

Evaluation of Magseed as  
Localization Device for Biopsy  
Proven Metastatic Axillary  
Lymph Nodes in Women with  
Breast Cancer.

NCT03718455

10/4/2018

## 1. PROTOCOL OVERVIEW

**Title:** Evaluation of Magseed as Localization Device for Biopsy Proven Metastatic Axillary Lymph Nodes in Women with Breast Cancer.

**Running Title:** Axillary Magseed Study.

**IRB Protocol Number:** 18-004803.

**Brief Study Description:** Pilot study to evaluate the safety and effectiveness of localizing biopsy proven metastatic axillary lymph nodes in women with breast cancer using Magseed markers as an alternative to the current practice of placing radioactive seed markers.

**Study Population:** Twenty patients with breast cancer will have a Magseed inserted into a biopsy proven metastatic axillary lymph node for pre-surgical localization.

## 2. STUDY BACKGROUND

Breast cancer patients with metastatic disease to the axilla historically have undergone a complete axillary lymph node dissection (ALND); however, this can result in significant morbidity. Alternatively, selective lymph node (SLN) surgery can be performed in patients who receive neoadjuvant chemotherapy (NAC) (1-3), since complete nodal response is seen in 41-74% of these patients (1, 4). The false negative rate of SLN surgery following NAC can be reduced by ensuring removal of a previously biopsy proven malignant lymph node (5). However, without preoperative localization, the biopsied lymph node is not obtained during the SLN surgery in around 23-25% of cases.

Currently at Mayo Clinic Rochester, breast cancer patients who are treated with NAC may have a biopsy clip placed in an axillary lymph node at the time or shortly after percutaneous sampling. Following 12-20+ weeks of NAC, preoperative localization of the sampled lymph node using a radioactive seed can be done up to 5 days prior to surgery. Localization of the sampled lymph node in patients with complete imaging response to NAC can be technically challenging if the biopsy clip is not sonographically visible, and has been shown to be successful in only 72% of cases (6). Here at Mayo, we place sonographically visually enhanced biopsy clips at the time of lymph node sampling; however, there is subset of patients where the clip is not readily identifiable particularly if there is an excellent response to the NAC. Mammographic localization can be achieved only if the biopsy clip can be included in the mammogram. If sonographic or mammographic localization of the biopsy clip is not possible, CT localization may be done, but this increases the cost of care, exposes the patient to a higher radiation dose, and potentially delays surgery.

An alternative to the radioactive seed is the Magseed (*Endomagnetics, Inc.*), a magnetic seed that uses an identical needle delivery system, that is FDA approved for long term placement into soft tissues prior to surgery. A recent study reported a 100% success rate of percutaneous preoperative localization of non-palpable breast lesions and surgical retrieval of the Magseed and intended breast target (7). However, given 3-4 cm of susceptibility artifact created by the Magseed on MRI, localization of the breast primary is recommended to be done only after all preoperative MR imaging is complete. The degree in which this artifact would interfere with the evaluation of the axilla is unknown as the axilla can also be evaluated with ultrasound to assess the response to NAC. MD Anderson currently is recruiting to an open label clinical trial evaluating placement of the Magseed into the axilla for preoperative localization after completion of NAC up to 30 days prior to surgery (NCT03038152). Recently, the Magseed was FDA cleared for soft tissues and long-term implementation, which means that the seed could be placed prior to initiation of NAC. Here at Mayo Clinic Rochester, the breast surgery group has a short-term trial approved to test the ease of use, intuitiveness, and accuracy of pre-surgical localization with the Magseed in the breast in our operating rooms, which would allow to also test the Magseed in the axilla.

Placement of a Magseed prior to NAC in the biopsy proven metastatic lymph node at or close to the time of the lymph node sampling would allow the lymph node to be identified at surgery following NAC without requiring the patient to undergo a second preoperative localization procedure. This would eliminate the need for the potentially time consuming and frustrating search for the axillary biopsy clip in patients with an excellent treatment response. Feasibility of localizing the sampled lymph node would be substantially higher prior to NAC, but it is unknown if this benefit outweighs the potential loss of information in assessing the axillary response to NAC on MRI due to the susceptibility artifact created by the Magseed in the axilla. It is expected that there would be negligible artifact to the ipsilateral breast tissue so the response to NAC for the breast primary could still be assessed accurately on MRI, but this may depend on both the location of the primary breast tumor(s) and the metastatic axillary lymph node, and requires further evaluation.

