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# Lymph node wire localization post-chemotherapy: Towards improving the false negative sentinel lymph node biopsy rate in breast cancer patients☆

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ABSTRACT

*Purpose:* To evaluate whether the disease status of the pre-neoadjuvant chemotherapy (NAC) core biopsied lymph node (preNACBxLN) in patients with node positive breast cancer corresponds to nodal status of all surgically retrieved lymph nodes (LNs) post-NAC and whether wire localization of this LN is feasible.

*Materials and methods:* HIPPA compliant IRB approved retrospective study including breast cancer patients (a.) with preNACBxLN confirmed metastases, (b.) who received NAC, and (c.) underwent wire localization of the preNACBxLN. Electronic medical records were reviewed. Fisher's exact test was used to compare differences in residual disease post-NAC among breast cancer subtypes.

*Results:* 28 women with node positive breast cancer underwent ultrasound guided wire localization of the preNACBxLN, without complication. There was no evidence of residual nodal disease for 16 patients, with mean 4.4 (median 4) LNs resected. 12 patients had residual nodal metastases, with mean 9.2 (median 7) LNs resected and mean 2.3 (median 2) LNs with tumor involvement. 11 patients had metastases detected within the localized LN. One patient had micrometastasis in a sentinel LN, despite no residual disease in the preNACBxLN. Patients with luminal A/B breast cancer more often had residual nodal metastases (86%) at pathology, as compared to patients with HER2 + (20%) and Triple Negative breast cancer (50%), though not quite achieving statistical significance ($p = 0.055$).

*Conclusion:* Ultrasound guided wire localization of the preNACBxLN is feasible and may improve detection of residual tumor in patients post-NAC.

## 1. Introduction

Management of the axilla in breast cancer patients has evolved greatly over the last few years. The American College of Surgical Oncology Group (ACOSOG) Z0011 trial recently found no survival benefit with axillary lymph node (LN) dissection (AxLND) over sentinel lymph node biopsy (SLNBx) alone for patients with stage 1 or stage 2 primary breast cancer with ≤ 2 axillary LN metastases, when undergoing breast conservation surgery with adjuvant whole breast radiotherapy and appropriate systemic therapy [1,2]. This may in part be accounted for by improvements in systemic therapy and inclusion of part of the axilla in the radiation field [3–6]. As a result conservative surgical management of the axilla has been favored. Less extensive LN dissection reduces surgical morbidity by decreasing lymphedema, arm immobility and paresthesia [7–9].

However for patients with locally advanced node-positive breast cancer, who receive neoadjuvant chemotherapy (NAC), AxLND rather than SLNBx has been the mainstay for assessing nodal disease for many years. The SENTINA (SENTinel NeoAdjuvant) study found increased false negative SLNBx rate after neoadjuvant chemotherapy, as compared to prior to treatment [10]. Furthermore the ACOSOG Z1071 trial found a 12.6% false negative SLNBx rate post-NAC, placing the role of SLNBx in this population in question [11]. LN disease status is important for predicting patient prognosis and helps to determine the

*Abbreviations:* NAC, neoadjuvant chemotherapy; preNACBxLN, pre-neoadjuvant chemotherapy biopsied lymph node; LN, lymph node; AxLND, axillary lymph node dissection; SLNBxSentinel, lymph node biopsy

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extent of LN dissection and need for radiation therapy [10,12]. Thus, studies sought to better assess LN stage with improved LN mapping to allow more conservative management of the axilla [8,13–15]. In the Z1071 trial, the false negative SLNBx rate decreased to < 10% when ≥ 3 LNs were removed and two tracers were used for intra-operative LN mapping. LN staging is further improved when the preNACBxLN is removed at surgery [16,17].

Ultrasound-guided wire or radioactive seed localization may be used to assist retrieval of the preNACBxLN during surgery [16,17]. Preoperative LN localization is currently performed by many practices [18–20]. Here we identify patients with node positive locally-advanced breast cancer who received NAC, and evaluate whether the disease status of the retrieved preNACBxLN corresponds to the nodal status of all surgically retrieved LNs at SLNBx or AxLND. Lastly, we assess whether ultrasound-guided wire localization of the preNACBxLN is feasible.

## 2. Materials and methods

A HIPPA-compliant, IRB approved retrospective study was performed, including breast cancer patients with LN confirmed metastases, who subsequently received NAC and underwent wire localization of the preNACBxLN between January 2015 and December 2016. The health information system at our institution was reviewed for all breast cancer patients. Once breast cancer was confirmed, LN core biopsy was performed on the most suspicious LN identified on imaging for patient staging. Suspicious LN features included cortical thickening greater than 3 mm [21], cortical thickness equal to or greater than the width of the fatty hilum [22] and loss of the fatty hilum. At the time of the LN core biopsy, a marking clip was routinely placed, which allowed re-identification of the biopsied node after NAC and subsequent wire localization under ultrasound guidance. Patients were excluded if pathology was unavailable, if the LN was positive for a second primary cancer, or if the preNACBxLN was negative for metastatic disease.

