Molecular and Functional Imaging of Breast Cancer

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Background: Significant efforts have been directed toward developing and enhancing imaging methods for the early detection, diagnosis, and characterization of small breast tumors. Molecular and functional imaging sets the stage for enhancement of current methodology.

Methods: Current imaging modalities are described based on the molecular characteristics of normal and malignant tissue. New molecular imaging methods that have the potential for clinical use are also discussed.

Results: Dynamic contrast-enhanced magnetic resonance imaging is more sensitive than mammography in BRCA1 carriers. It is used in screening and in the early evaluation of neoadjuvant therapy. Positron emission mammography is 91% sensitive and 93% specific in detecting primary breast cancers. Sentinel node scintigraphy is a key component of axillary lymph node evaluation. Other imaging modalities being studied include Tc99m sestamibi, radiolabeled thymidine or uridine, estrogen receptor imaging, magnetic resonance spectroscopy, and diffusion magnetic resonance imaging.

Conclusions: Molecular and functional imaging of the breast will likely alter clinical practice in diagnosing and staging primary breast cancer and assessing response to therapy since it will provide earlier information regarding the underlying biology of individual breast cancers, tumor stage, potential treatment strategies, and biomarkers for early evaluation of treatment effects.
The potential role of molecular imaging as a response biomarker is of particular interest because it may allow assessment of therapeutic efficacy that moves beyond simple anatomic measurements. That is, virtually all clinical therapies are currently evaluated by RECIST (response evaluation criteria in solid tumors), which is simply dependent on tumor size. Through molecular imaging, various physiologic or metabolic biomarkers are currently being evaluated to assess tumor response using both physiologic and anatomic criteria. This approach may prove critical not only as a method to assess tumor response quickly following therapy, but also as an early indicator or tumor adaptation and emergence of resistance.

This article reviews current imaging modalities that rely on molecular characteristics of tumor and normal tissue. Also included is a discussion about new technologies that may significantly impact the radiologic approach to breast cancer in the future.

Current Applications

**Evaluation of the Primary Tumor in the Breast**

Current imaging of a primary breast cancer is almost entirely dependent on anatomic characteristics of the tumor. Mammography detects tumors based on the presence of a mass, microcalcifications, or distortion of the normal breast architecture. Ultrasound can further characterize a mass as cystic or solid, and magnetic resonance imaging (MRI) adds information regarding tumor vascularity and blood flow. However, new imaging technologies that provide insight into cellular and even subcellular processes in tissue have been developed, and their role in breast imaging is being explored. As discussed below, most research in these modalities has investigated the role of these new technologies in improving sensitivity and specificity in detecting breast cancer. However, it remains to be seen if they also provide predictive or prognostic information about the cancer biology that can either guide therapeutic strategies or measure treatment results in a way that is more accurate or timely than standard anatomic data such as RECIST measurements.

**Magnetic Resonance Imaging**

MRI is a noninvasive imaging modality that can generate high-resolution, multiplanar, three-dimensional (3D) images of any organ of the human body with excellent soft tissue contrast. Signals acquired from water and/or fat are utilized to generate an image, and image contrast depends on intrinsic properties of the tissue, e.g., relaxation properties (T1- and T2-weighted images). The ability to modify image contrast simply by altering the parameters used for image acquisition is a major strength of MRI. Alternatively, image contrast can be improved by administration of an external gadolinium-based contrast agent. Heywang et al.1 were the first to use gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) for MRI of the breast. The technique is called contrast-enhanced MRI (CE MRI) or dynamic contrast-enhanced (DCE MRI), depending on the method of image acquisition after administration of the contrast agent. CE MRI helps in distinguishing benign from malignant lesions by improving the image contrast of high-resolution T1-weighted images acquired after injection of the gadolinium-based contrast agent.2,3 DCE MRI is used to evaluate various enhancement characteristics of the lesion by acquiring baseline images prior to contrast agent injection and multiple postcontrast images. This dynamic acquisition of data allows for the determination of vascular permeability through quantification of the volume transfer constant (Ktrans) of contrast agent between blood plasma and the extravascular extracellular space and the extravascular extracellular volume fraction (ve).4 Fig 1A is a DCE MRI image of a brightly enhancing breast tumor, and Fig 1B is a Ktrans map from the same patient showing elevated enhancement at the tumor periphery.

