Mammograms are Waldograms: Why we need 3D longitudinal breast screening

Richard Gordon, PhD and Radhika Sivaramakrishna, PhD

In this article, we postulate that research in breast imaging should be focussed toward routine three-dimensional (3D) screening of asymptomatic women.

In the "Where's Waldo?"* series of children's books, a small figure of Waldo is sought in a complex image. Using overlapping scenes containing Waldo, we aim to show how the detection of a small lesion in a projection image (i.e., in a standard mammogram) becomes an exceptionally difficult and unnecessary task, given the option of 3D imaging. This handicap is present in both film and digital mammography. With appropriate registration of longitudinal 3D images, Waldo, and perhaps small breast lesions, could be made to almost "jump out" of the picture. We briefly evaluate the future potential of four different 3D imaging modalities to detect small breast tumors: MRI, ultrasound, x-ray CT, and EIT. Any 3D modality that replaces mammography for standard screening would also, in the process, significantly reduce mortality.

Taibes[1] describes the frustrations of two opposing camps, both deeply concerned with the epidemic of breast cancer. The U.S. National Institutes of Health[2] was disposed to bring these parties to a consensus. There is now a consensus that for women over the age of 50 years, mammographic screening is of significant benefit, reducing mortality by about 30%. The remaining frustration and controversy lies in whether or not to regularly screen women 40 to 49 years old with mammography. Though the two camps take the opposing endpoints of "all or nothing," the underlying fact remains that traditional mammography has serious limitations, despite recent declines in mortality rates for breast cancer.[3] The technique still misses about 5% to 15% of all tumors.[4,5] Also, the overall yield of breast cancers per number of breast biopsies recommended on the basis of screening mammograms ranges between roughly 10% and 50%.[5,6] X-ray mammography is especially ineffective in detecting cancers in radiographically dense breasts.[7]

Additionally, there is a deeper and usually unspoken frustration, stemming from the fact that we have no useful screening technique for women younger than 40, except breast self-examination and clinical breast examination. Younger women are simply on their own,[8,9] though 21% of breast cancer cases are in women under 50 years of age. Spratt et al[10] suggest, "No subset of adult women has a risk so low as to permit their exclusion from an effective breast cancer control program."

While it is important to detect breast tumors early to reduce the likelihood of metastatic spread,[11,12] it is clear that we need to look beyond mammography in order to accomplish this.[13] The problems with mammography stem from its two-dimensional (2D) nature. A tumor is missed most probably because tissue present above and below it is superimposed together on a 2D projection in mammography.[14] We would like to demonstrate this using "Waldograms," and thus make a case for 3D longitudinal breast imaging. Perhaps, in the future, better diets, environmental cleanup,

Dr. Gordon is with the Departments of Radiology and Electrical and Computer Engineering at the University of Manitoba, Health Sciences Center in Winnipeg, Manitoba, Canada. Dr. Sivaramakrishna is in the Department of Biomedical Engineering at the Cleveland Clinic Foundation in Cleveland, OH.

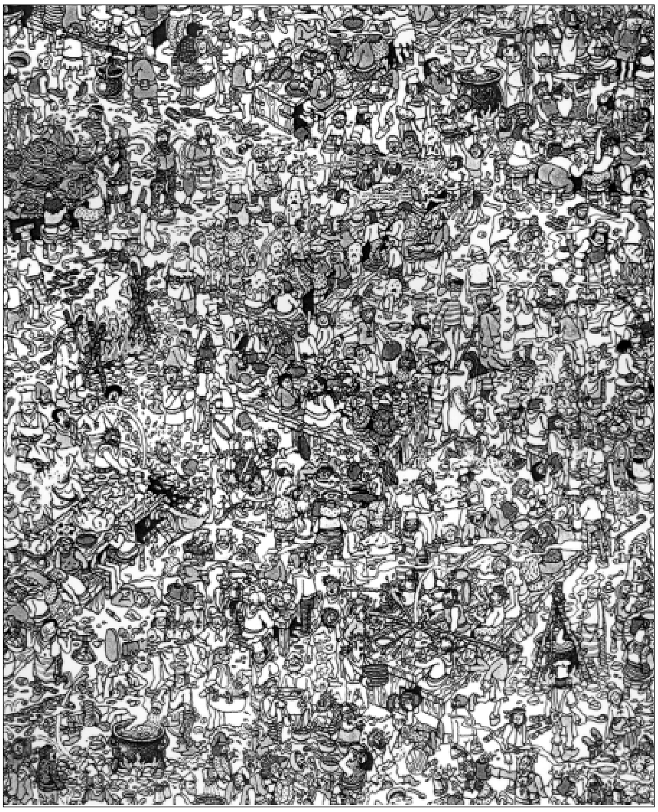

FIGURE 1. *A "Waldogram" (A) representing a plane through a woman's breast. Reprinted with permission from Walker Books Ltd.*

