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13. ABSTRACT *(Maximum 200 words)*

The major hypothesis of this project is that use of a combination of MRI, MRI with contrast, magnetization transfer contrast and proton MR spectroscopy 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) improved spatial localization for MR spectroscopy , 2) the development of multicoil spectral methods and 3) the design and construction of a MR guided needle localization device. In the first year of this study, measurements have been obtained on: (1) 18 patients undergoing breast-conserving surgery and definitive breast irradiation for treatment of early stage breast cancer; (2) 19 patients undergoing breast biopsy for suspicious breast abnormalities, but without a confirmed diagnosis of malignancy; and (3) 1 patient with locally advanced breast cancer.

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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: PROGRESS REPORT

A. Progress in Technical Areas

We have made progress in three important technical areas. These are: 1) improved spatial localization for MR spectroscopy , 2) the development of multicoil spectral methods and 3) the design and construction of a MR guided needle localization device.

Improved spatial localization for MR spectroscopy. The use of short echo, solvent suppressed localized proton MRS in studies outside the brain have been hampered by contamination of the spectra with resonances arising from lipids which are outside the region of interest. There have been a variety of remedies suggested for the minimization of this contamination. These include applying spatial presaturation pulses prior to executing the localization sequence, improving the spatial selectivity of the Radio Frequency (RF) pulses employed and eliminating contaminating magnetization by using spoiler gradient pulses or phase cycling schemes. These remedies may be used alone or in combination with each other. It is the purpose of this study to investigate which single remedy or combination of these remedies can effective remove lipid contamination. We constructed a phantom containing two compartments as shown below.

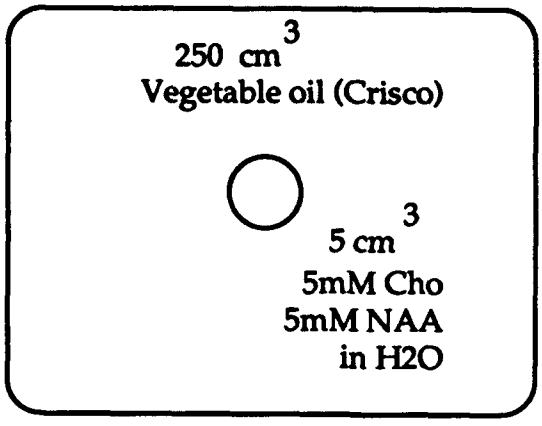

Figure 1. A schematic diagram of the phantom used in the localized MRS studies. The phantom contains N-acetylaspartate (NAA) and choline (Cho).

A cubic voxel measuring 7 mm per linear dimension was positioned against the inner edge of the phantom containing aqueous solution. Solvent suppressed proton spectra were obtained using the stimulated echo sequence (STEAM) with an interecho delay (TE) of 31 msec on a General Electric Signa 1.5 T scanner. The study was performed with a prototype receive-only breast coil (body coil transmit). Solvent suppression achieved by employing three chemically shift selective (CHESS) pulses before the three slice selective 90 degree STEAM pulses.

Using this phantom we tested three different options for reducing the lipid signal; 1) spatial presaturation (six sided); 2) phase cycling (2 and 8 step) and 3) the use of digitally crafted slice selective pulses (generated with the Shinnar-LeRoux algorithm) with very sharp and less sharp spatial profiles. For the sake of convenience we refer to these options as 1) sat or no-sat, 2) 2 PC or 8 PC (PC referring to phase cycling) , and 3) sharp or fuzzy.

It is important to note that even the pulses with less sharp spatial transition zones were superior to single lobe sinc pulses. All possible combinations of these options were also evaluated.

We found minimal lipid contamination with the use of the sharp pulses. Three of the spectra obtained are shown below.