Among all molecular imaging methods, DCE MRI is the most widely used technique for breast lesion detection and characterization.5 It has high sensitivity, 89% to 100%, for breast cancer, greater than any other imaging modality.3,6 DCE MRI of breast is routinely used in the
DCE MRI is recommended for screening women at high risk for breast cancer.\textsuperscript{5-7} A consistently high sensitivity of detection makes it an invaluable adjunct to mammography and ultrasound for screening breast cancer, particularly in high-risk women.\textsuperscript{3,6} Kuhl et al\textsuperscript{10} conducted a surveillance study of 529 symptomatic BRCA patients comparing mammography, ultrasound, and MRI. DCE MRI had higher sensitivity (91\%) and specificity (97\%) compared to mammography and ultrasound (33\% and 40\% sensitivity; and 97\% and 90\% specificity, respectively). The Magnetic Resonance Imaging Breast Screening (MARIBS) study compared MRI to mammography for screening in women with a strong family history of breast cancer or high probability of a BRCA1, BRCA2, or TP53 mutation.\textsuperscript{11} The sensitivity and specificity were 77\% and 81\% for MRI and 40\% and 93\% for mammography. MRI had higher sensitivity compared to mammography, particularly in BRCA1 carriers (92\% vs 23\%).\textsuperscript{11} The study concluded that annual screening combining CE MRI and mammography would detect most tumors in the high-risk patient group.\textsuperscript{11} Trecate et al\textsuperscript{12} screened 116 patients by mammography, ultrasound, and MRI over 5 years. Out of the 12 detected cancers, 6 were detected only by MRI.

Concerns about the cost associated with the use of MRI for breast cancer screening are significant and justifiable. However, MRI may prove to be a cost-effective modality for screening women at high risk, especially for the BRCA1 and BRCA2 subgroups.\textsuperscript{13} Recent guidelines of the American Cancer Society and European Society of Breast Imaging recommend the use of MRI for screening breast cancers.\textsuperscript{14,15}

The role of DCE MRI in the staging of breast cancer has also been evaluated.\textsuperscript{6,16-19} MRI provides superior estimates of tumor size relative to mammography and ultrasound.\textsuperscript{20,21} Lesion size as assessed by MRI correlates well with the pathologic specimen.\textsuperscript{22} However, MRI has been reported to overestimate the size of tumors that are greater than 2.0 cm.\textsuperscript{22} MRI has been used for an accurate assessment of the tumor extent.\textsuperscript{21-24} Uematsu et al\textsuperscript{24} suggested that MRI is the most accurate method for determination of tumor extent, although there is a risk of overestimation. The sensitivity, specificity, and accuracy of detection of intraductal spread by DCE MRI was 66.7\%, 64.2\%, and 65.6\%, respectively, which compares favorably to mammography (22.2\%, 85.7\%, and 50\%) and ultrasonography (20.6\%, 85.2\%, and 50\%).\textsuperscript{25} Although MRI is clearly superior to mammography in detecting breast cancer, its clinical utility is limited because its specificity remains low and virtually every tumor is surgically resected, allowing full pathologic staging. Thus, inclusion of MRI as a routine imaging modality for breast cancer staging is limited by its low specificity and lack of evidence of benefit in clinical management.\textsuperscript{8,26,27}

Many patients with locally advanced breast cancer are treated with neoadjuvant therapy. Thus, assessment of tumor response to chemotherapy may improve management of care in this patient group. MRI has been found to be the superior method for assessment of therapeutic response compared with clinical examination, mammography, and ultrasound.\textsuperscript{28-33} After one or two chemotherapy cycles, substantial changes were observed in the contrast enhancement pattern.\textsuperscript{34,35} Significant quantitative changes in several DCE MRI kinetic parameters were observed even before a measurable change in tumor volume occurred.\textsuperscript{36}

Conversely, an unchanged contrast enhancement pattern after two chemotherapy cycles strongly correlated to subsequent nonresponse based on standard size metrics.\textsuperscript{13,35,37} Johansen et al\textsuperscript{38} used DCE MRI to determine the early clinical response to primary chemotherapy in patients with locally advanced breast cancer. They found that a change in largest diameter of late enhancement during chemotherapy was the single most predictive MRI characteristic for tumor response.

