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An X-ray Computed Tomography/Positron Emission Tomography System Designed Specifically for Breast Imaging

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Abstract

Mammography has served the population of women who are at-risk for breast cancer well over the past 30 years. While mammography has undergone a number of changes as digital detector technology has advanced, other modalities such as computed tomography have experienced technological sophistication over this same time frame as well. The advent of large field of view flat panel detector systems enable the development of breast CT and several other niche CT applications, which rely on cone beam geometry. The breast, it turns out, is well suited to cone beam CT imaging because the lack of bones reduces artifacts, and the natural tapering of the breast anteriorly reduces the x-ray path lengths through the breast at large cone angle, reducing cone beam artifacts as well.

We are in the process of designing a third prototype system which will enable the use of breast CT for image guided interventional procedures. This system will have several copies fabricated so that several breast CT scanners can be used in a multi-institutional clinical trial to better understand the role that this technology can bring to breast imaging.

Keywords

Breast Cancer; Computed Tomography; Positron Emission Tomography; Equipment; Radiation Dose; Diagnostic Imaging

Introduction

Breast cancer mortality in the last two decades has seen excellent improvement, and this is attributed in part to the success of breast cancer screening. Mammography has evolved over this same period of time, through direct film, xerography, screen-film mammography, and finally full field digital mammography. While this evolution in mammography technology has resulted in impressive improvements in image quality, it is recognized by the breast

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imaging community that projection imaging of the breast has fundamental limitations. These limitations have led to a search for screening technologies with higher sensitivity.

One of the fundamental limitations of mammography is that it is a projection imaging technology, where the three dimensional breast is imaged to produce two dimensional images (the mediolateral oblique, MLO, and the cranial caudal, CC, projections). By collapsing three dimensions down to two, enormous data compression is achieved which considerably reduces the time required for mammogram interpretation by breast imaging physicians. However, this process also results in the superimposition of anatomy on the 2D mammogram, which can occasionally obscure the presence of a tumor by masking it within the normal breast parenchyma. This problem is worse for breasts with a high fibroglandular tissue content, as is typical in younger women. Thus, it is known that mammography has reduced sensitivity for cancer detection in younger pre-menopausal women. To overcome these issues unique to 2D imaging, many researchers have proposed 3D imaging technologies for breast cancer screening.

The many different tomographic technologies evaluated for potentially improving breast cancer screening sensitivity include magnetic resonance imaging (1,2), ultrasound imaging (3–5), tomosynthesis (6), breast CT (7–11), positron emission mammography (12–15), nuclear projection imaging (16–18), and optical imaging methods (19–20). In the interest of brevity, a complete review of all of these methods will not be presented. Rather, we focus here on our work in the development of breast CT, and will also touch on comparisons with both contrast enhanced breast MRI (CEB-MRI) and tomosynthesis. CEB-MRI and tomosynthesis are perhaps the two tomographic imaging modalities which are being seriously used as adjuncts to digital mammography by those in the international breast imaging community. While CEB-MRI is used routinely for screening high risk women in the United States, tomosynthesis has yet to be approved for use by the Food and Drug Administration and thus is currently used as a research tool in the U.S.

At present, there are three research groups in the U.S. that have developed breast CT systems for imaging intact breasts of live women, at the University of Rochester, Duke University, and University of California Davis. However, the first two groups have not yet published clinical results for their systems in the peer reviewed literature to our knowledge, and thus a knowledgeable presentation of their work is not possible. Therefore, out of necessity, most of the following discussion on breast CT will address the development and clinical testing at our own setting at the University of California, Davis.

System Fabrication

Prototype 1: Albion

The design of the first prototype scanner, dubbed Albion, at UC Davis began in the late 1990's. The scanner was fabricated in 2001, and was extensively tested on phantoms, eventually leading to clinical testing in patients which began on November 22, 2004. Figure 1 illustrates the basic geometry of the Albion scanner. This is a full cone beam breast CT scanner, which requires only one rotation of the gantry around the breast to acquire the necessary data for reconstructing the entire breast volume. This system uses a Varian PAXSCAN 4030CB flat panel detector, which has a native detector element size of 0.194 mm in a 2048 × 1536 array, resulting in a 400 mm × 300 mm field of view in the detector plane. At full resolution, however, the frame rate of this detector is 7.5 frames per second, which is too slow for breath hold breast CT. Thus, we use the flat panel in a 2 × 2 binning mode, which results in effective detector element size of 0.388 mm and reduces the matrix to 1024 × 768 pixels. With 2 × 2 binning, a frame rate of 30 frames per second is possible. The PAXSCAN flat panel detector is an indirect system which employs a CsI scintillator,

and at the detector plane the Nyquist frequency for the 0.388 mm detector element pitch is 1.28 mm^{-1} . With a 1.7 magnification factor for example, the Nyquist frequency at the scanner isocenter becomes 2.2 mm^{-1} .

Breast imaging with the women prone on a table with her breast to be imaged hanging pendant into the scanner field of view, requires a nearly half-cone geometry as seen in Figure 1B. Because both the detector and the x-ray tube need to be positioned as close to the bottom of the patient couch as physically possible, this means that the central ray must strike the detector near its top, resulting in the half cone geometry. Consequentially, the (half) cone angle in breast CT is generally larger than the half cone angles used in other medical imaging applications (such as dental) where the central ray can be positioned near the center of the flat panel detector. For example, in breast CT, for the central ray placed 10 mm from the top edge of the active flat panel surface which is mounted with the 300 mm dimension in the vertical direction, and with a 900 mm source to detector distance, the half cone angle approaches 18 degrees. By comparison, the half cone angle of a typical 64 slice whole body CT scanner is about 2 degrees.

The inside of the Albion scanner is pictured in Figure 2. This shows the flat panel detector positioned on a gantry arm, opposite the x-ray source. The rigid mounting of the detector and x-ray tube on the same rotating gantry system results in a 3rd generation, rotate-rotate CT acquisition approach. The gantry arm seen in Figure 2 is mounted on a motion control system (Kollmorgen, Radford, VA) which consists of the high precision bearing, angle encoder, and motor in the same unit. The motor housing is enclosed in a central hub, which serves as the cable take-up spool for the system.

