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TITLE: A New Perspective on DCIS Using MRI: Correlation of Tumor and Vessel Proliferation with MR Signal Enhancement

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13. ABSTRACT *(Maximum 200 Words)*

The purpose of this study is to correlate density of contrast enhancement on breast MRI images with pathology characteristics and markers of proliferation and angiogenesis in women with ductal carcinoma in situ (DCIS) of the breast. The specific aims of our study are two fold. 1) We will first develop a novel method for characterizing DCIS lesions based on cellular proliferative activity within the tumor surrounding vascular endothelium. Using immunohistochemical techniques, we will determine whether this proliferation is found in the DCIS itself, in the surrounding stroma, or in vascular endothelial cells and whether they are proximate. 2) Secondly, we will correlate this proliferative profile with MRI characteristics in order to determine whether MR can predict the biological characteristics of DCIS. Thus MR could potentially serve as a surrogate marker of biological behavior.

The two aims mentioned above toward this goal we wish to acquire a better understanding of the basis and timing for transformation of DCIS which would help us to find more optimal ways to treat DCIS, and indeed, help us to treat invasive breast cancer and develop strategies for prevention.

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Table of Contents

Introduction

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Body

Specific Aim 1: Stain a series of 75 DCIS lesions and 20 non-malignant controls with proliferative, epithelial, and endothelial markers

Accomplishments

We have obtained informed consent to analyze samples from patients with a diagnosis of Ductal Carcinoma in Situ (DCIS) who have had a prior MRI before definitive surgery (Appendix A)

Informed consent has been obtained to analyze samples and MR images from patients who are undergoing a preoperative MRI for a diagnosis of DCIS (Appendix B)

Task 1.1: Create a database of 75 patients with DCIS which includes details of physical findings and mammographic presentation.

We have created a database of patients with DCIS that includes details of physical findings and mammographic presentation. We have 90 patients in this database and are gathering information on their surgery type, MRI date, surgery date, age at diagnosis, size, type, grade, necrosis, extent, number of segments involved, pixel density, and pattern of enhancement.

Task 1.2 Identify 20 non-malignant controls

We are currently looking through cases to identify suitable controls. We should have this complete by February of 2002.

Task 1.3 Review all pathology in terms of grade, extent, size, and patterns of tumor vessels by H&E

We have begun to review all pathology but unfortunately the pathologist on this study, Dr. Sudilovsky, has left the university. We are interviewing pathologists to take over for Dr. Sudilovsky, and are currently discussing the protocol with Dr. Yun Li Chen who is likely to begin working on this study. In addition, our current breast surgery fellow, Veronica Shim, has begun to work on the project with us. All pathology will be reviewed by June of 2002.

Task 1.4 Stain tumor specimens using CD 34 and CD 105 in order to highlight vascularity of tumor lesions

A comparison of CD34 and CD 105 has been performed. CD34 will be used for the definitive analysis. It appears that a cut section is likely to be better than a core for quantitatively counting microvessels to assess angiogenesis.

Task 1.5 Add serial section stain and dual stain with proliferative markers to elucidate which areas of tumor are proliferating

We will add serial section stains rather than dual stains with proliferative markers (Ki67, cytokeratin, and MCM2) to elucidate which areas are proliferating (tumor vs. epithelial vs. endothelial).

Task 1.6 Compare proliferative patterns of tumor and blood vessels and correlate to grade, extent, and Her2/neu markers

We are in the process of assessing grade, Her-2, ER, and Cox-2 and will compare all of these to grade and extent..

Specific Aim2: Create a tissue arrray from DCIS cases to see if this technique can be used to capture the same data described in Specific aim 1

Task 2.1 Identify a tissue array from DCIS cases to see if this technique can be used to capture the same data described in Specific aim 1

A tissue array from the DCIS cases is underway by Karen Chew.

Task 2.2 Create tissue array composed of plugs from identified tissue blocks

The tissue array is being created.