The accuracy of MRI determination of pathologically complete response (pCR) varies according to the chemotherapy agent used and presumably its mechanism of action. MRI was more accurate in identifying pCR in patients who were receiving the HER2 inhibitor trastuzumab and less accurate in patients receiving bevacizumab, the anti-vascular endothelial growth factor drug.\textsuperscript{39} This suggests that imaging studies employed to measure pCR will need to be tailored to the specific drug being evaluated.

The accurate depiction of residual tumor in the postchemotherapy setting may guide selection of local treatment. Several studies have confirmed that compared to conventional imaging modalities, DCE MRI is much more sensitive and specific for assessing residual tumor extent after chemotherapy.\textsuperscript{38,39,40,41} Abraham et al\textsuperscript{38} showed that the RODEO (Rotating Delivery of Excitation Off-Resonance) breast imaging method accurately evaluates the residual tumor following completion of therapy compared to clinical examination, ultrasound, or mammography.\textsuperscript{28} A reduction of < 25\% in the largest diameter of late enhancement during neoadjuvant chemotherapy shows the potential to predict with high specificity any residual tumor after therapy.\textsuperscript{42} An insufficient (< 25\%) decrease in the largest diameter of late enhancement during chemotherapy was most indicative of residual tumor at final pathology.\textsuperscript{38} MRI has been shown to have a positive predictive value for residual disease up to 92\%.\textsuperscript{43,44} MRI findings of normal postoperative rim enhancement around a smoothly margined resection cavity are suggestive of the absence of residual tumor.\textsuperscript{45}

**Positron Emission Mammography**

Positron emission mammography (PEM) for breast cancer uses similar principles as the more generic and lower resolution cancer imaging modality positron emission tomography (PET). Both methods work...
through the introduction and detection of a positron-emitting glucose analog, \(^{18}\text{F}\)-2-deoxy-2-fluoro-D-glucose (\(^{18}\text{F}\)-FDG). Extensive clinical experience with PET imaging in cancer has demonstrated that the vast majority of primary and metastatic cancers take up more glucose than adjacent normal tissue takes up. This generally reflects a metabolic shift from oxidative metabolism of glucose to anaerobic pathways. The latter is much less efficient than the former — 2 moles of adenosine triphosphate (ATP) per mole of glucose for anaerobic metabolism vs 36 moles of ATP per mole of glucose for the aerobic pathway — and requires increased glucose flux (generally through upregulated membrane glucose transporters) to maintain adequate ATP concentration.

PET imaging exploits this difference in cancer and normal tissue metabolism through \(^{18}\text{F}\)-FDG, which is taken up like glucose and phosphorylated by an intracellular hexokinase, an enzyme that is also overexpressed in many cancers, but undergoes no further metabolism, thus allowing tracer buildup. The \(^{18}\text{F}\)-FDG analog decays by emitting a positron that is annihilated within a few millimeters, resulting in emission of two gamma rays that radiate in opposite directions and are detected by the PET instrument.

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Although whole body positron emission tomography (WB PET) is sensitive and effective in detecting advanced breast cancer and evaluating therapy response,51,52 due to its relatively low spatial resolution, breast lesions < 2 cm in diameter may not be detected. Moreover, the PET image format cannot easily be compared to conventional mammograms.

