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PROTOCOL TITLE

Pilot trial evaluating a miniature radiofrequency tag for localization of non-palpable
breast lesions for surgery

PROTOCOL NUMBER

LOCALIZER003

NCT03202472

Original Protocol Date: February 6, 2017

Revision Date: July 10, 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

WL	Wire localization
RSL	Radioactive seed localization
RFID	Radio Frequency Identification

1. STUDY SUMMARY

1.1 Study Population

Patients who require breast surgery of a non-palpable breast lesion and would otherwise require wire localization (WL) of the lesion on the morning of surgery.

1.2 Study Duration

The estimated duration of the study is one year.

1.3 Study Center(s)

UCLA Health System Sites

1.4 Objectives

This pilot study will evaluate the feasibility of utilizing a new FDA-cleared radiofrequency tag for localization of non-palpable breast lesions and provide preliminary data for a larger study.

1.5 Number of Subjects

The projected enrollment is 50 patients

1.6 Statistical Methodology

For binary outcomes, exact confidence bounds will be reported for all proportions. For the three Likert questionnaires, a total score will be computed for each and summary statistics will be reported for the total score and for each item as well as confidence bounds for the median or mean.

2. INTRODUCTION AND BACKGROUND

Wire localization (WL) has been the standard localization technique for guiding surgical excision of non-palpable breast lesions for over 20 years (1-3). It is effective in localizing the intended target with failure rates between 1-6.7% (4-6) but it carries risks inherent in the technique of placing a wire into a patient's breast. For one, a portion of the wire must reside outside of the breast so the surgeon can use the trajectory of the wire to guide the surgical resection. In this case, the wire can be inadvertently dislodged at any point following the wire placement and before the ultimate wire removal in the operating room (7). Also, given its external component, the WL procedure must be

performed on the same day of surgery, which can delay surgical start times and impede operating room efficiency.

The WL procedure is performed by the breast radiologist in the Imaging Center on the morning of surgery. The procedure is performed under local anesthesia in either the upright, supine or prone position, depending on the lesion location and the method of image guidance for wire insertion. Patients arrive at the facility on an empty stomach given that they are having surgery that same day. It is not uncommon for patients to experience lightheadedness and become vasovagal from the localization procedure. Despite these inconveniences for patients, WL has remained the primary method for localizing non-palpable breast lesions for surgery for both benign and malignant disease.

With screening mammography, the rates at which breast cancers are being diagnosed at a non-palpable, early stage has grown considerably, increasing the number of breast cancers that require image-guidance for excision. Although WL remains the most utilized method for localizing non-palpable breast cancers, the rates of positive margins varies widely with this approach ranging from 12-60% (8-10). Given this and the technical difficulties associated with WL, alternatives have been sought that may improve outcome for patients with breast cancer treated with breast conservation surgery.

Radioactive seed localization (RSL) has emerged as an alternate and possibly more favorable option for localization and has been a widely studied alternative. Unlike the wire, the radioactive seed is implanted entirely within the breast and this can be performed at any time within 5 days of surgery. Studies have demonstrated the effectiveness of RSL in appropriately targeting the lesion for removal (10,11). In addition, RSL appears to equal if not improve the negative margin rate and re-excision rate for lumpectomies for breast cancer compared to WL (12-14). Nonetheless, RSL has not been easy to adopt given the regulations necessary to manage and track the radioactive seeds, the special licensing necessary for handling radioactive material, and the coordination necessary between the different departments.

Other alternatives for lesion localization are under active investigation. A magnetic seed called the Magseed is currently being evaluated in a clinical trial at MD Anderson (Clinicaltrials.gov). Preliminary concerns include difficulty with the large size of the probe compared to incision size for seed detection and the interference from the metal surgical instruments which are used during surgery. In addition, presence of the magnetic seed is a contraindication for the higher power 3T MRI's used to evaluate breast lesions and may impose significant artifact if used with the 1.5T MRI's. For these reasons, we are seeking an alternative for lesion localization.