### 3. STUDY AIMS

**Aim 1:** Evaluate if Magseed is a viable alternative to radioactive seed as a localization method for biopsy proven metastatic breast carcinoma following neoadjuvant chemotherapy.

**Aim 2:** Determine the amount of artifact created by the Magseed in the axilla at MRI and identify imaging optimization to minimize the artifact produced by the magnetic clip.

**Aim 3:** Assess the success of retrieval of the Magseed and biopsy proven metastatic lymph node in the operating room compared to the current practice with the radioactive seed.

### 4. STUDY INCLUSION & EXCLUSION CRITERIA

**Study Population Target:** Twenty women with biopsy proven breast cancer and metastasis to an axillary lymph node

**Inclusion Criteria:**

1. Women 18 years or older
2. Neoadjuvant chemotherapy planned prior to surgical excision
3. Scheduled for target axillary lymph node dissection including the localized lymph node and sentinel lymph node

**Exclusion Criteria:**

1. Pregnant or nursing women
2. Allergy to lidocaine or gadolinium
3. Contraindication to MRI (i.e. pacemaker)
4. Axillary Infection
5. Prior axillary radiation
6. Known allergy to bone wax, beeswax or propolis

## 5. STUDY DESIGN

**Part 1:** Ten women with biopsy proven breast cancer and metastasis to an axillary lymph node will have a Magseed placed into the metastatic lymph node AFTER neoadjuvant chemotherapy (NAC) and just prior to surgery. These patients will have a non-contrast enhanced breast MRI development study to evaluate and identify ways to reduce the artifact in the axilla created by the Magseed. Efficacy of the localization with the Magseed will be available within a week of the placement.

**Part 2:** Ten additional women with biopsy proven breast cancer and metastasis to an axillary lymph node will have a Magseed placed into the metastatic lymph node BEFORE NAC. These patients will have routine contrast enhanced MRIs, mammograms, and ultrasounds before and after NAC to evaluate treatment response.

**Seed placement:** Once a patient has been identified eligible for the research study and has provided written informed consent they will have a Magseed placed into the biopsy proven lymph node. The Magseed delivery system is identical to our current practice using radioactive seeds. The seed is pre-loaded into the needle and is inserted into the lymph node following local anesthesia with 1% lidocaine. Once the seed is deployed, post procedure seed location is confirmed sonographically and mammographically with tomosynthesis.

**MRI:** Ten no-charge limited non-contrast breast MRIs for research development purposes are available for this study through the radiology department. Phase 1 participants will enroll in the study after their pre- and post-NAC imaging has already been performed per routine clinical practice. These participants will have a single non-contrast enhanced breast MRI using our

standard non-contrast sequences (axial ideal T1 and T2-weighted, axial STIR, and axial 3D vibrant using a dedicated breast coil, FOV 28 cm or to fit the patient size, and an image-thickness/image-increment of 5mm/1mm). A physicist will participate in the scanning of these patients to evaluate the extent of artifact in the axilla and adjacent breast tissue and optimize scanning parameters to reduce this artifact.

Phase 2 participants will enroll in the study prior to NAC and have routine contrast enhanced breast MRIs performed before and after NAC. Clinically indicated MRI scans will be charged to the patient's insurance company as this imaging is standard clinical practice. The MRI protocol will use our standard clinical sequences (axial ideal T1 and T2-weighted, axial STIR, and axial 3D vibrant using a dedicated breast coil). Once contrast is injected (gadobutrol 10mmol/10mL) 3D vibrant sequences will be obtained four times after contrast injection (FOV 28 cm or to fit the patient size, and an image-thickness/image-increment of 5mm/1mm).

**Mammogram:** Patients enrolled in the research study will have standard mammographic imaging before and after NAC, which will include both the breast and axilla as per routine clinical protocol.

**Ultrasound:** Patients enrolled in the research study will have standard sonographic imaging before and after NAC of the breast and axilla as per routine clinical protocol. Post-NAC ultrasound of the axilla will be a supplemental assessment to breast MRI as the Magseed artifact may obscure these findings.

**Seed Removal:** As per the current practice, patients will have targeted axillary lymph node dissection including both the localized lymph node and sentinel lymph node. Identifying the lymph node containing the Magseed will require the Sentimag handheld probe in the operating room. This device which functions similar to the gamma probe has been approved for an equipment trial starting in August of 2018. Once the lymph node has been excised a specimen radiograph will be obtained to verify removal.