PEM adapts the PET imaging techniques to the breast and is an effective technique for detecting and managing breast cancer.53 Similar to PET, PEM exploits the ability of \(^{18}\text{F}\)-FDG to characterize malignant lesions. However, the resolution is increased by allowing detectors to be placed directly on the breast, similar to mammography. A dual-detector system is used that consists of two flat, high-resolution detector heads mounted directly to compression paddles. Images can be acquired comfortably with gentle compression.54 Respiratory motion is not an issue with PEM imaging, as the breast is immobilized.55

Since mammographic positioning is used in this method, direct correlation of PEM images with mammography for both initial and recurrence imaging is allowed. The images can also be reconstructed into 3D for localization of abnormalities.54,55

This technique enables the capture of sharp, detailed, localized images of breast lesions (as small as 2 mm), and small foci of ductal carcinoma in situ (DCIS) can be detected. Unlike mammography, PEM does not depend on the presence of microcalcifications for DCIS identification.54 Several PEM studies were recently published.16,55-59 Fig 2 is a PEM image that clearly resolves a primary lesion in a breast with high mammographic density (left panel). This image correlated

![Fig 2. — FDG-PEM detection of primary lesion with high mammographic density (left panel) with brightly enhanced lesion (blue boxes) surrounded by bright (dense) breast tissue. Axilla (right panel) shows metastatic disease in lymph node (arrow). The primary lesion correlated with MRI. However, MRI did not detect disseminated disease. Images were provided courtesy of Kathy Schilling, MD, Boca Raton Community Hospital, Boca Raton, Florida.](image-url)
with MRI, but MRI did not detect associated lymph node metastases (right panel). The results of a large multicenter study examining the efficacy of PEM reported 91% sensitivity and 93% specificity.58

Raylman et al60 recently developed a high-resolution PEM/PET imaging and biopsy device to detect and guide the biopsy of suspicious breast lesions. The PEM/PET scanner consists of two sets of rotating planar detector arrays for the production of multi-angle tomographic images. Thus, high resolution images in all three dimensions can be achieved by multi-view data acquisition. Initial testing of PEM/PET showed that spatial resolution and detection sensitivity results are close to the value obtained for some small animal imagers. Multicenter studies are needed to further define the sensitivity of this new technique.

Breast Cancer Staging Through Sentinel Lymph Node Scintigraphy

Assessing the presence or absence of tumor in axillary lymph nodes is essential for staging of breast cancer. However, surgical axillary node dissection is costly and can be associated with significant morbidity such as lymphedema, reduced arm motility, and increased susceptibility to infections.51,62 To reduce unnecessary axillary lymph node dissections, lymphoscintigraphy is routinely used to identify the sentinel lymph node (SLN), which is then removed and examined for disease pathology. Examination of the SLN has proved to be an acceptable alternative to axillary lymph node dissection.63-65 The SLN is the node that first receives lymph from the area of the breast harboring the tumor. If the SLN is determined to be free of disease, it is assumed that all other axillary lymph nodes will be negative and axillary dissection can be avoided. Thus far, this assumption has been well supported by clinical observations.63,65 Lymphoscintigraphy uses a labeled compound that is typically engulfed by macrophages and then carried to draining lymph nodes. As a result, it is an effective method for the preoperative evaluation of the lymphatic basin and identification of the SLN.66-68

Conventional scintigraphy produces planar images that may not allow the distinction of separate overlapping radioactive sources located at different depths; which can lead to a false-negative result if the SLN is missed during biopsy.67 Since conventional lymph node imaging with planar techniques does not always determine the exact anatomic location of the SLN,69-72

Fig 3. — (A) In a patient with right breast cancer, planar lymphoscintigraphy depicts an internal mammary chain sentinel lymph node (ascending arrow) and a second-echelon node (descending node). (B) Axial-fused SPECT/CT and (C) 3D SPECT/CT maximum-intensity projection of thorax enable tracing of the sentinel node (arrow) underneath the rib at the second intercostal space close to the right border of the sternum. (D) In another breast cancer patient, axial SPECT/CT-fused image visualizes an interpectoral sentinel node (arrow). Reprinted by permission of the Society of Nuclear Medicine from: van der Ploeg IM, Valdés Olmos RA, Nieweg OE, et al. The additional value of SPECT/CT in lymphatic mapping in breast cancer and melanoma. J Nucl Med. 2007; 48(11):1756-1760. Figure 1.
Single photon emission computed tomography (SPECT) was developed to obtain the needed 3D information that can provide the depth of the SLN, improve the accuracy of node depiction and localization, and enable the separate visualization of closely approximated nodes with tracer activity. This method is especially advantageous for patients with a tumor in close proximity to the SLN. SPECT is a tomographic version of conventional scintigraphy that can provide increased image contrast and resolution. When SPECT is combined with the anatomical detail provided by CT, precise anatomic localization of the SLN is obtained to aid the surgical biopsy (Fig 3). Recent studies have reported improved anatomical localization of the SLN by SPECT/CT (89% to 100% localization) compared with conventional imaging (72% to 94% localization) in the same patients. SPECT/CT was recently used to provide high-quality anatomical localization of SLNs in patients with breast cancer via 3D image reconstructions.