FIGURE 2. *A "Waldogram" (B) representing another plane through a woman's breast. Reprinted with permission from Walker Books Ltd.*

drug treatment, and genetic screening will eventually make medical imaging irrelevant. For now, we argue that aggressive research toward 3D breast imaging and 3D registration, to permit 3D longitudinal digital subtraction, is the best path to detecting tumors small enough to reduce the likelihood of metastasis and to cure this disease.

For example, it was demonstrated that reliable detection and removal of tumors by the time they reach 4 mm in diameter corresponds to a 25-year metastasis rate of only 0.6%.[12] We would like to interpret this extrapolation of a French study[15] to mean a 99.4% cure rate, if we had an imaging tool that successful. Due to the cautions needed in interpreting epidemiological data, we have embarked on a further epidemiological study.[16] The predicted "cure rates" are 99.8% for 3 mm tumors and 98.8% for 5 mm tumors. We regard 4 mm as a reasonable compromise between these tentative estimates of "cure rate" and realistic expectations of future imaging capabilities, and take it as our target for research.

Because many of the normal structures found within the breast will likely be of the same size as the small tumors we are looking for, the most reliable way to detect small tumors is by their growth relative to local tissue. In order to do this, we need two longitudinal images of the breast which could be aligned with each other. Subtracting one from the other would reveal a tumor which has grown in the time interval between the two images. However, the loose and non-rigid nature of breast tissue almost guarantees that two images of the breast taken at different times will be not be exactly aligned. Hence, along with a good 3D imaging technique, a good 3D registration algorithm[17,18] also will be necessary to succeed in detecting small breast tumors.

We will demonstrate, using the popular cartoon character Waldo, that 3D longitudinal imaging with 3D registration and subtraction provides a pathway towards detection of small tumors in the breast.

Waldograms

Waldo is a cartoon character appearing in a series of children's books by the English cartoonist Martin Handford.[19] The idea is to find Waldo amongst myriads of other small-scale characters.

Figure 1 is a typical example of the problem of detecting Waldo, but already we encounter one handicap for radiologists: the original is in color, but we must deal in shades of gray. Let us call this "Waldogram" A. Figures 2 and 3 are two more Waldograms, B and C, and Figure 4 is the superposition of figures 1, 2, and 3, represented by D = A + B + C. Start by trying to find Waldo in D (figure 4), and you'll be confronting the problem of tumor detection in mammograms head on.

A, B, and C can be considered analogous to three planes through a woman's breast. While A may have a clear (albeit hard to find) picture of Waldo, that char-

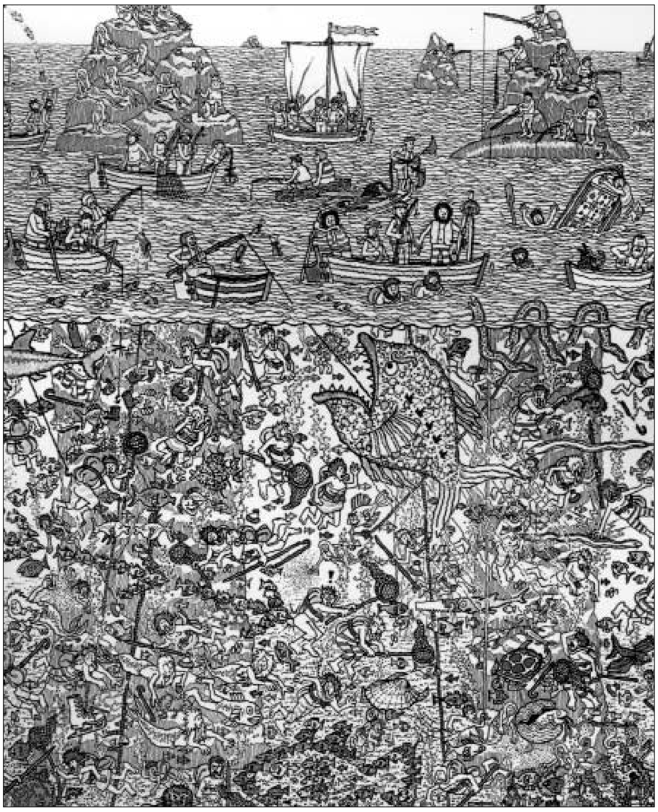

FIGURE 3. *A "Waldogram" (C) representing a third plane through a woman's breast. Reprinted with permission from Walker Books Ltd.*

