

Role of Ultrasound-Guided Fine-Needle Aspiration of Indeterminate and Suspicious Axillary Lymph Nodes in the Initial Staging of Breast Carcinoma

Savitri Krishnamurthy, M.D.¹

Nour Sneige, M.D.¹

Deepak G. Bedi, M.D.²

Beth S. Edieken, M.D.²

Bruno D. Fornage, M.D.²

Henry M. Kuerer, M.D., Ph.D.³

S. Eva Singletary, M.D.³

Kelly K. Hunt, M.D.³

¹ Department of Pathology, M. D. Anderson Cancer Center, Houston, Texas.

² Department of Radiology, M. D. Anderson Cancer Center, Houston, Texas.

³ Department of Surgical Oncology, M. D. Anderson Cancer Center, Houston, Texas.

Address for reprints: Savitri Krishnamurthy, M.D., Department of Pathology, The University of Texas M. D. Anderson Cancer Center, P.O. Box 53, 1515 Holcombe Blvd., Houston, TX 77030; Fax: (713) 794-5664; E-mail: skrishna@mdanderson.org

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BACKGROUND. Ultrasound (US) is more sensitive than physical examination alone in determining axillary lymph node involvement during preliminary staging of breast carcinoma. Due to occasional overlap of sonographic features of benign and indeterminate lymph nodes, fine-needle aspiration (FNA) of sonographically indeterminate/suspicious lymph nodes can provide a more definitive diagnosis than US alone. This study was undertaken to determine the diagnostic accuracy of US-guided FNA of indeterminate/suspicious/metastatic-appearing axillary lymph nodes during the initial staging of breast carcinoma.

METHODS. The cytology of 103 cases of US-guided FNA of nonpalpable indeterminate/suspicious/metastatic-appearing lymph nodes was compared with the final histopathologic status of the entire axilla after axillary dissection. The final axillary lymph node status was categorized as either negative when all lymph nodes were negative for metastasis or positive when there was evidence of metastasis in one or more lymph nodes. The sensitivity, specificity, diagnostic accuracy, and false-negative rate of US-guided FNA of nonpalpable axillary lymph nodes in the preliminary staging process were calculated.

RESULTS. In 51 of 103 cases (49.5%), the US-guided FNA and histopathology were both positive for metastasis. In 24 of 103 cases (23.3%), both were negative. The apparent false-positive FNA in 16 (15.5%) cases was explained by the complete response of the metastatic lymph nodes to neoadjuvant chemotherapy in the interval between FNA and axillary dissection. In 12 cases (11.6%), US-guided FNA was negative, but metastasis was seen in histologic sections. All cases with three or more lymph nodes with metastatic disease and 93% of those with metastatic deposit measuring more than 0.5 mm were detected by US-guided FNA. The probability of detecting lymph nodes with smaller metastatic deposit measuring less than 0.5 cm was 44%. The overall sensitivity of US-guided FNA was 86.4%, the specificity was 100%, the diagnostic accuracy was 79.0%, the positive predictive value was 100%, and the negative predictive value was 67%.

CONCLUSIONS. US-guided FNA of nonpalpable indeterminate and suspicious axillary lymph nodes is a simple, minimally invasive, and reliable technique for the initial determination of axillary lymph node status in breast carcinoma. The common causes of discrepancy between the initial and final axillary lymph node status include failure to visualize all lymph nodes during US examination, small-sized metastases, and preoperative neoadjuvant chemotherapy. *Cancer* 2002;95:982-8.

