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RESEARCH ARTICLE

A Validated Ultrasound-Based Scoring System to Stratify Risk of Axillary Metastasis in Breast Cancer: AX-RADS (Axillary Imaging Reporting and Data System)

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ABSTRACT

Introduction: Ultrasound is the imaging modality of choice for evaluation of axillary involvement in breast cancer, but is associated with variable sensitivity and specificity. Understanding the risk of axillary lymph node metastasis (ALNM) based on ultrasonographic and clinical features will inform treatment decisions. Our group aimed to create a scoring system to quantify the risk of ALNM based on ultrasound characteristics in breast cancer patients. We validated the model and tested it among different Memorial Sloan Kettering Breast Cancer Sentinel Lymph Node Metastasis Nomogram (MSK) subgroups.

Methods: The ultrasound score was developed using data collected at a single institution from 2019 to 2021 by allocating points based on the regression coefficients of variables found to significantly predict ALNM. We validated the test statistics of our score at an outside institution. The index and validation cohorts were combined: 358 pooled patients were stratified by predicted ALNM positivity according to a validated nomogram based on primary tumor characteristics.

Results: Between 2019 and 2021, in the validation cohort, the NPV for low risk (0–1) scores was 87%, while the PPV for high-risk (5 +) scores was 71%. Overall, in the combined cohort, 241 (67%) patients had low-risk (0–1) axillary ultrasound scores and 33 (9%) had high risk (5 +) scores. In this combined cohort, NPV was 84% (203/241 low-risk score patients were node negative), while PPV for high-risk scores was 85% (28/33 high-risk score patients were node positive). When stratified via the Memorial Sloan Kettering Breast Cancer Nomogram: Sentinel Lymph Node Metastasis predicted ALNM rates, the NPV of low-risk scores was 87%–89% for patients with < 50% predicted ALNM positivity. For patients with > 50% predicted ALNM positivity, the PPV of high-risk scores was 82%.

Conclusions: A scoring system to predict ALNM among biopsy-proven breast cancer patients undergoing upfront surgery was successfully developed from a multivariate model based on axillary ultrasound characteristics. Combining the axillary US scoring system with an additional validated nomogram based on primary tumor and patient characteristics may help foster better communication about ALNM risk to inform treatment decisions.

Abbreviations: ALNM, axillary lymph node metastasis; ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; FNA, fine needle aspiration; MSKCC, memorial Sloan Kettering Cancer Center; NPV, negative predictive value; PPV, positive predictive value; SLNB, sentinel lymph node biopsy.

Presentation: The index score development was a poster presentation at the Society of Surgical Oncology meeting in Dallas, TX, in March 2022. The validation cohort and score analysis was a poster presentation at the San Antonio Breast Cancer Symposium in San Antonio, TX, in December 2023.

Summary

- Recognizing ultrasound optimally evaluates axillary involvement in breast cancer, our group worked to identify specific ultrasound characteristics in our model that predicted axillary lymph node metastasis (ALNM).
- We then created and externally validated, a scoring system that quantified the risk of ALNM.
- Lastly, we incorporated our novel ultrasound method with an additional known validated nomogram to help foster better communication about ALNM risk to inform treatment decisions.

1 | Introduction

Breast cancer is the second leading cause of cancer death for women in the United States [1]. The treatment of breast cancer continues to evolve in ways that both improve outcomes and decrease treatment-related morbidity. Axillary lymph node metastasis (ALNM) is an important prognostic factor in breast cancer, with important implications for both local-regional recurrence and overall survival [2]. Based on the results of multiple landmark trials [3–8], the field of breast cancer surgery has moved to less aggressive surgical staging and management of the axilla. With these changes, however, there is a greater reliance on imaging of the axilla to guide locoregional therapies.

Assessment tools to stratify the risk of ALNM have been previously developed, one of the most widely used of which is the Memorial Sloan Kettering Cancer Center (MSKCC) breast cancer nomogram. The MSKCC nomogram assists in predicting the probability of sentinel lymph node metastasis [9] by incorporating clinicopathologic patient and primary tumor data such as age, tumor size, type and grade, and hormonal status. Like the development of the BI-RADS imaging stratification system to assist in surgical decision making surrounding the primary breast tumor, there is potential utility of incorporating axillary nodal ultrasound characteristics into risk stratification systems. A prior study at University of Massachussetts [10] used stepwise selection for lymph node variables that predicted sentinel node positivity. However, the population was small, limited to early-stage breast cancer, unvalidated, and was not formulated into a usable scoring system that can be interpreted by a broader population of treating providers.

