Update on Emerging Technologies in Breast Imaging

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Abstract

Despite mammography's proven efficacy, there continues to be interest in newer technologies in breast cancer detection and expanded use of established technologies, especially in women with dense breast tissue and those at high risk. This article reflects on the development in the last ten years of some of these modalities and their current use. (*JNCCN* 2012;10:1355–1362)

Digital Mammography and Breast Tomosynthesis

Ten years ago, most mammography units in the United States were using film screen technology. After the results of the Digital Mammographic Imaging Screening Trial (DMIST), proving digital mammography was as efficacious as film screen mammography, the number of facilities investing in digital technology rapidly increased. As of December 2011, according to the American College of Radiology (ACR), 81% of certified facilities have digital units and 82% of certified mammography units in the United States are digital (Marion Boston, personal communication, 2011). Women younger than 50 years, those who are premenopausal, and those with dense breast tissue were shown to experience the most benefit from digital technique.[1,2] However, detection of breast cancers in dense breast tissue remains a limitation of conventional mammography. Using digital technology, digital breast tomosynthesis mammography (DBT) is being developed for detection and characterization of breast lesions obscured by overlapping tissue, particularly in women with dense breast tissue.

The technology for digital breast tomosynthesis is the same as digital mammography, but with modifications to the digital mammography unit that enable acquisition of a 3-dimensional volume of thin-section data. Much like those used in CT, the images are reconstructed using reconstruction algorithms. The x-ray tube moves along an arc during the exposure, with the breast in compression in a standard plane.[3] The reconstructed images are then sent to a reading workstation.

The expected benefits of DBT are superior detection of noncalcified masses otherwise obscured by overlapping tissue and a decrease in recall rates. Preliminary reader performance studies with small numbers of cases have shown favorable results. In their initial experience with comparison of image quality of tomosynthesis and conventional digital mammography in 98 women, Poplack et al[4] showed equivalent or superior image quality of tomosynthesis compared with mammography in 89%. Other investigators have also found reader preference for DBT.[5–7] More mass detection by DBT has been demonstrated, including greater than 90% sensitivity.[8,9] Reader performance was also found to improve when DBT views were combined with digital mammography compared with digital mammography alone.[10,11] When adjusting for confounding variables, Poplack et al[4] found the recall reduction to be 40%. Gur et al[12] also showed a reduction in the recall rate with the combined use of tomosynthesis and full-field digital mammography (FFDM). This group also found longer interpretation times for DBT, with the longest mean time to view and rate an examination when FFDM and DBT were combined.[12] Good et al[6] also found that the mean time spent in reviewing, interpreting, and rating the exami-

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nation was greater for the DBT studies than with FFDM (mean time, 2.72 vs. 1.58 minutes).

Improved detection of calcifications on DBT does not seem as clear as for masses. Technical factors remain with tomosynthesis, which can limit the resolution for calcifications.[13,14] Poplack et al[4] found that 57% of cases with calcifications were seen better on FFDM, whereas only 14% were seen well with DBT. Other studies have found that calcifications were seen on both FFDM and DBT.[4,15,16] In the largest study so far (100 paired examinations), FFDM performed slightly better than DBT.[17]

Hologic now has FDA approval for a digital tomography unit for clinical use. However, protocols for the use of DBT have not been addressed, such as whether to use DBT and FFDM combined or DBT alone; or to use single-view tomosynthesis acquisition verses 2 views.[18] Also to date, no widely available means exists to biopsy findings found only on DBT or an optimal imaging technique to keep dose close to a single, 2-view mammogram.[18] Although there have been promising experimental trials for digital tomosynthesis, no large-scale, multi-institutional clinical trials comparing FFDM and DBT have been performed to determine the exact role tomosynthesis will have in breast imaging.

MRI

Over the past decade, the use of breast MRI has continued to increase, with a survey indicating that 73.8% (557/754) of practices in late 2006 offered the examination.[19] In this same period, many investigators have worked to further delineate the role of dynamic contrast-enhanced MRI (DCE-MRI) in breast cancer care. Nonetheless, the lack of breast MRI standardization has led to heterogeneous research studies, such that study results may not be universally applicable.

