Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

Utility of Preoperative Ultrasound for Predicting pN2 or Higher Stage Axillary Lymph Node Involvement in Patients With Newly Diagnosed Breast Cancer

Hiroyuki Abe[1]
David Schacht
Charlene A. Sennett
Gillian M. Newstead
Robert A. Schmidt

OBJECTIVE. The objective of our study was to report the positive predictive value (PPV) of ultrasound of the axilla to predict pN2 or higher disease in breast cancer patients.

MATERIALS AND METHODS. A retrospective study of 559 patients with newly diagnosed invasive breast cancer from 2005 through 2009 was performed. All patients underwent ipsilateral axillary ultrasound for staging purposes. Ultrasound findings were considered suspicious for metastasis if cortical thickening or nonhilar blood flow to the cortex was present. Suspicious lymph nodes were classified on the basis of their features as high, intermediate, or low suspicion. The standard of truth was confirmed pathologically.

RESULTS. Either pN2 or pN3 disease was found in 50 of 181 (28%) patients with positive findings on an ultrasound study and 10 of 378 (3%) patients with a negative ultrasound study ($p < 0.01$). When two or more lymph nodes of high suspicion or a total of three or more lymph nodes of any combination of high suspicion and intermediate suspicion were detected, patients were likely to have pN2 or pN3 disease (PPV, 82%). Either pN2 or pN3 disease was found in two of 122 (2%) patients whose primary cancers were up to 10 mm and 58 of 437 (13%) patients whose primary cancers were larger than 10 mm ($p < 0.001$). Ultrasound of the patient with tumors larger than 10 mm showing at least two highly suspicious nodes had a PPV of 87% for predicting pN2 or higher disease.

CONCLUSION. Ultrasound was useful for predicting pN2 or higher axillary disease in breast cancer patients. Preoperative ultrasound assessment for staging of axillary lymph nodes might help avoid underestimation at sentinel lymph node biopsy.

Keywords: breast cancer, lymph node, staging, ultrasound

DOI:10.2214/AJR.12.9036

Received April 6, 2012; accepted after revision July 18, 2012.

[1]All authors: Department of Radiology, The University of Chicago, 5841 S Maryland Ave, MC 2026, Chicago, IL 60637. Address correspondence to H. Abe (habe@radiology.bsd.uchicago.edu).

AJR 2013; 200:696–702

0361–803X/13/2003–696

© American Roentgen Ray Society

Axillary lymph node staging plays an important role in the management of breast cancer patients because the presence of axillary lymph node metastatic disease adversely affects the prognosis in those patients [1–3]. The staging of axillary lymph nodes is currently considered to be a key procedure because the extent of regional disease helps determine the need for adjuvant chemotherapy and radiation therapy. For pathologic staging of the ipsilateral axillary lymph nodes, the nodes are classified as pN1, pN2, or pN3, where pN1 means there are one to three metastatic lymph nodes; pN2, four to nine metastatic lymph nodes; and pN3, 10 or more metastatic lymph nodes. The distinction between pN1 and pN2 or higher disease is important in decision making for treatment because locally advanced breast cancer generally needs adequate adjuvant treatment [4].

Traditionally, axillary lymph node dissection (ALND) has been used for the evaluation and treatment of axillary metastases. However, ALND can be associated with significant side effects including upper extremity lymphedema, arm numbness and tingling, pain, impaired shoulder mobility, and arm weakness [5–8]. In addition, investigators have suggested that ALND is not a curative procedure but a staging procedure that should be used to obtain prognostic information [9, 10]. In this context, sentinel lymph node biopsy (SLNB) has become popular as a less invasive staging procedure [11, 12]. Furthermore, the results of the Z0011 Trial of the American College of Surgeons Oncology Group indicated that among patients with up to two metastatic lymph nodes, there was no survival benefit or reduction in local recurrence in patients who underwent ALND compared with those who underwent SLNB alone [13]. The results of that trial could promote a trend toward nonperformance of ALND when a small number of metastatic lymph nodes are seen at SLNB.

Although SLNB is a widely accepted procedure for assessing axillary lymph node status,

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

it is not immune to false-negatives [8, 14]. Ultrasound is widely used to evaluate the axillary lymph node status in the preoperative setting [15–25]. If ultrasound has the ability to predict pN2 or more advanced disease, underestimation of lymph node staging by SLNB alone could be avoided and patients with advanced stage disease could be triaged to receive the appropriate adjuvant treatment.

In this study, we evaluated the ability of axillary ultrasound to predict pN2 and pN3 disease in patients with newly diagnosed breast cancer.

Materials and Methods

This retrospective study was HIPAA compliant and was approved by the University of Chicago Institutional Review Board. The requirement for written informed patient consent was waived.

Patients

We retrospectively reviewed the ultrasound studies of the ipsilateral axilla in patients with newly diagnosed invasive breast cancer between January 1, 2005, and December 31, 2009. There were 559 consecutive patients in this review after excluding 10 patients who left our institution without undergoing treatment; 19 patients who did not receive surgical treatment because of systemic metastasis or other comorbidities; and 51 patients who received neoadjuvant chemotherapy, which could have modified the final pathologic results of lymph node staging.