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In the preliminary staging of newly diagnosed cases of breast carcinoma, based on the extent of the primary tumor and the presence or absence of lymph node involvement, various combinations of

surgery, radiotherapy, and chemotherapy are used to tailor the treatment. The routine staging process includes a thorough history and physical examination, ultrasound (US) of the breast and lymph node basins (axillary, internal mammary, infraclavicular, and supraclavicular), computed tomography (CT) scan of the abdomen, bone scan, and a chest X-ray. In the absence of distant metastatic disease, assessment of the status of the axillary lymph nodes is the most important component of the initial staging process because of their impact on subsequent management. In addition, the presence or absence of axillary metastases is the strongest prognostic indicator available for breast carcinoma. Physical examination alone is neither a sensitive nor reliable way to ascertain lymph node status, because metastatic lymph nodes are often not palpable and reactive lymph nodes may be mistaken for metastases.¹⁻³

Several imaging techniques are used to visualize the lymph nodes, including US, magnetic resonance imaging, CT scans, and nuclear medicine. US is the most useful of these techniques for the evaluation of local disease in the breast and regional lymph nodes.²⁻⁶ It visualizes not only alterations in the size, shape, and contours of the lymph nodes, but also changes in the cortical morphology and texture that can reflect the presence of underlying metastasis. However, these early signs of metastatic disease sometimes overlap with those of benign reactive changes, resulting in a label of "suspicious" or "indeterminate" for some lymph nodes. Other lymph nodes may be regarded as "metastatic" appearing when sonography shows compression or displacement of hyperchoic fatty hilum and lymph node enlargement. Fine-needle aspiration (FNA) of sonographically suspicious, indeterminate, or metastatic-appearing axillary lymph nodes provides a more definitive diagnosis compared with sonography alone. Our objective was to evaluate the accuracy of US-guided FNA of indeterminate and suspicious axillary lymph nodes in the initial staging of breast carcinoma.

MATERIALS AND METHODS

The cytology of all cases of US-guided FNA of nonpalpable indeterminate and suspicious axillary lymph nodes was compared with the final histopathologic status of the entire axilla after axillary dissection. US-guided FNA was performed at The University of Texas M. D. Anderson Cancer Center in 1999 during the preliminary staging of breast carcinoma. The sonographic criteria for selecting indeterminate, suspicious, or metastatic-appearing nodes were increased thickening and/or lobulation of the hypoechoic lymph node cortex compared with other ipsilateral or con-

tralateral lymph nodes, eccentric lobulation of the hypoechoic lymph node cortex with compression of the adjacent hilar fat, and complete disappearance of the hilar fat, which was replaced by hypoechoic cortex. In all cases, FNA was performed by a radiologist (D.G.B., B.S.E., and B.D.F.) under US guidance, using a 20-gauge or 21-gauge needle attached to a 10-mL or 20-mL plastic syringe. One percent xylocaine was used for local anesthesia. Under real-time visualization, the needle was directed into the cortical tissue of the lymph node. The tip of the needle was documented on a hard copy image as being within the target and one or two passes were made. Direct smears from the aspirate were fixed in alcohol and air-dried for Pap and Diff-Quik (American Scientific Products, McGraw Park, IL) staining. All of the slides were screened immediately for specimen adequacy by the cytopathologist and FNA repeated if necessary; all cases negative for metastasis in the preliminary screening were then screened thoroughly by the cytotechnologist and cytopathologist. The axillary lymph node status as determined using US-guided FNA in the preliminary staging process was compared with the final status following histopathologic examination of the axillary lymph nodes that were removed in the axillary dissection. For the purpose of analysis, the final axillary lymph node status was categorized as either negative when all of the histopathologically examined lymph nodes were negative for metastasis or positive when there was evidence of metastasis in one or more lymph nodes. Because the most abnormal-appearing lymph node was evaluated by FNA, its cytology represented the status of the entire axilla during preliminary staging and was compared with the histopathologic status of the whole axilla upon surgical dissection. The number of dissected axillary lymph nodes having metastasis and the size of each metastasis were noted. The discrepant cases were analyzed with respect to the tumor type, treatment with/without preoperative neoadjuvant chemotherapy, and the interval between US-guided FNA and subsequent surgery. Finally, the sensitivity, specificity, diagnostic accuracy, and false-negative rate of US-guided FNA of nonpalpable axillary lymph nodes in the preliminary staging process were calculated.

