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Original Article

The role of Strain Elastography in Evaluating Borderline Axillary Lymph nodes

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ABSTRACT

Background: Axillary lymph node (ALN) enlargement with diffuse cortical thickening and conserved echogenic hilum may represent a diagnostic and therapeutic challenge.
Sonographic strain elastography may help the characterization of borderline ALN.
Aim: To evaluate the strain elastography of borderline ALN and to calculate a cutoff value of strain ratio (SR) that can identify suspicious ALN with the highest sensitivity and specificity to reduce unnecessary invasive procedures.
Subjects and Methods: A prospective study included 45 patients who attended the Breast clinic in Oncology Teaching Hospital with borderline axillary lymphadenopathy (intact hilum and diffusely thickened cortex more than 3mm) who had normal ipsilateral breast, suspicious ipsilateral breast lesion, or who had ipsilateral mastectomy. B-mode sonography and elastography were performed for all participants. Four-point elasticity score (ES), and SR were obtained for the targeted lymph node followed by ultrasound-guided fine need aspirate (FNA) biopsy..
Results: Malignant ALN constituted 20% of the cohort. B mode measurements were not able to differentiate between cytologically confirmed benign and malignant ALN in terms of axis ratio (mean ± standard deviation, 0.46 ± 0.08 vs 0.50 ± 0.12) and cortical thickness (4.88 ± 1.93 vs 6.27 ± 2.46). The mean SR of all samples was 2.66 ± 2.25. Metastatic ALN depicted significantly higher SR ($P<0.0001$), with 88.9% exhibiting ES score 3 and 4. None of the metastatic ALN had ES score 1. ROC curve was used to investigate the utility of SR as a diagnostic tool. The area under the curve (AUC) was 0.906 with a 95% CI of 0.814-0.997, $P<0.001$. SR cutoff of 2.1 was chosen with 100% sensitivity and 66.7% specificity.
Conclusion: High proportion of borderline ALNs are not malignant. Strain elasticity can improve the risk stratification of such cases and prevent unnecessary invasive procedures. We suggested an algorithm that could better tackle borderline ALN which will need further evaluation

Introduction

Unilateral axillary lymph node (ALN) enlargement may represent a diagnostic and therapeutic challenge. Several infectious and inflammatory conditions are associated with unilateral ALN adenopathy (1). Although primary breast carcinoma presented as ALN adenopathy is relatively uncommon with a range of 0.3-1% (2), exclusion of metastatic disease remains the primary target in the evaluation of ALN adenopathy. In ultrasonography, a benign ALN appears ovoid, with a thin hypoechogenic cortex and hyperechogenic hilum due to the presence of lymphatic tissue cords and medullary sinusoids within connective tissue trabeculae (3). Features that render an ALN suspicious are thickening of the cortex, compression or absence of the hilum, altered vascular pattern, and change of the shape. A completely hypoechogenic ALN with absent fatty hilum is a specific alteration of metastatic disease that occurs usually in advance disease warranting presurgical biopsy (4). The real challenge is when an ALN shows alteration in cortical thickness in the presence of the hilum which may associate with early metastasis (3). Several cortical thickness cutoff values have been proposed to predict suspicious LN by imaging ranging between 2.3-3mm with various sensitivity and specificity ranging between 59%-95% and 44%-100% respectively (3, 5).

Sonographic strain elastography is a noninvasive, relatively new technique that uses the color map to demonstrate stiffness and homogeneity (6). It has been used to early detect and evaluate malignant lesions in addition to its value in the assessment of response to treatment as in thermal ablation and chemotherapy (6). Several studies demonstrate the ability of US elastography to identify early circumscribed malignant infiltration in cervical, axillary, and inguinal lymph nodes by demonstrating stiffness of the cortex and medulla (7, 8).

Different qualitatively US elastogram classifications have been proposed. A 4-point (9), 5-point (10), 6-point, 7-point (7), or 8-point rating scale (11, 12). In the 4-point rating scale, the metastatic LNs were mostly evaluated to score 3–4. According to several studies, strain ratio (SR) >1.5 or hard composition over 50% has been suggested as an indicator of malignancy (11). Nonetheless, elastogram evaluation remains an operative-dependent technique and reproducibility can be affected by commercial system design and settings.

