Assessment of Ultrasound Features Predicting Axillary Nodal Metastasis in Breast Cancer: The Impact of Cortical Thickness

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Key words
- ultrasound
- axilla
- adenocarcinoma
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- metastases

Abstract

Purpose: To evaluate the accuracy of axillary ultrasound (AUS) in detecting nodal metastasis in patients with early-stage breast cancer and to identify AUS features with high predictive power.

Materials and Methods: Prospective single-center preliminary study in 105 patients with a primary diagnosis of breast cancer and clinically negative axilla. AUS was performed using a 12 MHz linear-array transducer before ultrasound-guided needle biopsy. Nodal characteristics (shape, longitudinal-transverse [LT] axis ratio, margins, cortical thickness, hyperechoic hilum) were correlated with histopathological nodal status after SLNB or axillary lymph node dissection (ALND).

Results: Nodal metastases were present in 42/105 patients (40.0%). Univariate analyses showed that absence of hyperechoic hilum, round shape, LT axis ratio < 2, sharp margins and cortical thickness > 3 mm were associated with lymph node metastasis. Multivariate logistic regression analysis revealed cortical thickness > 3 mm as an independent predictive parameter for nodal involvement. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 66.7, 74.6, 63.6, 77.0% and 71.4% respectively when cortical thickness > 3 mm was applied as the criterion for AUS positivity. Axillary tumor volume was low in patients with pT1/2 tumors and negative AUS, since only 3.2% of patients had > 2 metastatic lymph nodes.

Conclusion: Cortical thickness > 3 mm is a reliable predictor of nodal metastatic involvement. Negative AUS does not exclude lymph node metastases, but extensive axillary tumor volume is rare.

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Introduction

Axillary lymph node metastasis is an important prognostic factor in early-stage breast cancer and remains crucial for individual treatment decisions. Axillary staging by sentinel lymph node biopsy (SLNB) represents the gold standard for patients with clinically negative axilla. Over the last 3 decades many studies have demonstrated the advantages offered by axillary ultrasound (AUS) for the detection of lymph node metastases in women with breast cancer [1,2]. It has also been shown that the sensitivity of AUS depends on the extent of axillary tumor burden [3–6]. However, most of the available studies were carried out to identify metastatic lymph nodes prior to surgery, either to avoid false-negative SLNB or to spare SLNB in cases where axillary lymph node dissection (ALND) was clearly necessary. Following release of the American College of Surgeons Oncology Group (ACOSOG) Z0011 and European Organisation for Research and Treatment of Cancer (EORTC) AMAROS trial data, the goal of AUS needs to be redefined [7–9]. As pointed out in a 2014 editorial by Hieken [10], patients should be stratified into 3 groups: (1) those for whom axillary surgery can be avoided altogether [this is the aim of the ongoing Sentinel Node vs. Observation after Axillary Ultrasound (SOUND) trial and the newly started Intergroup Sentinel Mamma trial (INSEMA); (2) those for whom SLNB is sufficient for nodal staging (patients with limited node-positive disease); and (3) patients who will derive benefit from ALND (directly or after positive SLNB) within the context of multimodality therapy [10–12].

Uncertainty persists as to which ultrasound criteria (e.g., size, morphology, cortical thickness, vascularity) should be used to define lymph node positivity. Of these, longitudinal-transverse (LT)

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axis ratio < 2, eccentric cortical thickening and/or absent fatty hilum as well as higher peripheral vascularity are reported to be the most reliable criteria for predicting lymph node metastasis [13, 14]. Recent retrospective data have indicated that a cortical thickness > 3 mm may be the most accurate ultrasonographic predictor of lymph node metastasis [15].

The aim of this prospective single-center study was to evaluate the impact of cortical thickness for the axillary staging of breast cancer patients, as compared with a conventional algorithm, and to determine a cut-off value that is predictive of nodal metastatic disease.