Prior international retrospective studies have also made such attempts [11–14]. Zong et al. [11] and Zhu et al. [14] evaluated only early-stage breast cancer patients. Zha et al. [13] and Zhou et al. [15] created a radiomics score, though this may be difficult to incorporate into clinical practice given technical and personnel requirements. As such, no formal methodology has been widely adopted to incorporate axillary imaging features into breast cancer care in the United States. An ultrasound-based, user-friendly, validated scoring system predicting ALNM could be an important, cost-effective tool in guiding axillary lymph node sampling and subsequent surgical therapy.

In this study, we hypothesized that individual axillary lymph node ultrasound characteristics would be associated with accurate prediction of ALNM as confirmed on biopsy (preoperative image-guided such as core needle biopsy (CNB) or surgically with SLNB or ALND). Based on our results, our objectives were to develop an ultrasound-based scoring system to assist in prediction of lymph node positivity and to validate this score in an external institutional cohort.

2 | Methods

2.1 | Patient Selection

Chart review for the single index institution was conducted for all patients treated for breast cancer between the years of 2019 and mid 2021 ($n = 362$). Chart review was similarly conducted for patients at the validating institution ($n = 140$). Individual institutional IRB approval was obtained at both institutions. Patients were excluded if a preoperative axillary ultrasound (routinely obtained per institutional protocol) or axillary sampling (core needle or sentinel lymph node biopsy) was not performed, or results were unable to be retrospectively reviewed. Additional exclusion criteria included a missing tumor board file or other variable data. Patients with ductal carcinoma in situ (DCIS) only were excluded, but those who were upstaged to breast cancer on final pathology were included. Finally, any patient who underwent neoadjuvant therapy before axillary ultrasound and biopsy was excluded.

Variables collected included age, gender, body-mass index, clinical and pathologic Tumor Nodal Metastasis and American Joint Commission on Cancer staging, tumor grade, tumor histology, number of positive nodes, status of sentinel lymph node biopsy, estrogen-receptor/progesterone-receptor/human epidermal growth factor 2 status, Ki67 percentage, presence of lymphovascular invasion, use and timing of neoadjuvant therapy, status of preoperative axillary imaging, date axillary ultrasound performed, status of axillary core needle lymph node biopsy, and lymph node biopsy results.

2.2 | Statistical Analysis

The scoring system at the index institution was developed using the SAS software program (Cary, NC). The axillary ultrasounds of patients were evaluated on several individual characteristics: nodal length and width, cortical thickness, preservation of hilum, shape, eccentricity, preservation of margin, presence of microcalcifications and number of abnormal appearing nodes (Figure 1).

The axillary ultrasounds were individually reviewed by a radiology team at the corresponding institution, who were informally blinded to the patient characteristics to include biopsy results. Six categorical and three continuous axillary lymph node ultrasound variables were used as covariates in the outcome of nodal positivity. The cutoff values for conversion of continuous variables (nodal length, nodal width, and cortical thickness) into categorical variables were determined by previous studies [16, 17] and clinical precedent or the LASSO statistical method from the index cohort data. Using these covariates, forward selection univariate and multivariate logistic regressions were used to determine independent predictors of ALNM. Backward selection, while referenced in other papers analyzing this topic, resulted in