This study aimed to evaluate the strain elastography of borderline ALN in a sample of Iraqi patients and to calculate a cutoff value of strain ratio that can identify suspicious ALN with the highest sensitivity and specificity to reduce unnecessary invasive procedures.

Subjects and Methods

A total of 45 patients visiting the Referral Training Center for Early Detection of Breast Cancer, Oncology Teaching Hospital, Medical City in Baghdad during the period between October 2020 and September 2021 were prospectively recruited. The study protocol was approved by the Ethical committee of the Oncology Teaching Hospital. Informed consent was given by all participants.

Inclusion criteria were: borderline axillary lymphadenopathy with intact hilum and diffusely thickened cortex more than 3mmin patients with normal ipsilateral breast, suspicious ipsilateral breast lesion, or patients with an ipsilateral mastectomy who completed medical treatment for more than one year and did not receive radiotherapy.

Exclusion criteria included highly suspicious ALN with lost hilum, ALN with cystic changes or calcific foci, patients with a history of ipsilateral radiotherapy of mastectomy site or as part of breast-conserving therapy (BCT), and also breast cancer patients who received chemotherapy in the last 12 months.

In a supine position, with the arm of the examined side lifted above the head, proper breast or mastectomy site sonographic evaluation was done, then the patient turned to supine oblique position for proper evaluation of the ipsilateral axilla. B-mode sonography and sonographic elastography were performed for all participants using the linear transducer 9L-D (2-8 MHz with FOV 44 mm) of a GE healthcare sonographic machine (LOGIQ S8 XD clear 2.0) by two Board-certified radiologists with at least 6 years of experience. After identification of the borderline ALN on B-mode sonography, important measurements were taken (LN short-axis and long-axis diameters with maximal cortical thickness), long-to-short axis (L/S) ratios were subsequently calculated.

Real-time elastography images of the lymph node were obtained by starting strain elastography after pressing the "Elasto" button at the console of the machine. The size of the box was adjusted to place the concerned LN at the center along with part of surrounding normal tissue. Manual compression over the lymph node with an ultrasound transducer for at least 5 seconds was used to catch a quality graph with consistent high (nearly flat, plateau-like) peaks to freeze the image for color analysis and measurement of the strain ratio.

A four-point elasticity score was obtained based on the percentage of high elasticity. The elastography color bar refers to soft lesions as red and the blue color denotes stiff lesions. According to this system ALN in our cohort were classified to: score 1 when ALN was predominantly red color with <10% of the area colored as blue; score 2 when elastography was predominantly red and green, with 10%-50% of the area shown as blue; Score 3 when predominantly (50%-90%) was blue and green; while score 4 refers to a stiff nodule that is predominantly (>90%) blue (13, 14).

The strain ratio, a pseudo-quantitative measurement, was calculated for each ALN in the cohort by taking the E-Indexes of the first (reference tissue) and the second (the lesion of interest). The reference selected was fatty areas of the axilla at nearly the same level as the LN (14). A strain ratio >1 indicates that the target lesion is less compressible than the normal reference tissue, indicating lower strain and greater stiffness.

Ultrasound-guided fine need aspirate (FNA) biopsy was performed for all the borderline ALN. Patients with cytology report positive for malignancy or granuloma were confirmed by histopathology. Patients with reactive cytology were followed up for 3-12 months within the period of the study, 16/26 retained the normal morphology while the rest did not show worsened morphology. Patients who were lost during the follow up were excluded from the study.

Statistical analysis

All statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) software version 25 (IBM Corp., Armonk, N.Y., USA). Continuous variables were expressed as mean, standard deviation, and range. Mann Whitney and Chi-Square tests were used to compare groups as required. Sensitivity was measured as the proportion of malignancies that were correctly identified. Specificity was measured as the proportion of benign diseases that were correctly identified as such. The positive predictive value (PPV) was measured as the proportion of positive for malignancy tests that were truly positive. Negative predictive value (NPV) was measured as the proportion of negative for malignancy tests that were true negative. The overall test accuracy was measured as the proportion of all results that were true. Receiver operating characteristic (ROC) curve analysis was performed for the strain ratio. A *P* value of less than 0.05 was considered statistically significant.

