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14. ABSTRACT The purpose of this postdoctoral training award is for the PI to be trained in every aspect of conducting a research breast cancer study in a clinical setting. This study aims to improve specificity of breast cancer detection by using a combined MRI/MRS protocol. In the past year, the first year of this award, the PI has laid the ground work for patient recruitment and data collection. The PI has constructed a breast phantom, drafted the IRB protocol, consent form and advertising pamphlet, been trained in MRI/MRS data acquisition, data analysis, consenting patients, and established working relationship with the involved radiologists and surgeons. Relevant preliminary data were published in the journal of radiology and presented in the Era of Hope 2005 – Department of Defense Breast Cancer Research Meeting. Data collection from human subjects will commence upon approval of the IRB protocol by the Army Surgeon General's Human Subjects Research Review Board.					
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Introduction

This is the annual report for the first year of a three-year Breast Cancer Research Program (BCRP) post-doctoral training grant, covering the period from June 2004 to June 2005.

The approved Statement of Work of this award is listed as the following:

- Task 1. Training in patient recruitment and MRI/MRS scanning protocol, Months 1-6:*
- a. Interacting with radiologists and surgeons at breast care center.*
 - b. Preparing advertising flyers and learning patient recruitment procedure.*
 - c. Learning consenting patients.*
 - d. Training in MR scanning of patients, including DCE MRI, ¹H MRS and perfusion MRI. Number of patients = 25.*
 - e. Training in MR data processing and correlation of MR data with biopsy results*
- Task 2. Extensive evaluation of the sensitivity and specificity of the proposed MRI/MRS protocol in detection of breast malignancy, Months 7-36:*
- a. Scanning 125 patients with the MRI/MRS protocol.*
 - b. Creating and maintaining data base for MR data and biopsy results.*
 - c. Coordinating between research subjects and their physicians in regards of clinical and research matters related to the study.*
 - d. Analyzing MR data, correlating MR results with biopsy results, computing overall sensitivity and specificity of the MR protocol in detection of breast malignancy.*
 - e. Preparing for publication of research results.*
 - f. Fine-tuning and optimizing the procedure of MR data acquisition and processing, establishing a clinically practical MR protocol with improved specificity for diagnosis of breast cancer.*

For the first year, we have accomplished Task 1 and more, except that we were unable to study patients under this grant award. As of July 2005, the IRB protocol for this project is still pending approval by the Army Surgeon General's Human Subjects Research Review Board. We expect the IRB to be approved by DOD in 3-4 months. With a vast patient pool at Stony Brook University, we will have no difficulty in meeting the goal of studying 150 patients with suspicious breast lesions by averaging two MRI/MRS scans per week.

Body

With the help of the mentor, Dr. Wei Huang, the collaborator, Dr. Paul Fisher, and the DOD representatives, the PI has been working with 100% effort on this project. The following progress has been made:

1. The PI and Dr. Fisher (Breast Radiologist, collaborator) have had bi-weekly meetings with the breast surgeons at the Stony Brook University Hospital to update the progress of the study and to set up the patient recruitment routines for this study. As soon as we obtain the final IRB approvals from both DOD and Stony Brook University, we will distribute the pamphlet in the offices of the breast surgeons and radiologists and the patient recruitment will start immediately. Since the MR protocol has already been set up and tested successfully, the data collection process will also commence.
2. The preliminary data presented in the application for this award were published in the journal of RADIOLOGY in August 2004 (1, appendix), entitled "Detection of Breast Malignancy: Diagnostic MR Protocol for Improved Specificity". The mentor on this project, Dr. Wei Huang, is the first and senior author. The PI is a co-author.
3. The preliminary data were also presented by the PI as both poster and platform presentations at the Era of Hope 2005 – Department of Defense Breast Cancer Research Meeting in Philadelphia, June 2005 (2, appendix). The abstract of the presentation is attached.
4. A breast phantom was constructed, which is consisted of vegetable shortenings and three ping-pong balls filled with 2, 5 and 10 mM choline chloride solutions, respectively. This phantom will be used to test the pulse sequences for dynamic contrast enhanced MRI, proton MR spectroscopy (MRS), and perfusion MRI, which are the main components of the proposed MR protocol for breast cancer diagnosis. This phantom will also serve the purposes of assuring MR scanner quality control and study reproducibility.
5. The preliminary data were collected using a 1.5T Marconi Edge scanner. In the summer of 2004, the 1.5T Marconi instrument was replaced with a 1.5T Philips Intera scanner at the Stony Brook University Hospital. We have successfully implemented the original pulse sequences that were used to collect the preliminary data and proposed for this project onto the new Philips scanner with the same data acquisition parameters. Tests of these sequences on the breast phantom have been successfully performed.
6. We have drafted an IRB protocol, consent form, and an advertising pamphlet for this project which have recently (July 2005) been approved by the local IRB committee. The PI is currently corresponding with Dr. Inese Beitins of DOD to further revise the language of the above mentioned documents so that our IRB protocol will meet the standard required by the Army Surgeon General's Human Subjects Research Review Board. The IRB protocol, consent form and advertising pamphlet are attached as appendices.
7. Under the local IRB that was used to collect the preliminary data that were used to apply for the grant, the PI has been trained by the mentor (Dr. Huang) on the

details of MRI/MRS data collection and analysis, from positioning patient on the MRI scanner table to analyzing proton spectrum. The PI has scanned more than 30 patients with the proposed MRI/MRS protocol in the past year. The PI has also worked together with Dr. Fisher to learn how to interact with patients who have suspicious breast lesions and to consent them for research study. The PI has learned how to securely access patients' clinical data base and obtain biopsy results, and how to calculate sensitivity and specificity based on the correlations between MR data and biopsy results.

Key Research Accomplishments

- Learned how to work with a team of radiologists and surgeons to conduct clinical research
- Learned how to collect MRI/MRS data in a clinical setting
- Learned how to analyze MR data and correlate with biopsy results
- Learned how to consent patient for clinical research
- Drafted IRB protocol, consent form and advertising pamphlet.
- Constructed a breast phantom for MR sequence testing and quality control
- Transferred the proposed MRI/MRS protocol from a 1.5T Marconi scanner to a 1.5T Philips scanner
- Contributed as a co-author in the publication of the preliminary data in the journal of Radiology
- Presented an abstract as both poster and platform presentations at the Era of Hope 2005 – Department of Defense Breast Cancer Research Meeting in Philadelphia, June 2005.

Reportable Outcomes

There is no reportable outcome from the patient studies, as the relevant IRB protocol is still pending approval by the Army Surgeon General's Human Subjects Research Review Board. However, we have accomplished the following in preparation for data collection from human subjects:

- Constructed a breast phantom for MR sequence testing and quality control
- Transferred the proposed MRI/MRS protocol from a 1.5T Marconi scanner to a 1.5T Philips scanner

As soon as the IRB protocol is approved by DOD, we will be able to start patient studies immediately under the support of this grant.

Conclusions

In the first year, we have laid the ground work for patient recruitment and data collection. The PI has drafted the IRB protocol, consent form and advertising pamphlet, been trained in MRI/MRS data acquisition, data analysis, consenting patients, and established working relationship with the involved radiologists and surgeons. As soon as the relevant IRB protocol is approved by the local IRB committee and the Army Surgeon General's Human Subjects Research Review Board (expected to be in late 2005), we will start human subject accrual and data collection.

References

1. Huang W, Fisher PR, Dulaimy K, **Tudorica LA**, O’Hea B, Button TM. Detection of breast malignancy: diagnostic MR protocol for improved specificity. *Radiology* 2004; 232: 585-591.
2. **Tudorica LA**, Fisher P, Dulaimy K, Huang W. Clinically practical magnetic resonance imaging/spectroscopy protocol for improved specificity in breast cancer diagnosis. Era of Hope 2005 – Department of Defense Breast Cancer Research Meeting, Philadelphia, PA; June 2005.

Appendices

Paper, Radiology 2004; 232: 585-591

Abstract, Era of Hope 2005 – Department of Defense Breast Cancer Research Meeting, Philadelphia, PA; June 2005.

IRB protocol

Consent form

Advertising pamphlet

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Abbreviations:

BIRADS = Breast Imaging Reporting and Data System
 Cho = choline-containing compounds
 DCE = dynamic contrast enhanced

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Detection of Breast Malignancy: Diagnostic MR Protocol for Improved Specificity¹

PURPOSE: To prospectively determine if a combined magnetic resonance (MR) protocol that includes T1-weighted dynamic contrast agent-enhanced (DCE) MR imaging, hydrogen 1 (¹H) MR spectroscopy, and T2*-weighted perfusion MR imaging improves specificity in the diagnosis of breast cancer.

MATERIALS AND METHODS: The combined MR imaging–MR spectroscopy protocol was performed in 50 patients after positive findings at mammography but prior to biopsy. Single-voxel proton MR spectroscopy and perfusion MR imaging were conducted only if DCE MR images showed rapid contrast enhancement in the lesion. Biopsy results were used as the reference for comparison with MR results and for calculation of sensitivity and specificity in the detection of breast malignancy.

