Use of a Radiofrequency Chip for Localization of Non-Palpable Breast Lesions: A Comparison to Wire Localization

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BIOMEDICAL RESEARCH PROTOCOL
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Project Title: Use of a Radiofrequency Chip for Localization of Non-Palpable Breast Lesions: A Comparison to Wire Localization
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Clinical Trial Phase: IV: Post Marketing Study
Clinicaltrials.gov Number: *Pending*
Study Drug/Study Device: LOCalizer

I. Research Objectives/Background

1. Include primary, secondary, and exploratory objectives.

   Part A: Physician Training:
   - Objective 1: To allow the breast radiologists and surgeons to become comfortable with RFID chip placement and retrieval.
   - Objective 2: Pilot the data collection surveys and chart review methodology.

   Part B: Randomized Controlled Trial:
   - Objective 3: Examine accuracy of RFID localization in comparison to traditional wire localization
   - Objective 4: Compare Operating Room utilization and procedure scheduling between RFID and wire localization
   - Objective 5: Compare satisfaction between RFID and wire localization in patients, surgeons, radiologists, and staff

2. Include background and rationale for initiating the study. Includes pre-clinical and clinical data, current experiences with procedures, drug, or device, and any other relevant information to justify the research.

   With increasing use of screening mammography, more breast lesions are identified prior to being clinically palpable. This has led to the increased use of radiologic localization to facilitate surgical excision. Localization is typically accomplished using image guided wire placement. However, this technique has several limitations and disadvantages. First, the wire must be placed on the same day as the surgical excision. This requires scheduling coordination between radiology and the surgical operating room (OR). Because of scheduling, no wire localization procedures can be scheduled in the OR as a first case. This limits the OR utilization. If there are difficulties with wire placement the OR start time may be further delayed. For the patient, this is another procedure that needs to be done on the day of surgery which prolongs the time before surgery and can increase anxiety. To further complicate a patient's surgery day, this wire localization may be done at a different facility than the planned surgical excision. This requires the patient to drive across town with a wire protruding from the breast. Wire migration, breakage, and dislodgement can occur and may result in inaccurate lesion removal and potential need for a second operative procedure. In addition to the disadvantage associated with

placement on the same day as surgery, there are also technical challenges. The wire insertion point may be distant from the lesion location which may increase the difficulty of lesion excision and alter surgical incision placement. Both can lead to an increased volume of breast tissue excision and decreased cosmetic outcome. For these reasons, alternatives to wire localization have been sought.

Radioactive seed localization (RSL) was introduced in 1999 and was the first widely used alternative to wire localization in the United States (Pouw et al., 2015). This technique involves placement of an iodine-125 impregnated titanium seed into the breast lesion. Advantages of RSL have been its technical ease and the ability to place up to 5 days prior to surgical excision. Despite these advantages RSL has not been adopted universally. This is in part due to the regulations regarding using a radioactive seed. Proper handling and disposal require the oversight of a Radiation Safety Officer and specific facility licensing. Training of all personal involved much be performed. This adds layers of complexity to the procedure. Also, an improperly placed seed requires removal (Goudreau et al, 2015).

In an effort to address the disadvantages of RSL, alternatives have been developed that retain the ease of placement similar to RSL, but without the associated radioactivity. There are currently three approved marketed devices that are alternatives to wire localization: Magseed, Savi Scout, and LOCalizer.

The Magseed device consists of a 5 x 1 mm paramagnetic steel and iron oxide seed. Using the Sentimag probe a magnetic field is generated that transiently magnetizes the iron oxide which is then detected by the probe (Harvey et al., 2018). A disadvantage of the Magseed device is the inability to use the localization probe intraoperatively in the presence of any metal instruments. As the majority of operating instruments are metal, this creates significant challenges.

Savi Scout is an infrared and electromagnetic localization system using a radar reflector activated with an infrared light. A large multi-site study of Savi Scout demonstrated overall good localization with improvement in surgeon satisfaction when compared to wire localization (Cox et al., 2016). Like the Magseed, the Savi Scout has its own limitations. Most notably is the ability to disable the reflector with contact with electrocautery. Also, there is the risk of transection of the antenna during dissection.

The most recent addition to the market for the localization of non-palpable breast lesions has been the LOCalizer. The LOCalizer device is a radiofrequency identification chip (RFID) which is implanted percutaneously in the breast, and then localized by a handheld reader device. Because the chip is not visible to the operator, the reader device makes an audible sound that increases in pitch as the device is moved closer to the chip's location. There is currently limited data available regarding the use of a radiofrequency identification chip for non-palpable breast lesions. A study examining proof of concept demonstrated that RFID was feasible for lesion identification when implanted < 6 cm deep (Reicher et al, 2008). This was followed by a clinical study involving 20 patients demonstrating no localization failures or chip migration prior to incision (Dauphine et al., 2015). To date there are no larger published series using this technology.

