New Technologies in Breast Imaging

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Abstract
Large, randomized controlled trials have proven the efficacy of mammography in reducing breast cancer mortality. However, the known deficiencies of mammography have led to the development of new technologies. Magnetic resonance imaging (MRI), digital mammography, computer-assisted diagnosis, positron-emission tomography (PET), technetium 99m sestamibi, and expanding roles for breast ultrasound have been explored as tools in breast cancer detection and evaluation. This article discusses these modalities and their current uses. (JNCCN 2003;1:272–278)

Mammography is currently the gold standard for breast cancer screening. Large randomized, controlled trials conducted over the past 40 years have shown significantly reduced mortality from breast cancer among women who have been offered screening mammography. The Swedish Two-County Trial found a 32% reduction in breast cancer mortality; the Health Insurance Plan (HIP) of Greater New York trial found a 23% reduction with a combination of screening mammography and clinical breast examination; and the Edinburgh Scotland Trial found a 29% reduction.

However, the limitations of mammography are well known. The sensitivity of mammography is reported to be 85% to 90%, but can be as low as 70%.

Despite advances in mammographic technique and interpretation, breast density, observer oversight, and subtle signs of tumors remain major limitations. Also, only 10% to 30% of lesions found by mammography prove to be malignant. Over the years, new technologies and expanding roles for existing technologies have been developed for breast imaging. This article describes these technologies as well as the current scientific basis for their application.

Breast Ultrasound
Until recently, the role of ultrasound in breast imaging was primarily evaluating mammographic and palpable abnormalities, particularly, determining the cystic or solid nature of an abnormality. However, recent investigations with high-resolution whole breast ultrasound have shown promise with the expanded use of ultrasound as a screening modality and to characterize solid lesions.

A limitation of screening mammography is that in women with dense breasts, cancer can be obscured by overlapping fibroglandular breast tissue. When whole breast ultrasound rather than targeted ultrasound was used in addition to mammography in women with dense breasts, the incremental cancer detection rate by ultrasound was 0.2% to 0.3%. The mean size of sonographically found invasive cancers was not significantly different from those detected by mammography. However, there was a subsequent decline in the specificity of lesions found, and potentially, many unnecessary biopsies could be performed. The positive predictive values for whole breast ultrasound have ranged between 11% and 12%, and are lower than for mammography (25% to 40%).

Mortality rates in the screening population, with or without additional sonography, should be compared. Any benefit must be weighed against the additional cost of screening and increase in the false positive rate.

Lesion characterization may be helpful in decreasing the number of unnecessary biopsies. Stavros et al prospectively classified 750 sonographically solid masses as benign, indeterminate, or malignant. The classification scheme had a negative predictive value of 99.5% and a sensitivity of 98.4%. Therefore, follow up was recom-
mended for those lesions meeting benign classification. However, ultrasound performance is operator dependent, and interobserver variability may limit the accuracy and reproducibility of breast ultrasound. Whole breast screening ultrasound has also been used as a tool for detecting multicentric, multifocal, and contralateral breast cancer. For ipsilateral cancers, a 14% to 15% increase in cancer detection and a 4% increase in contralateral cancers was shown. Some patients may choose mastectomy instead of lumpectomy based on finding additional foci of carcinoma. Moon et al also tried to characterize a subgroup of patient who may most benefit from preoperative whole breast ultrasound. Seventy-eight percent of additional cancers detected at ultrasound were in patients with index tumors 2 cm or larger, and 92% were found in dense breasts.

Breast Magnetic Resonance Imaging

In the past decade, faster and improved imaging techniques, dedicated radio frequency coils for the breast, and gadolinium contrast materials have made magnetic resonance imaging (MRI) a realistic imaging tool for the evaluation of breast abnormalities. Investigators have explored MRI for breast screening and for a possible role in breast cancer staging. Investigators also have explored a role for MRI in evaluating the breast in women who have axillary lymph nodes positive for metastatic disease, whose primary malignancy is mammographically and clinically occult.

However, many potential issues still must be resolved. Unlike mammography, breast MRI does not have a universally accepted standard technique or standard interpretation criteria. Currently, no clinical indications for MRI of the breast have been established. Finally, it remains to be seen if this expensive technology can become cost effective.

Use As a Screening Tool

The variable sensitivity of mammography has prompted the search for other imaging modalities to use in the detection of early breast cancer. The reported sensitivity of MRI for detection of breast cancer ranges between 88% and 97%. A recent study found that MRI failed to detect every carcinoma of the breast. In particular, small (<4 to 5 mm) invasive cancers, diffusely growing, or intraductal cancers were missed. The reportedly wide range of specificity of breast MRI, 37% to 97%, is problematic. However, many benign and malignant lesions will enhance with contrast material, as will normal breast tissue, especially in younger women. Lesion kinetics (Fig. 1), such as rate of enhancement or analysis of time-signal intensity curves and lesion morphology have been explored, with much overlap between benign and malignant lesions found. Probably, a combination of both kinetics and morphology of lesions will be needed for more accurate lesion diagnosis.