RESULTS: DCE MR imaging alone showed 100% sensitivity and 62.5% specificity. The specificity improved to 87.5% with the addition of ¹H MR spectroscopy and to 100% with the further addition of perfusion MR imaging. Twenty-eight patients underwent both MR spectroscopy and perfusion MR imaging. Two patients underwent MR spectroscopy but declined to undergo perfusion MR imaging. The remaining 20 patients had negative results at DCE MR imaging and therefore did not undergo the additional examinations.

CONCLUSION: The combined MR protocol of DCE MR imaging, ¹H MR spectroscopy, and perfusion MR imaging has high sensitivity and specificity in the diagnosis of breast cancer.

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Conventional mammography has been the primary screening and diagnostic tool for breast cancer for more than 20 years. While mammography has high sensitivity for malignancy, particularly in breasts with low-density tissue, it has poor specificity. The false-positive rate at mammography is typically reported in the range of 60%–80%. Because there is such a high false-positive rate, biopsies are often performed unnecessarily and, in a small percentage of patients, may result in complications that can include hemorrhage, abscess, or pain, or result in missed lesions. Complications may also result from general anesthesia induced in patients who are unsuited for local anesthesia, leading to unnecessary anxiety and expense. Therefore, to reduce the number of unnecessary interventions, there is a need for additional evaluation following a positive result at mammography.

In recent years, results of many studies have shown that the noninvasive techniques of magnetic resonance (MR) imaging have strong potential to improve sensitivity and specificity in the diagnosis and evaluation of breast cancer. MR imaging techniques, particularly those involving the administration of contrast agents, have been performed in selected patients for the diagnosis and evaluation of breast tumors. Dynamic contrast agent-enhanced (DCE) MR imaging, in which the passage of a contrast agent through mammary tissue is monitored after a bolus injection, is now an integral part of a proposed standard diagnostic protocol for breast cancer (1) when MR imaging is being performed. The advantages of this approach stem from the observation that even the qualitative time

courses of MR imaging signal intensity in a region of interest exhibit reproducible patterns that appear to be capable of enabling discrimination between benign and malignant lesions and even between different types of malignancy (2,3). Although the results of investigations have varied greatly, the sensitivity of T1-weighted DCE MR imaging for breast malignancy has been consistently reported to be excellent (88%–100%) (4–12). Qualitative analyses of the temporal changes in signal intensity after bolus contrast agent injection have shown that malignant tissues generally enhance early compared with benign tissue, with a large and rapid increase in signal intensity. This is presumably caused by the inherent leakiness of the tumor vasculature and/or by increased vascularization. However, the reported specificity of DCE MR imaging has been variable, ranging from 37% to 97% (4–13). Although there is good evidence that carcinomas tend to enhance faster and wash out earlier than do benign tissues, there are exceptions to this pattern, and there is considerable overlap in response between benign and malignant lesions. For example, fibroadenomas sometimes demonstrate an enhancement pattern similar to that of invasive cancer (14).

There exist a plethora of semiquantitative and quantitative analysis methods that have been applied to imaging data in an attempt to differentiate benign from malignant breast lesions (4–9,13,15,16). However, these methods assume an effectively infinitely fast rate of equilibrium transcytolemmal water exchange (equivalent to assuming that the linear relationship between $R1$ [$1/T1$] and contrast agent concentration holds) during contrast agent bolus passage through breast tissue; this assumption leads to substantial underestimation of pharmacokinetic parameters (17,18). Furthermore, quantitative methods require a lengthy process of data analysis and are not quite practical for breast cancer diagnosis in a clinical setting.

T2*-weighted perfusion MR imaging (19–22) and hydrogen 1 (1H) MR spectroscopy (23–26) have also been examined as promising tools for improving specificity in the detection of breast malignancy. The former technique is based on measurement of the increased perfusion that is typical in malignant tumors; the latter is based on the detection of the 1H nuclear MR of choline-containing compounds (Cho), which, when enhanced, serves as the marker of active tumors (27).

The purpose of this study was to prospectively determine if a combined MR protocol that includes T1-weighted DCE MR imaging, 1H MR spectroscopy, and T2*-weighted perfusion MR imaging improves specificity in the diagnosis of breast cancer.

MATERIALS AND METHODS

Patients

Fifty patients (age range, 34–71 years; mean age, 50.2 years) with positive diagnoses at mammography were recruited to participate in this study. Patients included women whose results on mammograms were scored, according to the Breast Imaging Reporting and Data System (BIRADS), as either BIRADS 4 (suspicious abnormality) or BIRADS 5 (highly suggestive of malignancy). The most important criterion for recruitment was that patients be scheduled to undergo excisional or core biopsies, on the basis of their positive mammographic findings, within 1 week following the MR examinations. All 50 patients met this criterion.

The MR examination protocol included T1-weighted DCE MR imaging, single-voxel 1H MR spectroscopy, and T2*-weighted perfusion MR imaging. In preparation for this study, a retrospective analysis was performed (results were not published). Clinical DCE MR imaging data (acquired with the same protocol used in our study) and pathologic results were compared in more than 30 patients who had mammographic scores of BIRADS 4 or BIRADS 5 at our institution. Results of this retrospective examination showed there were no false-negative findings when using the DCE MR imaging protocol alone. Therefore, to determine if our combined MR protocol would improve specificity in breast cancer diagnosis, 1H MR spectroscopy and perfusion MR imaging were performed only after positive findings were observed at DCE MR imaging. Prior to the MR examinations, informed consent was obtained from the patients once the nature of the procedures had been fully explained. This MR imaging–MR spectroscopy study was conducted with the approved institutional review board protocol.

MR Examinations

The MR imaging and MR spectroscopy data for all 50 patients were acquired by using a 1.5-T whole-body MR imager (Edge; Marconi Medical Systems, Cleveland, Ohio). The body coil was used as

the transmitter, and a dedicated four-channel phased-array breast coil (USA Instruments, Aurora, Ohio) was used as the receiver.

After pilot imaging had been performed, T1-weighted DCE MR imaging was performed by using a three-dimensional spoiled gradient-recalled echo pulse sequence to acquire eight frames (data sets) of sagittal volumetric images continuously over time, spatially covering the whole breast. Parameters were as follows: 9.0/3.8 (repetition time msec/echo time msec), 30° flip angle, 5-mm section thickness, 24-cm field of view, and 64×256 matrix size. Each frame of images typically contained 18–26 sections, depending on the breast size; this resulted in an acquisition time of 10.4–15.0 seconds for each frame (the temporal resolution of the DCE MR imaging study). At the start of the second frame data acquisition, the contrast agent (gadodiamide, Omniscan; Nycomed, Princeton, NJ) was delivered intravenously as a dose of 0.1 mmol per kilogram of body weight, at a rate of 2 mL/sec, by using an MR-compatible programmable power injector (Spectris; Medrad, Indianola, Pa); this was followed with a 15-mL flush of isotonic saline solution. The total injection time was less than 15 seconds. The first frame of the DCE MR images was subtracted from each frame of images by using commercial image-processing software (Breast Uptake; Marconi Medical Systems).

From the subtracted MR images, if contrast enhancement was observed in later frames in the lesion with positive mammographic diagnosis, a region of interest was drawn encompassing the enhanced lesion, and a plot of signal intensity-versus-image frame was obtained. Typically in this study, signal intensity that reached a plateau by the fourth frame was defined as a positive finding for malignancy at DCE MR imaging. If there was continuously increasing signal intensity in the enhanced region through eight frames of data acquisition or if there was no enhancement at all, this was defined as a negative finding. In case of lesion enhancement, two authors (either W.H. and K.D. or W.H. and P.R.F.) drew the region of interest independently to confirm the shape of the signal intensity curve. The study protocol was discontinued in patients with negative findings at DCE MR imaging. Patients with positive findings continued the protocol, undergoing further examination with 1H MR spectroscopy and perfusion MR imaging.

A single-voxel proton spectrum was

collected from the enhanced lesion with a point-resolved spectroscopic pulse sequence (2,000/135; 128 signals acquired). The subtracted DCE MR sections covering the enhanced lesion were used as pilot images for placement of the rectangular MR spectroscopy voxel, which encompassed the entire enhanced lesion area. The voxel size ranged from 1.6 to 9.0 cm³, depending on the size of the enhanced lesion that was being examined. With the commercial MR spectroscopy data-processing software (Marconi Medical Systems), the raw spectral data were processed by using 3-Hz line broadening, Fourier transformation, and phase and baseline corrections. The detection of an apparent Cho resonance peak at 3.23 ppm (signal-to-noise ratio, ≥ 2) was defined as a positive finding at MR spectroscopy, and a negative finding was defined otherwise.