Post-NAC, patients went on to wire localization of the preNACBx LN. Dual tracer (blue dye and 99mTc activity) was used for LN mapping. Patients not in the ALLIANCE A011202 trial had a SLNBx after removal of the wire-localized LN; while patients in the ALLIANCE A011202 trial were randomized to SLNBx or AxLND which was also performed immediately after removal of the wire-localized LN.

Upon surgical excision, resected biopsy clip and wire were immediately confirmed on specimen radiograph. The presence of the pre-NAC placed biopsy clip and biopsy site changes within the localized LN at pathology were used to confirm appropriate targeting. Both the targeted wire-localized LN and any additional resected LNs were identified. All LN specimens were evaluated by pathology with hematoxylin and eosin staining. Breast cancer staging post-NAC was performed at pathologic evaluation, in accordance with the American Joint Committee on Cancer Staging Manual, 7th edition. Treatment response and residual disease at pathology were recorded for both the resected axillary LNs and the primary breast cancer. Fisher's exact test was used to evaluate for significant differences in residual tumor within the breast or LNs among various breast cancer sub-types. Electronic medical records were reviewed for clinical, imaging and pathology findings.

## 3. Results

Twenty-eight women with a mean age of 49 years (range: 28–87 years) with locally advanced breast cancer (27 IDC; 1 ILC) and LN involvement confirmed on pre-NAC core biopsy met inclusion/exclusion criteria (Table 1). Breast cancer stages of the 28 included women were as follows: 17 T2N1, 8 T3N1, 1 T2N2, 1 T3N2, and 1 T4N1. For all cases, a Hydromark (Biopsy Sciences, Clearwater, Florida) (Fig. 1) was placed post-core LN biopsy to facilitate detection of the core biopsied LN on ultrasound. Upon completion of NAC, patients were evaluated for treatment response and surgical planning. Patients underwent post-NAC ultrasound-guided LN localization immediately prior to surgical resection. No complications were reported during or immediately post-wire localization.

**Table 1**
Patient characteristics.

| | | Nodal status | |
|---|---|---|---|
| Nodal disease at pathology | | No residual disease | Residual nodal disease |
| Patient characteristics | Number of patients | 16 | 12 |
| | Age | 47 (range 27–87) | 52 (range 39–79) |
| LNs | Total resected | 4.4 (median 4) | 9.2 (median 7) |
| | Residual tumor | 0 | 2.3 |
| | Wire-localized LN | 0 | 11 |

Seven patients underwent localization of the preNACBxLN with concomitant AxLND, with 5/7 found to have residual nodal metastases on pathology. All other patients (21) underwent SLNBx with dual tracer mapping, with 7/21 patients with residual nodal metastases at pathology. Definitive breast surgery was performed at the time of initial LN resection for all patients. Patients with residual nodal disease often had more LNs resected, since they had both more suspicious LNs and more often underwent AxLND (of 12 patients with residual nodal metastases, five underwent AxLND), as opposed to patients without residual nodal disease (of 16 patients without residual nodal metastases, two patients underwent AxLND). Median 4 LNs were removed at SLNBx, by utilizing dual tracer mapping, in accordance with ACOSOG Z1071 recommendations, to ensure appropriate excision of residual nodal disease.

For 93% (26/28) of cases appropriate LN targeting was confirmed by identifying a biopsy clip or biopsy site changes within the wire-localized LN on pathology. For the two cases in which the preNACBxLN was not appropriately targeted, biopsy site change was identified on pathology in a different surgically retrieved LN. For these two cases the biopsy clip was difficult to identify on axillary ultrasound. One case had no evidence of nodal disease at pathology, while the other case had nodal metastases in the wire-localized LN, as well as in the preNACBxLN.

HER2 + (ER/PR + or −) and Triple Negative (HER2 −/ER −/PR −) breast cancers more often responded to NAC, as compared to luminal A/B (HER2 −/ER +) breast cancers (Table 2). Post-NAC there was no pathologic evidence of invasive disease (ypN0 or N0i + with ypT0 or Tis) in the breast or axilla for 73% (11/15) of HER2 +, 50% (3/6) of Triple Negative, and 14% (1/7) of luminal A/B breast cancer. Twenty percent (3/15) of patients with HER2 + breast cancer had residual nodal metastases, compared to 50% (3/6) and 86% (6/7) of patients with Triple Negative and luminal A/B breast cancer, respectively. However, among the breast cancer sub-types, differences in response to NAC for residual primary invasive and nodal disease were not statistically significant ($p = 0.11$ and 0.055, respectively), likely due to the small number of patients evaluated.

For patients with no pathologic evidence of nodal disease (16), a median of 4 (mean 4.4; range 2–14) LNs were resected. For patients with residual nodal metastases (12), 67% had additional LNs with tumor involvement, with a median of 7 (mean 9.2; range 3–21) LNs resected and mean 2.3 LNs with tumor involvement (Table 1). Among patients with residual nodal disease, metastases were identified in the localized LN for 11/12 patients. Three patients had residual disease only within the wire-localized preNACBxLN. One patient had isolated tumor cells identified only in one non-localized sentinel LN; thus, for this case our localized LN was discordant with disease status among all resected LNs. This patient had luminal A (Ki67 15%) primary breast cancer, stage T3N1 and underwent NAC prior to mastectomy and