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Can Strain Elastography Improve the Diagnosis of Unilateral Axillary Lymphadenopathy?

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Abstract

Background: Prompt evaluation of unilateral axillary lymphadenopathy may be challenging. Though it is most commonly caused by benign disorders, it may be the first sign of breast cancer.

Aim of Study: To assess the diagnostic performance of strain elastography in the evaluation of unilateral axillary lymphadenopathy and whether it can improve the reliability of conventional ultrasound and avoid unnecessary interventional procedures.

Patients and Methods: This study included 77 female patients who were referred from the surgical outpatient clinic for the evaluation of unilateral, clinically palpable axillary lymphadenopathy. Gray scale ultrasound and strain elastography were performed, and final categorization of lymph nodes was done individually. The results were then compared to the histopathology results, sparing those who were categorized by imaging as non-specific lymph nodes, for whom follow-up was performed.

Results: In this prospective study, 51/77 (66.2%) lymph nodes were non-specific or reactive, and 26/77 (33.8%) lesions were malignant or metastatic. In comparison to strain elastography, which had a sensitivity of 86.36% and a specificity of 65.45%, and overall accuracy of 71.43%, ultrasound results analysis had a greater sensitivity of 92.7% and a comparable specificity of 64.3%, and a greater overall accuracy of 74.03%.

Conclusions: Strain elastography can be used as a complementary imaging tool to ultrasound examination in the evaluation of unilateral axillary lymphadenopathy. Guided by the patient's clinical data, it can increase our confidence in the diagnosis, allowing for short-interval follow-up with a subsequent reduction in the rate of interventional procedures.

Key Words: *Axillary lymph nodes – Ultrasound – Strain elastography.*

Introduction

UNILATERAL axillary lymphadenopathy can present a diagnostic dilemma. A range of benign and malignant disorders can cause it. The most frequently encountered axillary lesion is benign reactive lymphoid hyperplasia, which is caused by inflammation of the lymph nodes or surrounding organs (e.g., breast or lung). Collagen vascular disorders like rheumatoid arthritis and scleroderma may potentially be a cause as well [1].

On the other hand, it may be the first sign of malignancy that necessitates prompt evaluation of the breast while searching for a primary disease. Moreover, in breast cancer cases, the pathological status of axillary lymph nodes (ALN) plays a critical role in its staging and management [2]. Preoperative knowledge of lymph node status enables the decision of axillary lymph node dissection (ALND) to be made in the appropriate clinical setting. This allows cost reduction and minimizes the risk of post-operative complications [3]. Therefore, differential diagnosis of metastatic ALN is highly desirable.

The primary imaging modality used in the examination of axillary lymph nodes is ultrasound (US). Sono-elastography is a non-invasive imaging technique used to assess elasticity. Its theory is based on the fact that malignant masses have a higher cell density and thus a higher stiffness. This technique includes strain elastography (SE) and shear wave elastography (SWE) [4]. SE is a qualitative technique that uses ultrasound waves to

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List of Abbreviations:

ALN : Axillary lymph nodes.
ALND : Axillary lymph nodes dissection.
US : Ultrasound.
SE : Strain elastography.
SWE : Shear wave elastography.
SNB : Sentinel node biopsy.
LN : Lymph node.
ROI: : Region of interest.
PPP : Positive predictive value.

quantify relative tissue displacements based on stiffness and generate an elastographic map [5].

Our aim in this study was to assess the diagnostic performance and the added role of strain elastography in the evaluation of unilateral axillary lymphadenopathy and whether it could avoid unnecessary interventional procedures.

Patients and Methods

This study was a prospective analysis, approved by the ethics committee at our institute and was performed in the period from June 2020 to December 2021.

Patient population: This study included 77 female patients who were referred from the surgical outpatient clinic of our institute. Their age ranged between 25 and 62 years (mean age: 41.01).

Inclusion criteria:

Patients presented solely withunilateral, clinically palpable axillary lymphadenopathy with no associated breast or upper arm pathology.

Exclusion criteria:

- Previous history of surgical or interventional procedures.
- Patients with bilateral axillary lymphadenopathy.
- Patients with known systemic diseases (e.g., collagen vascular disease).

Gray scale ultrasound and strain elastography were performed to evaluate their possible impact on accurate diagnosis and consequent guidance for management planning.

Ultrasound examination:

All patients were examined with B-mode ultrasound. Examinations were performed using (GE LOGIQ S8 and GE LOGIQ P7) which includea multi-frequency linear probe operating at 7.5 to 12 MHz. On B-mode sonography, lesions were evaluated regarding their size, shape, cortical thickness, presence of fatty hilum, and calcifications.

