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Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

Robert Thomas Etnire
University of Nevada, Las Vegas

INVESTIGATION OF MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY FOR THE DETECTION OF BREAST CANCER

by

Robert Thomas Etnire

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ROBERT THOMAS ETNIRE

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[redacted]
Examination Committee Chair

[redacted]
Dean of the Graduate College

[redacted]
Examination Committee Member

[redacted]
Examination Committee Member

[redacted]
Graduate College Faculty Representative

ABSTRACT

Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

by

Robert Thomas Etnire

Dr. Phillip W. Patton, Examination Committee Chair
Associate Professor of Health Physics
University of Nevada, Las Vegas

Magnetic resonance imaging (MRI) of the breast offers an alternative to screening mammography which may benefit those women at high risk for breast cancer, women under the age of 40, and those with dense breast tissue. One concern with MRI is the number of high false positives. Coupling MRI with magnetic resonance spectroscopy (MRS) may lower the number of false positives, and thus improve the diagnostic capabilities of MRI for the clinician. MRS for breast imaging focuses on the total choline containing compounds in the spectra in the suspected breast lesion to analyze areas of concern. The results of the study indicate that MRI helps differentiate potential lesions in the breast from healthy tissue, which is clearly seen in scans containing contrast. Also, MRS helped to confirm if a lesion is malignant by determining the SNR of the lesions, with an SNR of greater than or equal to 2.0 indicating malignancy.

Keywords; magnetic resonance imaging, magnetic resonance spectroscopy, breast, mammography

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CHAPTER 1

INTRODUCTION

Effectively treating breast cancer continues to be an extremely difficult task. Imaging modalities and radiation therapy work jointly in order to accurately locate and then effectively treat tumors. While current therapies can be effective, they generally are unsuccessful in changing prognosis in the more common cancers (Allen et al. 2001). The clinical and pathological findings and the type of treatment to be performed varies with each individual patient. The effectiveness of different imaging modalities in detailing the various breast regions impacts the diagnosis and subsequent treatment options.

The American Cancer Society has issued new recommendations for women at different levels of risk of breast cancer (Saslow et al. 2007). The recommendations for the use of screening MRI is for those women with approximately 20-25% or greater increased lifetime risk of developing a form of breast cancer. This includes women with a family history of breast or ovarian cancer and women who have received previous treatment with chest irradiation, such as for Hodgkin's disease. In addition, a recent study found that MRI can detect cancer in the contralateral breast that may be missed by mammography, further enhancing the need for MRI (Lehman et al. 2007).

Anatomy of the Breast

The breasts rest on the pectoralis major, the chest muscle that covers the ribs. They are supported by and attached to the front of the chest wall on both sides of the sternum by ligaments (National Cancer Institute 2006). Even though the breasts sit on a major chest muscle, it has no muscle tissue itself. It is made up of a layer of fat that surrounds the glands and extends throughout the breast. Each breast is made up of approximately 15-20 lobes (National Cancer Institute 2007a). The lobes are made up of several smaller lobules. At the end of the lobules, there are tiny bulb-like glands where the milk is produced (National Cancer Institute 2006). The milk flows from the lobules through the ducts to the nipple. The fat that covers the lobes is what gives the breast its size and shape. Figure 1 details the anatomy of the breast.

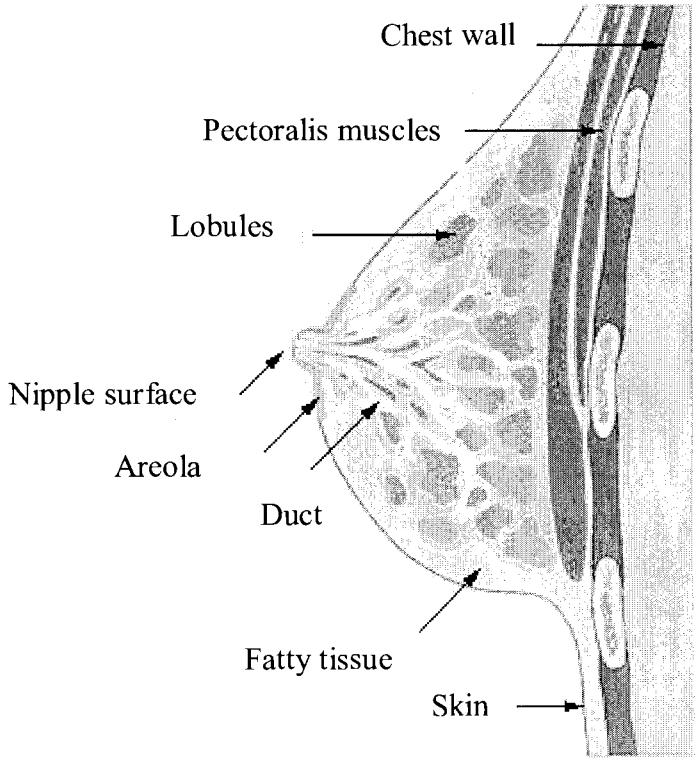


Figure 1. Detailed anatomy of the breast (National Cancer Institute 2006).

The breasts also contain lymph vessels which lead to the lymph nodes (National Cancer Institute 2007a). There are groups of lymph nodes located near the breast in the axilla, above the collarbone, behind the sternum, and other various locations throughout the body. Figure 2 illustrates the locations of lymph nodes in and surrounding the breasts. Breast tissue and breast cancer both appear bright when using mammography, which is part of the problem in detecting breast cancer using screening mammography.

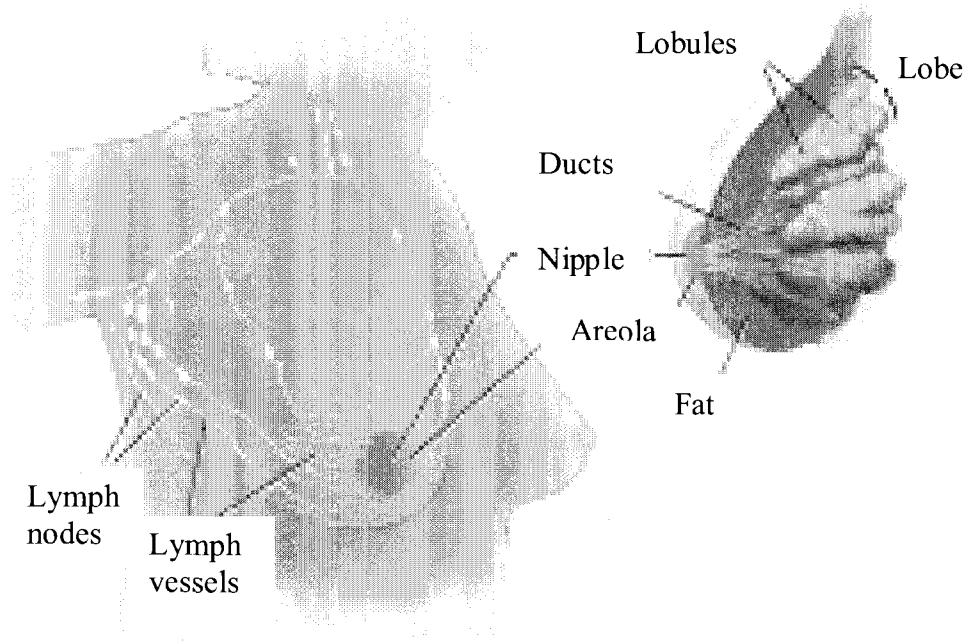


Figure 2. Lymph nodes in and surrounding the breast (National Cancer Institute 2007a).

Breast Cancer Statistics

The main locations of breast cancer include the breast or chest wall, the axilla, and the ipsilateral supraclavicular and internal mammary lymph nodes. Breast cancer typically starts in the ducts and then spreads to the lobules and lobes, and finally to the

lymph nodes. The number of breast cancer incidences from 2000-2003 was 199,479 for invasive cases and 44,913 for *in situ* cases (National Cancer Institute 2007b). Table 1 details the number of incidences by age and type. Using the previous data for 2005, the American Cancer Society estimated 211,240 new cases of invasive breast cancer would be diagnosed as well as 58,490 new cases of *in situ* breast cancer among women per year (American Cancer Society 2005). As a result of these case estimates, the American Cancer Society estimated 40,410 deaths from breast cancer yearly. Table 2 details the estimated number of new breast cancer cases and deaths in women by age for 2005.

The incomplete killing of malignant cancer cells that have spread throughout the body is a major failing in the management of breast cancer (Allen et al. 2003). There are several different options available for the treatment of breast cancer, such as chemotherapy, surgery, radiation therapy, and hormone therapy. Because of the different treatment options and the ongoing increase in breast cancer cases each year, an effective no/minimal risk imaging modality is needed in order to clearly identify tumors in and around the breast, so an effective treatment process can be implemented.

Table 1. Age Distribution (%) of breast cancer cases by site for all races, 2000-2003 (National Cancer Institute, 2007b).

	Age									
Site	<20	20-34	35-44	45-54	55-64	65-74	75-84	>85	All Ages	Cases
Invasive	0.0	1.9	10.6	22.1	22.8	20.4	16.8	5.4	100.0	199,479
In situ	0.0	0.8	11.5	27.6	25.0	20.3	12.5	2.2	100.0	44,913

Table 2. Estimated new breast cancer cases and deaths in women by age in the United States, 2005 (American Cancer Society 2006).

Age	In situ cases	Invasive cases	Deaths
Under 40	1600	9510	1110
40 and older	56890	201730	39300
Under 50	13760	45780	5590
50 and older	44730	165460	34820
Under 65	37040	123070	17470
65 and older	21450	88170	22940
All ages	58490	211240	40410

Breast cancer screening has been recommended for several decades and the majority of women over the age of 40 in the United States participate in screening activities (Elmore et al. 2005). There are rationales behind screening for a disease before it becomes clinically evident. They are primarily based on the principle that early detection allows for intervention that interrupts the natural history of the disease and prevents a detrimental outcome (Lee et al. 2004). The ideal screening test should be noninvasive or minimally invasive, be relatively inexpensive, and have both a low false-negative rate and low false-positive rate. In summary, the screening should produce more benefit than harm and do so at a cost that is affordable.

Imaging Modalities for the Detection of Breast Cancer

The primary imaging modality used to detect clinically occult breast cancer is mammography (Bluemke et al. 2004). However, due to the similarities of breast tissue and microcalcifications, mammography has limitations in both sensitivity and specificity which has led to the exploration of other imaging techniques. One of the most promising

substitutions for mammography is magnetic resonance imaging (MRI), which gives excellent soft tissue delineation with no radiation dose (Fig. 3).

