, although vaguely apparent on the conventional mammogram (arrow), is much better visualized on the 1 mm thick tomosynthesis image (B) (arrow). Note the clarity of the spicules and the separation from surrounding tissue.

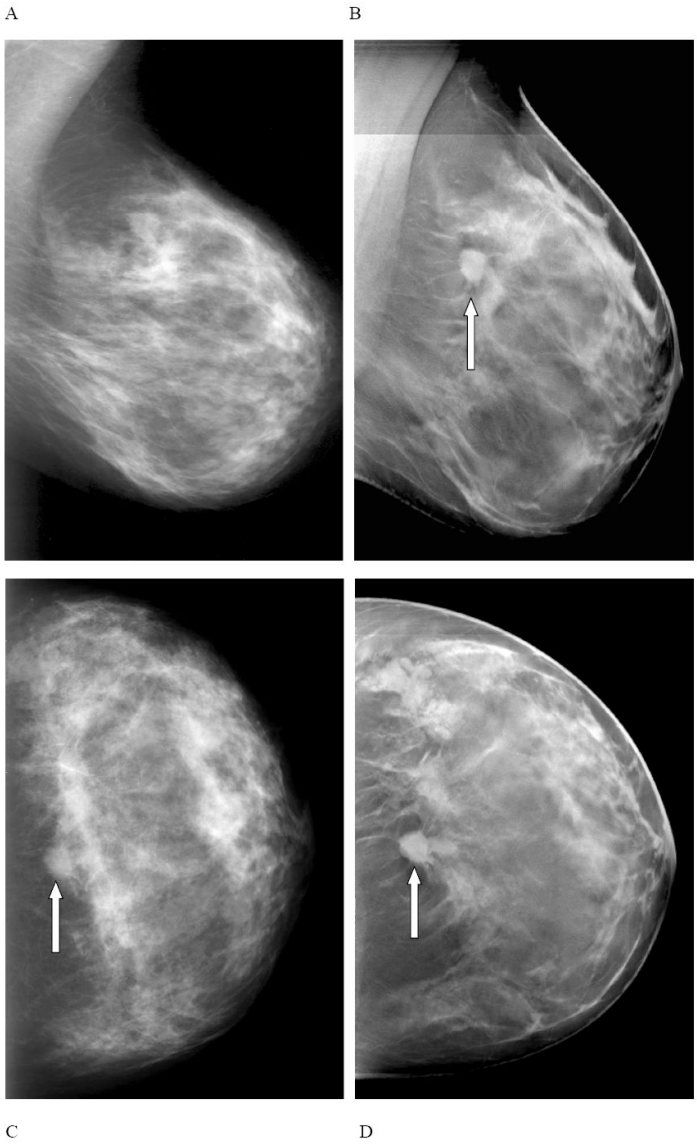
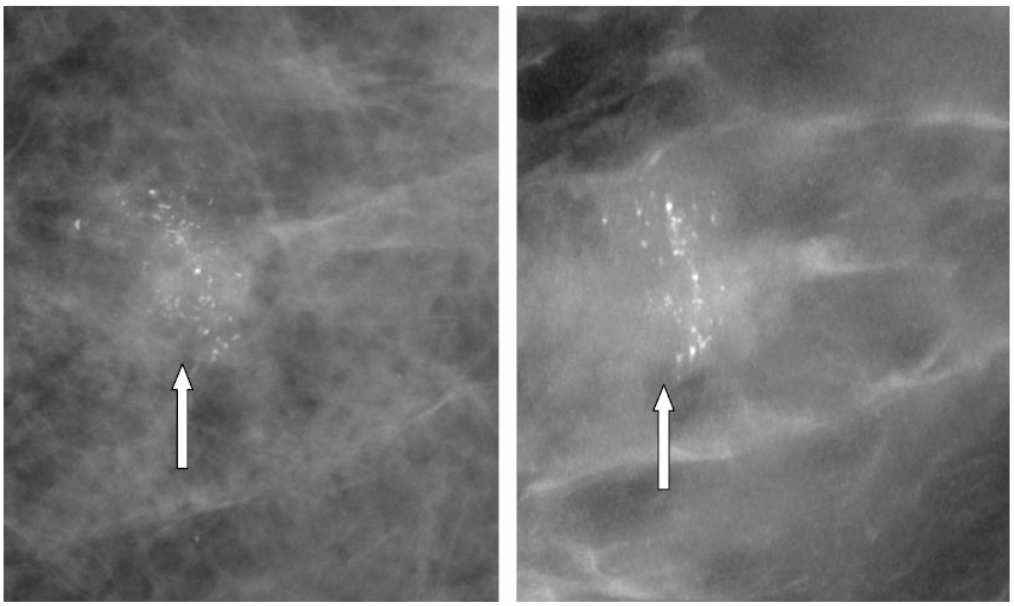


Figure 3.