After MR spectroscopy, T2*-weighted perfusion MR imaging was performed in a single 5-mm sagittal section containing the enhanced lesion. The location of this section was chosen to be approximately through the center of the enhanced lesion and was based on the analysis of the DCE MR imaging data. A fast low-angle shot sequence was employed for perfusion imaging, and parameters were as follows: 54/35, 10° flip angle, 24-cm field of view, 92 × 256 matrix size, and 40 frames. The temporal resolution of the data acquisition was about 5 seconds. Intravenous bolus injection of gadodiamide (0.1 mmol per kilogram of body weight) was carried out at 4 mL/sec at the beginning of the sixth frame data acquisition. The perfusion MR data were processed (PROPAK software; Marconi Medical Systems) by using the standard area-under-the-curve algorithm (28–32) to construct the relative blood volume map that corresponded to the breast image section. The MR signal intensity-versus-time curve was converted to the $\Delta R2^*$ -versus-time curve based on the following relationship: $\Delta R2^* = \Delta(1/T2^*) = -(1/TE) \ln(SI_t/SI_0)$, where TE is echo time, SI_t is the signal intensity at time t , and SI_0 is the baseline signal intensity prior to contrast material injection. The $\Delta R2^*$ -versus-time curve was analyzed by using gamma-variate fit, and the area under the curve was computed that was proportional to blood volume. When compared with enhancement in normal breast tissue on the same image section, the observation of striking enhancement in the lesion area (at least a fivefold increase in signal intensity when compared with normal breast tissue) on the relative breast blood

volume map was defined as a positive finding at perfusion MR imaging. No apparent enhancement (no enhancement at all or less than a fivefold increase in signal intensity when compared with normal breast tissue) was defined as a negative finding.

Statistical Analysis

The sensitivity and specificity in the detection of breast malignancy were calculated for each MR examination method and for the combination of methods; these calculations were based on the correlation of the MR data with the biopsy results used as the reference standard. The positive or negative findings at MR examinations were classified as true or false in comparison with pathologic findings. Sensitivity is the probability that results at imaging are positive in those patients who have the disease. Sensitivity is defined as $[TP/(TP + FN)] \cdot 100$, where TP is the total number of true-positive results and FN is the total number of false-negative results. Specificity is the probability that results at imaging are negative in patients who do not have the disease. Specificity is defined as $[TN/(TN + FP)] \cdot 100$, where TN is the total number of true-negative results and FP is the total number of false-positive results.

RESULTS

All 50 patients successfully underwent DCE MR imaging. Twenty of the 50 patients had negative findings at DCE MR imaging and did not undergo further examination at ¹H MR spectroscopy or perfusion MR imaging. Among the 30 patients who had positive findings at DCE MR imaging, two underwent MR spectroscopy but declined perfusion MR imaging because they were unwilling to receive additional contrast material injections. Thus, 28 of 30 patients underwent both MR spectroscopy and perfusion MR imaging.

In 39 of 50 patients, there was contrast enhancement in the suspicious lesions at DCE MR imaging. As an example, Figure 1a shows a sagittal DCE MR image of the breast obtained in a patient with a suspicious lesion at mammography that was later pathologically proved to be malignant. This image was the result of subtraction of a first frame image from the fourth frame image at the same location. The contrast-enhanced lesion is clearly visible on this image, and the placement of the MR spectroscopy voxel, encompassing the enhanced area, is also dem-

onstrated. Figure 1b shows the graph of signal intensity-versus-image frame from the enhanced lesion area in this patient. The curve rises rapidly and reaches a plateau by the fourth frame, which implies positive findings at DCE MR imaging. Figure 1c shows a DCE MR image similar to the one in Figure 1a, although this image was obtained in another patient. The lesion was clearly enhanced following contrast administration; however, the curve of signal intensity-versus-image frame (Fig 1d) of this lesion displays continuous signal intensity increase, which implies negative findings at DCE MR imaging in this patient. The lesion was later confirmed to be benign at biopsy. Of 20 patients with negative DCE MR imaging findings, 11 had images with no contrast enhancement at all. Typically, when contrast enhancement was observed in the lesion, curve shapes like those shown in Figure 1b and 1d were used to distinguish positive from negative findings (in nine patients) at DCE MR imaging.

Among the 30 patients who underwent MR spectroscopy, findings were positive in 22 patients. Figure 2a shows a representative magnified proton spectrum collected from the contrast-enhanced lesion area in a patient who had positive findings at DCE MR imaging. A Cho peak was detected with a signal-to-noise ratio greater than 2, which indicated positive findings at ¹H MR spectroscopy. The lesion was later pathologically proved to be malignant. As an example of negative findings at MR spectroscopy, Figure 2b shows a magnified proton spectrum in a patient for whom the biopsy result was negative. No apparent Cho peak was detected; there was only noise-level signal intensity at the Cho resonance frequency (3.23 ppm).

In 19 patients, findings at perfusion MR imaging were positive. As an example, Figure 3a shows a relative blood volume map of the breast, which was obtained at perfusion MR imaging in the same patient whose DCE MR image is shown in Figure 1a. Strong rim enhancement was observed in the lesion area on the map, revealing high vascularity of the tumor and positive findings at perfusion MR imaging. Figure 3b shows a representative blood volume map for negative findings at perfusion MR imaging (results were negative in nine patients). In the lesion area (indicated by arrow), where contrast enhancement was seen at DCE MR imaging, there was no obvious enhancement in comparison with normal breast tissue on the map. The biopsy

results obtained in this patient revealed a benign breast lesion.

MR imaging, MR spectroscopy, and pathologic findings in the 50 patients are summarized in the Table. The pathologic results were used as the reference standard. There were no false-negative findings at DCE MR imaging (all 20 patients with negative findings at DCE MR imaging had negative pathologic results), thus showing a 100% sensitivity for this method, or $[18/(18 + 0)] \cdot 100$. Twelve patients with positive findings at DCE MR imaging had benign lesions at biopsy, which resulted in a 62.5% specificity for this method, or $[20/(20 + 12)] \cdot 100$. Four patients who underwent ^1H MR spectroscopy had false-positive findings, which improved the specificity of our protocol in the detection of breast malignancy to 87.5%, or $[28/(28 + 4)] \cdot 100$. With the further consideration of perfusion MR imaging results (the two patients who declined to continue the study were excluded), if we consider one or two negative findings at both MR spectroscopy and perfusion MR imaging to be "final negative" with the combined MR protocol, there were no false-positive findings, and the specificity was further improved to 100%, or $[30/(30 + 0)] \cdot 100$.

DISCUSSION

Our results are consistent with those of previous studies (4–13); the results of our study demonstrate that DCE MR imaging has very high sensitivity for breast cancer diagnosis, but its specificity is rather unsatisfactory. Because of the high false-positive rate at conventional mammography and the noninvasive nature of MR procedures, it is very important to search for MR diagnostic protocols for breast cancer that have high specificity but are also clinically practical. The results of our study showed that the combined MR imaging–MR spectroscopy protocol, which consisted of DCE MR imaging, ^1H MR spectroscopy, and perfusion MR imaging, had 100% specificity in the detection of breast malignancy. It therefore possesses the potential to be used as a standard screening tool following positive mammographic diagnosis, to avoid the performance of unnecessary biopsy procedures. The MR techniques used in this protocol are now available on some commercial MR imagers and can be easily implemented with standardized data acquisition parameters. This grants an advantage to larger clinical trials of this method, as the MR data can be rigorously