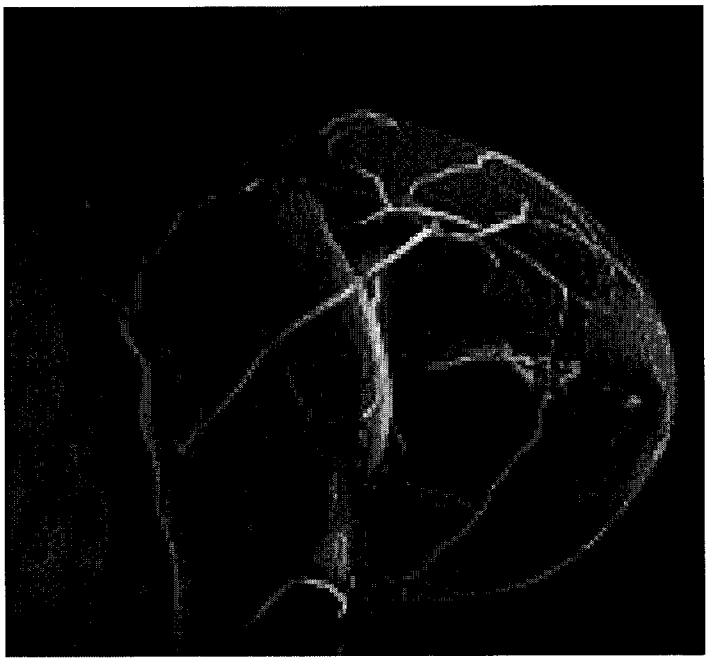


Figure 3. Side view MRI of the breast with contrast showing chest and blood vessels (MR Breast 2005).

The use of MRI for breast imaging has been approved by the United States Food and Drug Administration (FDA) to help diagnose breast cancer since 1991 (MR Breast 2005). Breast MRI is most commonly used to investigate breast concerns detected with mammography, physical exam, or other imaging modalities. MRI breast exams are likewise extremely useful in examination of the augmented breast. This includes both the breast implant and the surrounding tissue of the breasts. MRI is valuable for staging breast cancer, helping to determine the most appropriate treatment, and for patient follow-up after breast cancer treatment.

Researchers are investigating whether breast MRI would be useful in screening younger women at higher risk of developing breast cancer. Women younger than 40 years of age typically do not undergo mammography because of the high radiation exposure; monthly self breast examinations are considered sufficient. Some women, however, do suffer from a higher risk of breast cancer due to a strong family history or a mutated breast cancer gene, either BRCA 1 or BRCA 2. Women meeting these criteria should undergo some form of breast imaging before the age of 40. Since most young women have dense breast tissue, MRI may be a useful technology because of its effectiveness in distinguishing between dense tissue and tumors. However, currently the FDA has only approved mammography examinations to be used as a screening device for women with no symptoms of breast cancer. MRI is not approved by the FDA for younger women who may have an increased risk of breast cancer.

One of mammography's shortcomings is that it loses sensitivity when screening younger women, specifically those with dense breast tissue (Mitka 2003). Screening mammography is less effective in identifying breast cancer in dense breast tissue because dense breast tissue turns up as a bright region, similar to the appearance of cancerous tumors. As women age, the breast tissue tends to become less dense, thus increasing the effectiveness of screening mammography.

There has been recent debate about the amount of radiation dose a patient receives from routine screening mammography (Brenner et al. 2002). Glandular doses from screening mammography are typically low, usually less than 3 mGy of 26-30 kVp low-energy x-rays. The dose varies depending on the size of the breast, with larger breasts receiving a slightly higher dose.

Because mammography consists of ionizing radiation, there is an increased risk of developing breast cancer associated with screening exams. This risk is due to the exposure the breast receives from low energy x-rays which result in a factor of two increase for developing breast cancer (Brenner et al. 2002). However, it is highly unlikely that the radiation risk alone is cause for major concern for mammography for those women greater than 50 years of age.

While mammography uses low energy x-rays in imaging the breast, MRI uses powerful magnetic fields and radio waves to create images (MR Breast 2005). It is able to switch magnetic fields and radio waves to achieve views in any plane, yet mammography requires re-orientation of the breast and the mammography system for each view desired. Figure 4 depicts the normal breast imaging placement in MRI. The total MRI exam usually consists of a variety of T1 and T2 weighted sequences, which yields specific image orientations and specific types of contrast.

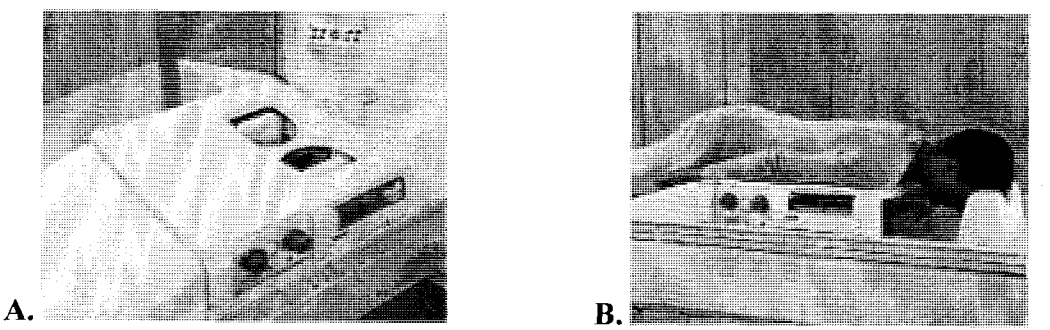


Figure 4. Image A shows a recent advancement in MRI breast imaging, the CP Breast Array Coil. This allows for bilateral breast imaging and improved differentiation between various breast tissues. With image B, the patient is placed directly on top of the table. The technologist has visual control of the breast position through a transparent window (MR Breast 2005).

Breast MRI has many benefits in helping to examine lesions and areas that may be missed by mammography, because MRI is highly sensitive to small abnormalities. A mammogram may reveal breast cancer in one area, but an MRI may show that the cancer is multi-focal, meaning small tumors are present in several areas of the breast. Determining the extent of breast cancer with MRI can help indicate the type of treatment the patient should undergo. Breast MRI is also useful in helping to determine how far the cancer has spread and to what areas, in addition to helping physicians determine cancer reoccurrences in women who have already been treated for breast cancer with lumpectomy.

While MRI has significant promise as a supplemental tool to mammography in the diagnosis of breast cancer, it still has several hurdles to overcome in order to gain wider acceptance and use (Mitka 2003). Breast MRI is not always able to distinguish between cancerous and non-cancerous abnormalities, more commonly known as false-positives. This can lead to unnecessary breast biopsies. Also, a biopsy of an MRI detected abnormality can be difficult. Physicians will have to learn how to use MRI to guide them to the abnormality. Researchers and manufacturers are continuously trying to develop new MRI systems and tools to allow for better MRI guided breast biopsy because the abnormality found with MRI may or may not be visible with mammography.

Breast MRI is unable to detect calcifications, while mammography can. Calcifications are tiny calcium deposits which can indicate the presence of breast cancer, typically associated with early stage breast cancers, such as ductal carcinoma in situ (DCIS).

Possibly the biggest drawback to using MRI, from a business perspective, is the cost. The average breast MRI costs approximately $1000. This is compared to approximately $100 per screening mammogram. Obviously to both the patient and insurance companies paying for the imaging procedure, a breast MRI needs to show significant benefits over mammography in order to justify the cost. Due to the current cost to benefit ratio, most community MRI centers do not perform breast MRI. However, new MRI systems designed specifically for the use of breast imaging are continuously being developed but are currently not widely available.

Magnetic Resonance Spectroscopy

MR Spectroscopy is the analysis of the shift, usually labeled as part per million (ppm), in resonance frequency of nuclei as a result of surrounding chemical bonds (Hendee and Ritenour 2002). Magnetic resonance spectroscopy (MRS) measures the differences in resonance frequencies among nuclei that occupy different positions in molecules. Each molecule resonates at a different frequency, due to their local magnetic fields. For example, on a 3.0 T spectrometer, N-acetyl aspartate (NAA) resonates at 2.0 ppm, creatine resonates at 3.0 ppm, and choline resonates at 3.2 ppm (Brown and Semelka 2003).

In spectroscopy, a broad range of radio frequencies is applied to the sample and a signal containing a range of frequencies is received (Hendee and Ritenour 2002). A Fourier transform is used on the return signal to determine what amplitude of each frequency is contained within the signal. All molecules and compounds are detected in the same magnetic field.

Proton MRS has started being used to help with breast cancer diagnosis. MRS provides the metabolic information about a visualized lesion in the breast (Lenkinski and Katz-Brull 2005). Thus, questionable lesions can be further examined without unnecessary biopsies. This not only helps the radiologist in their decision making, but also allows the patient to avoid the worry that is associated with questionable lesions. MRS coupled with MRI allows the radiologist to not only see the image of the lesion in the breast, but to also see the metabolic information of the lesion. A sample spectroscopy can be seen in Fig. 5.

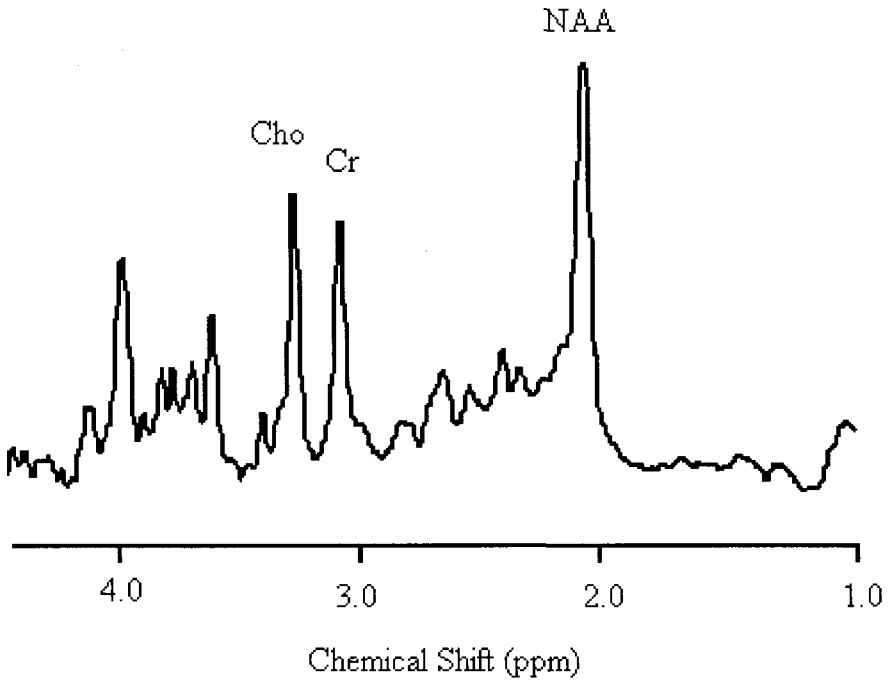


Figure 5. A proton spectra acquired on a 3.0 T system (Achieva 2007).