Ultrasound for axillary lymph node staging was performed either at the same time as the diagnostic breast ultrasound or after the diagnosis of breast cancer had been established. Patients ranged in age from 24 to 89 years (mean, 59 years). The histologic types of the primary lesions in the 559 patients were infiltrating ductal carcinoma (IDC) in 527 (94%) patients, infiltrating lobular carcinoma (ILC) in 30 (5%) patients, and others in two patients (sarcoma and adenoid cystic carcinoma). Among the 559 patients, 58 patients with IDC and two patients with ILC had pN2 or higher disease. There were 36 (6%) patients with primary cancer of 5 mm or smaller, 86 (15%) patients with primary cancer larger than 5 mm up to 10 mm, 213 (38%) patients with primary cancer larger than 10 mm up to 20 mm, 170 (30%) patients with primary cancer larger than 20 mm up to 50 mm, and 54 (10%) patients with primary cancer larger than 50 mm. The mean size of all primary cancers was 22.7 mm. The size of the primary lesions was obtained from the pathologic reports.

Ultrasound Examination

In our practice, we routinely perform an ultrasound survey of the axillary lymph nodes of patients with invasive breast cancer. Axillary ultrasound was performed ipsilateral to the known index cancer using an HDI 5000 ultrasound unit (ATL) or an IU 22 system (Philips Healthcare International) with a 5-12–MHz linear transducer or a 5-17–MHz linear transducer, respectively. The patient was placed in a supine or oblique position to flatten the axillary fossa on the table with the ipsilateral hand placed behind the head.

The goal of ultrasound scanning was to detect as many level 1 lymph nodes as possible; however, a minimum goal was to detect at least one lymph node. Ultrasound results were considered positive if a detected lymph node showed cortical thickening (including diffuse thickening, asymmetric thickening, and loss of hilum) without or with nonhilar blood flow to the cortex [22]. Cortical thickness equal to or greater than the width of the fatty hilum or cortical thickness of more than 3 mm was used as the standard for positive cortical thickening. Color Doppler ultrasound was performed with low-velocity (4.4 cm/s for ATL HDI 500 and 2.5 cm/s for IU 22) parameter settings and high gain by using a slow scanning technique. Ultrasound was performed by one or more of five radiologists who had 4–36 years' experience in breast imaging, including 4–18 years' experience in breast ultrasound, at the time of the study.

Histology

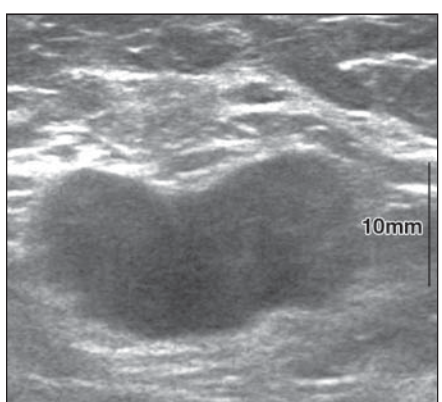
The final pathologic results were obtained by ALND in 174 patients and SLNB in 385 patients. SLNB was performed in the standard fashion with a combination of radioisotope and blue dye. The average number of lymph nodes examined for SLNB was 3 (range, 1–18 nodes) and for ALND, 20 (range, 8–49 nodes). Lymph nodes underwent serial sectioning with a slice thickness of 2–3 mm at pathologic examination and H and E staining. Immunohistochemical stains were used as indicated by the pathologist.

Retrospective Review

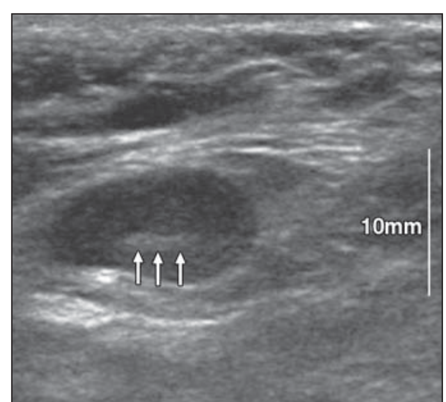
One radiologist retrospectively reviewed the ultrasound reports and ultrasound images to determine whether the ultrasound studies reported a suspicious lymph node or nodes and categorized the lymph nodes as normal or as suspicious with a grade of suspicion of high, medium, or low. The criteria for these categories are modified versions of criteria from a prior study [25] as follows: Lymph nodes of high suspicion have a complete absence or near complete absence of fatty hilum (Fig. 1); lymph nodes of intermediate suspicion have a cortical thickness greater than the width of the fatty hilum, a cortical thickness of more than 4 mm, a cortical thickness of between 3 and 4 mm with nonhilar blood flow, or asymmetric cortical thickening of more than 3 mm (Fig. 2); and lymph nodes of low suspicion have a 3- to 4-mm uniform cortical thickening (Fig. 3). The short axis of the cortex and that of the fatty hilum are used to measure the thickness to determine the abnormality (Fig. 4). The same radiologist also reviewed the pathologic reports to correlate the imaging results with the final histologic results, including the number of metastatically involved lymph nodes and the size of the largest metastatic deposit.

