Selective Surgical Localization of Axillary Lymph Nodes Containing Metastases in Patients With Breast Cancer
A Prospective Feasibility Trial

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IMPORTANCE Nodal ultrasonography with needle biopsy of abnormal lymph nodes helps to define the extent of breast cancer before neoadjuvant chemotherapy. A clip can be placed to designate lymph nodes with documented metastases. Targeted axillary dissection or selective removal of lymph nodes known to contain metastases (clip-containing nodes) as well as sentinel lymph nodes (SLNs) may provide more accurate assessment of the pathologic response after neoadjuvant chemotherapy.

OBJECTIVE To determine the feasibility of image-guided localization and resection of lymph nodes containing known metastases.

DESIGN, SETTING, AND PARTICIPANTS This prospective feasibility trial performed at MD Anderson Cancer Center, Houston, Texas, included 12 patients with axillary nodal metastases confirmed by results of fine-needle aspiration biopsy who had a clip placed in the lymph node targeted for biopsy from December 1, 2012, through November 30, 2013.

INTERVENTIONS Preoperative targeting of the clip-containing lymph node under ultrasonographic guidance consisting of wire localization in 2 patients and placement of radioactive iodine I 125 (125I)-labeled seeds in 10 patients. Surgeons removed the localized lymph node before completion axillary lymph node dissection and used radiography of the specimen to confirm removal of the clip-containing lymph node and seed.

MAIN OUTCOMES AND MEASURES Confirmation of the removal of the clip-containing lymph node.

RESULTS Image-guided localization and selective removal were successful in all 12 patients. Five patients underwent SLN dissection in addition to removal of the clip-containing lymph node. Placement of 125I seeds did not interfere with lymphoscintigraphy or intraoperative identification of SLNs. In 4 of the 5 patients (80%), the clip-containing lymph node was one of the SLNs. Ten patients completed neoadjuvant chemotherapy before surgery. Of the 9 patients who underwent lymph node dissection, 4 (44%) had residual nodal disease after chemotherapy; all had disease identified in the clip-containing lymph node.

CONCLUSIONS AND RELEVANCE Axillary lymph nodes marked with a clip can be localized and selectively removed to accomplish targeted axillary dissection, which is technically possible after chemotherapy and is easily performed with other axillary surgery, such as SLN dissection. The ability to add selective removal of the clip-containing lymph nodes to SLN dissection may identify patients for limited nodal surgery after chemotherapy with increased accuracy for determining residual disease compared with SLN identification alone.
he presence of lymph node metastases in patients with breast cancer is an important prognostic feature used to guide systemic and locoregional therapies. Neoadjuvant chemotherapy is often used in these patients to downsize the primary tumor, which increases the surgeon's ability to administer breast-conserving therapy and also allows for a smaller volume of breast tissue to be resected. Similarly, considerable interest exists in avoiding extensive axillary surgery when chemotherapy eradicates metastatic disease in the lymph nodes. At present, no clear consensus exists on a reliable mode of restaging the axilla after chemotherapy to confirm conversion to negative lymph node status. Although sentinel lymph node (SLN) dissection reliably identifies nodal metastases in women with clinically node-negative disease, this technique alone has had mixed results when performed in women with clinically node-positive disease who receive neoadjuvant chemotherapy. The recently published American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was designed to determine whether SLN dissection was accurate in staging the axilla after chemotherapy in patients presenting with node-positive disease. The trial had a prespecified false-negative rate (FNR) of 10% as the success benchmark. The overall FNR was 12.6%, which has sparked considerable conversation about how to achieve a more acceptable FNR. The ultimate goal is to provide optimal oncologic locoregional control with limited morbidity.

On subgroup analysis of ACOSOG Z1071, patients who had a clip placed in the lymph nodes after needle biopsy and who had documented removal of the clip-containing SLN had a lower FNR. Thus, perhaps SLN dissection with removal of the lymph node known to contain metastases (the clip-containing lymph node) may improve results of axillary staging after chemotherapy. In fact, the National Comprehensive Cancer Network recently revised their guidelines to recommend placement of clips in lymph nodes with biopsy-confirmed metastases. The guidelines also mandate that the marked lymph node be removed during surgery. The ability to selectively remove these clip-containing lymph nodes has enormous clinical potential to improve our ability to assess residual disease and to spare patients the considerable morbidity associated with axillary lymph node dissection (ALND).