The diagnostic performance of DCE-MRI has been better established over the past decade. A meta-analysis of 44 studies from 1985 to 2005 that excluded articles with only palpable or symptomatic lesions estimated that the pooled weighted sensitivity and specificity of DCE-MRI was 90% and 72%, respectively.[20] In 2011, another meta-analysis of 69 MRI studies from 1985 to 2010, excluding studies performed on high-risk patients, echoed similar results with a pooled sensitivity of 90%, specificity of 75%, accuracy of 91% for detecting cancer or high-risk lesions versus benign lesions, and positive and negative likelihood ratios of 3.64 (95% CI, 3.0–4.2) and 0.12 (95% CI, 0.09–0.15), respectively.[21]

Guidelines for using MRI as an adjunct screening tool for high-risk populations were established in 2007.[22] A meta-analysis[23] of 11 prospective nonrandomized screening MRI studies in high-risk populations calculated that combined MRI and mammography might rule out cancer better than mammography alone, lending further support to the American Cancer Society[22] and NCCN recommendations[24] (Table 1). However, even if they are eligible for adjunct MRI screening, women frequently opt against it. The ACR Imaging Network (ACRIN) 6666 protocol identified 1215 high-risk women who were eligible for MRI screening, but found that only 57.9% agreed to participate, with the largest percentage of nonparticipants (25.4%) refusing because of claustrophobia.[25] Therefore, alternative screening strategies may be considered for subpopulations not amenable to MRI.[25]

MRI has an established role in identifying otherwise occult primary breast cancers in women with axillary nodal adenocarcinoma or Paget disease of the nipple.[24] In patients with early-stage breast cancers, MRI has been used to evaluate the extent of disease. A 2008 meta-analysis reported a 16% median prevalence of incremental multifocal or multicentric disease detected by MRI, with a summary positive predictive value of 66% and true-positive/false-positive ratio of 1.91.[26] More extensive surgery was performed in 11.3% of women with additional biopsy-proven disease and 5.5% of women without additional disease.[26] In more advanced cancer cases, MRI remains the best imaging modality for assessing chest wall and pectoralis muscle tumor invasion by evaluating for enhancement in these structures[27]; involvement of the chest wall indicates a T4-stage tumor, whereas information about pectoralis muscle involvement can impact surgical planning.

Screening the contralateral breast for occult malignancy in patients with newly diagnosed cancer has served as another motivation for performing preoperative MRI. A 2009 meta-analysis of 22 studies estimated that MRI detects 4.1% of incremental contralateral breast cancers; 35.1% of these were pure ductal carcinoma in situ and 64.9% represented invasive cancer.[28]

Despite the incremental cancer detection that MRI offers, recent clinical and surgical outcomes

Table 1 Recommendations for Adjunct MRI Screening

Annual Screening MRI Recommended for Women With
BRCA mutations and their untested first-degree relatives[a]
Lifetime risk of ≥20%, defined by BRCAPRO or other Mendelian risk prediction model[a]
History of chest radiation between ages 10 and 30 years (Hodgkin survivors)[b]
Tumor suppressor gene mutations (p53/PTEN) and their untested first-degree relatives; (Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes)[b]
Insufficient Evidence to Recommend For or Against MRI in Women With
Personal history of breast cancer or high-risk lesions
Lifetime risk between 15% and 20%
Heterogeneously or extremely dense mammograms[c]
Recommend Against MRI Screening for Women With Lifetime Risk <15%

[a]Based on evidence from nonrandomized screening trials and observational studies.
[b]Based on expert consensus opinion of the American Cancer Society advisory panel.
[c]According to Breast Imaging Reporting and Data System.
Data from Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89; and Bevers TB, Bonaccio E, Buys SS, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. Version 1, 2012. Available at: NCCN.org. Accessed March 7, 2012.

studies suggest that it may not be routinely indicated for patients with newly diagnosed cancer. In 2004, a retrospective study reported a significant reduction in recurrence rates when preoperative MRI was performed. However, this study had a short mean follow-up time (3.4 years) and did not adjust its results for differences in tumor- or therapy-related variables between the MRI (n=121) and non-MRI groups (n=225); the latter group was disadvantaged by higher-stage cancers, which may have influenced study results.[29] In 2008, a nonrandomized, retrospective, single-institution study reported no significant differences in the 8-year rates of overall survival, local recurrence, metastatic disease, or contralateral breast cancer between women who had (n=215) and had not (n=541) undergone MRI before breast-conserving surgery with radiation.[30] The 2 groups in this study were also not matched, with the MRI group advantaged by younger women with smaller tumors. The authors acknowledged that their study was underpowered to detect an incremental improvement in the already-low baseline recurrence rate (4%). Both of these studies may reflect the impact of older (1990s) MRI technology.