A-D – Mediolateral oblique conventional mammogram (A) of a patient with invasive ductal cancer. The cancer was not apparent on the conventional MLO projection but could be vaguely seen on the cranial caudal view (C) as a density (arrow). 1 mm thick tomosynthesis images in both the MLO (B) and CC (D) view not only show the cancer (arrow) but also the margins



A B

Figure 4.
A, B – Conventional cranial-caudal digital mammogram (A) and tomosynthesis 11 mm thick MIP image (B) of microcalcifications proven to represent ductal carcinoma in situ. Both conventional and DBT images show calcifications well (arrows). The MIP image does not necessarily show microcalcifications above or below the 11 mm thick slice.

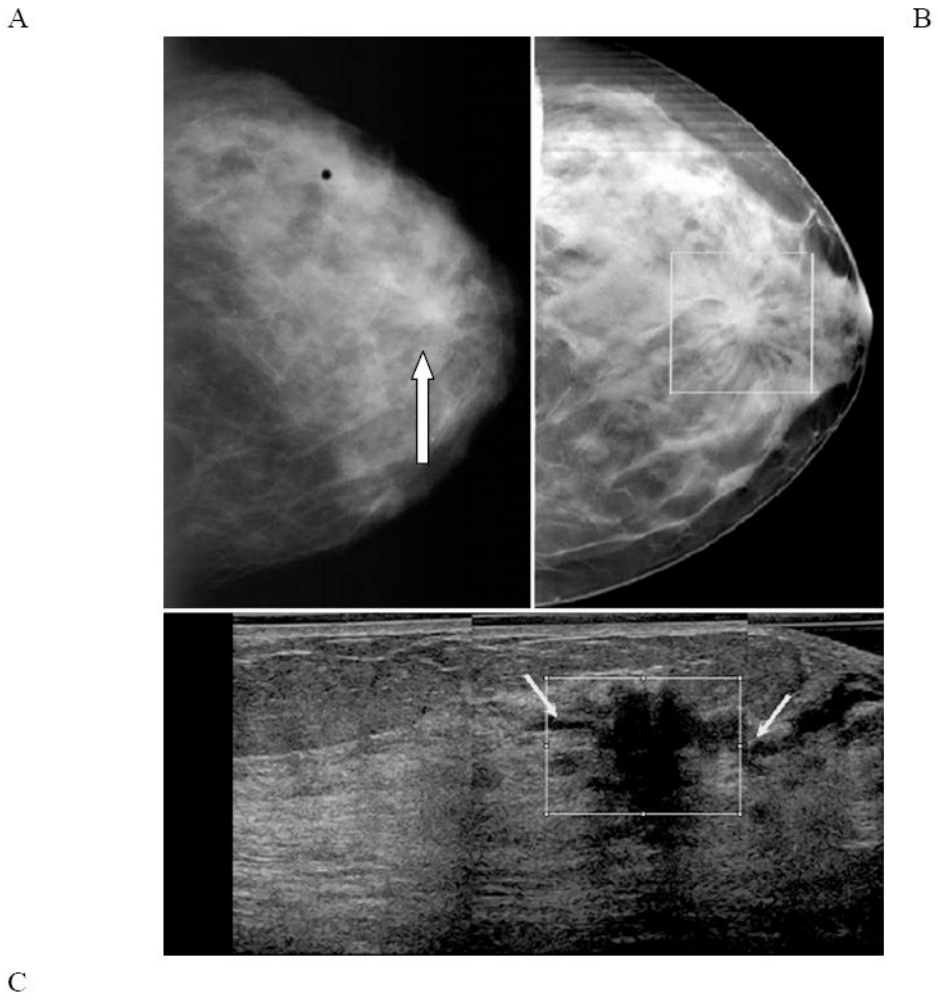


Figure 5.
(A-C)– Images from a combined DBT and ultrasound system. The DBT and US image were obtained automatically during a single compression. Conventional film screen (CC) mammogram (A), DBT 1 mm thick image (B) and the corresponding automated ultrasound image (C) of a patient with invasive cancer. The cancer is subtle on conventional mammogram (arrow) and apparent on the DBT (within box) and very apparent on ultrasound image (within box, arrows).