We hypothesized that targeted axillary dissection (TAD), which includes removing the SLNs and the clip-containing lymph nodes positive for disease at presentation, may constitute a more reliable approach to restaging the axillary nodal basin after chemotherapy. The goal of this study was to determine the feasibility of localizing clip-containing lymph nodes in patients with known axillary metastases. A secondary end point was to determine the feasibility of performing this procedure in conjunction with dual-tracer SLN dissection.

### Methods

This single-institution prospective feasibility study was approved by the institutional review board of the MD Anderson Cancer Center, Houston, Texas. All patients provided written informed consent. We designed the study to determine the methods for localizing and selectively removing axillary lymph nodes containing clips in patients with breast cancer (clinicaltrial.gov identifier: NCT01880645). All patients underwent surgery from December 1, 2012, through November 30, 2013. Patients with confirmed axillary metastases and a clip in the sampled lymph node were offered participation in the trial. Patients were eligible if they underwent surgery after neoadjuvant chemotherapy or if they underwent surgery first. We obtained clinicopathologic data prospectively from source documentation in the electronic medical record (clinical notes and reports from the radiology and pathology departments).

#### Nodal Ultrasonography and Clip Placement

Per our institutional practice, real-time ultrasonography of the ipsilateral regional lymph nodal basins, including the axillary, infraclavicular, and internal mammary nodal basins, was performed in patients with a diagnosis of breast cancer. Abnormal axillary lymph nodes (ie, with eccentric cortical thickening, hilar compression, displacement, effacement, and irregular nodal margins) were identified, and patients underwent ultrasonography-guided fine-needle aspiration biopsy using a 21-gauge needle. Immediate cytologic evaluation was performed. When the evaluation demonstrated metastasis, a clip marker (HydroMark T3; Devicor Medical Products) was placed within the cortex of the sampled lymph node under ultrasonographic guidance (Figure 1).

#### Radiologic Localization

Before surgery, the clip-containing lymph node was reidentified using gray-scale ultrasonography. A standard radioactive iodine I125 (125I)-labeled titanium seed with activity rang-
ing from 0.100 to 0.300 mCi (to convert to millibecquerels, multiply by 3.7×10^{10}) or a hook wire was used to target the clip-containing lymph node, as confirmed by postprocedural mammography. The 125I seed has a half-life of 60 days and was placed within 5 days of the planned surgery (usually the day before).

**Surgical Procedure**
In the 2 patients who underwent wire localization, an axillary incision was made in accordance with the planned ALND. The localized lymph node was then removed separately and underwent radiographic examination to confirm that the lymph node contained the clip. In the 10 patients with 125I seed localization of the clip-containing lymph node, the planned axillary incision was made and the axilla was explored using a handheld gamma probe optimized to 125I, which is distinct from the activity setting used for SLN identification. The clip-containing lymph node was identified using the probe and removed. Intraoperative radiography confirmed that the excised lymph node contained the clip and the seed. After the localized lymph node was removed, the remaining axillary contents were removed per standard surgical technique.

A proportion of patients underwent SLN dissection at the same operation. This procedure was added after we determined that selective removal of the clip-containing lymph node was safe and feasible.

**Pathologic Handling**
On arrival at the pathology laboratory for intraoperative assessment, the specimen underwent accession and gross pathologic examination in a separate section of the laboratory that is designated for handling specimens containing radioactive materials. Before sectioning, a gamma probe was used to identify the location of the radioactive seed in the specimen. The specimen then underwent radiography to confirm and document the presence of the seed and the clip in the specimen. The radioactive seed was removed and placed in a dedicated lead-shielded container for storage and subsequent disposal. The removal and storage of the explanted seed was recorded in an inventory log. The lymph node with the marker clip was serially sectioned and placed in a separate cassette for routine processing similar to that of the non–clip-containing lymph nodes. Formalin-fixed and paraffin-embedded tissue blocks of the lymph nodes were sectioned at a thickness of 5 μm and stained with hematoxylin-eosin for histopathologic examination by a dedicated breast pathologist (including S.K.). The histopathologic changes in the clip-containing lymph node, including the presence or absence of residual metastatic carcinoma, were given in the final pathology report.

**Results**
Twelve patients with node-positive disease at diagnosis were included in this study, meeting the study’s planned accrual. Clinicopathologic characteristics of the trial participants are summarized in the Table. Two patients underwent wire localization, and 10 patients underwent localization using 125I radioactive seed placement in the clip-containing lymph node under ultrasonographic guidance. All patients had successful radiologic localization of the clip-containing lymph node and surgical removal of the clip-containing lymph node with radiographic confirmation (Figure 2).

