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# Does a Positive Axillary Lymph Node Needle Biopsy Result Predict the Need for an Axillary Lymph Node Dissection in Clinically Node-Negative Breast Cancer Patients in the ACOSOG Z0011 Era?

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## ABSTRACT

**Background.** American College of Surgeons Oncology Group (ACOSOG) Z0011 defined clinical node negativity by physical examination alone. Although axillary ultrasound with biopsy has a positive predictive value for lymph node (LN) metastases approaching 100 %, it may not appropriately identify clinically node-negative women with ≥3 positive LNs who require axillary lymph node dissection (ALND). We sought to identify the total number of positive LNs in women presenting with cT1–2N0 breast carcinoma with a positive preoperative LN biopsy to evaluate the potential for overtreatment when ALND is performed on the basis of a positive needle biopsy in patients who otherwise meet ACOSOG Z0011 eligibility criteria.

**Methods.** Patients with cT1–2N0 breast cancer by physical examination with a positive preoperative LN biopsy were identified from a prospective institutional database. Clinicopathologic characteristics and axillary imaging results were compared between women with 1 to 2 total positive LNs and ≥3 total positive LNs.

**Results.** Between May 2006 and December 2013, a total of 141 women with cT1–2N0 breast cancer had abnormal axillary imaging and a preoperative positive LN biopsy (median patient age 51 years, median tumor size 2.4 cm, 86 % ductal histology, 79 % estrogen receptor positive). Sixty-six women (47 %) had 1 to 2 total positive LNs, and 75 (53 %) had ≥3 total positive LNs. Women with ≥3 total positive LNs had larger tumors (2.4 vs. 2.2 cm, $p = 0.03$), fewer tumors with ductal histology (79 vs. 94 %, $p = 0.01$), more lymphovascular invasion (80 vs. 61 %, $p = 0.01$), and higher median body mass index (29.2 vs. 27.1 kg/m$^2$, $p = 0.04$). Having >1 abnormal LN on axillary imaging was significantly associated with having ≥3 total positive LNs at final pathology (68 vs. 43 %, $p = 0.003$).

**Conclusions.** Axillary imaging with preoperative LN biopsy does not accurately discriminate low- versus high-volume nodal disease in clinically node-negative patients.

Axillary management for early-stage breast cancer patients continues to evolve, with the goal of optimal oncologic safety coupled with nominal surgical morbidity. Four trials evaluating axillary management in clinically node-negative breast cancer patients have established the safety of omitting a completion axillary lymph node dissection (ALND) in select pathologically node-positive patients.[1–5] The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial reported equivalent outcomes for sentinel lymph node biopsy (SLNB) alone compared to completion ALND for women with 1 to 2 positive sentinel lymph nodes undergoing breast-conserving surgery, whole-breast radiotherapy, and systemic therapy.[3,4] In the ACOSOG Z0011 trial, a clinically negative axilla was defined by physical examination alone. However, some studies suggest that axillary ultrasound (US) and needle biopsy of abnormal-appearing nodes can appropriately allocate node-positive women to an up-front ALND, avoiding a 2-step axillary procedure.[6,7] Although



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axillary US and needle biopsy has a positive predictive value for the detection of nodal metastases approaching 100 %, it may not appropriately identify clinically node-negative women who require ALND.[8] In the ACOSOG Z0011 era, axillary US and needle biopsy to select patients for ALND has utility only if it appropriately discriminates between women with 1 to 2 positive sentinel lymph nodes (LNs) and those with >2 positive sentinel LNs.

In this study, we sought to determine if a positive preoperative LN needle biopsy in clinically node-negative women with T1–2 tumors identified a population of women who require ALND and to evaluate the potential for overtreatment when ALND is performed on the basis of a positive needle biopsy in patients who otherwise meet ACOSOG Z0011 eligibility criteria.