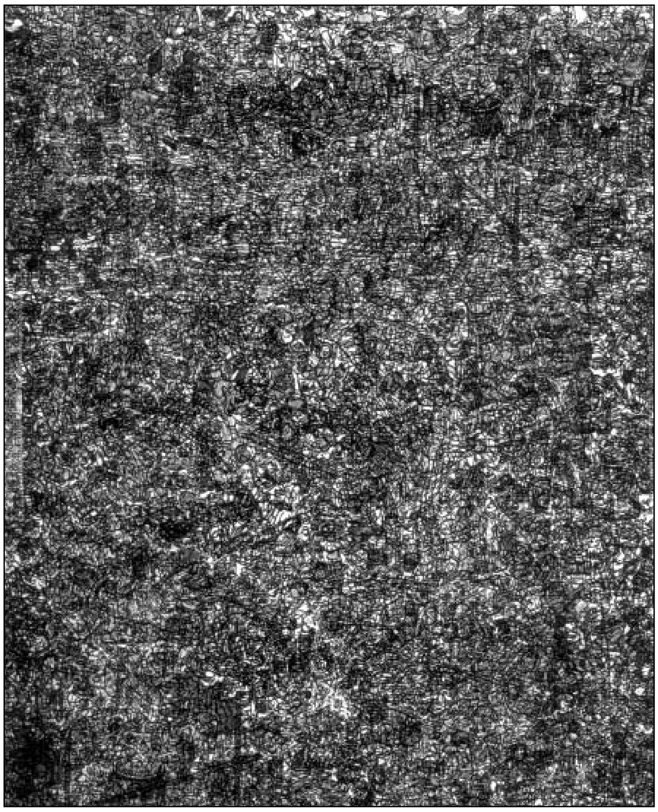

FIGURE 4. *This image (D) represents the superposition of A, B, and C.*

acter is nearly indiscernible when covered up by the uncorrelated structure added to the image by B and C in D (figure 4).

One approach to the problem of finding Waldo is by digital subtraction. We created another picture from A by eliminating Waldo; let us call it A – W. We then superimposed A – W, B, and C to yield a picture A + B + C – W. The negative of this was made [i.e., W – (A + B + C)]. Now, when we superimpose D and this negative, we should get:

$$E = A + B + C + W - (A + B + C) = W$$

E is shown in figure 5. But where is Waldo? If you are a practiced Waldo finder, you can probably see him. However, there are many Waldo-sized artifacts in the difference image E.

We took care to align A + B + C – W and A + B + C as accurately as possible before superimposition. The small registration errors lead to many artifactual errors in E ("false positives"). If we were dealing with a woman's breast imaged at two different times, our inability to align it the same way twice would produce small registration errors. Any attempt to locate a small tumor that grew in the time interval between the two mammograms, by subtraction imaging, is then also likely to fail.

Suppose we were working in three dimensions and therefore could isolate corresponding planes. If we add the negative of A – W to A we get

$$F = A + (W - A) = W$$

Again, A – W and A were aligned as accurately as possible before superimposition.

This time Waldo jumps out at us in F (figure 6). Certainly, there is still much background registration error, but it does not overlap Waldo and it is quite distinguishable from him.

The Waldogram demonstration suggests that breast tumors are missed by mammography because of its two-dimensional nature and that if we were to routinely image the breast in 3D we might detect small, growing tumors reliably, by registration of 3D longitudinal images and their digital subtraction.