Task 2.3 Stain tissue sections as in Specific aim 1 and correlate individual sections with tissue arrays

Ongoing

Specific Aim 3: Define MRI characteristics of DCIS

Task 3.1 Examine and compare all MR images; create a stratification and standards of patterns seen based on extent, density, and intensity of contrast enhancement of the first fifty patients

All MR images are being analyzed for morphological and kinetic data. We are currently working on refining the method for identifying the pixels to count for a MRI density measure.

Task 3.2 Categorize each image according to these patterns of extent, density, SER, and imaging phenotype

Will be accomplished by April 2002

Specific Aim 4: Investigate associations between MR proliferative markers, and standard pathologic prognostic features.

Task 4.1 Correlate MRI characteristics to pathologic and proliferative characteristics identified in specific aim 1

We will correlate MRI characteristics to all pathologic and proliferative characteristics identified above.

Task 4.2 Determine if proliferative activity is associated with standard prognostic features alone

We will analyze all data and try to determine if proliferative activity is a property of grade and or size or if it is a biologic parameter which might act as a trigger point for progression

Conclusions

We anticipate that the project will be completed on time. We hope to have our database complete by March 2002. The staining and final results will be performed by June of 2002. We will analyze the data and prepare a final report by September 2002.

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Appendix A
Human Subjects Protocol
submitted to the
Committee on Human Research
Category 4: Expedited Review

A New Perspective on DCIS using MRI: Correlation of Tumor and Vessel Proliferation with MR Signal Enhancement

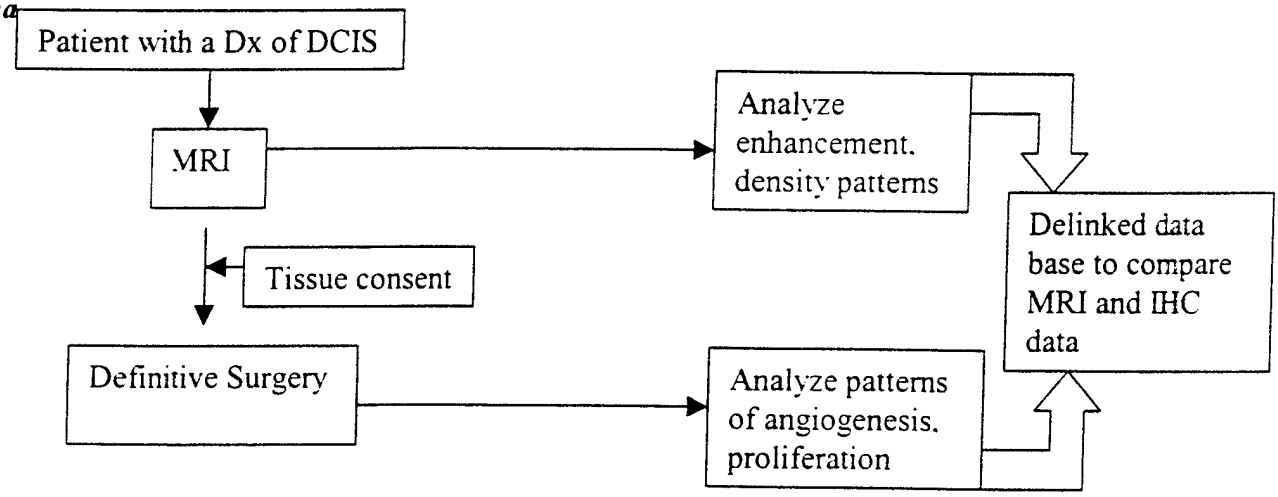
Laura J. Esserman, MD, MBA-Principal Investigator

1. Study Aim, Background, and Design

The purpose of this study is to correlate density of contrast enhancement on breast MRI images with pathology characteristics and markers of proliferation and angiogenesis in women with ductal carcinoma in situ (DCIS) of the breast. The specific aims of our study are two fold. 1) We will first develop a novel method for characterizing DCIS lesions based on cellular proliferative activity within the tumor surrounding vascular endothelium. Using immunohistochemical techniques, we will determine whether this proliferation is found in the DCIS itself, in the surrounding stroma, or in vascular endothelial cells and whether they are proximate. 2)Secondly, we will correlate this proliferative profile with MRI characteristics in order to determine whether MR can predict the biological characteristics of DCIS. Thus MR could potentially serve as a surrogate marker of biological behavior.

