Value of Axillary Ultrasound after Negative Axillary MRI for Evaluating Nodal Status in High-Risk Breast Cancer

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BACKGROUND: It is assumed that axillary ultrasound (AxUS) is the best method for axillary nodal evaluation in newly diagnosed breast cancer patients. However, few have evaluated the efficacy of preoperative axillary MRI. We compared the statistical accuracy of AxUS and MRI in detecting nodal metastases among breast cancer patients who were selected for neoadjuvant chemotherapy.

STUDY DESIGN: We retrospectively analyzed 219 breast cancer patients undergoing neoadjuvant chemotherapy from 2007 to 2015, all of whom had AxUS and breast MRI before chemotherapy. Two breast radiologists, blinded to clinical, pathologic, and AxUS findings, re-reviewed all breast MRIs, specifically focusing on axillary nodal characteristics. We correlated clinico-pathologic characteristics, AxUS, and MRI findings, and quantified predictive values of both imaging modalities.

RESULTS: Overall, 101 of 219 (47%) patients had T2 tumors. The most common abnormal nodal finding was size >10 mm. Axillary ultrasound and MRI agreed on nodal status in 192 of 219 patients (87.6%). When correlated with pre-chemotherapy needle biopsy in 129 patients, AxUS and axillary MRI performed similarly (sensitivity of 99.1% vs 97.4% and specificity 15.4% vs 15.4%, respectively). Only 4 of 129 (3.1%) patients had a negative MRI and positive AxUS; 3 of 4 of these patients (75%) had a positive biopsy and 2 of 3 had positive lymph nodes on final pathology, therefore suggesting MRI missed clinically significant disease in only 2 of 129 (1.5%) patients.

CONCLUSIONS: In a high-risk patient population, AxUS and MRI have similar statistical profiles in evaluating axillary nodal status. Routine use of AxUS after a normal axillary MRI is not warranted. (J Am Coll Surg 2019;228:792–797. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Breast cancer is the most commonly diagnosed malignancy in women.[1] The presence of lymph node metastases is the most important factor in predicting long-term survival.[2] Traditionally, axillary lymph node status has been assessed by sentinel lymph node biopsy (SLNB) and axillary lymph node dissection, which are invasive and may result in post-surgical complications. Unfortunately, differentiating between benign and malignant axillary nodes by noninvasive methods is challenging. Physical examination alone is associated with a 30% to 45% false negative rate in detecting axillary lymph node metastases.[3] Therefore, imaging assessment by ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) have been used to enhance the sensitivity of clinical examination in assessing axillary lymph node status.[4-9] The 2 most commonly used imaging modalities in this setting are US and MRI. Ultrasound has been used extensively in the evaluation of axillary lymph node status in breast cancer patients due to its practicality, accessibility,

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Abbreviations and Acronyms
AxUS = axillary ultrasound
LN = lymph node
PPV = positive predictive value
SLNB = sentinel lymph node biopsy
US = ultrasound

dynamic observation, and lack of radiation. However, the sensitivity and specificity of US for nodal metastasis detection are variable, ranging from 45% to 100% and 50% to 89%, respectively.[10-13]

Compared with US, MRI has shown higher sensitivity and specificity in detecting axillary nodal metastases in breast cancer patients ranging from 78% to 96% and 75% to 96%, respectively.[14-16] In addition, MRI offers the benefit of improved evaluation of extent of primary disease in patients with newly diagnosed breast cancer or in detecting mammographically occult multifocal/multicentric disease in the ipsilateral (16% to 20%) and contralateral breasts (4% to 5.5%).[17-20] The pathologic complete response of axillary nodal metastases after neoadjuvant therapy is estimated at 17% to 97%.[17,20-23] Despite this response rate, treatment of axillary lymph nodes remains unsettled, with the standard of care based on nodal status at initial diagnosis regardless of response to neoadjuvant treatment. Robust prospective data demonstrate excellent nodal pathologic complete response rates and improved outcomes in those with nodal and breast pathologic complete response, suggesting that final pathologic staging is the most important prognostic indicator for patients. These axillary interventions are the subjects of ongoing clinical trials (A11202, NRG/NSABP B-51). Therefore, determining the most sensitive, accurate, and efficient imaging algorithm for axillary lymph node staging at diagnosis is critical.

