D0928

A Study to Evaluate the Use of Supine MRI Images In Breast Conserving Surgery

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SUMMARY

Section 1. INTRODUCTION

Most women with breast cancer have their tumors detected by screening mammography or breast MRI, before the tumors become clinically palpable. Most of these women with small breast cancers will choose breast conserving surgery. The goal of breast conserving surgery is to completely resect the tumor with negative margins and simultaneously preserve the shape of the breast. The standard technique for breast conserving surgery for patients with non-palpable breast cancer is to place a wire into the cancer pre-operatively (in Radiology under mammographic, ultrasound or MRI guidance) and then, in the Operating Room, to excise the tissue around the wire. This technique, initially developed in the 1970's, has several limitations. It adds a separate procedure to the surgical resection, thereby complicating and lengthening the process. Standard localization involves placement of one wire as close as possible to the clip left at the time of diagnostic core biopsy, or close to residual masses or calcifications. Mammographic images are then taken in two projections and the surgeon must then estimate the location of the cancer from these wire localization films. In many cases this imprecisely localizes the cancer, resulting in positive margin rates from 30-50% (1,2). Additional precision can be gained by placing additional wires, but this increases the length of time for the localization procedure (3). Wire localization is an inefficient and imprecise technique.

Because of these limitations, efforts have been made to find alternatives to wire localization. Intra-operative ultrasound has been evaluated and been shown to be superior to wire localization (4-6), but over half of mammographically visible invasive cancers and most ductal carcinoma in situ lesions are not visible on US. Targeting the resection at the hematoma left from the initial core biopsy

has had some success in early retrospective studies (7,8). Neither of these techniques has been widely adopted.

MRI of the breast has been shown by multiple studies to be more sensitive than mammography (9-12) for the detection of breast cancer. Furthermore, several studies have demonstrated the ability of MRI to detect mammographically and clinically occult foci of cancer in the ipsilateral breast in approximately 25% of patients (9,13-15). In many cases the local extent of the tumor is better defined by MRI, while in some cases additional foci of cancer are seen in other quadrants of the breast.

While it seems intuitive that a surgeon would want to precisely know the extent of disease prior to lumpectomy, some argue that MRI is not justified unless it is shown to have a significant clinical impact, i.e., that MRI appropriately changes the surgical management, or that the positive margin rate is decreased, or that the local recurrence rate is less in patients who undergo pre-op MRI. The retrospective studies described above did demonstrate that MRI resulted in a change in surgical management in 25% of patients (performing larger lumpectomies so as to try to completely resect the tumor or excising additional multicentric tumors in the breast). These studies did not address whether the positive margin rate was decreased by the use of MRI. This will be addressed in the Comparative effectiveness of MRI in breast cancer (COMICE) trial in Great Britain, where 1600 patients were randomized to receive MRI or no MRI prior to breast conserving therapy. Two studies retrospectively evaluated whether the local recurrence rate in breast conservation patients undergoing MRI was lower than that seen in concurrent patients not receiving MRI. These studies had conflicting results. In one, 215 women who had MRIs had a LR rate of 3%, which was not significantly different than the rate of 4% in 541 women not undergoing MRI (16). In contrast, Fischer found a lower rate of in breast recurrence in pts who had MRI (1% vs 7%) (17). In summary, breast MRI has been shown to better define the local extent of the breast cancer than mammography and results in changes in surgical management, but has not yet been demonstrated to decrease the positive margin rate or the rate of local recurrence. While it is

being used as part of the initial diagnostic evaluation for patients newly diagnosed with breast cancer in many centers, and is reimbursed in NH and VT, it is not yet considered to be standard of care.

A limitation of all of these MRI studies is that the MRI exams are performed with the patient prone and the breasts in a pendant position, which is markedly different than the position of the breast when the patient is supine on the Operating Room table. The spatial information the surgeon receives from the prone MRI about the site of the tumor in the breast is hard to mentally translate into the actual site of the tumor in the breast of a supine patient prepared for surgery. Of particular interest is a recent Japanese study that evaluated resections based on supine MRI in 24 patients with DCIS and compared them to 28 patients who had prone MRI and wire localized resections (18). The positive margin rate was lower in the supine MRI group (12% vs 39%, p=0.03) and the volume of breast tissue removed was less (27 vs 57 cm3, p=0.001). In this study the supine MRI image was correlated to the position on the OR table by taking plain xrays in the OR and lining up a metallic button on the surface of the breast with a clip left at the time of biopsy.