The ideal for a screening study is to detect malignancy in its earliest stages. Mammography has proven to be very sensitive for the detection of ductal carcinoma in situ (DCIS). However, the specificity for DCIS remains low. The use of MRI in the evaluation of DCIS in the breast has shown variable results, with sensitivities ranging between 45% and 100%. Different techniques and patient populations probably account for these results. These studies included tumors with invasive components. Teifke et al found that 65% of purely intraductal carcinomas were not detected with MRI.

Although the sensitivity of MRI of the breast for invasive carcinomas (and possibly for DCIS) is promising, limited knowledge of the efficacy of MRI as a breast cancer screening tool is available. There are ongoing trials involving women identified as high risk: those who are known carriers of a BRCA 1 or 2 mutation, who have a family member known to carry a BRCA 1 or 2 mutation, who have a personal or family history suggestive of BRCA 1 or 2 involvement, or...

Figure 1 Gadolinium-enhanced MRI of the breast shows an irregular enhancing mass with kinetics curve. The Y scale is the percent enhancement, and X scale is time.
who have at least a 25% to 30% estimated lifetime risk for developing breast cancer. At present, MRI for breast cancer screening should be performed within clinical trials after careful risk assessment.

Staging
Given the high sensitivity of MRI and its ability to detect cancers not found at mammography, investigators have evaluated the potential role that MRI may have in staging breast cancer. Harms et al found clinically and mammographically unsuspected cancer in 37% of patients with a known breast cancer, while Orel et al found that MRI detected one or more mammographically occult cancers in 34%. In 20%, the cancers were mammographically and clinically occult multifocal or diffuse disease.

MRI has been promising for breast cancer staging given its high sensitivity, especially for invasive cancers. However, some significant questions remain. For example, the clinical importance of additional foci of carcinoma detected by MRI and whether they can be effectively treated remains to be seen. Also, the patients who will benefit from MRI staging, possibly such as those with palpable cancers or dense breasts, have not been identified. Careful, prospective clinical trials are still needed to answer these questions.

Although occult cancer presenting as ipsilateral axillary metastasis accounts for less than 1% of breast carcinomas, breast MRI has shown some promise in detecting mammographically and clinically occult primary breast carcinoma. In approximately one third of patients who present with axillary metastasis, no tumor is found at mastectomy. In the two largest series, 75% and 86% of primary breast cancers, respectively, were detected using breast MRI. Treatment of these patients is controversial, but breast conservation may be offered if the lesion can be localized with either MRI or ultrasound guidance and a specimen radiograph documenting lesion removal can be obtained.

Digital Mammography
Despite advances in film screen technology and film processing, there are still limitations in subtle lesion detection with mammography, particularly in women with dense breasts. In this system, film is not only an image receptor, but also the display and storage medium. A loss in image contrast in the film-screen system can lead to lower optical density (the ability to detect a contrast difference between adjacent breast tissue and a breast lesion).

Digital mammography separates image acquisition from image display and storage. The digital detectors use a phosphor material to absorb x-ray photons, converting them to an electronic charge that is then sent to an analog-to-digital converter. The converter changes it to a digital signal. With the steps of image acquisition, display, and storage separated, each can potentially be optimized. Spatial resolution is defined as the number of pixels in the image, and contrast is defined as bit depth. Studies are ongoing to determine the spatial and contrast resolution requirements of a digital detection system in different clinical settings, such as for screening, diagnosis, and intervention.

To date, only one large clinical screening trial has attempted to evaluate full-field digital mammography (FFDM). This study compared FFDM and film screen (FS) mammography in a screening cohort. The protocol was designed to limit bias from a verification of findings detected with FS mammograms by recommending imaging work-up or biopsy based on positive screening results with either FFDM or FS mammography. The recall rate, or the number of women called back for evaluation of a finding on the screening examination, was 11.8% for digital mammography and 14.9% for FS mammography (P < .001). No statistically significant difference in sensitivity was found (P > .01), although more cancers were detected with FS mammography. The number of biopsies resulting from FS mammography was higher than for digital mammography (P < .001), but the area under the ROC curve for the two modalities was not significantly different (P = .18). Future clinical studies also will be needed to determine whether more contrast or spatial resolution is better for breast cancer detection.

Computer-Assisted Detection and Diagnosis
Reasons for the potentially high false-negative rate of mammography include interpreter perception and interpretation error. Because individuals can interpret the same images differently, there is evidence that double reading (by more than one individual) will increase the detection rate of cancers. However, this also may result in higher recall and biopsy rates and increases in the cost of screening. Thus far, the Food and Drug Administration has only given approval for computer-aided detection, not diagnosis.
Software has been developed to help radiologists decrease the false-negative rate of mammographic interpretation. The computer uses an image analysis algorithm to evaluate a mammographic image and will mark or highlight areas that could be abnormal (Fig. 2). Studies using computer-assisted detection (CAD) show increased sensitivity for detection of both spiculated masses and calcifications. In evaluating CAD for screening mammography, a retrospective, blinded study found that CAD reduced the false-negative rate by 77%, without a significant increase in the recall rate. The only prospective study to date involved 12,860 patients in community breast centers. In this study, CAD increased the number of cancers detected by 19.5%, increased the proportion of early stage cancers found, and only modestly increase the recall rate (6.5% to 7.7%). Also, no change was noted in positive predictive value (PPV) for biopsy. The increase in the number of cancers detected was explained by the calcification cases (87%; most were DCIS), suggesting that radiologists overlook calcifications more frequently than masses or that mass detection is more problematic for CAD. A higher sensitivity for calcifications than for masses was shown with CAD. The higher call-back rates are probably due to CAD’s low specificity.