RESULTS

One hundred three (103) cases were identified in the cytopathology files of M. D. Anderson Cancer Center as having undergone US-guided FNA of one or more nonpalpable, sonographically indeterminate or suspicious axillary lymph nodes followed by complete axillary dissection in 1999. Of the primary tumors, 89 were invasive ductal carcinomas, 2 were invasive lob-

TABLE 1
Discrepancy between US-Guided FNA and Axillary Lymph Node Dissection^a

Preliminary axillary lymph node status following US-guided FNA	Final axillary lymph node status following axillary dissection		
	Positive (%)	Negative (%)	Total
Positive	51 (49.5)	16 (15.5) ^b	67 (65)
Negative	12 (11.6)	24 (23.3)	36 (34.9)
Total	63	40	103

US: ultrasound; FNA: fine-needle aspiration.

^a Sensitivity, 86.4%; specificity, 100%; diagnostic accuracy, 79%; False-negative rate, 11.6%; Positive predictive value, 100%; Negative predictive value, 67%.

^b All 16 patients received neoadjuvant chemotherapy in the interval between FNA and axillary dissection.

ular carcinomas, and 12 were carcinomas of no specified type. Of the 103 cases, 65 received preoperative neoadjuvant chemotherapy. Table 1 provides details of the comparison between preliminary staging and final status of the axillary lymph nodes.

Of the 67 cases in which metastatic adenocarcinoma was exhibited in the cytologic smears, one or more lymph nodes were identified as histologically positive for metastasis after axillary lymph node dissection in only 51. However, all 16 of 67 cases that appeared at first to be false-positive for metastasis had received preoperative neoadjuvant chemotherapy. Moreover, the tissue sections of one or more of their dissected axillary lymph nodes revealed areas of fibrosis with or without hemosiderin pigment deposition and infiltration by histiocytes, which are features consistent with probable complete response of metastatic disease to neoadjuvant therapy. Figure 1 is an example of one such case where the smears showed metastatic carcinoma but the subsequent axillary dissection was negative. Therefore, these 16 cases were not truly false-positive cases.

All cases with three or more lymph nodes with metastatic disease and 93% of those with metastatic deposit measuring more than 0.5 mm were detected by US-guided FNA. The probability of detecting lymph nodes with smaller metastatic deposit measuring less than 0.5 cm was 44%.

In the 12 discrepant cases diagnosed as being negative by preliminary US-guided FNA, there was histologic evidence of metastasis in one or more of the dissected axillary lymph nodes. The primary tumor in these 12 discrepant false-negative cases was ductal in type. Table 2 shows the details of the size of the metastases and the interval between FNA and axillary dissection in these 12 cytologically false-negative cases. Four of these patients received preoperative

neoadjuvant therapy, underwent axillary dissection 3 to 7 months after the primary diagnosis, and the mean size of the metastasis was 0.9 cm (range, 0.4–2.0 cm). The remaining eight patients did not receive preoperative chemotherapy, axillary dissection was performed 0.2–3.6 months after the primary diagnosis, and the mean size of the metastases was 0.4 cm (range, 0.1–1.6 cm). Figure 2 is an example of a discrepant case where the cytology smears were negative, but axillary dissection showed a single lymph node containing micro-metastasis measuring 0.2 cm in maximum dimension.

The overall sensitivity of US-guided FNA was 86.4%, the specificity was 100%, diagnostic accuracy was 79.0%, positive predictive value was 100%, negative predictive value was 67%, and the false-negative rate was 11.6%. The false-negative rate in the 38 patients who did not receive preoperative chemotherapy was 21.0%.

