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ORIGINAL ARTICLE – BREAST ONCOLOGY

Prospective Registry Trial Assessing the Use of Magnetic Seeds to Locate Clipped Nodes After Neoadjuvant Chemotherapy for Breast Cancer Patients

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ABSTRACT

Background. Targeted axillary dissection (TAD) involves locating and removing both clipped nodes and sentinel nodes for assessment of the axillary response to neoadjuvant chemotherapy (NAC) by clinically node-positive breast cancer patients. Initial reports described radioactive seeds used for localization, which makes the technique difficult to implement in some settings. This trial was performed to determine whether magnetic seeds can be used to locate clipped axillary lymph nodes for removal.

Methods. This prospective registry trial enrolled patients who had biopsy-proven node-positive disease with a clip placed in the node and treatment with NAC. A magnetic seed was placed under ultrasound guidance in the clipped node after NAC. All the patients underwent TAD.

Results. Magnetic seeds were placed in 50 patients by 17 breast radiologists. All the patients had successful seed placement at the first attempt (mean time for localization was 6.1 min; range 1–30 min). The final position of the magnetic seed was within the node (n = 44, 88%), in the cortex (n = 3, 6%), less than 3 mm from the node (n = 2, 4%), or by the clip when the node could not be adequately visualized (n = 1, 2%). The magnetic seed was retrieved at surgery from all the patients. In 49 (98%) of the 50 cases, the clip and magnetic seed were retrieved from the same node. Surgeons rated the transcutaneous and intraoperative localization as easy for 43 (86%) of the 50 cases. No device-related adverse events occurred.

Conclusions. Localization and selective removal of clipped nodes can be accomplished safely and effectively using magnetic seeds.

Clinically node-positive breast cancer patients often are treated with neoadjuvant chemotherapy (NAC), which can eradicate nodal disease for 40–75% of patients.[1–5] Considerable interest is focused on developing surgical techniques that can reliably assess nodal response to therapy in order to avoid axillary lymph node dissection (ALND) for patients who achieve a nodal pathologic complete response (pCR).

Recent trials evaluating the use of sentinel lymph node dissection (SLND) for clinically node-positive patients who received NAC have reported a false-negative rate (FNR) of 11.9–14.2% when SLND was used alone.[1,6–8] The American College of Surgeons Oncology Group

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(ACOSOG) Z1071 trial noted that a subset of patients had a clip placed in the node with metastatic involvement at the time of biopsy. When this clipped node was retrieved as a sentinel lymph node (SLN), the FNR was reduced to 6.8%, suggesting that ensured evaluation of the node known to contain metastasis at the time of diagnosis (the biopsied node) might be a critical aspect of assessing nodal response.[9]

This finding led to the development of targeted axillary dissection (TAD), with selective localization and removal of the clipped node in addition to the sentinel nodes. The initial studies of TAD used radioactive seeds placed the day before surgery under ultrasound guidance to facilitate removal of the clipped node.[10,11] When TAD was performed, the FNR was reduced to 2%.[10]

A survey of the American Society of Breast Surgeons showed that 82% of respondents considered placement of a clip in biopsied nodes with ensured removal as critical to minimally invasive axillary staging.[12] However, techniques for this have been challenging in many settings that do not use radioactive seeds, which have a large associated regulatory burden.

This trial aimed to evaluate whether magnetic seeds, which do not carry the regulatory challenges associated with radioactive seeds, can be used for localization and selective removal of clipped nodes in clinically node-positive patients undergoing TAD after completion of NAC.

METHODS

Study Design

This single-institution, prospective registry study enrolled breast cancer patients who had biopsy-proven axillary metastases with a clip placed in the biopsied node and were treated with NAC. The study excluded patients with distant metastasis, inflammatory breast cancer, a history of axillary surgery or ipsilateral breast cancer, a pacemaker, or a pregnancy. Patients were enrolled any time before surgery after providing written informed consent. The institutional review board approved this study.

Magnetic Seeds

Magseed (Endomag; Endomagnetics Ltd, London, England, UK) was used as the magnetic seed in this trial. The Magseed marker is a small (5 × 0.9 mm) metallic marker that becomes magnetic when exposed to a magnetic field. It is identified intraoperatively using the SentiMag (Endomagnetics Ltd, London, England, UK) handheld magnetometer probe, which gives an audible and visual signal reflecting the distance from the Magseed.