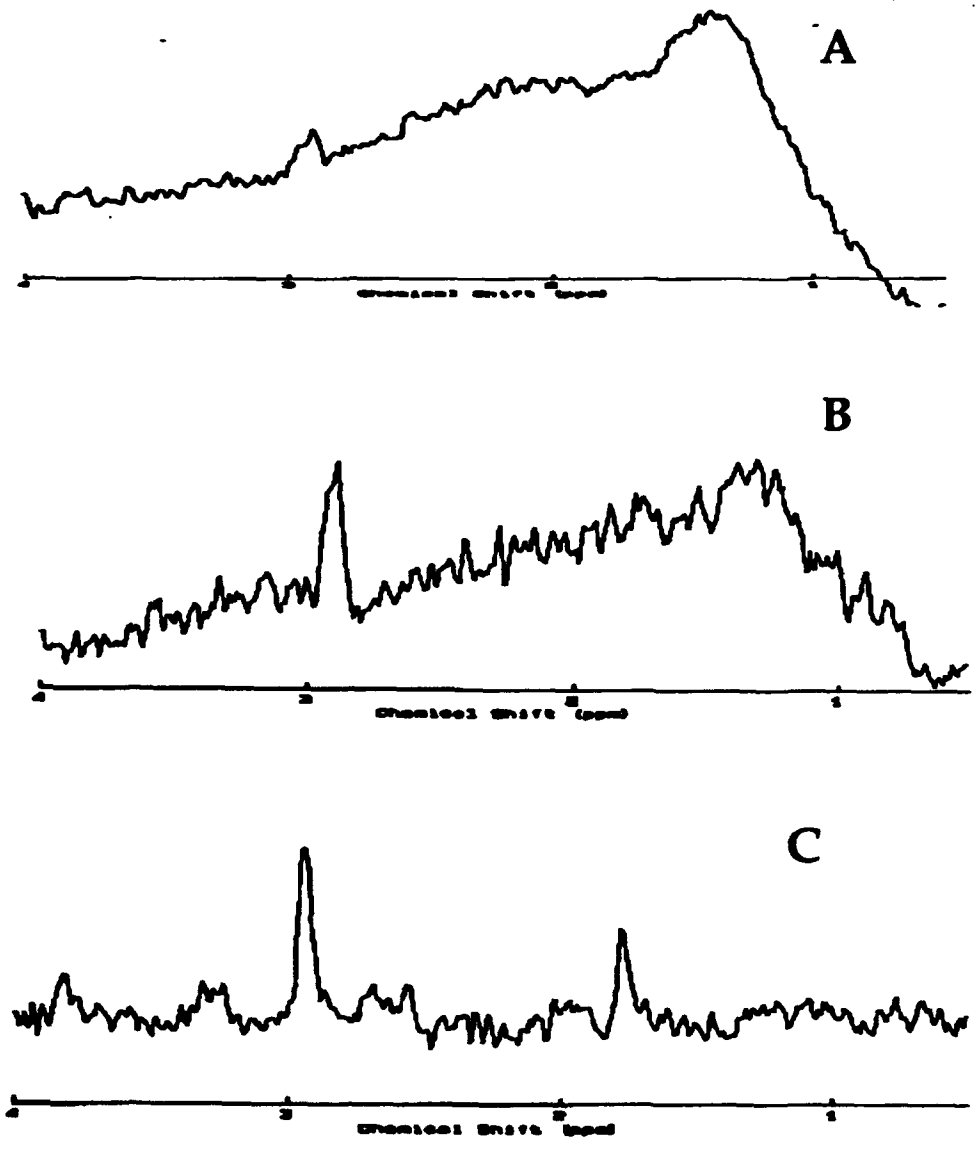

Figure 2. Proton spectra obtained using the phantom shown in figure 1. Spectrum A was obtained with two step phase cycling and fuzzy pulses; B was obtained with eight step phase cycling , fuzzy pulses and outer volume saturation ; C was obtained with eight step phase cycling , sharp pulses and outer volume saturation.

The use of sat reduced the intensity of the lipid peak by about a factor of four. We also found that the use of 8 step phase cycling (8 PC) improved the baseline. Note that the combination of fuzzy, and 2 PC produced a spectrum (spectrum A) with considerable lipid signal. The combination of fuzzy , 2 PC, and no-sat gave a spectrum with reduced lipid signal (spectrum B). The best results were obtained with sharp, 8 PC and sat (spectrum C) although the improvement over sharp, 8 PC and no-sat was minimal.

Our results indicate that the most important factor in reducing lipid contamination is the use of digitally crafted RF pulses with sharp spatial transition zones. These pulses require more time to play out than pulses with broader transition zones. This may mean that the minimum echo delay is somewhat lengthened. For MRS applications in tissues like the breast which contain or reside in fat, the elimination of out of voxel lipid signal is critical in obtaining interpretable solvent suppressed proton at short echo delays.