The x-ray tube used in a pendant geometry breast imaging system needs to have the x-ray focal spot positioned near the physical end of the tube housing, in order to allow the x-ray focus to be as close to the bottom of the patient as physically possible. This geometry is required in order to produce CT images as far posterior in the breast as possible, so that all of the tissue up to the pectoralis major ("chest wall") can be captured in the scanner's field of view (FOV). Recognizing this as a priority in the design of the scanner, a Comet industrial x-ray tube (Comet AG, Flamatt, Switzerland) was selected for use in the Albion scanner. This is a 640 Watt x-ray tube, which means that at 80 kVp it can run continuously at 8.0 mA, and at 64 kVp it could run at 10 mA. This tube has a 0.4 mm focal spot which is positioned 47 mm from the top of the tube housing. As we shall see later, this represents one of a number of system design compromises that are required when building a prototype breast imaging system with off-the-shelf components. While the form factor of the Comet x-ray tube is desirable, this is a stationary tungsten anode system and therefore uses a water cooled anode, thereby requiring the coupling of water hoses to and from the x-ray tube on the rotating frame. In addition, this x-ray tube cannot be pulsed due to the limited focal spot loading, and thus it must be operated in continuous (essentially fluoroscopy) mode. The top of the x-ray tube housing is seen in Figure 2, with the metallic cylinders protruding from both sides of the tube housing. These metal cylinders are high current solenoids used to rapidly activate an x-ray shutter system, which is used to turn on and off the x-ray beam during the CT scan acquisition. The actuation time is approximately 133 ms, and thus is acceptable for activating the x-rays before and after the 17 second scan, but do not have the temporal resolution to mechanically pulse the x-ray system.

The issue of whether a slip ring design, which would eliminate the cable handling issues, is necessary for a cone beam scanner is worth discussion. Certainly a slip ring is inherently more elegant of a design than the use of a system which incorporates a cable handling system as seen in Figure 2, and all modern commercial whole body CT scanners use slip ring designs. A slip ring system is absolutely required when a helical scanning geometry is

used, as with all modern whole body scanners. However, for a cone beam system which requires only one complete revolution of the gantry around the object (breast in this case), helical scanning is not necessary. Furthermore, the water cooled x-ray system used on our scanner would be hard to position on a slip ring design. Thus, while slip ring designs are necessary for helical CT scanning, the simplicity and low cost of a cable connection make sense for prototypical breast CT scanners designed in the academic environment.

Prototype 2: Bodega

A second prototype breast CT scanner, dubbed Bodega, was fabricated in the 2006 time frame. This system used a 1000 Watt Comet x-ray tube, allowing 12.5 mA operation at 80 kVp, for example. The Bodega scanner is physically taller than the earlier prototype, which allows more comfortable access on the part of the mammography technologist in positioning the breast. The larger dimensions of this scanner (Figure 3A) also allowed the incorporation of PET detectors, as discussed later, but the additional height required a few steps to be incorporated into the design, as seen in the picture. In addition to being slightly larger, the second prototype also incorporated an additional degree of freedom into its design. The x-ray tube was mounted on a vertical ball drive, allowing vertical motion during the rotational motion of the tube. Thus, instead of the strictly circular motion of the Albion system, Bodega is capable of any number of scan geometries, such as a “potato chip” trajectory, circle – line, etc. These other trajectories have the potential to overcome some of the Fourier sampling limitations of cone beam CT. While we do have an active research program in this area, non-circular acquisition trajectories will not be further discussed in this article.

Dedicated Breast PET/CT Hardware

PET hardware (Figure 3B) was installed into the Bodega breast CT scanner. The PET component, described in detail by Wu *et al.* (21), utilizes 32 detector blocks arranged in 2 square panels. Each block consists of a 9 by 9 array of 3mm × 3 mm × 20 mm lutetium oxyorthosilicate (LSO) crystals, coupled by a tapered fiber light guide to a position-sensitive photomultiplier tube (R5900-C8, Hamamatsu Photonics). A resistive network reduces the output of the 16 blocks in each panel to four position signals (15). Triggering is accomplished using standard NIM electronics while pulse shaping is achieved using a custom-built fast spectroscopy amplifier. Data is acquired using a PCI PowerDAQ board PD2-MFS-2M/14 (United Electronic Industries, Inc., Walpole, MA) characterized for PET applications by Judenhofer *et al.* (22). Random coincidences are estimated using a delayed channel approach.

The detector heads are mounted on a gantry that allows radial translation, vertical translation and rotation about the breast. When not in use, the detector heads are retracted behind lead shields to avoid exposure to X-ray flux. Data is acquired in “step and shoot” mode, and a typical scan takes approximately 10 minutes (23). Spatial resolution under optimal circumstances is approximately 2.5 mm FWHM, typical energy resolution is 25% at 511 keV, and sensitivity is approximately 1.7% at the center of the field of view (21).

Calibration and Reconstruction

Flat panel detector systems have a characteristic structured noise pattern which is due to the use of multiple different gain channels on the electronics, among other issues which affect the gain of an individual detector element. To correct for this, an automated detector calibration process was implemented. Under computer control, with the gantry completely stationary, a series of individual exposures at increasing mA levels are performed. The system automatically steps through 15 different mA settings, from 0.2 mA to 10 mA. At each kerma rate to the detector (a linear function of the mA), 300 frames are acquired and

the mean gray scale (GS) value for each pixel on the image is computed. Once the detector response is determined for every (2×2) detector element over the entire kerma rate range of the system, linear regression is used to determine the slope (units of GS/mA) and intercept (units of GS) of the linear response (Figure 4A). While non-linear approaches are possible for detectors in general (24), we have found that the PAXSCAN 4030CB is robustly linear and so non-linear methods are not required. While a look-up table of dead pixels is stored for each detector system, this calibration procedure is also a surveillance technique for finding bad detector elements. For example, empirical study has helped to define the acceptable range of linear correlation coefficients and slope values for acceptable detector element performance. Detector elements which are identified as laying outside an acceptable range are corrected for by interpolation with surrounding data.