Methods

Patients

This prospective single-center study in patients with primary invasive breast cancer and clinically negative axilla was conducted between January 2010 and January 2011 at the Breast Cancer Center of Rostock University Hospital. Ethical approval was granted by our institutional review board. A total of 105 patients were enrolled. Patients who were scheduled for neoadjuvant chemotherapy or in whom AUS did not reveal any lymph nodes were excluded. Patient charts were reviewed for demographic data, primary tumor histology, grade, stage, hormone receptor status, HER-2 status, lymphovascular invasion (LVI), number of lymph nodes removed, and number of positive nodes on histological examination after axillary surgery. Lymph node involvement was defined as present if macrometastases were described on histological examination.

Ultrasound

B-mode ultrasound of the breast and axilla was carried out by an experienced examiner (AS, SH, MD, JS) using a high-end device with a multi-frequency linear-array transducer (5–12 MHz; Philips iU22, Bothell, WA, USA). Ultrasound examination of the axillary region followed a standardized protocol. The patient was placed in a supine position with the ipsilateral hand behind the head. The axilla was scanned in a longitudinal and transverse direction. The most suspicious lymph node was selected. If all lymph nodes appeared normal, the most representative lymph node in the lower part of the axilla was chosen for further analysis. Lymph nodes were measured in the longitudinal plane, and the longitudinal and transverse dimensions were determined and documented as the Solbiati Index (LT axis ratio). The hilum (2 axes) and cortical thickness were also measured. Finally, the following qualitative criteria were described: oval or round appearance, absent fatty hilum, sharpness of margins, and focal thickening of the cortex. In accordance with local hospital guidelines, lymph nodes were regarded as abnormal if a fatty hilum was absent or the Solbiati Index was < 2 and the cortical thickness was eccentric. Patients with sonographically abnormal lymph nodes were referred directly for ALND, whereas SLNB was performed in patients with normal AUS.

Statistics

Statistical analysis was conducted in collaboration with an independent statistician (ÄG) using the SPSS 20.0 software package (IBM Ehningen, Germany). Specimen histology (SLNB or ALND) was used as the gold standard for defining metastatic lymph nodes.

Descriptive statistics were computed for continuous and categorical variables. The computed statistics included mean and range for continuous variables, and frequencies and relative percentages for categorical factors. Clinical, histological and sonographic parameters were compared using the chi-square test or Fisher's exact test. A logistic regression model was applied to assess the independence of the occurrence of lymph node metastases from prognostic factors. First, univariate analyses were used to reveal unadjusted associations between prognostic variables and outcome. Thereafter, variables yielding significant p-values in univariate analyses were entered in the multivariate model to highlight some adjusted associations between outcome and covariates.

In order to further evaluate the diagnostic performance of cortical thickness in discriminating between negative and metastatic lymph nodes, a receiver operating characteristic (ROC) analysis was carried out to compare the areas under the curve (AUC).

The diagnostic sensitivity, specificity, positive and negative predictive values and accuracy were calculated for subjective AUS and for cortical thickness > 3 mm.

All tests were 2-tailed and $p < 0.05$ was considered to be statistically significant.

Results

Demographic data and tumor parameters

The 105 patients who took part in this study had a mean age of 61.1 years (range: 34–89 years). 67 patients (63.8 %) had pT1 tumors, 28 patients (26.7 %) were diagnosed in tumor stage pT2, and 10 patients (9.5 %) had tumors > 5 cm (pT3). Regarding histological subtypes, 75 tumors were invasive ductal carcinomas (IDC), 11 were invasive lobular carcinomas (ILC), 12 were mixed invasive ductal and lobular carcinomas (IDLC), and the remaining 7 cases included rarer subtypes, e. g., mucinous or medullary carcinomas. Postoperative histological examination revealed that 42 (40 %) out of 105 patients had nodal metastases. Of these, one patient had micrometastatic nodal involvement, 21 patients had metastases in 1–3 axillary lymph nodes (pN1a), 15 patients had metastases in 4–9 axillary lymph nodes (pN2a), and 5 patients had metastases in 10 or more axillary lymph nodes (pN3a). The prevalence of nodal involvement according to clinicopathological characteristics is summarized in **Table 1**. Nodal metastases were significantly more frequent in pT2/3 tumors, in high-grade (G3) tumors, in tumors with LVI and multifocal growth as well as in tumors with a high proliferation index (Ki-67 > 14 %). Multivariate analysis showed large tumor size and LVI to be independent predictors of positive lymph nodes (**Table 2**).