Magnetic Resonance Physics

Every proton and neutron of a nucleus has a magnetic field because of their nuclear spin and charge distribution. When placed in an external magnetic field, the nucleus will resonate (Bushberg et. al 2002). This is because of the properties of the nuclei spin quantum number. Both protons and neutrons have a spin quantum number of ½ and thus, because hydrogen has one proton, it has two energy states (Brown and Semelka 2003). Those nuclei that have an odd number of nucleons have a magnetic moment, which is the magnitude and direction of the magnetic field with respect to the nucleus.

A nuclear magnetic moment is generated from the nucleus of an atom since it is a spinning charged particle (Bushong 2003). Because the magnetic moment varies based on mass, charge of the particle and the rate at which it spins, each spin state has a different magnetic moment. Each spin state possesses the same energy until an external magnetic field is applied, at which point the spin states change energies.

In the external magnetic field, the spin state is typically in the lowest energy state possible. This allows the spin states to be in equilibrium with the magnetic field. When an electromagnetic pulse is applied to the field that has the equal energy to that of the particles spin state energy gap, some of the particles in the lower energy state are excited to a higher energy state. As the pulse terminates, the spins in the higher energy field return to the lower energy state. This process of returning to the lower energy states is what produces the magnetic resonance signal.

Review of Related Literature

There have been a few studies conducted that couple MRI with MRS to develop a more efficient way of detecting breast cancer. These studies have primarily been conducted on either 1.5 T or 4.0 T MR systems. The purpose of these studies was to improve the specificity of MR while maintaining the sensitivity. Sensitivity is how well an imaging system can detect subtle differences in anatomy, while specificity is the ability to precisely identify the reason for such differences (Bushong 2003). Magnetic resonance imaging of the breast is reported to have a sensitivity of 94-100% with variable specificity of 37-97% (Meisamy et al. 2005). Coupling MRI with MRS should increase the specificity.

In these studies, patients underwent an imaging protocol that consisted of a T1-weighted, a T2-weighted scans, and a spectroscopy scan. The studies measured success in different ways. One method measured success by discovering if elevated levels of choline reflect an incidence of breast cancer (Bolan et al. 2003). Another method tried to discover if the elevated levels of choline could distinguish between benign and malignant breast lesions (Roebuck et al. 1998). Another method used known results of breast lesions and had radiologists determine the type of treatment that should be taken based on only looking at the MR images, and then looking at the MR spectroscopy with the MR image and determining if there should be a change in treatment (Meisamy et al. 2005). These previous studies have shown that there is a cutoff for tCho concentration of 1.03 mmol kg^{-1} for distinguishing between benign and malignant lesions. A tCho concentration greater than 1.03 mmol kg^{-1} suggested malignancy and a concentration less than 1.03 mmol kg^{-1} suggested benignity. One other research method showed the

appearance of choline resonance peak based on the signal to noise ratio (SNR) of greater than two (Huang et al. 2004). An SNR equal to or greater than two was defined as a positive finding and a negative finding was defined as any SNR less than two.

Choline is an amine which is found in the breast. The total choline containing compounds (tCho) consists of several different choline compounds: choline, phosphocholine, glycerophosphocholine, phosphatidylcholine, and sphingomyelin. Since elevated levels of tCho have also been found in a variety of human tumors, a measure of the tCho level can help radiologists determine if a lesion is cancerous (Roebuck et. al 1998). The elevated levels of tCho vary, since different amounts of tCho are produced in the body depending on the individual.

The goal of this research is to determine whether MRI coupled with MRS is an effective imaging protocol for the detection of breast cancer using a 3.0 T Philips spectrometer, the highest clinically approved magnetic field strength. Success of this study will be determined by accurately comparing mammography diagnosis with the diagnosis from MRI coupled with MRS. Further aim of this study is to show comparable results obtained from the 3.0 T system to a 4.0 T system. A favorable comparison between the two would show that MRI coupled with MRS for the detection of breast cancer is applicable today, instead of having to wait for the approval of a 4.0 T system for clinical use.

CHAPTER 2

MATERIALS AND METHODS

Patient Preparation

Two groups of women between 18-80 years of age were imaged on a 3.0 T Philips Achieva MR spectrometer. The first group consisted of those women who were diagnosed cancer free, while the second were diagnosed with a form of breast cancer through conventional methods, i.e. mammography. Some women had a prior incidence of breast cancer and are currently in remission. These women were considered to be in the diagnosed cancer free group.

A Philips Achieva 3.0 T clinical spectrometer located at the Nevada Imaging Center Spring Valley - Amigenics was used for imaging and spectroscopy scans on all subjects. MR imaging and MR spectroscopy measurements were made using a Philips bilateral breast coil. The coil is designed to have the patient lie in the prone position.

The protocols used for each subject were a T1-weighted, a T2 SPAIR SENSE scan which is a fat suppression scan, a spectroscopy scan, dynamic thrive scan, and a thrive post scan. The last two scans were conducted after contrast was injected into the patient. The contrast agent was gadolinium diethylenetriamine pentaacetic acid (GDPA). GDPA is the most commonly used contrast agent for MR Imaging. There are potential risks involved with it. Gadolinium based contrast agents can cause nephrogenic systemic fibrosis (NSF) which causes fibrosis in different tissues throughout the body. It most

commonly occurs in those individuals with acute or chronic severe renal insufficiency or dysfunction. However, the chance of developing an anaphylactoid reaction as the result of GDPA is 0.03-0.1%. While the risk is low, no patient was imaged who had any history of renal problems. All patients choosing to participate in the study were informed of the potential side effects by a physician before beginning the scans. The TR and TE used for each of the scans can be seen in Table 3.

Table 3. MR scans parameters.

Scan	TR (ms)	TE (ms)
T1-weighted	425	8.0
T2 SPAIR	5874	120
Spectroscopy	1500	420
Dynamic Thrive	4.2	2.1
Thrive Post	1.8	2.5

The field of view varies with each patient. The total time for the MR imaging scans was approximately 20 minutes. Single voxel proton MR spectroscopy was performed using a slice of interest from the T2 SPAIR SENSE scan. The long echo time was used to help identify the choline peak, since this metabolite has a long T2 relaxation time. The long echo time also helps to eliminate the broad components of the water resonance. Water suppression was used to filter out the water resonance peak. With the water suppression, the total spectroscopy scan was approximately 10 minutes. The overall scan time varied for each patient depending on the size of the patient, the amount of tissue, the amount of fat, and the amount of water in the breast.

Radiologist Performance Study

Two radiologists specializing in the area of breast cancer diagnosis participated in reading the MRI scans for this study. Both readers were blinded to any medical information about the participants. Current diagnosis from the last mammography scan was not known to the radiologists. Each patient's MR images were read by each participating radiologist. The radiologists made their recommended diagnosis without referring to one another, based on MR images. A recommended patient treatment follow-up was also provided. These results were compared to the diagnosis made from the mammograms. The MR Spectroscopy scans recommendations were determined using the SNR from the choline peak on the graph.

CHAPTER 3

RESULTS

Patients

Recruitment fliers were mailed out to patients of the Nevada Imaging Center Spring Valley - Amigenics, where the imaging scans took place. Six patients were chosen to participate in the study, one of which was not a patient of Nevada Imaging Center Spring Valley – Amigenics, but referred by a doctor employed with the imaging center and familiar with this study. The mean age of the patients was 53 years with an age range of 43-69 years. All patients underwent a mammogram within the past year prior to their MR Imaging and Spectroscopy scans. All patients underwent an MRI scan on the Philips 3.0 T Spectrometer except for the patient who was referred to us. The IRB protocol and their rights were explained to each patient.

While a total of six patients were chosen to participate in this study, only four of the patients' results were included in the final analysis. This is due to a variety of reasons. The fifth patient who participated in this study was not included due to issues with digitizing her mammograms. The patients provided their most recent mammography scans, which were scanned into the computer database system at the Nevada Imaging Center Spring Valley – Amigenics. During the time period when the radiologists were preparing to read the scans, and before the scans were transferred to each of the radiologist's computer system, the computer containing all of the patients' MRI, MRS,

and mammography scans became inoperable. All of the scans for each patient were lost at this time. Eventually, after rebuilding the system, the information was recovered. However, the information for patient five was corrupt and incomplete. Much time was spent trying to recover and restore the original scans for this patient, but some of the data was permanently lost. The rest of the data that wasn't corrupt contained not enough information to be able to send to the radiologists for their readings. Since further inconveniencing the patient was not an option this patient was removed from the study.

Patient six was excluded from this study due to major difficulties handling outside MRI and mammography image data sets. While it was possible to examine the mammography and MRI scans and load them into the computer system at the imaging center, it was not possible to anonymize the scans. Since anonymizing the patient's scans was part of the protocol to both maintain patient privacy and abide by the Health Insurance Portability and Accountability Act (HIPAA), it was not possible to have this patients MRI and mammography results analyzed by the radiologists. Therefore, patient six was not included in the final results for this study.

There were also minor complications with the remaining four patients; however these complications did not prevent them from participating in this study. Out of the remaining four patients, only two of them, patient two and four, completed all of the scans. That is, they had a mammography completed within the year prior to undergoing the MRI and MRS and were able to deliver the films and radiologist's report from the mammography scan. They also both had MRI and MRS scans that were completed with the MRI results being read by two radiologists.

To determine which imaging protocols were ideal for breast MR Imaging coupled with MR Spectroscopy, different scans were investigated. Patient two completed all aspects of the study, but an additional T2-weighted scan was also performed. This patient was imaged early in the study while the imaging protocols were still being developed. At that time, it was thought the T2-weighted scan would help in identifying a suspicious lesion for a spectroscopy scan on because water and other fluid containing tissues are bright on this scan. The T2 SPAIR SENSE is a fat suppression scan which also made these tissues bright. After seeing the results of the T2-weighted scan and comparing it to the T2 SPAIR SENSE scan, it was decided to delete the T2-weighted scan, as it offered no benefit for either the MR technician performing the scan or for the radiologists reading the scan. It was decided to proceed with the patients from that point forward without the T2-weighted scan. The MR technician who conducted the imaging scans did not perform spectroscopy during the development of the protocol, and therefore one patient did not receive it. Once a final protocol was established with the MR Imaging and MR Spectroscopy scans, no additional scans were conducted and all of the scans in the protocol were performed.