Historically, many proposed sentinel node biopsy before beginning chemotherapy to accurately stage the axilla, but this practice has largely fallen out of favor due to associated comorbidities. Today, most clinicians favor axillary imaging, with or without biopsy, before neoadjuvant therapy for staging and diagnostic purposes, given that imaging is less invasive and highly accurate. Therefore, finding the optimal noninvasive imaging algorithm to evaluate axillary nodal status is important. Multiple studies have investigated the diagnostic accuracy of US or MRI for evaluating the axilla in breast cancer patients.[4-6,8] These have demonstrated variable sensitivity and specificity between the modalities.

Patients with high-risk disease necessitating neoadjuvant chemotherapy are more likely to have lymph node metastases. Patients undergoing neoadjuvant chemotherapy tend to undergo multiple imaging studies for extent of disease, including MRI, but other than axillary US, few routinely assess the axillary status. As a result, we sought to assess the utility of performing axillary US after a negative evaluation of the axilla on MRI, by correlating US and MRI findings with results of lymph node biopsy. We hypothesized that status of the axillary region on pretreatment MRI will be the same as that of an axillary ultrasound. This would suggest that a dedicated targeted axillary ultrasound after diagnosis of breast cancer would be unnecessary in patients undergoing breast MRI.

METHODS

After institutional review board (IRB) approval was obtained, a HIPAA-compliant retrospective analysis was performed of consecutive patients with stage I to III breast cancer, who were selected to undergo neoadjuvant chemotherapy and had both AxUS and MRI within 60 days of diagnosis and before beginning neoadjuvant chemotherapy, from January 2007 to September 2015. Two fellowship-trained breast imaging radiologists reanalyzed the entire breast MRIs, with specific attention to the axillary lymph nodes; radiologists were blinded to clinical, pathologic, and AxUS findings. Patient demographics, intraoperative characteristics, AxUS and MRI interpretations, and pathology data were collected and analyzed.

Axillary US was performed by a dedicated breast ultrasound technologist and a dedicated breast imaging radiologist. Sonographic criteria for a suspicious axillary LN included the following established features: size >10 mm, cortical thickness > 3 mm, abnormal shape, heterogeneous hyperechoic cortex, peripheral revascularization, perinodal fat infiltration, and replaced hilum.

Breast MR images included both sagittal and axial T1 and T2 weighted sequences, which were obtained before and after contrast administration using a Siemens 1.5T magnet. Magnetic resonance imaging criteria for a suspicious axillary LN included established features: size > 10 mm, cortical thickness > 3 mm, irregular edges, abnormal shape, and replaced hilum. Breast imagers performed all nodal biopsies when indicated via ultrasound guidance using either a 14- or 18-G core needle.

Because this was a mixed cohort of patients who were diagnosed at our institution or referred for second opinion evaluation, there was no consistency in the diagnostic process as to whether AxUS or MRI was performed first. Also, practice patterns differed concerning whether AxUS was completed at the time of initial diagnostic breast US (before breast biopsy was performed) or as a

Table 1. Demographics and Staging

Characteristic	Total (n = 219)
Age, y, median (range)	53.0 (23–80)
BMI, kg/m^2, median (range)	27.6 (20–51)
Tumor size	
Missing, n	4
cTx, n (%)	16 (7.4)
cT1, n (%)	11 (5.1)
cT2, n (%)	101 (47.0)
cT3, n (%)	56 (26.0)
cT4, n (%)	31 (14.4)
Nodal involvement	
Missing, n	4
cNx, n (%)	3 (1.4)
cN0, n (%)	81 (37.7)
cN1, n (%)	118 (54.9)
cN2/N3, n (%)	13 (6.0)
Tumor type, n (%)	
Invasive ductal carcinoma	194 (88.6)
Invasive lobular carcinoma	25 (11.4)

second procedure at a later time after the diagnosis of breast cancer had been confirmed. The majority of patients had the 2 imaging modalities within 2 to 4 weeks of each other. Descriptive statistics for categorical variables are reported as frequency and percentage; continuous variables are reported as mean (standard deviation) or median (range), as appropriate. Agreement of the 2 imaging modalities was analyzed using receiver operating characteristic (ROC) methods and McNemar's test. All statistical tests were 2-sided, with alpha level set at 0.05 for statistical significance.