Ultrasound data

Of the 105 patients analyzed, 27 cases revealed abnormal ultrasound findings while the axillary lymph nodes were regarded as normal in 78 cases. Compared with the histological examination of lymph nodes after SLNB or ALND, the sensitivity and specificity of AUS were 45.2 and 87.3 % respectively. Subsequently, qualitative and quantitative lymph node features were analyzed in detail. Of 40 patients with a reduced LT axis ratio (Solbiati Index < 2), 23 were node-positive. The absence of fatty hilum was observed in 26 patients, 18 of whom had nodal metastases. Of 46 patients with a focally thickened cortex, nodal involvement was present in 25 cases. Finally, metastatic lymph nodes

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occurred in 28 of 44 patients with cortical thickness > 3 mm (**Table 3**). ROC analysis identified a cut-off cortical thickness value of 3.0 mm that yielded sensitivity of 66.7 % and specificity of 74.6 %. The AUC was 0.68 (95 % CI 0.56; 0.79).

Univariate and multivariate analysis

The risk of occurrence of axillary lymph node metastasis associated with each parameter was estimated by univariate logistic regression, using the presence of histologically confirmed lymph node metastasis as the dependent variable. All of the described ultrasound parameters were significantly associated with the risk of node-positive disease. Multivariate analysis revealed that only a cortical thickness > 3 mm was an independent ultrasound parameter for the prediction of lymph node metastasis (**Table 4**). The diagnostic performance of AUS using a cortical thickness > 3 mm as the criterion for suspicious lymph nodes is summarized in **Table 5** in comparison with our previous local institutional guidelines. The overall accuracy of AUS increased from 61.0 to 71.4 % when cortical thickness was used as the parameter to predict nodal metastatic disease.

Table 1 Clinicopathological characteristics and axillary lymph node metastasis in patients with early-stage invasive breast cancer (n = 105).

	n	pN+	%	p-value
Size of tumor				< 0.001 *
pT1	67	15	22.4	
pT2/3	38	27	71.1	
Grade of differentiation				0.001#
G1	20	1	5	
G2	56	25	44.6	
G3	29	16	55.2	
Tumor histology				0.010#
Ductal	75	27	36.0	
Lobular	11	7	63.6	
Mixed	12	8	66.7	
Other	7	0	0	
Receptor status				0.834
HR positive/HER2 negative	87	34	39.1	
HER2 positive	8	4	50.0	
Triple negative	10	4	40.0	
LVI				< 0.001 *
Negative	59	8	13.6	
Positive	46	34	73.9	
Number of foci				< 0.001 *
Unifocal	87	28	32.2	
Multifocal/multicentric	18	14	77.8	
Ki-67				0.009 *
≤ 14 %	52	14	26.9	
> 14 %	53	28	52.8	
Surgery				< 0.001 *
BCS	67	14	20.9	
Mastectomy	38	28	73.7	
Total	105	42	40.0	

BCS: breast-conserving surgery; LVI: lymphovascular invasion

* Fisher's exact test #chi-square test

Prediction of extended axillary tumor volume

This study subgroup was selected on the basis of the ACOSOG Z0011 criteria. After the exclusion of 10 pT3 tumors, 17.9 % of patients had > 2 lymph node metastases. This was an unsuspected finding in 7.4 % of cases on AUS. When a cortical thickness ≤ 3 mm was applied as the criterion for negative AUS, only 3.2 % of the study group revealed unexpected extended axillary disease (**Table 6**).