Our proposed study is a pilot study to evaluate a recently FDA-approved radiofrequency tag for Radio Frequency Identification (RFID) of non-palpable breast lesions for surgery. RFID technology is already widely used outside of medicine, most commonly in the microchip for pet identification. The radiofrequency tag (or microchip) is passive and has no internal energy source unlike the radioactive seed. The LOCalizer probe used to read the tag in the operating room emits a signal that then completes a circuit with the tag that allows for localization and detection. Similar to the radioactive seed and unlike the wire, the RFID tag is inserted completely within the breast allowing uncoupling of the localization procedure from the day of surgery. But, unlike the radioactive seed, there is no concern for signal decay so the RFID tag can be inserted up to 30 days prior to surgery. This allows for more flexible scheduling for tag insertion and allows for scheduling of surgeries for first case start times, improving overall operating room efficiency. Also, since the RFID tag is not radioactive, it does not require special handling and tracking. And, unlike any other localization method currently available, RFID with the LOCalizer can read distance in millimeters from the tag, which in theory will help guide surgical dissection and possibly reduce rates of positive margins.

Radiofrequency technology has been approved by the FDA for implantation in humans for purposes of identification. Further studies have expanded this technology for use as a localization method as well. In the medical field, RFID tags have been evaluated for their use in guiding positioning of endotracheal tubes for intubation (15) and locating surgical sponges in body cavities (16). Proof of concept studies have also been performed demonstrating the feasibility of using RFID technology for localizing tumors (17).

A prospective clinical study evaluating the safety of RFID technology for localization of non-palpable lesions in the breast was performed at Harbor UCLA (18). In this safety analysis study, 20 patients underwent both wire placement and radiofrequency tag insertion for the localization of non-palpable breast lesions. The radiofrequency tag was successfully identified *in vivo* with the LOCalizer device and the tag and targeted lesions were removed successfully in all 20 patients. All cases were performed with IRB approval as a Non-Significant Risk device.

We believe that a pilot study evaluating this new technology without concomitant placement of a wire is necessary to ensure that surgeons can successfully use RFID technology alone to locate non-palpable breast lesions. In addition, a preliminary assessment of patient experience and physician experience, evaluation of positive margin rates for malignant lesions and determination of volume of tissue removed would be helpful for initial evaluation of this technology as a non-inferior alternative to WL. Results from this study will inform study design for a larger prospective institutional study.

3. STRATEGY

We plan to enroll 50 patients with non-palpable breast lesions that require surgical removal through the UCLA Health System. The patients may have a diagnosis of breast cancer and be undergoing a lumpectomy or they may have a benign lesion requiring localization for surgical excisional biopsy. Patients will undergo image-guided placement of the radiofrequency tag by our breast radiologists by either mammographic or sonographic guidance within 30 days of surgery rather than a wire localization on the morning of surgery. The RFID tag will be provided at no cost to the patient. The patients will undergo surgery as planned and the surgeons will use a handheld device (LOCALizer) to localize the tag during surgery. Retrieval of the marker will be confirmed by specimen radiography performed per standard protocol at the time of surgery. Three breast surgeons will be participating and enrolling through 2 UCLA sites.

4. AIMS

4.1 Primary Study Endpoints

- a) Percentage of patients with successful placement of the RF tag under radiographic guidance confirmed by mammography
- b) Percentage of patients with successful retrieval of the RF tag confirmed by specimen radiography

4.2 Secondary Study Endpoints

- a) Patient experience with image-guided placement of tag
- b) Radiologist's experience placing radiofrequency tag compared to WL
- c) Surgeon's experience using radiofrequency tag to guide resection compared to WL
- d) Percentage of patients with positive margins on initial lumpectomy using RFID technology
- e) Percentage of patients with cancer requiring re-excision
- f) Volume of tissue removed with specimen with tag (not including shave margins, if taken)
- g) Days prior to surgery of insertion of marker
- h) Percentage of patients with documented migration of marker

5. SUBJECT SELECTION

Patients over the age of 18 who require breast surgery and localization of non-palpable breast lesions for surgery will be enrolled. The vast majority will be women given that screening mammograms are performed primarily in women and women are diagnosed with breast cancer at rates significantly higher than men.