The flat field technique is illustrated in Figure 4B. The flat field correction image shown in Figure 4B is actually the 768×1024 matrix of the slope terms for each 2×2 binned detector element. Division by this value, which is in the units of GS/mA, results in a corrected image which is scaled in the units of mA – this is an arbitrary distinction at this point, because the preprocessing before image reconstruction requires that the log ratio be computed. The images after flat field correction are stored as 4 byte floating point numbers, and so the mA scaling fits well within this storage class.

The various dimensions and angles of the breast CT scanner need to be determined with utmost accuracy, in order that the reconstruction algorithm perfectly emulates the acquisition geometry of the data. In order to determine these geometrical parameters, a calibration procedure is performed each day prior to scanning patients. The calibration procedure involves the placement of a simple ball bearing (BB) phantom (Figure 5A) in the scanner field of view, and scanning it. Software was written which tracks the trajectory of a series of BB's on each projection image over the 2π CT scan. The trajectory of each BB follows an elliptical path, as seen in Figure 5A. By fitting these individual paths using algebra, five key geometrical parameters are determined. These parameters include the x and y coordinate of the ray that is normal to the detector in both the vertical and horizontal dimensions, the rotation angle of the detector columns around this point, and the source to isocenter distance (SIC), and the source to detector distance (SID) (Figure 5B).

Image Reconstruction

Once the acquired data from the CT scan is flat-field corrected, it needs to be preprocessed prior to filtered backprojection. As shown in Figure 6A, a 30×60 pixel region of interest (ROI) is selected outside the breast, and this corresponds to I_0 . Each of the pixel values $I(x,y)$ on each projection image is then scaled as:

$$\mu t(x,y) = \ln[I_0/I(x,y)] \quad [1]$$

This produces the logged projection data seen in Figure 6B, which is then used in the filtered backprojection reconstruction process, described below. We have been using an 80 kVp x-ray spectrum, with either 0.3 mm or 0.2 mm of Cu filtration – a relatively “hard” beam. Thus, in breast tissue which is primarily adipose (density $\sim 0.93 \text{ g/cm}^3$), there is very little beam hardening. Nevertheless, we do apply a beam hardening correction which is commonly used in the CT industry. A look-up table is computed which maps the computed values $\mu t(x,y)$ from Equation 1 into $\mu' t(x,y)$. These values are then used in the reconstruction algorithm. The lookup table is computed by knowing the x-ray spectrum used (25) and the average attenuation properties of breast tissue (26). Although the look-up table is nearly linear, it does theoretically correct for the polyenergetic x-ray spectrum used in the breast

CT scanner. The fact that there are no bones in the breast and that the tissue path lengths through the breast are relatively short (typically 14 cm to 18 cm as a maximum) further reduces the impact of beam hardening in breast CT.

With the projection data corrected to $\mu' t(x,y)$, these data are then used in a Feldkamp (27) style filtered backprojection cone beam reconstruction algorithm (Figure 6B). Each projection image is Fourier transformed in the horizontal direction, and the Fourier data is multiplied by the selected kernel in the frequency domain. We generally use a Shepp-Logan kernel, but also make use occasionally of the RAMP kernel. A voxel-based cone beam backprojection algorithm, written in our laboratory, is used. The known x-ray source location is used with the centroid of each voxel coordinate in the breast reconstruction matrix $B(x, y, z)$, and the linear projection of these two three dimensional points in space is extrapolated onto the plane of the projection image $\mu' t(x,y)$. This location on the detector surface in general is located between actual pixel coordinates, so interpolation is used to weight the projection value from the four surrounding pixel values on the projection image. This weighted value is then added to the appropriate voxel in the reconstructed volume data set $B(x,y,z)$. Iteration of this process over each voxel, and over all ~500 projection images, results in the reconstructed volume data set $B(x,y,z)$.

Radiation Dose in Breast CT

The radiation dose in screening mammography is the only radiation dose level regulated by an act of the United States Congress through the Mammography Quality Standards Act (MQSA). While it is a fair question to ask whether the dose levels defined by MQSA are scientifically justifiable (in either direction), we have taken the approach in our research that the radiation dose from breast CT should be *equal* to that of two view mammography. We are engaged in a number of clinical trials in breast CT, most of which have a comparative arm with two view mammography. In order to make scientifically-based detection performance comparisons with the current state of the art for breast cancer screening, mammography, the radiation dose levels used between the comparative arms should be equal. In order to accomplish this, the following methods were pursued.

The methods for computing the mean glandular dose to the breast in the geometry of breast CT, with the women prone, breast pendant, and the x-ray tube rotating 2π around the breast, were not available at the start of our investigation. We engaged in a Monte Carlo exercise which led to the development of methods for dose computation in the breast CT geometry (28). and these methods were subsequently reproduced by Thacker (29). These methods allow the selection of breast CT acquisition parameters, based on the diameter of the breast being imaged and with general knowledge of the glandular fraction (based on mammographic findings), which deliver the *exact same* mean glandular dose as two view mammography. Caveats to this are described below:

The dose in breast imaging is very small for small breasts, and in mammography increases in a sub-exponential manner (because kVp's are increased as breast diameter increases) as the breast diameter increases. We measured the mean glandular dose (MGD) on all of our (screen-film Lorad Mark IV) imaging systems as a function of breast composition (0%, 50%, and 100% glandular) and compressed thickness (2, 4, 6, and 8 cm), using standard breast dosimetry methods.

Based on the mammography dose data for two view imaging, we used the technique factors which affect breast dose (basically kVp, filtration, and mAs) computed previously (30), and adjust the breast CT technique factors to deliver the *same* radiation dose as in two view mammography. We make one exception to this for small breasts, where the technique factors would call for low radiation levels and the radiation dose to the detector is so low

that electronic noise issues become important. Consequently, we have adapted a minimum mA level of 2.0 for the smallest of breasts, and this means that the very low radiation dose levels to women with smaller breasts are increased slightly.