Study Protocol

Per institutional standard, all the patients with invasive breast cancer had a mammogram and ultrasound imaging of the breast as well as regional lymphatics at the time of diagnosis. Needle biopsy was performed when abnormal nodes were seen, and a clip was placed in the biopsied node.[13] The patients eligible for this study received NAC at the discretion of the treating medical oncologist. The NAC consisted of anthracycline, taxane-based regimens, or both. Human epidermal growth factor receptor 2 (HER2)-positive patients also received HER2-targeted therapy.

After completion of NAC, a magnetic seed was placed in the clipped node under ultrasound guidance by a dedicated breast radiologist up to 30 days before surgery, with mammographic axillary views performed to confirm placement (Fig. 1a). At surgery, all the patients underwent

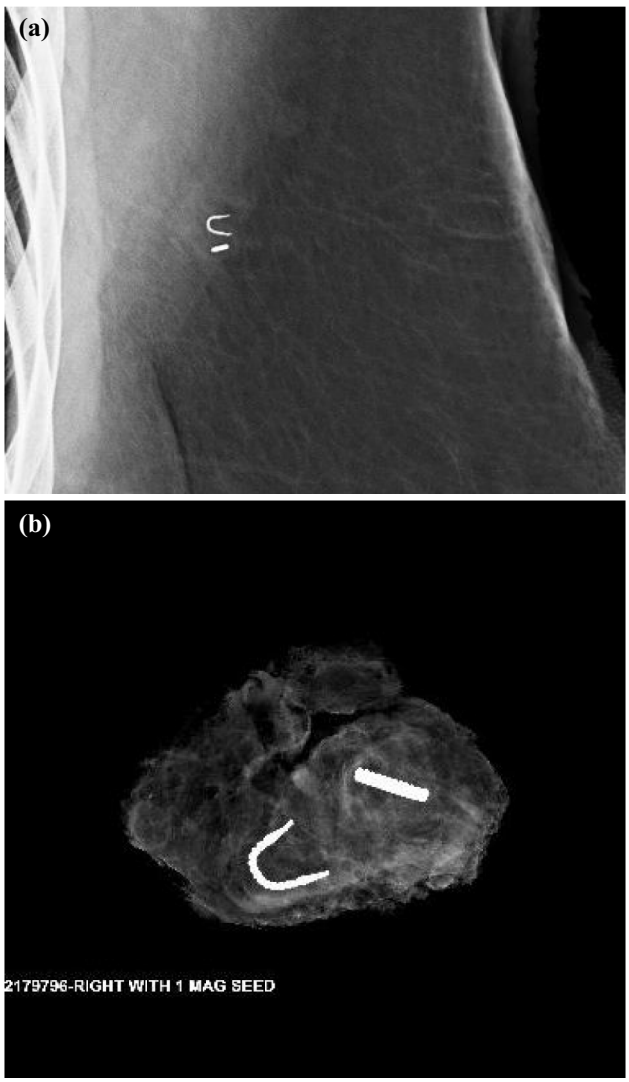

FIG. 1 **a** Placement of magnetic seed in a clipped lymph node. **b** Radiograph of clip and magnetic seed in the same surgical specimen

TAD with or without completion ALND. The clipped node containing the magnetic seed was located intraoperatively using the SentiMag probe. A specimen x-ray was performed to confirm removal of the clip and the magnetic seed (Fig. 1b). Sentinel nodes were identified using the dual-tracer technique (^{99}technitium sulfur colloid and blue dye) unless contraindicated.

The primary end point of the study was the proportion of patients who had the clipped node and magnetic seed retrieved in the same surgical specimen. The secondary end point was ease of transcutaneous and intraoperative localization of the magnetic seed by surgeons, which was assessed via a 5-point Likert scale ranging from easy to difficult.

Data Collection and Analysis

Clinicopathologic features were obtained from review of electronic medical records. The radiologic details of the procedure included time for magnetic seed placement and final position of the magnetic seed. Surgical reports were reviewed to evaluate the number of nodes retrieved with the magnetic seed, whether the magnetic seed was found within the node, and whether an ALND was performed. All the patients were assessed by the clinical team within 30 days after surgery to evaluate for adverse events. Data were summarized using descriptive statistics such as frequency distribution, mean, and median.

RESULTS

Informed consent for participation was provided by 53 patients in this trial. Three of these patients could not be evaluated due to a change in surgical plan (n = 1), radioactive seed placed instead of magnetic seed (n = 1), and clip not visualized by ultrasound after NAC (n = 1). Consequently, 50 patients were evaluable (Fig. 2).