The development of multicoil spectral methods. We have developed 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 demonstrated below:

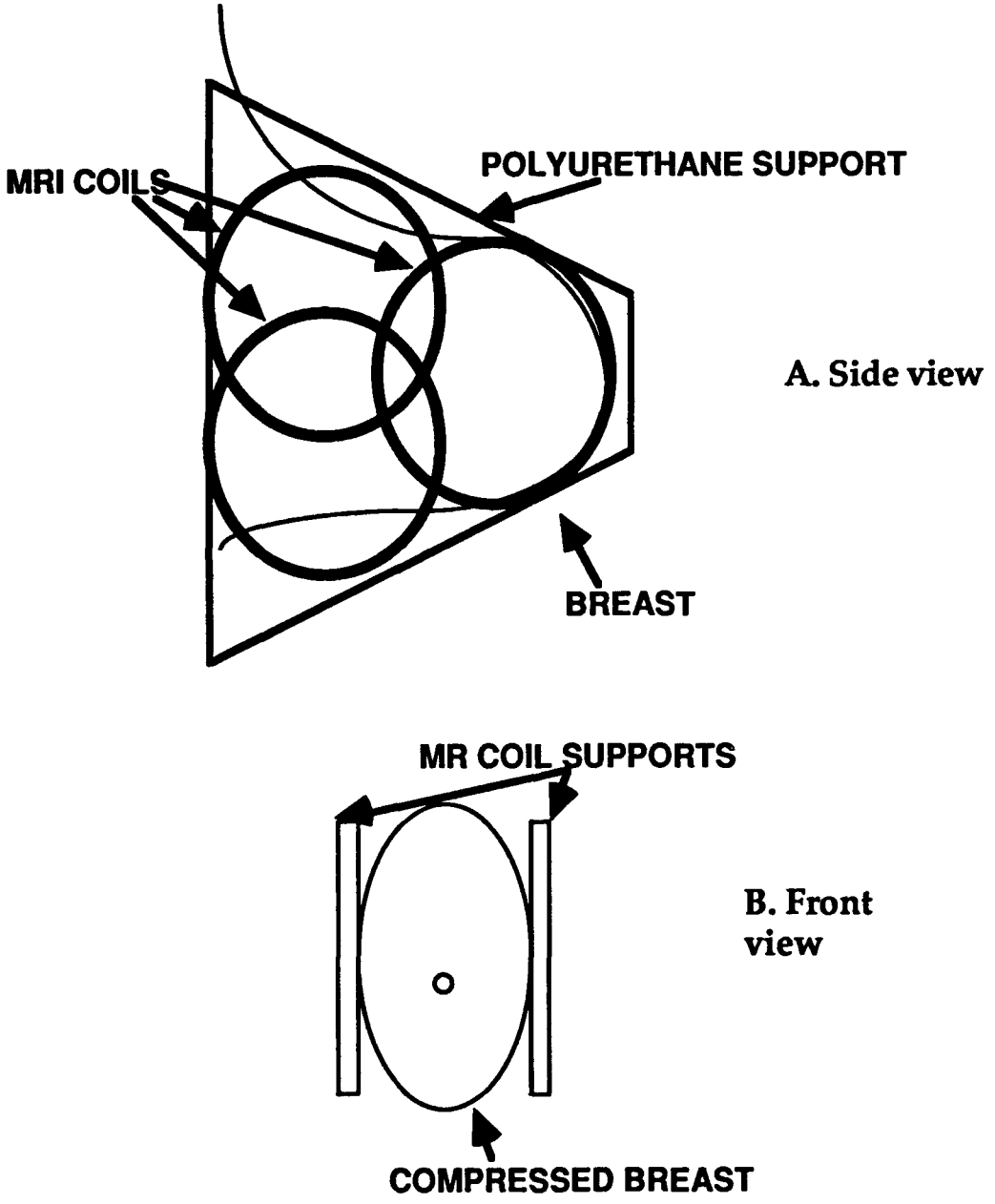

Figure 3. A schematic diagram of the breast multicoil device currently used in our studies.

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 it is possible to acquire solvent suppressed proton spectra using this multicoil array. The spectra are acquired and stored as four separate data files; one spectrum from each coil. In this mode there are two advantages of the multicoil array over conventional surface coils. The first advantage is that each spectrum has the potential signal-to-noise of a small coil. This feature taken together with the compression of the breast which places the tissue proximal to the coils has meant that we can acquire spectra from structures with volumes of about 0.3 cm^3. The combined spectra can improve the signal-to-noise of the resultant spectra by as much as $\sqrt{2}$. This extra signal-to-noise results in improved spectra quality and decreased acquisition times. The second advantage is spatial coverage. Since we do not know the location of the lesion beforehand the use of the multicoil spectral feature allows us to obtain spectra from each lesion without repositioning of the coil.