## MATERIALS AND METHODS

After receipt of institutional review board approval, patients clinically staged as having T1–2N0 invasive breast cancer with a positive preoperative axillary LN needle biopsy (fine needle aspiration or core needle biopsy) were identified from a prospective institutional database. Clinical nodal status was confirmed by chart review. Patients undergoing neoadjuvant chemotherapy or managed with a SLNB alone were excluded. Patient and tumor characteristics including age, body mass index, tumor size, tumor histology, nuclear grade, presence of lymphovascular invasion, multifocality, estrogen and progesterone receptor status, HER2/neu amplification, and breast surgery were collected. Type of axillary surgery and the total number of positive LNs were determined. Axillary imaging results from mammogram, US, and magnetic resonance imaging (MRI) were abstracted from radiology reports. All outside imaging was reviewed by specialist breast imagers before surgery. We do not routinely obtain axillary US for clinically node-negative patients at our institution. Axillary USs were performed at the discretion of an outside physician before presentation at Memorial Sloan Kettering Cancer Center (MSKCC) or were done as additional workup for abnormal LNs seen on mammogram or MRI. For US performed at MSKCC, a high-resolution transducer was used by a trained US technician to perform contiguous radial and antiradial scanning; a breast radiologist rescans any questionable findings. For each imaging modality, it was determined whether abnormal axillary LNs were identified, and the number of abnormal LNs was categorized as 1 or >1. Clinicopathologic characteristics and axillary imaging results were compared between women with 1 to 2 total positive LNs and those with ≥3 total positive LNs.

Clinical characteristics were summarized using frequency and percentage for categorical covariates, and median and range for continuous covariates, and were compared between the group with 1 to 2 positive LNs and the group with ≥3 positive LNs by chi-square tests for categorical covariates (Fisher's exact test in the case of small call frequencies) and *t* tests for continuous covariates (Wilcoxon rank sum test for tumor size). All statistical analyses were performed in SAS 9.2 (SAS Institute, Cary, NC), and $p$ values of <0.05 were considered significant.

## RESULTS

Between May 2006 and December 2013, a total of 904 breast cancer patients had a positive preoperative LN needle biopsy; 151 of these women were staged as having cT1–2N0 disease by physical examination. Ten women underwent SLNB alone and were excluded, leaving 141 women in the study population. Median patient age for the cohort was 51 years (range 25–91 years), median pathologic tumor size was 2.4 cm (range 0.8–9.5 cm), 86 % of tumors were of ductal histology, and 79 % of tumors were estrogen receptor positive. Lumpectomy was performed in 51 women (36 %), while 90 (64 %) underwent mastectomy (Table 1). All patients had an ALND.

Sixty-six women (47 %) had 1 to 2 total positive LNs (34 with 1 positive node, 32 with 2 positive LNs), and 75 (53 %) women had ≥3 total positive LNs. Table 1 compares clinicopathologic features between these two groups. Women with ≥3 total positive LNs had larger tumor size (2.4 vs. 2.2 cm, $p = 0.033$), fewer tumors with ductal histology (79 vs. 94 %, $p = 0.012$), a higher rate of lymphovascular invasion (80 vs. 61 %, $p = 0.011$), and a higher median body mass index (29.2 vs. 27.1 kg/m$^2$, $p = 0.045$).

All 141 patients had at least 1 abnormal axillary LN seen on US, and 60 (43 %) had abnormal axillary LNs identified on mammogram. A total of 89 women (63 %) were also imaged with breast MRI; 16, 49, and 35 % had 0, 1, or >1 abnormal LNs identified, respectively. Table 2 compares axillary imaging results among women with 1 to 2 total positive nodes and those with ≥3 total positive nodes. A significantly greater proportion of women with ≥3 total positive nodes had >1 abnormal LN identified on preoperative axillary imaging compared to women with only 1 to 2 total positive LNs (53 vs. 29 %, $p = 0.0032$). Among women with >1 abnormal LNs identified on preoperative axillary imaging, 68 % had ≥3 total positive LNs at final pathology (Fig. 1).