Statistical Analyses

The positive predictive value (PPV) of ultrasound findings of lymph nodes in terms of grade of suspicion for detecting pN2 and pN3 disease was obtained. The Fisher exact test was used to compare the number of patients with positive or negative ultrasound findings among the patients who had



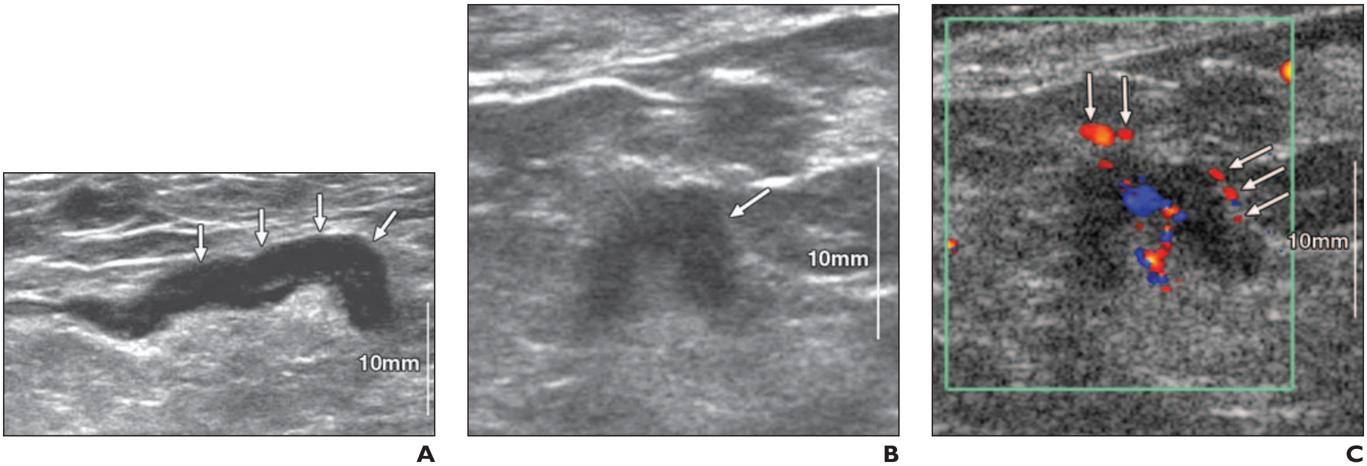
A



B

Fig. 1—Ultrasound images of metastatic axillary lymph node in patients with infiltrating ductal carcinoma.
A, Metastatic axillary lymph node in 49-year-old woman with IDC shows complete absence of fatty hilum. Long- and short-axis measurements are 28 and 12 mm, respectively.
B, Metastatic axillary lymph node in 67-year-old woman with IDC shows near complete absence of fatty hilum (*arrows*). Long- and short-axis measurements are 14 and 8 mm, respectively.

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved



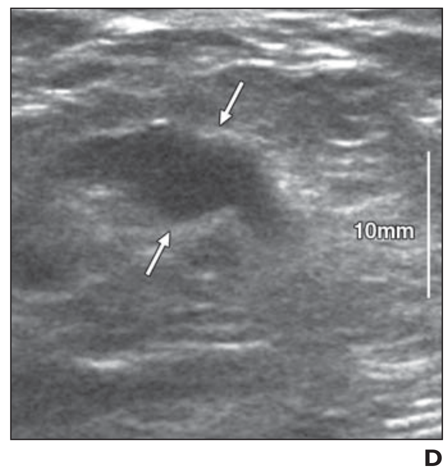


Fig. 2—Ultrasound of metastatic axillary lymph node in patients with invasive carcinoma.
A, Metastatic axillary lymph node in 65-year-old woman with infiltrating ductal carcinoma (IDC) shows uniformly thickened cortex (*arrows*) (cortical thickness = 4.6 mm).
B and **C,** Metastatic axillary lymph node (*arrow*, **B**) in 67-year-old woman with invasive lobular carcinoma shows mildly thickened cortex (cortical thickness = 3.2 mm) with nonhilar cortical blood flow (*arrows*, **C**).
D, Metastatic axillary lymph node in 68-year-old woman with IDC shows asymmetric cortical thickening (*arrows*) (maximum cortical thickness = 6.2 mm).

pN2 and pN3 disease and to compare the number of patients with primary cancer up to 10 mm and the number of patients with primary cancer larger than 10 mm among those who had pN2 and pN3 disease. Of the patients whose pathologic data about the size of metastatic deposits were available, the number of patients whose largest metastatic deposit was up to 5 mm was compared with the number of patients whose largest metastatic deposit of was larger than 5 mm. A subset analysis of ultrasound PPV was performed for tumor size of more than 10 mm. A $p < 0.05$ was considered to indicate a significant statistical difference. Statistical calculations were performed using SPSS software (version 11.01 J, LEAD Technologies).