The second patient who also completed all aspects of the study was patient four. This patient was imaged during the later stages of the study. For both patient two and patient four, the spectroscopy scan was conducted before the contrast injection so there would be no chemical interference with the selected voxel. A physician discussed the benefits and potential drawbacks of the contrast with each patient. A licensed technician performed the contrast injections and a physician was present during and after the entire scan time, in case the patient had a late reaction to the contrast agent. The mammography and MR

Imaging with and without contrast scans were all read by two radiologists. The MR Spectroscopy scan was analyzed by using previous literature, specifically the study conducted by Huang et al. 2004.

The other two patients whose results were chosen to be read by the radiologists had incomplete scans. Patient one was the first patient who was scanned as part of this study. The patient had a mammography scan within the year prior to having the MRI scan, but a copy of the films was never received from the patient and repeated attempts to obtain them were unsuccessful. It was decided to continue with the MRI scan with the hope of receiving the mammography films at a later date, but the films were still never received from the patient. Also during the scan, the MR technician did not perform the spectroscopy scan. The results from the MR Imaging scan were analyzed by both radiologists, but obviously no comparison can be made to the missing mammography scans. The lack of spectroscopy prevented the verification of the BI-RADS (Breast Imaging Reporting and Database System) diagnosis with the MRI scans.

The other patient who had incomplete results was patient three. The patient had incomplete results for different reasons than the first patient. This patient did deliver the mammography films to be scanned into the computer system at the imaging center. The patient then had both the MR imaging and spectroscopy scans completed with contrast. All scans were confirmed to be present. However, there was a problem with the data when the computer system crashed. While the mammography films that had been scanned in and the MR Imaging scans with the contrast agent were able to be recovered, the spectroscopy scan was lost. Again, a great deal of time was spent trying to discover why the MR Imaging scans were able to be recovered while the spectroscopy was not. It

was decided to proceed with only the mammography and MR Imaging scans. While there were two patients who had complete results that were going to be analyzed by the radiologists, both of those patients were thought to have either benign tumors, cysts, or no findings, patient three was known to have a BI-RADS diagnosis of 5 with malignant tumors present from the mammography scan. Having this patient's spectroscopy scan would have helped to confirm the malignant tumors seen in the mammography scan by analyzing the choline level as well as helping to measure the effectiveness of MR imaging coupled with spectroscopy. Table 4 lists the different BI-RADS categories and the respective diagnosis and criteria for each one.

Table 4. BI-RADS Scores (American College of Radiology 2003).

Category	Diagnosis	Criteria
0	Incomplete	Not enough information to make a diagnosis
1	Negative	Nothing to comment on
2	Benign	Definite benign finding
3	Probably benign	Finding has high probability of being benign
4	Suspicious abnormality	Reasonable probability of being malignant
5	Highly suspicious of malignancy	High probability of being malignant
6	Known biopsy proven malignancy	Known to be malignant

In regards to patient three it should be noted that mammography did not miss the malignant tumors. Upon talking to the patient about their medical history, it was discovered the patient had not undergone a mammography scan in over five years.

MR Imaging and Spectroscopy Results

Table 5 shows the results of each patient scanned. As can be seen in the table, only two of the four patients completed all aspects of the study. The mammography BI-RADS reading, two MRI BI-RADS reads by radiologists, and the spectroscopy level are all included. The spectroscopy level is determined using the SNR. An SNR of greater than or equal to 2.0 indicates a positive finding and an SNR of less than 2.0 indicates a negative finding. Any of the exams where patients' results were unavailable or not completed are marked with an X.

Table 5. Mammography and MRI findings using BI-RADS score. MRS findings used SNR score. MR Imaging scans were read by two radiologists.

Patient	Mammography	MR Imaging 1	MR Imaging 2	MR Spectroscopy
Patient 1	X	3	3	X
Patient 2	2	2	2	1.3
Patient 3	5	5	5	X
Patient 4	1	1	1	0.1

An X signifies exam either not completed or unavailable

Patient 1 received a BI-RADS score of 3 from each radiologist reading the MRI scans. Mammography and spectroscopy were unavailable for this patient. The BI-RADS score of 3 indicates that lesions are present in the breast and have a high probability of being benign. Figure 6 shows selected slices from each of the scans the patient underwent. The bright spots in the images indicate the lesions in the breast and help the radiologist diagnosis. Since the tumors are probably benign, a six month follow-up is recommended.

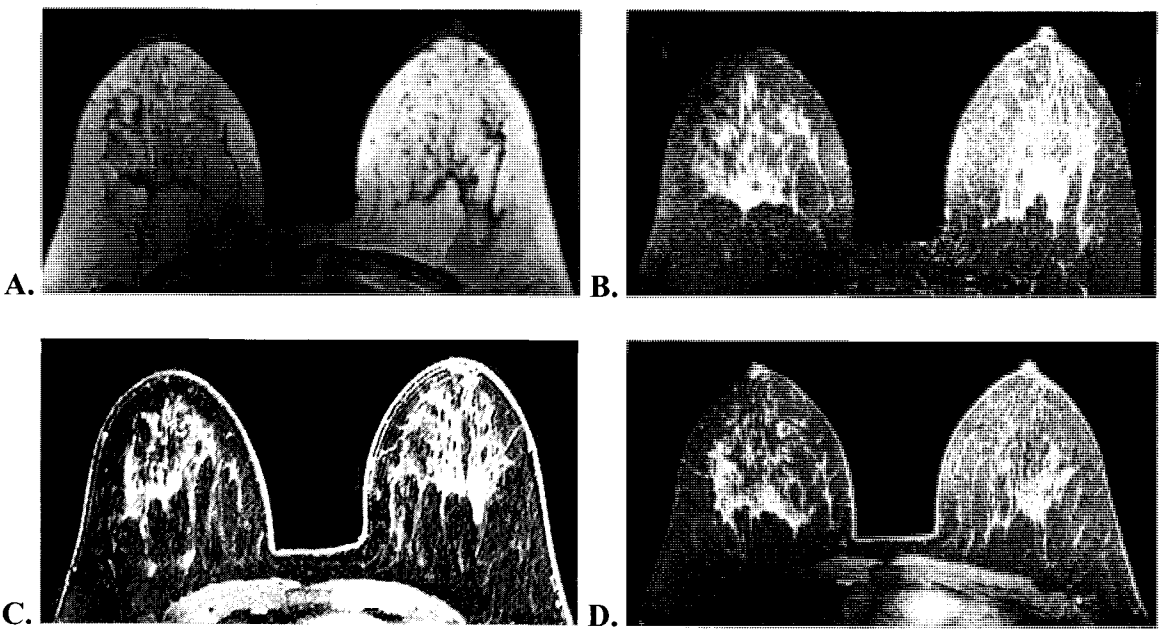


Figure 6. Patient 1 images from each scan performed. A) is slice 34 from the T1-weighted scan. B) is slice 34 from the T2 SPAIR scan. C) is slice 317 from the Dynamic Thrive scan. D) is slice 116 from the Thrive Post scan.

Patient 2 received a BI-RADS score of 2 from the radiologist reading the mammography scan and a BI-RADS score of 2 from each of the radiologists reading the MRI scans. The BI-RADS score of 2 indicates lesions or calcifications are present in the breast but are definitely benign. Figure 7 shows selected slices from each of the MR scans the patient underwent. The bright spots in the images indicate the presence of the benign lesions in the breast. Because the tumors are known to be benign, annual routine screening is recommended, corresponding to the SNR of 1.3 for the spectroscopy scan.

Spectroscopy results were only available for two of the four patients. The patients whose results were available were patient 2 and 4 as listed in Table 5. The results from the MR image for patient 2 show the possibility of tiny cysts within the selected voxel. The spectroscopy conducted on this patient shows a SNR of 1.3, indicating a negative finding. Based on the mammography scan, both radiologists' reads of the MR imaging

scans, and the low SNR level, a recommendation of continued annual screening mammography was recommended. Figure 8 shows the MR image of patient 2 as well as its corresponding MR Spectroscopy scan.

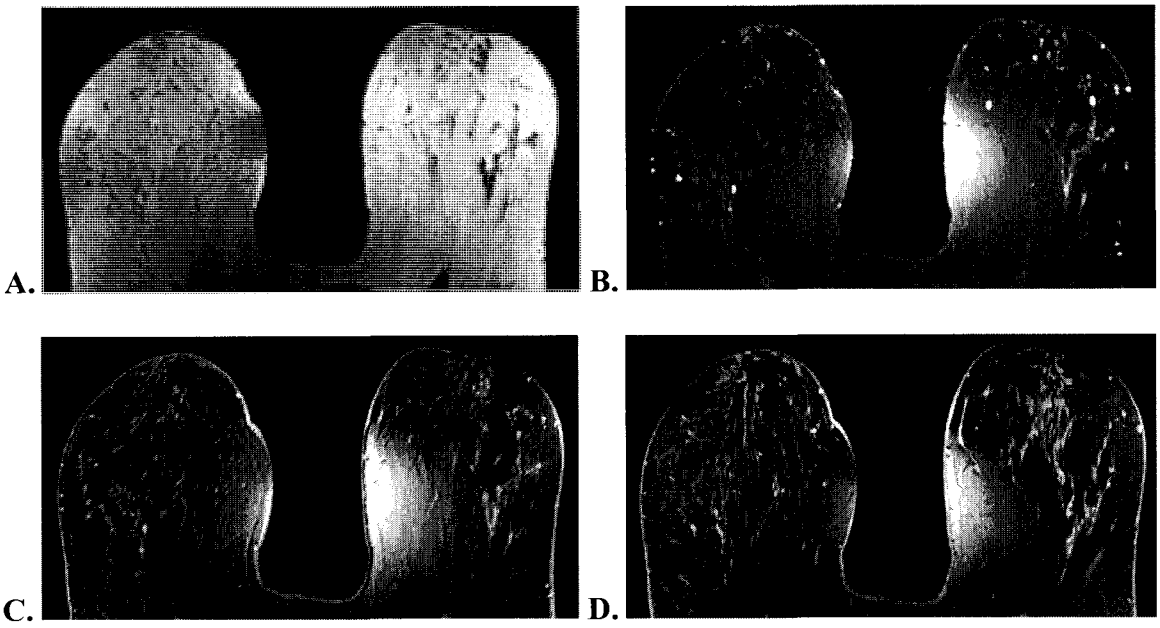


Figure 7. Patient 2 images from each scan performed. A) is slice 34 from the T1-weighted scan. B) is slice 34 from the T2 SPAIR scan. C) is slice 405 from the Dynamic Thrive scan. D) is slice 95 from the Thrive Post scan.