The initial ultrasound showed a single abnormal node in 19 patients (38%), two abnormal nodes in 8 patients (16%), three abnormal nodes in 12 patients (24%) and four or more abnormal nodes in 11 patients (22%). The clinicopathologic characteristics are summarized in Table 1. Nodal pCR was experienced by 22 patients (44%).

Magnetic Seed Placement

Magnetic seeds were placed in the clipped nodes by 17 breast radiologists. The size of the clipped node after NAC ranged from 0.5 to 3 cm. Placement of the magnetic seed was successful for all the patients at the first attempt. The mean time required for seed placement was 6.1 min (median, 5 min; range, 1–30 min). The final position of the magnetic seed was within the node for 44 patients (88%), in the cortex for 3 patients (6%), less than 3 mm from the node for 2 patients (4%), and by the clip for one patient (2%), whose node was not well-visualized (Table 2). The mean distance from skin to the magnetic seed was 15 mm (range, 5–22 mm).

Surgical Procedure

Ten fellowship-trained breast surgical oncologists participated in the trial. The sentinel node procedure used a radioisotope in all cases, with the addition of blue dye in 47 cases (94%). The clipped node was an SLN in 80% (40/50) of the patients. In six cases (12%), the clipped node was the only node retrieved as a part of the TAD procedure (i.e., no additional sentinel nodes were identified). Residual nodal disease was identified in 21 of the 30 patients who underwent ALND. This group had no false-negative results from evaluation of the clipped node.

For all the patients, the magnetic seed was retrieved during surgery. The mean number of nodes retrieved with the magnetic seed was 1.3 (range, 1–6). From 49 patients (98%), the clip and magnetic seed were retrieved in the same specimen. From one patient, the clip and magnetic seed were retrieved from different nodes (Table 3). No adverse events resulted from the use of magnetic seeds.

The surgeons were asked to rate the ease of localization on a scale from 1 (easy) to 5 (difficult). When asked about transcutaneous localization, 86% (43/50) of the surgeons categorized it as a 1, 10% (5/50) as a 2, and 4% (2/50) as a 5 (difficult). Both cases of difficult transcutaneous localization occurred during the surgeon's first three cases using the magnetic seeds for TAD, and both surgeons reported a score of 1 for subsequent cases, suggesting a learning curve. When asked about the intraoperative ease of localization, 86% (34/50) of the surgeons classified it as a 1, 6% (3/50) as a 2, 6% (3/50) as a 3 or 4, and 2% (1/50) as difficult (Table 4).

DISCUSSION

This prospective trial demonstrated that magnetic seeds can be safely and effectively used to locate and remove clipped nodes from clinically node-positive patients undergoing TAD after completion of chemotherapy. Additionally, in a majority of cases, the surgeons reported that the localization procedure was easy to perform.

For localization of breast lesions, the use of magnetic seeds as an alternative to wires or radioactive seeds has been studied previously. Schermers et al.[14] reported that magnetic seeds were feasible and safe for this purpose in a pilot study of 15 patients who had radioactive and magnetic