5.1 Inclusion Criteria

- a) Able to give written informed consent to participate in the study
- b) Patients over the age of 18
- c) Patients with breast lesions that are non-palpable that require surgical removal
- d) Lesions and/or clip targetable with image guidance

5.2 Exclusion Criteria

- a) Multicentric breast cancer
- b) Stage IV breast cancer
- c) Pregnant or lactating females

5.3 SUBJECT RECRUITMENT

Patients will be identified by the treating surgeon during their surgical consultation visits. The study will be discussed with them at the time of surgical planning in a private room. When potential patients are identified, the treating surgeon will explain the study purpose, obtain informed consent, and provide the patient with a signed copy. The patient's surgery and localization procedure will then be scheduled.

6. STUDY PROCEDURE

Enrollment Random unique number assigned	Radiofrequency tag placed under radiologic guidance	Patient completes patient questionnaire regarding marker placement. Radiologist completes physician questionnaire	Breast surgery performed and RF tag removed	Surgeon completes physician questionnaire	Post-operative visit and end of Study
≤ 8 wks	≤ 24 hrs	< 30 days	≤ 24 hrs	≤ 2 wks	

- a) Questionnaires: Each subject will complete a patient questionnaire (attachment 12.1) following placement of the radiofrequency tag. The questionnaires will be completed in a private room immediately following the procedure and no later than 24 hours. The questionnaires will be labeled with the unique patient identifying number so that clinical outcome can be associated with patient reported outcome for data analysis. The radiologist will also complete a questionnaire (attachment 12.2) following placement of the marker, and the surgeon will complete a questionnaire (attachment 12.3) following the breast surgery.

7. DATA MANAGEMENT AND EVALUATION

7.1 Sample Size Determination

Sample size for this pilot study was selected at 50 patients. Since this is not a comparative study, the sample size is based on the width of the confidence interval, not power. Our primary outcomes are successful placement and successful retrieval of the RFID tag. We anticipate 100% success for both outcomes. Assuming this is true, a sample size of $n=50$ allows establishment of the lower 95% confidence bound at 94.2%.

The sample size is also based on pragmatics of recruitment and patient flow and budgetary constraints. This is a pilot study to determine feasibility of patient recruitment for a larger study, implementation of a new FDA-cleared device, and modification of the logistics of the study protocol.

7.2 Statistical Methods

For binary outcomes, exact confidence bounds will be reported for all proportions. For the three Likert questionnaires, a total score will be computed for each and summary statistics (mean, median, range, proportion who are 1,2,3,4,5) will be reported for the total score and for each item as well as confidence bounds for the median or mean.

7.3 Safety Analysis of Individual Adverse Experience Reporting

The procedure involved in placing the radiofrequency marker for the research study will be included in the safety analysis for adverse event reporting by the participant. All adverse events due to these procedures will be recorded and reported to the IRB.

Image-guided localization is standard for localizing breast lesions that are not palpable and that require surgical removal. The most common localizing device is a hooked wire. We are studying a radiofrequency marker as an alternative. The patient and/or her insurance will be billed for the standard of care procedure of insertion of the localizing device, the localization mammogram, the specimen mammogram and the surgery but there will be no cost to the patient or her insurance for the RFID tag itself.

Some risks associated with the localization procedure (regardless of the device placed) include pain, bruising, bleeding, swelling, infection, lightheadedness and dizziness. Less common risks include implant rupture, pneumothorax (punctured/collapsed lung) or movement (migration) of the marker after placement and before surgery. The placement of marker may not be successful due to inadequate visualization of the abnormality or difficult location of the abnormality (too close to the skin surface or too deep in the breast) which precludes safe and accurate placement of the marker. In this case, if placement of the standard wire is also considered technically impossible then the breast imager and surgeon will discuss alternatives for lesion localization, such as intraoperative ultrasound localization, placement of skin marker, etc. such as is standard protocol when wire placement is unsuccessful.