Strain elastography:

Elastography images were obtained by placing the transducer with coupling gel on the skin and then the considered lymph node was focused upon. After activating the strain elastography function, images were obtained by applying repeated compression and decompression at a sustained frequency. Color coding is superimposed on the translucent B-mode images. To get a correct elastography map, the process was repeated until a stable image was obtained.

The strain indices of the lesions were determined to evaluate the elastography images. To accurately determine the degree of stiffness of the lesion, an internal reference was elicited approximately at the same level as the concerned area and was selected as channel 1, and the region in the lymph node was selected as channel 2; the region of interest was chosen as the thickest part of the cortex. The strain ratio was calculated automatically as the strain observed on channel 1 divided by the strain measured on channel 2.

Image analysis:

The recorded findings were analyzed by two experienced breast radiologists with at least 10 and 12 years of field experience, who were blinded to the patients' clinical background, as well as each other's results, and agreement was achieved in consensus. Final diagnosis was correlated to the pathology results (obtained by cytology, core biopsy, and/or following a surgical procedure)in all cases sparing those categorized by imaging as non-specific lymph nodes that were found in 11/77 (14.3%) cases.

On ultrasound examination, lymph nodes were classified into four groups: Non-specific, reactive, indeterminate, or pathological based on their morphological criteria. Average cortical thickness (<3mm) with preserved fatty hilum was considered non-specific. Concentric diffuse cortical thickness-with preserved fatty hilum was considered reactive. Focal cortical thickening of any size and/or focal indentation or displacement of the fatty hilum were considered indeterminate. Globular and/or hypoechoic lymph node with lost fatty hilum were considered pathological. Non-specific and reactive lymph nodes were considered benign, while indeterminate and pathological lymph nodes were considered suspicious.

On strain elastography, qualitative analysis, using the color scale, and semi-quantitative analysis, using the strain ratio, of the examined axillary lymph nodes were performed. The lymph node was given an elasticity score ranging from 1 to 5 based on the percentage of stiff areas that were colored in blue (either absent or very small, <50%, >50%, almost occupying all of the cortex, almost occupying all of the cortex with a green line at the periphery). Lymph nodes with a score of 1 or 2 were regarded benign, whereas those with a score of 3, 4, or 5 were suspicious. A strain ratio was obtained from the most concerning nodes and compared to normal tissue nearby. We used a strain ratio of 3 as a cut-off value between malignant and reactive lymph nodes based on the literature and previous research [6]. The final categorization was based on a combination of semi-quantitative and qualitative analysis, with the most suspicious finding taken into account.

Pathological analysis:

The diagnosis was established by means of a core needle biopsy or cytology (considered as the standard reference) except in 11/77 (14.3%) cases in which non-specific lymph nodes were assigned by imaging. To ensure benign pathology, short-term follow-up (1 month) was done in cases with biopsy proven reactive lymph nodes. In cases with pathologically proven malignant lymph nodes, reference to the final surgical pathology was made.

Statistical analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 22. Epi calc Qualitative data was presented by number and percentage, while quantitative data was presented by mean, standard deviation, median, and range. Statistical tests with ROC curve analysis were done to detect sensitivity, specificity, positive predictive value, and negative predictive value. The Parametric *t*-test and ANOVA were performed, and the non-parametric Chi-square test was also performed. The level of significance was considered if the *p*-value was equal to or below 0.05. A correlation was done using the Pearson correlation coefficient and the level of significance was considered equal to or below 0.05.

Results

This prospective study included 77 female patients with unilateral axillary lymphadenopathy who underwent ultrasound examination and real time ultrasound elastography. According to the final histopathological results, 51/77 (66.2%) lymph nodes were found to be non-specific or reactive, while 26/77 (33.8%) lymph nodes were found to be malignant or metastatic.

Gray scale ultrasound:

Based on the combined US criteria, a final diagnosis of the examined lymph nodes was assigned, whether they were non-specific or reactive, indeterminate or pathological lymph nodes. Thirty-five out of 77 lymph nodes were diagnosed as benign, either non-specific (11/35 cases, 31.4%) or reactive (24/35 cases, 68.6%), out of which 2/24 (8.3%) cases were malignant as verified by pathology (false negative).

Conversely, 42/77 (54.5%) lymph nodes were considered suspicious, out of which 24/42 (57.1%) lymph nodes were considered indeterminate and 18/42 (42.9%) lymph nodes wereconsidered pathological. Among the assigned suspicious lymph nodes, 18/42 (42.9%) lymph nodes were benign as verified by pathology (false positive), as emphasized in Tables (1,2). Based on our results, the calculated sensitivity of the ultrasound examination was 92.3%, the specificity was 64.7%, and the total accuracy was 74.0%, as illustrated in Table (3).