There are a number of interesting findings from the breast CT images that we have acquired, which relate to the radiation dose in the breast from mammography. In most Monte Carlo simulations which focus on computing the so-called “DgN” values for mammography, the researchers used the assumption of a layer of skin over the breast that was 4 or 5 mm thick (31,32). Images from breast CT, however, demonstrate that the skin layer in the breast is about 1.5 mm thick (33). This implies that existing DgN values for mammography (where the x-ray energies are low) are too low, because the “shielding” effect from a thick layer of skin is reduced. In addition, many medical physicists assume a generic “50% – 50%” breast, meaning 50% adipose and 50% glandular, for breast dosimetry. Recent observations (in press) however have revealed the fact that the average volume glandular fractions are much smaller, with the average volume glandular fraction falling somewhere in the 15% to 20% range. This, too, leads to higher DgN coefficients. Finally, there are ICRP recommendations which suggest a radiation quality factor of 1.3 for x-ray energies 25 keV and lower, which is the case for mammography. However, this weighting factor has not been used in the United States as part of mammography dosimetry. The implications of the above observations are that the dose to the breast from mammography is higher than previously thought – perhaps 50% higher. This means that the radiation levels in breast CT could be increased from the levels that we are currently using, to be equal to two view mammography.

Technical Performance

Spatial Resolution

Figure 7A shows the measured modulation transfer functions (MTFs) of the Albion breast CT system (34). The resolution degrades towards the periphery of the field of view (at larger radius from the isocenter), due to the combined effects of the motion of the (continuously on) x-ray tube around the breast and the 33 ms frame time of the detector. Figure 7B illustrates the worst-case computer simulation results for the MTF when a continuous x-ray system is used (35), these are determined at the maximum radius (about 7 cm) from isocenter, along the circumferential direction (the direction of tube motion). As the number of views decreases in Figure 7B, the integration length along circumferential arcs increases (2π tube rotation is assumed in each case), and therefore the MTF degrades with fewer views. A pulsed system gives the best MTF results, not surprisingly, corresponding to about 3000 views (*i.e.*, a blur distance of only 0.14 mm at 7 cm radius) with a continuous x-ray source.

The degradation in the MTF at greater radial extent, as seen in both Figures 7A and 7B, is the consequence of using a continuous x-ray source. Interestingly, all commercial whole body scanners also employ a continuous source design, and thus the resolution degradation towards the periphery of the field of view is a common phenomenon in continuous source CT. These observations have prompted the search for a pulsed x-ray system capable of high kVp operation, with the desirable form factor discussed previously.

Contrast Resolution

The noise power spectrum (NPS) is shown in Figure 8. A polyethylene cylinder 156 mm in diameter was scanned at the same dose levels used for breast imaging, and the data was reconstructed as usual using a Shepp-Logan kernel. Regions of interest (ROIs) measuring 256×256 pixels were selected inside the reconstructed cylinder, the ROI was spatially filtered using a Hamming filter, the data was renormalized to zero mean, and the two dimensional Fourier Transform was computed. A total of four overlapping 256^2 ROIs were

evaluated on each CT slice, over 29 CT slices, resulting in an NPS averaged from 116 ROIs. An inset image of the 2D NPS is illustrated in the figure. Recognizing the rotational symmetry of the 2D data NPS(x,y), it was recomputed to a one dimensional NPS(r) using:

$$r = \sqrt{x^2 + y^2} \quad [2]$$

The family of curves in this figure corresponds to different CT slice thicknesses. Because the NPS is essentially the frequency-dependent variance in the image, the variance increases linearly as the slice thickness decreases, reflecting the fact that reducing the slice thickness results in the same proportionate reduction in the number of x-ray photons contributing to that image.

Image Display

In both screen-film and digital mammography, all four images from both breasts are displayed simultaneously during radiologist interpretation. This is generally not practical with breast CT image data sets, given that there can be >500 images per breast. Therefore, the interpreting radiologist needs a robust visualization platform in order to efficiently evaluate the breast CT images. We have spent considerable effort in developing such a platform, in close consultation with breast imaging radiologists. Figure 9 illustrates the display interface. The breast image data set of one breast is loaded into the memory of the graphics processing unit (GPU), and once loaded the observer can use the mouse to rapidly pan through the breast image data in three dimensions.

One of the key features of the visualization tool for breast CT is that it allows image averaging in three dimensions. The voxel dimensions (Δx , Δy , Δz) in breast CT are quite small, and although this is good from the standpoint of spatial resolution, small voxels at low radiation dose levels mean that some noise will also be present. To accommodate this, the visualization tool allows the user to adjust the slice thickness simultaneously in three dimensions. The coronal image displays the (x , y) projection through the data set, integrated along Δz , the sagittal displays the (y , z) integrated along Δx , and the axial displays the (x , z) along Δy . With one adjustment, the observer changes the amount of voxels averaged along the line of sight of the observer. The image remains unaltered in pixel size in the three display orientations, but is smoothed in the orthogonal dimension in each case.

Other key features of the visualization tool include the ability to make measurements, and to annotate images. The window level feature shows the image histogram which has some intuitive advantages. It can toggle between imaging averaging and maximum intensity projection. Because the breast CT data set is coherent, meaning it is a true 3D volume data set acquired of the entire breast in one position, the axial (x , z), sagittal (y , z) and coronal images (x , y) have a well-defined spatial relationship between each other. This allows the observer to click on an area of suspicion in one view, and the viewer then instantly presents the other two orthogonal views which intersect that same point of suspicion. This feature allows the observer to rapidly search the 3D volume data set in an interpretive mode. The rapidity of the visualization tool working with the GPU hardware, combined with the display features mentioned above, allow the radiologist observer to comprehend the image data not as separate 2D images as with mammography, but rather as a coherent 3D volume of image data.

Clinical Imaging Performance

Clinical Trial

We initially (2004) performed a phase I clinical trial involving 10 healthy volunteers, which allowed us to optimize the breathing routine as well as modify the patient table slightly for comfort. Since 2005, we have been involved in a Phase II clinical trial, in which women initially diagnosed as BIRADS 4 or 5 based on mammography and other imaging procedures are invited to participate. We have performed breast CT imaging at UC Davis on over 220 women (late 2009), with over 50 cases performed both with and without the addition of iodinated contrast. These women are scheduled for their breast CT procedure just prior (a few minutes) to their scheduled breast biopsy, and thus pathological status of virtually all lesions imaged by breast CT has been determined.