Results

The mean age of the patient was 42.15 ± 11.5-year ranging between 22-71 years, 91% of them were women. Symptomatic patients with palpable or tender axillary lumps represented 64.4% of the cohort, while the rest were on surveillance for benign or malignant breast lesions as shown in Table 1.

Table 1 Demographic characteristics and diagnostic impression of the study cohort

Parameter	Number	Rate
Age		
≤ 30	5	11.1
31-39	16	35.6
≥40	24	53.3
Gender		
Female	41	91.1
Male	4	8.9
Chief complaint		
Palpable axillary lump	11	24.4
Axillary tenderness	18	40
Follow up for benign breast lesion	5	11.1
Cancer patient surveillance	11	24.4
Radiological impression		
Axis ratio (short/wide axis)		
<0.5	27	60
> 0.5	18	40
Cortex thickness		
3-6mm	31	68.9
≥6mm	14	31.1
Cytological impression		
Reactive	29	64.4
Granulomatous	7	15.6
Malignant	9	20.0

The mean short/long axis ratio in all cases was 0.47 ± 0.09, ranging between (0.32-0.8). The mean of long and short axes of cytologically confirmed metastatic ALN was greater than that of the reactive ALN, however, statistically, that was not significant as shown in Table 2. The mean cortical thickness of all cases was 5.16 ± 2.09, ranging between (3-11) mm. Cortical thickness of 6mm and more was seen in 5/9 (55.6%) metastatic ALN compared to only 16% of the benign/ inflammatory ALN (P=0.077). The mean SR of all samples was 2.66 ± 2.25 ranging between (0.6-11.0). SR was significantly higher in metastatic ALN (P<0.0001), with 88.9% exhibited elasticity score (ES) 3 and 4. None of the metastatic ALN had ES 1 as shown in Table 2, Figure 1 shows examples of elasticity studies of malignant and benign ALN.

Table 2 B-mode and elastography features of the reactive and metastatic axillary lymph nodes.

Sonography Criteria	Reactive (n=36)	Malignant (n=9)	P-value
Long axis (Mean ± SD)	19.83 ± 8.13	21.00 ± 8.13	0.293
Short axis (Mean ± SD)	8.91 ± 3.02	10.11 ± 3.72	0.211
Axis ratio (short/ long axis) (Mean ± SD) <0.5 No (%) ≥0.5 No (%)	0.46 ±0.08 22 (61.2) 14 (38.9)	0.50 ±0.12 5 (55.6) 4 (44.4)	0.761
Cortical thickness (Mean ± SD) <6 No (%) ≥6 No (%)	4.88 ±1.93 27 (75.0) 9 (25..0)	6.27 ±2.46 4 (44.4) 5 (55.6)	0.077
Strain ratio (Mean ± SD) <2.1 No (%) ≥2.1 No (%)	2.01 ±1.35 24 (66.7) 12 (33.3)	5.46 ±3.36 0 (0) 9 (100)	<0.0001
Elasticity score No (%) 1 2 3 4	 9 (25) 22 (61.1) 3 (8.3) 2 (5.6)	 0 1 (11.1) 2 (22) 6 (66.7)	<0.0001
Elasticity score No (%) 1 &2 3&4	 31 (86.1%) 5 (13.9%)	 1 (11.1%) 8 (88.9%)	<0.0001

