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REVIEW ARTICLE

Future Directions in Breast Imaging

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INTRODUCTION

Breast cancer imaging has improved dramatically over the last decade, with higher and more uniform quality standards for mammography, the increasing use of sonography and magnetic resonance imaging (MRI), and the widespread availability of imaging-guided percutaneous biopsy for clinically occult disease. This review paper describes the limitations that exist in the current state of the art for breast cancer imaging for detection and diagnosis. Four broad areas of future investigation are described in detail. First, we discuss the use of newer versions of mammography, such as digital mammography, with tomosynthesis and digital subtraction mammography. Secondly, new screening for occult disease might be improved through individualized strategies that stratify by patient risk, for example, through more rigorous screening with new and different tools for women at high risk. Third, the use of tools that might be useful for less invasive therapy of breast cancer with imaging to monitor the efficacy of the therapy is discussed. Finally, we describe the use of imaging to monitor and adjust neoadjuvant chemotherapy regimens in the course of therapy for advanced breast cancers when the risk of death is high.

NEW TYPES OF X-RAY MAMMOGRAPHY

Digital mammography holds great promise for breast cancer screening, but to date, the available results have been somewhat mixed. One large screening trial showed statistically significantly improved specificity with a nonstatistically significant lower sensitivity for digital compared to traditional film mammography.[1] Another large Norwegian study showed no difference in cancer detection rates between digital and film mammography with worse specificity for digital.[2] These trials were limited in that they included only one digital equipment manufacturer, General Electric (General Electric Medical Systems, Milwaukee, WI). The American College of Radiology Imaging Network's Digital Mammographic Imaging Screening Trial (sponsored by the National Cancer Institute), which enrolled 49,528 women in 34 centers in the United States and Canada over a 24-month period, should definitively determine how the sensitivity and specificity of digital and film mammography compare in the screening setting across multiple machine types. Those results are expected in the spring of 2005. Table 1 presents a summary of the clinical trials data on digital mammography.

Of course, there are other ways in which digital mammography might allow improved diagnostic accuracy compared to film mammography. First, once mammography is digital, tomography can more easily be performed, at a dose that is comparable to a two-view mammogram.[3] This might be an ideal tool for screening. Second, perhaps the limitations of mammography in radiographically dense breasts can be overcome through the use of tomograms and three-dimensional reconstructions. Third, perhaps mammography can be performed with less compression. Of course, clinical trials are needed to prove these hypotheses. To date, the General Electric tomosynthesis system is being tested at Massachusetts

Table 1. Clinical Trials Data on Digital Mammography

	Lewin et al[1]	Skaane et al[2]	DMIST†
No. of participants			
Digital	4,521	6,997	49,528
Film	4,521	17,911	49,528
Sensitivity, %			
Digital	63	Not reported	
Film	79	Not reported	
Positive biopsy rate, %			
Digital	28*	Not reported	
Film	23*	Not reported	
Recall rate, %			
Digital	12*	4.6*	
Film	15	3.5*	
Cancer detection rate per 1,000 women			
Digital	5.9	5.9	
Film	7.5	4.1	
Area under the ROC curve			
Digital	0.72	Not reported	
Film	0.78	Not reported	

Abbreviations: DMIST, Digital Mammographic Imaging Screening Trial; ROC, receiver operating characteristic.
*Indicates a statistically significant difference.
†Results not presented or published yet.

General Hospital (Boston, MA) and the Uniformed Services Academy (Bethesda, MD). Other manufacturers (Hologic Inc, Bedford, MA; and Sectra, Stockholm, Sweden) are also working on tomography digital mammography products with various levels of mammographic compression, dose, and visualization tools. There are currently no published peer-reviewed papers describing clinical trials data for tomosynthesis.

Another tool that might bring added value to digital mammography for patients is digital subtraction angiography.[4,5] Two different methods for this technique have been described. One uses intravenous contrast with a precontrast image followed by a series of contrast-uptake images, with the precontrast images subtracted digitally from the postcontrast images and a contrast-uptake curve used for assessment of potential malignancies, just as such curves are used in MRI of the breast.[4] The other method obtains images at two different energy levels after the administration of an iodinated contrast agent with a weighted subtraction of the logarithmic transform of these images, so as to create an image that shows iodine.[5] These methods have been demonstrated to be feasible. Their effects on diagnostic accuracy have yet to be carefully assessed, especially in comparison to the more widely available MRI.