Typically, axillary node imaging in patients with breast cancer is performed following peritumoral or subareolar injection of Tc99m-labeled colloids. In some cases, peritumoral injection may be more accurate in identifying lymph nodes subject to drainage from a given breast tumor (eg, parasternal lymph nodes are not detected by the subareolar injection route). However, identification of the SLN by peritumoral injection can be limited by breast and tumor size or the existence of multifocal or nonpalpable tumors. Subareolar injection has several advantages over peritumoral injection; it is easier to perform because it does not require radiographic localization of nonpalpable tumors, and lymphatic drainage to the axilla is faster. As a result, dynamic acquisitions and visualization of draining lymph vessels can be performed using a lower dose of radiotracer. Interestingly, parasternal accumulation in internal mammary lymph nodes is found in 10% to 15% of patients. However, since detection of internal mammary lymph node involvement has no therapeutic advantage, biopsies are not usually performed in these nodes.

**Future Directions**

**Breast Cancer Mitochondrial Imaging With Breast-Specific Gamma Imaging**

Technetium (Tc99m) sestamibi may have value in detecting breast cancers and distinguishing between benign and malignant masses discovered by other imaging modalities. Sestamibi is taken up by active mitochondria and accumulates in breast cancers that generally have high mitochondrial activity when compared to surrounding tissues. Due to the absence of breast compression and the inability to locate the detector close to the breast, Tc99m sestamibi imaging in the breast generally has had poor sensitivity for small lesions (<1 cm in diameter). To overcome this, imaging devices have been designed by two different groups with high-resolution gamma camera detectors and the ability to position detectors on the breast with light compression in a similar orientation as used for mammography. These new imaging systems allow for both the standard mammographic views and the orthogonal views for precise location of lesions within the breast.

Brem et al advanced this potential approach using a high-resolution gamma camera to measure Tc99m ses-

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**Fig 4.** Abnormal breast-specific gamma imaging (BSGI) scintimammograms of (A) left craniocaudal, (B) right craniocaudal, (C) left mediolateral oblique, and (D) right mediolateral oblique projections demonstrating marked focal radiotracer uptake (arrows). Pathologic examination demonstrated 9-mm infiltrating ductal carcinoma. From Brem RF, Rapelyea JA, Zisman G, et al. Occult breast cancer: scintimammography with high-resolution breast-specific gamma camera in women at high risk for breast cancer. *Radiology.* 2005;237(1):274-280. Reprinted with permission by Radiological Society of North America and Rachel F. Brem, MD.
tamibi uptake of abnormal tissue in the breast, called breast-specific gamma imaging (BSGI) (Fig 4). This camera utilizes position-sensitive photomultiplier tubes and has subcentimeter resolution. Preliminary results of clinical studies evaluating BSGI are promising. Sensitivity of BSGI detection compared to traditional gamma camera methods improved from 85% to 92% for lesions > 1 cm and from 47% to 67% for lesions < 1 cm, and tumors as small as 0.3 mm have been detected. A more recent study reported 96.4% and 59.5% sensitivity and specificity, respectively, for BSGI.

Rhodes et al developed a semiconductor-based gamma camera system for detection of malignant breast lesions < 2 cm termed molecular breast imaging (MBI). The sensitivity and specificity of Tc99m sestamibi imaging were increased compared to conventional imaging, and malignant breast lesions < 1 cm were detected with 86% sensitivity. A second MBI study was conducted that included 100 patients with suspicious lesions < 2 cm in diameter as measured by mammography or sonography. Sensitivity of detection for tumors < 5 mm, 6 to 10 mm, and ≥ 11 mm in diameter was 29%, 86%, and 97%, respectively. Of 47 patients with no evidence of cancer at biopsy or surgery, 36 true negatives and 11 false positives were identified by MBI scans. An overall sensitivity of 74% for tumors < 1 cm in size was reported, representing a 30% improvement in sensitivity compared with previous reports.