The two aims mentioned above toward this goal we wish to acquire a better understanding of the basis and timing for transformation of DCIS which would help us to find more optimal ways to treat DCIS, and indeed, help us to treat invasive breast cancer and develop strategies for prevention. We have been awarded a grant from the Department of Defense USAMRMC (proposal #SR990030) to study 75 patients with DCIS using MRI at UCSF.

Study Schema



2. Subject Population *Inclusion/Exclusion Criteria*

Women of all races and ethnic groups over 18 years of age will be eligible for the study. It is expected that 30% of the patients recruited into the trial will be less than 50 years old. The proposed participants are UCSF/Mt Zion Carole Franc Buck Breast Care Center (BCC) female patients who have had an MRI of the breast as part of clinical care or another CHR approved study and have a diagnosis of ductal carcinoma in situ (DCIS) of the breast

We propose to analyze our existing data base of women diagnosed with intraductal carcinoma who have had an MRI prior to definitive surgical treatment of either partial or total mastectomy. We currently have 70 patients with a diagnosis of DCIS who have been imaged and treated. However, several of these cases showed no residual disease and some turned out to be invasive cancer. We have nearly 50 patients with clear cases of DCIS.

Criteria for Inclusion are as follows

Patients with DCIS who have had a MRI of the breast as part of another study and signed a tissue consent form prior to their surgery. These patients will be included in the retrospective study group if their pathological examination of surgical excision specimen reveals residual DCIS.

3. Procedures to be Done for the Purpose of the Study

We will create a database of all patients who have had a MRI of the breast as part of a research protocol who had a diagnosis of DCIS. We will identify those patients who had residual disease at the time of surgical resection. We will identify those patients who had residual disease at the time of surgical resection. We will identify which patients signed a tissue consent and create a second linked data base without patient identifiers to include only those patients with residual DCIS and a tissue consent. Tissue blocks will be pulled and IHC stains performed and recorded and data from MRI film recorded. Analysis of data will be performed on the latter data database.

4. Risks: Potential Risks /Discomforts to Subject, Including Possible Loss of Confidentiality, and Methods of Minimizing These Risks

Records will be kept in a confidential form at UCSF. Strict data security measures have been implemented to assure confidentiality, including password protection of all dial-up access to the database. During their required reviews, representatives of the FDA, DOD-USAMRMC, or other organizations that have a role in the conduct of this study may have access to medical records and data that contain the patient identity. However, no information by which the patient can be identified will be released or published. All data will be stored using ID numbers as opposed to patient names as the primary means of identification. All published reports will refer to patients only by number.

5. Benefits: Potential Direct Benefits to Subjects and General Benefits to a Subject Group, Medical Science and/or Society

MRI is a very low risk procedure. The procedures performed in this protocol are identical to those of routine medical tests. The benefits of MRI in breast cancer detection are a subject of current research, but it appears to have value for tumor detection in women for whom mammography is difficult, such as younger women with radiologically dense breast tissue and where interventions have occurred, and for treatment management once tumors have been detected. We hope that this research will ultimately lead to extension of these benefits to broader groups of patients, including monitoring those with high genetic risk for breast cancer and with previous history of cancer.

6. Consent Process and Documentation

We will include data only from patients who signed our global research consent prior to their MRI and the tissue consent prior to surgery. Patients will not be contacted regarding this retrospective study.

7. Qualifications of Investigators

Dr. Laura Esserman is the Medical Director of the Carol Franc Buck Breast Care Center at UCSF/Mount Zion Medical Center and Clinical Leader of the Breast Oncology Program at the UCSF Cancer Center. She is an Associate Professor of Surgery and Radiology. Dr. Esserman, along with Dr. Hylton, has been a pioneer in identifying appropriate clinical applications of Breast MRI. She will direct the project, screen subjects for inclusion, and in collaboration with Drs. Hylton, Wolverton, Hwang, and Sudilovsky, correlate MRI characteristics with pathologic and proliferative changes identified by histopathology. She will monitor the project's pace of work, making sure that milestones are met according to the timeline set forth in the proposal. She will be responsible for running monthly team meetings to review data.