RESULTS

Demographic data, tumor size, and nodal involvement are summarized in Table 1. Of note, the majority of patients, 199 of 219 (91%), had T2 to T4 disease, and 131 of 219 (60%) had a clinician-detected palpable lymph node at presentation. In total, 157 of 219 (72%) patients had abnormal lymph node(s) by MRI compared with 146 of 219 (67%) by US. Axillary LN >10 mm was the most common abnormal finding in both MRI and US. The specific abnormal nodal findings detected on AxUS and MRI are summarized in Table 2; MRI detected more abnormal lymph nodes. Among 219 patients, AxUS and MRI agreed on nodal status in 192 of 219 (87.6%, kappa 0.59) and disagreed in 27 (AxUS abnormal/MRI normal, n = 8, AxUS normal/MRI abnormal, n = 19).

Overall, 129 of 219 (58.9%) patients underwent preoperative needle biopsy under US guidance. Among these patients, AxUS and MRI were both abnormal in 122 of 129 (95%). The remaining 7 patients undergoing biopsy had the following axillary imaging results: AxUS normal/MRI abnormal (n = 2), both normal (n = 1, biopsy done for clinical findings), AxUS abnormal/MRI normal (n = 4). Collectively, 116 of 129 (90%) patients had a positive biopsy (Table 3). Ultrasound and MRI had similar accuracy, sensitivity, specificity, and positive predictive value (PPV) (Table 4). Of the 4 of 129 (3.1%) patients with a normal MRI and an abnormal AxUS, 3 of 4 (75%) had a positive needle biopsy; 2 of these had positive lymph nodes on final surgical pathology, therefore suggesting that MRI missed clinically significant disease in only 2 of 129 (1.5%) patients. At final pathology, 90 of 219 patients had positive lymph nodes. These patients

Table 2. Descriptions and Frequencies of Abnormal Lymph Nodes by Imaging Type

	Abnormal AxMRI, 157 of 219 (71.6%)		Abnormal AxUS, 146 of 219 (66.6%)	
Variable	n	%	n	%
No. of suspicious lymph nodes				
1	32	20.4	61	41.8
>1	125	79.6	85	58.2
Lymph node characteristic				
>10 mm	149	94.9	121	82.9
Cortical thickness >3 mm	143	91.1	57	39.0
Abnormal shape	94	59.9	4	2.7
Replaced hilum	95	60.5	14	9.6
Irregular edge	38	24.0	NA	
Hyperechoic cortex	NA		2	1.4
Peripheral vascularization	NA		5	3.4
Other (perinodal fat infiltration, hypoechoic area)	NA		8	5.6

Ax, axillary; US, ultrasound.

Table 3. Comparison of Axillary Ultrasound and Axillary MRI in 129 Women Undergoing Axillary Lymph Node Biopsy

Characteristic	No. of LN biopsy positive	No. of LN biopsy negative
AxUS abnormal	115	11
AxUS normal	1	2
MRI abnormal	113	11
MRI normal	3	2

AxUS, axillary ultrasound; LN, lymph nodes.

included 21 of 90 (23%) patients who did not undergo pre-chemotherapy needle biopsy; 14 of these had an abnormal MRI and only 9 had an abnormal AxUS.

DISCUSSION

In breast cancer patients, accurate assessment of axillary LN status before initiation of chemotherapy is important for staging and may change treatment and surgical options offered or clinical trial eligibility available to patients. Because of the importance of nodal status in diagnosis and treatment, assessment of axillary LN status in those receiving neoadjuvant chemotherapy has been the subject of many studies evaluating surgical (SLNB vs axillary lymph node dissection, pre-chemotherapy SLNB) and imaging (axillary US) approaches.[24,25] We therefore sought to study a high risk patient population because these patients were more likely to have significant nodal disease burden, so discordance (missing disease) between the 2 imaging modalities could be more clinically significant and impactful to decision making.

