AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6702

A MULTI-CENTER STUDY EVALUATING THE UTILITY OF DIFFUSION WEIGHTED IMAGING FOR DETECTION AND DIAGNOSIS OF BREAST CANCER

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ABSTRACT

Magnetic resonance imaging (MRI) has become an important tool for breast imaging. Conventional breast MRI is highly sensitive for detecting cancer, but can also result in many false positives. Diffusion weighted imaging (DWI) can provide complementary information for lesion characterization by measuring the mobility of water molecules in tissue allowing an indirect assessment of tissue microstructure. Single center studies have shown promise for adding DWI to breast MR examinations to improve specificity; however, differences in study design have caused variable results and there is no consensus on the optimal approach. To determine the added value of DWI for reducing false positives of breast MRI, it is important to validate these findings in a multi-center study with DWI implemented across a variety of systems (manufacturers/models/magnet strengths). Furthermore, it is essential to use a standardized approach to breast DWI acquisition and analysis to identify optimal apparent diffusion coefficient (ADC) thresholds for discriminating benign from malignant breast lesions.

For this study, we plan to evaluate DWI scans performed in women with breast lesions identified by conventional breast MRI. We will determine whether an ADC threshold can be defined for distinguishing benign and malignant lesions on DWI, assess the difference in ADC cutoffs for mass and non-mass lesions, and investigate the potential improvement in accuracy using techniques such as nonzero minimum b-value (to remove perfusion effects in the ADC measures) and normalized ADC measures (to account for variations in water content and other factors).

The outcomes of this study are potentially significant because if results are positive and DWI is found to be valuable for distinguishing benign from malignant breast lesions, (1) DWI could be easily implemented into routine clinical breast MR examinations (including screening exams) to improve specificity and reduce the number of unnecessary biopsies while adding only a few minutes to the exam and requiring no additional contrast or hardware, (2) the study will answer essential questions for implementing breast DWI in the multi-center clinical setting, such as establishing optimal ADC cutoff values and developing standardized image acquisition, data quality assurance, and interpretation methodologies, and (3) the study will provide valuable preliminary data and methodology to support a larger prospective Phase 3 trial to validate the improvement in diagnostic performance achieved by incorporating DWI into conventional breast MRI assessments. A negative result of the study will indicate that this technology is not yet ready for incorporating into standard breast MRI assessments and more work must be done to address specific issues identified by the study.

BACKGROUND AND SIGNIFICANCE

Conventional Breast MRI

Breast cancer is the second leading cause of cancer death among women in the United States, and earlier detection through screening is a fundamental way to improve survival. Dynamic contrast enhanced (DCE-MRI) of the breast has a high sensitivity for breast cancer detection and is the most sensitive technique for screening high-risk women and detecting contralateral or multifocal disease in patients with recently diagnosed breast cancer.

However, overlap in the appearance of benign and malignant breast lesions on DCE-MRI can produce many false positives. In high-risk women, data from 9 studies have shown that MRI screening prompts a biopsy in approximately 7.8% of women, of which 40% are found to have
cancer (MRI positive predictive value \[PPV\] = 40.3\%). In women with newly diagnosed cancer, data from 16 studies have shown that MRI prompts biopsy for additional lesions in 16\% of women, of which 66\% are confirmed to be additional cancer (PPV=66\%). Particularly in light of recent American Cancer Society guidelines recommending annual MRI screening for high risk women, estimated to affect up to 1.8 million women in the US, there is a clear and quickly growing need to improve the specificity of breast MRI in order to limit the number of unnecessary biopsies that will result from expanded use of this highly sensitive screening tool.

**DWI of the Breast**

Diffusion weighted imaging holds strong potential as an adjunct MRI technique for improving the specificity of conventional breast MRI. By measuring the mobility of water molecules in tissue, DWI indirectly assesses tissue microstructure and provides complementary information to DCE-MRI for lesion characterization. DWI is a short MRI sequence (< 5 minutes) that can be incorporated into a standard breast MRI protocol on clinical scanners. Numerous groups have demonstrated restricted water diffusion in breast malignancies and significant differences in ADC values of benign and malignant lesions. Further, recent single center studies report that ADC measures are complementary to DCE-MRI parameters for discriminating benign and malignant breast lesions and can increase the accuracy of conventional breast MRI assessment.