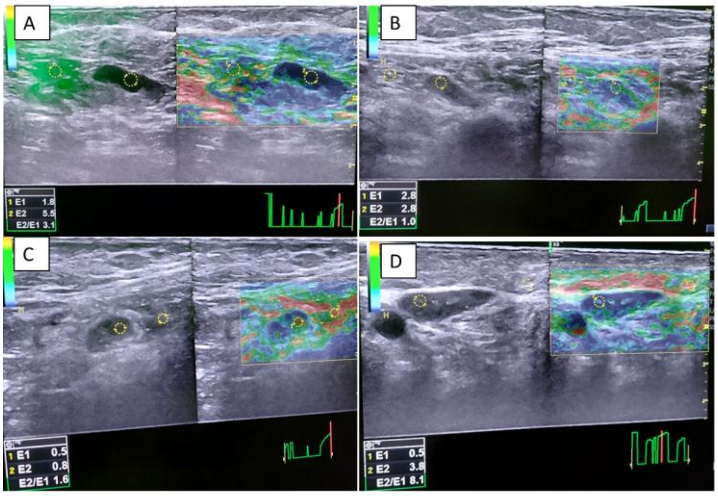


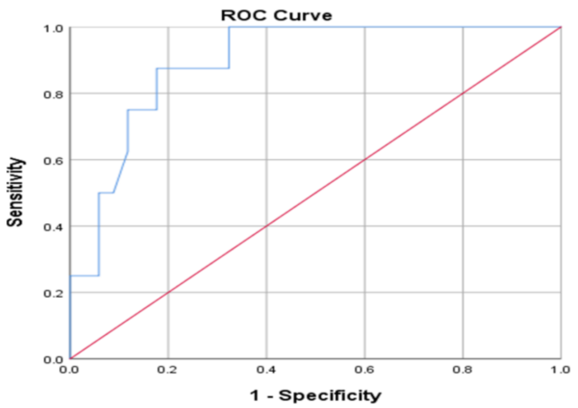
Figure 1 Elastography study of axillary lymph nodes. A) A patient with newly diagnosed breast cancer had enlarged ipsilateral axillary LN, elasticity score was 3, strain ratio was 3.1, FNA revealed malignancy that was proved after excisional biopsy. B) A patient complained of left axillary pain, the ultrasound revealed an infected sebaceous cyst with an ipsilateral enlarged axillary lymph node, elasticity score 2 and the strain ratio was 1, cytology impression was reactive, reduction in cortical thickness was noted at the follow up visit. C) A patient complained of a palpable lump at the left axilla after COVID 19 vaccination, the ultrasound revealed left axillary lymphadenopathy with an elasticity score of 2 and a strain ratio of 1.6, the cytology impression was reactive, reduction in cortical thickness was noted at the follow up visit. D) A patient complained of right axillary pain, ultrasound revealed right axillary lymphadenopathy with an elasticity score of 3 and the strain ratio of 8.1 with no ipsilateral breast abnormality. The radiological impression was suspicious, cytology revealed reactive lymphadenopathy confirmed by excisional biopsy (False positive).

ROC curve was used to investigate the utility of SR as a diagnostic tool. The area under the curve (AUC) was 0.906 with a 95% CI of 0.814-0.997, P<0.001, Figure 2. By reviewing the sensitivity and the specificity of the different cutoff values, we found that SR which could efficiently identify the metastatic ALN was 2.6 with a sensitivity of 88.9% and specificity of 83.3%, however, in screening tests, the aim is to achieve the higher sensitivity, therefore, we considered an SR cutoff of 2.1 with 100% sensitivity but lower specificity of 66.7%. When predictive values and accuracy of the calculated SR cutoff (2.1) were compared to the literature suggested value of 1.5, the former had higher overall accuracy (73.3% vs 62.2%). Combined elasticity score and ratio improved individual test specificity to 88.9 and PPV and NPV to 66.7% and 97.7% respectively, as shown in Table 3.

Table 3 validity of elasticity score and ratio using the proposed cutoff value and literature proposed cutoff value

	Sensitivity	Specificity	PPV	NPV	Accuracy
ES 1&2 vs 3&4	88.9%	86.1%	61.5%	96.9%	86.7
SR >1.5 vs ≤ 1.5	100%	52.8%	34.6%	100%	62.2
SR≥2.1 vs <2.1	100%	66.7%	42.9%	100%	73.3
SR > 2.6 vs ≤2.6	88.9%	83.3%	57.1%	96.8%	91.1
SR >1.5 and ES>2	88.9%	86.1%	61.5%	96.9%	86.7
SR≥2.1 and ES>2	88.9%	88.9%	66.7%	97.0%	88.8
SR >2.6 and ES>2	88.9%	91.7%	72.7%	97.7%	91.1

Abbreviations: ES, elasticity score; SR, strain ratio; PPV, positive predictive value; NPV, negative predictive value.



Area	Std. Error	P	95% Confidence Interval
0.906	.047	.000	0.814-0.997

Figure 2 ROC curve of elasticity ratio

Discussion

Borderline ALN can be frequently seen during breast cancer patient surveillance as well as nonmalignant conditions. In the absence of radiological features such as lost echogenic hilum and focally thickened cortex, the suspicion level is reduced yet focal malignancy cannot be excluded mandating further invasive procedures (15). Sentinel ALN is recommended in such cases during the first diagnosis of breast cancer while in the absence of malignant breast lesion adding further evaluating tools may reduce the need for unnecessary surgery. The utility of elastography in identifying focal malignant changes is established in many of the internal organs (16, 17). This study examined the benefit of incorporating strain elasticity to predict early malignant changes in borderline ALN.