Five patients underwent an SLN dissection at the same operation. Presence of the 125I seed in the lymph node did not interfere with preoperative lymphoscintigraphy (demonstrated in Figure 3). Iodine I 125 has a gamma emission at 35 keV compared with the 140 keV seen with technetium. Lymphoscintigraphy cameras capture 120 to 150 keV, thus not detecting the 125I emission. Sentinel lymph nodes were identified in all patients in whom SLN dissection was attempted. The mean number of SLNs retrieved was 2.4 (range, 1–6). The clip-containing lymph node was also an SLN in 4 of 5 patients (80%).

We used a variety of techniques to resect the seed-containing lymph nodes and SNLS. One approach started with the gamma probe on the technetium setting to identify the
SLNs with an increased radioisotope count. When nodes with increased technetium counts (ie, “hot” nodes) were removed, the gamma probe was then changed to the $^{125}$I setting to determine whether the lymph node contained the radioactive seed. Some surgeons started with the $^{125}$I setting and identified the clip-containing lymph node first, then changed the probe setting to assess the technetium counts. Both techniques were equally successful. Selective removal of the clip-
containing lymph node did not interfere with the planned completion ALND.

Ten patients underwent chemotherapy before their axillary surgery, and 2 patients underwent surgery first. One patient refused ALND and underwent removal of the clip-containing lymph node (which was also an SLN) and 1 additional SLN; no residual disease was identified in the lymph nodes. In the remaining 9 patients who had neoadjuvant chemotherapy and completion ALND, 4 had residual disease identified in the clip-containing lymph node and 5 had no residual disease. All patients with residual axillary metastases had disease identified in the clip-containing lymph node.

No adverse events were reported intraoperatively. Two patients had postoperative complications that were not attributable to the specific removal of the clip-containing lymph node. One patient had a skin-sparing mastectomy with placement of a tissue expander at the same operation as the axillary procedure. She presented with a hematoma on postoperative day 5, and surgical exploration revealed a source of bleeding on the pectoralis muscle. One patient underwent total mastectomy at the time of axillary surgery and was noticed to have postoperative cellulitis, which was managed with oral antibiotics in an outpatient setting.

Discussion

We present here a novel surgical technique to localize clip-containing lymph nodes in patients with breast cancer and documented axillary metastasis at initial presentation. The technique was successful in a variety of patients, was easily performed by multiple surgeons, and could be performed in conjunction with any breast or axillary surgical procedure. We propose that the selective removal of lymph nodes with confirmed metastases in addition to SLN dissection, that is, TAD, may improve the ability to accurately stage the axilla after chemotherapy. This study was designed to explore the feasibility of localizing clip-containing lymph nodes and was not designed to assess the FNR of TAD, although a prospective study to assess this issue is now ongoing (MD Anderson study protocol No. PA11-1087).

In the first 2 patients, we used wire localization to identify the clip-containing lymph node. We transitioned to 125I seed localization because this technique became more common for localization of breast lesions. Several advantages to using the 125I seed include patient comfort, increased ease of surgical scheduling, decreased risk for displacement, and the potential for decreased risk of injuring the surrounding vascular structures during the time from localization to surgery. The seeds are made of titanium and contain 125I, which emits 35 keV of gamma radiation and has a half-life of 60 days.12,13 Our institution has limited the number of seeds inserted in a patient to 4 to limit excess radiation exposure; this number allows for placement of the seed in the axillary lymph nodes even when multiple seeds are needed to localize breast lesions. Standard handheld gamma probes used for SLN detection can be used to localize the 125I seed and radioisotope-containing SLNs by changing the energy mode. Several institutions14-17 have now reported on their initial experience using 125I seeds in breast localization, with results showing the procedure to be a safe and oncologically successful approach.

The surgical technique for removing the seed-containing lymph nodes is straightforward for surgeons experienced with SLN dissections. In fact, participating surgeons believed that identifying the seed-containing lymph node was easier because the expected count was greater than 10,000 with no background counts. In a trial from the Netherlands describing the use of radioactive 125I seeds to mark lymph nodes for selective removal,18 the authors reported similar technical success. Fifteen patients had 125I seeds placed in sampled lymph nodes after the initial diagnostic biopsy. Patients then completed chemotherapy with the seed in place and underwent selective removal after completion of chemotherapy. Similar to our preliminary results, Straver et al18 found that the clip-containing lymph node correctly identified patients with residual nodal disease in all cases. Our trial has the added advantage of showing that the localization and removal of the clip-containing lymph node can be performed with SLN dissection. We also show that the seed can be placed in the perioperative period instead of before chemotherapy, which limits radiation exposure to the patient.