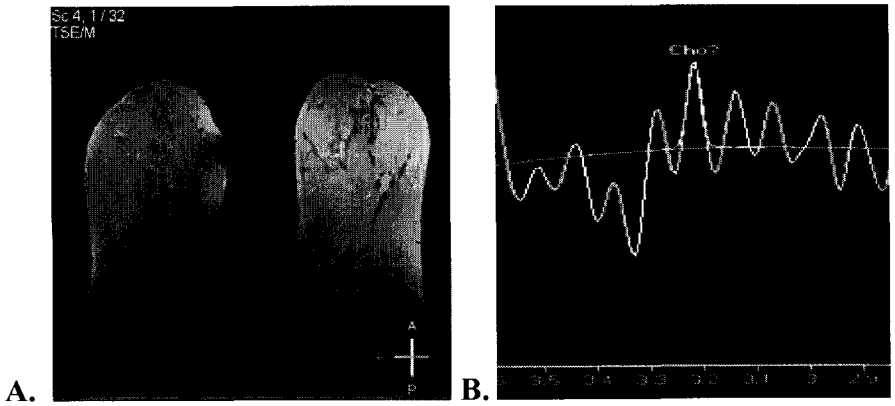


Figure 8. The MR image and spectroscopy results for patient 2 are shown in A) and B). The MR image in A) shows the voxel that was chosen outlined in the box on the left breast. In B), the choline peak is highlighted in the spectroscopy graph at 3.2 ppm, the position of tCho in a 3.0 T spectrometer. The SNR of 1.3 indicates a negative finding.

Patient 3 received a BI-RADS score of 5 from the radiologist reading the mammography scan and a BI-RADS score of 5 from each of the radiologists reading the MRI scans. The BI-RADS score of 5 indicates lesions are present in the breast and have a high probability of being malignant. MR images can be seen in Figure 9. A fairly large tumor can be seen in the left breast in the T2 SPAIR scan. The same tumor is seen even more clearly in the two contrast scans along with several other small lesions. For this diagnosis, appropriate action should be taken, whether it includes immediate surgery without biopsy, oncology treatment, or a different treatment method. Ultimately, the treatment method will be different for each patient. Spectroscopy was unavailable for this patient. Figure 9 shows selected slices from each of the scans the patient underwent.

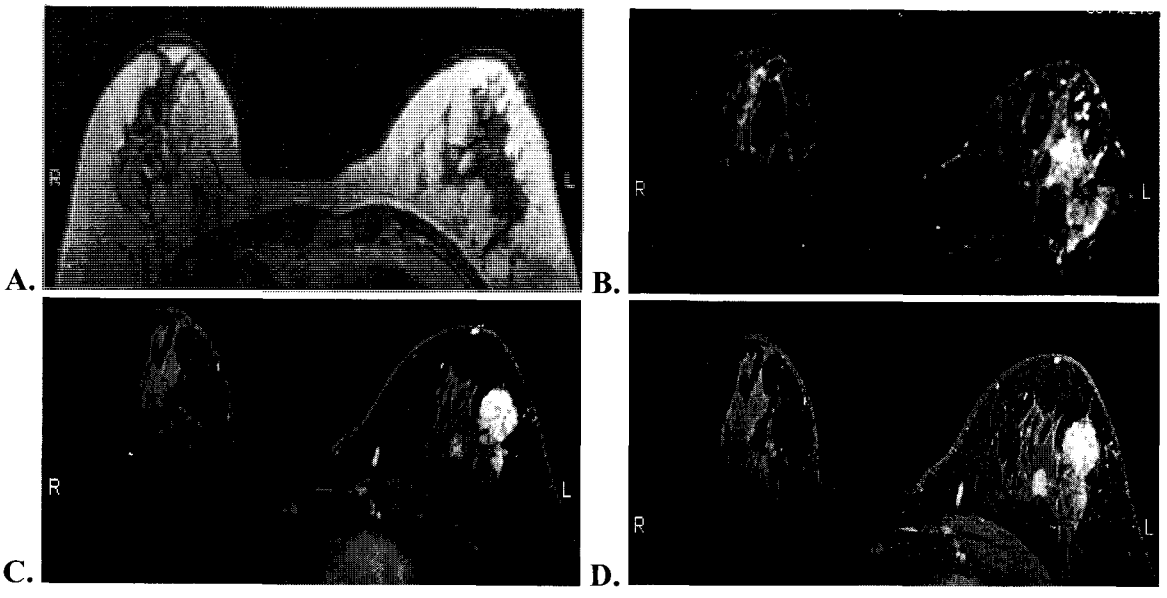


Figure 9. Patient 3 images from each scan performed. A) is slice 34 from the T1-weighted scan. B) is slice 34 from the T2 SPAIR scan. C) is slice 317 from the Dynamic Thrive scan. D) is slice 77 from the Thrive Post scan.

Patient 4 received a BI-RADS score of 1 from the radiologist reading the mammography scan and a BI-RADS score of 1 from each of the radiologists reading the

MRI scans. The BI-RADS score of 1 indicates there are no lesions or suspicious calcifications present in the breast and therefore nothing to comment on. Since no masses are seen, annual routine screening is recommended, corresponding to the SNR of 0.1 for the spectroscopy scan. Figure 10 shows selected slices from each of the scans the patient underwent.

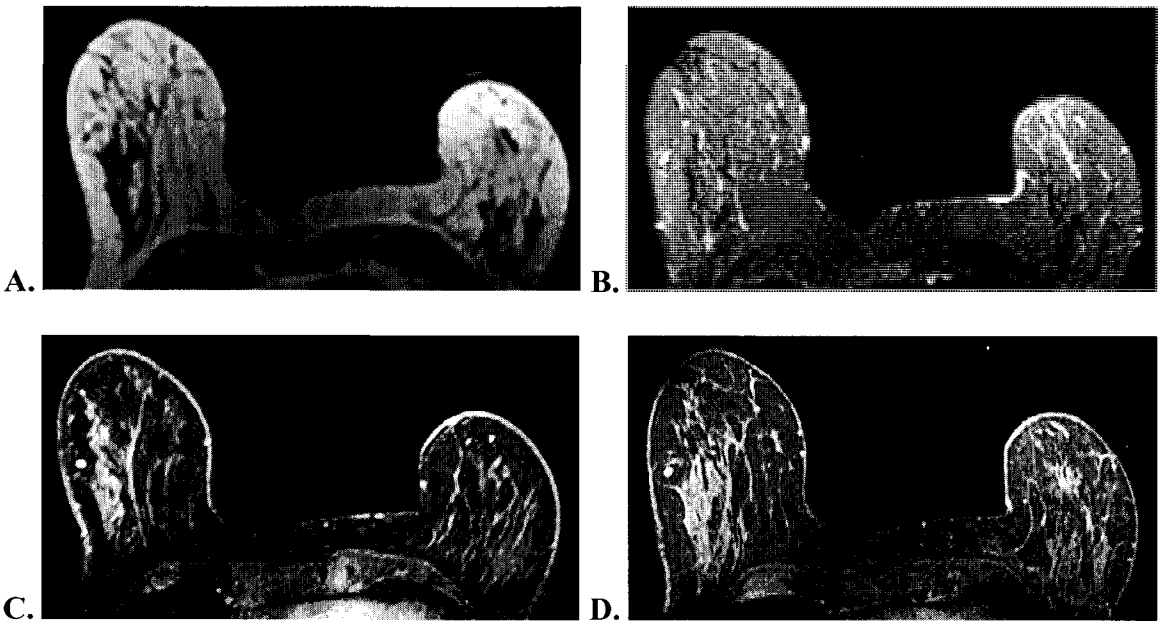
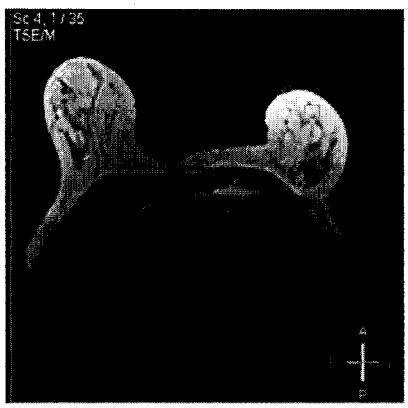


Figure 10. Patient 4 images from each scan performed. A) is slice 34 from the T1-weighted scan. B) is slice 34 from the T2 SPAIR scan. C) is slice 317 from the Dynamic Thrive scan. D) is slice 77 from the Thrive Post scan.

The results from the MR image for patient 4 identified no tumors or cysts. Spectroscopy was performed on the patient and an SNR of 0.1 was found, indicating a negative finding. Based on the mammography scan and both radiologists' reads of the MR imaging scans, and the low SNR level, a recommendation of continued annual screening mammography is still recommended. Figure 11 shows the MR image of patient 4 as well as its corresponding MR Spectroscopy scan.

A. 

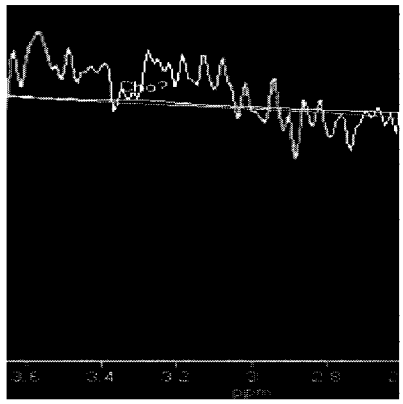
B. 

Figure 11. The MR image and spectroscopy results for patient 4 are shown in A) and B). The MR image in A) shows the voxel that was chosen outlined in the box on the left breast. In B), the choline peak is highlighted in the spectroscopy graph at 3.2 ppm, the position of tCho in a 3.0 T spectrometer. The SNR of 0.1 indicates a negative finding.

It is also possible to have a false positive with MR Spectroscopy. An SNR of greater than 2 can still be a negative finding, but it would be unknown whether it was a negative finding until after a biopsy was performed. A high SNR indicating the presence of a tumor could be due to several reasons, such as interference from other breast tissue in the voxel or the voxel not being an appropriate size for the suspected lesion.