Toward this end, we present below brief evaluations of four potential technologies for 3D breast screening with respect to the detection of 4 mm tumors.[13,20] The four modalities are MRI (magnetic resonance imaging), 3D ultrasound, EIT (electrical impedance tomography), and CT mammography. We are not evaluating optical tomography, positron emission tomography (PET), thermography, or nuclear medicine imaging of the breast,[13] because it is not clear that these modalities can attain sufficient resolution to screen for and detect small breast tumors.[21]

It must be stated here that in proposing modalities for 3D longitudinal imaging, there are two considerations from an imaging point of view. First, the method must have sufficient spatial resolution to detect 4 mm tumors. Second, although it would be helpful to have adequate contrast resolution (i.e., density or gray level contrast relative to surrounding tissue) this is not absolutely

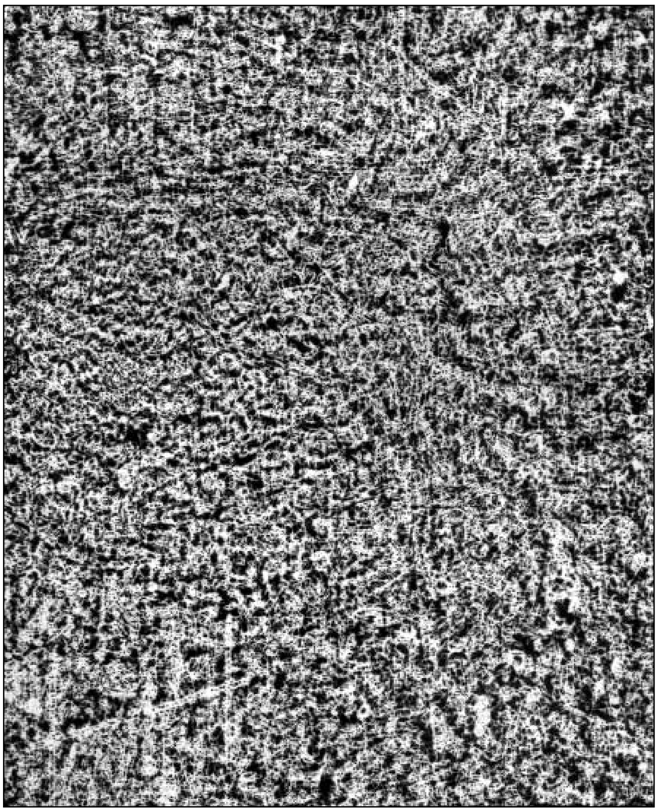

FIGURE 5. *This image (E) was obtained by the equation E=A+B+C+W–(A+B+C)=W representing a digital subtraction mammogram which, if perfect, should show Waldo (W). It is peppered with "registration noise" of comparable magnitude and texture.*

FIGURE 6. *This image (F) was obtained by the equation F=A+(W–A)=W representing digital subtraction between corresponding planes isolated by a 3D imaging modality. While some registration noise persists, Waldo stands out clearly.*

essential, as the local architectural distortion caused by a small growing tumor may be sufficient to locate it by 3D longitudinal registration and subtraction.

Our evaluations on MRI, 3D ultrasound, and EIT will be short for the following reasons: the role of MRI in breast cancer screening has already been discussed adequately in the literature, and we shall merely indicate relevant articles in the literature; 3D ultrasound is just taking off and has a long way to go before it could routinely achieve 4 mm detection capability; and EIT of the breast is still in its infancy. However, CT of the breast is the natural extension of mammography to 3D. Thus, the desirable x-ray characteristics of breast tissue can still be retained with this modality. However, it has never been seriously considered as a screening technique due to the large x-ray doses involved. Recent literature in relation to CT mammography has only described it as a useful diagnostic tool and not as a primary screening tool. We therefore discuss CT of the breast in greater detail to see what techniques could be used to reduce the dose to acceptable levels while still aiming for 4 mm lesion detection.

It might be argued that even if an imaging modality is able to detect all 4 mm lesions, it may not be able to detect microcalcifications, which are heavily used by mammographers for diagnosis. Since microcalcifications are typically in the range of 0.1 mm, it would seem that this would place a big demand in terms of resolution on any imaging technique which attempts to replace mammography. Even if the contrast were available, all current commercially available 3D imaging techniques like MRI, ultrasound, and CT of the breast do not approach 0.1 mm spatial resolution, though micro-CT units which have spatial resolutions ranging from 25 to 100 µm have been reported.[22,23]

It must be pointed out that microcalcifications mostly occur with accompanying lesions or inside a "bed" of dysplastic/hyperplastic cells and actually represent the calcium secretions of these cells.[24] Let us call this entire "bed" of cells a "lesion" for simplicity. In mammography, because the visibility of a lesion is occluded by overlapping tissue above and below a lesion, often only the calcium deposits inside a lesion are visible, due to their high contrast, and the lesion itself is not seen directly. The shapes and other attributes of microcalcifications are used diagnostically to evaluate whether the accompanying lesion is benign or malignant. However, an important question would be: If one had an imaging technique which could delineate all lesions and indicate their presence reliably, would we still need to image microcalcifications? This is a controversial issue and needs further investigation and evaluation.