We have a commercial tomosynthesis unit from Hologic Corporation located in our laboratory, and are engaged in a clinical trial comparing breast CT with tomosynthesis in the same women.

With the PET system, we are also engaged in a number of small clinical trials studying the uptake of ^{18}F fluoro deoxy glucose (FDG) in various populations. We have used injected doses of 10 mCi of ^{18}F FDG with a delay before imaging of approximately 45 minutes.

All of our clinical studies are of course performed under proper authority of the institutional review board.

Acquisition Protocol

The woman is placed prone with the breast to be imaged hanging into the hole at the center of the table. The woman is encouraged to extend her breast as far as possible into the depression in the table. We have tried having the patient hyperventilate for 15 seconds just prior to the acquisition, however more recently we have abandoned that approach as the vast majority of women have no problem holding their breath for the 17 seconds required for CT image acquisition. For contrast studies, we perform non-contrast breast CT on the unaffected and then the affected breast, inject the contrast, and then perform breast CT on the affected and then the unaffected breast. For contrast, 100 ml of Visopaque is injected at 4 ml/s, into the brachial vein using a power injector. The delay between start of injection and scan has been varied, with an average of about 100 seconds.

Breast CT images

A medley of breast CT images showing various tumors is shown in Figure 10. These images illustrate that breast CT does an excellent job at demonstrating mass lesions. Although microcalcifications are clearly visible in some of these breast CT images, microcalcification detection performance could be improved. Improvements in the spatial resolution with the design of a pulsed x-ray source system should improve this case. In an analysis of 69 of our earlier non-contrast breast CT cases, Lindfors (36) found in a preliminary study employing a single non-blinded radiologist and a subjective scoring system that breast CT was superior to mammography for the detection of mass lesions in the breast ($p = 0.002$), but mammography remained significantly better ($p=0.006$) in the depiction of microcalcifications. Nevertheless, only a significant minority of breast cancers are seen based upon microcalcifications alone, and thus the superior mass detection of breast CT may compensate in part for its reduced performance in microcalcification detection performance. Even with the anticipated improvements in spatial resolution that a pulsed x-ray system will bring, and even with the reduced kVp used for breast CT by other investigators⁹, it is unlikely that breast CT detection of microcalcification-based lesions will ever be equal or better than mammography

without contrast injection. Indeed, mammography (including digital mammography) has been optimized over 3 decades to have exquisite depiction of microcalcifications.

Esserman has published a recent high profile criticism (37) of the early detection strategies used for breast cancer, claiming that mammographic screening leads to the over treatment of breast cancer in some women. The suggestion was that many of the cancers detected by mammography are indolent and would never result in a loss of life for some women. This criticism falls squarely on “cancers” such as ductal carcinoma in situ (DCIS), which typically are detected as patterns of microcalcifications. The fact of the matter is that physicians do not fully understand which DCIS lesions will progress to invasive cancer and which ones will not, and so there is a necessary over treatment. Nevertheless, breast CT’s better detection performance for masses and slightly compromised performance for finding the smallest of microcalcifications may partially address the concerns of Esserman and her colleagues, however at this point in time *we* are clearly not advocating compromised detection performance of any type of lesion.

Contrast Enhanced Breast CT

The use of iodinated contrast in breast CT leads to a substantial increase in the diagnostic effectiveness of this modality, and this trend is consistent with experience in breast MRI as well – that injected contrast contributes greatly to lesion detection and characterization. Figure 11 illustrates two examples of pre- and post contrast breast CT images. The enhancement of the lesion by contrast injection acts to significantly increase its contrast in the breast CT images. While the upper case demonstrates this effect for a mass lesion, the lower pair of images illustrates how contrast injection leads to the enhanced detection of a lesion characterized by small microcalcifications. Therefore, with the injection of contrast agent, it is likely that the compromised microcalcification detection performance of breast CT relative to mammography will become superior to mammography performance.

Figure 12 shows pre- and post- contrast images, as well as the subtraction image between them. The use of subtraction imaging, similar to that used in breast MRI, can lead to significant delineation of the lesion as the anatomical background contrast is reduced.

Mathematically Modeled Imaging Performance

While almost 300 women have been imaged on our two prototype breast CT scanners, the logistical impediments of performing a radiologist observer performance comparison between breast CT and mammography are considerable. In our phase II trial, all of the patients recruited for breast CT imaging had their lesions identified initially by screening mammography. Therefore, the selection criteria for this Phase II trial favors mammography (this is the nature of a Phase II trial). Furthermore, the vast experience of breast imaging radiologists with mammography and their lack of experience with breast CT adds a considerable bias to such a comparison. Because of these issues, we have focused (at least in the short term) on non-radiologist based, mathematical comparisons between breast CT and mammography.

Figure 13 illustrates the noise power spectra (NPS) of the anatomic noise background of breast CT images, versus mammograms of the same women (38). This data stems from earlier work on Burgess (39), who showed that the NPS of the breast anatomical background in mammography obeys a power law:

$$\text{NPS}(f) = \alpha f^{-\beta} \quad [3]$$

The β term is the slope of the curve on a log-log plot (Figure 13). Burgess found for his set of digitized mammograms, that the β value was 2.8. He predicted that if β could be reduced in magnitude, that the detection performance of breast cancer would improve. Figure 13 shows the NPS of one specific case, where the NPS(f) of the mammogram resulted in a β of 3.1, very near Burgess' value of 2.8. The β value for the corresponding breast CT data set of this same women was 1.9, significantly lower. A theoretical evaluation developed by Craig Abbey in Metheany *et al.*,³⁸ showed that for breast CT, the value of β should be that of mammography minus one. To a reasonable approximation ($3.1 - 1 \approx 1.9$), this is what our experimental results demonstrated. As the NPS flattens out, Burgess predicts that lesion detection performance will improve. This is an exciting preliminary result which suggests that breast CT may have a future in breast cancer screening.