Protocols

The breast MRI and MRS protocol took some time to develop because the Nevada Imaging Center Spring Valley – Amigenics does not offer breast MRI or MRS. A mixture of scans were initially used, but eventually discarded because they either revealed no beneficial information or had similar parameters to other scans and were therefore unnecessary. After several different scans were added or subtracted from the protocol, the researcher for this study decided on the final protocol that consisted of a T1-weighted, T2 SPAIR, Spectroscopy, Dynamic Thrive, and a Thrive Post scan. All four patients underwent each of the scans with the exception of patient 1 who did not have

spectroscopy conducted. Patient 3 completed all of the scans but the spectroscopy was lost when the computer system was inoperable.

Figures 6, 7, 9, and 10 show selected slices from each of the patients. The slices represented for each patient were chosen based on the image from each scan showing the most detail. Image A) in each of the figures is the T1-weighted scan. Each of the T1-weighted images appears bright, emphasizing the fat in the breast. The fat is easily seen in each patient, enabling the radiologist when looking at other scans to easily see if a potential lesion is actually fat by referring to the T1-weighted scan. Water and other fluids in the breast appear as dark intensity in each of the figures.

Image B) in each of the figures is the T2 SPAIR scan. Fat appears as a dark intensity and water and other fluids appear as bright intensities. The T2 SPAIR is a fat suppression scan which helps to emphasize the water in the breast as well as enhance any lesions that might be present. Since fat and water have different resonances, the fat is suppressed by introducing a prepulse to eliminate the quadrupole effects on fat suppression. The fat suppression adds to the overall scan time, but is vital in order to achieve the image quality seen in the images. With the fat suppressed, lesions appear bright and are easier to differentiate from water and other fluids that are present.

Image C) in each of the figures is the Dynamic Thrive scan. This is a T1 scan that has had gadolinium added as a contrast agent. The dynamic thrive scan is a quick scan showing the uptake of the agent in the breast almost immediately after it has been administered. Since the contrast agent is typically seen in the malignant and benign lesions in the breast before any other areas, a quick scan can help the radiologist easily differentiate the lesions from other areas in the breast.

Image D) in each of the figures is the Thrive Post scan. It is also a T1 scan aided with the use of a gadolinium contrast agent. This scan is an appropriate follow-up scan to the Dynamic Thrive scan because it still has the benefits of the contrast agent uptake in the lesions, but also the contrast has been absorbed by the rest of the breast by this point in the scanning protocol. It offers more detail to the overall breast while still showing the lesions as bright spots.

CHAPTER 4

CONCLUSIONS

MR imaging for the detection of breast cancer has shown promise but there are issues still associated with it, such as time of exam, cost, and false positives, that overall make it an imaging modality that does not currently offer the screening benefits of mammography. The use of MR spectroscopy for the detection of breast cancer is still a fairly new concept and is not widely utilized. However, MR imaging coupled with MR spectroscopy is showing promise.

While there were only a small number of patients scanned for this study, there are positives voiced by the patients. All of the patients liked the fact that the MRI offered an alternative to the breast compression associated with mammography scans in order to produce the best possible image. The ease of the entire exam was also cited as a positive by all patients. The patients also expressed enthusiasm with regards to the fact that there is no radiation dose from the MR imaging or spectroscopy exams as is the case with mammography.

There were also some negatives about the exam that some of the patients noted. The primary concern about the exam was the length of time. While a mammography scan can take as little as 10 or 15 minutes, the MRI and MRS exams take approximately 30-40 minutes. The patients that received a contrast injection also cited this part of the exam as a negative. Specifically, the patients didn't like the fact that the needle was placed into

their hand during the prep before the scan took place, and then they had to wait until the part of the scanning protocol to receive the injection before the needle was removed. The MRI bore can also get extremely loud during some of the exams and this was noted as more of an annoyance as opposed to a negative.

One major complication with regards to this study was the lack of patients. This was due to several reasons. The most common complaint from potential patients was the time the imaging and spectroscopy scans would take place. Most of the exams had to be conducted at night. This was because the Philips 3.0 T spectrometer is in high demand due to the rarity of the magnetic strength in the Las Vegas valley and the quality of images that can be seen from it. The MRI is in use seven days a week for approximately 16 hours a day, leaving only a small window at night when it was available to be used for research purposes. Many potential patients said the only time available for them to volunteer for the study was during normal day time hours. Therefore the time of the exams was a turnoff for many potential patients. Several potential patients were unable to be imaged due to metal objects being located inside their bodies and the concern the magnets could potentially cause physical harm.

Because of the small number of patients and the incomplete scans for a couple of them, it is hard to measure the diagnostic performance of MR spectroscopy. The two patients who completed all the scans, mammography, MR imaging, and MR spectroscopy, show MR imaging and spectroscopy to be effective methods. Both patients MR images read by the radiologists confirmed the recommendations of the radiologist who read the mammography scans. The results from the spectroscopy graphs also

confirmed these results, indicating that MR imaging coupled with spectroscopy is an effective imaging modality for diagnosing breast cancer.

MR Spectroscopy helps to determine the diagnosis and recommended follow-up for the patient, but does have a drawback seen in this study. Patient four had been diagnosed as a BI-RADS 1 from the mammography scan, indicating a negative finding. Since a negative finding means there is nothing to report, it is difficult to run spectroscopy if there are no lesions present. The use of MRI does help to see lesions that may go undetected with mammography, but could also produce the same result. In these cases where the patient clearly has no lesions present and is a negative finding, it is probably not worth the either the MR technologist or the patients' time to undergo this scan. More research is needed to determine if this is valid conclusion or just a rare case that appeared in this study.

Though the number of patients was low, some findings can be noted. Both of the radiologists were in agreement with each other as to the BI-RADS diagnosis. While MRI for the detection of breast cancer is not widely used, radiologists coming to the same conclusion while not previously seeing a large number of MRI breast scans shows promise that these image sets are not too complicated to analyze for the inexperienced. This is especially a good sign since the four patients each had a different diagnosis, yet the radiologists still came to the same conclusions.

The use of the gadolinium contrast agent is a definite must for any breast MRI protocol. The contrast agent uptake in the breast by the lesions clearly helps the radiologist identify not only obvious larger lesions seen in the T1-weighted and T2 SPAIR scans, but also smaller lesions that may have gone unnoticed. The T1-weighted

and T2 SPAIR scans should also be included in the protocol due to the benefits of differentiating the tissue relaxation times in the breast. The fat tissue appearing as a bright intensity in the T1-weighted scan and water and other fluids appearing as bright intensity in the T2 SPAIR again help to differentiate the different tissues and fluids that make up the breast and aid the radiologist in making a better diagnosis and recommended follow-up.

Previous studies of MR imaging coupled with spectroscopy for the detection of breast cancer have been primarily conducted on 1.5 T spectrometers, with a few studies conducted on a research based 4.0 T spectrometer. Obviously the number of patients used in the study is not ideal, and a larger volume would produce more complete results, the few patients that imaged show positive results and incentive to continue the research on a broader scale. The MR image exams were consistent with the mammography BI-RADS results. The spectroscopy results both confirmed that any suspected lesions discovered and analyzed within the voxel area were negative findings.

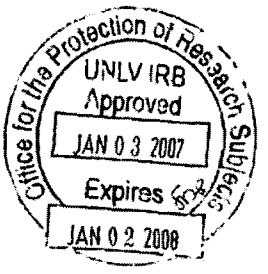
There needs to be continued research conducted with MR Imaging coupled with MR Spectroscopy, but the use of a contrast agent is essential for helping to emphasize potential lesions in the breast. Continued research on a 3.0 T spectrometer will help to conclude whether MR Imaging coupled with Spectroscopy is an effective imaging modality for the detection of breast cancer.

APPENDIX I

IRB APPROVAL LETTER

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

Biomedical IRB – Expedited Review Approval Notice



NOTICE TO ALL RESEARCHERS:

Please be aware that a protocol violation (e.g., failure to submit a modification for any change) of an IRB approved protocol may result in mandatory remedial education, additional audits, re-consenting subjects, researcher probation suspension of any research protocol at issue, suspension of additional existing research protocols, invalidation of all research conducted under the research protocol at issue, and further appropriate consequences as determined by the IRB and the Institutional Officer.

DATE: January 8, 2006

TO: **Dr. Phillip Patton**, Health Physics

FROM: Office for the Protection of Research Subjects

RE: Notification of IRB Action by Dr. Charles Rasmussen, Co-Chair
Protocol Title: **Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer**
Protocol #: 0611-2139

This memorandum is notification that the project referenced above has been reviewed by the UNLV Biomedical Institutional Review Board (IRB) as indicated in regulatory statutes 45 CFR 46. The protocol has been reviewed and approved.

The protocol is approved for a period of one year from the date of IRB approval. The expiration date of this protocol is 2, 2008. Work on the project may begin as soon as you receive written notification from the Office for the Protection of Research Subjects (OPRS).

PLEASE NOTE:
Attached to this approval notice is the **official Informed Consent/Assent (IC/IA) Form** for this study. The IC/IA contains an official approval stamp. Only copies of this official IC/IA form may be used when obtaining consent. Please keep the original for your records.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

Should the use of human subjects described in this protocol continue beyond 2, 2008 it would be necessary to submit a **Continuing Review Request Form** *60 days* before the expiration date.

If you have questions or require any assistance, please contact the Office for the Protection of Research Subjects at OPRSHumanSubjects@unlv.edu or call 895-2794.

Office for the Protection of Research Subjects
4505 Maryland Parkway • Box 451047 • Las Vegas, Nevada 89154-1047
(702) 895-2794 • FAX: (702) 895-0805

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

INFORMED CONSENT

Department of Health Physics

TITLE OF STUDY: Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

INVESTIGATOR(S): Robert Etnire, Phillip Patton

CONTACT PHONE NUMBER: 702-895-3555 (Phillip Patton), 702-869-5889 (Rob Etnire)

Purpose of the Study

You are invited to participate in a research study. The purpose of this study is to investigate Magnetic Resonance Imaging (MRI) as a new methodology for identifying breast cancer using various imaging procedures.

Participants

You are being asked to participate in the study because your mammography scans have indicated the possibility of breast cancer, or you are healthy and have not been previously diagnosed with breast cancer and are between the ages of 18 and 80 with no known medical conditions such as pregnancy, metal implants, claustrophobia, etc., that would prevent you from being imaged by MRI.

Procedures

If you volunteer to participate in this study and are selected, you will be asked to do the following: lie on your stomach for approximately 45-60 minutes while the imaging procedure is occurring and complete a questionnaire about your medical history and a questionnaire about the procedure.

Benefits of Participation

There *may not* be direct benefits to you as a participant in this study. However, we hope to learn that Magnetic Resonance Imaging coupled with Magnetic Resonance Spectroscopy is effective for the diagnosis of breast cancer, thus reducing the radiation exposure women receive from their annual mammograms.