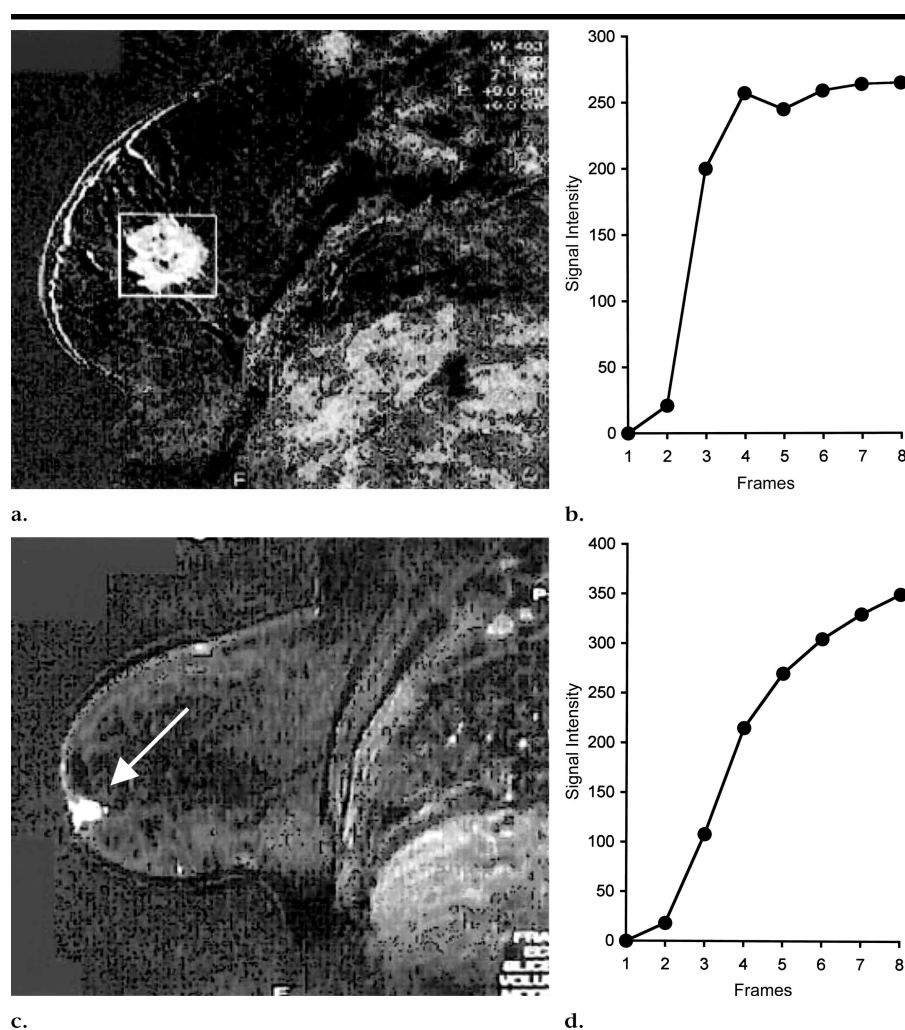


Figure 1. (a) Sagittal DCE MR image in a patient (age, 55 years) with a pathologically proved malignant breast tumor. The image was obtained with subtraction and a spoiled gradient-recalled-echo sequence (9/3.8, 30° flip angle). The rectangular box encompassing the enhanced lesion demonstrates the voxel placement for the single-voxel ^1H MR spectroscopy examination. (b) Plot of signal intensity-versus-frame number obtained in the enhanced lesion area shown in a. The curve rose rapidly following contrast injection, reaching plateau by the fourth frame. (c) The same type of image as in a, obtained in a patient (age, 50 years) with a pathologically proved benign breast lesion. Contrast enhancement was seen in the lesion (arrow). (d) Plot of signal intensity-versus-frame number obtained in the enhanced lesion area shown in c. The curve rose continuously through the time course of DCE MR data acquisition.

compared among different clinical sites. The total imaging time, including all three sequences, is usually less than 40 minutes, and the procedures are tolerable for patients. The total contrast agent dose used is no more than 0.2 mmol per kilogram of body weight, which is a dose well below the limit approved by the U.S. Food and Drug Administration. All 50 patients whom we studied underwent successful DCE MR imaging and had no complaints. Only two patients who had positive findings at DCE MR imaging declined to undergo perfusion MR imaging. Furthermore, this is a relatively qualitative protocol and there is no complicated

quantitative data analysis involved. Therefore, we believe that this combined MR imaging–MR spectroscopy protocol is practical for breast cancer diagnosis in clinical settings.

Despite the exciting progress that has been made in DCE MR imaging methods for breast cancer diagnosis, based on the characteristics of the time course of signal intensity change following bolus contrast media injection, there have been considerable difficulties with reproducibility from one MR imaging acquisition or pulse sequence to another and from site to site. Because of the variable results, no single standardized and gen-

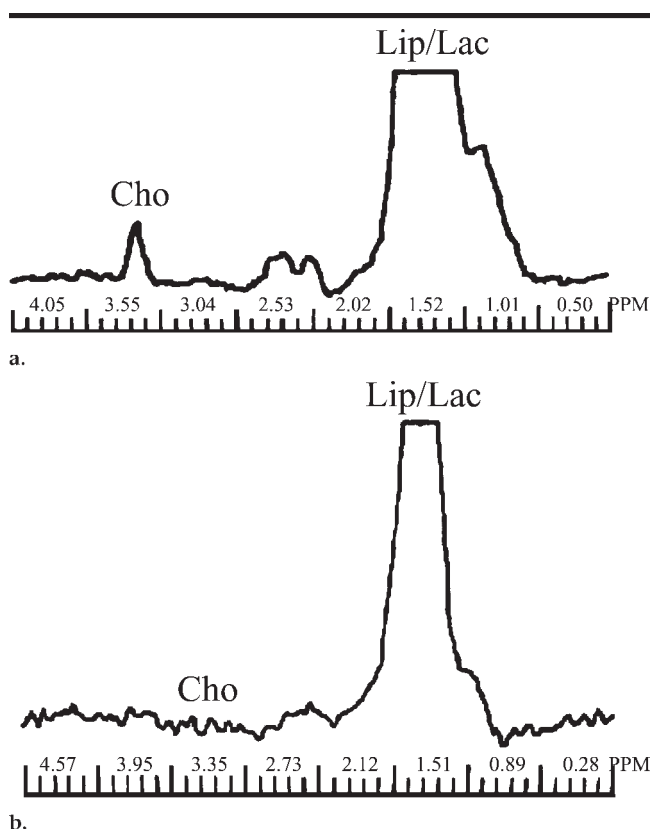


Figure 2. Magnified proton spectra obtained with a point-resolved spectroscopic sequence (2,000/135). (a) Spectrum obtained from the contrast-enhanced lesion area in a patient (age, 48 years) with a pathologically proved malignant breast tumor. An apparent Cho peak was detected at 3.23 ppm with a signal-to-noise ratio greater than 2. (b) Spectrum obtained from the contrast-enhanced lesion area in a patient (age, 59 years) with a pathologically proved benign breast lesion. No Cho peak was detected, and there was only noise-level signal at 3.23 ppm. *Lac* = lactate, *Lip* = lipid.

erally accepted technique has emerged for DCE MR imaging. This has caused difficulties in making meaningful comparisons between different cancer types and between data from different imaging sites (33,34). There are discrepancies with regard to sequence parameter choices, numbers of sections, speed of acquisition, and dose of contrast medium; these discrepancies are based on available hardware and software, clinical indications, desired results, and personal experience. Therefore, it is desirable to perform quantitative analysis of the DCE MR imaging data to extract fundamental pathophysiologic quantities, such as microvascular perfusion and permeability of the breast lesion. These values are independent of MR data acquisition methods and parameters and may be used to differentiate malignant from benign breast lesions. Most semiquantitative and quantitative DCE MR data analysis methods employ the two-compartment Kety-

Schmidt model (17,35) to compute pharmacokinetic parameters, which assumes an effectively infinitely fast rate of equilibrium transcytolemmal water exchange and, thus, a linear relationship between R_1 and tissue contrast concentration during bolus contrast agent passage through breast lesions. However, these assumptions do not always reflect the actual physiologic environment, given the inhomogeneous nature of tumors, and lead to substantial underestimation of the pathophysiologic quantities (17,18). As a result, there have been no clearly defined thresholds for pathophysiologic quantities that can be used to differentiate benign from malignant breast tumors. Another drawback of quantitative analysis is that the data processing is complicated and lengthy, which may delay the diagnostic process. Also, the results of quantitative analysis may be more difficult to understand and interpret. At this time and in the near future, qualitative MR

protocols with high sensitivity and specificity, such as the one we used for this study, may be the tools of choice for breast cancer diagnosis in clinical practice.

The target of MR data collection was well defined in this study; it was the breast lesion with a positive diagnosis based on conventional mammography. The lesion could be easily located on MR images according to geometric information on mammograms. In clinical practice, however, there are other complications to take into account when using this combined protocol of DCE MR imaging, ^1H MR spectroscopy, and perfusion MR imaging, such as a patient's menstrual cycle or the presence of multiple enhancing lesions. It has been shown (36,37) that both diffuse and nodular contrast enhancement of breast parenchyma can occur at DCE MR imaging during all phases of the menstrual cycle, especially during week 1 and week 4. There is less enhancement during weeks 2 and 3, especially during week 2. Since the breast lesion of interest was predefined in our study, menstrual cycle was not an issue of concern. If this breast MR protocol is to be employed for clinical purposes, we believe examination should be scheduled for the 2nd week of the patient's cycle, whenever possible, to avoid potential complications. Although the DCE MR imaging technique involves the use of a three-dimensional sequence to collect data in the whole breast, the MR spectroscopy and perfusion MR imaging techniques used in this study are limited to data collection from one contrast-enhanced lesion and one image section containing the enhanced lesion, respectively. In reality, multiple contrast-enhanced lesions are often observed at different locations in one breast. In such cases, multisection or three-dimensional MR spectroscopic imaging techniques and multisection echo-planar MR imaging techniques are desirable to measure Cho level and relative blood volume in all the enhanced lesions. The echo-planar MR imaging method (21) enables data collection in the whole breast while maintaining or even shortening the acquisition time in comparison with that of the perfusion MR imaging method used in this study. There may be an extra 10–15 minutes required for MR spectroscopic imaging data acquisition, compared with the acquisition time of single-voxel MR spectroscopy. The possibility of using the MR spectroscopic and echo-planar MR imaging sequences in our meth-