DISCUSSION

Initial staging of newly diagnosed cases of breast carcinoma is a routine practice for selecting the appropriate protocol for treatment. Determination of the axillary lymph node status in this process plays a particularly important role in guiding the surgeon and oncologist in planning the management of breast carcinoma patients. For patients with locally advanced breast carcinoma with evidence of metastases to the regional lymph nodes or distant spread, neoadjuvant chemotherapy is offered as first-line therapy, which then is followed by surgery.^{7–9} In patients with smaller (T1 and T2) breast carcinomas, when there is no evidence of metastasis to the axillary lymph nodes in the preliminary staging process, segmental mastectomy (lumpectomy) and sentinel lymph node mapping are preferred instead of complete axillary lymph node dissection.^{10–12}

Physical examination alone is very unreliable in assessing axillary lymph node status because metastatic lymph nodes cannot always be distinguished from normal or reactive ones. Specifically, the overall false-negative rate of physical examination alone has been reported to be as high as 32–33%.¹ US examination can improve the sensitivity of clinical examination in assessing axillary lymph node status in this preliminary staging process. There are several sonographic features that are used to categorize a lymph node as benign, suspicious, or metastatic. Some of the sonographic features that favor a benign lymph node include a predominantly hyperechoic lymph node due to fat replacement, the presence of a thin homogeneous symmetrical cortical rim around the hyperechoic hilar fat, and symmetric cortical lobulations similar to contralateral axillary lymph nodes.¹³ When