However, despite such promising findings from a variety of institutions, ADC measures have not been incorporated into clinical breast MRI interpretations or BI-RADS recommendations. Prior to widespread adoption of DWI for breast tumor assessment, well-controlled multi-center trials are required to validate the single center findings and define recommendations.

**Rationale for Selected Approach**

The techniques used to acquire DW images, including the choice of b-values, vary considerably across studies in the literature. There is also wide variation in image quality of breast DWI due to the frequency of inadequate fat suppression and other imaging artifacts. Furthermore, DWI data analysis techniques vary widely including post-processing to include noise filtering, image registration, methods for region of interest (ROI) measurement (sub-region versus whole tumor characterization) and ADC calculation (tumor versus normalized). As a result, there are considerable differences in the reported ADC values of similar breast pathologies using different techniques.

Our goal is to develop a standardized approach to breast DWI, identify optimal ADC thresholds for discriminating benign and malignant breast lesions, and investigate the potential of DWI for reducing false positives of breast MRI in a multi-center trial.

**STUDY OBJECTIVES/SPECIFIC AIMS**

**Primary Aim**
- To determine whether the Apparent Diffusion Coefficient (ADC), when used systematically in conjunction with conventional DCE-MRI, can reduce the biopsy rate by at least 20\% while maintaining sensitivity.

**Secondary Aims**
- To determine whether optimal ADC cutoffs are different for mass and non-mass lesion types;
- To determine whether site-generated ADC values differ significantly from those obtained by central review;
- To determine whether the use of a nonzero minimum b-value to reduce perfusion effects
in ADC calculation can increase the AUC for differentiating benign and malignant lesions;

- To determine whether the use of a normalized ADC measure (tumor/normal ratio) to account for inter- and intra-subject variations in water content and other factors can increase the AUC for differentiating benign and malignant lesions;
- To determine whether ADC with nonzero minimum b-value and/or normalized ADC can reduce the biopsy rate while maintaining sensitivity.

**Primary Endpoint**
Biopsy rate

**Secondary Endpoints**
False positive rate, area under the ROC curve, sensitivity, specificity, and positive predictive value.

**STUDY OVERVIEW**

This is a single arm multi-institution study with the primary objective of determining whether DWI can decrease the biopsy rate of conventional breast DCE-MRI. The study design incorporates observational analysis of DWI in women undergoing breast MRI. ADC values will be measured for breast lesions identified on DCE-MRI (BI-RADS 3, 4, or 5) to evaluate the ability to distinguish benign and malignant lesions based on ADC. We plan to recruit 100 women with breast lesions (BI-RADS 3, 4, or 5) identified by conventional breast DCE-MRI requiring either biopsy, surgical excision or short-interval imaging follow-up. We anticipate accrual for the study will take 12 months, with approximately 10 participating ACRIN-approved sites that acquire DWI in their standard clinical MRI protocol. Site qualification for study participation will require passing quality control (QC) requirements. At participating sites, all potentially-eligible participants will be informed of the study and, if interested, will be consented prior to undergoing clinical breast MRI to include a DWI scan. Sites will use a standardized acquisition sequence per the study protocol. At the time of interpretation, the site radiologists will record a BI-RADS assessment to determine study eligibility prior to reviewing DWI. Those with lesions identified on MRI as BI-RADS 3, 4, or 5 will be enrolled in the study. Participants who do not have lesions assessed as BI-RADS 3, 4, or 5 will not be enrolled in the study. Sites will measure the lesion and normal-appearing breast tissue ADC values, and all images, measures, and associated clinical and pathological data will be sent to the ACRIN Core Laboratory. All enrolled participants will be followed at 30 days, 6 months, and 12 months post-MRI. ACRIN will perform a centralized read of DWI to measure lesion ADC and normal tissue ADC values, with researchers blinded to lesion outcomes and site ADC measurements. Data analysis will then be performed to compare ADC values in benign and malignant lesions and address the study objectives.

