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The major hypothesis of this project is that use of a combination of Magnetic Resonance Imaging (MRI), MRI with contrast, magnetization transfer contrast and proton Magnetic Resonance spectroscopy (MRS) will lead to improved detection and characterization of breast cancer. At present mammography detects lesions which have about an 80% false positive rate for malignancy. There are strong preliminary indications that the combination of MRI with dynamic contrast uptake studies can both detect lesions and provide improved characterization over mammography. The addition of the metabolically based MRS parameters into an approach based on multivariate classification should improve the characterization even further. Technical progress has been made in three areas: (1) the development of a breast array for bilateral imaging of the breast, (2) the development of B1 mapping methods and (3) improvements in the use of multicoil MRS. In the second year of this study, additional measurements have been obtained on: (1) 25 patients undergoing breast-conserving surgery and definitive breast irradiation for treatment of early stage breast cancer; (2) 18 patients undergoing breast biopsy for suspicious breast abnormalities, but without a confirmed diagnosis of malignancy; and (3) 2 patient with locally advanced breast cancer.

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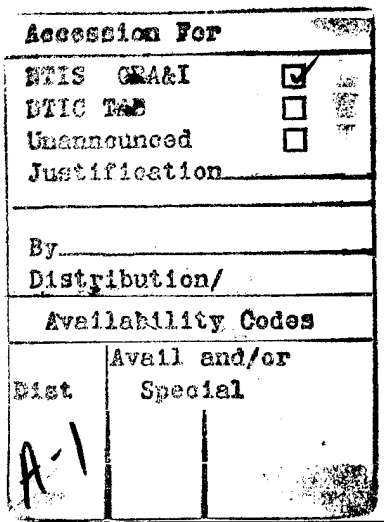

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Early Detection of Breast Cancer and Recurrence Following Therapy with Magnetic Resonance Imaging and Spectroscopy

Robert. E. Lenkinski, Ph.D; Lawrence Solin, M.D.,

Principal Investigators

ANNUAL REPORT

MARCH 1993 - MARCH 1994

Early Detection of Breast Cancer and Recurrence Following Therapy with Magnetic Resonance Imaging and Spectroscopy

Contract #: DAMD17-93-C-3086

Principal Investigator: Robert E. Lenkinski, Ph.D. and Lawrence Solin M.D.

INTRODUCTION: RESEARCH OBJECTIVES

The rising incidence of breast cancer has reached epidemic proportions. In a recent National Institutes of Health consensus development conference (June, 1990), it was emphasized that during the 1990's, more than 1.5 million women in the U.S. will be diagnosed with breast cancer and that approximately 30% of them will die of the disease (1). It is estimated that 1 out of every 9 women will develop breast cancer during her lifetime. While the etiologies of breast cancer remain unclear, several risk factors have been implicated, including hormonal factors, family history, and previous history of breast cancer (2). However, three quarters of women who will develop breast cancer have no known risk factors (3).

Although there are ways to reduce an individual's risk for breast cancer, there is no known way to categorically prevent the disease. Once the disease is disseminated, treatment options offer little hope for long-term survival. Yet, data has accumulated showing a benefit to detecting and treating breast cancer early in its growth. In general, the smaller the lesion is at the time of detection, the better the prognosis (4). While it was readily demonstrable that mammography could detect

early, clinically occult breast cancers (5), long term studies were needed to show the efficacy of screening as a means of reducing breast cancer mortality.

The beneficial effect of screening mammography was initially shown in a study undertaken by the Health Insurance Plan of New York (HIP), begun in 1963 (6). This study was the first randomized control study to evaluate the efficacy of screening. By the most recent follow-up evaluation 18 years after the start of the study, a 23% reduction in breast cancer mortality was found for the screened population.

In the 1970's, the National Cancer Institute in conjunction with the American Cancer Society undertook the Breast Cancer Demonstration Project (BCDDP) in attempt to show that population screening could be performed (5,7,8). Detection rates for breast cancer were twice as high as in the HIP study due to improvements in technology. Of all the cancers, 88% were seen on mammography, 42% of cases detected only by mammography. While not a randomized control study, the BCDDP data strongly suggests a substantial mortality reduction for screened women ages 35-74 (8).

An ongoing randomized control study in Sweden has shown at least a 40% reduction in breast cancer mortality with screening (9). Dutch case control studies have shown a 50% reduction in breast cancer mortality with screening (10).

Typical screening programs include annual physical examination and mammography, supplemented with self examination. Although controversial, current recommendations suggest a baseline mammogram between the ages of 35-40, a mammogram every 1-2 years between the ages of 40-50, and a mammogram every year after age 50. In our hospital, mammograms are reported as: no suspicious findings; probably benign but warrants close follow-up; well defined mass that requires additional evaluation with ultrasound; or suspicious for malignancy, biopsy recommended. The follow-up algorithm for probably benign lesions is an initial follow-up mammogram at a 6 month interval, then yearly mammography for a period of 3 years. When a lesion of concern is identified mammographically, the only

non invasive method for tissue characterization is high resolution ultrasound. If the lesion can be shown to be a simple cyst by ultrasound, a biopsy can be averted.