Failure in this study is defined as inability to localize the lesion with the RFID tag but successful localization with the wire. If both approaches are unsuccessful then this would reflect an inability to localize the lesion in general, which is a risk of image-guided localizations but not a failure of the tag itself. In the case of defined failure, the patient will require a second procedure for wire placement prior to surgery. Failure would also be defined as inability to retrieve the tag and/or the lesion. In this case, the patient would require a second localization procedure and surgery.

The risks from participation in this study are minimal. Participation is voluntary and participants can withdraw any time after consent but prior to placement of the research device without fear of any change in medical treatment.

An interval analysis will be performed after enrollment of the first 20 patients to ensure that the radiologists are able to successfully place the device for appropriate lesion localization, surgeons are able to successfully retrieve the device, and patients do not experience significant adverse side effects from placement of the tag.

The assessment of safety will be based primarily on the frequency of AE's. The research device will most likely be placed within 7 days of surgery but can be placed on the morning of surgery out to 30 days prior to surgery. The patient will be contacted by study personnel on the day following device insertion (unless within 24 hours of surgery) to inquire about adverse events and an AE report form will be completed (attachment 12.4). A follow-up visit within 2 weeks of surgery will also occur and will be the final study visit.

This study will involve two sites, and study personnel will be notified immediately regarding any documented AE's or concerns that impact patient safety or continuation of the study.

Given the low risk of this study, there is no anticipated toxicity.

7.4 Data Collection

All subjects will be assigned a unique identifying number upon signing their consent. All data will be identified using this number. No data will be collected or stored attached to any identifying information. Personal/medical history data will be kept unidentified according to HIPAA. Personal information and the codes associated with the personal information will be maintained in a password protected file by the PI, on her computer that is password protected and located in a secure office with limited access. The random unique number will be used to identify subjects in all electronic spreadsheet collating results.

7.5 Privacy and Confidentiality

No information that identifies a subject will be released without separate consent except as specifically required by law. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and in accordance with all institutional review board requirements, and all applicable policies of the institution. Participants will be assigned a unique study identification number which will be the only marker attached to their data collection forms. Participants will complete questionnaires in the privacy of a closed room. Only the PI will have access to the key linking names and contact information with the primary and complete set of data collected, by study identification number, and this key will be kept in a password protected computer file. All paper records for individual participants will be coded as noted above, handled with privacy and confidentiality in mind, and kept in a locked file cabinet in the PI's office. All participant identifiers are removed from

Excel tracking spreadsheets. Medical record review will be limited to the patients of the investigators listed on this study.

7.6 Consent Process

When potential subjects are identified, the treating surgeon will discuss the study with the patient and obtain informed consent. Informed consent discussion will be performed in a private room/office. A copy of the signed consent will be given to the patient. They will be welcome to review the forms at home and have an opportunity to discuss their participation in the research with whomever they wish. The consenting physician will question the prospective subject during the consent process to make certain the subject understands the research study as well as the risks and benefits of the study. They will also be available for questions.

8. STUDY FINANCES

8.1 Funding Source

All product for the RFID localization procedure will be provided by Faxitron Biopics, LLC but this is not an industry-sponsored study.

8.2 Subject Compensation

There will be no monetary compensation for participation.

8.3 Commercial Ramifications

There are no commercial ramifications.

9. ADVERSE EXPERIENCE REPORTING

9.1 Investigator Responsibility

The Code of Federal Regulations, 21 CFR .150(a)(1) states that: An investigator shall submit to the sponsor and to the reviewing IRB (Institutional Review Board) a report of any unanticipated adverse effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

9.2 Sponsor Responsibility

The Code of Federal Regulations, 21 CFR 812.150(b)(1) states that: A sponsor who conducts an evaluation of an unanticipated adverse effect under §812.46(b) shall report the results to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. This study has no sponsor outside of UCLA.

For reported deaths, the investigator should supply the IRB with any additional requested information (e.g. autopsy reports and terminal medical reports).