Computer-aided diagnosis attempts to classify lesions as either benign or malignant. Computer analysis schemes are being developed using either human-extracted features or computer-extracted features. The performance of radiologists in terms of the area under the ROC curve was significantly improved for differentiating between benign and malignant calcifications with computer-aided diagnosis as well as for benign and malignant masses. Also, Huo et al showed that the greatest improvement in the area under the ROC curve and sensitivity was seen in community radiologists versus radiologists with more mammographic experience. However, no improvement in specificity was shown. Although promising, CAD and computer-assisted diagnosis must be compared with double reading by experienced radiologists to evaluate it for cost-effectiveness.

**Positron-Emission Tomography and Technetium-99m Sestamibi**

Mammography, ultrasonography, and MRI rely on morphologic changes in the breast to diagnose breast disease. Functional imaging of the breast using positron-emission tomography (PET) also has been used to evaluate breast tumors, detect axillary and metastatic disease, and monitor response to chemotherapy. When a positron is emitted from an isotope and interacts with a tissue electron, the energy given off in two 511KeV photons and detected by a PET camera. These photons produce lines of “coincidence” that can be reconstructed into tomographic images using algorithms like those used for computed tomography (CT) scan reconstructions. The glucose analogue, 2-[18F]-fluorodeoxy-D-glucose (FDG) is the most commonly used radiopharmaceutical in PET imaging of the breast. In neoplastic cells, which have a higher metabolic rate than non-neoplastic cells, there is a preferential uptake of FDG.

Reported sensitivities of PET for primary breast carcinomas range between 68% to 94% and specificities range between 84% and 100%. The spatial resolution of PET limits the evaluation of tumors less
than 1 cm.\textsuperscript{51,54,56} PET has shown promise in detecting axillary nodal metastases in breast cancer (Fig. 3), with sensitivities between 79\% and 100\%\textsuperscript{,57–59} and specificities between 66\% and 100\%.\textsuperscript{57–59} However, in regard to actual staging of breast cancer with PET, the false-negative rate remains uncertain without large prospective studies.\textsuperscript{50}

Whole-body PET imaging is capable of showing distant metastatic disease,\textsuperscript{54,55} but large studies defining the accuracy of PET at lesion detection in different organ systems have not been completed.\textsuperscript{50} Finally, PET holds some promise in monitoring response of breast cancer to neoadjuvant chemotherapy. Two studies evaluating the role of PET in women with locally advanced breast cancer may predict who will respond to neoadjuvant chemotherapy early in treatment, thereby potentially reducing toxic effects of chemotherapy and avoiding delay in a more beneficial regimen and surgery.\textsuperscript{60,61}

The role of PET in the management of breast cancer patients is evolving. The expense and availability of radiopharmaceuticals as well as the lack of high spatial resolution devices probably will limit the use of PET breast imaging in many centers.

Scintimammography with the lipophilic cation technetium-99m sestamibi has received much attention in the past 10 years. Originally used as an imaging agent for myocardial perfusion, it is the only radiopharmaceutical approved for use in radionuclide breast imaging. The first relatively large series evaluating the use of this agent for detecting breast cancer showed a sensitivity of 96\%, specificity of 87\%, a PPV of 82\%, and a negative predictive value (NPV) of 97\%.\textsuperscript{62} Several other large series were summarized by Taillefer,\textsuperscript{61} who noted sensitivities between 50\% and 95\%, specificities between 58\% and 100\%, PPVs between 67\% and 100\%, and negative predictive values between 55\% and 97\%. In two more-recent studies, the values also fell within these previously noted range.\textsuperscript{64,65} If a combination of mammography and scintimammography are analyzed, the sensitivity, specificity, PPV, and negative predictive value increased to 93\%, 72\%, 80\%, and 90\%, respectively. The area under the ROC curve showed that the combination of the modalities was significantly more accurate than either test alone (\(P < .05\)).\textsuperscript{65}

Unlike mammography, the sensitivity of technetium 99m sestamibi does not appear affected by dense fibroglandular tissue, which can limit evaluation with mammography.\textsuperscript{62,66} However, lesions smaller than 1 cm have been the lower limit of scintimammography sensitivity,\textsuperscript{63,64,67,68} and therefore, it has not been advocated as a screening tool.\textsuperscript{61}

**Conclusions**

The emerging technologies discussed may show promise in the future as adjunctive tools to mammography. With further research, they may improve the sensitivity and specificity of breast cancer detection.

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