Two recent trials1,2 evaluated the accuracy of SLN dissection to stage the axilla after chemotherapy in patients who present with clinically node-positive disease. The ACOSOG Z1071 trial required pathologic confirmation of axillary metastasis by results of fine-needle aspiration biopsy or core biopsy before chemotherapy. Although that trial did not meet the prespecified FNR end point, it identified technical aspects that could improve the accuracy of SLN dissection. For instance, the use of dual tracers (radioisotope and blue dye) improved the FNR to 10.8% compared with 20.3% when a single tracer was used (P = .05). The removal of more SLNs also improved the accuracy from an FNR of 31.5% when 1 SLN was examined to 21.1% when 2 SLNs were examined and 9.1% when 3 or more...
SLNs were examined ($P = .007$). This improvement is not surprising because one would expect that sensitivity would increase with a larger number of sampled lymph nodes. One preliminary subgroup analysis presented at the 2012 American Association for Cancer Research San Antonio Breast Symposium revealed that 96 patients had a clip placed in the lymph node after their initial needle biopsy. When the clip-containing lymph node was identified in one of the SLNs, the FNR was reduced to 7.4% (95% CI, 2.0%-17.9%). This finding led to revisions to the National Comprehensive Cancer Network guidelines, which now recommend marking lymph nodes that have undergone biopsy with clips when metastases are confirmed and removing all clip-containing lymph nodes during surgery.

The European Sentinel Neoadjuvant (SENTINA) Study also examined the use of SLN dissection in patients with clinically node-negative disease after neoadjuvant chemotherapy. The trial did not require pathologic confirmation of axillary metastases at presentation, with only 149 of 592 patients undergoing needle biopsy of suspected abnormal lymph nodes. Similar to the ACOSOG Z1071 trial, these investigators reported an overall FNR of 14.2% (95% CI, 9.9%-19.4%), which improved from 24.3% with a single SLN removed to less than 10% with 3 or more SLNs removed. They also reported a trend toward an improved FNR when dual tracers were used compared with a single mapping agent (8.6% vs 16%). Investigators from both trials hypothesize that SLN dissection could stage the axilla accurately after chemotherapy in select patients if technical aspects are optimized.

Targeted axillary dissection requires a multidisciplinary team that works together from the first diagnostic nodal ultrasonographic examination to the completion of the pathologic examination after surgical removal. First, radiologists must place a clip in axillary lymph nodes when metastases are confirmed by results of the needle biopsy. In addition, radiologists must be available and able to place a wire or an $^{125}$I seed accurately in the clip-containing lymph node preoperatively. Surgeons who are comfortable using gamma probes to identify radioisotope-containing SLNs should be able to accurately identify the seed-containing node intraoperatively, although precautions must be in place when using radioactive material similar to that used when $^{125}$I seeds guide segmental mastectomy. Removal of the clip-containing lymph node is confirmed by intraoperative radiography, which requires a participating pathologist and radiologist. Similar to intraoperative assessment for breast localization, handling and disposing of the $^{125}$I seed must also be performed in concordance with radioactive safety guidelines.

There are limitations to this pilot feasibility trial. Although the small number of patients enrolled established the feasibility of the technique, we cannot evaluate its efficacy in identifying patients with residual nodal disease. Trials to assess this efficacy are currently accruing data at our institution. This technique may benefit patients who are not receiving neoadjuvant chemotherapy and otherwise fit ACOSOG Z0011 eligibility criteria but who have a single suspected abnormal lymph node seen on ultrasonography if removal of the clip-containing lymph node and evaluation of the SLNs reveal only 1 or 2 positive lymph nodes; however, the application of the ACOSOG Z0011 criteria in this case is unclear and will need further investigation. Last, placing an $^{125}$I seed preoperatively incorporates a procedure for patients that involves added risk and extra radiation exposure and should be implemented into practice only if a potential benefit exists.

**Conclusions**

Documented axillary lymph nodes containing metastases that are marked with a clip can be localized safely and removed at the time of breast surgery. This procedure can be performed with wire localization or with placement of a radioactive $^{125}$I seed; it can be performed with other axillary surgical procedures, including SLN dissection and ALND. Although ongoing studies must be completed to determine whether adding this targeted surgical technique to SLN dissection improves our ability to identify patients whose nodal disease is eradicated by chemotherapy, its potential for use in breast cancer and possibly other disease sites remains exciting.

**REFERENCES**