In order to overcome the limitations of wire localization at our institution, we will evaluate the proposed benefits of the LOCalizer system for successful localization of non-palpable breast lesions in patients undergoing breast surgery. We hypothesize that the use of an RFID is non-inferior to the use of a guide wire for localization of breast lesions. Further, we hypothesize that the RFID chip will improve operating room utilization and efficiency while improving staff and patient satisfaction.

II. Drugs/Biologics/Devices

1. Include the product, dose, route, and regimen.
   - LOCalizer by Health Beacons and Faxitron Bioptics LLC - LOCalizer uses a miniature radiofrequency chip designed to be implanted into the breast up to 30 days before surgery.

2. Include the rationale for choosing the drug/biologic and dose, or for choosing the device to be used.
   - The RFID was chosen as a way to improve operating room efficiency and patient satisfaction. Many other institutions have transitioned from wire localization to radioactive seed localization. However, radioactive seed localization requires multiple steps in the regulatory process due to the radioactivity. The goal of trialing the RFID was to get the benefits of a radioactive seed localization including ease of scheduling, decreased risk of migration, and improved patient comfort while avoiding the challenges of using a radioactive implant.
   - Another localization device currently on the market is the MagSeed. The reason the LOCalizer RFID was chosen over the MagSeed is the MagSeed would require purchasing all new instruments for the operating room. The MagSeed is a magnetic chip. The detector device for the MagSeed requires that all instruments nearby be non-magnetic. This would translate into needing to replace all retractors and other instruments with either a non-magnetic metal or with plastic instruments.
   - Savi Scout is an infrared and electromagnetic localization system using a radar reflector activated with an infrared light. The Savi Scout reflector can be inactivated by contact with electrocautery. Also, there is the risk of transection of the antenna during dissection.
   - Due to the limitations of the other localization techniques, the RFID was selected for assessment in this study.

3. Include the standard reference therapy against which the study product is being compared, or if the reference is a placebo. Include justification for inclusion of a placebo or non-treatment group.
   - No placebo group
   - The reference therapy is wire localization

4. Include justification and safety information.
   - LOCalizer is a wireless radiofrequency identification (RFID) breast lesion localization system. It uses a RFID chip and a handheld reader with probe. The RFID is designed to be implanted in the lesion up to 30 days before surgery and is free of radioactivity. It was awarded 510k clearance by the FDA on 5/1/17

5. If an IDE (for investigational devices) or IND (for investigational drugs) is not necessary, provide justification.
   - Not applicable

III. Recruitment Process

1. Describe the recruitment process; including how and where recruitment will take place.
   a. Recruitment will occur in the Ellis Fishel Breast Center.
   b. All women with non-palpable breast lesions needing localization prior to excision will be screened for participation by the breast surgery clinic.

2. Describe any screening/baseline procedures.
   a. The screening of patients will occur by the breast surgery clinic at the time of scheduling the excision of a breast lesion requiring radiologic localization.

IV. Consent Process

1. Describe the consent process; including who will be approached for consent and what type of consent will be obtained from each subject population, if there is more than one.

Consent:

- Standard of Care Consent: The localization procedure, excisional breast surgery and follow up post surgery are standard of care and participants will sign the standard clinical consents for these procedures.
- Research Consent: Participants will sign a research consent form for the use of the RFID chip and/or wire for localization and for completion of the surveys.

V. Inclusion/Exclusion Criteria

1. List the inclusion and exclusion criteria.
    a. Inclusion criteria:
        i. Women requiring image guided pre-operative breast lesion localization for any reason (i.e. not restricted to cancer patients)

    b. Exclusion criteria:
        i. Lesions deeper than 6 cm from the skin surface
        ii. More than one lesion requiring localization
        iii. Lesions requiring bracketing
        iv. Lesions requiring MRI localization
        v. Inability to complete survey
        vi. Pregnancy

2. Describe restrictions on participation and appropriate screening procedures to ensure that the restrictions are maintained, including pregnancy testing.
    a. Pregnancy testing: If participants are post-menopausal or if pregnancy is not possible based on medical history, then no pregnancy testing is performed. In all other cases, a urine pregnancy test will be performed at the baseline visit in the breast surgery clinic, or in the radiology department prior to undergoing the localization.
    b. Either the PI, Co-Investigators, or the research staff will ensure that all enrolled subjects fit criteria.

