Diagnostic Utility of MRI in Female Patients with Nipple Discharge: A Prospective Trial

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Research Summary

1. **Protocol Title:**
   Diagnostic Utility of MRI in Female Patients with Nipple Discharge: A Prospective Trial

2. **Purpose of the Study:**
   The purpose of this prospective study is to determine the diagnostic value of MRI for the evaluation of patients with pathologic nipple discharge.

3. **Background & Significance:**
   Nipple discharge, one of the most common reasons for referral to the breast imaging service, is often investigated by diagnostic mammography and sonography to evaluate for an underlying malignancy, the reported incidence of which ranges from 3 to 29% (1-7). If conventional imaging is negative, the patient may obtain further imaging with MRI, undergo ductography or ductoscopy, proceed to duct exploration and excision, or be observed (6, 8). Findings on breast MRI, in addition to the patient's symptomatology (frequency and volume of discharge) and risk of breast cancer, are used to inform the decision about whether to pursue surgery or watchful waiting (8).

   Limited research suggests that MRI may have a role in the evaluation of patients with nipple discharge because of its ability to identify mammographically- and sonographically-occult disease and to guide surgical excision (2, 9-16). Previous research has drawn conclusions from small retrospective patient cohorts, and there is relatively wide variability in the reported diagnostic utility of MRI. Consequently, duct exploration and excision remains the gold standard diagnostic approach (6, 8, 17). However, duct excision is an invasive procedure that can be technically challenging, especially if the affected duct cannot be localized or if the intraductal lesion is located far posteriorly in the breast, and can result in complications, such as interruption of the neurovascular supply to the nipple-areolar complex, cosmetic deformity, and breastfeeding limitations (18).

   Many women with nipple discharge and a negative conventional imaging workup undergo surgical excision, but few actually have underlying malignancy. MRI may be useful to improve patient selection in this setting; in particular, a high negative predictive value of MRI may obviate the need for invasive surgery in patients who do not require intervention for symptomatic relief (8, 9, 17). Our research group previously performed a retrospective study on this topic, which is currently under review for publication. The negative predictive value of MRI was found to be 100%, but this study was significantly limited by selection bias; that is, only certain patients, at the discretion of the breast surgeon, underwent MRI as part of their workup.

   The purpose of the proposed prospective study is to determine the diagnostic value of MRI for the evaluation of patients with pathologic nipple discharge.

4. Design & Procedures:

Referral for breast MRI in patients with pathological nipple discharge has changed in recent years. Discussion with our breast surgeons indicate that referral for breast MRI has become routine for patients who present with pathological nipple discharge when in the past, referral was at the discretion of the breast surgeon. For our study, patients with pathologic nipple discharge (unilateral and bloody or unilateral and clear) will be identified in either surgery clinic with presenting symptoms or in breast imaging clinic in one of 2 ways: 1) on the requisition under the "indication for exam" as specified by the referring clinician, or 2) by the technologist who asks routine questions to the patient. These patients will undergo conventional imaging with mammography and breast sonography first. If conventional imaging is negative or non-diagnostic, the patient will be seen in surgical clinic (Clinic 2-2 next door to ours) and contrast-enhanced breast MRI will be ordered by the surgeon as part of clinical care. All patients will see a breast surgeon first before being approached for the study. Once a patient is identified as having a planned contrast MRI, they will be approached by a CRC or resident/fellow participating in the study. Our experience, based on a prior retrospective nipple discharge study, has shown that approximately 100 patients per year are encountered at our breast imaging clinic for evaluation of nipple discharge. We expect that approximately 75% will agree to participate in the study. This will yield a recruitment rate of 75 patients per year, hence the number specified in the study proposal. Bracco Diagnostics will provide seed funding for 2 years for an anticipated total of 150 patients.

We will only be obtaining data prospectively on patients who receive MRI's for clinical purposes (symptoms of pathological nipple discharge). When the clinical team notifies us that an MRI has been ordered for that purpose, we will consent the patients to document the results and follow-up. We will not be obtaining any MRI's on patient's for research purposes only. For that reason, we will be following clinical guidelines for obtaining creatinine, pregnancy tests, etc.