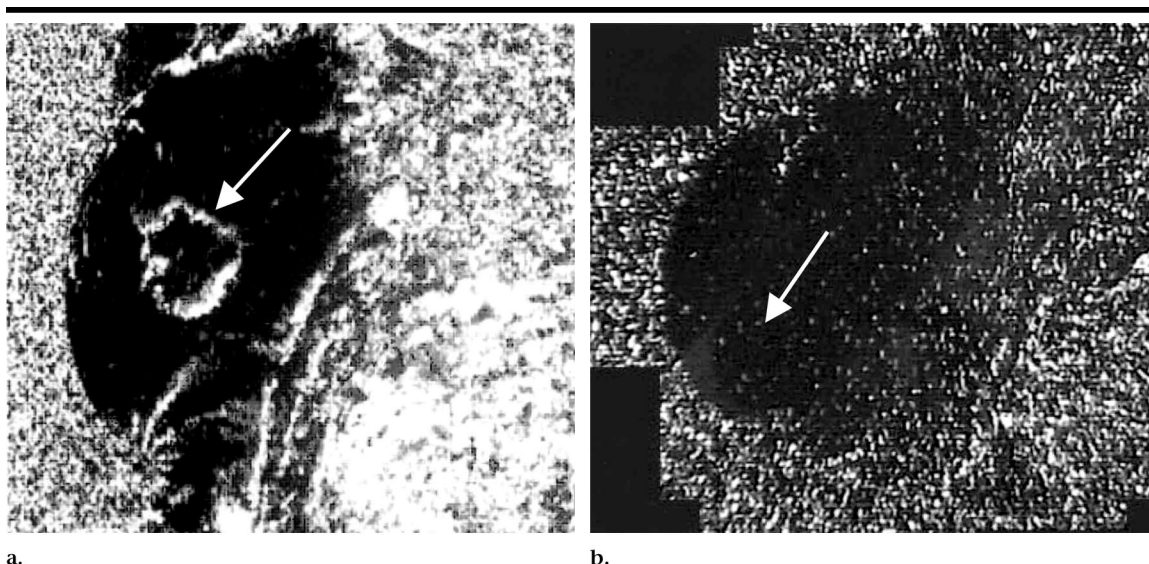


Figure 3. Relative breast blood volume maps reconstructed from the single-section perfusion MR images (fast low-angle shot sequence, 54/35, 10° flip angle). (a) Image obtained in the same patient as in Figure 1a. Striking rim enhancement (arrow) is clearly visible in the lesion area on the map, compared with normal breast tissue. (b) Image obtained in a patient (age, 42 years) with a pathologically proved benign breast lesion. The lesion was contrast enhanced at DCE MR imaging. No enhancement was observed in the lesion (arrow), compared with normal breast tissue.

ods for whole breast study is being investigated.

A limitation of this study was the patient population chosen. All patients had positive findings at mammography with either possible malignancy or a high probability of malignancy. To determine if this MR imaging–MR spectroscopy protocol may potentially be used as a standard screening tool for the general patient population following positive mammographic diagnosis but prior to biopsy, we hope to conduct a study among patients whose positive ratings at mammography are lower than BIRADS 4 and BIRADS 5.

Results of one study (19) showed that the addition of T2*-weighted perfusion MR imaging to a DCE MR imaging study substantially improved specificity in the diagnosis of breast cancer, which is consistent with our findings. In that study, there was an interval of about 15 minutes between T1-weighted DCE MR imaging and T2*-weighted perfusion MR imaging to allow sufficient time for washout of the contrast agent injected during DCE MR imaging. Since the MR signal changes in opposite directions for these two techniques, excessive residual contrast material from the DCE MR imaging procedure will severely compromise the robustness of the signal change during bolus contrast material passage at perfusion MR imaging. In our experience, patients usually feel anxious and restless in the MR imager during idling time. This may lead to body movement and cause misplace-

Findings at DCE MR Imaging, MR Spectroscopy, and Perfusion MR Imaging in Patients with Breast Lesions

No. of Patients	DCE MR Imaging	MR Spectroscopy	Perfusion MR Imaging	Pathologic Evaluation
20	Negative	NA*	NA*	Benign
18	Positive	Positive	Positive	Malignant
7	Positive	Negative	Negative	Benign
2	Positive	Positive	Negative	Benign
1	Positive	Negative	Positive	Benign
2	Positive	Positive	NA†	Benign

Note.—Findings are scored as positive or negative for malignancy. NA = not applicable.

* The MR protocol was discontinued due to negative findings at DCE MR imaging.

† The MR protocol was discontinued at the patient's request.

ment of the image section at single-section perfusion MR imaging. In our study, the addition of MR spectroscopy (about a 15-minute examination) between DCE MR imaging and perfusion MR imaging had the following advantages: (a) It allowed us to obtain more information to improve specificity in the detection of breast malignancy, (b) it allowed time for the washout of contrast agent, and (c) it made patients more at ease and thereby reduced the possibility of body movement. However, there is a limitation to MR spectroscopy. Because of the low signal-to-noise ratio and the impracticality of increasing the number of signals acquired and thus lengthening the imaging time, the MR spectroscopy data for lesions smaller than 1 cm³ are usually not reliable. Therefore, the diagnosis of small

lesions needs to be based on data obtained at DCE MR imaging and perfusion MR imaging. In our study, the patients with false-positive findings at MR spectroscopy all had pathologically proved fibroadenomas. It appears, on the basis of our results, that the false-positive findings at MR spectroscopy can be corrected by taking perfusion MR imaging data into account.

In conclusion, results of this study in 50 patients with positive mammographic findings showed that a combined protocol of T1-weighted DCE MR imaging, ¹H MR spectroscopy, and T2*-weighted perfusion MR imaging had high sensitivity and specificity in the diagnosis of breast cancer. We believe this protocol is easy to implement at clinical MR imaging sites and has the potential to be used as a tool

to help prevent unnecessary biopsies following positive mammographic diagnosis.

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CLINICALLY PRACTICAL MAGNETIC RESONANCE IMAGING/SPECTROSCOPY PROTOCOL FOR IMPROVED SPECIFICITY IN BREAST CANCER DIAGNOSIS

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Conventional mammography is known to have high false positive rate (60-80%) in detection of breast malignancy, resulting in unnecessary biopsies. The increasingly popular dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) technique demonstrated high sensitivity (88-100%), but rather variable specificity (37-97%) in diagnosis of breast cancer. In this study, a combined MRI/MR spectroscopy (MRS) protocol including DCE MRI, ^1H MRS, and perfusion MRI was used to examine patients with suspicious breast lesions. By correlating MR data with pathology results, we sought to determine if this clinically practical MRI/MRS protocol improves the specificity in detection of breast malignancy.

48 patients with positive mammography findings were recruited to participate in this MR study thus far. Biopsy was performed after but usually within a week of the MR examination. The MRI/MRS protocol was conducted with a 1.5 T MR scanner. For DCE MRI, 8 series of sagittal volumetric images of the whole breast with suspicious lesions were acquired with a temporal resolution of about 15 sec. Gadolinium-based contrast agent (0.1 mmol/kg dose) was delivered by intravenous (IV) injection at the start of the second series acquisition. Rapid contrast enhancement in lesions with signal intensity reaching plateau by the fourth series was defined as positive finding. Any enhancement with continuous rising of signal intensity through eight series or no enhancement was defined as negative finding. The study was discontinued for patients with negative findings. Patients with positive findings continued to undergo single voxel ^1H MRS and perfusion MRI examinations. The detection of an apparent choline (Cho) peak (signal-to-noise ratio > 2) at 3.23 ppm was defined as positive finding for the MRS study. An IV injection of contrast agent (0.1 mmol/kg) was administered during perfusion MRI acquisition. The relative blood volume map was generated from the perfusion imaging data. The striking enhancement in the lesion area on the map compared to normal tissue area was defined as positive finding for the perfusion MRI study.

By correlation with the pathology results as the reference standards, there were no false negative findings from DCE MRI studies, showing 100% sensitivity of this method. The specificity of DCE MRI was 67%. With the addition of ^1H MRS data, the specificity improved to 90%. With further addition of perfusion MRI results, the specificity improved to 100%.

This study shows that while DCE MRI has very high sensitivity in diagnosis of breast cancer, its specificity is unsatisfactory. The MRI/MRS protocol of combined use of DCE MRI, ^1H MRS and perfusion MRI substantially improves specificity and may help to reduce unnecessary biopsies following positive mammograms. With its technology easy for implementation at any imaging site and short scanning duration, this MRI/MRS protocol may have the potential to become the standard screening tool following positive mammographic findings.

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Clinically Practical Magnetic Resonance Imaging/Spectroscopy Protocol for Improved Specificity in Breast Cancer Diagnosis

1.0 PROTOCOL SUMMARY

Our aim is to perform a combined MR protocol of a dynamic contrast enhancement (DCE) MRI, ^1H MRS and perfusion MRI on 150 patients with positive mammography findings and who are scheduled for excisional or core biopsy. The MRI/MRS will be administered at Stony Brook Hospital, Radiology Department, Stony Brook, New York 11794, within a week prior to scheduled biopsy.

2.0 OBJECTIVES AND SPECIFIC AIMS

1. To examine the sensitivity and specificity of DCE MRI in detection of breast malignancy.
2. To test the hypothesis that the addition of ^1H MRS and perfusion MRI improves specificity in detection of breast malignancy.
3. To establish a reliable and easy-to-implement MR protocol with high sensitivity and specificity for the diagnosis of breast cancer.