FIG. 2 Trial schema

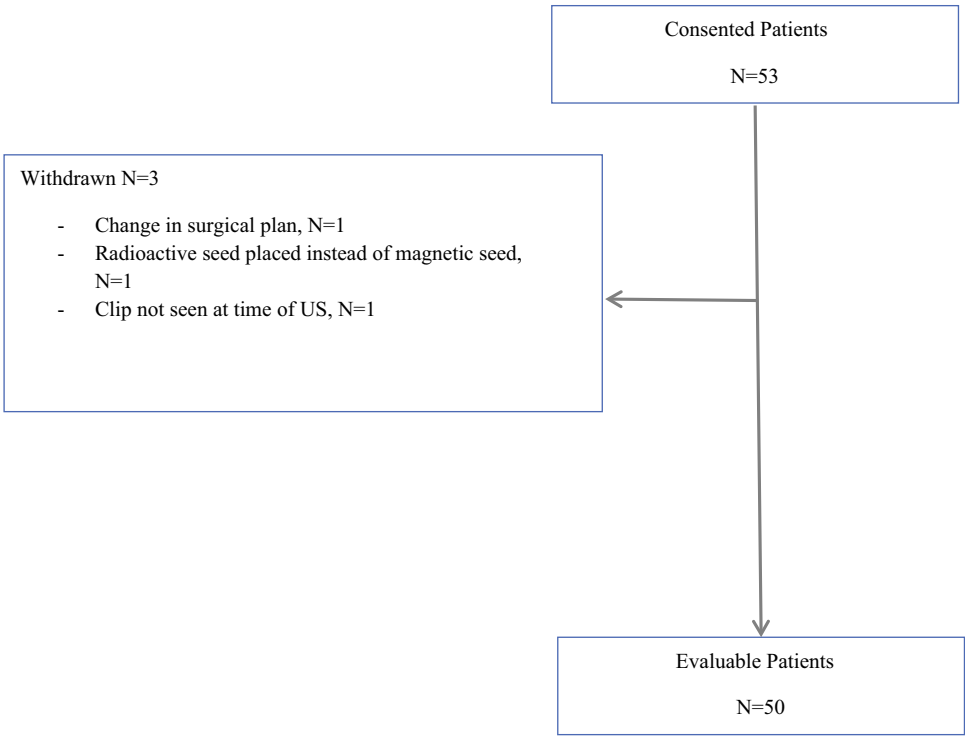

TABLE 1 Clinicopathologic characteristics

	n = 50 *n* (%)
Clinical T category	
T1	13 (26)
T2	27 (54)
T3	8 (16)
T4b	2 (4)
No. of abnormal nodes on initial ultrasound	
1	19 (38)
2	8 (16)
3	12 (24)
≥ 4	11 (22)
Tumor histology	
Ductal	47 (94)
Lobular	3 (6)
Tumor subtype	
HR+/HER2−	26 (52)
HR+/HER2+	10 (20)
HR−/HER2+	5 (10)
HR−/HER2−	9 (18)
Size of clipped node when biopsied (cm)	Mean 2.2
	Range 0.8–3.7

HER2 human epidermal growth factor receptor 2

TABLE 2 Radiologic details of the procedure

	n = 50 *n* (%)
No. of radiologists placing magnetic seeds	17
Time for magnetic seed placement (min)	Mean 6.1
	Median 5
	Range 1–30
Size of clipped node on last US (cm)	Mean 1.5 cm
	Range 0.5–3 cm
Distance to skin (cm)	Mean 1.6
	Range 0.5–2.4
Magnetic seed placed on first attempt	50 (100)
Final position of seed in relation to node	
Within the node	44 (88)
In the cortex	3 (6)
< 3 mm from node	2 (4)
By clip (node not well-visualized)	1 (2)
Days between seed placement and surgery	
1	44 (88)
2–5	5 (10)
6–10	0
11–15	1 (2)
> 15	0

US ultrasound

TABLE 3 Surgical details of the procedure

	n = 50 *n* (%)
No. of nodes retrieved with the magnetic seed specimen	Mean 1.3 Median 1 Range 1–6
Seed and clip in same specimen	49 (98)
Seed stayed in the node for retrieval	50 (100)
Clipped SLN	40 (80)
ALND performed	30 (60)

SLN sentinel lymph node, *ALND* axillary lymph node dissection

TABLE 4 Ease of transcutaneous and intraoperative localization of the magnetic seed, as rated by surgeons

	n = 50 *n* (%)
Transcutaneous localization	
1 (easy)	43 (86)
2	5 (10)
3	0
4	0
5 (difficult)	2 (4)
Intraoperative localization	
1 (easy)	43 (86)
2	3 (6)
3	2 (4)
4	1 (2)
5 (difficult)	1 (2)

seeds were placed in unifocal breast lesions. These authors reported that the magnetic seed could be identified with the probe in 100% of the cases. This study has been followed by a few observational cohort studies, all reporting a 100% retrieval rate and excellent accuracy of seed placement (< 1 cm from the lesion).[15–17]

In a study comparing 100 consecutive patients undergoing wire-localization and 100 patients with magnetic seed localization, no significant differences were found in the re-excision rate, the specimen weight, the specimen volume, or the tumor-to-specimen volume ratio.[18] A prospective trial at our institution enrolling 107 patients with 124 magnetic seeds placed to locate breast tumors demonstrated that the seeds were retrieved in all cases, with a median operative time of 15 min for specimen removal.[19]

Although the use of magnetic seeds for breast localization has been reported, few studies have evaluated their use to locate clipped lymph nodes. One retrospective analysis demonstrated a retrieval rate of 97% (37/38 magnetic seeds).[20] The current prospective study demonstrated a similar retrieval rate (100%), with the magnetic seed and clip identified in the same node in 98% of the cases.

The optimal method for axillary staging after NAC for clinically node-positive patients is evolving. Traditionally, all patients underwent ALND. However, a significant proportion of these patients will convert to pathologically node-negative status and may not benefit from extensive axillary surgery.