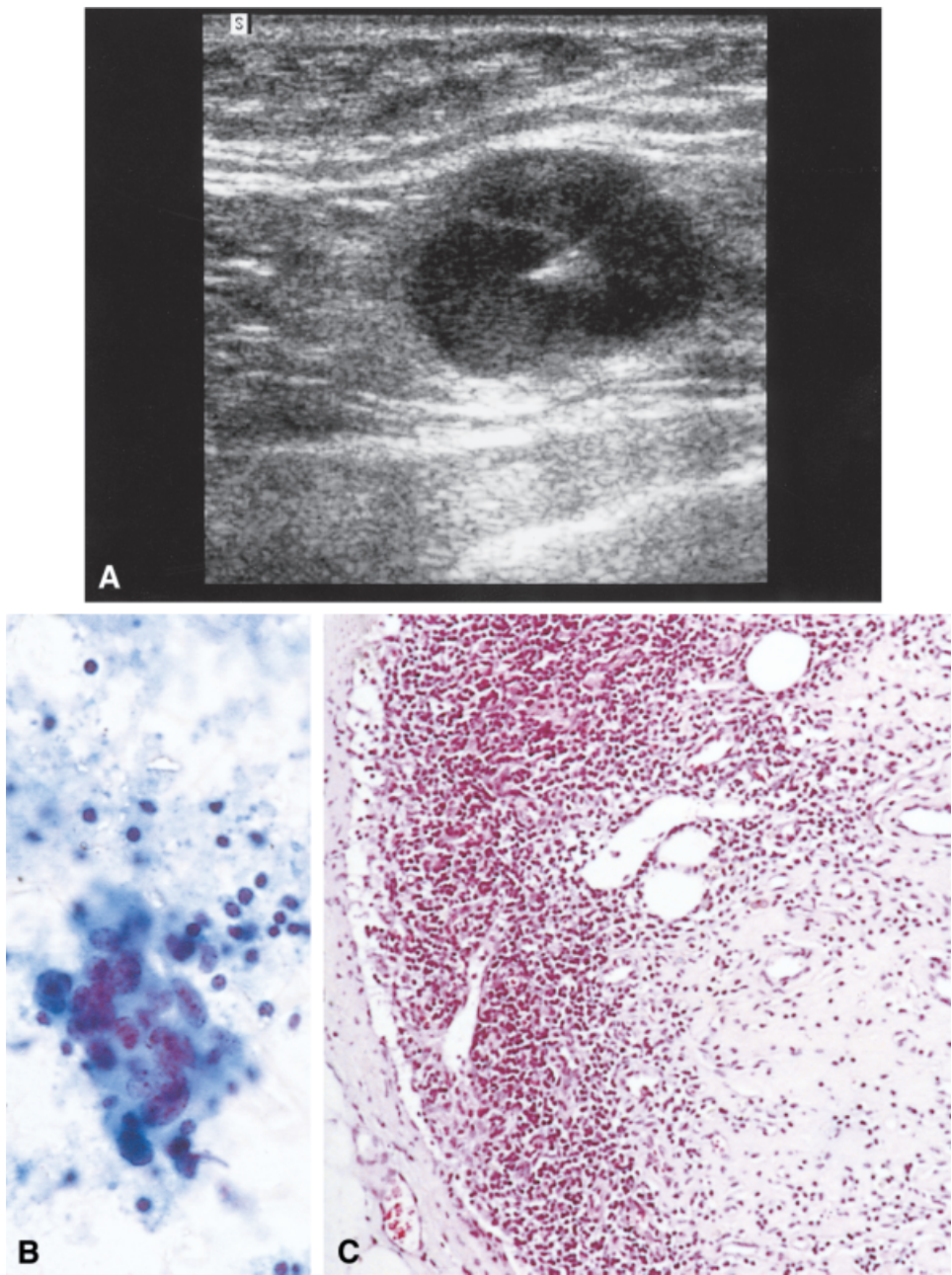


FIGURE 1. (A) Sonographically suspicious lymph node. There is eccentric cortical lobulation although the hyperechoic fatty hilum is still seen. (B) Fine-needle aspiration cytology smear of the same lymph node showing a cluster of malignant cells. (C) Section of a lymph node obtained from axillary dissection several weeks later is negative for metastasis, but shows fibrosis, consistent with complete response to neoadjuvant chemotherapy.

there is thickening or eccentric lobulation of the hypoechoic cortical rim, compression or displacement of the fatty hyperechoic hilum, or complete replacement of the hilar fat by hypoechoic tissue, the lymph node is categorized sonographically as suspicious or metastatic appearing. These criteria have been studied further and refined by in vitro sonography of 170 dissected axillary lymph nodes in breast carcinoma patients, focusing on the cortical morphology and dividing the lymph nodes into various subtypes with a progressive increase in the probability of metastasis.¹⁴

The overall sensitivity and specificity of US alone

TABLE 2
Details of the 12 False-Negative Cases

False-negative cases	Size of metastases (cm)	Duration between FNA and surgery (mos)
No neoadjuvant chemotherapy (<i>n</i> = 8)		
Range	0.1–1.6	0.2–3.6
Mean	0.4	1.6
Neoadjuvant chemotherapy (<i>n</i> = 4)		
Range	0.3–2	3–6.7
Mean	0.9	4.9