The results suggest that MBI and BSGI may have a future role as an adjunct to MRI for the evaluation of patients in whom the sensitivity of mammography is decreased by the density of the breast parenchyma. MBI has been successfully employed in screening of high-risk women with a family history of breast cancer or who have had prior chest or mantle irradiation. It may also be helpful for surveillance in women following breast surgery. However, like other radionuclide-based imaging, these techniques require an injection of radiotracer with resulting radiation exposure. Multicenter studies are needed to further define the sensitivities of these developing techniques for both in situ and invasive subcentimeter lesions.

**New Molecular Imaging Agents for Breast Cancer**

The introduction of new PEM agents for further molecular characterization of target site activities may offer new opportunities for diagnosis and staging of breast cancer. These agents can provide anatomic localization as well as measurements of key tumor parameters that may provide information on prognosis, predict optimal therapeutic strategies, and evaluate the results of treatment. These include agents that measure cell proliferation such as radiolabeled pyrimidine and purine (thymidine or uridine), which incorporate into DNA or RNA, e.g., 18F-adenosine-PET and 18F-fluoro-L-thymidine (FLT)-PET. In addition, several compounds are in development that target critical components of the microenvironment including angiogenesis, cell metabolism, and hypoxia.

Perhaps one of the most promising new radiotracers is FLT. Tissue uptake of this radiopharmaceutical is correlated with thymidine kinase-1 (TK-1) activity, which is closely related to DNA synthesis during S-phase. In one study, the tumor-to-normal breast tissue ratio for FLT (17.4) was higher than that of FDG (12.4) so that contrast is potentially greater for FLT-PET/PEM than FDG. FLT has an additional potential advantage because of its increased uptake in the presence of inflammation compared to that of FDG. Thus it can be useful in patients who have received needle biopsy shortly before imaging. Finally, because FLT uptake is closely correlated with cell proliferation, changes in activity may be used to monitor the tumor response to cytotoxic or cytostatic agents.

Development of other targets to guide or monitor therapy is an active area of study. For example, agents have been developed to target the estrogen receptor (ER) to predict response to hormonal therapy. Other
compounds can determine HER2 expression in vivo to predict response to targeted therapies.\textsuperscript{98} Agents for tumor receptor imaging may have unique properties\textsuperscript{99} since high-affinity ligands can be developed for these targets and images can be generated with nanomolar or picomolar amounts of the probe.

This high level of sensitivity is apparent in the promising results of ER imaging for predicting and evaluating clinical response to hormonal therapy.\textsuperscript{99,100} For example, the ER imaging agent $16\alpha$-[\textsuperscript{18}F]-fluoro-17\textbeta\textendash estradiol (FES)\textsuperscript{101,102} has binding characteristics similar to estradiol\textsuperscript{103,104} and diagnostic images can be obtained with injection of < 5 \textmu g of FES.\textsuperscript{105}

Nuclear medicine imaging has great flexibility and potential for the development and use of different kinds of positron-emitting radiotracers that could lead to significantly improved lesion detection compared to other imaging modalities.

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) is a unique and powerful technique used to assess metabolite levels in tissues in vivo. The ability to detect metabolites in vivo and the potential to perform it during routine MRI examinations make it an attractive emerging technology for breast cancer evaluation. MRS was developed as a localized single voxel technique that can provide a single metabolite value for a single large volume of tissue. However, it is now possible to measure the distribution of a particular metabolite in a volume of interest by

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![Image of MRSI tCho map](image-url)

**Fig 6.** — Overlay of MRSI tCho map on an MRI image of an axial slice of a breast with a large tumor (panel B). The tCho map in panel B corresponds to the large square area indicated in panel A. Voxel 1 in panel A is within the tumor, and the corresponding spectrum is shown in panel C with a large tCho resonance signal. The corresponding spectrum for voxel 2, which is outside the tumor, is shown in panel D with no detectable choline. Reprinted from Hu J, Yu Y, Kou Z, et al. A high spatial resolution $^1$H magnetic resonance spectroscopic imaging technique for breast cancer with a short echo time. Magn Reson Imaging. 2008;26(3):360-366. © 2008, with permission from Elsevier.
acquisition of spectra from multiple voxels (usually about 1 cm³), providing an image map of metabolite levels within the tissue. This method is called chemical shift imaging (CSI) or MR spectroscopic imaging (MRSI).