## 6. STUDY RISKS

**Seed Placement:** The Magseed is placed in an axillary lymph node using local anesthesia in an outpatient environment. There is a small risk of discomfort associated with the local anesthetic. There is a minor risk of infection and bleeding or bruising with the needle entry that is similar to a blood draw. Damage to adjacent structures including vessels or the lung are extremely rare with image guidance.

**MRI:** There is no radiation associated with MRI, but patients with metal devices in their body like pacemakers, cannot have an MRI and will not be able to participate in the study.

Patients with claustrophobia may feel trapped in the MRI scanner and may not tolerate the examination. If the patient feels too confined in the MRI scanner the technologist will stop the examination.

The MRI machine makes loud noises, which can damage hearing. Because of this known risk all patients are required to wear ear protection during the MRI scan that will minimize the discomfort and keep the noise levels at a safe level.

Gadolinium is FDA-approved and routinely used for breast MRI exams. Gadolinium can cause discomfort, warm tingling feeling in the body, metallic taste in the mouth, nausea, or headache in about 1 in 100 patients. These side effects usually last only for a very short time and completely resolve. Severe allergic reactions to gadolinium are extremely rare and occur in about 1 in 300,000 people. The needle placed in the patient's vein may cause minor pain, bruising, or infection at the injection site. Studies have shown that small amounts of gadolinium may remain in the body of patients who have received these injections. The effect of this, if anything, is unknown at this time.

Gadolinium may harm a fetus and therefore, pregnant women will not be allowed to enroll on this study. Women of reproductive age will undergo urine pregnancy testing.

Magseed placement will interfere with visualizing the axilla on MRI. The extent to which the artifact could interfere with visualizing the adjacent breast tissue is unknown. This is way phase 1 will consist of ten patients who have already had all their standard breast imaging. The one-time limited non-contrast MRI will allow us to optimize scanning parameters and decrease the artifact for phase 2 participants receiving their standard MRI after Magseed placement.

**Mammogram:** Inherent risks include added radiation dose. The MQSA (Mammography Quality Standards Act) recommended average glandular dose limit for screening mammography to 3mGy per view, which equals 12 mGy for a standard 4-view mammogram. There is no set limit for average glandular dose for diagnostic mammography. This is because the number of mammographic views for each patient varies based upon the images necessary to work up any particular finding. All diagnostic mammography will be within current clinical guidelines and well below levels that are known to cause long term side effects.

**Magseed:** The Magseed needle contains bone wax, which contains natural beeswax. There is a potential for a very minimal risk for an allergic reaction or a foreign body reaction (granuloma). To further minimize this risk, patients with known allergies to bone wax, beeswax or propolis will be excluded from the study.

## 7. IMAGE INTERPRETATION

Experienced breast radiologists from our institution will place the Magseed into the axilla and interpret the MRI, mammographic and sonographic imaging as per current clinic practice. This

work flow will remain the same. The non-contrast enhanced breast MRI will be evaluated by both the study investigators and physicists.

## 8. END OF STUDY DEFINITION

A participant is considered to have completed the study once the Magseed has been removed from the axilla.

## 9. SAFETY MONITORING

**Adverse Events (AE):** Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

**Serious Adverse Events (SAE):** An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Death
- Life threatening, even if temporary in nature, requiring inpatient hospitalization
- Results in permanent impairment of a bodily function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure
- Results in an increased level of care (unscheduled admission, transfer from a routine inpatient bed to an intensive care unit, etc.).

**Severity of AE:**

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

**AE relationship to the study intervention:**

- Definitely Related – The AE *is clearly related* to the study intervention.
- Probably Related – The AE *is likely related* to the study intervention.
- Possibly Related – The AE *may be related* to the study intervention.
- Unlikely Related – The AE *is doubtfully related* to the study intervention.

- Not Related – The AE *is clearly NOT related* to the study intervention.

**Expectedness:** Principle investigators and co-investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

- Expected Adverse Events
  - Seed Placement: Minor discomfort, bleeding, infection, bruising
  - MR: Anxiety, stress, claustrophobia
  - Mammography: Anxiety, stress, discomfort
  - Surgical excision of Magseed: Expected discomfort from the operation, bleeding, and infection

**Time Period and Frequency for Event Assessment and Follow-up:** For this study, the study treatment follow-up period is defined as 30 days following the removal of the Magseed. Unanticipated AEs deemed as unrelated or AEs in the mild/grade 1 category do not need to be reported as study data for this study.