## DISCUSSION

Among a cohort of clinically node-negative breast cancer patients identified as having abnormal axillary

**TABLE 1** Clinicopathologic features of patient population based on extent of nodal involvement

| Characteristic | Total population ($n = 141$) | 1–2 positive LNs ($n = 66$) | ≥3 positive LNs ($n = 75$) | $p$ |
|---|---|---|---|---|
| Age, years, median (range) | 51 (25–91) | 51.5 (31–80) | 51 (25–91) | 0.80 |
| BMI, kg/m$^2$, median (range) | 27.7 (17.7–48.6) | 27.1 (17.7–41.4) | 29.2 (18.4–48.6) | 0.0448 |
| Tumor size, cm, median (range) | 2.4 (0.8–9.5) | 2.2 (0.8–4.5) | 2.4 (0.9–9.5) | 0.0329 |
| Tumor histology | | | | 0.0121 |
| Ductal | 121 (86 %) | 62 (94 %) | 59 (79 %) | |
| Lobular | 12 (9 %) | 1 (2 %) | 11 (15 %) | |
| Mixed ductal and lobular features | 7 (5 %) | 3 (5 %) | 4 (5 %) | |
| Metaplastic | 1 (1 %) | 0 (0 %) | 1 (1 %) | |
| Nuclear grade | | | | 0.92 |
| Low/intermediate | 43 (38 %) | 23 (39 %) | 20 (37 %) | |
| High | 70 (62 %) | 36 (61 %) | 34 (63 %) | |
| Missing | 28 | 7 | 21 | |
| LVI present | 100 (71 %) | 40 (61 %) | 60 (80 %) | 0.0114 |
| Multifocal | 62 (44 %) | 26 (39 %) | 36 (48 %) | 0.30 |
| ER status | | | | 0.81 |
| Positive | 112 (79 %) | 53 (80 %) | 59 (79 %) | |
| Negative | 29 (21 %) | 13 (20 %) | 16 (21 %) | |
| PR status | | | | 0.64 |
| Positive | 102 (72 %) | 49 (74 %) | 53 (71 %) | |
| Negative | 39 (28 %) | 17 (26 %) | 22 (29 %) | |
| HER2/neu status | | | | 0.41 |
| Not amplified | 36 (26 %) | 19 (29 %) | 17 (23 %) | |
| Amplified | 105 (74 %) | 47 (71 %) | 58 (77 %) | |
| Total positive nodes, median (range) | 3 (1–53) | 1 (1–2) | 6 (3–53) | NA |
| Total nodes removed, median (range) | 21 (7–60) | 21 (7–53) | 20 (10–60) | 0.83 |
| Final breast procedure | | | | 0.45 |
| Lumpectomy | 51 (36 %) | 26 (39 %) | 25 (33 %) | |
| Mastectomy | 90 (64 %) | 40 (61 %) | 50 (67 %) | |

*LN* lymph node, *BMI* body mass index, *LVI* lymphovascular invasion, *ER* estrogen receptor, *PR* progesterone receptor

imaging with a subsequent positive preoperative LN needle biopsy, nearly half (47 %) had only 1 to 2 total positive LNs at the time of axillary surgery. During this time period, almost all patients with a positive LN needle biopsy finding were managed with an up-front ALND, with only 4 % of patients having a SLNB followed by completion ALND. On the basis of final LN pathology, our results suggest that at least half of these patients could be safely managed with SLNB alone if treated according to ACOSOG Z0011 criteria. Furthermore, because the number of positive LNs is the total number of positive nodes from an axillary dissection specimen rather than number of positive sentinel LNs, this is likely an underestimate of the number of women who would be spared a completion ALND if managed according to ACOSOG Z0011 criteria.

Although some suggest that axillary US and needle biopsy are essential in the preoperative workup of breast cancer patients to help dictate surgical management, the role of preoperative axillary staging is shifting in the ACOSOG Z0011 era.[9–11] Houssami et al. assessed the utility of preoperative axillary US and needle biopsy in discriminating low versus high nodal disease burden based on needle biopsy results in an analysis of seven studies and reported results similar to our findings. In this analysis, high nodal disease burden was defined as >3 positive LNs in six studies and ≥2 positive LNs in one study. The pooled odds ratio for high nodal disease burden with a positive versus negative needle biopsy was 4.38, with the proportion of patients with a positive needle biopsy having a high nodal disease burden estimated to be 59 %. Conversely, these results suggest that 41 % of patients with a positive preoperative needle biopsy would have only 1 to 2 total positive LNs and do not require additional axillary surgery.[12]