In 2009, another single-institution (single-surgeon) study of women who underwent breast-conserving surgery with radiation found no significant differences in achievement of negative margins at initial lumpectomy, re-excision rates, or ipsilateral recurrence rates (median follow-up, 4.5 years) between those who did (n=127) and did not (n=345) undergo preoperative MRI.[31] After adjusting for patient, tumor, and therapy variables, this study still found no statistical difference in the 5- and 8-year actuarial ipsilateral breast recurrence rates between the groups.[31] However, the recurrence rate of 2.2% was lower than the 10-year local recurrence rates of 3.5% to 6.5% reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP),[32] possibly reflecting the short follow-up interval and one surgeon's style. In 2010, a multicenter randomized controlled trial (COMICE) conducted between 2002 and 2007 found that incremental MRI was not significantly associated with a reduced reoperation rate in women who were assigned to MRI (n=816) compared with those who were not (n=807).[33] The total reoperation (re-excision and mastectomy) rate of 19% in both groups is comparable to the 20% rate found within the English National Health Service (NHS) trusts (n=55,297)[34] but lower than rates reported in US studies (31%–50%).[35–38] The 10% and 11% re-excision rates in the 2 groups are also comparable to the 10.7% rate in the NHS trusts[34]; however, these rates are again lower than that reported in US studies (22.9%–26%).[35,36] These differences presumably reflect regional variations in initial surgical approaches. Therefore, whether the results of COMICE are universally applicable remains unclear. Furthermore, recurrence and survival rates were not study end points and therefore, prospective random-

ized controlled trial data still do not exist on the impact that preoperative MRI may have on clinical outcomes.

Although the utility of routine preoperative MRI may be growing more controversial, certain patient subgroups, such as those with invasive lobular carcinoma, are thought to benefit from the information it provides.[39] Currently, NCCN 1) does not advocate for or against the use of routine preoperative breast MRI for the assessment of ipsilateral or contralateral breast cancer; 2) suggests that decisions to use MRI be made in concert with the multidisciplinary treatment team; and 3) recommends against alteration in surgical management without additional tissue sampling of MRI findings.[24]

The literature on using MRI to assess response to neoadjuvant chemotherapy is heterogeneous but is generally supportive. DCE-MRI provides not only anatomic information for assessment of tumor dimensions but also information about tumor vascularity and cellular permeability, although nonenhancement does not exclude residual tumor. New means to identify early responders include evaluating for alterations in pharmacokinetic parameters and increases in apparent diffusion coefficient values on diffusion-weighted MRI.[40,41] However, the optimal method for using MRI to monitor response to neoadjuvant chemotherapy has yet to be determined.

Ultrasound: Hand-Held and Automated

Ultrasound in breast imaging has always been an inexpensive adjunctive tool, allowing easy access, increased patient comfort, and o radiation use. During the past 8 years, the use of ultrasound has increased in screening for and staging of breast cancer, particularly in women with dense breasts. Dense breast tissue can obscure breast cancers. Additionally, dense breast parenchyma alone has been shown to increase the risk of developing breast cancer.[42] Recent legislation in Connecticut and Texas now requires women to be informed of their breast parenchymal density at their mammogram to allow them the choice of requesting whole breast screening ultrasound.[43]

Before 2003, the prevalence of cancer in patients who had undergone supplemental ultrasound after mammography ranged between 0.27% and 0.47%.[44–47] Since then, an additional 12,202 patients with dense breasts have been evaluated with ultrasound, with similar cancer detection rates.[48–50] The ACRIN 6666 trial is the largest trial of screening ultrasound in which mammography and ultrasound were performed and read independently. The diagnostic yield and performance of screening with ultrasound plus mammography versus mammography alone were evaluated in women with elevated risk of breast cancer. In 2637 eligible participants, an additional 1.1 to 7.2 cancers per 1000 women were detected with ultrasound (cancer detection yield increase of 4.2/1000).[51] A mix of film-screen and digital mammography techniques were used. The false-positive rate in this study was 4.4% for mammography alone, 8.1% for ultrasound alone, and 10.4% for both. Of the women recalled for biopsy after routine mammography, the positive predictive value (PPV) was 23%, compared with 8.9% for ultrasound and 11.2% for combined modalities. The median size of the invasive cancers seen only on ultrasound was 10 mm, and 89% of patients were node-negative. The recall for mammography in this series was within accepted parameters (10.5%), whereas the recall for ultrasound was lower than expected at 5.4%, probably because these studies were physician-performed and could assess lesions directly in real time. The short-term follow-up recommendation after ultrasound in 8.6% of participants was similar to that in other series.[44,46,47] The study by Berg et al[51] validates the detection benefit of a single screening ultrasound in women at high risk of breast cancer. However, this was also associated with a risk of higher false-positive results, as evidenced by a large number of benign biopsy results and short-term follow-up evaluations.[51] Ultrasound elastography may help in this regard.[52] Evaluation of the incidence of annual screening ultrasound is a continuing part of this ACRIN trial, and will need to be evaluated in light of subsequent screening trials of breast MRI, which has been shown to outperform combined mammography and ultrasound.[53–56]