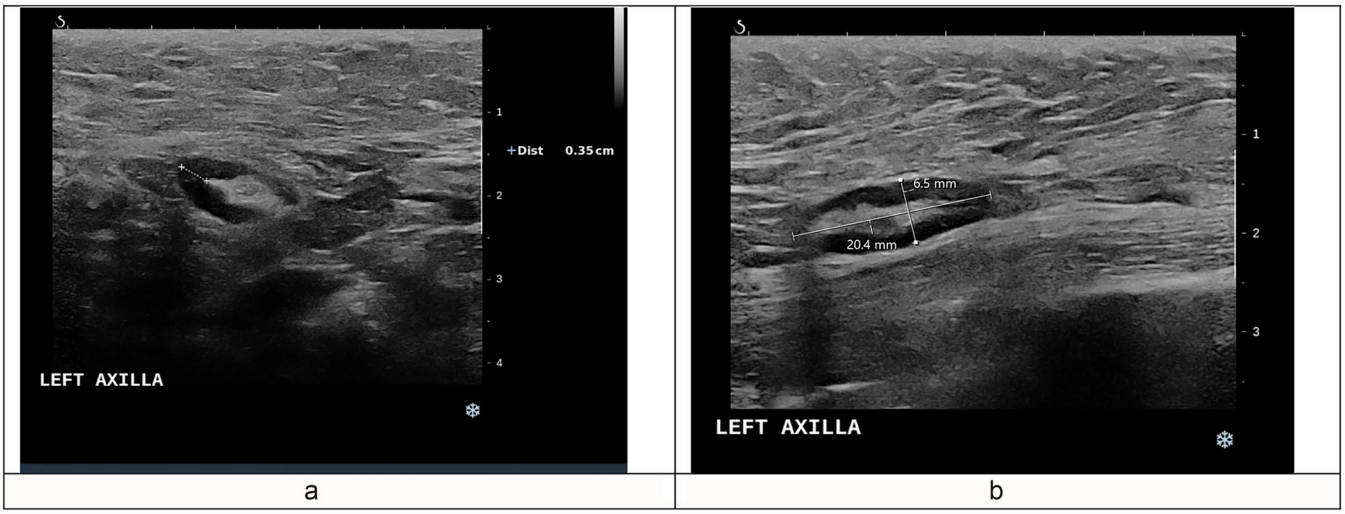

FIGURE 1 | (a) Lymph node with thickened cortex > 3 mm. (b) Lymph node length > 20 mm.

TABLE 1 | Scoring system for likelihood of ALNM based on ultrasound characteristics.

Predictor	Level	Score value
Ultrasound Length (mm)	≤ 10 mm	0
	≤ 20 mm	1
	> 20 mm	2
Cortical Thickness (mm)	≤ 3 mm	0
	> 3 mm	1
Presence of Hilum	Yes	0
	No	2
Shape	Oval	0
	Irregular	1
	Round	4

errors of quasicomplete separation likely due to over-specification of the model. The regression coefficients of variables that acted as independent predictors of ALNM were converted into score values for application of a novel scoring system. The regression coefficients were rounded up to the nearest whole number to ensure unique score Values (Table 1). Area under the curve of a receiver operator curve created from the independent predictors, 0.776, showed appropriate discrimination of the index model covariates for nodal positivity.

After development of the scoring system, logistic regression was performed to determine probability of nodal positivity given certain score amounts. Using a tree-based statistical model (PROC HPSPLIT), the scoring system was optimally stratified into risk categories from the outcome response (Table 2).

The ultrasound scoring system was tested at a validating institution. After confirming reproducible results, patients were pooled from both institutions and score performance in different MSK subgroups was evaluated.

TABLE 2 | Novel ultrasound scoring system.

Risk category	Total ultrasound score
Low	0–1
Indeterminate	2–4
High	5–9

3 | Results (Score Creation and Validation)

The clinicopathologic and surgical treatment characteristics of both the index and validating institutions are demonstrated in Table 3.

This scoring system was first applied to 218 patients at the index institution. The NPV (negative predictive value) for low-risk scores was 82% and the PPV (positive predictive value) for high-risk scores was 89%. Subsequent evaluation of the scoring system with 140 patients at the validating institution found the NPV for low-risk scores was 87% and the PPV for high-risk scores was 71%. After completing validation, the cohorts were combined, and 358 pooled patients demonstrated the NPV for low-risk scores was 84% (203/241 patients were node negative), and the PPV for high-risk scores was 85% (28/33 patients were node positive).

The combined cohort was then stratified by predicted ALNM positivity according to patient and primary tumor clinicopathologic data from the MSK nomogram. After stratifying according to level of MSK-predicted ALNM rates, axillary imaging data from our novel score was again evaluated. For patients with < 50% predicted ALNM positivity via MSK nomogram, the NPV of low-risk ultrasound scores was 87%–89%. For patients with > 50% predicted ALNM positivity via MSK nomogram, the PPV of high-risk scores was 82% (Table 4).

4 | Discussion

In this study, individual axillary nodal ultrasound characteristics were successfully implemented into a multivariate model to derive a novel scoring system to predict ALNM in patients

TABLE 3 | Clinicopathologic characteristics of both the index and validating institutions.