Section 2. OBJECTIVES

We propose to use a novel technique (optical scanning) to correlate the supine MRI image to the surgical position in the OR and then to confirm and extend the Japanese study described above. In the first phase of the study, 5-25 patients with palpable invasive breast cancer will undergo pre-operative supine MRI and optical scanning in the surgical position. The purpose of this phase will be ensure that the images created from the optical scanner-adjusted supine MRI images closely correspond to the location of the palpable tumors in these breasts. All patients will then have their tumor resected using the standard method of either palpation or image guided wire localization.

In the second phase of the study, patients with non-palpable invasive breast cancer or DCIS who desire breast conservation will be randomized to either a usual care group, or a group receiving a supine MRI in addition to conventional imaging (mammogram and prone MRI) and undergoing breast cancer resection without the wire localization technique.

The primary objective will be to determine whether the addition of supine MRI to conventional imaging with mammography and or sonography and prone MRI will result in a lower positive margin rate in patients undergoing breast conserving surgery.

Our secondary objectives will be to determine:

1. whether there are differences between the two groups in the volume of breast tissue removed.
2. whether diagnostic information obtained from a supine MRI is equivalent to that obtained from the prone MRI.

Section 3. ELIGIBILITY CRITERIA

Inclusion Criteria Phase 1

1. Age $\geq$ 18 years
2. Histologic diagnosis of palpable invasive breast cancer or ductal carcinoma in situ
3. Patient desire to undergo breast surgery
3. Patients will have provided informed consent to participate, documented by their signature on the study consent form
4. The cancer enhances on breast MRI imaging.

Inclusion Criteria Phase 2

1. Age ≥ 18 years
2. Histologic diagnosis of invasive breast cancer or ductal carcinoma in situ
3. The tumor is visible and enhances on prone MRI and is ≥ 1 cm in greatest diameter.
5. Determination by the surgeon that the neoplasm is non-palpable. A patient with a palpable hematoma from core biopsy, but a non-palpable neoplasm, will be eligible for study
6. Patient desire to undergo breast conserving surgery
7. Patients will have provided informed consent to participate, documented by their signature on the study consent form. The process of informed consent will be documented in the medical record and a copy of the signed consent form will be given to the patient.

Exclusion Criteria (Phases 1 and 2)

1. Absolute contraindication to MRI, including presence of implanted electrical device (pacemaker or neurostimulator), aneurysm clip or metallic foreign body in or near eyes
2. Severe claustrophobia
3. Contraindication to use of gadolinium based intravenous contrast, including life threatening allergy or compromised renal function (creatinine > 2.0)
4. History of median sternotomy
5. Pregnancy (Patient attestation that they are not pregnant will be acceptable, as per standard policy for MRIs at DHMC)
6. Multicentric breast cancer, defined as two or more tumors in different quadrants of the breast.

An eligibility worksheet will be completed for each patient prior to enrollment and will be signed and dated by the surgeon investigator.

Section 4. TREATMENT PLAN

Phase 1 Patients with a percutaneous core biopsy demonstrating invasive carcinoma or ductal carcinoma in situ will undergo contrast enhanced bilateral breast MRI in the prone position, as is the current clinical standard at Dartmouth. At the time of surgical consultation, patients with palpable invasive breast cancer or DCIS who desire breast surgery will be invited to be a part of the study. Prior to surgery these patients will undergo a contrast enhanced supine MRI and an optical scan. The optical scan will be done with the patient in the surgical position. This image will be used to adjust the MRI image obtained pre-operatively into a highly accurate representation of the breast and the MRI-defined tumor mass to correspond to the position of the patient at the time of surgery. This image will be projected on a screen above one side of the patient's head for easy viewing. This image display will indicate the distances at a particular radian (measured in terms of clock hours and minutes) from the nipple to all aspects (cranial, caudal, medial, lateral) of the tumor. The image display will also indicate the distances from the skin to the tumor and from the tumor to the chest wall. Measurements of the distance from the nipple to these edges of the palpable tumor at specified, measured radians will also will be made by the surgeon and will be compared to the optical scanner adjusted supine MRI images.

Phase 2. Patients with histologic evidence of invasive carcinoma or ductal carcinoma in situ will undergo bilateral breast MRI in the prone position, as is the current standard at Dartmouth. At the time of surgical consultation, patients with non-palpable breast cancers who desire breast conservation will be invited to be a part of the study. Consenting patients will undergo randomization, stratified by DCIS vs invasive cancer and for invasive lobular cancer vs invasive ductal cancer. Patients in Group W will undergo wire-localized partial mastectomy.

Patients randomized to Group S will undergo a contrast enhanced supine MRI and optical scan, followed by partial mastectomy using the image guidance system we developed and verified in Phase I (19).