3.0 BACKGROUND AND RATIONALE

Conventional mammography has been the primary screening and diagnostic tool for breast cancer for more than 20 years. While highly sensitive for malignancy, particularly in breast with low-density tissues, its specificity is poor. The current false positive rate of mammography is typically reported in the range of 60-80%. Because of such high false positive rate, unnecessary biopsies are often performed and cause complications that include: hemorrhage, abscess, pain, missed lesions and complications resulting from general anesthesia for patients unsuited for local anesthesia. In addition, invasive breast procedures can leave scars that make subsequent mammographic interpretation difficult in 50% of patients (1). The topic of false positive mammography has been a volatile subject in the literature with one study finding that women following the NIH screening recommendations may have a 24% chance of a false positive mammographic finding (2) over a ten-year period. These false positive results lead to tremendously unnecessary anxiety and expense. While stereotactic- and ultrasound-guided breast biopsy has reduced the morbidity of definitive tissue diagnosis, they may lead to prolonged mammographic surveillance and subsequent anxieties. Therefore, there is a need for additional evaluation following a positive mammogram, but prior to biopsy, to reduce unnecessary interventions.

In recent years, many studies have shown that the noninvasive techniques of MRI have strong potential to improve the sensitivity and specificity in the diagnosis and evaluation of breast cancer. MRI scans for breast tumors, particularly those involving the administration of contrast agents, have been rapidly gaining in popularity. It was recently estimated that the use of such agents has grown to 30-40% of all types of clinical MRI investigations (3). These contrast agents – small hydrophilic, paramagnetic gadolinium (Gd) chelates – constitute “one of the safest classes of drugs ever developed” (4). Of particular interest for breast cancer is the so-called “dynamic-contrast-enhancement (DCE) study, in which contrast agent passage through mammary tissue is monitored following a bolus injection. The popularity of this approach stems from the observation that even the qualitative time-courses of MRI signal intensity in a region-of-interest (ROI) exhibit reproducible patterns that appear capable of discriminating benign from malignant lesions, and even different type of malignancies (5). Thus, such a DCE MRI study now forms an integral part of a proposed standard breast cancer diagnostic protocol (6). Furthermore, NCI (National Cancer Institute) solicitations for Letter-of-intend on human trials evaluating new antiangiogenetic drugs now call for a DCE MRI study to be included in the protocol.

Although the results of investigation to date have varied greatly, the sensitivity of breast DCE, T1-weighted MRI for malignancy has consistently been reported to be excellent (88-100%) (7-15). Qualitative analyses of the temporal changes in signal intensity following bolus CR injection have shown that malignant tissues generally enhance early, with rapid, large increase in signal intensity as compared with benign tissues. The latter generally show a slower increase in signal intensity. This is presumably due to the inherent leakiness of the tumor vasculature and/or increased vascularization. However, the specificity of DCE MRI has been rather variable, ranging from 37-97% (7-16). Recently, T2*-weighted perfusion MRI (17-19), as well as the technique of ¹H MR spectroscopy (MRS) (20-22) have also been examined as promising tool for improving the specificity of breast malignancy detection. The former is based on the measurement of increased perfusion typical in malignancy, the latter is based on the detection of the ¹H nuclear magnetic resonance of choline-containing compounds (Cho) which, when enhanced, serves as the marker of active tumor (23).

4.0 OVERVIEW OF STUDY DESIGN

4.1 Design

In this study we propose to improve the sensitivity and specificity in detection of breast malignancy using DCE MRI, ¹H MRS, and perfusion MRI. The preliminary data collected so far have shown encouraging results.

The hypothesis is that DCE MRI provides high sensitivity and the addition of ¹H MRS and perfusion MRI improves specificity in detection of breast malignancy.

We expect that DCE will provide satisfactory sensitivity, but unsatisfactory specificity in detection of breast malignancy, and that the addition of ^1H MRS and perfusion MRI scans will substantially improve the specificity.

In order to examine the sensitivity and specificity of DCE MRI in breast malignancy detection we will correlate the DCE MRI results with the biopsy results.

To test the hypothesis that the addition of ^1H MRS and perfusion MRI improves specificity in detection of breast malignancy we will correlate the ^1H MRS and perfusion MRI results with the biopsy results.

The ultimate objective is to establish a reliable and easy-to-implement MR protocol with high sensitivity and specificity for the diagnosis of breast cancer. This aim can be achieved after scanning a large population of patients with the proposed MR protocol.

4.2 Methods

The MRI/MRS protocol will be performed using a 1.5 T Philips Intera whole-body MR scanner with the body coil as the transmitter and a dedicated phased array breast coil as the receiver. Following pilot scanning, DCE T1-weighted MRI will be performed using a 3D spoiled-GRASS (SPGR) pulse sequence to acquire 8 frames of sagittal volumetric images of the whole breast with suspicious lesions, with 30° flip angle, TE = 3.8 ms, TR = 9 ms, 5 mm slice thickness, 24 cm field of view (FOV) and 64x256 matrix size. Usually each frame contains 18-26 slices and the acquisition time for each frame is less than 15 sec. Gadolinium contrast agent (0.1 mmol/kg) is delivered intravenously at 2 cc/sec by a programmable power injector (Medrad, Indianola, PA) at the start of the second frame data acquisition. The first frame of images is subtracted from each frame of images using Philips image processing software. Contrast-enhanced lesions with signal intensity reaching plateau by the fourth frame are defined as **positive** findings for the DCE MRI study. Any enhancing areas with continuous rising of signal intensity through eight frames or no enhancement at all are defined as **negative** findings. The scanning protocol is discontinued for patients with negative DCE MRI findings. Patients with positive findings will continue to undergo ^1H MRS and perfusion MRI examinations.

Single-voxel proton spectrum will be collected from the enhanced lesion with a PRESS pulse sequence, TE = 135 ms, TR = 2000 ms, and 128 scan averages. Perfusion T2*-weighted MRI will be performed on a 5-mm single sagittal slice containing the enhanced lesion with a FLASH sequence, 10° flip angle, TE = 35 ms, TR = 54 ms, 24 cm FOV, 92x256 matrix size, and 40 frames. Intravenous bolus injection of Gd contrast agent (0.1 mmol/kg) will be carried out at 4 cc/sec at the beginning of the sixth frame data acquisition. The detection of an apparent Cho peak at 3.23 pp (signal-to-noise ratio > 2) is defined as the **positive** finding for the MRS study. Philips perfusion imaging processing software will be used to construct a relative breast blood volume (rBBV) map from the 40 frames of images, which is similar to how the cerebral relative blood volume

map is generated from perfusion MRI data. Compared with normal breast tissue area, the observation of striking enhancement in the lesion area on the rBBV map is defined as the **positive** finding for the perfusion MRI study.

Even if a patient undergoes all three MR scanning techniques, the total scanning time is less than 40 min, which is tolerable for average patients based on our previous experience. The total contrast dose administered can be more than 0.2 mmol/kg, which is well below the FDA approved limit.

The biopsy results will be used as the “gold” standard to correlate with the MR data. The sensitivity and specificity in detection of breast malignancy will be calculated for each or the combination of the MR methods.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any patient, who is 18 years or older undergoing a diagnostic imaging breast exam and having a positive finding will be eligible.

5.1 Subject Inclusion Criteria

- Patient need to be 18 years or older
- Patient had a positive mammographic finding
- Patient is scheduled for a biopsy

5.2 Subject Exclusion Criteria

- Patients who would be normally excluded from undergoing an MRI examination: patients with a pacemaker, aneurysm clip or any other condition that would warrant avoidance of a strong magnetic field
- Patients who are pregnant
- Patients who are unable to comply or complete the MRI exam due to claustrophobia or high levels of anxiety.

6.0 RECRUITMENT PLAN

Participants will be pre-selected by a surgeon or by a radiologist at the Carol Baldwin Breast Care Center from the patients with breast cancer or women with clinical and/or mammographic findings suspicious for breast masses. Any known breast lesion is appropriate for evaluation with the proposed protocol.

Potential research subjects will be identified by a breast surgeon or by a radiologist from the Carol Baldwin Breast Care Center. The radiologist investigator will screen the patient’s medical records for suitable research study participants and discuss the study

and their potential for enrolling in the research study. Potential subjects contacted by their breast surgeon will be referred to the investigator staff of the study.

The patients will be approached and informed about the study by the surgeon or by the radiologist at the time of their visit at the Carol Baldwin Breast Care Center (CBBCC). During the initial conversation between the investigator/ research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at CBBCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. In most cases, the initial contact with the prospective subject will be conducted by the investigator or by the research staff. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log.

On the day of the MRI examination at Stony Brook University Hospital a consenting professional will explain this study and ask them to attend earlier than their scheduled appointment. The Consenting Professional will explain the procedure and obtain the informed consent.

For non-English speaking patients a pre-arranged in-house translator will be made available for the duration of the study. The translator assists the person obtaining consent and serves as a witness. The witness and subject/patient must sign the Consent Form.