The selection criteria of our cohort were strict, excluding all highly suspicious lymph nodes and focusing on relatively small ALN with a diffuse increase in cortical thickness and subtle shape change regardless of breast pathology. Among the 45 collected cases, cytology/histopathology diagnosed 80% as benign. B mode US evaluation showed no significant difference in these parameters in metastatic ALN compared to reactive/ inflammatory ALN. Cohort characteristics explain the disagreement with the results of Choi et al.(18) who concluded that cortical thickness, absent hilum and S/L access were significantly different in metastatic ALN, as he have included breast cancer patients with looser selection criteria, including highly suspicious ALN.

We adopted the four-tiered elasticity score which is easier to conduct and interpret with a good predictive value compared to the 5 and 6 tiered adopted by other studies (19, 20). Our results showed a significantly higher prevalence (88.9%) of metastatic ALN in elasticity scores 3 and 4 compared to (11.1%) score 2, whereas score 1 did not associate with any metastatic ALN. This was in agreement with Choe et al. 2011 who used a 4 tired score modified from Alam's5-tiered score (18, 19).

Strain elasticity ratio, in our cohort, was referenced to axillary fat as recommended by many studies (18, 21). Mean SR was significantly higher in metastatic ALN. In the literature, different cutoff values were suggested depending on the cohort characteristics, referenced tissue, and the targeted predictive value. To reduce unnecessary invasive procedures in borderline ALN, we were aiming for the highest sensitivity and compromising on specificity. Therefore we suggested a cutoff value of 2.1 with an NPV of 100% and a specificity of 66.7% which was higher than the specificity of cutoff value (1.5) proposed by Lyshchik et al. (20).

Based on our findings, we proposed an algorithm for borderline ALN management, figure 3, by stratifying the risk into, a low-risk group with an elasticity score of 1 or 2 and SR< 2.1 who could be followed up for 6 months. A high-risk group with an elasticity score of 3 or 4 and strain ratio ≥ 2.1 should undergo FNAC. The intermediate-risk group includes two categories when ES is 1 or 2 but the SR is 2.1 or higher or when the ES is 3 or 4 but the SR is lower than 2.1. In both situations, FNA is recommended if a suspicious breast lesion (BIRADS IV or V) was identified in the ipsilateral side, otherwise, the patient would be scheduled for following up. A prospective study with a calculated sample size, however, would be required to evaluate the validity of this algorithm.

The study limitations included small sample size and a small number of participants in some subgroups. For better differentiation of benign lymph nodes from one another such as granuloma for reactionary purposes more cases in subgroups would be required.

Conclusion

A high proportion of borderline ALN is not malignant. Strain elasticity can improve the risk stratification of such cases and prevent unnecessary invasive procedures. We suggested an algorithm that could better tackle borderline ALN which will need further evaluation.

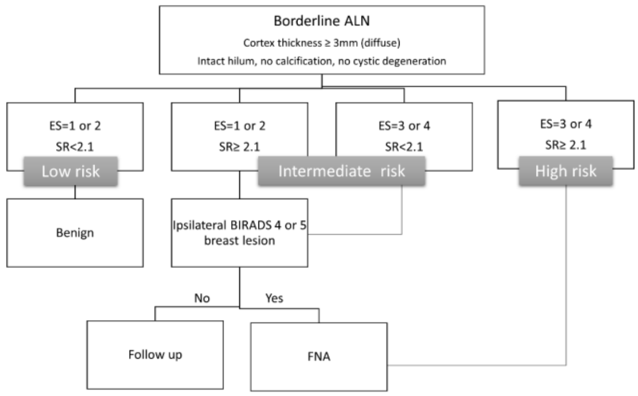


Figure 3. A flow chart illustrates a management algorithm for borderline axillary lymph nodes. Abbreviation, axillary lymph nodes (ALN), elasticity score (ES), strain ratio (SR).

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Conflict of Interest

No conflict of interest

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