An observer performance study was conducted on 388 breast CT volume data sets. A pre-whitened ideal observer was modeled, and a signal-known-exactly study using simulated spherical lesions spanning in size from 2 mm to 15 mm in diameter was performance. For each volume data set and each lesion diameter, 500 lesions and 500 "non-lesions" were placed into the breast volume. Considerable effort, described elsewhere (submitted for publication), went into the design of this study and the accurate placement of breast lesions into the volume data set. The placement of lesions (to compute sensitivity) and non-lesions (used to compute specificity) allowed receiver operation characteristic (ROC) curve analysis to be performed for each breast volume data set at each lesion diameter. The ROC curve parameters were then used here to compute the more pertinent performance parameter, sensitivity at 95% specificity – corresponding to a reasonable operating point on the ROC curve. The lesions were analyzed two ways – as lesions in the native thin slice (0.3 mm) breast CT volume data, and the breast CT images were also integrated in one dimension, generating "thick-slab", mammogram-like images, which had an integration path length of 43 mm. The results of this study are shown in Figure 14, and here the breast CT sensitivity is significantly improved over that of "mammography". For example, for 2 mm lesions, the sensitivity went from 21% in mammography to 75% in breast CT, a factor of 3.57 (75/21) improvement. For a 5 mm lesion, the sensitivity of breast CT was a factor of 1.36 (83/61) improvement over mammography. Even for larger 11 mm lesions, the improvement of breast CT over mammography in terms of sensitivity was a factor of 1.17.

While it is likely that human observer studies are eventually needed to validate the performance of breast CT, the ideal observer results shown in Figure 14 do show that conceptually, the tomographic nature of breast CT should lead to superior lesion detection performance that mammography.

Other Breast Imaging Modalities

Tomosynthesis

A state of the art, commercial tomosynthesis system (Hologic Corporation) has been recently sited in our laboratory. Tomosynthesis is currently not approved for clinical use in the United States, but under a research protocol we have been imaging women with suspicious lesions using both breast CT and tomosynthesis. Comparison images for one women are shown in Figure 15. The MLO and CC views from the tomosynthesis images are shown on the left, with the three orthogonal breast CT images shown in the right. This happens to be an easy case where the lesion is well seen in a predominately adipose breast, but the figure does show the comparison between tomosynthesis and breast CT.

Breast MRI

Many of the women who have had breast CT studies in our laboratory have gone on to have breast MRIs for staging and further diagnosis. Figure 16 illustrates a contrast enhanced

breast MRI, along side of the contrast enhanced breast CT image. It is our observation that these images are equivalent in terms of their diagnostic information, and this has been our general observation over the growing population of women in which we have breast MR and breast CT comparison images. If this observation holds, breast CT will have an important role to play in breast imaging by replacing the far more expensive breast MRI, and by allowing the co-location of the system in the breast imaging clinic which would significantly improve access issues.

Breast PET/CT

Images from the PET/CT of a patient with extensive disease are shown in Figure 17. The PET information was colorized and overlaid onto the anatomical backdrop provided by the CT images. The uptake of FDG, which the PET images depict, shows numerous focal lesions at the displayed planes in the breast. The breast PET data highlighted regions which were not highlighted in the non-contrast CT performed on this women, showing the additional diagnostic data that PET/CT may add over CT, at least in the non-contrast CT setting.

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References

1. Agnese DM. Advances in breast imaging. *Surg Technol Int* 2005;14:51–56. [PubMed: 16525954]
2. Bartella L, Morris EA. Advances in breast imaging: magnetic resonance imaging. *Curr Oncol Rep* 2006;8:7–13. [PubMed: 16464397]
3. Cassano E, Rizzo S, Bozzini A, Menna S, Bellomi M. Contrast enhanced ultrasound of breast cancer. *Cancer Imaging* 2006;6:4–6. [PubMed: 16478698]
4. Nelson TR, Pretorius DH. Three-dimensional ultrasound imaging. *Ultrasound Med Biol* 1998;24:1243–1270. [PubMed: 10385948]
5. Greenleaf JF, Gisvold JJ, Bahn RC. Computed transmission ultrasound tomography. *Med Prog Technol* 1982;9:165–170. [PubMed: 7162487]
6. Niklason LT, Christian BT, Niklason LE, Kopans DB, Castleberry DE, Opsahl-Ong BH, Landberg CE, Slanetz PJ, Giardino AA, Albagli RD, DeJule MC, Fitzgerald PF, Fobare DF, Giambattista BW, Kwasnick RF, Liu J, Lubowski SJ, Possin GE, Richotte JF, Wei CY, Wirth RF. Digital tomosynthesis in breast imaging. *Radiology* 1997;205:399–406. [PubMed: 9356620]
7. Boone JM, Kwan AL, Yang K, Burkett GW, Lindfors KK, Nelson TR. Computed tomography for imaging the breast. *J Mammary Gland Biol Neoplasia* 2006;11:103–111. [PubMed: 17053979]
8. JM; Boone Breast, CT. Its prospect for breast cancer screening and diagnosis. In: Karellas, A.; Giger, ML., editors. *Syllabus: Advances in Breast Imaging Physics, Technology, and Clinical Applications*. Radiological Society of North America; Oak Park, IL: 2004. p. 165-177.
9. Chen B, Ning R. Cone-beam volume CT breast imaging: feasibility study. *Med Phys* 2002;29:755–770. [PubMed: 12033572]
10. Chen Z, Ning R. Why should breast tumour detection go three dimensional? *Phys Med Biol* 2003;48:2217–2228. [PubMed: 12894980]
11. Glick SJ, Breast CT. *Annu Rev Biomed Eng* 2007;9:501–526. [PubMed: 17506654]
12. Jagaru A, Masamed R, Keesara S, Conti PS. Breast MRI and 18F FDG PET/CT in the management of breast cancer. *Ann Nucl Med* 2007;21:33–38. [PubMed: 17373334]
13. Avril N, Rose CA, Schelling M, Dose J, Kuhn W, Bense S, Weber, Ziegler WS, Graeff H, Schwaiger M. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. *J Clin Oncol* 2000;18:3495–3502. [PubMed: 11032590]