Dr. Shelley Hwang (Co-PI) is an Assistant Professor of Surgery at UCSF and Attending Surgeon at the Carol Franc Buck Breast Care Center. She has been working with Dr. Esserman, Hylton, and Kinkel to define MR characteristics of DCIS. She will work to review surgical reports and reconstruct the anatomical location of tissue specimens at the time of surgical dissection. She will participate in data review and in the correlation of pathology and radiology findings. Dr. Hwang will also work with Dr. Sudilowsky to identify cases of sections of contiguous DCIS in order to create tissue arrays.

Dr. Nola Hylton (Co-PI) an Associate Professor of Radiology at UCSF and a leader in the development of breast MRI. She will be responsible for screening and reviewing all MRI films. She will create the automated readouts of density and peak enhancement and continue to retool developmental software to better characterize DCIS lesions.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO BE A RESEARCH SUBJECT
A NEW PERSPECTIVE ON DCIS Using MRI:
Correlation of Tumor and Vessel Proliferation with MR Signal Enhancement

Appendix B

A. PURPOSE AND BACKGROUND

Laura Esserman, MD, MBA in the department of surgery and radiology and Nola Hylton, PhD in the department of radiology are conducting a research study to investigate the usefulness of MRI (magnetic resonance imaging) for characterizing ductal carcinoma in situ (DCIS). This research is being done in hopes that this study will result in a new use for MRI, an imaging technique, to detect and diagnose DCIS. You are being asked to take part in this study because you have ductal carcinoma in situ (DCIS) and will undergo core biopsy or breast surgery.

B. PROCEDURES

We are asking for permission to review your MRI and mammogram records that are taken as part of your treatment in this research study. If you agree to be in the study, the following will occur:

1. You will have 1 MRI examination. The MRI exam will be before you have surgery.
2. You will have mammograms as part of your clinical care.

C. RISKS/DISCOMFORTS

We are requesting you get 1 MRI examination in this study. As we are asking permission to review your medical records and plan to correlate our findings on MRI and mammogram with pathologic features of DCIS, the risks involved are the normal risks associated with MRI.

1. Risks Associated with MRI (Magnetic Resonance Imaging)
The MRI unit is noisy. Some patients feel claustrophobic in the MRI magnet.

2. Risks Associated with Gadolinium
Headaches and nausea. Allergic reactions are less likely.

3. Reproductive risks: You should not be or become pregnant while on this study. If there is a chance that you are pregnant, you should have a pregnancy test prior to entering on this study.

4. Confidentiality: Participation in research will involve a loss of privacy; however, your records will be handled as confidentially as possible. Records of your progress while on the study will be kept in a confidential form at this institution. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)*, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

D. BENEFITS

There will be no direct benefit to you from participating in this study. However, the information that you provide may help health professionals investigate the usefulness of MRI for characterizing ductal carcinoma in situ (DCIS). We hope this study will result in a new application of Magnetic Resonance Imaging techniques to detect and diagnose DCIS.

E. COSTS

There will be no costs to you as a result of taking part in this study.

F. QUESTIONS

You have talked to Dr. Esserman, Dr. Hylton, or the person who signed below about this study and have had your questions answered. If you have further questions, you may call the Clinical research nurse coordinator, Lorna Beccaria at (415)502-3702.

If you have any comments or concerns about participation in this study, you should first talk with the researchers. If for some reason you do not wish to do this, you may contact the Committee on Human Research, which is concerned with the protection of volunteers in research projects. You may reach the committee office between 8:00 and 5:00, Monday through Friday, by calling (415) 476-1814, or by writing: Committee on Human Research, Box 0962, University of California, San Francisco/San Francisco, CA 94143.

G. CONSENT

You will be given a copy of this consent form to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You are free to decline to be in this study, or to withdraw from it at any point. Your decision as to whether or not to participate in this study will have no influence on your present or future status as a patient.

If you agree to participate you should sign below.

Date	Signature of Study Participant
Date	Signature of Person Obtaining Consent