Detection and diagnosis are two separate issues. The first is to be able to detect every lesion which develops inside a woman's breast. The next step would be to decide how to diagnose each of these lesions. Needle biopsy can provide the true histologic nature of a lesion, with a failure rate of less than 1%.[25] Future developments in imaging may even reach the point where malignant and benign lesions may be distinguished with a similar failure rate. For now, we address the issue of detection of all 4 mm tumors and put aside the issue of how they will be diagnosed; without detection, there can be no diagnosis.

Brief evaluations of 3D imaging modalities

Magnetic resonance imaging (MRI)—Increasingly, MRI has been used as a diagnostic tool to resolve mammographically ambiguous lesions, as well as for cancer staging.[25] The development of dedicated surface coils resulted in the ability to image smaller lesions than was traditionally possible with standard mammography.[26] The use of dedicated surface coils, under homogeneous magnetic fields, has allowed spatial resolutions close to 5 mm, with slice thicknesses in the same range.[27] However, with current 3D imaging techniques,[28] the entire breast can be imaged without gaps at a 1 to 2 mm slice thickness. Also, 3D imaging techniques allow nearly cubic voxels. While the tomographic quality of these images has an obvious advantage (because the exact location of a lesion can be known in three dimensions), the question as to whether MRI can be used for breast cancer screening has been addressed by several researchers[25,29] and the general consensus appears to be that the high cost for imaging and long examination time prevent it from becoming a screening modality. The nearly standard use of gadolinium contrast agents, which are mildly neurotoxic,[30] also makes MRI of the breast an invasive procedure.

The issue of examination time has been solved with current fast 3D imaging techniques, which allow complete signal acquisition in a short time;[28] fast 3D gradient echo (GE) sequence images of the entire breast can be acquired in about a minute.[31]

Even if, as explained earlier, we set aside the fact that MRI cannot image microcalcifications, cost continues to remain a stumbling block. Quoting Harms and Flamig,[25] "The cost of the contrast medium alone for breast MR imaging is about double the current cost of screening mammography." To reduce these costs, the use of contrast agents could be avoided by using coils co-axial to the breast and shielding the chest from the breast.[32] It remains to be seen, however, whether future development of technology and development of superior imaging sequences will obviate the need for the use of contrast agents, as well as bring down the cost for an examination. Until such time, MR screening will not be able to replace mammography.

3D ultrasound—Ordinary B-mode ultrasound is not reliable for breast cancer detection.[33,34,35] However, Moskalik et al[36] suggest that 3D compound ultrasound images obtained from multiple views can be registered to correct for refraction artifacts, as well as motion during image acquisition. They also propose image registration of 3D longitudinal ultrasound compound images "to display growth of abnormalities." Further studies need to be performed to determine the limiting resolution of this technique.

Ultrasound computed tomography (UCT), introduced at least 20 years ago,[37] uses standard CT algorithms to obtain 3D images of the breast, where changes in gray level between voxels indicate changes in acoustical properties of the tissue. In reflection-mode UCT, the transducer is used both to transmit pulses and receive the echoes. In transmission-mode UCT, two transducers are used, one to transmit pulses and the other on the opposite side of the breast to receive echoes. Another possibility is to measure the time taken for the pulses to travel between the transmitter and receiver and construct a speed-of-sound image based on these measurements.[5] However, due to artifacts introduced as a result of attenuation and refraction along the path of the pulses, the resolution with transmission-mode UCT is much lower than with reflection-mode UCT.[38] Another major problem with transmission UCT is the time needed to gather the projections and reconstruct the image.

Problems due to long imaging times with UCT have been tackled by a hybrid technique which fuses information from a compound B-scan image and a limited speed-of-sound CT image[39] to produce an image which depicts both tissue morphology and acoustic properties. The algorithm uses the Fourier back-projection (FBP) algorithm, although given the limited number of views (4 to 64), an iterative algorithm may have done better.[40] A voxel size of 1 mm^3 was used, although no studies have been performed to quantitate the achievable resolution. It is clear that further research is warranted to evaluate 3D ultrasound as a screening modality to detect small breast tumors.