While mammography has clearly become the gold standard in the detection of early, clinically occult breast cancer, it has limitations. First, not all cancers will be detected mammographically. There are several reasons why breast cancers will be missed, but approximately 30-50% of the false negative mammograms are unavoidable, as the tumor does not produce changes visible with current techniques (2).

Perhaps the most significant limitation of mammography is the relatively low specificity of mammographically detected abnormalities. It is this issue which we plan to address in this proposal. The positive predictive value for biopsies based on mammographically detected abnormalities is approximately 15%-30% (11,12), similar to the rate for biopsy of palpable abnormalities (20-25%). This low positive predictive value for mammographically detected abnormalities reflects an overlap in the mammographic appearance of benign and malignant lesions. If it is estimated that 150,000 new cases of breast cancer will be diagnosed each year (1), assuming a 25% true positive biopsy rate, approximately 600,000 surgical biopsies will be performed to make these diagnoses. The cost of each biopsy including procedural costs, pathology costs, short stay hospitalization, operating room costs and preadmission testing is approximately $3,000 (the cost is $4,500 in our institution). This implies that approximately 1.8 billion dollars each year is being spent on excisional breast biopsies in the United States. If it is estimated that only 25% of these biopsies yield malignant tissue, this suggests that over 1.4 billion dollars are being spent on negative biopsies. Thus, not only does the lack of specificity of mammography subject many women with benign breast disease to unnecessary surgery, it does so at a large financial cost to the health care system. In fact, it is estimated that the expense of excisional biopsies is

the major cost of screening mammography programs, accounting for 32.2% of this cost, slightly more than the cost of the mammograms (13).

The major goal of this proposal is to characterize breast lesions as either benign or malignant based on a comparison of a number of anatomical, functional and metabolically based Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) parameters.

The specific hypotheses to be tested are:

1. The rate of uptake of an MRI contrast agent, Gadolinium diethylene triaminepentaacetic acid (Gd-DTPA), is greater in breast carcinomas than in benign lesions of the breast.

2. The peak uptake of Gd-DTPA is greater in malignant tissue than in benign lesions.

3. There is no significant increase in the uptake of Gd-DTPA in cysts and normal breast tissues.

4. The magnetization transfer ratio of cysts is smaller than malignant carcinomas and/or fibroglandular tissues.

5. Micro calcification can be detected by signal losses due to susceptibility differences visualized on gradient-echo sequences.

6. The appearance of the interface between normal tissue and cysts or fibroadenomas is smooth whereas this interface is irregular for malignant or fibroglandular tissue.

7. Malignant tissue will have higher choline levels on MRS than either normal or benign tissue.

8. Some malignant tissue will have elevated levels of lactate whereas benign lesions will have normal levels.

BODY

A. Progress in Technical Areas

We have made progress in three important technical areas. These are: 1) the development of a method for employing multicoil to provide high resolution bilateral MR images of the breast, 2) the development of B_1 mapping methods for MR image enhancements and 3) improvements in multicoil spectral methods.

The development of a method for employing multicoil to provide high resolution bilateral MR images of the breast. We have previously described the development of a multicoil array specifically for imaging the breast. This array has the advantage of eliminating the requirement of accurate coil placement, while providing adequate sensitivity to support high resolution studies. We have three 1.5 Tesla Signa (General Electric, Milwaukee, Wisc) systems equipped with the multicoil package. This consists of 4 separate NMR receivers, and the software to simultaneously acquire data from 4 separate receive channels. There are connections for up to 6 coils, with the ability to select up to 4 of the 6 coils for image acquisition. The 4 separate images that are acquired by the 4 separate receiver channels are combined together, weighting the data according to the relative signal within the 4 channels in each pixel. This has the effect of maximizing the signal to noise ratio in the composite image, by minimizing noise contributions from channels in areas outside their sensitive volume. The net result is an image that has the spatial coverage of 4 receiver coils, and the signal to noise ratio of that from a single surface coil.

The actual design for a breast array consists of 6 coils, 3 on either side of the breast. The coils are arranged on a planar surface in the geometry shown below:

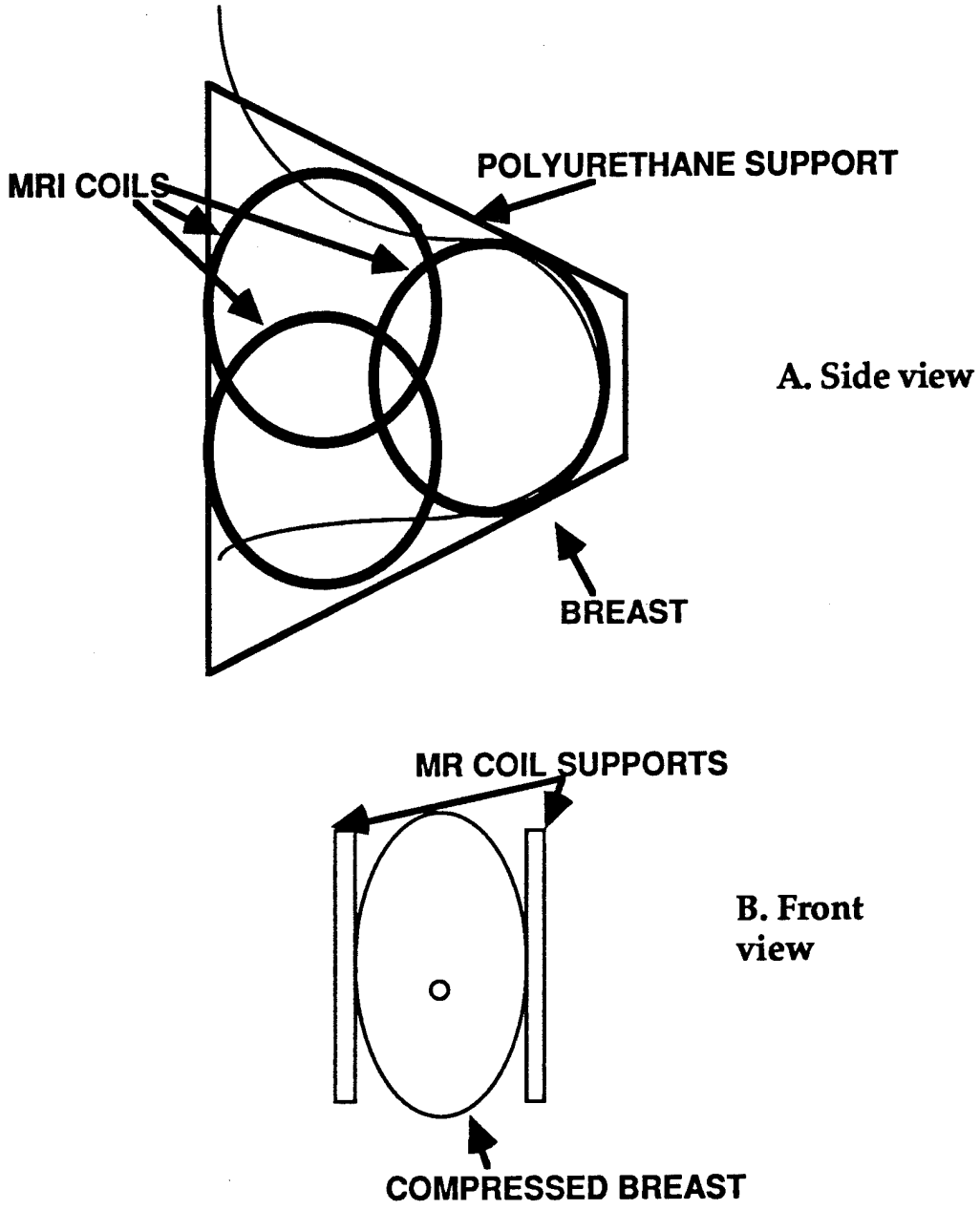

Figure 1 A schematic diagram of the breast multicoil device currently used in our studies.

The coil is applied to the breast similar to the compression planes in the medial-lateral oblique mammographic projection (B). This provides the ability to examine the maximal amount of breast tissue, including the axillary tail. Compression is applied

with care taken not to cause patient discomfort. Compression serves several purposes. First, it effectively limits the size of the breast in 1 dimension. This makes it easier to identify the suspicious region of the breast, since the required spatial coverage in the compression dimension is limited. Second, the geometry of the compressed breast is more suitable for surface coil MR imaging. The reduced distance between the surface and the center of the breast allows for the use of smaller coils without the center of the breast being outside the sensitive volume of the coils. Smaller coils provide a higher signal to noise ratio, and thus support higher resolution imaging. The reduced spatial coverage of the smaller coils can be offset by the use of a multicoil array as described above. In addition, gentle compression also holds the breast in a fixed position relative to the coil, therefore fixing the coils will stabilize the breast and reduce motion artifacts.

We have found that contiguous slice three dimensional (3D) acquisitions using localized receive coils is a preferred technique to acquire post contrast high resolution MR images of the breast. We have successfully used this technique in conjunction with a specially designed four coil compression breast array to acquire unilateral high resolution saggital breast images. Bilateral MR imaging of breasts requires the use of an axial field of view (FOV) large enough to cover both breasts, thus limiting resolution. In addition, the maximum number of receivers in our standard multiple coil MR scanner is four, making it impossible to use our compression breast array to image both breasts simultaneously.

Smaller FOV's can be used if the exam is performed by taking saggital slices through each breast. This, however, is time consuming since separate scans must be set up for each breast. Furthermore, this makes it impossible to image both breasts dynamically following a single bolus of intravenous contrast.

We have recently implemented a slab-interleaved, double volume 3D fast gradient echo (FGRE) pulse sequence which also controls dynamic switching (multiplexing) of a

multiple coil array of eight coils (four coils per 3D volume) to four receivers. With a high speed, high field strength gradient system, repetition times (TR's) of less than 10 ms are achievable for FGRE pulse sequences. With TR's in this range, two 3D volumes, one centered on each breast can be acquired with temporal resolution equal to or better than that attainable for a single breast examination on a standard imaging system.