Similarly, Schipper et al. examined the nodal disease burden in women evaluated with preoperative axillary US

**TABLE 2** Axillary imaging results based on extent of nodal involvement

| Imaging results | 1–2 positive LNs ($n = 66$) | ≥3 positive LNs ($n = 75$) | $p$ |
|---|---|---|---|
| Mammogram with abnormal LNs | | | 0.75 |
| No | 37 (56 %) | 44 (59 %) | |
| Yes | 29 (44 %) | 31 (41 %) | |
| No. of abnormal LNs on US | | | 0.016 |
| 1 | 52 (79 %) | 45 (60 %) | 3 |
| >1 | 14 (21 %) | 30 (40 %) | |
| MRI performed | | | 0.0266 |
| Yes | 48 (73 %) | 41 (55 %) | |
| No | 18 (27 %) | 34 (45 %) | |
| No. of abnormal LNs on MRI ($n = 88$)[a] | | | 0.083 |
| 0 | 8 (17 %) | 6 (15 %) | |
| 1 | 28 (58 %) | 15 (38 %) | |
| >1 | 12 (25 %) | 19 (48 %) | |
| No. of abnormal LNs on US/MRI axillary imaging[b] | | | 0.0032 |
| 1 | 47 (71 %) | 35 (47 %) | |
| >1 | 19 (29 %) | 40 (53 %) | |

*LN* lymph node, *MRI* magnetic resonance imaging, *US* ultrasound

[a] Results unknown for 1 patient who underwent MRI

[b] Greatest number of abnormal LNs seen on either US or MRI for each patient

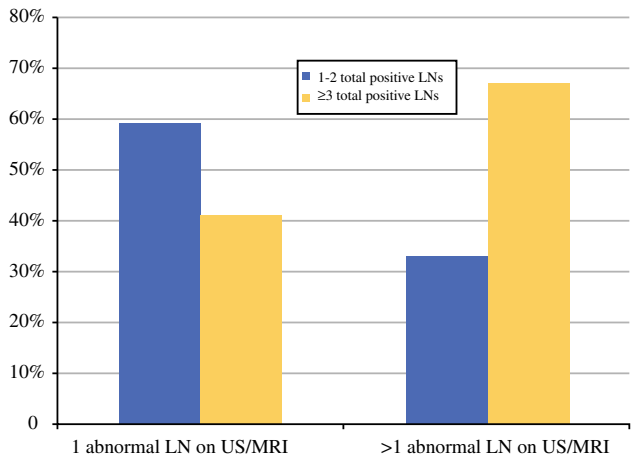


**FIG. 1** Total positive lymph nodes (LNs) for women with a positive preoperative needle biopsy with 1 or > 1 abnormal axillary LNs identified by ultrasound (US) or magnetic resonance imaging (MRI)

and needle biopsy.[13] In a cohort of 40 clinically node-negative breast cancer patients with an abnormal axillary US and positive LN needle biopsy, 25 (62.5 %) were pN1, while 15 (37.5 %) had pN2–3 disease at final pathology. In a subset of women with T1–2 tumors undergoing breast-conserving surgery, 12 of 278 cases had abnormal axillary US and needle biopsy. ALND pathology of these 12 patients revealed 1 to 2 positive LNs in 6 cases, supporting the notion that a positive LN needle biopsy does not predict the need for ALND in clinically node-negative patients.

Studies by Caudle et al. and Verheuvel et al. have also compared node-positive patients identified by US and needle biopsy to women with negative axillary imaging found to have a positive node with a SLNB and concluded that women diagnosed with positive nodes by needle biopsy are higher risk for heavy nodal disease burden and should not be managed according to ACOSOG Z0011 criteria.[14,15] Women with a positive needle biopsy had higher risk tumor characteristics, with larger tumor size as well as more high-grade tumors with lymphovascular invasion and hormone receptor negativity. Although women identified as being node positive by US and needle biopsy were at higher risk for heavy nodal disease burden, 37–52 % had only 1 to 2 total positive LNs. Furthermore, while survival was expectedly worse in the needle biopsy cohort reported by Verheuvel et al. that presented with more advanced-stage disease, there was no difference in regional recurrence, with only one isolated regional relapse in each group. A meta-analysis including six additional studies also reported a higher percentage of pN2 disease in women with a positive needle biopsy finding compared to those with negative axillary imaging with a positive sentinel LN (46 vs. 30 %).[16] These studies concluded that SLNB may not be appropriate for women diagnosed with nodal disease by US and needle biopsy because this represents a higher-risk population; however, these studies do not represent women meeting ACOSOG Z0011 criteria, yet 30–52 % of patients had low-volume nodal disease and in the appropriate context could be spared ALND.