Results

Ultrasound detected at least one suspicious lymph node in 181 patients, including 112 (62%) patients with true-positive findings and 69 (38%) with false-positive findings. For the 112 patients with true-positive findings, positive pathologic results for metastatic lymph nodes were confirmed with ALND in all cases except three patients who underwent SLNB. For the 69 patients with false-positive ultrasound examinations, negative pathologic results for metastatic lymph nodes were confirmed with SLNB in all patients except one who underwent ALND.

Of the 378 patients with negative ultrasound studies, pathologic results indicated that 87 (23%) patients had a metastatic lymph node or nodes and 291 (77%) did not. Among the 291 patients with true-negative findings, results were confirmed with SLNB in all patients except two who underwent ALND. Of the 87 patients with false-negative ultrasound findings with metastatic lymph nodes pathologically, 62 patients underwent ALND and 25 had only SLNB.

Table 1 summarizes the relationship between the pN stage and positive or negative ultrasound study. Among them, 50 of 181 (28%) patients with a positive ultrasound study had pN2 or pN3 disease and 10 of 378 (3%) patients with a negative ultrasound study had pN2 or pN3 disease. This difference was statistically significant ($p < 0.01$). Overall the negative predictive value (NPV) of ultrasound in excluding pN2 or pN3 disease was 97% (368/378). Subset analysis based on the type of primary tumor was performed and there was no statistical difference between NPV for patients with ILC versus IDC. Specifically, the NPV for excluding pN2 and pN3 disease in patients with ILC was 96% (25/26) and the NPV for excluding pN2 and pN3 disease in patients with IDC was 97% (341/350).

Table 2 summarizes the relationship between the size of the primary cancer and the pN stage. There were only two patients with pN2 or pN3 disease among 122 patients

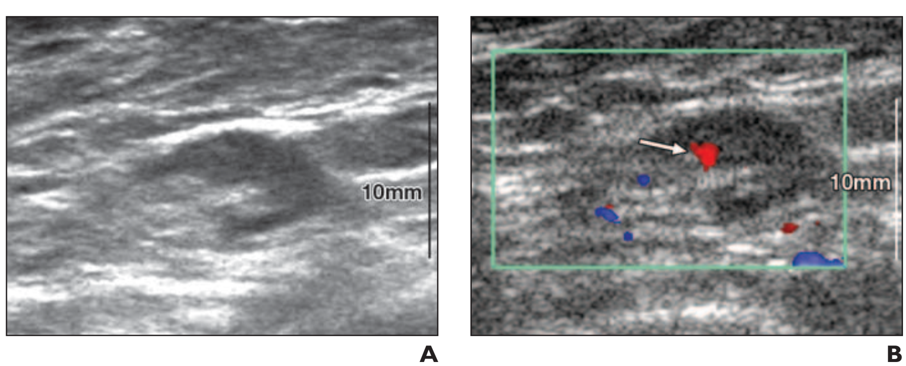


Fig. 3—Ultrasound images of 72-year-old woman with infiltrating ductal carcinoma.
A and **B,** Metastatic axillary lymph node shows mildly thickened cortex (cortical thickness = 3.0 mm) with normal hilar blood flow (*arrow*, **B**).

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

whose primary cancers were up to 10 mm, and there were 58 patients with pN2 or pN3 disease among 437 patients whose primary cancers were larger than 10 mm. There is a statistically significant difference between those two groups ($p < 0.001$).

Table 3 shows the relationship between the largest nodal metastatic deposit and a positive or negative ultrasound study. Seventeen patients were excluded because the pathologic size of metastatic deposits could not be obtained from the records. As a result, 182 patients were included in this analysis. The sensitivity of ultrasound for detecting a lymph node with a metastatic deposit of larger than 5 mm was shown to be significantly higher than the sensitivity for the detection of a lesion that was 5 mm or smaller ($p < 0.001$). Ultrasound failed to detect positive lymph nodes in 26 patients with metastatic deposits larger than 5 mm including 11 patients with metastatic deposits larger than 10 mm. The primary cancer of all but one of those 26 patients was IDC. Among the 70 lymph nodes with a metastatic deposit of 5 mm or smaller, a micrometastasis was identified in 32 lymph nodes.

The relationships between pN stage and ultrasound findings of lymph nodes in terms of grade of suspicion among patients with positive ultrasound findings are summarized in Table 4, which shows the number of lymph nodes of high suspicion detected by ultrasound in relation to the pN stage on final pathology. Among 181 patients with positive ultrasound findings, ultrasound detected at least one lymph node of high suspicion in the ipsilateral axilla in 71 patients. Among them, 27 of 33 patients who had two or more lymph nodes of high suspicion were proven to have pN2 or pN3 disease (PPV, 82%), and 10 of 11 patients who had three or more lymph nodes of high suspicion were proven to have pN2 or pN3 disease (PPV, 91%). Table 4 shows the number of lymph nodes of any combination of high suspicion and intermediate suspicion detected by ultrasound in relation to the pN stage on final pathology. Among them, 18 of 22 patients who had three or more such lymph nodes were proven to have pN2 or pN3 disease (PPV, 82%).