**PARTICIPANT SELECTION/ELIGIBILITY CRITERIA**

Eligible participants are women 18 years or older who undergo a clinical breast MR examination (including both DCE and DWI scans) by which a previously undiagnosed lesion (BI-RADS 3, 4, or 5) is identified. Women undergoing high risk screening and local staging for a recently diagnosed breast cancer (in whom an additional lesion distinct from the known cancer is detected on MRI) may be the most common candidates, but others meeting the criteria will not be excluded. Outcomes (benign or malignant) will be determined for each study lesion by means of biopsy, surgical excision and/or follow-up assessment at 30 days, 6 months and 12 months after the MRI.
Inclusion Criteria
- Willing and able to provide written informed consent;
- 18 years of age or older;
- Successful completion of breast MR examination with DWI required by protocol;
- Undiagnosed breast lesion (BI-RADS 3, 4, or 5) identified on MRI. The BI-RADS assessment must refer to a focal finding within the breast (i.e. mass, non-mass, or focus) as opposed to diffuse processes (e.g. background parenchymal enhancement, skin thickening) or lesions outside the subcutaneous breast (e.g. axillary lymph nodes, focal skin lesions, osseous lesions, etc.).

Exclusion Criteria
- Participants with current or recent history (within 6 months prior to the MRI) of chemotherapy for cancer;
- Neoadjuvant chemotherapy between MRI and confirmation of lesion outcome (study lesions must be biopsied prior to undergoing any chemotherapy);
- Pregnant (if a female is of childbearing potential - defined as a pre-menopausal female capable of becoming pregnant - confirmation of pregnancy status per the site’s standard of practice should be done prior to MRI);
- Unwilling or not suitable to undergo MRI or use the contrast agent gadolinium. Sites will comply with their institutional standard policies and procedures for performance and assessment of conducting MRI and the use of gadolinium in their patients.

Inclusion of Women and Minorities
Women of all ethnic groups are eligible for this trial. Based on US 2011 Census ethnic and racial demographics, and in conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown below:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
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<td>17</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
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<td>83</td>
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<td><strong>Ethnic Category: Total of all participants</strong></td>
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<table>
<thead>
<tr>
<th>Racial Category</th>
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</thead>
<tbody>
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<td>American Indian or Alaskan Native</td>
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<tr>
<td>Asian</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Black or African American</td>
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<td>14</td>
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<tr>
<td>Native Hawaiian or other Pacific Islander</td>
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</tr>
<tr>
<td>White</td>
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<td>78</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all participants</strong></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

In order to target and recruit women from diverse ethnic communities, we will include sites from a range of geographic locations serving a variety of socioeconomic groups.
SITE SELECTION

Institution Requirements
The potential sites for this study are ACRIN-participating institutions that perform DWI as part of the clinical breast MRI protocol and meet qualifications for participating in this study. All sites must be either previously approved to participate in ACRIN clinical trials by having a General Qualifying Application (GQA) on file approved by the ACRIN Institutional Participants Committee (IPC), or submit a GQA for IPC review. In addition, each institution must submit a Protocol Specific Application (PSA), which documents that sites have the necessary personnel, equipment, and referral base to carry out the requirements specific to the ACRIN 6702 protocol.

Sites also must obtain ACRIN DWI qualification for the scanner(s) that will be used for scanning trial participants. In addition, test images of the breast DWI scan per protocol specifications must be reviewed and approved prior to participant enrollment.

Regulatory Requirements and Documentation
Prior to the recruitment of a patient for this study, investigators must be registered members of the Cancer Trials Support Unit (CTSU). Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status.

Each CTSU investigator or group of investigators at a clinical site must also obtain IRB approval for this protocol and submit IRB approval and the supporting documentation to the CTSU Regulatory Office before they can enroll patients.

All sites must have study-specific, initial full-board Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB overseeing the study for the site.

Requirements for ACRIN 6702 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on ACRIN 6702
- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- Site must meet institution requirements as listed above

STUDY PROCEDURES
Sites will recruit potential participants scheduled for a clinical breast MRI examination including both DCE and DWI scans. These participants should be consented for potential participation in the trial. Only participants with lesions deemed probably benign (BI-RADS 3) or malignant (BI-RADS 4 or 5) by conventional MRI will qualify for the study. After the potential participant has been deemed eligible, confirmed by conventional MR images (without DWI), sites will register the participant to the trial in Medidata Rave. Participants who do not have MRI-detected lesions assessed as BI-RADS 3, 4, or 5 are not eligible and will not be registered. Sites will comply with their institution’s IRB requirements in maintaining a screening log of consented potential participants.
Each site will maintain all documentation of the screening and eligibility assessments, as well as documentation for all clinical procedures, as related to the trial and study-related procedures for source verification.