Standard radiologic images (mammograms, ultrasounds, prone MRI images) will be available to the surgeon at the time of surgery for all patients. Patients in Group W, the usual care group, will undergo standard of care breast conserving surgery as practiced at our institution for non-palpable breast cancers.

Patients in Group S will undergo a supine MRI at a convenient time within a week of surgery. They will have an optical scan of the breast surface while on the OR table on the day of surgery. Using the methods described and validated in Phase I, the scan data will be used to adjust (coregister) the supine MRI image volume obtained pre-operatively into a highly accurate representation of the breast and MRI defined tumor mass at the time of surgery. This coregistered image will be projected on a screen for easy viewing by the surgeon. A hand held, sterile stylus pointer will be tracked during surgery and will allow the surgeon to point to a specific location on the breast and see exactly where that point is on the screen image display. The image display will indicate the distances from the nipple to all aspects (cranial, caudal, medial, lateral) of the tumor, as well as the distances from the tumor to the skin and from the tumor to the chest wall. Guided by the coregistered image information the surgeon will mark on the surface of the breast the extent of resection. The sterile stylus probe may be used during the procedure to relate points in the surgical field to their corresponding location on the coregistered supine MRI image. The surgeon will resect the breast tumor volume that is identified by the image guidance system.

The surgical specimens will be water displaced to determine their volume. The specimen will then be inked by the surgeon with 6 different colors to orient the specimen (black: deep, blue: superficial, green: caudal, orange: cranial, yellow: lateral and red: medial), and will undergo specimen mammography. Specimens will then be sent to Pathology. Margins for invasive cancers will be considered positive if cancer cells are present at the edge. Margins will be

considered positive for DCIS if there are tumor cells < 1 mm from the edge. The distance to the nearest margin will be determined in all cases.

At the end of patient accrual, prone and supine MRIs from patients in Group S will be separately interpreted by two radiologists. The cases will be divided in halves. One radiologist will initially interpret half of the supine and half of the prone MRIs, the other will initially interpret the other half. After a 6-week interval, each Radiologist will interpret the other half of the images. Concerning lesions on each study will be identified, and then a comparison will be made between the supine and prone images to determine if lesions identified on the supine images are concordant with the number and size of lesions identified on the prone images.

Section 5. POTENTIAL TOXICITY

Supine MRIs are administered according to standard-of-care practice for prone breast MRI and represent no more additional risk than would be experienced by women receiving these exams as part of their (non-research) breast care. The risk of contrast enhanced MRI is very low, reflecting the minute risk of life threatening allergy and development of nephrogenic sclerosis related to gadolinium based intravenous contrast. Patients deemed to be at higher risk for gadolinium induced nephrogenic sclerosis because of compromised renal function will not be eligible for participation. Patients who experience a significant allergic reaction to gadolinium based intravenous contrast at the time of their clinical prone MRI will also be considered ineligible for study participation.

Optical scans will be performed using a GO!Scan 3D optical scanner (Creaform, Levis, Quebec, Canada). This scanner will be able to scan the entire breast in 1 minute. It uses white light (LED) to form the image, like a flashlight. There are no anticipated risks associated with the use of this scanner.

Section 6. DRUG FORMULATION AND PREPARATION

Not applicable.

Sections 7 and 8. Clinical ENDPOINTS AND STATISTICAL ANALYSIS

The primary objective of the first phase will be to determine how closely the optical scan adjusted images of the tumor location correspond with the location as identified by intraoperative tumor palpation and measurement. Precise distances from the nipple to the superior, inferior, medial and lateral edges of the tumor will be taken from the adjusted MRI images and then marked on the patient's skin. The surgeon will then palpate the tumor and measure the distance between the palpable superior, inferior, medial and lateral tumor edges and the spots located by MRI. An adjusted image will be considered acceptable if all 4 image guided measurements are < 1 cm from the palpable tumor edge. We will enroll at least 5 patients on this phase of the study. We will move on to Phase II when 90% of the measurements in the previous 5 patients are acceptable, as defined above. If by technical modifications we cannot meet these criteria for moving to phase II after 25 patients the protocol will be closed.

The primary objective of the second phase is to determine whether the addition of supine MRI to conventional imaging with mammography and prone MRI will result in a lower positive margin rate in patients undergoing breast conserving surgery. Following informed consent and enrollment, patients will be assigned to usual care or usual care plus supine MRI. A permuted block randomization will be used within strata defined by DCIS and type of invasive cancer to achieve balance in treatment totals within strata. The positive margin rate in the two groups will be computed and compared using a chi-squared statistic.