**Spectral Characteristics of Breast MRS:** The ¹H MRS spectrum of the normal breast is primarily dominated by resonances arising from lipid protons with little contribution from water. In general, the single water resonance is spatially separated from a number of lipid-based resonances at the opposite end of the spectrum. In between these two major signals is a cluster of resonances that correspond to choline-containing compounds. Resonance signals arising from glycerophosphocholine (GPC), phosphocholine (pCho), and choline (Cho) form a composite peak at 3.2 ppm, generally termed total choline (tCho).[106,107] Fig 5 shows an image-localized MRS spectrum.

Choline compounds are soluble intermediates of the phosphatidylcholine (PtdCho) biosynthetic pathway. PtdCho is the major phospholipid component of the cellular plasma membrane. These upstream intermediates, primarily pCho,[108] are found to be elevated in malignant breast tumors. This is likely caused by an increased tumor cellular proliferation due to defective contact inhibition.[109] Many reports have demonstrated that malignant lesions can be distinguished from benign by increased tCho levels, as observed by MRS.[110-117] Katz-Brull et al[115] reported the sensitivity and specificity of MRS to detect malignancy as 83% and 85%, respectively, in a pooled analysis of five clinical studies.[115] The combined use of MRI and MRS showed increased specificity compared with MRI alone for detection of malignant disease.[116] The study revealed that the factors limiting the sensitivity of MRS were primarily technical and can be improved by technological advancements in detection of the choline signal.[115] The availability and use of 3T magnetic field MR systems for clinical use will increase the signal to noise ratio, thereby resulting in improvement in choline detection. The addition of quantitative analysis of choline resulted in higher sensitivity, specificity, accuracy, and increased agreement to distinguish benign from malignant breast lesions.[116] In vivo 2D correlation spectroscopy of the breast has been reported to separate and quantify the individual resonances within the composite tCho signal.[118] Choline MRSI is a recent addition to breast imaging that may allow improved localization and detection of tumor boundaries.[119,120] Fig 6 shows a tCho map (panel B) overlay on an MRI image of an axial slice of a breast with a large tumor, providing high morphological registration. Voxel 1 (panel A) within the tumor corresponds to the MRS spectrum in panel C showing a large tCho resonance. Voxel 2 outside the tumor corresponds to the spectrum in panel D with no tCho signal detected.

MRS-detected choline has also been evaluated for response to breast cancer therapy. Jagannathan et al[114] observed that tCho levels were reduced in 89% of subjects undergoing chemotherapy. Meisamy et

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**Fig 7.** — (A) Apparent diffusion coefficient of water (ADCw) map (center slice) of a breast cancer xenograft tumor before treatment with docetaxel, (B) ADC map of corresponding slice of the same tumor 48 hours post-treatment with increased ADC values throughout the tumor, and (C) post-treatment histology of the corresponding center slice demonstrating the heterogeneity of cellularity.
observed significant changes in tCho within 24 hours between responders and nonresponders. These metabolic changes were more pronounced than changes in tumor size. Recently, MRS was used to determine therapy response in a preclinical study.109