The design and construction of a MR guided needle localization device. Although not specifically planned for this study, we have found it important to perform needle localization of lesions seen on MRI examination of the breast. We have designed and used a multicoil array with that requirement. We have placed an alpha numeric grid of holes within the plastic that supports the coil . The holes are marked by small droplets of copper sulfate solutions placed within the plastic itself. This is then be used as guide to place localizing needles in MRI detected lesions.

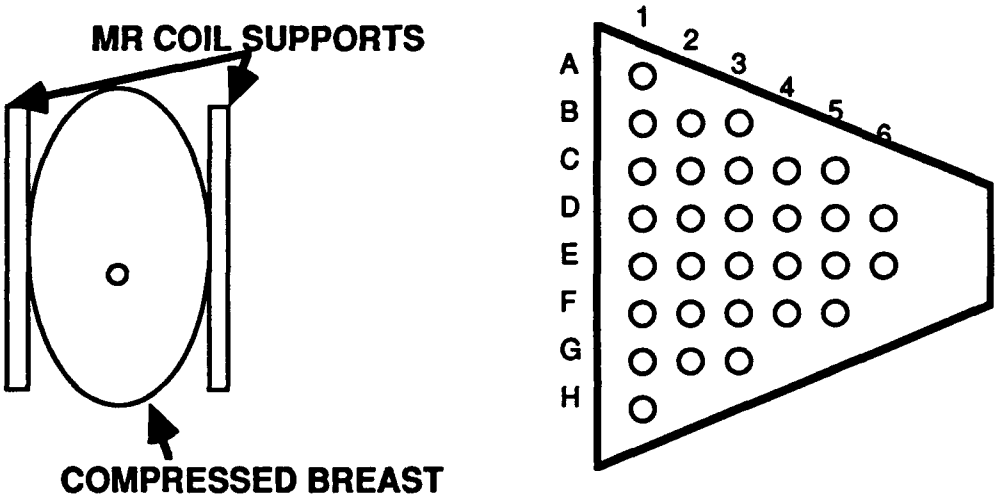

Figure 4. A diagram of the MRI device developed for needle localization of MR detected breast lesions.

B. Clinical Studies

In the first year of this study, measurements have been 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. Patients who have undergone 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 has not previously been described, and this study will be the first such description. The findings from 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.

For the patients in group one, 18 patients have undergone imaging using near infrared optical radiation and 17 of these 18 patients have also undergone baseline MRI study. Follow up studies approximately three weeks after completion of radiation treatments were performed in 11 patients. A second follow up study approximately six months after completion of radiation therapy was performed in 5 patients. Therefore, a total of 34 studies have been performed in these 18 patients. The distribution of diagnoses for these patients is as follows:

STAGE	NO. OF PATIENTS
0	6
I	9
II	3

Review of the 18 patients shows that clinical management was altered in 4 patients (22%). In 2 patients, the MRI findings precipitated needle localization breast biopsy after completion of definitive breast irradiation. These two biopsies both were benign. One patient was found to have a clinically and mammographically unsuspected focus of disease prior to excision. Based on the MRI findings, needle localization of this second focus of disease was performed through a surgical biopsy which encompassed the primary tumor, as well as the unsuspected focus found on MRI study. The clinically unsuspected focus was confirmed pathologically as being ductal carcinoma in situ. The fourth patient underwent an MRI-directed core biopsy which showed a benign fibroadenoma. Thus, of the four biopsies precipitated by MRI findings, one (25%) was positive for disease which was unsuspected clinically and mammographically.

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.

Nineteen patients have undergone imaging for a clinically suspicious abnormality, but without the diagnosis of malignancy. All these patients underwent biopsy subsequent to imaging. The pathologic findings on breast biopsy from these patients are as follows:

CARCINOMA	NO. OF PATIENTS
Yes	4
No	15

Review of these 19 cases shows that the clinical management was not changed in any of these cases. That there was no change in clinical management may reflect the small total number of cases (n=19) or the small number of carcinomas detected (n=4).

Only one patient has undergone a pretreatment study for locally advanced breast cancer. No conclusions can be based on this one patient at the present time.

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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