		Index institution ($n = 218$)	Validating institution ($n = 140$)
Age (mean)		55.4 years	65.1 years
Clinical			
T	Unk	9 (4.1%)	2 (1.4%)
	CIS	5 (2.3%)	7 (5.0%)
	1	125 (57.3%)	95 (67.9%)
	2	56 (25.7%)	32 (22.8%)
	3	16 (7.3%)	4 (2.9%)
	4	7 (3.2%)	0 (0%)
N	Unk	11 (5.0%)	0 (0%)
	0	153 (70.2%)	128 (91.4%)
	1	44 (20.2%)	12 (8.6%)
	2	5 (2.3%)	0 (0%)
	3	5 (2.3%)	0 (0%)
M	Unk	12 (5.5%)	0 (0%)
	0	199 (91.3%)	140 (100%)
	1	7 (3.2%)	0 (0%)
AJCC clinical stage			
Unk		10 (4.6%)	3 (2.1%)
0		2 (0.9%)	7 (5.0%)
1		136 (62.4%)	114 (81.4%)
2		37 (16.9%)	13 (9.3%)
3		27 (12.4%)	3 (2.1%)
4		6 (2.8%)	0 (0%)
Grade			
Unk		30 (13.8%)	0 (0%)
1		49 (22.5%)	34 (24.3%)
2		83 (38.1%)	76 (54.3%)
3		56 (25.7%)	30 (21.4%)
4		0 (0%)	0 (0%)
ER pos		162 (74.3%)	126 (90%)
PR pos		138 (63.3%)	114 (81.4%)
HER2 pos		31 (14.2%)	11 (7.9%)
MSK Risk % (mean)		40.7	31.4

with breast cancer. This model was created using inclusive selection criteria, as opposed to prior studies only investigating early-stage breast cancer where rates of ALNM may be lower. Additionally, this model was created and subsequently validated with an external cohort.

The landscape for axillary surgery is rapidly progressing. SLNB was modernized by Morton and Veronesi to include isosulfan blue and technetium 99 m, respectively [18, 19]. While NSABP B-32 established SLNB as standard of care in patients with clinically node negative breast cancer, the ACOSOG Z0011 and AMAROS trials [5, 20] demonstrated ALND can be safely omitted in clinically node negative patients and low volume positive sentinel node patients (i.e., 2 or fewer positive nodes). Historically, the results of these two trials have been challenging to apply, as many patients have preoperative ultrasound findings concerning for positive lymph nodes but are clinically negative on exam. Even now, work continues to investigate nonoperative management of the axilla, such as the recent SOUND [21] trial advocating omission of SLNB in patients without findings concerning for axillary node involvement on axillary ultrasound.

The MSK nomogram is now widely in practice [9], as well as other scoring systems that were either developed independently [22, 23] or expanded from MSK [24]. These systems incorporate pathologic features of the patient's primary breast tumor only, however. Attempts have also been made to incorporate imaging modalities (CT [25], MRI [26, 27], CT lymphography [28]) to predict ALNM. Despite a widely known drawback of operator dependency, ultrasound has many benefits over other imaging techniques: it is less expensive, often more convenient and efficient, and does not provide radiation. Many of the existing studies evaluating ultrasound as a modality to predict ALNM were conducted outside the United States (limiting generalizability), use radiomics instead of multivariable analysis (limiting ease of interpretation), and restrict the study to only patients with early-stage breast cancer, a population where concern for ALNM is usually low [10–15].

Others use radiomics instead of multivariable analysis. Radiomics is a technologically and mathematically advanced concept which aims to use artificially enhanced imaging analysis to extract certain "hidden" image features that may better predict clinical endpoints. The future of radiomics may be large, but at the current time many pitfalls exist [29]. Image acquisition is still plagued by variability from different scanners, imaging protocols or acquisition technique (i.e. operator-based ultrasound). Image segmentation, selecting the region of interest to be analyzed, is also affected by manual operator segmentation or non-standardized automated segmentation techniques. Most notably, a lack of standardized features to extract from images by radiomic packages has hindered clinical application. Ultimately, these factors limit the ease of interpretation with radiomic-based approaches.

To our knowledge, our study is the first to evaluate ultrasound at a US institution and include advanced stages of breast cancer, making our study more generalizable to the population at greatest risk. We additionally developed a scoring system which may be more readily incorporated into clinical practice than other methods, particularly radiomic scoring strategies proposed in the prior studies. Lastly, we demonstrated that our novel scoring system can be incorporated with other already widely used adjunct risk calculators (i.e., MSK).

This study has multiple limitations. It is a retrospective study. It has been evaluated at two separate institutions with a total of 358 patients, however multicenter validation and greater

TABLE 4 | *** A portion of patients were lost due to lack of applicable data when subcategorizing by MSK scores. Further, two categories from the MSK score (1. Multifocality, 2. If tumor was confined within the upper inner quadrant of the breast) were excluded as these data points were not collected in the initial analysis.