Upon the patients arrival at the MRI suite a consenting professional will approach the patient. The patient will be informed that, due to the high sensitivity of the MRI exam, there is a possibility of observing additional lesion(s) other than those already shown by the mammography and/or ultrasound exams. Should such situation occurs, the referring physician will be informed of such findings, and the radiologist may recommend further follow-ups with clinical breast MRI exam which provides more diagnostic information than the research procedure. Any decision of additional biopsies, if there is, will be fully based on the results of clinical examinations, not on the results from this research study. The patient is also told that at any given time can choose to withdraw without consequence.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team, he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at Stony Brook in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

7.0 PRETREATMENT EVALUATION

Not Applicable

8.0 TREATMENT/INTERVENTION PLAN

Not Applicable

9.0 EVALUATION DURING TREATMENT/INTERVENTION

Not Applicable

10.0 TOXICITIES/SIDE EFFECTS

The sequences will conform to the standard heating and patient safety guidelines the Philips adheres to for all product pulse sequences.

Even if the patient undergoes all three MR scanning sequences, the total contrast dose administered will be no more than 0.2 mmol/kg, which is well below the FDA approved limit.

Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and all subjects death will be promptly reported by

phone (301) 619 2165, by e-mail (hsrrb@det.amedd.army.mil), or facsimile (301) 619 7803 to the Army Surgeon General's Human Subjects Research Review Board. A complete written report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZR-QH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

11.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Not applicable

12. CRITERIA FOR REMOVAL FROM STUDY

If a subject decides to discontinue exam there will be no penalty or loss of benefits to which the patient is entitled.

12.1 TERMINATION

Termination from the study will occur if you are unable to complete the entire MR examination.

13.0 PROTOCOL MODIFICATIONS

Any modifications to the protocol will be reviewed by the Stony Brook IRB. The informed consent document will be revised to concur with any protocol modifications, and will also be reviewed and approved by the IRB. Once approved, the modifications and revised informed consent document will be forwarded to the Human Subject Research Review Board (HSRRB) for review and approval. No protocol modification will be implemented prior to approval from both the IRB and the HSRRB.

13.1 PROTOCOL DEVIATIONS

Any deviations from the approved protocol will be reported by the Principal Investigator and the Investigators.

14.0 BIOSTATISTICS

In this protocol we wish to study the utility of DCE MRI, MRS and Perfusion MRI to discriminate between malignant and nonmalignant lesions identified by MRI. Typically the MRI identifies one lesion per patient and a third of them are expected to be malignant. We will assess the diagnostic accuracy of the quantitative measure obtained from MRS using receiver operating characteristic (ROC) curve methodology. We will use the area under the ROC curve as the measure of accuracy, which can range from 0.5 for a marker no better than tossing a coin to 1.0 for a perfect marker. A study with 150 patients will enable us to estimate the area under the ROC curve with 95% confidence intervals for various true areas given by: 0.6 (0.50-0.69), 0.7 (0.61-0.79), 0.8 (0.72-0.87) and 0.9 (0.84-0.95). We see that a 150 patients study gives area estimates with 10% and 5% accuracy for true areas of 0.6 and 0.9 respectively.

Estimated annual accrual: 50 evaluable patients

Target initiation date: June 2005

Target completion date: January 2007

Estimated sample size: 150

15.0 SUBJECT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Subject Registration

The following person(s) can obtain informed:

Paul R Fisher, MD

Mark Wagshul, PhD

Terry Button, PhD

Luminita A Tudorica, PhD

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written Informed Consent, by following procedures defined in section entitled Informed Consent Procedures.

15.2 Randomization

Not Applicable

16.0 DATA MANAGEMENT ISSUES

Imaging and spectroscopy data will be collected by the study coordinator (L. Tudorica). The responsibilities of the study coordinator include project compliance, data collection,

abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol team.

The data for this study will be entered into a secure database within Stony Brook University by all consenting professionals on this study. Each patient will be identified by number and MRI/MRS scan date. Source documentation will be available to support computerized patient record.

The data for this study will be stored until the study is completed, analyzed, and published.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

The quality assurance of the MRS data will be achieved by:

1. The full width at half maximum (FWHM) of the water peak after shimming should be less than 20 Hz. If the results of auto-shimming during pre-scan are not satisfactory, manual shimming will be performed to make sure the FWHM of the water is less than 20 Hz. This assures that excellent water suppression will be achieved and the Choline (Cho) peak will not be obscured by the residual water signal and the generally large lipid peak, as the Cho peak is usually miniscule compared to the water and lipid peaks.
2. We will use a phantom in which three ping-pong balls are immersed in vegetable shortening. These balls are filled with choline chloride solutions of 2.5, 5.0, and 10 mM. Single voxel (voxel size $1.6 \times 1.6 \times 1.6 \text{ cm}^3$) proton spectrum will be acquired from the 2.5 mM solution once every other week on each MR scanner to make sure there is no dramatic drop in S/N ratio of the Cho peak. The pulse sequence and parameters used for the phantom study will be the same as those used for the human study.

Reproducibility and Validity

The reproducibility and validity of the MRS measurements can be achieved by:

1. Complete step 2 of quality assurance.
2. Once per month, MRS data will be collected from all three choline chloride solutions as described above. Using the [Cho] quantification method mentioned above, the [Cho] values calculated from the spectral data should match the actual choline concentration. The standard deviation of [Cho] from multiple MRS measurements over time should be within 10% of the mean value.

16.2 Data and Safety Monitoring

The study coordinator (LT) is assigned to the study. The responsibilities include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.3 MRI Scanner Monitoring

Every morning the MRI scanner is tested and the test results are recorded on a data sheet in accordance with Philips on a daily basis.

17.0 PROTECTION OF HUMAN SUBJECTS

MRI is considered a minimal risk device. The risk from exposure to the prototype sequence should not be considered any greater than conventional MRI. Since the patients will be having conventional MR sequences, these should not pose a hazard.

The subjects will not be charged for the MRI study. The patients will not be compensated for their participation. Every effort will be made to keep study records private. No identifiers will be used in any reports or publications resulting from this study.

The representatives of the U.S. Army Medical Research and Materiel Command may review research records as part of their responsibility to protect human subjects in research as part of the Department of Defense (DOD).

This protocol does not include children because this disease process does not occur in children.

17.1 Privacy

Stony Brook University's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Informed Consent Form. The use and disclosure of protected health information will be limited to the individuals described in the Informed Consent Form.

As a part of the U.S. Army Medical Research and Materiel Command's (USAMRMC) responsibility to protect human subjects in research, representatives of the USAMRMC are eligible to review research records.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE will be reported to the IRB as soon as possible but no later than 7 days. The IRB requires a memo sent to the IRB Chairman containing the following:

1. The initials of the subjects, patient MRN#, protocol # and title
2. The date of the event occurred
3. A description of the SAE
4. An explanation of how the SAE was handled
5. A description of the subject's condition
6. Indication if the subject remains on the study
7. Indication if the event is considered related to the treatment (drug, device, intervention)
8. Indication if an amendment will need to be made to the protocol and/or consent form as a result.

All SAE must be entered into the Research Database page.

18.0 Informed Consent Procedures

Consenting individuals will be radiologists or researchers who have had extensive experience with the consent process from prior protocols. The consent will be done in person on the day that the patient arrives in the MRI suite.



Department of Radiology

INFORMED CONSENT
Clinically Practical Magnetic Resonance Protocol for Improved
Specificity in Breast Cancer Diagnosis

Principal Investigator: Paul Fisher, M.D.

You are being asked to be a volunteer in a research study:

You are encouraged to take your time in making your decision. Discuss this study with your friends and family.

The purpose of this study is:

To evaluate the role of magnetic resonance imaging (MRI) of the breast in the detection and treatment of breast cancer. In addition to the usual diagnostic imaging procedures of mammography and ultrasound, you will also undergo one or more MRI studies of the breast.

If you decide to participate, your part in the research project will involve:

Having an initial breast MRI performed and possibly additional breast MRI studies at a later date to follow the breast and/or response to treatment. Each MRI session will take about 1 hour. Before you undergo MR scanning procedures, you will be asked to fill out a standard questionnaire, which is the same as the one used for the clinical breast MRI.

Risks:

The MRI procedure may induce claustrophobia in some subjects. Two series of MRI images will also include an i.v. injection of a contrast agent. This involves inserting a needle into a vessel in your arm. This may cause fainting, minor discomfort and swelling, as well as bruising or bleeding. The contrast agent that is injected is safe and has already been approved for general use, but some people do experience a minor headache, rash, nausea or burning after the injection.

Due to high sensitivity of the MRI exam, there is a possibility of observing additional lesion(s) other than those already shown by your mammography and/or ultrasound exams. Should such situation occurs, we will inform your physician of such findings, and we may recommend further follow-ups with clinical breast MRI exam which provides more diagnostic information than the research MRI procedure you will undergo, or other clinical studies. Any decision of additional biopsies, if there is, will be fully based on the results of clinical examinations, not on the results from this research study.

Benefits:

The investigators believe that breast MRI may improve the detection and treatment management of breast cancer patients. It is unclear, however, that you will derive any direct benefit from this study. However, one potential benefit for you is when the MRI exam in this research protocol detects additional lesion(s)

which is not identified on your mammogram. In this case, additional clinical procedures may be prescribed by your doctor for early diagnosis and/or early treatment of potentially malignant tumor.

Confidentiality/Protecting the Privacy of Your Health Information:

The following procedures will be followed in an effort to keep your personal information confidential in this study: Your identity will be held confidential, and all data will be kept in a secured, limited access location. Your identity will be numerically coded. Your identity will not be revealed in any publication or presentation of the results of this research.