14. Kumar R, Alavi A. Fluorodeoxyglucose-PET in the management of breast cancer. *Radiol Clin North Am* 2004;42:1113–1122. ix. [PubMed: 15488561]
15. Doshi, NK.; Silverman, RW.; Shao, Y.; Cherry, SR. A dedicated mammary and axillary region PET imaging system for breast cancer. *IEEE Nuclear Science Symposium Conference Record*; 2001. p. 29-44.
16. Bagni B, Franceschetto A, Casolo A, De SM, Bagni I, Pansini F, Di LC. Scintimammography with ^{99m}Tc-MIBI and magnetic resonance imaging in the evaluation of breast cancer. *Eur J Nucl Med Mol Imaging* 2003;30:1383–1388. [PubMed: 12910383]
17. Buscombe JR, Holloway B, Roche N, Bombardieri E. Position of nuclear medicine modalities in the diagnostic work-up of breast cancer. *Q J Nucl Med Mol Imaging* 2004;48:109–118. [PubMed: 15243412]
18. Gommans GM, van der Zant FM, van Dongen A, Boer RO, Teule GJ, de Waard JW. (99m)Technetium-sestamibi scintimammography in non-palpable breast lesions found on screening X-ray mammography. *Eur J Surg Oncol* 2007;33:23–27. [PubMed: 17126524]
19. Tromberg BJ. Optical scanning and breast cancer. *Acad Radiol* 2005;12:923–924. [PubMed: 16087089]
20. Fantini S, Heffer EL, Pera VE, Sassaroli A, Liu N. Spatial and spectral information in optical mammography. *Technol Cancer Res Treat* 2005;4:471–482. [PubMed: 16173819]
21. Wu Y, Bowen SL, Yang K, Packard N, Fu LG, Burkett J, Qi, Boone JM, Cherry SR, Badawi RD. PET characteristics of a dedicated breast PET/CT scanner prototype. *Phys Med Biol* 2009;54:4273–4287. [PubMed: 19531852]
22. Judenhofer MS, Pichler BJ, Cherry SR. Evaluation of high performance data acquisition boards for simultaneous sampling of fast signals from PET detectors. *Phys Med Biol* 2005;50:29–44. [PubMed: 15715420]
23. Bowen SL, Wu Y, Chaudhari AJ, Fu L, Packard NJ, Burkett GW, Yang K, Lindfors KK, Shelton DK, Hagge R, Borowsky AD, Martinez SR, Qi J, Boone JM, Cherry SR, Badawi RD. Initial characterization of a dedicated breast PET/CT scanner during human imaging. *J Nucl Med* 2009;50:1401–1408. [PubMed: 19690029]
24. Kwan AL, Seibert JA, Boone JM. An improved method for flat-field correction of flat panel x-ray detector. *Med Phys* 2006;33:391–393. [PubMed: 16532945]
25. Boone JM, Seibert JA. An accurate method for computer- generating tungsten anode x-ray spectra from 30 to 140 kV. *Med Phys* 1997;24:1661–1670. [PubMed: 9394272]
26. Boone JM, Chavez AE. Comparison of x-ray cross sections for diagnostic and therapeutic medical physics. *Med Phys* 1996;23:1997–2005. [PubMed: 8994164]
27. Feldkamp LA, Davis LC, Kress JW. Practical cone-beam algorithm. *J Opt Soc Am A* 1984;1:612–619.
28. Boone JM, Shah N, Nelson TR. A comprehensive analysis of DgN(CT) coefficients for pendant-geometry cone-beam breast computed tomography. *Med Phys* 2004;31:226–235. [PubMed: 15000608]
29. Thacker SC, Glick SJ. Normalized glandular dose (DgN) coefficients for flat-panel CT breast imaging. *Phys Med Biol* 2004;49:5433–5444. [PubMed: 15724534]
30. Boone JM, Kwan AL, Seibert JA, Shah N, Lindfors KK, Nelson TR. Technique factors and their relationship to radiation dose in pendant geometry breast CT. *Med Phys* 2005;32:3767–3776. [PubMed: 16475776]
31. Boone JM. Glandular breast dose for monoenergetic and high-energy X-ray beams: Monte Carlo assessment. *Radiology* 1999;213:23–37. [PubMed: 10540637]
32. Wu X, Barnes GT, Tucker DM. Spectral dependence of glandular tissue dose in screen-film mammography. *Radiology* 1991;179:143–148. [PubMed: 2006265]
33. Huang S-Y, Boone JM, Yang K, Kwan ALC, Packard N. Evaluation of skin thickness from 46 dedicated breast CT examinations. *Medical Physics*. 2007 Ref Type: In Press.
34. Kwan AL, Boone JM, Yang K, Huang SY. Evaluation of the spatial resolution characteristics of a cone-beam breast CT scanner. *Med Phys* 2007;34:275–281. [PubMed: 17278513]
35. Yang K, Kwan ALC, Boone JM. Computer modeling of the spatial resolution properties of a dedicated breast CT system. *Medical Physics*. Jan 1;2007 Ref Type: In Press.

36. Lindfors KK, Boone JM, Nelson TR, Yang K, Kwan AL, Miller DF. Dedicated Breast CT: Initial Clinical Experience. *Radiology*. 2008
37. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA* 2009;302:1685–1692. [PubMed: 19843904]
38. Metheany KG, Abbey CK, Packard N, Boone JM. Characterizing anatomical variability in breast CT images. *Med Phys* 2008;35:4685–4694. [PubMed: 18975714]
39. Burgess A. On the noise variance of a digital mammography system. *Med Phys* 2004;31:1987–1995. [PubMed: 15305451]

Figure 1. The basic geometry of the dedicated breast CT system is illustrated. Figure 1A shows the top view of the scanner, while Figure 1B illustrates the side view.

Figure 2.