Scans were performed on our prototype GE Signa 1.5T scanner equipped with high field strength, gradient amplifiers and GE Gradient Ramp Accelerator Modules (GRAM's) providing a ramp time of 150 microsec to a full scale gradient amplitude of 2.2 gauss/cm. A standard 3D FGRE pulse sequence was modified to allow acquisition of two separate 3D volumes by exciting each volume independently and sampling data from each volume in an interleaved fashion.

A bilateral breast coil array was designed and built comprising eight individual coils. With this array the patient can be studied in the prone position. Each breast can be compressed between one set of two coils located medially and another set of two coils located laterally. Each coil is connected to an independent preamplifier. The pulse sequence software provided signals to control a digital circuit which in turn controlled the dynamic switching of an eight line to four line multiplexer circuit. A schematic diagram of the circuit is shown in Figure 2.

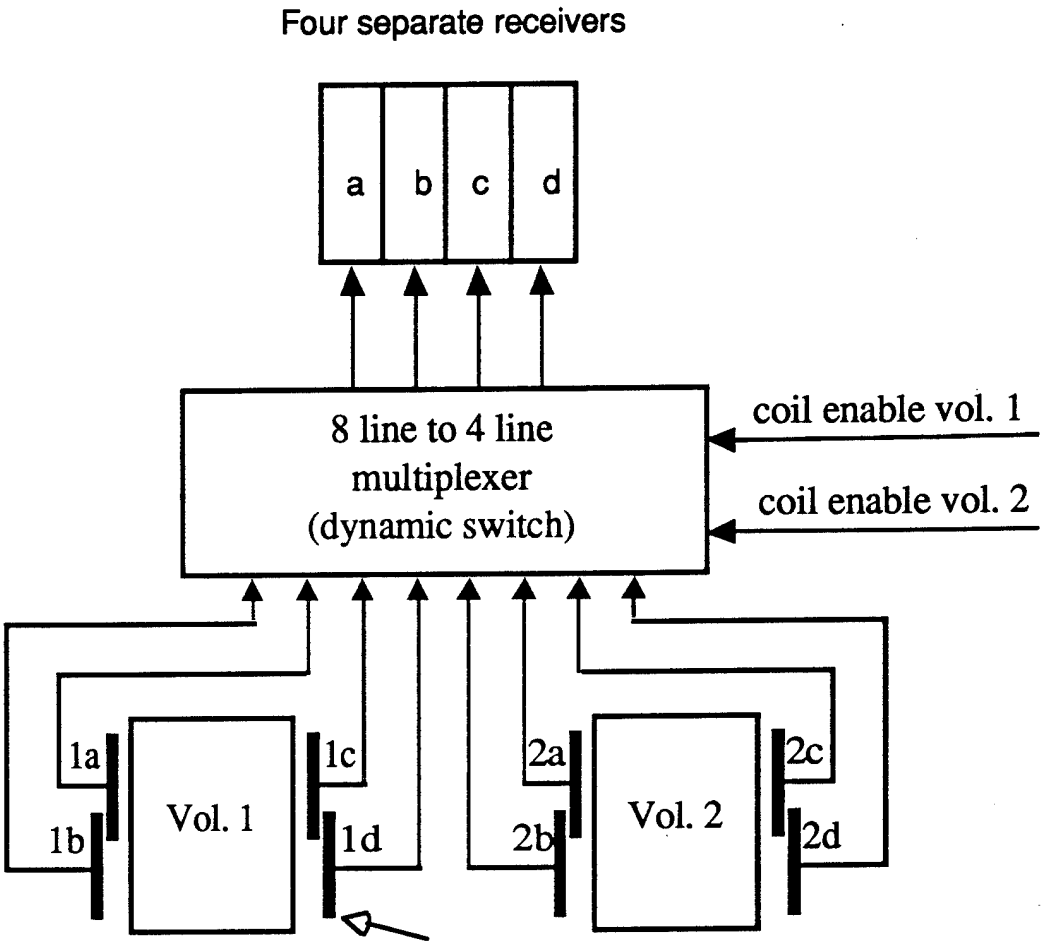

Figure 2. The schematic diagram of the coil switching scheme.

The pulse sequence along with the coil switching control signals is shown in Figure 3.