Table 5 shows the number of suspicious lymph nodes in patients with primary cancer larger than 10 mm in relation to pN stage. When two or more lymph nodes of high suspicion were detected by ultrasound, 26 of 30 patients were proven to have pN2 or pN3 disease (PPV, 87%) and when three or more lymph nodes of high suspicion were detected, 10 of 11 patients were proven to have pN2 or pN3 disease (PPV, 91%). When three or more lymph nodes of any combination of high suspicion and intermediate suspicion were detected, the PPV for pN2 or pN3 disease was 89% (17/19).

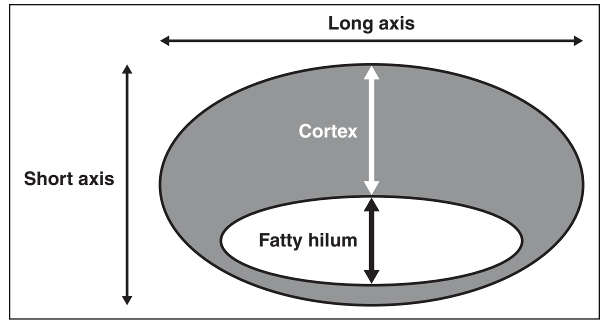


Fig. 4—Drawing shows short axis of cortex (*white arrow*) and short axis of fatty hilum (*black arrow*) which are used to measure thickness to determine abnormality.

Discussion

In the TNM system, breast cancer patients with pN2 or pN3 disease without systemic metastasis are classified as stage III, which is considered to be locally advanced disease. A combination of systemic and locoregional therapies is the preferable treatment option for these patients. Patients with stage III breast cancer treated with local therapy followed by postoperative adjuvant chemotherapy have a better survival rate than those treated with local therapies alone [26, 27]. Dose intensification of primary or postoperative chemotherapy improves the survival of patients with locally advanced breast cancer [28]. The results of two studies suggested that increasing numbers of involved lymph nodes in breast cancer patients were significant for increasing the rate of locore-

TABLE 1: Relationship Between the pN Stage and Ultrasound Findings

Ultrasound Findings	pN0	pN1	pN2	pN3	Total
Positive	69 (68)	62 (3)	32	18	181 (71)
Negative	291 (289)	77 (25)	8	2	378 (314)
Total	360 (357)	139 (28)	40	20	559 (385)

Note—Numbers in parentheses are for sentinel lymph node biopsy only.

TABLE 2: Relationship Between the Size of the Primary Cancer and pN Stage

Size of Cancer (mm)	pN0	pN1	pN2	pN3
0–5	32	4	0	0
> 5–10	68	16	1	1
> 10–20	147	51	12	3
> 20–50	98	46	13	12
> 50	15	22	14	4
Total	360	139	40	20

TABLE 3: Relationship Between the Largest Metastatic Deposit Within the Lymph Node and Ultrasound Findings

Largest Metastatic Deposit (mm)	Ultrasound Findings		Total	Sensitivity (%)
	Positive	Negative		
< 2	5	27 (14)	32 (14)	16
2–5	10 (1)	28 (8)	38 (9)	26
> 5–10	32	15	47	68
> 10	54 (1)	11 (1)	65 (2)	83
Total	101 (2)	81 (23)	182 (25)	

Note—Numbers in parentheses are numbers of lymph nodes that underwent sentinel lymph node biopsy only.

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

gional failure [29, 30]. Because radiotherapy is used to reduce the rate of locoregional failure, knowing the number of involved axillary lymph nodes is an important factor in deciding whether radiotherapy is needed.

Currently, the definitive staging procedure for axillary lymph node is surgical, either ALND or SLNB. However, because significant complications are often associated with ALND, SLNB has become more popular as a less invasive staging procedure especially with the evidence that ALND alone does not improve survival [6, 11, 31]. SLNB is based on the premise that sentinel lymph nodes are the first nodes to receive the lymph flow from the tumor; thus, these lymph nodes must be the first nodes to have metastatic deposits. Therefore, if sentinel lymph nodes are proven to be negative, the other remaining lymph nodes will also be negative. In addition, traditionally, if sentinel lymph nodes are positive, ALND is necessary to obtain an accurate axillary stage [32].

TABLE 4: Number of Lymph Nodes of High Suspicion and of Any Combination of High and Intermediate Suspicion in Relation to pN Stage

No. of Lymph Nodes	pN0	pN1	pN2	pN3	Total
High suspicion					
0	64 (63)	32 (3)	8	6	110 (66)
1	3 (3)	26	7	2	38 (3)
2	2 (2)	3	11	6	22 (2)
3	0	1	6	3	10
4	0	0	0	1	1
Total	69 (68)	62 (3)	32	18	181 (71)
Any combination of high and intermediate suspicion					
0	33 (32)	5 (2)	1	2	41 (34)
1	27 (27)	40 (1)	8	3	78 (28)
2	8 (8)	14	12	6	40 (8)
3	1 (1)	3	11	3	18 (1)
4	0	0	0	4	4
Total	69 (68)	62 (3)	32	18	181 (71)

Note—Numbers in parentheses are numbers of lymph nodes that underwent sentinel lymph node biopsy only.