VI. Number of Subjects

1. Include anticipated enrollment number in this study. Include a break-down in numbers if there is more than one subject population.
    - Part A: Nine subjects (3 for each of the 3 breast surgeons) will undergo dual RFID and wire localization prior to breast lesion excision. To account for screen failures, approximately 12 subjects may be enrolled.
    - Part B: Goal recruitment of 60 with 30 each for RFID and wire localization. To account for screen failures, approximately 72 subjects may be enrolled.

2. Include statistical analysis or other justification for the number of subjects enrolled.
    - No sample size calculation was performed as this is a pilot study.

VII. Study Procedures/ Design/Treatment Plan

1. Include study procedures/design/plan; include the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care). Include study duration and number of study visits required.

Standard of Care:

- Ultrasound or Mammographic guided localization
- Excisional breast surgery
- Follow-up visit in breast surgery clinic

Research:

- Use of RFID chip for localization procedure
- Surveys
- Urine Pregnancy test

Part A: Prospective trial to master the technique of RFID placement and retrieval.

- On the day of surgery prior to going to the operating room, the RFID placement will be performed first to allow radiologists to become familiar with placement of the RFID localizer. Participants will then immediately undergo wire localization (either ultrasound or mammogram guided at the discretion of the performing radiologist). The wire localization procedure is standard of care; the RFID device placement is for research and not charged to the patient.
- Data Collection: The same data that will be collected in the randomized controlled trial of RFID chip (Part B) will be collected (as below).

Part B: Prospective trial to examine safety, efficacy, OR utilization patterns, and satisfaction with RFID versus wire localization

- Randomization technique: Prior to randomization, subjects will be stratified based on technique of localization (either US guidance or mammographic guidance)
    - We will have a series of envelopes containing a card indicating either wire localization or RFID localization. We will have three different groups of envelopes to stratify based on the localization technique
        - Red envelopes – To be used for the first 20 patients undergoing mammographic localization. 10 will be wire localization and 10 will be RFID
        - Blue envelopes – To be used for the first 20 patients undergoing US localization. 10 will be wire localization and 10 will be RFID
        - White envelopes – To be used for patients undergoing either mammographic or US localization. 10 will be wire localization and 10 will be RFID
        - This technique will allow us to ensure that we have 30 patients undergoing RFID and 30 patients undergoing wire localization. It will also ensure that both the RFID and wire localization will have a minimum of 10 patients undergoing mammographic placement and 10 patients undergoing US placement.
- Study Time-line:
    - Breast surgery clinic appointment – Study enrollment
        - Consent
        - Patient Questionnaire #1
        - Radiology Nurse Form
        - Surgery Clinic Nurse Form
    - Radiology procedure appointment
        - Patient Questionnaire #2
        - Radiologist Form
        - Radiology Nurse Pregnancy Test results (if needed)
    - Surgical procedure day
        - Surgeon Form

    - Post-op visit
        - Study Completion Form
        - Patient Questionnaire #3
- Study Duration
    - There will be four visits: one pre-op breast surgery visit in which enrollment will occur (approximately one to two hours), one radiology procedure visit for localization (approximately one hour), one OR visit for surgery (approximately 6-8 hours), and one post-operative visit (approximately 30 minutes to one hour). This is the same number of visits as all patients not participating in this trial and standard of care.
    - For each study participant the expected duration is one month from enrollment until the post-operative visit.
    - Full accrual is expected to take 12 months.

2. Blinding, including justification for blinding or not blinding the trial. Describe un-blinding procedures.
    - No blinding
3. Justification of why participants will not receive routine care or will have current therapy stopped.
    - n/a: participants will be receiving routine care
4. Definition of treatment failure or participant removal criteria.
    - If there is a concern for the participant's health
    - If the participant's underlying disease gets worse
    - Participant has localization performed but does not undergo surgical excision
    - The study is closed for safety, administrative or other reasons
5. Description of what happens to participants receiving therapy when study ends or if participation in the study ends prematurely.
    - Participants will continue to receive routine care.
6. Include sub-studies or banking information (correlative/special studies)
    - n/a

VIII. Potential Risks/Adverse Events

1. Describe reasonably foreseeable risks or discomforts to the subjects and steps to minimize risks.

Risks of RFID: Potential pain and discomfort, migration or lost functionality of device. Failure of localization.

Risks of Survey: The potential exists for breaches of confidentiality for the survey data collected as part of the study. We expect this risk to be minimal.