Diffusion MRI
The contrast in diffusion-weighted (DW) images is generated by the diffusion properties of water molecules in tissues. The diffusivity of water molecules in tissues is quantified by the apparent diffusion coefficient (ADC) calculated from DW images. Tissue ADC provides information about the tissue architecture and cellularity. Several investigators have reported significantly reduced ADC values for malignant tumors compared with benign and normal tissue.122-128 ADC threshold values have been used to discriminate malignant lesions from benign. Marini et al129 achieved a specificity of 81% and sensitivity of 80% using an ADC threshold value of 1.1 × 10^{-3} mm²/s, while using a cutoff value of 1.31 × 10^{-3} mm²/s yielded a specificity of 67% and sensitivity of 100% to distinguish malignant from benign lesions. Woodhams et al130 obtained a sensitivity of 95% for breast cancer using a threshold < 1.6 × 10^{-3} mm²/s. Rubesova et al127 obtained specificity of 100% using a threshold of 0.95 × 10^{-3} mm²/s. Lower ADC values for malignant tissues are associated with increased cellularity. The increased cellularity results in restricted diffusivity that is manifested as reduction in ADC. This inverse correlation between ADC and tumor cellularity is observed in breast cancer.125,124

Preclinical studies have demonstrated that ADC has potential for use as an early noninvasive biomarker for therapy response. Morse et al131 reported that early changes in ADC may be a generalized measure of cytotoxic response to chemotherapy. There is evidence to show that ADC changes occur earlier than the morphologic changes. Fig 7A-B shows the ADC map (center slice) of a breast cancer xenograft tumor prior to treatment with docetaxel and 48 hours after treatment. Note that the posttreatment tumor has a marked increase in ADC throughout the tumor. Fig 7C shows the histology of the corresponding center slice of the tumor after resection, reflecting the heterogeneity of cellularity observed in the ADC maps. Galons et al132 investigated the chemotherapy response of human breast cancer tumor xenografts that were sensitive or resistant to paclitaxel by monitoring early changes in the ADC. Early increases in ADC were observed before significant changes in tumor volume had occurred in successful treatment of drug-sensitive tumors, while no ADC change was observed in resistant tumors.132 Lee et al133 showed the efficacy of DW imaging for early assessment of tumor response in mice implanted with human breast cancer (MX-1) and treated with cyclophosphamide.133

ADC has been used in the clinic as a biomarker capable of providing an indication of early response to treatment prior to measurable changes in tumor size. Pickles et al134 observed changes in ADC as early as the first-cycle time point, while a reduction in the longest diameter was observed only at the second-cycle time point. Sharma et al135 concluded that ADC may be a better predictor of early tumor response to neoadjuvant chemotherapy compared to morphological measurements. Theilmann et al136 carried out MRI before therapy and at 4, 11 and 39 days after therapy and found that ADC can predict response by 4 or 11 days after initiation of therapy. Yankeelov et al137 reported that Ktrans and ADC are the most sensitive parameters to change during neoadjuvant chemotherapy in breast cancer.

It is expected that the use of higher-field instruments will increase the capability of ADC measurements to distinguish malignant from benign lesions. Although there is no significant difference in ADC values measured at 1.5T and 3T, the use of a 3T system may increase the visibility of small cancers by DW imaging compared to 1.5T.138 It has been reported that specificity of malignant breast lesion detection by DW imaging increases to more than 90% at 3T.139

Conclusions
Imaging remains an integral tool for clinical detection, staging, and management of breast cancer. While significant improvements in anatomic resolution have been achieved, screening mammography continues to yield significant numbers of false positive and negative studies. Furthermore, traditional anatomic breast cancer imaging (ie, size and morphology) provides limited information about the underlying tumor biology. A clear challenge for breast cancer imaging is to move beyond anatomic techniques to find new directions that not only improve detection, but also provide guidance for therapeutic strategies and accurate, rapid evaluation of response to treatment.

New strategies using targeted molecular agents and advanced imaging technology are rapidly emerging. These techniques increasingly allow reproducible clinical imaging of the molecular components of tumor and/or normal tissue in the breast. While these are exciting and potentially important advances, much work will be required to identify the technologies that truly increase diagnostic accuracy and improve patient outcomes.

References
8. Orel S. Who should have breast magnetic resonance imaging evalu-
preoperative chemotherapy.


chemotherapy for palpable breast cancer.

tumor volume predict response to neoadjuvant chemotherapy and recur-

rence-free survival.


Br J Cancer. 2007;97(10):1300-1307.


Cancer. 2008;112(2):145-152.


Eur J Oncol. 2008;41(9):901-901.