Electrical impedance tomography (EIT)—EIT works by surrounding the breast with many electrodes either by direct skin contact or by immersing the breast in a conducting fluid. One pair of electrodes is chosen to drive a weak, harmless current through the breast. This current is below the threshold of sensation and does not cause tissue damage. Voltage measurements are taken simultaneously from all the other electrodes. Then, another pair of electrodes is chosen for current injection, to yield another "view." An image of the electrical resistance or impedance by varying the frequency of the current can be reconstructed using an appropriate algorithm.[41] To date, EIT has been a low-resolution imaging method, probably due to the small number of electrodes used (16 to 32)[42,43] and imprecise reconstruction algorithms, which presume that the electric current follows straight line paths.[44] The ultimate physical resolution may be limited by thermal fluctuations in the electric currents (Hoult D, personal communication, 1997).

Breast tumors have high impedance contrast.[45,46,47] Currently, computer simulations are being developed of many more electrodes, to predict if EIT spatial resolution could be competitive with CT, MRI, and 3D ultrasound.

Guardo et al[48] experimented with the back-projection reconstruction algorithm and were able to detect a 3 mL plastic sphere at the center of a torso-sized cylinder of saline. Shahidi et al[49] reported that simulation results with a 3D finite element method show that a 10-mL edema region with a conductivity equal to that of blood can be detected at a 40 dB signal-to-noise ratio (SNR). Furthermore, detection of a smaller volume, in the order of 2 mL, should be possible by improving either the instrumentation to achieve a 60 dB SNR or the performance of the reconstruction algorithms.[49] These results, scaled to the size of the breast, indicate that even small breast tumors (less than 4 mm in diameter) should detectably alter surface potentials. However, future research into this imaging modality is needed to determine if this is practicable and will lead to images of sufficient resolution.

X-ray computed tomography (CT)—CT mammography, while the obvious extension of mammography to 3D, has remained controversial because of the supposedly high doses required for full breast imaging. There was considerable enthusiasm for CT mammography in the late 1970s. Initial clinical trials using dedicated and conventional CT scanners suggested that several benign lesions could be distinguished from malignant lesions by imaging the breast twice: once before and once after intravenous iodide administration.[50] Radiological contrast agents created a 5% increase in CT numbers for breast cancers compared to benign lesions.[51,52] But, enthusiasm for CT mammography was not sustained because of concerns regarding radiation exposure, as well as the need for the use of contrast agents. The earlier experiments, however, used a low spatial resolution (1 voxel = 1 mm × 1 mm × 1 cm).

With the introduction of spiral or helical scanning, which allow the imaging of the whole breast in less than a minute, recent studies have begun focusing once again on CT breast imaging.[53] Raptopoulos et al[14] assessed the performance of high-resolution CT (slice thickness of 1 to 2 mm) on breast biopsy specimens following conventional x-ray specimen mammography. They conclude that, with fatty breasts, CT and mammography performed equally well. However, for masses in radiographically dense tissue, CT performed much better. This is because the masses are not occluded by the presence of overlapping tissue. Raptopoulos and coworkers thus concluded that CT could be used selectively for patients with dense, difficult-to-evaluate breasts where mammography has proved ineffective. They also stated that because of the averaging effect of the large voxels used in CT, microcalcifications would be poorly detected or missed. Nevertheless, if the lesion itself is visible in the image, do the microcalcifications really need to be imaged? Also it may be possible to image microcalcifications in the following way: Let us say we use 50 µm voxels and 50 µm wide detectors over a 30-cm cube volume. We would need a reconstruction volume of 6000^3 (large, but attainable). The readings along a line of detectors could be run length encoded,[54] and the runs used to create variable ray widths for an iterative CT algorithm. This should allow preservation of microcalcifications, while retaining full SNR for each ray sum. Again, this warrants further evaluation.