In this picture of our first prototype breast CT scanner, the flat panel detector is shown mounted opposite of the x-ray tube. The two cylinders projecting out from the x-ray tube are solenoids used to actuate the x-ray shutter on the system. The system currently does not employ a slip ring, and the cable tray which connects the rotating gantry with the stationary reference plane is seen in this photograph. The cable housing glides on a layer of ultra high molecular weight polyethylene, which presents a low coefficient of friction. The gantry is powered by a digitally controlled motor at the center, which is also a high precision bearing and angle encoder system.

Figure 3.

(A) The second prototype breast CT system developed at University of California Davis is illustrated. This system has mostly the same type of components as the first prototype, however this system is taller to allow better technologist access to the breast. The stairs allow the patient to access the table top more comfortably. This system also houses PET detectors. (B) The PET hardware installed into the second prototype breast CT system is illustrated. These PET heads consist of a 36 by 36 array of 3 mm $\times$ 3 mm $\times$ 20 mm LSO crystals, coupled to arrays of position sensitive photomultiplier tubes. The two PET heads rotate 180° around the breast on a separate gantry system, which in turn sits on top of the CT gantry.

Figure 4.

(A) The calibration of the flat panel detector makes use of a number of different exposure levels (typically 15), which allow the characteristic curve of each detector element to be measured and characterized. The characteristic curve of each of the $786,432 \times 2$ binned detector elements is measured and fit using linear regression. The “gain” image is the slope coefficient of each detector element. The characteristic curves (and fit line) for three specific detector elements (coordinates indicated) are shown. **(B)** The calibration process makes use of the gain image described in Figure 4A, and an offset image (with no x-rays incident on the detector) is acquired just prior to the acquisition. The gain and offset images are used in a process usually referred to as “flat field correction”, as described in this graphic.

Figure 5.

(A) The geometric calibration of the scanner is performed by imaging a phantom consisting of a vertical row of Pb ball bearings (BB's), seen in the inset in this figure. The position of each BB is tracked over a 2π acquisition of images, and their positions over the period of acquisition is illustrated for each BB in this image. (B) The calibration data shown in Figure 5A is fit to a series of equations, and five key geometric calibration parameters are determined algebraically. The parameters include the (x_0, y_0) coordinate on the panel where the doubly normal ray penetrates the imager, the rotation angle θ of the panel around this point, and the source-to-isocenter distance and the source-to-detector distance.

Figure 6.

(A) Once the projection images are flat field corrected, they are preprocessed prior to CT reconstruction. A 30×60 patch of pixels is identified automatically away from the breast silhouette, and the average intensity is computed in this region. This value is then used to compute the log ratio image, seen on the right. (B) The post-processed projection images are used in a cone beam CT reconstruction algorithm to produce a high resolution $\sim 512^3$ CT volume data set.

Figure 7.

(A) The measured MTFs from the center (*black line*) to the edge (*blue line*) of the scanner field of view are shown. Due to the motion of the gantry and the continuous x-ray output, there is circumferential motion blur that reduces the resolution of the system towards the periphery of the field. (B) The spatial resolution of the breast CT scanner, as characterized by the Modulation Transfer Function (MTF), was modeled mathematically and a family of MTFs are shown in this figure. With continuous x-ray imaging (as opposed to pulsed x-rays), blurring occurs at distances away from the isocenter of the scanner due to the interplay between the x-ray tube rotation around the breast and the detector frame time of 33 ms.

Figure 8.

The two dimensional noise power spectrum (NPS) was computed by imaging a 15 cm diameter cylinder of polyethylene. The inset shows the 2D NPS, and the individual curves were produced by integrating the 2D NPS radially. The data show that, as expected, thinner CT slices result in higher noise levels.

Figure 9.

CT imaging of the breast produces a high resolution large volume data set, which is best visualized using multiple viewing angles. A three dimensional viewer was written to take advantage of the graphics processing unit (GPU), and so when the data is loaded into the GPU the viewer allows extremely rapid paging through the image data set.

Figure 10.

This figure shows a series of breast CT images from different women, with no iodinated contrast. These images are all coronal sections through the breast, and represent the native reconstruction plane of the image data sets. The difference in the characteristic parenchyma pattern for each women is noted. A large spiculated mass is seen in the upper left image, with associated microcalcification. The breast CT image on the lower right has a large field of microcalcifications at 6 O'clock.

Figure 11.

Two pairs of pre- and post- contrast enhanced breast CT images are shown. In both cases, the use of iodinated contrast agent enhances the visualization of the lesion. The presence of iodine suggests that contrast is pooling at these locations, and this enhanced permeability and retention (EPR) is suggestive of malignant processes.

Figure 12.

With the pre- and post- contrast images, image subtraction is possible, as illustrated in this figure. Image A was subtracted from Image B to produce the subtracted image C. By suppressing the constant background parenchyma, subtraction tends to better illustrate the site of a suspicious enhancing lesion.

Figure 13.

The noise power spectrum of the anatomic images in breast CT and mammography were computed. A number of regions of interest (Figure 13A) were positioned on the image data, and the NPS was computed. The NPS follows a power law as proposed by Burgess³⁹, and the breast CT images have a slope which is approximately $\beta - 1$, compared to mammography's slope of β . This result is an indirect measure which suggests that breast CT may have better detection performance.

Figure 14.

Computer simulations using over 300 breast volume data sets were performed using a pre-whitening ideal-observer signal-known-exactly construct. Both thin section images (breast CT) and thick section images (mammography) were generated for each breast volume for each lesion diameter. ROC curves were generated, and the sensitivity at 95% specificity was computed, as shown in this figure. These data suggest that breast CT should have superior lesion detection performance for mass lesions.

Figure 15.

Tomosynthesis images and breast CT images of the same breast are shown. These images did not make use of contrast agent.

Figure 16.

It is possible that with the use of iodinated contrast agent, breast CT may convey most if not all of the information currently realized in contrast enhanced breast MRI. These images show breast CT (left) and breast MRI (right) of the same breast, in both cases with contrast agents. The diagnostic information is largely similar.

Figure 17.

Fused PET/CT images, produced on the dedicated breast PET/CT system designed and fabricated at UC Davis, are illustrated. The metabolic information from the PET images is colorized and overlaid on top of the gray scale image provided by the CT scan. The PET activity in this patient corresponds to a number of high grade tumors.