All data and medical information obtained about you, as an individual, will be considered privileged and held confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

Confidentiality cannot be guaranteed; your personal information may be disclosed if required by law. This means that there may be rare situations that require us to release personal information about you, e.g., in case a judge requires such release in a lawsuit, if you tell us of your intent to harm yourself or others (including reporting behaviors consistent with child abuse).

As a result of being in this study, identifiable health information about you will need to be used, generated, and or reported for the purpose(s) outlined in this consent form, and/or as required by law. Federal law protects your rights to privacy concerning this information. As such, there is certain specific information you need to know.

Individually identifiable health information (IIHI) under the federal privacy law is considered any information from your medical record, or obtained from this study, that can be linked to you, and that relates to your past, present, or future physical or mental health or condition. The following IIHI will need to be used, generated, or disclosed (reported) for the purpose of this study:

- Information from your medical record, including information about your medical history, results of physical examinations, laboratory (specimen pathology) test, x-rays (mammography) and other diagnostic medical procedures (ultrasound, biopsies)
- Information obtained from this study, including pre- and post-contrast agent MR images, dynamic contrast-enhanced MR images, MR spectroscopy results, and perfusion MR images

Your IIHI will be shared with any person or agency when required by law, and by:

- the research team for this study at Stony Brook University
- the sponsor(s) of this study, Department of the Army, US Army Medical Research Acquisition Activity
- your insurance company (if the routine MRI part of this study, including pre- and post-contrast MRI and dynamic contrast-enhanced MRI, is applicable and allowed to bill insurance carrier)
- Stony Brook University's Committee on Research Involving Human Subjects, and/or applicable officials of SBU
- The Federal Office of Human Research Protections for the purpose of assessing compliance associated with the conduct of this study.

Use and disclosure of your health information will be necessary for an indefinite period of time.

You need to know that some of the individuals or groups referenced above are not obligated to protect the privacy of your IIHI. As an example, the sponsor, Department of the Army and the Office of Human Research Protections do not have the same obligation to protect your IIHI, and as such, the federal privacy laws no longer protect it from further disclosure. **It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.**

You have the right to revoke (withdraw) your authorization for the use or disclosure of your IIHI at any time in writing. If you revoke this authorization, you may no longer participate in this research activity. Revoking your authorization means that all access to, and collection of your IIHI will be halted, unless the information concerns an adverse event (bad effect) you experienced related to the study. Your IIHI that was collected before you withdrew your authorization can continue to be used and reported.

When you sign the consent form at the end, it means that you have read this section and authorize the use and or disclosure of your individually identifiable health information in the manner explained above. Your signature also means you have received a copy of SBU's Notice of Privacy Practices.

Cost to Subject:

The cost of a routine MR with contrast agent will be billed to your insurance carrier, if applicable and allowed. There will be no additional "out-of-pocket" expense if your insurance company will not pay.

Payment to You:

Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research.

In Case of Injury:

If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly cause by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, Dr. Paul Fisher, (631) 444-3652. If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221.

If you are injured as a result of participating in this research project you should immediately notify Dr. Paul Fisher, (631) 444-3652. SUNY Stony Brook's University Hospital will be open to you in case of such injury. However, you or your insurance company will have to pay for any resulting treatment and/or hospitalization.

Your Rights:

- You do not have to be in this study if you don't want to be.
- You have the right to leave this study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a copy of this consent form.
- You do not waive any of your legal rights by signing this consent form.

Questions about the Study or Your Rights as a Research Subject

- If you have any questions about the study, you may contact Dr. Paul Fisher, at (631) 444-3652.
- If you have any questions about your rights as a research subject, you may contact Ms. Judy Matuk (Committee on Research Involving Human Subjects) at (631) 632-9036.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you are volunteering to participate in this study.

Name of Subject (please print)

Signature of Subject

Date

Signature of Person Obtaining Consent

Date

Advanced Magnetic Resonance Mammography (AMRM)

Breast cancer is the most common form of cancer among women in the United States. A report from the National Cancer Institute (NCI) estimates that about 1 in 8 women in the United States (approximately 12.8 percent) will develop breast cancer during her lifetime. The incidence of breast cancer has been rising for the past two decades, while mortality has remained relatively stable since the 1950's. More women with breast cancer are surviving in the face of the growing number of cases, most likely as a result of earlier detection, treatment improvements, and an overall increase in breast cancer awareness.

Mammography has been the gold standard screening tool for breast malignancy for more than a decade. While mammography is highly sensitive for malignancy, the current false positive rate for mammography is typically reported to be 70%. With this high false positive rate, unnecessary surgical biopsies are performed.

Mammography has been quite volatile with one publication suggesting that a woman following the FDA screening recommendations has a 10% chance of

a false positive finding at some point of her life.

The scientists at the MRI Research Center are evaluating the role of a new imaging technology, Advanced Magnetic Resonance Mammography (AMRM) as a potentially new high technology non-invasive diagnostic tool for breast malignancy.

The purpose of this study is to evaluate the role of Breast AMRM in the detection and treatment of breast cancer.

Magnetic Resonance Imaging (MRI) is an advanced technology that lets physicians see internal organs, blood vessels, muscles, joints, tumors, areas of infection and more. MRI is very safe; in fact, it makes use of natural forces and has no known harmful effects. It is important to know that MRI will not expose you to any radiation.

MRI can provide very early detection of many conditions, so treatment can be more effective. The excellent quality of MRI images can also provide the best possible information if surgery is required.

Conventional breast MRI has the capability of detecting breast cancer, however, at the same time it has a high false positive rate. Here at Stony Brook University Hospital we are trying to improve breast MRI specificity utilizing the AMRM protocol, which includes the MR spectroscopy looking for active

tumor marker, and perfusion MRI studying the Blood Perfusion in the lesion.

This new protocol has the potential to reduce the number of negative biopsies, thus saving women from the anxiety of worrying about breast lesions that turn out to be non-cancerous. It also has the potential to identify women who should be referred for early biopsy.

Frequent AMRM Questions and Answers

Where is the AMRM given?

For this study all MRI examinations are performed at Stony Brook University Hospital, Level 4, in the MRI Section of Radiology.

How long does the scan take?

The examination can last anywhere from 30 minutes to usually no more than one hour.

Will I feel any different after the examination?

Well, you may feel very well rested since you have just been lying on a table and doing absolutely nothing. In fact, some people even fall asleep during the examination. Other than that, you will feel perfectly normal and can go back to your everyday activities.

What is the procedure like?

There are many varieties of MRI scanning machines. To begin the examination, you will lay prone on the scan table. When the machine starts to work, you will hear some loud knocking sounds. These sounds occur whenever the MRI pictures are being taken. The MRI facility will provide earplugs to help block out the knocking sounds.

Although it is noisy, an MRI examination is completely painless. The only thing you must do is **HOLD STILL**. When you take a picture with a camera, your subject must keep still or the picture will come out blurry. It is the same with an MRI machine. If you move, the scans will be out of focus and you may have to repeat the examination.

You will be injected once or twice (depending on the outcome of the first injection) with a solution called “contrast agent”. This allows the radiologist to see the images more clearly. MRI contrast agents are safe and FDA approved. Typically there are few or no side effects. Some patients may experience a cold sensation at the injection site. Minor side effects may include headache, hives and itching.

What are the risks and benefits?

There are no risks and the investigators believe that breast MRI may improve the detection and treatment management of breast cancer patients.

Are there any restrictions with the examination?

Yes. Because the MRI machine uses a strong magnetic field, which will move objects made with iron or steel.

Let your doctor and the technologist know if you have:

- A pacemaker
- Aneurysm Clips
- Cochlear implants
- A neuro-stimulator (tens-unit)
- Metal implants
- Steel surgical staples or clips
- Any implant made partially or wholly of iron or steel

Also, if you are pregnant, let the doctor know.

Even metal objects not made of iron or steel can interfere with the examination, so please do not bring any of the following items into the examination room:

- Coins
- Jewelry
- Watches
- Keys
- Dentures or partial plates
- Hearing aids

Magnetic waves can also erase the code on bankcards and credit cards; so do not bring any to the examination room.

In order to participate in this project, is there a criteria that has to be met?

Yes. You have to be scheduled for an excisional or core biopsy after the MRI examination. Also, you must also be diagnosed with suspicious or highly suspicious mammography findings.

Where would someone call if they were interested in participating in this study?

As this study will be conducted at Stony Brook University Hospital's MRI Research Center you may call (631) 444-2409 for appointment.

For an appointment or more information about participating in this research study, please call the MRI Research Center at Stony Brook University Hospital at (631) 444-2409.

The State University of New York at Stony Brook is an equal opportunity/affirmative action educator and employer. This publication can be made available in

alternative format. If you need disability-related accommodations, please call (631) 444-2409.



**Magnetic Resonance Imaging
Research Center/Department of
Radiology at
Stony Brook University Hospital**

Advanced Magnetic Resonance Mammography (AMRM)

***Research Study Seeks
Volunteers***