The dose constraint for standard screening mammography (average glandular dose/view) given by the 1995 draft protocol of the Commision of the European Communitie,[55] is 2 mGy with grid. Thus, it is about 4 mGy for 2 views. Teifke et al[53] estimated that the average glandular dose for helical CT scanning using slices which are 6 mm in thickness is about 10 mGy, with in-slice resolution of 1 to 2 mm. Thus, it is seen that resolutions close to our 4 mm target are already available at only about 3 times the dose of standard mammography. This also agrees with the calculations of Muller,[56] who determined the dose of CT mammography to be three to six times that of diagnostic x-ray mammography. Niklason et al,[57] using digital tomosynthesis with data collected by a full-field digital mammography camera, obtained images with 1.5 to 3 mm pixels with "a total radiation dose of 0.89 to 1.74 times that in conventional mammography in the same specimen." Tomosynthesis uses simple back-projection, and can be improved upon by the use of CT algorithms.

In order for CT to be used on a regular basis for screening of asymptomatic women, the dose will have to be reduced even further.[58] The dose problem can be tackled in several ways[11]: In commercial x-ray CT machines, 180 or more views are taken in order to "overdetermine" the equations; most commercial CT scanners use variants of the FBP algorithm. The curve of image quality versus number of views peaks earlier for iterative algorithms than for FBP, at least under most conditions. Thus, a switch to iterative algorithms might reduce the number of views required. The original objection of increased computer time has been alleviated by much faster computers, and a new approach to algebraic reconstruction technique algorithms in particular produces converged images in one or two iterations.[40]

Reconstruction of images from limited data has been studied extensively in the literature.[59,60] Dhawan et al[61] obtained significantly improved images, compared to standard algorithms, using as few as 3 views, with Weiner deconvolution of the point spread function (PSF) of a CT algorithm. It should be possible to extend this to allow for a spatially varying PSF, which occurs in nonlinear CT algorithms such as ART.

Because the total dose is proportional to the number of views multiplied by the number of photons per view, another new approach is to use a large number of views with relatively few photons per view, at the level where one can do photon counting at each detector. A CT algorithm based on single photon data, such as has been devised for PET,[62] also is under development.

Substantial dose reduction by a factor of 10 also may be possible by performance of CT mammography with monochromatic x-rays.[63,64] Dose reduction should be attainable using steered x-ray microbeams.[65-67]

It is thus entirely possible that, with these approaches, CT dose could be reducible to levels at or below that of mammography. A voxel width of 0.5 mm is already available in commercial CT scanners,[68] though the x-ray peak energy is not optimized for mammography. Whether this voxel size is adequate to reliably detect 4 mm tumors remains to be seen. A new kind of CT scanner could potentially be built with substantially smaller voxel widths using detectors currently used in full-field digital mammography units.[69,70] Thus, future research of 3D CT mammography as a standard tool for breast imaging can be anticipated, of course operating at the appropriate energy range. If we combine all the tricks we know, can we squeeze out sufficient image quality at an acceptable x-ray dose to detect tumors at a small enough size to make a significant impact on mortality? Our guess is "yes," but much work lies ahead.

Discussion

It can be argued that high resolution breast imaging will result in many small "lesions" and "false positives." Is itbetter to ignore them all until some show up as larger tumors? If our extrapolation[12] of empirical data[15] to small tumor sizes is correct, then all small tumors should be removed. Leaving them in with a "wait-and-watch" policy only increases their size and thus their probability of metastasis.[71] If we succeed in imaging small tumors reliably, control studies could then be undertaken to determine whether "wait-and-watch" or "excise when found" is best.

It could also be argued that the image registration procedure will uncover normal changes in the breast occurring during the time interval between the two images, due to pregnancy and lactation, aging, menstruation, surgery, etc., which could be confused with a growing tumor. Once the image registration procedure detects all changes (normal and abnormal) in the breast, deciding which are abnormal becomes a classification and diagnosis issue. By conducting well-designed studies using healthy volunteers, it may be possible to evaluate how normal changes in the breast over time appear on an image.[72] It may then be possible to develop classification criteria to separate these normal changes from those that occur due to a growing tumor. This should be the focus of future research.

Standardization of breast position (most likely pendant) may be necessary to avoid the internal slippage of tissue that appears to occur on breast compression.[73] This is, again, a topic for future research.

Another reason for detecting and possibly removing tumors early is the bimodal nature of recurrence of breast cancer.[74] According to this new model, many large tumors produce angiostatin, an anti-angiogenic factor, which keeps distant micrometastases in an avascular state. However, surgical removal of the tumor removes the source of angiostatin, causing micrometastases to grow. Since smaller tumors will probably not produce enough angiostatin to suppress distant micrometastases, removing them should not cause an early recurrence. In fact, removing them may prevent the formation of distant micrometastases in the first place.