Another potential modality that is more easily used with digital mammography than with film is computer-assisted diagnosis and detection (CAD). For film, this technique is available only after digitization of the images. For digital mammography, the CAD systems can be applied more readily and easily to the raw digital data. One study has demonstrated the sensitivity of R2 Image Checker (R2 Technologies, Sunnyvale, CA) with General Electric digital mammograms (General Electric Medical Systems) in a test set of 63 histologically proven cancers as 89% for calcifications and 81% for masses, slightly worse than this CAD product performs with digitized film mammograms.[6] In addition, there is evidence to believe that image processing could further improve the visibility of lesions in digital mammograms.[7] Again, there are commercially available systems that render second opinions of digital mammograms. Unfortunately, to date, very little has been published on these methods with digital mammography, and the utility of CAD and image processing together has not been widely utilized or explored. Clinical trials exploring these adjunctive methods that are available with digital mammography are definitely needed before these techniques can be more broadly adopted.

EARLIER/BETTER BREAST CANCER DETECTION USING SCREENING METHODS TAILORED TO INDIVIDUAL RISK

The report from the Institute of Medicine titled, Integration and Innovation: A Framework for Progress in Early Detection and Diagnosis of Breast Cancer, is an independent review that again shows screen-film mammography to be the principal element of breast cancer screening.[8] Early detection of breast cancer by this method has been shown to save lives over the last 40 years in seven screening trials in four countries, especially for women older than 50 years of age.[9] Despite the well-known controversies about screening mammography, particularly between the ages of 40 and 50 years, multiple independent reviews of the literature agree that it is a very useful way to look for breast cancer.[10] Current major reviewing organizations are the WHO International Agency for Research on Cancer (March 2002), the Global Mammography Summit (June 2002), and the US Preventive Health Task Force (September 2002).[11,12] The estimated screening-related decrease in mortality ranges from 20% to 30%[13] to 50% or more,[14,15] with at least some of the reduction in mortality undoubtedly due to improvements in therapy.

The sensitivity estimates for screening mammography are 83% to 95%, with specificity 90% to 98%.[16] With dense breast tissue, sensitivity is lower, perhaps as low as 48%.[17] Thus, many women with breast cancer are diagnosed only after a palpable mass is located by the patient herself, a family member, or her physician. Since about 40,000 women and 400 men die of this disease each year in the United States, according to the American Cancer Society, improved detection is clearly a necessary goal.[18]

The elimination of false positives at screening is also essential, since now 10%[9] to 50%[19,20] of women screened for 10 years will have an abnormal exam. The current widely accepted US screening guidelines include all women 40 years and older, but there are some women who may not need to be screened and some who need much better screening methods than we now have. Low serum estradiol

may safely exclude some from the general screening population, whereas women with known risk factors could be helped by improved tools.[21] The American College of Radiology Imaging Network (ACRIN) 6667 breast MRI study has enrolled 1,007 women older than 18 years of age who had a diagnosis of breast cancer in one breast and a normal mammogram of the opposite breast. The goal of that study is to determine the accuracy of MRI in screening the opposite breast in this population. Other recently published studies have demonstrated increased cancer detection in high risk women with breast MRI.[22,23]

ACRIN 6666, the Screening Breast Ultrasound Trial for High-Risk Women, is assessing the utility of screening sonography in high-risk women. High risk is defined in this trial as asymptomatic women over age 25 years with heterogeneously or homogeneously dense breasts by mammography who have a known *BRCA1* or *BRCA2* mutation, or a personal history of breast cancer, or a prior biopsy showing lobular carcinoma-in-situ, aypical ductal hyperplasia, atypical lobular hyperplasia or atypical papillary lesion who are not on chemoprevention, or have a prior history of chest, mediastinal, or axillary irradiation before age 30 years and at least 8 years before study entry, or a lifetime risk of breast cancer by the Gail or Claus models of at least 25%, or a 5-year risk by the Gail model of at least 2.5%, or a 5-year risk by the Gail model of at least 1.7% with at least 75% dense breast tissue by a prior mammogram. More detailed information on this trial, which is currently open to accrual, can be found at the ACRIN Web site (www.acrin.org).