In our study, the sensitivity of US (99.1%) is higher than that reported in the literature.[10-13] This could be explained by the high risk (larger tumors, clinically palpable lymph nodes) population we elected to study (those planning neoadjuvant chemotherapy), the likelihood that these patients had higher volume disease at presentation, or the fact that 60% of patients had clinically abnormal lymph nodes. However, we also considered any node >10 mm to be abnormal, which may overestimate the sensitivity of US and lead to an increase in the false positive findings (and lower specificity of 15.4%). We did not specify the >10 mm measurement to be along the short axis or the longest diameter. It is likely that simply having a node >10 mm may be relatively common or nonspecific if found in isolation. Regardless, US has historically been prone to wide sensitivity ranges due to interoperator variability, as well as difficulties in detecting the deeper level II and III axillary nodes.[26,27]

Historically, US has been more commonly used due to its availability, in-plane resolution, capacity to facilitate biopsy, and patient and operator comfort with the technology. However, increased use and availability of MRI has demonstrated equivalent sensitivity and improved visualization of deep axillary nodes with MR imaging, raising the question of MR as an equivalent staging exam.

We also demonstrated high axillary MRI sensitivity and positive predictive value at 97.4% and 91.1%, respectively, and low similar specificity to US (15.4%). Again, this low specificity may be due to our liberal definition of an abnormal LN (size > 10 mm in any direction). Harnan and colleagues[4] conducted a meta-analysis evaluating MRI assessment of axillary LNs in breast cancer and revealed mean sensitivity and specificity of 90%. Kuijs and coauthors[28] also conducted a meta-analysis of 16 studies and found that axillary nodal staging by MRI approaches the negative predictive value of SLNB (negative predictive value of 95.0% and high median sensitivity of 84.7%).[28]

Having dedicated breast radiologists re-review the MRIs and remain blinded to the clinical history and axillary US findings significantly improves the reliability of our data and truly allows for assessment of the nodal status by MR imaging. The MRI performed well, missing clinically significant disease in only 2 of 129 (1.5%) patients. It is assumed with the benefit of clinical information, MRI performance could be further improved. These results are similar to results from another retrospective study of 271 patients, showing that in those with negative MRI but a subsequent positive axillary US, only 1 of 23 (4%) had metastatic disease after pathologic correlation.[29] In another study of 373 patients with both breast MRI and axillary ultrasound, van Nijnatten and associates[30] concluded that breast MRI and axillary ultrasound were comparable in staging axillary lymph nodes. They suggested that patients undergoing breast MRI preoperatively needed only axillary ultrasound for biopsy if MRI revealed suspicious lesions.[30] The authors also suggested that using breast MRI to stage the axillary lymph nodes would eliminate the need for supplemental

Table 4. Agreement Statistics among Axillary Ultrasound and Axillary MRI in 129 Women Undergoing Axillary Lymph Node Biopsy

Modality	Accuracy, %	Kappa	Sensitivity	Specificity	PPV	NPV	AUC
US	90.7	0.22	99.1	15.4	91.3	66.7	0.57
MRI	89.1	0.18	97.4	15.4	91.1	40	0.56

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; US, ultrasound.

dedicated axillary imaging, similar to our conclusions, but in a more specific high-risk cohort.

Finally, we found axillary US and MRI were concordant (agreed on nodal status) in 88% of patients. Mattingly and colleagues[31] reported similar results in a prospective trial of 43 patients, with agreement between axillary MRI and US in 95% of patients, with moderate strength of agreement (kappa 0.49).[31] Our study has multiple limitations, including its retrospective nature, relatively small number of patients, and relatively selective population (only those undergoing neoadjuvant therapy). The blinded re-review of the MRIs, however, was a novel process for assessing these data.

CONCLUSIONS

Magnetic resonance imaging is highly sensitive in detecting axillary LN metastases. A growing amount of evidence suggests that MRI should be considered as an equivalent axillary staging modality to axillary US. Our study suggests the routine use of axillary US after negative MRI is low-yield and therefore, may be unnecessary, specifically in breast cancer patients undergoing neoadjuvant therapy. Eliminating the redundancy of performing this US can reduce unneeded patient workups and anxiety, limit strain on resources in radiology, and reduce delays to surgery or treatment. Future studies with larger numbers of patients, a prospective design, and perhaps a normal risk population, are warranted to further validate the elimination of axillary US in the setting of a negative MRI.

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