TABLE 5: Number of Lymph Nodes of High Suspicion and of Any Combination of High and Intermediate Suspicion in Relation to pN Stage in Patients With Primary Cancer Larger Than 10 mm

No. of Lymph Nodes	pN0	pN1	pN2	pN3	Total
High suspicion					
0	50 (49)	26 (3)	8	6	90 (52)
1	2 (2)	23	6	2	33 (2)
2	1 (1)	2	11	5	19 (1)
3	0	1	6	3	10
4	0	0	0	1	1
Total	53 (52)	52 (3)	31	17	153 (55)
Any combination of high and intermediate suspicion					
0	26 (25)	4 (2)	1	2	33 (27)
1	21 (21)	38 (1)	7	3	69 (22)
2	5 (5)	9	12	6	32 (5)
3	1 (1)	1	11	2	15 (1)
4	0	0	0	4	4
Total	53 (52)	52 (3)	31	17	153 (55)

Note—Numbers in parentheses are for sentinel lymph node biopsy only.

Although SLNB is proven to be accurate in predicting axillary lymph node status, a false-negative rate of up to 15% has been reported in which patients with negative SLNB results had other affected lymph nodes in the same region [11]. These false-negative cases occur because the SLNB assessment is based solely on the few surgically removed lymph nodes, not on the remaining nonsentinel lymph nodes. SLNB may also be unreliable in patients who had preoperative chemotherapy; investigators have reported that 33% of these patients have an increased risk of false-negative results [33]. It is especially concerning that positive lymph nodes might be missed given the current trend toward the use of preoperative chemotherapy to increase the chances of performing breast-conservation therapy.

Recently, the results of the Z0011 Trial of the American College of Surgeons Oncology Group have been published [13]. The results of that study showed that among patients with up to two metastatic lymph nodes, there was no survival benefit or reduction in the local recurrence rate in patients who underwent ALND compared with the patients who had SLNB alone [13]. These results could change the current clinical pathway of lymph node staging in which a positive SLNB must be followed by ALND. However, the risk for underestimation of nodal staging becomes even higher if ALND is not performed after positive SLNB.

To minimize the risk of underestimation of axillary disease by SLNB, the data regarding the role of preoperative imaging should be considered. Among the various imaging modalities, ultrasound is useful for detecting metastatic axillary lymph nodes, especially when combined with ultrasound-guided fine-needle aspiration (FNA) or core needle biopsy [21, 25]. Reported sensitivity and specificity in detecting metastatic axillary lymph nodes with ultrasound alone has ranged from 49% to 87% and from 56% to 97%, respectively, whereas the sensitivity and specificity with the combination of ultrasound and ultrasound-guided FNA and core needle biopsy ranged from 31% to 63% and from 95% to 100%, respectively [24]. Investigators have reported that preoperative axillary ultrasound accurately excluded pN2 and pN3 axillary disease for 96% of patients with IDC [4]. Here, we show similar results: There were only 10 of 378 patients with

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

pN2 or higher disease on final pathology when ultrasound findings were normal. Thus, a negative ultrasound study of the ipsilateral axilla suggests that the patient will have a pathologic N1 stage at worst and that therefore SLNB is likely to be sufficient staging. In this study, there was no significant difference in NPV for excluding pN2 and pN3 disease between patients with IDC and those with ILC. Previously, Neal et al. [4] reported that the false-negative rate for excluding N2 and N3 disease in patients with ILC was significantly higher than that for patients with IDC. Thus, they argued against the use of axillary ultrasound for this purpose [4]. Most likely the differences between this work and the Neal study on this issue are because of the small sample sizes. In our study, among the 30 patients with ILC, only two patients had pN2 or higher disease. In the Neal study, eight of 47 patients with ILC had pN2 or higher disease. Because the numbers of patients with pN2 or pN3 and ILC are small in both of these studies, further research with a larger number of these patients may be needed to clarify this issue.

In our study, when there are at least two lymph nodes of high suspicion in the ipsilateral axilla, pN2 or higher disease is highly likely (PPV, 82%) and is even more likely when the tumor is larger than 10 mm (PPV, 87%). This information could help avoid underestimation of axillary disease when SLNB is being considered. Because of the nature of SLNB, the number of positive lymph nodes proven pathologically can never be more than the number of lymph nodes removed at SLNB. Therefore, if two lymph nodes are obtained at SLNB, the number of positive lymph nodes is at most two, which falls into the criterion of the Z0011 Trial not to perform ALND. However, if surgeons know that a preoperative ultrasound suggests pN2 or higher disease, they can perform a careful evaluation of the axilla at SLNB and obtain not only sentinel lymph nodes but also nonsentinel lymph nodes to avoid underestimation.

Although there are no universally accepted criteria in ultrasound features for metastatic lymph node, the presence of cortical thickening is the principal feature in assessing lymph nodes. An absent or near absent fatty hilum is widely considered as a strong indicator for metastasis. Published studies have reported its PPV as 86–90% [19, 25]. Because the sign is easily perceived, there is likely low interobserver variability in interpretation.