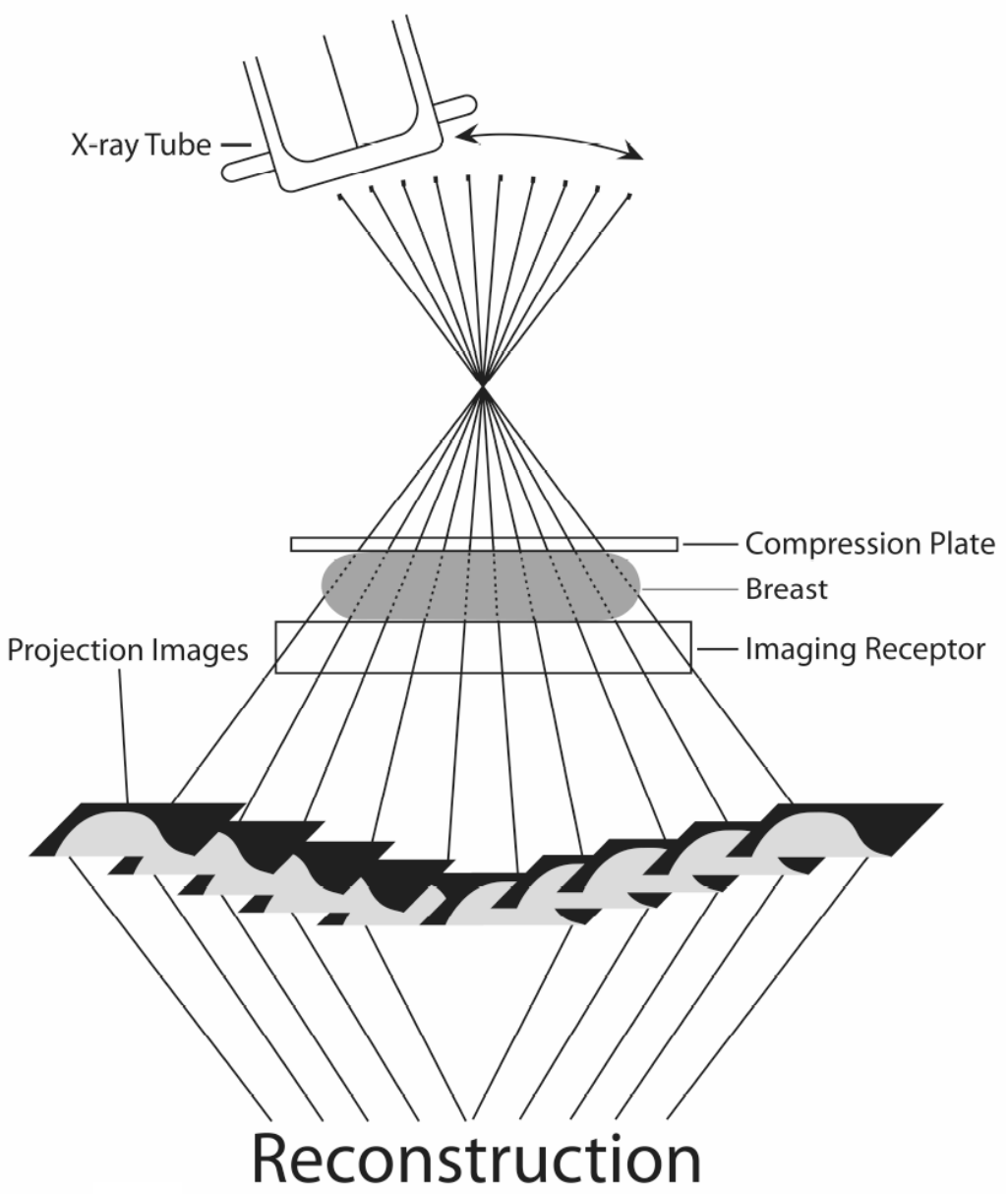


Illustration 1.
Schematic view of digital breast tomosynthesis. The X-Ray tube moves through a narrow arch while the breast is in compression. A series of exposures results in multiple projection image data sets. Each exposure is a fraction of the dose of a conventional mammographic view. Projection image data sets are reconstructed into multiple thin slice images (example 1 mm thickness) for interpretation by the radiologist.