Discussion

The role of AUS in the preoperative planning of surgery in early-stage breast cancer patients has been extensively examined. However, wide variability exists in the criteria for defining suspicious axillary nodes and for performing axillary FNA/UNB [1,2]. The present study analyzed sonographic lymph node criteria (size, LT axis ratio, hilum sign, cortical asymmetry and cortical thickness) in clinically node-negative breast cancer patients. Using a cortical thickness > 3 mm as the criterion for iN+, we achieved a sensitivity and specificity of 66.7 and 74.6 %, respectively, compared with 45.2 and 87.3 %, respectively, when previous local institutional guidelines were used. Moreover, the overall accuracy was substantially improved when the cortical thickness parameter was included. This is in accordance with the retrospective results presented by Choi et al. [15], who reported a sensitivity and specificity of 68.8 and 72.9 %, respectively, and stands in contrast to those of Lee et al. [4] who described a sensitivity and specificity of 56.3 and 92.3 %, respectively, when a cortical thickness > 3.8 mm was applied as the criterion [4,15]. Thickening of the cortex is indicative of early metastatic changes, whereas an absence of fatty hilum, which is regarded as highly specific for lymph node metastases, reflects later metastatic changes. In our study a hypoechoic hilum was observed in only 42.9 % of pN+ patients. Other qualitative morphological lymph node variables, such as focally thickened cortex, were non-predictive in the multivariate analysis. LT axis ratio is a quantitative variable with a widely accepted cut-off value of 2. Our results showed sensitivity of 54.8 % and specificity of 73.0 % when an LT axis ratio < 2 was defined as suspicious for nodal metastasis.

Lymph nodes with a cortical thickness > 2.3 mm combined with positive FNA have been categorized as suspicious by other study groups [5]. Definition of the cut-off point for cortical thickness depends primarily on the intended purpose of AUS. Until the ACOSOG Z0011 era, AUS was carried out to identify patients with node-positive disease who could be sent directly for ALND and in whom SLNB could be spared, especially in light of the

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p-value	OR	95 % CI	p-value
pT2/3 vs. pT1	8.51	3.44–21.06	< 0.001	3.58	1.16–10.98	0.026
LVI positive	18.06	6.68–48.81	< 0.001	11.09	3.50–35.17	< 0.001
G3 vs. G1	17.70	2.27–138.27	0.001	1.872	0.12–27.93	0.649
Multifocal disease	7.38	2.22–24.46	0.001	2.63	0.62–11.15	0.189
Ki-67 > 14 %	3.04	1.34–6.88	0.012	1.26	0.31–5.08	0.747

OR: odds ratio; 95 % CI: 95 % confidence interval

Table 2 Logistic regression model showing clinicopathological predictors of lymph node metastasis.

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higher false-negative rate of SLNB if lymph nodes are completely destroyed by metastases. As shown by the meta-analysis of Houssami et al. [2], the sensitivity and specificity of AUS can be increased by the use of FNA/UNB to 79.6% (95% CI 74.1–84.2) and 98.3% (95% CI 97.2–99.0), respectively. However, the sensitivity was strongly dependent on the underlying prevalence of nodal metastases, since studies with a metastatic node prevalence < 39% on excision histology had a sensitivity of 69.9% (95% CI 54.9–81.2) compared with 79.8% (95% CI 72.3–85.7) when more than 47% of the study population were node-positive [2]. This finding is important in view of the low prevalence of 20–30% lymph node metastases in early-stage breast cancer patients qualifying for SLNB. It may actually even be disadvantageous to identify all patients with limited axillary tumor burden prior to SLNB since, according to the meta-analysis of Houssami et al. [2], 55.2% (95% CI 41.8–68.2) of women with metastatic axillary nodes were triaged directly to ALND when AUS/UNB were used preoperatively. However, recent studies have demonstrated that patients with even small-volume metastatic lymph nodes detected preoperatively by AUS/FNA had a higher axillary tumor burden than patients found to be SLN-positive [16–19]. In a retrospective study, Caudle et al. [17] compared 708 node-positive T1 and T2 invasive breast cancer patients, stratified by whether metastases were identified by positive AUS confirmed by FNA (AUS criterion: cortical thickness < 2.3 mm; n = 190) or by SLNB alone (n = 518). SLNB patients had significantly fewer positive nodes (2.2 vs. 4.1), smaller metastases (5.3 vs. 13.8 mm) and a lower incidence of extranodal extension (24 vs. 53%) than the AUS group. Even when AUS identified ≤ 2 suspicious lymph nodes, 45% of patients had a substantial axillary tumor burden (≥ 3 metastatic lymph nodes). The authors concluded that patients with AUS/FNA-detected node-positive disease may not be comparable with patients in the ACOSOG Z0011 trial. Similar results were reported by Hieken et al. from the Mayo Clinic [18], with 51.6% of patients having ≥ 3 positive nodes after ALND when axillary metastatic disease had been identified preoperatively by AUS. Conversely, 22% of patients who were AUS-negative were SLN-positive at operation, but only 4% had 3 or more metastatic lymph nodes after ALND. In the present study, where a cortical thickness ≤ 3 mm was defined as AUS node-negative, only 3.2% of patients had 3 or more metastatic lymph nodes at operation.