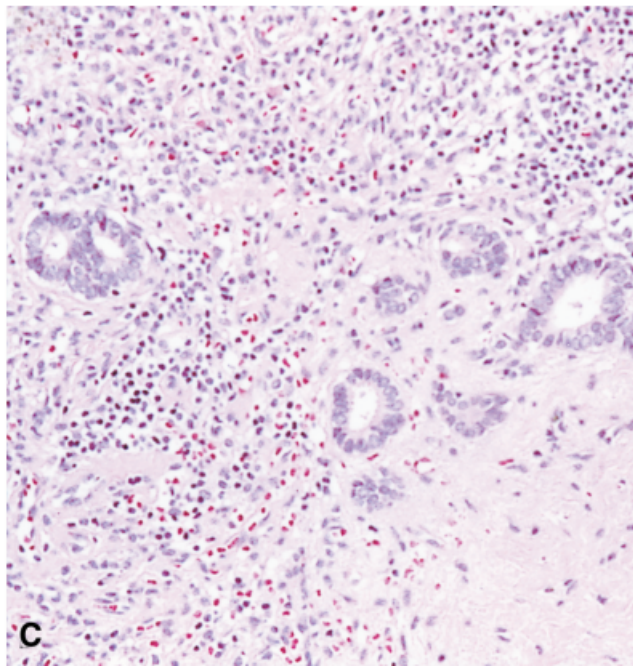
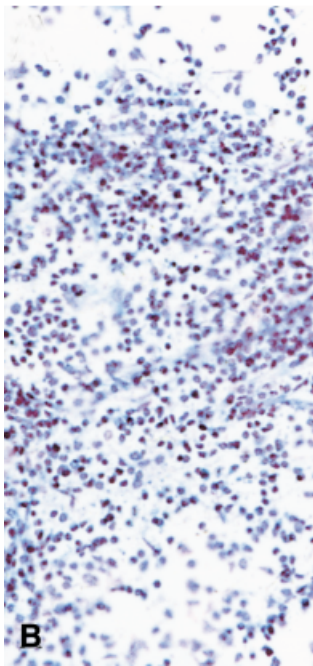
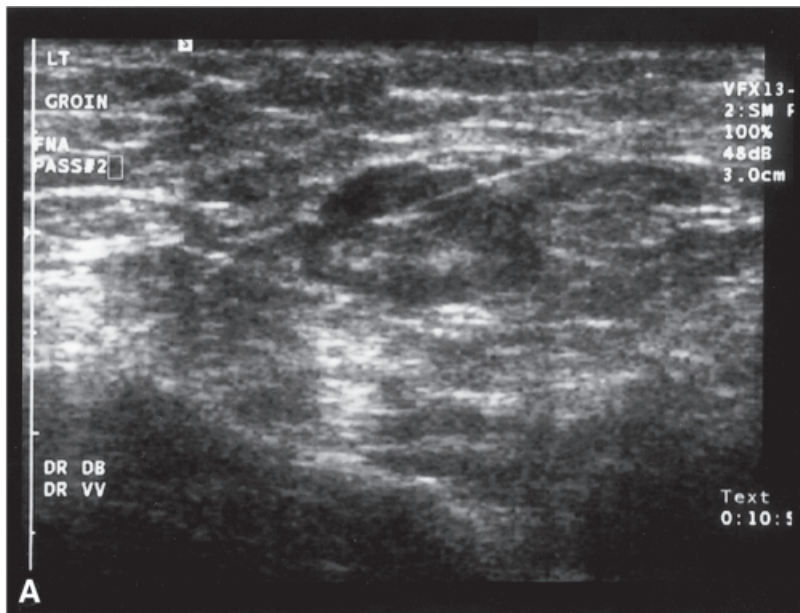


FIGURE 2. (A) Sonographically indeterminate axillary lymph node. The FNA is directed into an area of asymmetrically thickened cortex whereas the hyperechoic hilar fat is still visible. (B) Fine-needle aspiration cytology smear of the same lymph node shows a polymorphous population of lymphoid cells without any evidence of metastatic carcinoma. (C) Tissue section of a lymph node from the axillary dissection of the same case showed a single lymph node containing micrometastasis measuring 0.2 cm in maximum dimension.

in detecting axillary lymph node metastasis range from 42% to 56% and from 70% to 90%, respectively.¹⁵ It is generally well recognized that the rate of detection of suspicious lymph nodes increases significantly as the number of lymph nodes visualized on US examination of the axilla increases. Some authors have described specific sonographic features to be particularly helpful. Bonnema et al.¹⁵ used the echogenic pattern at the center of lymph nodes, thereby classifying lymph nodes having a hyperechoic center as benign and those having a hypoechoic center or inhomogeneous architecture as malignant; they found a

sensitivity of 36% and a specificity of 95%. Kanter et al.¹⁶ also found this criterion to be helpful in detecting malignancy. However, in their study, 30% of the lymph nodes believed to be benign using this criterion proved to be malignant using either cytology or histology. When size greater than 5 mm was used as a criterion for diagnosing metastatic lymph nodes, Bonnema et al.¹⁵ found an increase in sensitivity to 87% but a significant reduction in specificity to 56%. Feu et al.¹⁷ studied 158 excised axillary lymph nodes in 40 patients surgically treated for breast carcinoma in vitro using a 7.5-MHz US probe in a water bath. They