2. Describe any stopping rules.

- If there is a concern for the participant's health
- If the participant's underlying disease gets worse
- The study is closed for safety, administrative or other reasons

3. Include the plan for reporting unanticipated problems or deviations. This plan must include a five-day reporting requirement to the IRB once becoming aware of an event.

All unanticipated problems and deviations will be reported to the IRB within 5 business days of first learning of the event.

IX. Anticipated Benefits

1. Include both direct and indirect benefits for either the individual or society.
    a. There are no benefits to the participants.
    b. Potential benefits to society/breast patients include increased efficiency allowing more patients to be treated, decreased anxiety about procedures, less surgical complications, easier recovery, and improved satisfaction with operative procedure.

X. Compensation

1. Describe the amount, method, and timing of disbursement. Compensation can include checks, cash, gifts, extra/course credit, etc.
    - All participants will be compensated a total of $50 once they complete the study, by check. Should a participant not complete all four visits, the payment will be prorated as follows: Visits 1, 2 and 3: $10.00 each; Visit 4: $20.00.

XI. Costs

1. Detail costs of study procedures, drugs, biologics, or devices and identify who will cover the cost.

    - Costs for the localization procedure, pregnancy test, and excisional surgery are charged to the participant and/or their insurance. There is no charge to the participant for the RF chip. The chip is provided free of charge by the manufacturer/marketer.

XII. Data Safety Monitoring Plan

Describe the plan to monitor the data, if necessary. A plan is required for treatment and/or intervention studies, sensitive data are being collected, there is a possibility for subjects to experience adverse events, etc.

1. Either the PI, Co-Investigators or the research staff will ensure that all enrolled subject surveys and data are collected and secured prior to patient getting discharged.
2. If there is a failure of localization (intended purpose of the device) – this incidence needs to be reported.
3. PI, Co-Investigators or the research staff will monitor the study after every 10 subjects.
4. University statisticians will be contacted for analysis and interpretation of the data
5. If patients refuse to the finish the entire study – these subjects and reason why will be collected and not included in the main data and these will be unfinished cases with no comparison available.
6. If there is more than four incidence of failure of localization with RFID – study will be stopped.
7. If the case of study termination, IRB will be made aware of the reasons and course of action by the PI, Co-Investigators, or research staff.

XIII. Multiple Sites

1. Specify who is the lead site and describe the roles of each site in the study.
2. Indicate that all required approvals are already in place or will be in place at each site prior to project implementation. If the study will utilize a reliance agreement or a single IRB, please describe which institution(s) will be relying on another IRB for review, and which institution will be responsible for the IRB oversight of the relying IRB(s).
3. Describe the plan that is in place to manage information obtained from multiple sites that may be relevant to the protection of human subjects such as reporting unanticipated problems, protocol modifications, and interim results.

- Not applicable – Single site study

XIV. References/Appendices

1. Include findings from a literature search or pilot study must be outlined including appropriate detailed references to earlier studies and data.

   References:

Cox, C.E., Russell, S., Prowler, V., Carter, E., Beard, A., Mehundru, A., Shivers, S.C. (2016). A prospective, single arm, multi-site, clinical evaluation of a nonradioactive surgical guideance technology for the location of nonpalpable breast lesions during excision. *Ann Surg Onc*, 23, 3168-3174.

Dauphine, C., Reicher, J.J., Reicher, M.A., Gondusky, C., Khalkhali, I., & Kim, M. (2015). A prospective clinical study to evaluate the safety and performance of wireless localization of nonpalpable breast lesions using radiofrequency identification technology. *AJR*, 204, W720-W723.

Goudreau, S.H., Joseph, J.P., & Seiler, S.J. (2015). Preoperative radioactive seed localization for nonpalpable breast lesions: Technique, pitfalls, and solutions. *RadioGraphics*, 35, 1319-1334.

Harvey, J.R., Lim, Y., Murphy, J. et al. Breast Cancer Res Treat (2018) 169: 531. https://doi.org/10.1007/s10549-018-4709-y

Hayes, MK (2017). Update on Preoperative Breast Localization. Radiol Clin North Am. 2017 May;55(3):591-603.

Pouw, B., De Wit-van der Veen, L.J., Stokkel M.P.M., Loo, C.E., Vrancken Peeters, M.T.F.D., Valdes Olmos, R.A. (2015). Heading toward radioactive seed localization in non-palpable breast cancer surgery? A meta-analysis. *J Surg Onc*, 111, 185-191.

Reicher, J.J., Reicher, M.A., Thomas, M., & Petcavich, R. (2008). Radiofrequency identification tags for preoperative tumor localization: Proof of concept. *AJR*, 191, 1359-1365.

2. Additional references to supporting data or additional information may be included in an appendix.