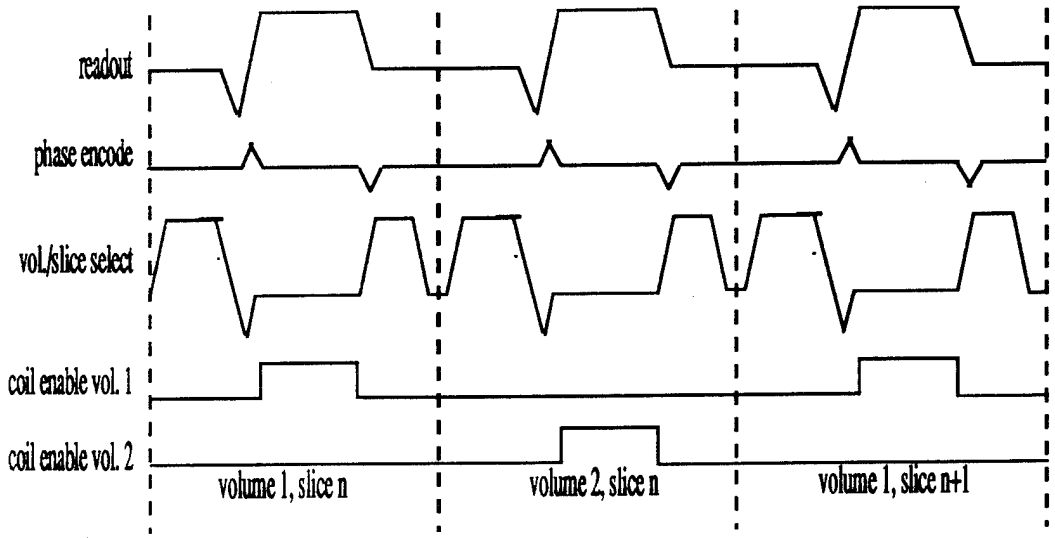

Figure 3. The pulse sequence for bilateral acquisition.

While data is being acquired from one volume, the four coils located at the other volume are electronically detuned to avoid coupling of the signal from one volume into another. All eight coils are detuned whenever any radio frequency pulse is applied to ensure patient safety and to avoid damage to the electronic circuits.

Fat suppression is accomplished by applying a spectrally selective inversion recovery pulse, which, when tuned to the frequency of the fatty tissue in the breast, will not affect the signal enhancement of tumors by contrast agents.

Image quality and signal-to-noise ratio of this method were determined using doped water and lipid phantoms. Scans of two healthy volunteers were also performed. Twenty 2 mm slices were acquired from 3D volumes centered on each breast with a resolution of 256X512, TE=1.6 ms, TR=9 ms, flip angle=40 degrees. The total scan time was 2 minutes and 3 seconds.

A 3D two volume pulse sequence has been executed for bilateral breast imaging. For a TR of 19 ms both single and double volume scans require identical scan times. Of equal significance, no sacrifice of SNR/resolution is incurred by adding a second

volume due to the interleaved nature of the pulse sequence and additional localized receive coils. The value of TR employed, 19 ms, is not the minimum TR achievable with this sequence. Therefore, it is possible to simultaneously acquire a20 slice volume for each breast in under 2 minutes.

Interleaved double volume bilateral breast imaging provides resolution equivalent to unilateral studies while preserving dynamic contrast information. It does so in the same time required for conventional unilateral studies. This allows bilateral, high resolution, post contrast breast examinations to be performed without any degradation in image quality when compared to a unilateral exam.

The development of B_1 mapping methods for MR image enhancements. One of the major problems with the use of surface coils or multicoils is the non-uniform intensity profile produced on the MR images. An example of a high resolution image of the front of the brain obtained with a four coil array is shown in Figure 4a.

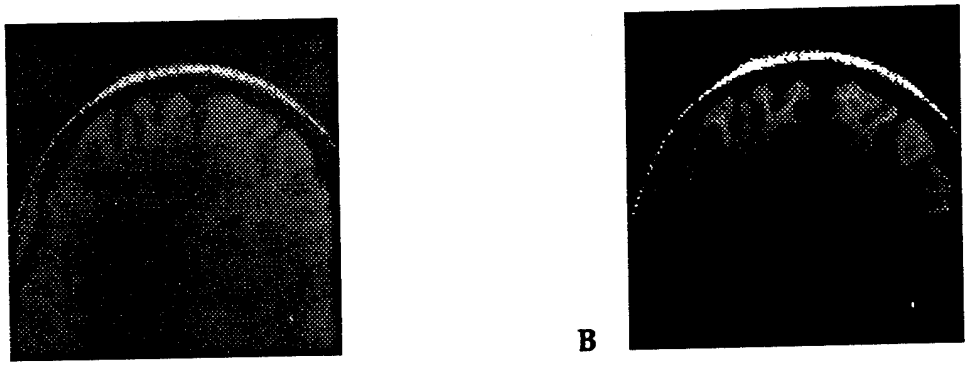

Figure 4. An example of a multicoil image of the head illustrating the non-uniform intensity profile.

The same image windowed to illustrate the non-uniform sensitivity profile is shown in Figure 4b. We have developed a method for generating a B_1 profile of this array . This B_1 profile is illustrated in Figure 5.

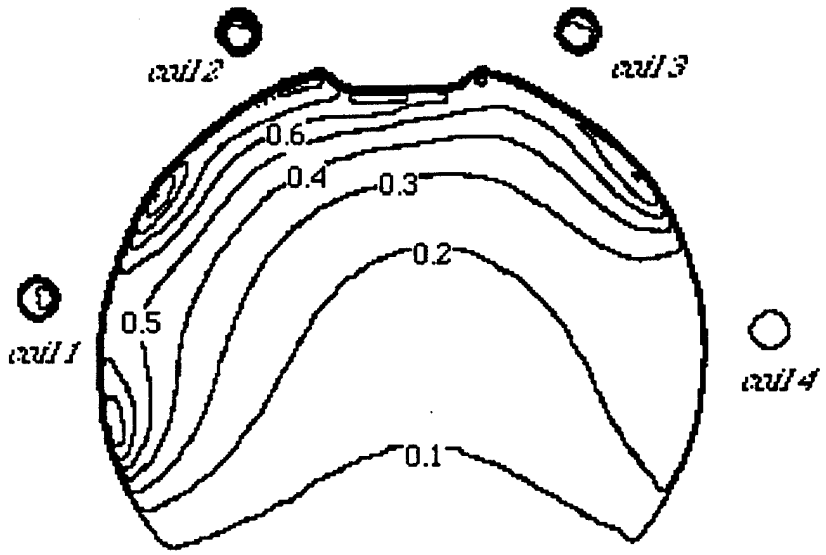

Figure 5. A contour plot of the B1 profile of the coil array employed to obtain the images shown in Figure 4.