Serum proteomic markers and genetic tests may also become useful for screening, as may the following imaging tools: digital subtraction mammography, CAD/computer-aided classification (CAC) capabilities, and tomosynthesis. Some of these tools may be proven and available in a few years.

NONSURGICAL TREATMENT OF EARLY/SMALL BREAST CANCERS

Percutaneous ablation of these small cancers may be possible using laser therapy, cryoablation, radiofrequency ablation, microwave phased-array thermotherapy, and high-intensity focused ultrasound (HIFU).

Laser therapy through a laser needle inserted under local anesthesia, with stereotactic mammographic guidance, showed 70% complete tumor ablation in one study of 54 women with invasive and in situ breast cancer. All had wire localization of residual tumor and surgical excision.[24]

Sonographically guided cryoablation under local anesthesia has been successful for fibroadenomas.[25] The experience with this technique for invasive breast cancers, limited so far, gives reason for hope.[25-28] This technique will need evaluation in multiple centers, to include post-treatment imaging with MRI and surgical/pathologic correlation.

Radiofrequency ablation is done through a 2-cm probe, placed under ultrasound guidance, which sends high-frequency alternating current into a breast mass. Again, this procedure can be done with local anesthesia, in outpatient clinics. Ten patients with invasive cancers showed good tumor killing and pathologic-imaging correlation on post-therapy MRI in a study reported by Burak et al.[29] Patients treated this way under general anesthesia have shown similar results.[30,31]

For microwave phased-array thermotherapy, under local anesthesia, a catheter is placed into the compressed breast while the patient lies prone. Eight of the 10 patients with larger cancers showed decrease in tumor size or tumor necrosis in one study.[32] Further study is needed, correlated with post-treatment imaging.

MRI guidance is used for HIFU, with the high-frequency ultrasound placed into the breast with no need for invasive devices such as needles. One randomized clinical trial included 48 women with invasive breast cancer and compared mastectomy to HIFU with subsequent mastectomy.[33] Another trial included 24 patients who could not be treated surgically or who refused surgery, showing correlation between residual tumor at core biopsy and post-therapy MRI.[34]

So the future holds the possibility of less invasive treatments for early/small breast cancers. How and how much imaging will be involved in these treatments and their monitoring is uncertain. So far, imaging has been useful for correlation with surgical results. Effectiveness of such therapies must be compared to the current standard treatments. Before certainty regarding the efficacy of these therapies can be reached, further randomized trials will be needed.

MONITORING BREAST CANCER THERAPY RESULTS WITH IMAGING

MRI may have an important role in monitoring response to therapy. MRI may help determine if a particular chemotherapy regimen is working for a patient, or if other drugs should be tried. This is likely to be most useful in women with locally advanced breast cancer or large tumors. In such patients, clinical response to neoadjuvant chemotherapy predicts for long-term outcome, for example, survival.[35] It is conceivable that MRI could be better than physical examination in monitoring response. ACRIN 6657/Cancer and Leukemia Group B (CALGB) Intergroup Trial 49808, Contrast-Enhanced Breast MRI for Evaluation of Patients Undergoing Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer, is evaluating the utility of MRI in patients who are receiving an anthracycline-based regimen only or followed by a taxane and enrolled in CALGB correlative science study 150007. These women undergo MRI at the time of diagnosis, after the anthracycline therapy, and after the taxane therapy/before surgery.

This use of MRI as a chemotherapy monitoring tool is in its early stages. Those responding to their drug regimen may show typical enhancement patterns over time. Decreased MRI sensitivity during chemotherapy has also been shown.[36] Interpretation criteria for MRI during chemotherapy may need to be quite different from prechemotherapy MRI. Published studies to date have included 30 or fewer patients.[36-39] In the future, chemotherapy monitoring in this patient population may also include MRI spectroscopy, positron emission tomography scanning with new agents, digital mammography with contrast, and sonography.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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