9.3 Principal Investigator Obligations

Maggie DiNome, M.D., F.A.C.S., is the Principal Investigator. All co-investigators participating in this research study shall be qualified by education, training and experience to assume responsibility for the proper conduct of the study, shall meet all the qualifications specified by the applicable regulatory requirement(s) and shall provide evidence of such qualifications through up-to-date curriculum vitae. Prior to the initiation of the study, the investigator and any co-investigators will supply UCLA with their curriculum vitae, including a list of publications and any other relevant documentation requested by the sponsor, the IRB (Institutional Review Board) and/or any other prevailing regulatory bodies.

a) Data

The Principal Investigator is responsible for the accuracy of the information collected and entered into the database. All data must be available for review. The PI will also allow representatives of the IRB to review the information reported in the database and reconcile the data with source documents.

b) Confidentiality of Subjects

The PI must assure that the subjects' anonymity will be maintained. All documents should identify subjects by identification code only. The PI will maintain a separate log of the subjects' codes, names and center identification code and keep it in a locked cabinet.

10. PUBLICATION PLAN

The publication plan will be in accordance with UCLA's publication policy

11. LITERATURE CITED

1. Leeming R, Madden M, Levy L. An improved technique for needle localized biopsies of the breast. *Surg Gynecol Obstet* 1993;177:84-6.
2. Greenlee JA, Gubler KD, Goepfert CJ, Ragland JJ. Surgical margins after needle-localization breast biopsy. *Am J Surg* 1995;170(6):643-5.
3. Jones MK, Vetto JT, Pommier RF, et al. An improved method of needle localized biopsy of nonpalpable lesions of the breast. *J Am Coll Surg* 1994;178:548-52.
4. Shetty MK. Presurgical localization of breast abnormalities: an overview and analysis of 202 cases. *Indian J Surg Oncol* 2010;1(4):278-83.
5. Jackman RJ, Marzoni FJ. Needle localized breast biopsy. Why do we fail? *Radiology*;1997;204(3):677-84.

6. Abrahamson PE, Dunlap LA, Amarnoo MA, Schell MJ, Braeuning MP, Pisano ED. Factors predicting successful needle-localized breast biopsy. *Acad Radiol* 2003;10(6):601-6.
7. Davis PS, Wechsler RJ, Feig SA, et al. Migration of breast biopsy localization wire. *AJR Am J Roentgenol* 1988;150:787-8.
8. Langhans L, Jensen MB, Talman MM, Vejborg I, Kroman N, Tvedskov TJ. Reoperative rates in ductal carcinoma in situ vs invasive cancer after wire-guided breast-conserving surgery. *JAMA Surg* 2017;152(4):378-84.
9. Medina-Franco H, Abarca-Perez L, Garcia-Alvarez MN, Ulloa-Gomez JL, Romero-Trejo C, Sepulveda-Mendez J. Radioguided occult lesion localization (ROLL) versus wire-guided lumpectomy for nonpalpable breast lesions: a randomized prospective evaluation. *J Surg Oncol* 2008;97(2):108-11.
10. Gray RJ, Salud C, Nguyen K, et al. Randomized prospective evaluation of a novel technique for biopsy or lumpectomy of nonpalpable breast lesions: radioactive seed versus wire localization. *Ann Surg Oncol* 2001;8(9):711-15.
11. McGhan LJ, McKeever SC, Pockaj BA, et al. Radioactive seed localization for nonpalpable breast lesions: review of 1,000 consecutive procedures at a single institution. *Ann Surg Oncol* 2011;18:3096-101.
12. Gray RJ, Pockaj BA, Karstaedt PJ, Roarke MC. Radioactive seed localization of nonpalpable breast lesions is better than wire localization. *Am J Surg* 2004;188(4):377-80.
13. Dryden MJ, Dogan BE, Fox P, Wang C, Black DM, Hunt K, Yang WT, Imaging factors that influence surgical margins after preoperative ¹²⁵I radioactive seed localization of breast lesions: comparison with wire localization. *AJR* 2016;206(5):1112-8.
14. Hughes JH, Mason MC, Gray RJ, et al. A multi-site validation trial of radioactive seed localization as an alternative to wire localization. *Breast J* 2008;14(2):153-7.
15. Reicher J, Reicher D, Reicher M. Use of radio frequency identification (RFID) tags in bedside monitoring of endotracheal tube position. *J Clin Monit Comput* 2007;21:155-8.
16. Rupp CC, Kagarise MJ, Nelson SM, et al. Effectiveness of a radiofrequency detection system as an adjunct to manual counting protocols for tracking surgical sponges: a prospective trial of 2,285 patients. *J Am Coll Surg* 2012;215:524-33.
17. Reicher J, Reicher M, Thomas M, Petcavich R. Radiofrequency identification tags for preoperative tumor localization: proof of concept. *AJR Women's Imaging* 2008;191:1359-65.
18. Dauphine C, Reicher J, Reicher M, Gondusky C, Khalkhali I, Kim, M. A prospective clinical study to evaluate the safety and performance of wireless localization of nonpalpable breast lesions using radiofrequency identification technology. *AJH Women's Imaging* 2015;204:W720-3.