Using these data the non-uniform sensitivity can be corrected to remove problems that impact on image quantitation.

Improvements in multicoil spectral methods. Multicoils provide a means of simultaneously acquiring data from several closely positioned coils. Appropriate recombination of these data offers the signal-noise ratio (SNR) of a surface coil over FOV's normally associated with volume coils. Multicoils have been used to improve SNR in single voxel proton MR spectroscopy (MRS) and Chemical Shift Imaging (CSI). In order to determine the optimal method for processing multicoil MRS data two recombination schemes were tested using simulations and ^{1}H-MRS data acquired with a 4 channel multicoil. Substantial SNR improvements are possible using weighted sums to recombine the data.

Simulations were performed to assess the SNR improvements possible using multicoils. In Figure 6, uncorrelated noise was added to 4 single resonance spectra. The

peak heights of 3 spectra ranged from 0 - 1 in increments of 0.1; the height of the fourth spectrum was fixed to 1 as a reference.

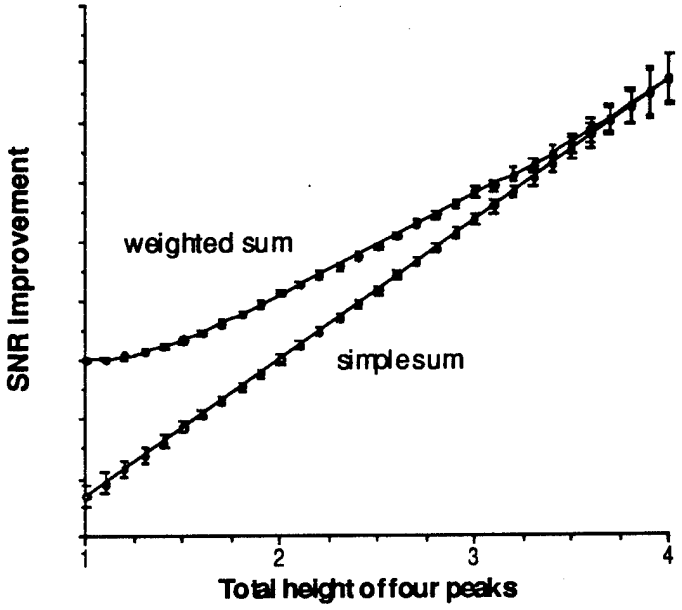

Figure 6. The SNR improvement obtained over a single coil using a multicoil array. The SNR for all combinations was evaluated using two approaches: a simple sum and a weighted sum. In the weighted sum, the contribution of each spectrum to the sum is weighted by its height. In the simple sum, all of the spectra are equally weighted. SNR comparisons are made relative to the reference. In Figure 7, uncorrelated noise was added to N single resonance spectra, each having unity peak height.

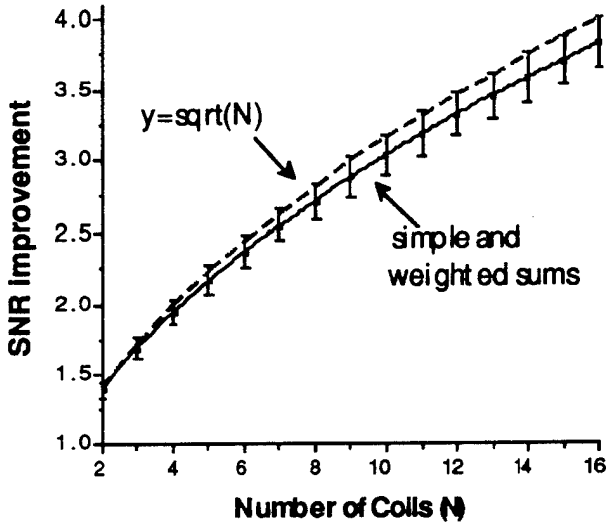

Figure 7. The SNR advantage as a function of the number of coils in the multicoil.

Figure 8 shows the multicoil positioned over a phantom containing 10 mM creatine, 10 mM N-acetylaspartate and 5 mM glutamine. Markers show the center of each coil. Coils 1 and 4 are each 8X7 cm while 2 and 3 are 10X4.5 cm. Solvent suppressed spectra (TR 2000, TE 31) were acquired from (2 cm)^3 voxels at the locations shown. Spectra from voxel B are shown in Figure 9 their order (from bottom to top) is coils 1-4, simple sum, and weighted sum.