The following data will be collected and analyzed: patient age, characteristics of the discharge (laterality, spontaneous versus expressed, duration of time, color, presence of blood), imaging workup and findings, BI-RADS final assessment categories, pathology results from core biopsy and/or surgical excision, and clinical and radiologic follow-up data during the two years after presentation.

5. Selection of Subjects:

See above detailed paragraph

Inclusion criteria: female patients with unilateral and bloody nipple discharge OR unilateral and clear nipple discharge; clinical decision to have contrast enhanced MRI.
Exclusion criteria: male gender, non-English speakers, age < 21 years, lack of capacity to give legally effective consent

Note: It is highly unusual for lactating patients to present with pathologic discharge and therefore will likely not be identified for the study. There is a very small potential

risk associated with absorption of contrast medium into the breast milk, but there is insufficient evidence to exclude women who are currently lactating from the study.

Note: The costs of MRI will be covered by insurance. In the unlikely event that a patient's insurance denies coverage, the patient will be excluded from the study.

6. **Subject Recruitment & Compensation:**
   The patient will be seen in surgical clinic (Clinic 2-2 next door to ours) and contrast-enhanced breast MRI will be ordered by the surgeon. Potential subjects will be contacted and introduced to the study by the designated Clinical Research Coordinator or resident/fellow participating in the project.

   Recruitment will begin after approval of IRB and conclude after recruitment of approximately 150 subjects. No financial compensation to subjects will be provided.

7. **Consent Process:**
   Please see Section 14 of the e-IRB submission form.

8. **Subject's Capacity to Give Legally Effective Consent:**
   Subjects who do not have the capacity to give legally effective consent will not be included in this study.

9. **Study Interventions:**
   Patients who choose to participate in our trial will have undergone mammography, breast sonography, and will be planning to have a contrast-enhanced breast MRI for evaluation of nipple discharge. The study interventions are collection of clinical data for research purposes.

10. **Risk/Benefit Assessment:**
    Participation in this study poses minimal risk to patients. Risks to the subjects include loss of confidentiality.

    Loss of confidentiality is unlikely because the study data will be stored in the PI's office and a shared drive.
    There will not be any direct benefit to the subjects; however, this research may help improve the diagnostic workup of nipple discharge in future patients.

11. **Costs to the Subject:**
    There is no cost to the subject as a result of this study. The costs of the MRI will be covered by insurance. No financial compensation will be provided.

12. **Data Analysis & Statistical Considerations:**

As discussed above, a high negative predictive value of MRI may obviate the need for invasive surgery in patients who do not require intervention for symptomatic relief. Based on a statistical consultation with Dr. Kingshuk Roy Choudhary, we can achieve a negative predictive value of MRI of 95% with a margin of error of +/- 4.3%, if we recruit 100 subjects. Our goal is to recruit approximately 150 subjects, with the expectation that some patients will not receive adequate two-year follow-up.

The following data will be collected and analyzed: patient age, characteristics of the discharge (laterality, spontaneous versus expressed, duration of time, color, presence of blood), imaging workup and findings, BI-RADS final assessment categories, pathology results from core biopsy and/or surgical excision, and clinical and radiologic follow-up data during the two years after presentation.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for MRI for the detection of malignancy will be calculated using standard formulas. MRIs classified as BI-RADS categories 4 and 5 will be considered "positive," while those classified as BI-RADS categories 1, 2, and 3 will be considered "negative." For purposes of the analysis, MRI will be considered to be "false positive" imaging if the biopsied and/or excised lesion does not reveal malignancy. MRI will be considered "false negative" imaging if there is no suspicious finding on imaging (BI-RADS 1, 2, or 3) but subsequent pathology reveals malignancy.

13. Data & Safety Monitoring:

Consent forms will be stored in the PI's office. Patient names and medical record numbers will be recorded in a database on a shared drive only accessible by study researchers. Once data collection is completed, these identifiers will be discarded. Only basic demographic information (age) will be retained.

14. Privacy, Data Storage & Confidentiality:

Please see Section 12 of the e-IRB submission form.

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