On the other hand, an argument could be made that: 1) there are many benign "lesions" that never get large but could be confused with small tumors; and 2) there are many small tumors that never grow and are therefore not harmful to the patient. It could be the latter that show up in autopsies of women who died of causes other than breast cancer.[75] Let us grant these two possibilities. Small tumors that grow slowly, do not grow, or regress can be distinguished from faster growing tumors by rate of growth (low, zero, or negative, respectively). Thus two 3D longitudinal registered breast images could be used to estimate rate of growth.

A recent article described the normal appearance of "lesions" in contrast-enhanced breast images which appear and disappear throughout the menstrual cycle and across consecutive cycles.[76] Kuhl et al[76] noted that contrast-enhancing foci are normal in healthy premenopausal breasts. These foci may even fall within formal malignancy criteria with regard to "enhancement velocity" (the rate at which the "lesion" uptakes the contrast agent), but may disappear in the next menstrual cycle, indicating the benign, transient nature of most of these "lesions." Exact localization of the "lesions" in 3D will allow us to track the size and location of each lesion versus time to determine whether it is a transient or a persistent lesion requiring further diagnosis. The latter would, we presume, be indicative of a tumor, shifting a study (in a clinical setting) from screening to diagnosis. Small lesions that appear transiently could require at least three registered 3D breast images taken at consecutive times to distinguish them from faster growing tumors that keep on growing. On the other hand, gating to the menstrual cycle might take care of this problem.

Recent literature suggests that prostate specific antigen (PSA), used to signal the presence of prostate cancer in men, is also present in fluid extracted from the nipple of a woman's breast, as well as in the serum.[77,78] However, like other chemical markers, this is present in only 30% to 40% of tumors. Hence, even if the presence of cancer were inferred through monitoring the changes in the antigen level, 3D breast imaging would have to be performed subsequently to find the location of the lesion. Whether 4 mm tumors can be reliably detected (but not located) by chemical tests is not yet known.

We have ignored all methods which attempt to visualize the vascular bundle around a breast tumor. With our goal of detecting 4 mm tumors, it is possible that many of these have little or no vascularization. Kallinowski and colleague's[79] model using implantation of human breast cancer in nude mice showed a 10-fold variation in tumor perfusion, thus indicating the existence of a large variation in the degree of angiogenesis in small cancers. Recent studies have also suggested that vascularity is not a reliable indicator of malignancy, as several benign lesions also display vascularity.[29,80] In a study performed by Nakata et al,[80] 8% of malignant tumors larger than our 4 mm goal did not display vascularity. We anticipate that this figure would increase as tumor size decreases and, hence, the role of vascularity in breast screening is questionable.

Throughout our discussion of different imaging modalities, we have indicated minimum pixel and voxel sizes used by different researchers. However, in most of these studies, quantitative measurements of resolution, as well as studies to estimate the minimum detectable size of a lesion, have not been performed. As Williams and Fajardo[70] point out, "The pixel-to-pixel spacing merely puts an upper limit on the achievable resolution. For this reason, the common (and incorrect) equating of pixel size with spatial resolution usually leads to an overly optimistic prediction of imaging performance for a digital system." Hence, it is clear that for all the imaging modalities discussed above, quantitative studies will have to be undertaken to obtain estimates of the actual spatial resolution achievable in each case.

We thus conclude that rigorous pursuit of small tumors via 3D screening, and subsequent registration and subtraction of longitudinal images, should be a top priority in breast cancer research. As we learn to handle such 3D images, we will likely gain the experience to distinguish potentially malignant tumors from benign small tumors and/or transient "lesions," as well as possible normal changes in the breast.

Conclusion

Reliable detection of all breast cancers before they reach 4 mm in diameter could potentially reduce the likelihood of metastasis to less than 1%, which we tentatively take to mean a potential cure rate of greater than 99%. We have presented an argument, using the popular cartoon character Waldo, that mammography misses tumors primarily because of its two-dimensional nature. We have also presented a brief evaluation of four different 3D imaging modalities which can potentially be used for 3D longitudinal breast screening. Small tumors could then be detected by registration and subtraction of these longitudinal images.

While none of these modalities have yet reached reliable detection of 4 mm tumors, we believe that future research in breast imaging should be directed toward this goal. The criteria to select an appropriate imaging modality would include safety, ability to detect small tumors, and cost. *AR*

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