**Adverse Event Reporting:** It is the responsibility of the principal investigator to document the grade and attribution of all Adverse Events (AEs) which occur during the course of the study.

The PI will document all AEs that occur within the first 24 hours. AEs will be recoded within the study participant's medical record. The nature of each event, date, time of onset, outcome, frequency, action taken and attribution will be recorded.

**Serious Adverse Event Reporting:** When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The principal investigator will evaluate the event and determine the necessary follow-up and reporting required.

**Definition of Unanticipated Problems:** The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the Institutional Review Board (IRB)-approved research protocol and informed consent document. A problem or event is "unexpected" when it occurs at an increased frequency or at an increased severity than expected
- Related to participation in the research. A problem or event is "related" if it is possibly related to the research procedures.
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**Unanticipated Problem Reporting:** The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

## 10. DATA MANAGEMENT & STATISTICAL CONSIDERATIONS

**Data Management:** The principle investigator and co-investigators will supervise the data collection management.

**Outcome analysis:** The successful placement of the Magseed into the metastatic axillary lymph node will be evaluated and recorded by the radiologist performing the procedure. This information will be document into the electronic medical records as per normal clinical practice, in addition this information stored in the database.

The degree in which the artifact created by the Magseed in the axilla obscures the axillary or adjacent breast findings will be evaluated and recorded by the radiologist interpreting the MRI. Treatment response based on mammographic and sonographic evaluation of the axilla will be evaluated and recorded by the radiologist. The radiologist will determine if the supplemental imaging with mammography and sonography adequately replaces visualization of the axilla on MRI. Imaging results will be records in standard radiological reports as well as the database.

The successful retrieval of the Magseed into the metastatic axillary lymph node will be evaluated by the surgeon and radiologist. These results will be reported in both the patients operative report as well as the research database.

**Adverse events:** Adverse events occurring during the research study will be recorded into the electronic medical records and recorded into the research database.

## 11. ETHICAL CONSIDERATIONS

**Informed Consent:** Institutional Review Board (IRB)-approved consent forms will be given to the participants. That participants will asked to read the form. The research study will be explained to the participant and all questions will be answered by the principle investigators, co-investigators, and/or study coordinator. A verbal explanation will be provided in terms

suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

**Confidentially:** Protected patient health information will be kept in a locked file cabinet. An enrollment log will be maintained confirming informed consent was obtained. A key linking patient identifiers to their research study identifier will be kept secure. Identifiable information will not appear on any reports, publications, or other disclosures of the study outcomes. Every effort will be made to keep medical information confidential.

**Records:** The principal investigator will maintain records and essential documents related to the conduct of the study as outlined in the Mayo Clinic Research Policy Manual – "Retention of and Access to Research Data Policy" [http://mayocontent.mayo.edu/research-policy/MSS\\_669717](http://mayocontent.mayo.edu/research-policy/MSS_669717) . These will include subject case histories and regulatory documents.

**Data:** Study data will be used to design the data collection instruments and patient data will be entered into a SDMS Database by the study coordinator or other members of the study team. The data collected in will later be exported to the appropriate software for statistical analyses.

**Publications:** Results from this study will be published in a peer reviewed journal.

## 11. REFERENCES

1. Boguey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *Jama*. 2013; 310(14):1455-61.
2. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *The Lancet Oncology*. 2013; 14(7):609-18.
3. Boileau J-F, Poirier B, Basik M, et al. Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: The SN FNAC Study. *Journal of Clinical Oncology*. 2015; 33(3):258-64.

4. Dominici LS, Negron Gonzalez VM, Buzdar AU, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer*. 2010; 116(12):2884-9.
5. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). *Annals of surgery*. 2016; 263(4):802-7.
6. Nguyen TT, Hieken TJ, Glazebrook KN, Boughey JC. Localizing the Clipped Node in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy: Early Learning Experience and Challenges. *Annals of surgical oncology*. 2017; 24(10):3011-6.
7. Price ER, Khoury AL, Esserman LJ, Joe BN, Alvarado MD. Initial Clinical Experience With an Inducible Magnetic Seed System for Preoperative Breast Lesion Localization. *American Journal of Roentgenology*. 2018:W1-W5.