Although the use of minimally invasive techniques such as SLND are appealing, studies reporting FNRs ranging from 11.9 to 14.2% suggest that an opportunity exists to improve surgical assessment of the axilla.[1,6–8] One tenet has been that marking nodes with biopsy-proven metastasis might allow for selective removal of that node to assess response. Similar to marking breast lesions at the time of biopsy, this approach allows for assurance that the node with proven metastasis is examined pathologically. Several studies have shown the benefit of evaluating this node. For example, a group from the Netherlands has developed the MARI (Marking Axillary nodes with Radioactive Seeds) procedure, in which a radioactive seed is placed in the node at the time of biopsy, left in place through chemotherapy, and removed at surgery. Their MARI procedure has a reported an FNR of 7%.[21] A prospective registry study from our institution also showed that specific evaluation of the clipped node alone after chemotherapy had a low FNR (4.2%).[10]

In the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, a subset of 170 patients had a clip placed to mark the biopsied node. When this clipped node was retrieved as an SLN, the FNR was decreased from 12.6 to 6.8%. In that trial, the clipped node was found in the ALND specimen in 24.1% of the cases, which means that relying on evaluation of the SLNs alone would have missed assessment of the node with biopsy-confirmed disease at the beginning of therapy in these cases.[9] Studies

from multiple institutions have demonstrated similar proportions of cases in which the clipped node was not retrieved as a sentinel node in 20% to 25% of cases.[10,22–25]

This finding suggests that combining SLND with ensured removal of the clipped node could improve accuracy of axillary response assessment. In fact, a meta-analysis showed that techniques involving removal of SLNs in addition to clipped nodes more accurately reflect axillary status.[26] Targeted axillary dissection, which involves locating and removing clipped nodes in addition to removing SLNs, is associated with an FNR improvement of 2%.[10] Several trials, including the German SenTa trial[27] and the French GANEA-3 trial,[28] currently are accruing patients with the goal to assess this approach. In addition, the ongoing Dutch multicenter RISAS trial aims to validate the combination of MARI with SLND, similar to TAD, for a cohort of 225 clinically node-positive patients.[29]

All the initial trials assessing removal of marked nodes have used radioactive seeds, which have several disadvantages. First, the use of radioactive seeds warrants extensive safety precautions. In the United States, radioactive seeds can be left in place for a limited time only by precluding their placement before initiation of NAC. This results in the need to place a clip before NAC followed by a second procedure to place the radioactive seed after NAC. Using magnetic seeds can overcome both of these issues.

Although the magnetic seed was placed after chemotherapy in the current trial, we currently are conducting the prospective, multi-institutional MAGELLAN (Magnetic-seed Enabled Long-term Localization of Axillary Nodes) trial to assess the placement of magnetic seeds before NAC.[30] If this procedure proves to be equally accurate, a second procedure to locate the clipped node after NAC will no longer be necessary.

The use of magnetic seeds requires specific technical considerations. Because metal instruments may distort the magnetic field, nonmetal instruments must be used when the SentiMag probe is applied to detect the magnetic signal. Surgeons at our institution have navigated this by using commercially available plastic retractors or by removing the metal instruments from the field when using the probe. In addition, magnetic seeds cause artifacts on MRI. In the current trial, the magnetic seeds were placed after NAC, so their use did not impede evaluation of treatment-response with MRI. This may be a consideration in the future if magnetic seeds are considered before initiation of chemotherapy in cases with MRI used to assess response.

Magnetic seeds and the probes to detect them can involve more expense than other localization techniques, although the costs to maintain the regulatory burdens associated with radioactive seeds may offset this when expense is considered from an institutional perspective. This is a potential area for future cost-analysis studies and a factor that institutions should consider when deciding whether to invest in this technology.

This trial was limited by its small sample and single-center study design. Additionally, this trial involved only dedicated breast cancer radiologists and surgeons experienced in using magnetic seeds and in performing TAD. Therefore, these results may not be generalizable to all practices. However, both radiologists and surgeons found the use of magnetic seeds comparable with the use of radioactive iodine seeds.

In conclusion, selective removal of clipped nodes can be accomplished safely and effectively with magnetic seed localization. Both seed placement and retrieval during surgery were successful for all the patients, with no associated adverse events. Magnetic seeds allow for the convenience of seed localization without the regulatory burden associated with radioactive seeds. Future studies should focus on patient-satisfaction and the cost-effectiveness of magnetic seeds compared with other localization techniques.

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