Another important question is the impact of ignoring axillary disease on the survival of breast cancer patients. From studies conducted prior to the SLNB era, it is well-known that omitting axillary surgery in early-stage breast cancer neither substantially increases the axillary recurrence rate (range: 2.5–9%) nor has any negative impact on disease-free and overall survival [20–22]. After SLNB, with an accepted false-negative rate of about 10%, axillary lymph node recurrence ranges from 0 to 3% [23–25]. Currently, axillary surgery for breast cancer is considered as a staging procedure. Adjuvant systemic treatment decisions are made on the basis of the biological behavior of the primary tumor. As a consequence, Gentilini and Veronesi initiated the SOUND trial to establish whether SLNB is really necessary for cN0 and iN0 patients with T1 tumors [11].

Noninvasive new imaging techniques such as ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) and magnetic resonance imaging (MRI) offer diagnostic performance comparable with that of AUS [26,27]. Because of their higher costs and possible side-effects, PET/CT and MRI do not have a place in routine staging. New ultrasound techniques, including contrast-enhanced ultrasound (CEUS) and US elastography, have been deployed for lymph node evaluation. CEUS provides detailed visualization of the vascularity of lymph nodes and may thus be helpful in differentiating between benign and malignant nodes [28]. With regard to axillary staging, only a small number of studies have been published, with very preliminary results [29,30]. US elastography allows in vivo assessment of relative elasticity differences. A recent meta-analysis of superficial lymph nodes revealed quite accurate diagnostic values for the elasticity score (ES) and strain ratio (SR) [31]. For the ES, a role has been suggested as an additional method alongside AUS in the prediction of breast cancer metastases, whereas the SR does not improve diagnostic accuracy [32,33]. Shear wave elastography (SWE) allows quantitative measurement of stiffness, yielding initial results in the evaluation of lymph nodes prior to SLNB [34]. However, US elastography is strongly dependent on the experience of the examiner and cannot be recommended for routine clinical use. Overall it must be remembered that exclusion of

Table 3 Ultrasonographic findings in 105 patients with documented lymph nodes.

	Patients (n)	pN+	%	p-value *
LT axis ratio				
≥ 2	65	19	29.2	0.007
< 2	40	23	57.5	
Hilum				
Hyperechoic	79	24	30.4	0.001
Hypoechoic	26	18	69.2	
Cortex				
Thin	59	17	28.8	0.010
(Focally) thickened	46	25	54.3	
Margin				
Vague/blurred	52	15	28.8	0.028
Sharp	53	27	50.9	
Cortical thickness				
≤ 3 mm	61	14	23.0	< 0.001
> 3 mm	44	28	63.6	
Total	105	42	40.0	

* Fisher's exact test

Table 4 Logistic regression model showing AUS predictors of lymph node metastasis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
L/T ratio < 2	3.28	1.44–7.47	0.008	1.5	0.43–5.27	0.53
Hypoechoic hilum	5.16	1.97–13.5	0.001	1.8	0.42–7.65	0.42
Focally thickened cortex	2.94	1.31–6.60	0.014	0.31	0.59–1.65	0.17
Sharp margin	2.56	1.14–5.74	0.035	1.0	0.31–3.22	0.99
Cortical thickness > 3 mm	5.88	2.49–13.83	< 0.001	8.1	1.91–34.38	0.005

OR: odds ratio; 95% CI: 95% confidence interval

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Table 5 Diagnostic performance of AUS: comparison of previous and new local institutional guidelines.