Risks of Participation

There are risks involved in all research studies. This study may include minimal risks. It is possible that some participants may experience claustrophobia during the procedure. Additionally, participants may fall while getting on or off the imaging table. Subjects may feel uneasy about the medical history questionnaire as well.

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

INFORMED CONSENT

Department of Health Physics

TITLE OF STUDY: Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

INVESTIGATOR(S): Robert Etnire, Phillip Patton

CONTACT PHONE NUMBER: 702-895-3555 (Phillip Patton), 702-869-5889 (Rob Etnire)

Cost /Compensation

There *will not* be a financial cost to you to participate in this study other than time and money needed to travel to and from the imaging center. The study will take approximately 45 - 60 minutes of your time. You *will not* be compensated for your time. *The University of Nevada, Las Vegas may not provide compensation or free medical care for an unanticipated injury sustained as a result of participating in this research study.*

Contact Information

If you have any questions or concerns about the study, you may contact **Robert Etnire** at **702-869-5889** or **Phillip Patton, PhD** at **702-895-3555**. For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, you may contact **the UNLV Office for the Protection of Research Subjects at 702-895-2794.**

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may stop participating in this study at any time for any reason without prejudice to your relations with the university. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality

All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for at least 3 years after completion of the study. After the storage time the information gathered will be shredded.

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

INFORMED CONSENT

Department of Health Physics

TITLE OF STUDY: Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

INVESTIGATOR(S): Robert Etnire, Phillip Patton

CONTACT PHONE NUMBER: 702-895-3555 (Phillip Patton), 702-869-5889 (Rob Etnire)

Participant Consent:

I have read the above information and agree to participate in this study. I am at least 18 years of age with no medical conditions (pregnant, metal implants, claustrophobia, etc.) that prevent me from being imaged using a magnetic resonance imaging spectrometer. A copy of this form has been given to me.

_____ _____

Signature of Participant Date

_____

Participant Name (Please Print)

Participant Note: Please do not sign this document if the Approval Stamp is missing or is expired.

APPENDIX II

MRI IMAGE ACQUISTION STEPS

Imaging and Spectroscopy Scans

1. Select 'Patient' on the menu bar.

2. Select 'New Exam.'

3. Enter the following information:
    a. Patient's coded name.
    b. Registration number.
    c. Patient's date of birth (MM/DD/YYYY).
    d. Patient gender as female.
    e. Patient's weight (in kg).
    f. Any additional comments.
    g. The other fields can be left blank.

4. Clink 'Enter.'

5. Click 'Proceed.' The system will not automatically switch to scan mode.

6. Select the 'Hospital' folder in the Exam Cards.

7. Select the folder 'User Defined 3.'

8. Scroll down and select the 'Breast' folder.

9. Select the first scan list 'Breast.'

10. Copy the scans and paste them in the Exam Cards.

11. Delete all scans except the Survey, Ref_SBrst, sT1W_TSE_Tra, sT2W_TSE_Tra, DYN_THRIVE SENSE, THRIVE_HR POST SENSE. These are the only imaging scans that are needed.

12. Next, add the spectroscopy scan.

13. Select the 'Hospital' folder in the Exam Cards

14. Select the 'Thorax' folder.

15. Copy and paste the 'Breast Spectroscopy' scan into the Exam Cards, placing it after the sT2W_TSE_Tra scan and before the DYN_THRIVE SENSE scan. The scan is named SV_PRESS_270.

16. In the Exam Cards, click on 'Status' for the Survey scan to open up the scan. Click 'Proceed' to start the Survey scan. The Survey scan will now begin.

17. When the Survey has finished, click on 'Status' in the Exam Cards for the Ref_SBrst to open up the scan. Click 'Proceed' to start the Ref_SBrst scan. The Ref_SBrst scan will now begin.

18. When the Ref_SBrst has finished, click on 'Status' in the Exam Cards for the sT1W_TSE_Tra to open up the scan. Select the 'Parameter Editor' on the Exam Cards Toolbar. Under the 'Initial' tab, use the Survey scan as a guide and adjust the field of view (FOV) to the size of the breast. Under the 'Geometry' tab, turn SENSE off and change the Matrix scan to 256. Click 'Proceed' to start the sT1W_TSE_Tra scan. The sT1W_TSE_Tra scan will now begin.

19. Repeat the steps used for the sT1W_TSE_Tra for the T2 SPAIR SENSE, DYN_THRIVE SENSE, and THRIVE_HR POST SENSE. The previous scans do not need to be finished to edit the following scans, with the exception of the SV_PRESS_270 scan. If the previous scan has not finished and the edit has been completed for the following scan, click 'Proceed' for this scan. It will start automatically once the previous scan has finished.

20. Once the T2 SPAIR SENSE has been completed, click on 'Status' in the Exam Cards for the SV_PRESS_270 to open up the scan. Select a slice from the T2 SPAIR SENSE that shows the suspicious area where the spectroscopy will be performed. A red box will appear in about 10-20 slices. This is the voxel box where the spectroscopy will be performed. Try to conform the voxel box to the exact size of the suspected area. Click 'Proceed' to start the SV_PRESS_270 scan. The SV_PRESS_270 scan will now begin.

21. The software will automatically adjust for the water suppression.

22. Following the water suppression, the scan will now begin.

23. When the SV_PRESS_270 scan has been completed, the contrast should be administered. Once the injection is complete, start the DYN_THRIVE SENSE scan. The scan preparation should have already been completed as stated in step 19.

24. Once the DYN_THRIVE SENSE scan has been completed, the THRIVE_HR POST SENSE will begin. This is the last scan in the protocol.

25. Once the protocol is completed, click on the 'Advance Processing Button' next to the patient name.

26. Double click on the figure of the peaks. This will load the spectroscopy curve into the main window.

27. Click 'Run Script.' This will load the graph for the voxel.

The protocol being used consists of the following scans

Survey

Ref_SBrst

Reference scan for bilateral SENSE Breast coil

-The sensitivity information obtained in this scan is used for all CLEAR reconstructions during the entire exam.

Tip:

If large patient movement has occurred, the reference scan should be repeated.

sT1W_TSE_Tra

A T1 weighted turbo spin echo (TSE) sequence of the breast

- The 's' stands for single shot
- Due to CLEAR, the axillae can also be clearly visualized
- Randomized shots are used to minimize motion artifacts

T2 SPAIR SENSE

A T2 fat suppression scan

SV_PRESS_270

MR spectroscopy scan

DYN_THRIVE SENSE

T1 weighted scan with contrast

THRIVE_HR POST SENSE

T1 weighted scan with contrast

Patient Positioning

1. Place the couch in the parking position by using the Out/Down tumble switch on the control panel. If imaging a heavy patient, do not place the couch in the parking position. Instead, place a couch about 15 cm from its lowest point.

2. Place the breast coil on the couch. Do not plug the coil into the scanner at this time. For comfort, place a few pillows at the head of the couch for the patient to rest their head on and place the coil directly behind these pillows. Place the breast mattress directly behind the coil. Add any other mattress as needed for patient comfort. Be sure the patient is as comfortable as possible to minimize motion artifacts. Blankets or sheets may be used as the room may become cool during the procedure.

3. Have the patient remove any metal items they are wearing. Give the patient a gown to wear with the opening in the front. The patient must not wear a shirt or bra during the procedure. Give the patient earplugs for their protection. The acoustic noise levels may cause some discomfort for patients without earplugs.

4. Have the patient lie down in the prone position on the couch. The breasts should be placed in holes in the coil and hang freely. The gown can hang on the sides of the coil, but cannot be in the coil holes.

5. Press the 'light visor' button on the control panel. This will activate the laser beams. Raise the couch using the Up/In tumble switch. Using the laser beams, place the patient so the breasts lie in the middle of the illuminated cross. Press 'Travel-to-scanplane' button on the control panel. The laser beams will turn off automatically. Use the Up/In tumble switch to place the patient into the tube. The couch will stop moving once the isocenter has been reached. The coil may now be plugged into the scanner.

6. Once all the scans have finished, remove the patient from the tube. Use the Out/Down tumble switch on the control panel until the couch is in the parking position. If imaging a heavier patient, stop the couch at about 15 cm above the lowest level.

APPENDIX III

MRI DEFINITION OF TERMS

CLEAR

- Stands for Constant LEvel AppeaRance
- Provides a superb uniformity correction
- It is automatically implemented in all SENSE protocols
- Requires that a reference scan be performed. The reference scan provides a sensitivity map of the coil enabling the system to calculate the exact signal contribution to each pixel of the image.

SENSE

- Stands for SENSitivity Encoding
- Potential benefits include:
    - Shorter scan times
    - Higher temporal resolution
    - Improved spatial resolution
    - Less motion and susceptibility artifacts

SPAIR

- Stands for SPectral Attenuated Inversion Recovery
- Fat suppression technique

SNR

- Stands for Signal to Noise ratio
- Measure of image quality

THRIVE

- Stands for T1 High Resolution Isotropic Volume Excitation
- Used with contrast for dynamic studies

APPENDIX IV

COPYRIGHT PERMISSION LETTERS

National Cancer Institute

-----Original Message-----
From: NCI Cancer.gov Staff <cancer.gov_staff@mail.nih.gov>
To: re182@aim.com; Re182@aol.com
Sent: Fri, 9 Mar 2007 11:28 am
Subject: RE: Cancer.gov Inquiry - Copyright Information

This follow-up message is in response to the e-mail you recently sent to the
National Cancer Institute's (NCI) Web site, http://www.cancer.gov, regarding
acknowledgement requirements for the use of content on our site. We apologize
for the delayed response. Both of the illustrations you mentioned
(http://www.cancer.gov/cancertopics/wyntk/breast/page2 and
http://training.seer.cancer.gov/ss_module01_breast/unit02_sec01_anatomy.html)
are in the public domain and may be used freely. Acknowledgement of the sources
is appreciated, but not required.

We prefer the following format when referencing content in the "What You Need To
Know About(tm) Cancer" publications:

National Cancer Institute. What You Need To Know About(TM) Breast Cancer
(http://www.cancer.gov/cancertopics/wyntk/breast). Posted 07/30/2005.

Source acknowledgement for information from the SEER Training Web site may be
stated as follows:

From http://www.training.seer.cancer.gov; funded by the U.S. National Cancer
Institute's Surveillance, Epidemiology, and End Results (SEER) Program, via
contract number N01-CN-67006, with Emory University, Atlanta SEER Cancer
Registry, Atlanta, Georgia, U.S.A.