When evaluating nodal disease burden by number of abnormal LNs identified, we found that women with >1 abnormal LNs by US or MRI were more likely to have >3 positive total LNs than women with only 1 abnormal LN on axillary imaging (68 vs. 43 %, $p = 0.003$). Hieken et al. also compared final nodal pathology for women with 1 vs. >1 abnormal LN on preoperative axillary imaging and found a greater percentage of pN2 disease in women with >1 abnormal node on US (31 vs. 14 %, $p > 0.001$).[17] While >1 abnormal LN is a predictor of higher nodal disease burden, we have previously reported that finding multiple abnormal axillary LNs on preoperative axillary imaging is extremely uncommon in a cohort of clinically node-negative patients meeting ACOSOG Z0011 eligibility criteria. Among 425 women treated with breast conservation found to have a positive sentinel LN, >1 abnormal LN was identified in 15 women (6 %) by US and 20 women (12 %) by MRI, with only 10 women (2 %) having >2 abnormal LNs by US or MRI.[18] Although finding multiple abnormal LNs is uncommon among women meeting ACOSOG Z0011 criteria, for women with multiple abnormal LNs and a positive preoperative needle biopsy, frozen section could be performed in the operating room to document the number of nodal metastasis to obviate a return to the operating room for a completion ALND in a population of women at high risk for requiring additional axillary surgery.

This study is limited by the retrospective nature of the data collection and a paucity of information regarding indication for axillary imaging. Although axillary imaging was not routine for clinically node-negative patients at our institution, many women undergo axillary US before presentation, and others have breast MRI at the surgeons' discretion. There were a variety of clinical situations among this patient population that led to the recommendation for LN needle biopsy. Some women underwent workup with biopsy before presentation. Others were undergoing mastectomy and had workup of an abnormal-appearing LN to obviate the need for 2-step axillary surgery. Last, some patients were treated before the adoption of ACOSOG Z0011 criteria and therefore would not have been candidates for a SLNB with a positive axillary LN. From 2006 to 2010, all women with a positive LN needle biopsy underwent an up-front ALND. In 2012 to 2013, women undergoing breast conservation had an attempted SLNB and a completion ALND for >2 positive sentinel LNs. Additionally, while we abstracted axillary LN imaging results from mammogram and MRI reports, it is notable that these imaging modalities are not performed to specifically evaluate the axilla and that review of US images is limited by the static nature of the films. As previously noted, while the presenting clinical stage is consistent with a population of patients meeting ACOSOG Z0011 criteria, many patients were treated with mastectomy and ALND, and therefore this cohort does not represent a population of women managed according to ACOSOG Z0011 criteria. However, in a recent study from our institution evaluating the role of axillary imaging in a consecutive cohort of women presenting with cT1–2N0 invasive breast carcinoma and treated according to ACOSOG Z0011 criteria, similar results were reported. Among a small group of women ($n = 11$) with a positive preoperative needle biopsy finding, 5 (45 %) of 11 women required completion ALND, while 6 (55 %) of 11 had 1 to 2 positive sentinel LNs and were spared additional axillary surgery.[18]

Although this is a relatively small study, the results strongly suggest that a positive axillary node needle biopsy is insufficient to warrant ALND. On the basis of the total number of positive axillary LNs identified in this cohort, it appears that approximately half of women presenting with clinically node-negative disease and a positive preoperative LN needle biopsy are likely overtreated if managed with up-front ALND, questioning the utility of axillary imaging and needle biopsy in select early-stage breast cancer patients.

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