found the absence of hilum to be the most specific sonographic feature for the diagnosis of metastasis. The increase in the long-to-short axis ratio was the finding that caused the most false-negative interpretations, indicating that lymph nodes appearing elongated or ovoid can be metastatic. In addition, they found that signs of malignancy were more accurate when lymph nodes measured 10 mm or more in comparison to those that measured less than 10 mm. Two other studies by Kanter et al.¹⁶ and Verbanck et al.¹⁸ also reported on the utility of US-guided FNA in the preliminary staging of breast carcinoma. The true false-negative rate of US-guided FNA is, however, not apparent from their data. We believe that our criteria based on cortical morphology are a refinement of those described before and are more accurate because cortical changes predate the secondary effects on the central fatty hilum. The true overall sensitivity of US alone was not our objective because we aspirated only indeterminate, suspicious, or metastatic-appearing lymph nodes.

Due to overlapping sonographic features of benign/reactive and suspicious/metastatic lymph nodes, a large number of lymph nodes that would otherwise be categorized as indeterminate for metastasis can be more definitively diagnosed if US is combined with FNA. Using cytomorphology of Diff-Quik and Pap-stained smears of US-guided FNA samples of indeterminate and suspicious lymph nodes alone without using ancillary cytokeratin immunostaining, we found the sensitivity and specificity of this test to be 86.4% and 100%, respectively. This is comparable to the results of Bonnema et al.¹⁵ who performed US-guided FNA of 122 lymph nodes obtained from 81 axilla and found a sensitivity of 80% and a specificity of 100%. The false-negative rate in their study was 12%, which was also similar to the overall false-negative rate for the whole group in our study. However, the false-negative rate for the group of patients who did not receive neoadjuvant chemotherapy in our study was 21%. Seventy-percent of the false-negative cases in the study by Bonnema et al. had only one dissected lymph node involved with metastatic tumor. Therefore, they concluded that a significant cause of discrepancy between US-guided FNA and subsequent axillary dissection was the occurrence of a small number of lymph nodes with metastasis. Our findings agree with those of Bonnema et al. in that the majority of our false-negative cases (67%) also had only one dissected lymph node positive for metastasis. However, all cases with involvement of three or more lymph nodes with metastatic tumors were detected by this test.

None of the studies in the literature reporting the utility of US-guided FNA of nonpalpable axillary

lymph nodes comment on the influence of the size of metastases in false-negative cases. We found that in the majority of our false-negative cases (8 of 12 cases, 66%), the size of the metastases ranged from 0.1 to 0.5 cm. Therefore, US-guided FNA failed to detect only small metastatic deposits in an axillary lymph node. Conversely, we detected 93% of cases with metastasis measuring more than 0.5 mm.

In conclusion, US-guided FNA of nonpalpable indeterminate and suspicious axillary lymph nodes is a simple, minimally invasive and reliable technique for the initial determination of axillary lymph node status in breast carcinoma patients. The positive predictive value of 100% and the negative predictive value of 67% in our study indicate that the predictive power of a positive result is excellent. That of a negative result, although much lower, is still acceptable. The results compare favorably with those of axillary dissection, thereby lending immense credibility to the procedure in the preliminary staging process. FNA of nonpalpable axillary lymph nodes can improve markedly the specificity of both physical examination and US alone in detecting metastatic lymph nodes. When US-guided FNA is positive, the patient need not undergo sentinel lymph node mapping, thereby saving time and expense during surgery. The common causes of discrepancy between the initial and final axillary lymph node staging are the failure to visualize lymph nodes during US examination of the axilla, a small number of lymph nodes positive for metastases, small-sized metastases, and neoadjuvant chemotherapy in the interval between FNA and lymph node dissection.

The high sensitivity and specificity and relatively low false-negative rate of US-guided FNA of nonpalpable axillary lymph nodes indicate that it is a useful procedure in the initial staging of breast carcinoma and can be immensely valuable in planning the appropriate management of patients.

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