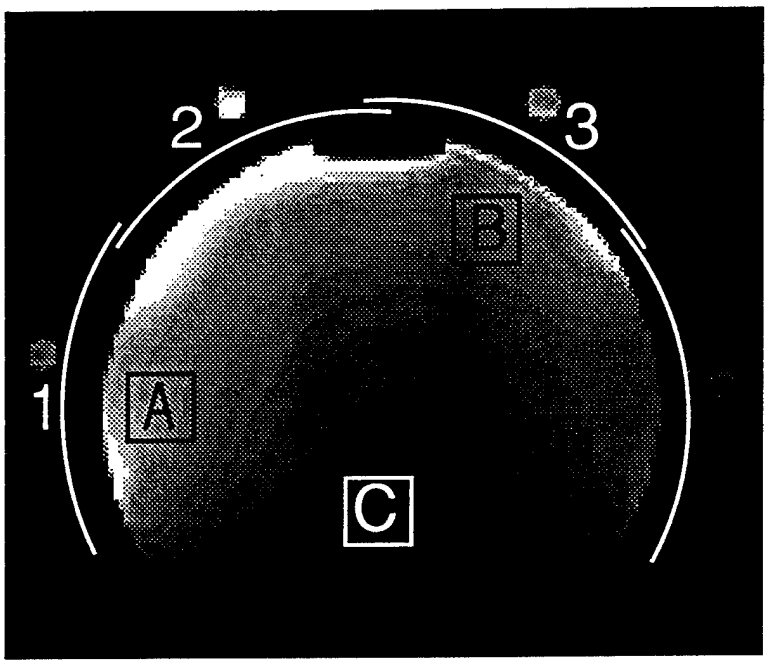

Figure 8. The arrangement of the multicoil and the voxels (A,B,C) sampled for MRS.

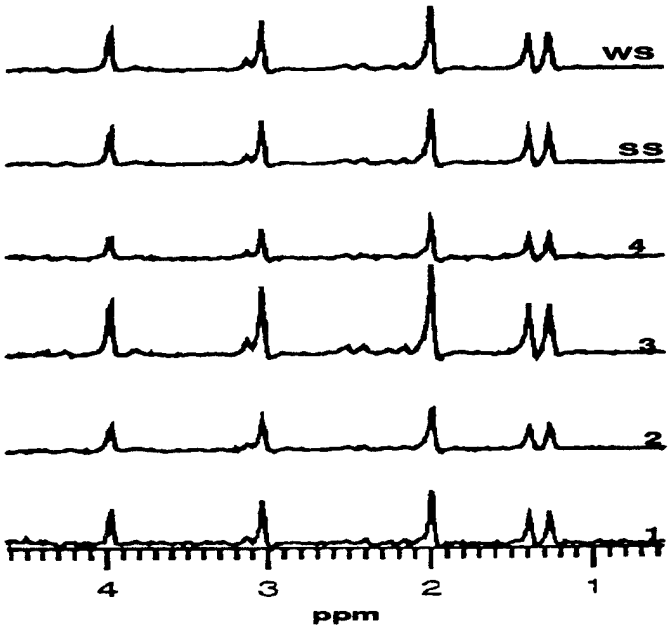

Figure 9. Localized MR spectra obtained from the voxels shown in Figure 8.

Figure 6 shows the weighted sum provides better SNR improvement than the simple sum, particularly when the difference in relative heights of the component spectra is large. In Figure 7 , all component spectra have unity height so the two approaches are identical. This models the situation where the signal is the same in all spectra (e.g., voxel is equidistant from all coils in a symmetric, well-decoupled multicoil). Figure 7 shows the SNR improvement approaches $\sqrt{N}$ where N is the number of coils in a multicoil.

The simulations model experiments where the individual coils in the multicoil are completely decoupled from one another and thus, the noise in each signal is uncorrelated from the others. This can be achieved to a large extent with planar geometry's but is harder to realize with complex geometry's such as the multicoil used in this study. Even so, the 20% improvements in SNR demonstrated here are commonly seen with the greatest improvements occurring when the signals in each coil are approximately equal.

B. Clinical Studies

In the first year of this study, measurements were obtained on: Group (1) 18 patients undergoing breast-conserving surgery and definitive breast irradiation for treatment of early stage breast cancer; Group (2) 19 patients undergoing breast biopsy for suspicious breast abnormalities, but without a confirmed diagnosis of malignancy; and Group (3) 1 patient with locally advanced breast cancer. In the second year of this project studies were obtained on an additional: Group (1) 25 patients; Group (2) 18 patients and Group (3) 2 patients. Patients who have undergone breast-conserving surgery and definitive breast irradiation will continue to have follow up studies as scheduled. This study will prove to be invaluable in the future for distinguishing local recurrences from normal scar evolution. Should any of the study patients in this study ultimately prove to develop a local recurrence, then the relative merits of MRI,

optical imaging, mammography, and clinical examination can be compared. At present it is difficult to make any conclusions since the patients are still early in their course. For the patients with locally advanced disease, conventional treatment modalities include chemotherapy, radiation therapy, and mastectomy. This study will determine the impact of conventional treatment modalities within the breast. It is known that there is a small group of patients for which mastectomy does not need to be performed, but for which conventional imaging is inadequate for this determination. MRI may prove to be useful for this determination. Finally, the large majority of patients undergoing surgical biopsy in the absence of a diagnosis prove to have benign disease. It is hoped that the addition of MRI to optical imaging and to mammography and clinical examination can spare some of these surgical biopsies by confirming a benign diagnosis on an imaging basis alone.