	Ultrasound score category	Index institution ($n = 218$)	Validating institution ($n = 140$)	Combined data ($n = 358$)
	Low risk	(113/138) 82% NPV	(90/103) 87% NPV	(203/241) 84% NPV
	Intermediate risk	(22/49) 45% NPV (27/49) 55% PPV	(23/30) 77% NPV (7/30) 23% PPV	(45/79) 57% NPV (34/79) 43% PPV
	High risk	(23/26) 89% PPV	(5/7) 71% PPV	(28/33) 85% PPV
MSK stratification***				
0%–25% MSK category	Low risk	(40/49) 82% NPV	(56/59) 95% NPV	(96/108) 89% NPV
	Intermediate risk	(9/11) 82% NPV (2/11) 18% PPV	(11/13) 85% NPV (2/13) 15% PPV	(20/24) 83% NPV (4/24) 17% PPV
	High risk	No high risk pts	(0/1) 0% PPV	(0/1) 0% PPV
26%–50% MSK category	Low risk	(44/48) 92% NPV	(21/27) 78% NPV	(65/75) 87% NPV
	Intermediate risk	(4/8) 50% NPV (4/8) 50% PPV	(8/13) 62% NPV (5/13) 38% PPV	(12/21) 57% NPV (9/21) 43% PPV
	High risk	(3/3) 100% PPV	(3/3) 100% PPV	(6/6) 100% PPV
> 50% MSK category	Low risk	(17/28) 61% NPV	(12/16) 75% NPV	(29/44) 66% NPV
	Intermediate risk	(4/14) 29% NPV (10/14) 71% PPV	(4/4) 100% NPV (0/4) 0% PPV	(8/18) 44% NPV (10/18) 56% PPV
	High risk	(7/8) 88% PPV	(2/3) 66.7% PPV	(9/11) 82% PPV

statistical power is needed. We analyzed the ultrasound images via chart review; therefore, only the images saved by the sonographer at the time of exam were available and pertinent information from other imaging slices may have been omitted. ALNM was a binary factor in our study and the degree of metastasis was not evaluated, which could be investigated in future studies. We were unable to perform certain subgroups of interest, such as hormonal positivity, due to sample size. The study was conducted during the COVID pandemic with potential lymphadenopathy due to both disease and vaccination. We intentionally stopped data collection before vaccine availability to limit this variability, but the pandemic nonetheless may have impacted selection of who received ultrasonography and what imaging results were obtained [30]. When we calculated the MSK value for our patients, two variables in the MSK score were omitted as they were not a part of our initial data collection (1. multifocality, 2. If tumor was confined within the upper inner quadrant of the breast). While these two variables are conversely associated with ALNM, the weight of them to the MSK score is unknown and this likely applied small differences to the patient MSK scores we derived. Our validation cohort was not powered enough for advanced stage cancer and overall, despite our inclusive selection criteria, our data is relatively skewed to earlier stage breast cancer. Lastly, similar to the pitfall of feature extraction in radiomic packages, the selected ultrasound characteristics are not standardized. However, the characteristics carry standing clinical precedent, as grey-scale nodal size and architecture have long been considered concerning malignant features and only recently has radiomics proposed more in-depth features such as texture, intensity, and volumetric differences. Our ultrasound characteristics are also available for validity/testing and standardization nationwide, while many radiologic trainees demonstrate limited literacy in radiologic AI and radiomics, additionally radiomics research can take longer due to the multiple processes and personnel involved [31].

5 | Conclusions

Management of the axilla is evolving. The importance of axillary ultrasound in the pretreatment staging of breast cancer has gained increasing importance, particularly with its inclusion in clinical trials and movements to limit surgical staging of the axilla. This creates an opportunity to standardize the criteria for what is sonographically abnormal and standardize communication of results between radiologists and clinicians. Retrospective studies, such as this one, provide valuable information for patients and providers regarding discussion surrounding surgical decision making. Further validating this scoring system could lead to clinical adoption. Additionally, characteristics evaluated in our retrospective models may provide advantageous framework when designing future prospective trials.

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The authors have nothing to report.

Disclosure

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policy or position of Brooke Army Medical Center, the US Army Medical Department, the Department of the Army, Department of the Air Force, Department of Defense, or the US Government. The voluntary, fully informed consent of the subjects used in this study was obtained as required by 32 CFR 219 and DODI 3216.02_AFI40-402.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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