The ACRIN 6666 trial has shown promising results of breast ultrasound in high-risk women. However, barriers to implementing screening ultrasound include median physician time needed to perform bilateral breast ultrasound (found to be 19 minutes) and potential qualified physician shortages.[52] Notably, the studies evaluating ultrasound for screening before the ACRIN study compared it with mammography using film-screen technique,[44–50] but digital

mammography has shown a benefit in young women, particularly those with dense breasts. Therefore, future clinical studies may not show supplemental ultrasound to have as much benefit compared with digital mammography.[57]

To help reduce operator time needed to perform handheld whole breast ultrasound and provide a standardized examination, automated whole breast ultrasound (ABUS) is being investigated. Automated whole breast ultrasound involves robotic guidance of an ultrasound transducer or probe over the breast, with presentation of the acquired images in the axial or coronal plane on a reading work station.[58] In a study of 6425 mammography-ultrasound pairs comparing the performance and diagnostic yield of mammography alone and with ABUS, ABUS was found to increase the diagnostic yield of mammography from 3.6 per 1000 to 7.2 per 1000. The PPV for biopsy of ABUS was 38.4%.[59] The average interpretation times have been reported to be between 7 and 8 minutes; this is separate from the imaging times of 10 to 20 minutes for each patient.[58] These results are promising, but potential costs of reviewing and storing multiple generated images and increased exposure to malpractice will need to be reviewed.[51] Combined ABUS and digital mammography systems have also been investigated,[60–62] potentially allowing simultaneous screening and diagnostic imaging.

Molecular Breast Imaging

Nuclear medicine modalities for molecular breast imaging have shown some promise in breast cancer detection in the past decade. These modalities would include positron emission mammography (PEM) using 18F-fluorodeoxyglucose (FDG) radionuclide and a dedicated, high-resolution PET scanner, with the ability to position the breast similar to mammography, and scintimammography (dual-head gamma or breast-specific gamma imaging [BSGI]) using technetium 99m (Tc99m) sestamibi. Molecular imaging involves exposure of ionizing radiation to the whole body, making these technologies unsuitable for annual use. Investigators will need to address the radiation-induced cancer risk of these modalities.[63] A single BSGI or PEM examination is estimated to induce a lifetime risk of fatal cancer greater than or equal to that of a lifetime of annual screening mammography.[63] Furthermore, none have standard interpretive criteria. Currently, no recommendation exists to use molecular imaging for breast cancer screening.

Berg et al[64] found PEM to be highly accurate in depicting primary breast cancer, with sensitivity improving when it was added to mammography, ultrasound, and the clinical examination, without reducing accuracy. The group's results support PEM use in defining extent of disease, aiding in surgical planning, and problem solving in difficult mammographic cases. In a separate study comparing the effectiveness of MRI and PEM in evaluating the contralateral breast of women with newly diagnosed breast cancer, PEM depicted cancer in 73% of women. However, most were not prospectively detected or misinterpreted as probably benign, highlighting the need to view lesions seen on PEM as suspicious unless known to correlate with a benign finding on MRI, ultrasound, or mammography.[65]

Two other molecular imaging techniques, dedicated dual-head gamma imaging and high-resolution BSGI, have been investigated for their adjunctive role to mammography. The dedicated dual-head gamma imaging uses a gamma camera system with a cadmium-zinc-telluride (CZT) semiconductor detector in place of a conventional sodium iodide detector. Both use the radiotracer Tc99m sestamibi. A prototype dual-head gamma camera showed a high sensitivity for malignant lesions smaller than 2 cm, with an 86% sensitivity for lesions smaller than 1 cm.[66] Adding gamma imaging using this technology to mammography increased the detection of node-negative cancer in dense breasts by 7.5 per 1000 women screened.[67] Early experience with a high-resolution small-field-of-view gamma camera (BSGI) in 50 patients showed the greatest improvement in detection of nonpalpable lesions and lesions smaller than 1 cm,[68] and in a retrospective study BSGI showed a high sensitivity of 96.4% with a moderate specificity of 59.5% for the detection of breast cancers.[69] In a multicenter patient registry to determine the impact of BSGI, the greatest benefit found was in women with negative or indeterminate mammographic findings.[70] Technical improvements to the breast-optimized cameras will potentially allow reduction of radionuclide to a dose comparable to that delivered by a screening mammogram, and trials are under way to determine the clinical impact of dose reduction.[67,70]

Conclusions

Continued development of digital technologies, including breast tomosynthesis, expansion of breast ultrasound technology, and molecular imaging, and the refined use of breast MRI, may continue to improve the early detection of breast cancer.

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