	Evaluation according to previous local institutional guidelines		Evaluation according to new local institutional guidelines (cortical thickness > 3 mm)	
	%	95 % CI	%	95 % CI
Sensitivity	45.2	31.2–60.1	66.7	51.6–79.0
Specificity	87.3	76.9–93.4	74.6	62.7–83.7
PPV	70.5	51.5–84.1	63.6	48.9–76.2
NPV	70.4	59.6–79.5	77.0	65.1–85.8
Accuracy	61.0	49.1–72.9	71.4	54.5–88.4

PPV: positive predictive value; NPV: negative predictive value

Table 6 Axillary tumor burden in patients with clinically node-negative axilla and pT1/2 tumors (n = 95).

	pN + n (%)	AUS-negative n (%)	Cortex ≤ 3 mm n (%)
≤ 2 positive LN	17 (17.9)	12 (12.6)	8 (8.4)
> 2 positive LN	17 (17.9)	7 (7.4)	3 (3.2)
Total	34 (35.8)	19 (20.0)	11 (11.6)

LN: lymph node(s)

nodal metastatic infiltration is impossible with any imaging technique since about 25 % of nodal metastases are ≤ 5 mm in size and are therefore below the reliable limit of detection [3].

Numerous studies have been performed to define factors predictive of axillary involvement [35], and the strong relationship between pathological tumor size and lymph node metastasis is well established [36]. A multi-variable approach involves the application of so-called nomograms, first introduced by Bevilacqua et al. from the Memorial Sloan-Kettering Cancer Center (MSKCC). Using 9 preoperatively assessable variables associated with SLN metastases, the test showed good accuracy, with an AUC of 0.75 in 1 545 sequential SLN biopsies [37].

In the present study, node-positive disease was strongly associated with tumor size, with only 22.4 % pN + in pT1 tumors vs. 71.1 % pN + in pT2-3 tumors. In the light of our study we have adapted our own local institutional guidelines, defining lymph nodes as suspicious (= indication for axillary UNB) if AUS reveals a cortical thickness > 3 mm or an absent fatty hilum. For indeterminate nodes a tumor size > 2 cm is considered to be an indication for UNB. This is supported by the work of Mainiero et al. who studied 226 AUS-guided FNA procedures in breast cancer patients [13]. These authors classified lymph nodes as benign if the cortex was even and measured < 3 mm, indeterminate if the cortex was even but measured ≥ 3 mm or measured < 3 mm but was focally thickened, and suspicious if the cortex was focally thickened and measured ≥ 3 mm or the fatty hilum was absent. The sensitivity of AUS-guided FNA was 11 % for normal-appearing lymph nodes, 44 % for indeterminate lymph nodes and 93 % for suspicious lymph nodes.

The principal limitation of the present study is that it cannot be guaranteed that the lymph nodes evaluated by AUS matched the lymph nodes sent for histopathological examination. However, by using a standardized protocol for AUS and evaluating the most representative lymph node in the lower part of the axilla, it was assumed that we were describing the potential SLN [15]. Furthermore, lymph nodes were matched by size (data not shown). A recent feasibility study by Caudle et al. has demonstrated successful image-guided localization and selective removal of clip-marked lymph nodes in a neoadjuvant setting [38]. In our opinion, however, from an ethical standpoint, this approach incorporating lymph node excision in addition to SLN dissection is not transferable to a study population with a low risk of nodal metastasis. A further limitation of our work is the small number of cases, rendering further subgroup analyses (e.g., for histological subtypes) impossible. The strength of the presented study is its prospective character in advocating a standardized protocol for AUS.

Conclusion

Among a range of AUS criteria, cortical thickness > 3 mm is the most reliable for defining suspicious lymph node metastases. This measurement can be obtained using a simple and reproducible procedure. Results should be confirmed by FNA or UNB to stratify patients either directly to ALND or – in the case of negative FNA/UNB – to SLNB. Ongoing and future studies such as the SOUND or INSEMA trials will establish whether it is possible to avoid axillary surgery altogether in definitely low-risk breast cancer patients.

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