### Study Procedures Table

<table>
<thead>
<tr>
<th>Study Procedure</th>
<th>VISIT 1: Screening/Eligibility</th>
<th>VISIT 2: 30 Day Follow-Up (± 3 days)</th>
<th>VISIT 3: 6 Month Follow-Up (± 4wks)</th>
<th>VISIT 4: 12 Month Follow-Up (± 4wks)</th>
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<tbody>
<tr>
<td>Informed Consent Form</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Screening/Eligibility Review</td>
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<td>Medical History</td>
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<td>MRI with DCE and DWI¹</td>
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<td>Clinical MRI Assessment to Determine Final Eligibility: BI-RAD 3, 4, or 5</td>
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<tr>
<td>ACRIN Participant Registration</td>
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<tr>
<td>Collection of Histopathology Report(s)²</td>
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<td>Follow-Up of All Study-Identified BI-RAD 3, 4, or 5 Lesions</td>
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<tr>
<td>AE Assessment</td>
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</tbody>
</table>

¹: DWI should be performed prior to contrast administration for clinical DCE-MRI and should be performed in the same examination.
²: When available.

### IMAGING PROTOCOL

#### Imaging Requirements and Parameters

**MRI Procedures:** All participating sites will use a standardized DWI acquisition sequence. The sequence will incorporate multiple b-values and good spatial resolution while maintaining adequate fat suppression and signal-to-noise. DWI will be acquired prior to DCE-MRI using a diffusion-weighted spin–echo echo planar imaging sequence. Scanning will be performed in the axial orientation, with diffusion gradients applied in three orthogonal directions to measure isotropic ADC. The sequence will employ parallel imaging (reduction factor ≥ 2) and fat suppression. The optimal technique for fat suppression (SPAIR, STIR, etc.) may vary between scanners. DWI will be performed using multiple b-values including 0, 100, and 800 s/mm².

**Magnet field strength:** There is no theoretical dependence of ADC on field strength, although differences may arise related to field inhomogeneity effects, signal-to-noise and severity of artifacts. Both 1.5 and 3 tesla field strengths will be allowed in ACRIN 6702, and identical QC criteria will be applied.

**Image Processing and Analysis:** ADC measures (in units mm²/s) will be performed in BI-RADS 3, 4, and 5 breast lesions identified on DCE-MRI. Sites will perform lesion ADC measurements according to the ROI measurement procedures described below. ADC maps generated from DW images and screen capture images showing ROI placement will be submitted in addition to originally acquired data to ACRIN Headquarters following each MRI exam.
**Lesion ADC measurement:** ADC measures will be performed by ROI by the site radiologist. An ROI will be drawn over the largest solid tumor region on DWI, with tumor size and location determined from corresponding DCE-MRI images. Areas of necrotic, cystic, or adipose tissue will be avoided by referencing to T1- and T2-weighted images and ADC maps in defining the ROIs. An additional ROI will be placed in a region of normal-appearing fibroglandular tissue for comparison. A screen capture will be saved in each case to illustrate ROI placement for reporting.

**Site Qualification and Quality Control:** Sites enrolling in ACRIN 6702 will be required to perform phantom QC testing and submit two DWI cases from human participants acquired using the multi-b value sequence outlined in the Imaging Manual. The DWI data from both QC and patient scans must meet specific quality criteria (e.g., artifacts, distortion, signal-to-noise ratio) for acceptance. Qualification must be performed for each scanner used for ACRIN 6702 participants and must be repeated after any major scanner upgrade or change of breast coil.

Regular quality-control (QC) scans will be performed at each site using a standardized phantom to evaluate consistent DWI performance. DWI scans for submitted study cases will be reviewed by the ACR Imaging Core on a regular basis for ongoing QC, and if artifacts or inconsistencies are identified the site will be contacted to help resolve the problem.

**ETHICAL CONSIDERATIONS**

This study is to be conducted according to International Conference of Harmonisation guidelines, U.S. federal regulations, standards of Good Clinical Practice, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study.

The investigator will provide ACRIN with the institution’s Federalwide Assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s) and copy(s) of annual renewal(s).

All potential participants invited to join this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study. The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the local IRB for approval and to ACRIN PDRC for review and filing.