While the number of patients studied so far is small, these findings may have significant clinical implications. One patient was found to have a clinically and mammographically unsuspected focus of ductal carcinoma in situ clearly separate from the primary tumor mass. Such foci of disease, clearly separate from the primary tumor mass, have been well described on pathologic studies of mastectomy specimens (16). In the absence of the MRI study, this focus of ductal carcinoma in situ would not have been excised surgically, but would have been treated with radiation alone. It is not certain whether or not the surgical excision has improved this patient's chance for local control of disease in the breast. However, the phenomenon of local recurrence after definitive breast irradiation is well established, and local recurrence in the breast can be distant from the primary tumor site. Thus, this patient might have been at high risk for recurrence in the breast using conventional imaging and treatment methods.

Over thirty patients have undergone imaging for a clinically suspicious abnormality, but without the diagnosis of malignancy. All of these patients underwent biopsy

subsequent to imaging. The pathologic findings on breast biopsy from these patients are as follows:

CARCINOMA	NO. OF PATIENTS
Yes	11
No	26

Review of these cases shows that the clinical management was not changed in any of these cases. We have begun to analyze the MRS data obtained on these cases. Our first level of analysis has involved using the strategy for combining the multicoil MRS data described above. Using these combined spectra we asked the following question: Is the fat/water ratio different in benign vs malignant masses. Scatter grams made from these data are shown in Figure 10.

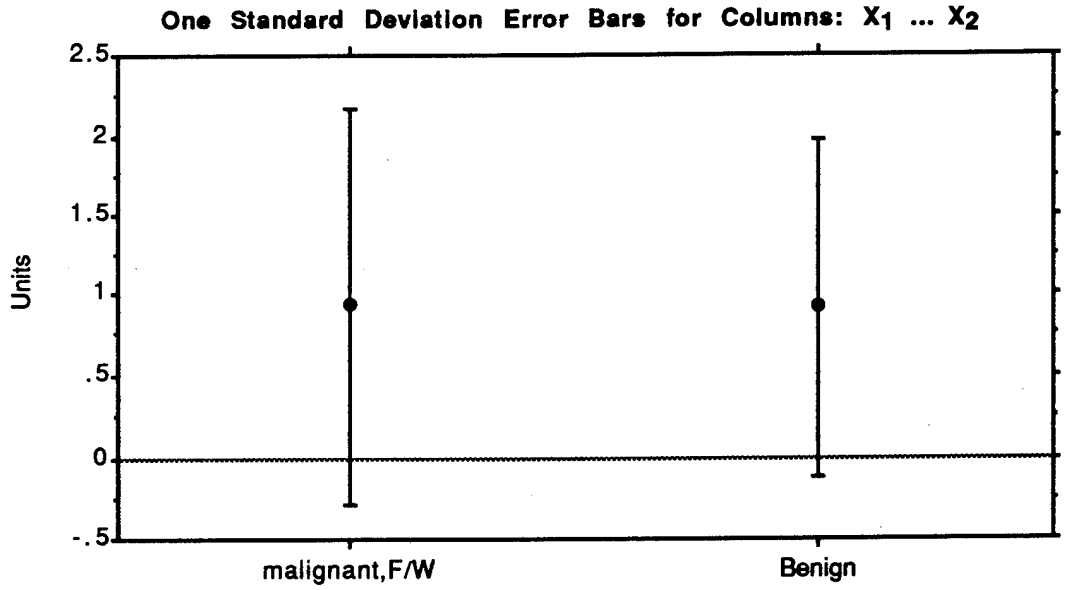

Figure 10. Scatter gram of Fat/Water ratios in the spectra of benign and malignant lesions.

These results clearly indicate that fat/water ratios cannot distinguish benign from malignant disease. We are currently carrying out a blinded analysis of the proton MR spectra obtained from these masses to see whether choline or lactate peaks can be used to make this distinction.

CONCLUSIONS

The research program has made substantial progress, and the work is progressing as planned. Additional patients will be accrued from all of the categories of patients. Patients who have undergoing breast-conserving surgery and definitive breast irradiation will continue to have follow up studies as scheduled. This follow-up may prove to be extremely valuable. The natural evolution of the radiation-treated breast as seen on MRI may prove to be invaluable in the future for distinguishing local recurrences from normal scar evolution. Should any of the study patients ultimately prove to develop a local recurrence, then the relative merits of MRI, optical imaging, mammography, and clinical examination can be compared. For the patients with locally advanced disease, the impact of conventional treatment modalities can be determined. It is known that there is a small group of patients for which mastectomy does not need to be performed, but for which conventional imaging is inadequate for determination. MRI imaging may prove to be useful for this determination. Finally, the large majority of patients undergoing surgical biopsy in the absence of a diagnosis prove to have benign disease. It is hoped that the addition of MRI and optical imaging can spare some of these surgical biopsies by confirming a benign diagnosis on an imaging basis alone.

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