A continued role for preoperative axillary lymph node biopsy is also suggested by this study. The utility and technique for ultrasound-guided axillary lymph node biopsy has been documented elsewhere [18, 21, 24, 25, 34, 35]. Exclusion criteria for the Z0011 Trial were clinically positive axillary examination, three or more positive sentinel nodes, and T3 tumors. Therefore, when ultrasound suggests pN2 or higher disease or when abnormal nodes are seen in the context of large tumors, axillary biopsy should still be considered. Clinically node positive patients can also continue to have ultrasound-guided core biopsy when clinicians prefer.

A limitation of our study was that we reviewed ultrasound images retrospectively. Ultrasound is a real-time study and an operator evaluates the lesion fully at the time of the scanning. However, captured images are "snapshots" and usually only a few images are acquired for each lesion. Therefore, it is sometimes difficult to evaluate the lesions retrospectively with the limited number of images retained. In addition, ultrasound study is well known to be operator dependent. The ultrasound images obtained for each case are the results of an operator's subjective assessment at the time of the diagnostic study. Therefore, the obtained images are somewhat biased by the operator's impression. Although the radiologists in this study are all experienced, interoperator variability is inevitable. With 3D ultrasound images, more accurate evaluation could have been performed. Another limitation concerns the final pathologic diagnosis, which was obtained with SLNB in more than half of the patients (69%, 385/559). As discussed earlier, SLNB is not a perfect procedure to assess axillary disease. In fact, we did not mark or localize the sonographically suspicious lymph nodes for removal at SLNB. Therefore, whether the sonographically suspicious lymph nodes were actually sampled during SLNB is not known and our results might reflect inaccuracies caused by false-negatives in those patients whose final diagnosis was made by SLNB, not ALND. Additionally, the exclusion of 51 patients who underwent neoadjuvant chemotherapy could have affected the overall results. However, it is likely that if pretherapy ultrasound studies of these patients had been included in this analysis, the PPV of ultrasound would have been, if anything, strengthened.

In this study, a relatively large number of lymph nodes exhibited micrometastasis at final histology. Current ultrasound systems are not expected to provide visualization of metastatic deposits of this size (< 2 mm). On the other hand, ultrasound failed to detect some lymph nodes with relatively large metastatic deposits. Specifically, ultrasound missed 11 patients who had metastatic deposits larger than 10 mm. There are two possible reasons for these misses. First, the inherent operator dependence with ultrasound could add errors that might have been avoided by either scanning a larger FOV or by performing a more careful examination. Second, the limited range of visualization afforded by ultrasound scanning makes detection of deep lymph nodes or nodes located behind the pectoral muscles very difficult even with meticulous scanning. More advanced technology, such as elastography or microbubble contrast enhancement, might improve the sensitivity for characterization of metastatic lymph nodes [36–38]. Furthermore, a sentinel lymph node can be detected with contrast-enhanced ultrasound with intradermal injection of microbubbles [39]. This technique could bridge the gap between axillary ultrasound and SLNB and might impact the current process of lymph node staging.

In conclusion, we found that ultrasound was useful in predicting pN2 or higher disease in the unilateral axilla in breast cancer patients. When there are at least two lymph nodes of high suspicion or a total of three lymph nodes of high and intermediate suspicion, it is likely that the patient will have pN2 or higher disease (PPV, 82%). Preoperative ultrasound assessment in staging of axillary lymph nodes of patients with newly diagnosed breast cancer might help avoid underestimation of nodal involvement based on SLNB.

References

1. Fisher B, Bauer M, Wickerham D, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: an NSABP update. *Cancer* 1983; 52:1551–1557
2. Banerjee M, George J, Song EY, Roy A, Hryniuk W. Tree-based model for breast cancer prognostication. *J Clin Oncol* 2004; 22:2567–2575
3. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors on early-stage breast cancer. *Oncologist* 2004; 9:606–616
4. Neal CH, Daly CP, Nees AV, et al. Can preoperative axillary US help exclude N2 and N3 metastatic breast cancer? *Radiology* 2010; 257:335–341
5. Veronesi U, Paganelli G, Viale G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. *J Natl Cancer Inst* 1999; 91:368–373
6. Swenson K, Nissen MJ, Ceronsky C, Swenson L, Lee MW, Tuttle TM. Comparison of side effects

Downloaded from www.ajronline.org by 143.167.102.119 on 04/24/18 from IP address 143.167.102.119. Copyright ARRS. For personal use only; all rights reserved

between sentinel lymph node and axillary lymph node dissection for breast cancer. *Ann Surg Oncol* 2002; 9:745–753

7. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; 98:599–609
8. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; 349:546–553
9. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985; 312:674–681
10. Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer. *N Engl J Med* 1992; 327:390–398
11. Fraile M, Rull M, Julian FJ, et al. Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: an approach to its validity. *Ann Oncol* 2000; 11:701–705
12. McMasters KM, Giuliano AE, Ross MI, et al. Sentinel-lymph-node biopsy for breast cancer: not yet the standard of care. *N Engl J Med* 1998; 339:990–995
13. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; 305:569–575
14. Hulvat MC, Hansen NM, Jeruss JS. Multidisciplinary care for patients with breast cancer. *Surg Clin North Am* 2009; 89:133–176, ix
15. Vaidya JS, Vyas JJ, Thakur MH, et al. Role of ultrasonography to detect axillary node involvement in operable breast cancer. *Eur J Surg Oncol* 1996; 22:140–143
16. Deurloo EE, Tanis PJ, Gilhuijs KGA, et al. Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer. *Eur J Cancer* 2003; 39:1068–1073
17. Podkrajsek M, Music MM, Kadivec M, et al. Role of ultrasound in the preoperative staging of patients with breast cancer. *Eur Radiol* 2005; 15:1044–1050
18. Swinson C, Ravichandran D, Nayagam M, et al. Ultrasound and fine needle aspiration cytology of the axilla in the pre-operative identification of axillary nodal involvement in breast cancer. *Eur J Surg Oncol* 2009; 35:1152–1157
19. Cho N, Moon WK, Han W, Park IA, Cho J, Noh DY. Preoperative sonographic classification of axillary lymph nodes in patients with breast cancer: node-to-node correlation with surgical histology and sentinel node biopsy results. *AJR* 2009; 193:1731–1737
20. Britton P, Moyle P, Benson JR, et al. Ultrasound of the axilla: where to look for the sentinel lymph node. *Clin Radiol* 2010; 65:373–376
21. Baruah BP, Goyal A, Young P, et al. Axillary node staging by ultrasonography and fine-needle aspiration cytology in patients with breast cancer. *Br J Surg* 2010; 97:680–683
22. Yang WT, Chang J, Metreweli C. Patients with breast cancer: differences in color Doppler flow and gray-scale US features of benign and malignant lymph nodes. *Radiology* 2000; 215:568–573
23. Rajesh YS, Ellenbogen S, Banerjee B. Preoperative axillary ultrasound scan: its accuracy in assessing the axillary nodal status in carcinoma breast. *Breast* 2002; 11:49–52
24. Alvarez S, Añorbe E, Alcorta P, López F, Alonso I, Cortés J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *AJR* 2006; 186:1342–1348
25. Abe H, Schmidt RA, Kulkarni K, Sennett CA, Mueller JS, Newstead GM. Axillary lymph nodes suspicious for breast cancer metastasis: sampling with US-guided 14-gauge core-needle biopsy—clinical experience in 100 patients. *Radiology* 2009; 250:41–49
26. Jaiyesimi IA, Buzdar AU, Hortobagyi GN. Inflammatory breast cancer: a review. *J Clin Oncol* 1992; 10:1014–1024
27. Horfobagyi GN. Multidisciplinary management of advanced primary and metastatic breast cancer. *Cancer* 2009; 74(suppl 1):416–423
28. Antman KH. Dose-intensive therapy in breast cancer. In: Armitage JO, Antman KH, eds. *High-dose cancer therapy*. Baltimore, MD: Williams & Wilkins, 1992:701–718
29. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999; 17:1689–1700
30. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997; 337:949–955
31. Fisher B, Jong-Hyeon J, Anderson S, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002; 347:567–575
32. Edge SB, Niland JC, Bookman MA, et al. Emergence of sentinel node biopsy in breast cancer as standard-of-care in academic comprehensive cancer centers. *J Natl Cancer Inst* 2003; 95:1514–1521
33. Nason KS, Anderson BO, Byrd DR, et al. Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. *Cancer* 2000; 89:2187–2194
34. Abe H, Schmidt RA, Sennett CA, Shimauchi A, Newstead GM. US-guided core needle biopsy of axillary lymph nodes in patients with breast cancer: why and how to do it. *RadioGraphics* 2007; 27(suppl 1):S91–S99
35. Koelliker SL, Chung MA, Mainiero MB, Steinhoff MM, Cady B. Axillary lymph nodes: US-guided fine-needle aspiration for initial staging of breast cancer—correlation with primary tumor size. *Radiology* 2008; 246:81–89
36. Taylor K, O'Keeffe S, Britton PD, et al. Ultrasound elastography as an adjuvant to conventional ultrasound in the preoperative assessment of axillary lymph nodes in suspected breast cancer: a pilot study. *Clin Radiol* 2011; 66:1064–1071
37. Choi JJ, Kang BJ, Kim SH, et al. Role of sonographic elastography in the differential diagnosis of axillary lymph nodes in breast cancer. *J Ultrasound Med* 2011; 30:429–436
38. Rubaltelli L, Corradin S, Dorigo A, et al. Automated quantitative evaluation of lymph node perfusion on contrast-enhanced sonography. *AJR* 2007; 188:977–983
39. Sever AR, Mills P, Jones SE, Mali W, Jones PA. Sentinel node identification using microbubbles and contrast-enhanced ultrasonography. *Clin Radiol* 2012; 67:687–694