12. ATTACHMENTS

- 12.1 Patient Questionnaire
- 12.2 Radiologist Questionnaire
- 12.3 Surgeon Questionnaire

ATTACHMENT 12.1

Patient Questionnaire

PATIENT QUESTIONNAIRE

Please do your best to answer the following questions about the localization procedure. Please circle one number per line to indicate your response as it applies.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	The procedure was not very painful	1	2	3	4	5
2.	The procedure was easier than the biopsy	1	2	3	4	5
3.	I did not feel lightheaded or dizzy during the procedure	1	2	3	4	5
4.	The procedure was easier than I expected	1	2	3	4	5
5.	The procedure went smoothly	1	2	3	4	5

ATTACHMENT 12.2

Radiologist Questionnaire

RADIOLOGIST QUESTIONNAIRE

Please do your best to answer the following questions about the localization procedure. Please circle one number per line to indicate your response as it applies, and please use the wire localization procedure as the comparison

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	The procedure took less time than a wire localization	1	2	3	4	5
2.	The needle was easy to handle	1	2	3	4	5
3.	The radiofrequency tag was easy to deploy	1	2	3	4	5
4.	The targeted lesion was successfully localized with the tag	1	2	3	4	5
5.	The marker seed was easy to visualize on post-procedural imaging	1	2	3	4	5
6.	The ID# was easy to read after tag placement	1	2	3	4	5

Method of Localization (circle):

Ultrasound

Mammogram

RFID #: _____

ATTACHMENT 12.3

Surgeon Questionnaire

SURGEON QUESTIONNAIRE

Please do your best to answer the following questions about the surgical procedure. Please circle one number per line to indicate your response as it applies, and please use the wire localization procedure as the comparison

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	The procedure was quicker than wire localized surgery	1	2	3	4	5
2.	The RF tag was easy to detect with the LOCALizer probe during surgery	1	2	3	4	5
3.	Having the distance gauge was helpful in guiding the surgical resection	1	2	3	4	5
4.	The RF tag was as easy and reliable as the wire in directing the surgical excision	1	2	3	4	5
5.	The RF tag and the clip/lesion was successfully removed with surgery	1	2	3	4	5

Closest depth measurement of tag from the overlying skin: _____

Radial distance of tag from the incision: _____

ATTACHMENT 12.4

Adverse Event Reporting Form

Pilot trial evaluating a miniature radiofrequency tag for localization of non-palpable breast lesions for surgery:

Adverse Event Report Form

Subject ID: _____

Patient Initials: _____

Date of RFID insertion: ____/____/____

Date of assessment: ____/____/____

Since the beginning of the trial, has the patient experienced any of the following?

CTCAE Adverse Events	Grade					Attribution Code
Hematoma	1	2	3	4	5	
Device related infection	1	2	3	4	5	
Vasovagal reaction	1	2	3	4	5	

Other Adverse Events	Grade					Attribution Code
	1	2	3	4	5	
	1	2	3	4	5	
	1	2	3	4	5	

Attribution codes:

1. Unrelated (AE not related to protocol treatment)
2. Unlikely (AE doubtfully related to protocol treatment)
3. Possible (AE may be related to protocol treatment)
4. Probable (AE likely related to protocol treatment)
5. Definite (AE clearly related to protocol treatment)

Comments:

Person completing form: _____