Our senior breast Pathologist, Dr. Wendy Wells, has performed a detailed analysis of the surgical margins for patients who had a core biopsy which was positive for cancer or DCIS and then underwent partial mastectomy at Dartmouth in the year 2005. A total of 125 patients with invasive ductal carcinoma were identified: 31 (25%) had positive margins. Twenty six of 53 patients undergoing partial mastectomy for DCIS had positive margins (45%). Overall, 57/178

patients (32%) had positive margins. A two-thirds decrease in the positive margin rate (i.e., from 32% to 11 percent or less) would be clinically meaningful. The primary analysis will consist of computing the positive margin rate observed in the two groups and comparing them with a chi-squared test. Based on a chi-squared test with a significance level of 0.05 and a power of 80%, a sample size of 69 patients will be required in each group.

We will adopt a sequential testing procedure to assure that possible increases in the expected margin rate are detected. After 10% of the patients are enrolled, or 7 in each group, an exact test for proportions will be applied. If proportion of positive margins is greater than 32% and the p-value for the test is less than 0.004, the trial will be stopped as possibly increasing the rate. This procedure maintains the significance level at 0.05 and the power at 80% using Pocock boundaries for the Lan and Demets alpha spending function.[20]

Annually at Dartmouth we care for approximately 300 patients with invasive ductal cancer and 100 patients with DCIS. Approximately ⅔ of these patients (266) will undergo breast conserving surgery. Approximately ¾ of these patients will have non-palpable tumors (200). We anticipate that it will be possible to accrue one third (67) of these patients per year. Thus, we expect that it will take 2 years to complete accrual.

Secondary endpoints will be analyzed as follows. The mean specimen volume from Group S will be compared to the mean specimen volume from Group W using t - statistics. The concordance between lesion volumes identified on the supine MRI images and the prone MRI images will be evaluated through correlation and regression analysis.

Relevant data will be saved in Velos case report forms. The NCCC Safety and Data Monitoring Committee will monitor this trial quarterly.

Section 9. HUMAN SUBJECTS

The patients for this study will be accrued from the population treated at the Dartmouth-Hitchcock Medical Center. All patients will sign an informed

consent, which describes the treatment to be performed and discusses the risks and benefits of participation in the study.

Risk/Benefit analysis:

Risks associated with the experimental arm of this study include the risks of an additional MRI and all participants have potential confidentiality risks. The risk of an additional MRI is negligible and reflects the minute risk of life threatening allergy and development of nephrogenic sclerosis related to gadolinium based intravenous contrast. Patients deemed to be at higher risk for gadolinium induced nephrogenic sclerosis because of compromised renal function will not be eligible for participation. Patients who experience a significant allergic reaction to gadolinium based intravenous contrast at the time of their clinical prone MRI will also be considered ineligible for study participation.

Risk of breach of confidentiality of the medical records of participants will be minimized. Subject identity is numerically coded and is not available to research investigators or otherwise stored on the databases maintained by the researchers to archive the clinical encounters accrued as part of the studies conducted under this protocol. In this regard, all conventional clinical image data is de-identified prior to its use for analysis. Databases which are used to store subject-sensitive information, even though completely de-identified as stored, are password-protected and encrypted during file/data transfers from viewing terminals. As further safe-guard, the Data Safety Monitoring and Accrual Committee of the Norris Cotton Cancer Center will oversee the conduct of the trial.

The potential benefits associated with the experimental arm of this study include lower positive margin rates, smaller excision volumes, and less discomfort since they will avoid the wire placement.

The importance of the knowledge to be gained and the ultimate potential for benefit for future patients if this new technology is effective far outweighs the nominal risks experienced by the women who participate in this clinical study.

Pregnant women will be excluded due to the potential risk of gadolinium to the fetus.

Women with child-bearing potential are eligible for enrollment into the study. The risks of participating in the imaging sessions for these women is no greater than for any other participant. Risks associated with breast surgery vis-à-vis child-bearing potential is outlined as part of standard of care. Thus, any woman of child-bearing years enrolled in this protocol would already understand (and have accepted) the surgical risks to her fertility.

Only women will be enrolled in the study because breast cancer is predominantly a female disease. The imaging apparatus is design to accommodate the size and shape variations associated with the adult female breast. While a very small proportion of breast cancer appears in males, the imaging systems are not designed to image the male breast. All racial and ethnic categories will be recruited commensurate with the racial/ethnic composition of the DHMC patient catchment area.

Patients will be considered “on study” and will be monitored for adverse events by the operating surgeon from the time of registration until 2 weeks after surgery.

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