We hope this information is helpful.

National Cancer Institute Staff

NOTE: You may get an error message when clicking on the URL link(s) in this
e-mail. If you copy and paste the full URL into your browser window, you should
not have a problem opening the link.

From: re182@aim.com [mailto:re182@aim.com]

Sent: Monday, March 05, 2007 7:31 PM
To: NCI Cancer.gov Staff
Subject: Re: Cancer.gov Inquiry - Copyright Information

Thank you for your help. I look forward to your reponse.

Robert Etnire

-----Original Message-----
From: cancer.gov staff@mail.nih.gov
To: Re182@aol.com
Sent: Mon, 5 Mar 2007 1:06 PM
Subject: RE: Cancer.gov Inquiry - Copyright Information
This message is in response to the e-mail you recently sent to the National Cancer Institute's (NCI) Web site, http://www.cancer.gov, regarding the use of content posted on our site.

We are trying to find out if the two illustrations you mentioned are in the public domain. If they are in the public domain, no copyright forms
will need to be completed. If the illustrations are not in the public domain, we will try to provide contact information for the owner of the illustrations.

We apologize for the delay and will send a response as soon as possible.
Thank you for your patience.

National Cancer Institute Staff

NOTE: You may get an error message when clicking on the URL link(s) in this e-mail. If you copy and paste the full URL into your browser window, you should not have a problem opening the link.

-----Original Message-----
From: Re182@aol.com [mailto:Re182@aol.com]
Sent: Wednesday, February 28, 2007 11:34 AM
To: NCI Cancer.gov Staff
Subject: Cancer.gov Inquiry - Copyright Information

Message: To whom it may concern:

I am a graduate student at UNLV. I am currently working on my thesis and I would like to include two images from your website in my research paper. In order to do so, I would need permission from you to use the image. The images I would like to use can be found at these websites: http://www.cancer.gov/cancertopics/wyntk/breast/page2 and http://training.seer.cancer.gov/ss module01 breast/unit02 sec01 anatomy
.
html. I can send the copyright page that would need to be filled out, signed, and mailed to me as an attachment in an email. The copyright page will be included in my thesis granting me permission. If possible,
can you please send a reply to my email address letting me know about your decision. Also, if you do grant me permission, the sooner I

receive the filled out copyright form, the better. Thank you in advance
for your help.

Robert Etnire
7937 Terrace Rock Way #101
Las Vegas, NV 89128

re182@aol.com

American Cancer Society

March 12, 2007

American Cancer Society

Attention: Reprints

To whom it may concern,

My name is Robert Etnire and I am a graduate student at the University of Nevada, Las Vegas. I am currently working on my thesis and will like to include some information from your website in it. I am researching the use of MRI coupled with MRS on a 3.0 T spectrometer for the detection of breast cancer. The research is in support of my thesis to earn my Master of Science degree in Health Physics.

I am requesting to use a table from the pdf file titled "Breast Cancer Facts and Figures 2005-2006." Specifically, I am requesting the use of Table 2. Estimated New Breast Cancer Cases and Deaths in Women by Age, US, 2005. The document is located at the web address: http://www.cancer.org/downloads/STT/CAFF2005BrFacspdf2005.pdf and a copy of the table is on page 3 of this document. Page 3 from this document has been included as part of the fax.

The table will be included in its entirety in my thesis as background information detailing the number of people by age stricken with breast cancer, as well as the number of deaths from it. The table will be cited both in the text and in a references page at the end of the thesis. In addition, a copyright page will be included in a separate section, detailing that permission was granted from the American Cancer Society to reprint the table.

The copyright page that I need filled out is included as part of this fax. It will either need to be mailed to me since it requires a signature, or scanned into a document and emailed. If the table from the document requested is public domain, then no copyright form is needed. However, I still need confirmation stating the document and the table requested is public domain. Proper citation will still be given as previously mentioned.

A final copy of the thesis will be shelved in the library at UNLV, as well as placed on microfilm. The thesis will not be sold, but may be referenced to in the future by other researchers.

Thank you for your help regarding my thesis. If there is any other information needed, please feel free to contact me by any of the methods listed below. Also, if there is anything I can do to speed up the request process, please let me know that as well. Thank you again.

Sincerely,
Robert Etnire

7937 TERRACE ROCK WAY #101
LAS VEGAS, NV 89128
PHONE: 702-869-5889
EMAIL: RE182@AOL.COM

REFERENCES

Achieva 3.0T Philips Medical System. 3.0T Intera Philips Medical Systems Clinical Benefits [online]. Available at: http://www.mr.ethz.ch/3t/clinical_benefits.html. Accessed on 21 January 2007.

Allen BJ, Rizvi S, Li Y, Tian Z, Ranson M. In vitro and preclinical targeted alpha therapy for melanoma, breast, prostate and colorectal cancers. Critical Reviews in Oncology/Hematology. 39:139-146; 2001.

Allen BJ, Tian Z, Rizvi SMA, Li Y, Ranson M. Preclinical studies of targeted alpha therapy for breast cancer using 213Bi-labelled-plasminogen activator inhibitor type 2. British Journal of Cancer. 88: 944-950; 2003.

American Cancer Society. Breast cancer facts and figures 2005-2006 [online]. Available at: http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf. Accessed 14 March 2006.

American College of Radiology. Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas) [online]. Available at: http://www.acr.org/SecondaryMainMenu Categories/quality_safety/BIRADSAtlas.aspx. Accessed 14 April 2009.

Bartella L, Morris EA, Dershaw DD, Liberman L, Thakur SB, Moskowitz C, Guido J, Huang W. Proton MR spectroscopy with choline peak as malignancy marker improves positive predictive value for breast cancer diagnosis: preliminary study. Radiology. 239: 686-692; 2006.

Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, Heywang-Köbrunner SH, Hylton N, Kuhl CK, Lehman C, Pisano ED, Causer P, Schnitt SJ, Smazal SF, Stelling CB, Weatherall PT, Schnall MD. Magnetic resonance imaging of the breast prior to biopsy. Journal of the American Medical Association. 292: 2735-2742; 2004.

Bolan PJ, Meisamy S, Baker EH, Lin J, Emory T, Nelson M, Everson LI, Yee D, Garwood M. In vivo quantification of choline compounds in the breast with 1H MR spectroscopy. Magnetic Resonance in Medicine. 50: 1134-1143; 2003.

Brenner DJ, Sawant SG, Hande MP, Miller RC, Elliston CD, Fu Z, Randers-Pherson G, Marino SA. Routine screening mammography: how important is the radiation-risk side of the benefit-risk equation? International Journal of Radiation Biology. 78: 1065-1067; 2002.

Brown MA, Semelka RC. MRI basic principles and applications, 3rd ed. Hoboken, New Jersey: John Wiley and Sons, Inc.; 2003.

Buchholz TA, Strom EA, McNeese MD. The breast. In: Cox JD, Ang KK, eds. Radiation oncology: rationale, technique, results, 8th ed. St. Louis, MO: Mosby; 2003: 333-385.

Bushberg JT, Seibert JA, Leidholdt EM, Boone JM. The essential physics of medical imaging, 2nd ed. Philadelphia, PN: Lippincott Williams & Wilkins; 2002.

Bushong SC. Magnetic resonance imaging, 3rd ed. St. Louis, MO: Mosby; 2003.

Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. Journal of the American Medical Association. 293: 1245-1256; 2005.

Hendee WR, Ritenour ER. Medical imaging physics, 4th ed. New York: Wiley-Liss, Inc.; 2002.

Huang W, Fisher PR, Dulaimy K, Tudorica LA, O'Hea B, Button, TM. Detection of breast malignancy: Diagnostic MR protocol for improved specificity. Radiology. 232: 585-591; 2004.

Lee CH, Weinreb, JC. The use of magnetic resonance imaging in breast cancer screening. Journal of the American College of Radiology. 1: 176-182; 2004.

Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, Peacock S, Smazal SF, Maki DD, Julian TB, DePeri ER, Bluemke DA, Schnall MD. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. The New England Journal of Medicine. 356: 1295-1303; 2007.

Lenkinski RE, Katz-Brull R. Breast magnetic resonance spectroscopy. In: Morris EA, Liberman L, eds. Breast MRI. New York, NY: Springer; 2005: 266-272.

Magnetic Resonance Breast Imaging. Imaginis: The Breast Health Resource [online]. Available at: http://imaginis.com/breasthealth/mri.asp. Accessed 12 April 2005.

Meisamy S, Bolan PJ, Baker EH, Pollema MG, Le CT, Kelcz FK, Lechner MC, Luikens BA, Carlson RA, Brandt KR, Amrami KK, Nelson MT, Everson LI, Emory TH, Tuttle TM, Yee D, Garwood M. Adding in vivo quantitative 1H MR spectroscopy to improve diagnostic accuracy of breast MR imaging: preliminary results of observer performance study at 4.0 T. Radiology. 236: 465-475; 2005.

Mitka, M. Researchers seek mammography alternatives. Journal of the American Medical Association. 290: 450-451; 2003.

National Cancer Institute. What you need to know about breast cancer [online]. Available at: http://www.cancer.gov/cancertopics/wyntk/breast/page2. Accessed January 21, 2007a.

National Cancer Institute. SEER cancer statistics review 1975-2003 [online]. Available at: http://seer.cancer.gov/cgi-bin/csr/1975_2003/search.pl#results. Accessed January 2, 2007b.

National Cancer Institute SEER's training website. Breast cancer [online]. Available at: http://training.seer.cancer.gov/ss_module01_breast/unit02_sec01_anatomy.html. Accessed 14 November 2006.

Roebuck JR, Cecil KM, Schnall MD, Lenkinski RE. Human breast lesions: characterization with proton MR spectroscopy. Radiology. 209: 269-275; 1998.

Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S, Smith RA, Warner E, Yaffe M, Andrews KA, Russell CA. American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA A Cancer Journal for Clinicians. 57: 75-89; 2007.

VITA

Graduate College
University of Nevada, Las Vegas

Robert Thomas Etnire

Home Address:
7937 Terrace Rock Way #101
Las Vegas, Nevada 89128

Degrees:
Bachelor of Science, Health Physics, 2005
University of Nevada, Las Vegas

Thesis Title: Investigation of Magnetic Resonance Imaging and Spectroscopy for the Detection of Breast Cancer

Thesis Examination Committee:
Chairperson, Dr. Phillip W. Patton, Ph. D.
Committee Member, Dr. Steen Madsen, Ph. D.
Committee Member, Dr. Ralf Sudowe, Ph. D.
Graduate Faculty Representative, Dr. Harvey Wallmann, Ph. D.