Table (1): Correlation between final categorization by ultrasound examination and final pathology.

Ultrasound Diagnosis	Operative findings			
	Negative		Positive	
	Count	%	Count	%
Non specific	11	100	0	0
Reactive	22	91.7	2	8.3
Indeterminate	14	58.3	10	41.7
Pathological	4	22.2	14	77.8

Table (2): Correlation between the final diagnosis by ultrasound examination and strain elastography with final pathology.

	True positive	True negative	False positive	False negative
- Diagnosis by ultrasound	24	33	18	2
- Diagnosis by strain elastography	19	36	19	3

Table (3): Diagnostic indices of ultrasound examination versus strain elastography in the diagnosis of axillary lymph nodes.

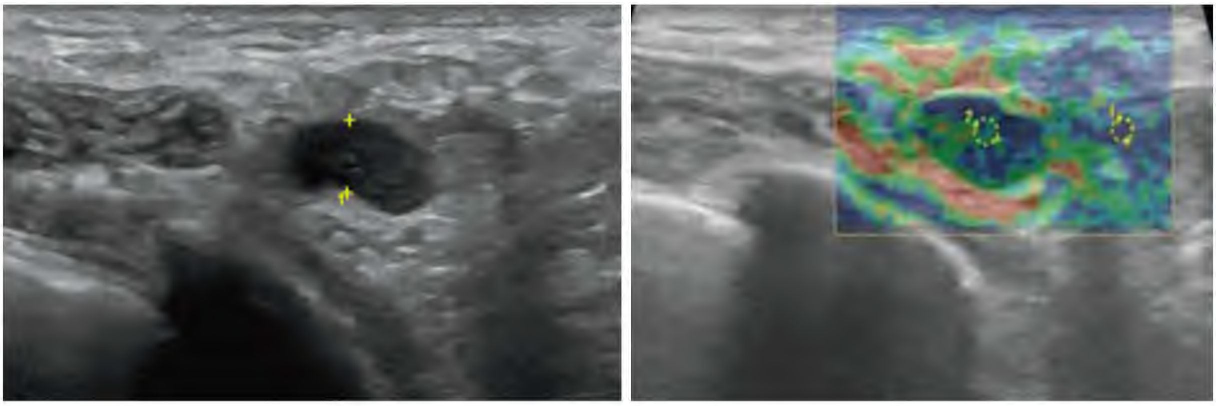
Statistics	Ultrasound (95% CI)	Strain Elastography (95% CI)
- Sensitivity	92.31% (74.87% to 99.05%)	86.36% (65.09% to 97.09%)
- Specificity	64.71% (50.07% to 77.57%)	65.45% (51.42% to 77.76%)
- Positive Predictive Value (*)	57.14% (47.50% to 66.27%)	50.00% (40.13% to 59.87%)
- Negative	94.29% (81.10% to 98.45%)	92.31% (80.47% to 97.22%)
- Predictive Value (*) Accuracy (*)	74.03% (62.77% to 83.36%)	71.43% (60.00% to 81.15%)

Considering the cortical thickness, it was observed that malignant lymph nodes had significantly higher maximal cortical thickness compared to benign lymphnodes. Based on the analysis of the depicted hilar changes in this study (present/absent), there was a significant positive correlation between lost fatty hilum and malignant lymph nodes (p-value <0.05, r:0.6405) (Fig. 1).

Strain elastography:

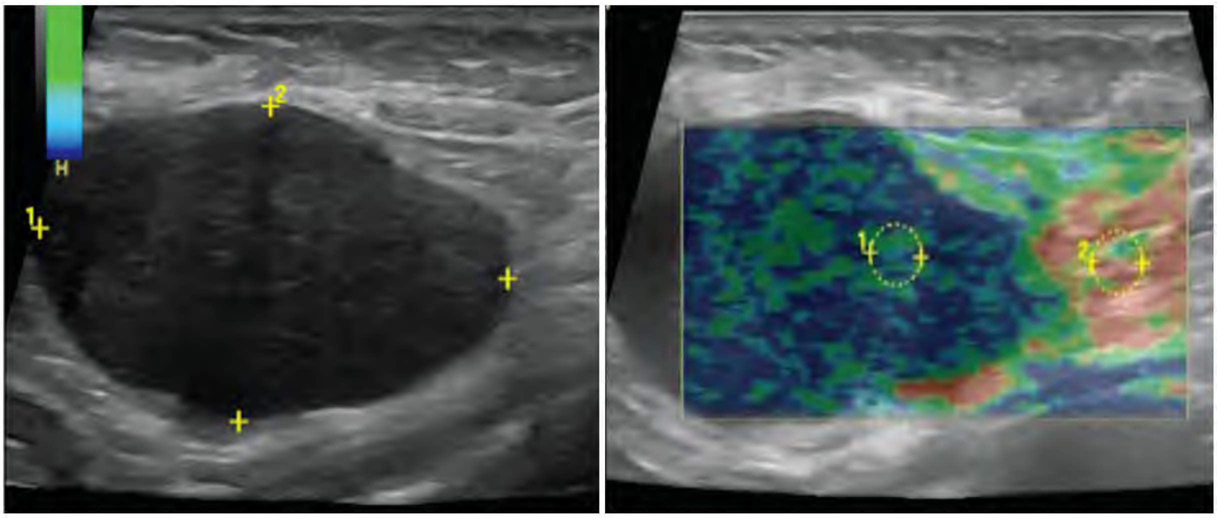
Based on the color-coded score map, 13/77 (16.9%) nodes had a score of 1, 26/77 (33.8%) had a score of 2, 21/77 (27.3%) had a score of 3 (blue >50%), and 17/77 (22.1%) had a score of 4 and 5. Based on the analysis of strain ratio, 37/77 lymph nodes had an estimated strain ratio of >3 (used as a cut-off value). Final categorization was based on combining both quantitative and qualitative analysis.

Thirty nine (39/ 77, 50.6%) lymph nodes were considered benign, out of which 3/39 (7.7%) were malignant by pathology (false negative) (Fig. 1). Conversely, 38/77 (49.4%) lymph nodes were considered suspicious; out of which 19/38 (50%) were benign by pathology (false positive), as shown in Table (2). The mean strain ratio for both reactive and malignant LNs was obtained. It was found that the mean SR for malignant lesions (3.723±2.604) was significantly greater than that for benign lesions (mean, 2.402±1.904) (p-value 0.045) (Fig. 2). On correlation to the final pathological results, the calculated sensitivity and specificity were 86.36% and 65.45%, whereas the overall accuracy was 71.4%. This was emphasized in Table (3).



(A) (B)

Fig. (1): A 50-year-old female with pathologically proven non-Hodgkin lymphoma. (A): Axillary ultrasound shows pathological axillary LN with lost fatty hilum (true positive). (B): SE shows enlarged axillary lymph node with elasticity score 2 and calculated strain ratio of 0.3 (false negative).



(A) (B)

Fig. (2): A 65-year-old female with pathologically proven metastatic axillary lymph node. (A): Axillary ultrasound shows pathological axillary LN with lost fatty hilum (true positive). (B): SE shows an enlarged axillary LN with elasticity score 3 and calculated strain ratio of 3.8 (true positive).

Discussion

Unilateral axillary lymphadenopathy is a more concerning clinical scenario than bilateral axillary lymphadenopathy. Despite its more common association with benign disorders, excluding an occult malignancy is crucial. There is no standardized management in this setting, varying from ultrasound follow-up to interventional procedures.

Moreover, the prediction of axillary lymph node (LN) status remains an important issue in the preoperative assessment of breast cancer patients. Sentinel node biopsy (SNB) is the standard option for women who are staged with a negative nodal status **[7]**. Nevertheless, the presence of preoperative axillary metastases will obviate the need for SNB and necessitate axillary LN dissection (ALND) with a resultant risk of significant increase in morbidity, such as lymphedema or paresthesia of the arm **[8,9]**.

Ultrasound remains the most suitable method for assessing the nodal status. Technical advances like ultrasound elastography, tissue harmonic imaging, andincreasing frequencies may allow better diagnostic performance **[10]**. Our study encompassed patients with unilateral axillary lymphadenopathy, and aimed to highlight the added role of strain elastography in diagnosis and nodal staging in cases of breast cancer.

On ultrasound examination, morphologic criteria, such as shape, cortical thickening, and hilar effacement were carefully analyzed. It was noted that the pathologically proven malignant LNs showed significantly higher maximal cortical thickness compared to benign lymphnodes. That was in accordance with Wojcinskil et al. **[11]**, who stated that the cortex for the metastatic lymphnodes was significantly broader (4.2mm versus 1.4mm, $p<0.001$). Similar findings have been reported by a study done by Rotim et al. **[12]**, who stated that cortical thickening of more than 5.1mm was associated with 87% sensitivity and 67% specificity for malignant disease. Also, Abe et al. **[13]** reported that cortical thickening was the most sensitive for the detection of axillary lymph node metastases.

A substantial positive correlation between lost fatty hilum and malignant lymph node was found in the current study (p-value 0.05). According to Abe et al. **[13]**, the lack of a fatty hilum had the highest positive predictive value and was the most specific indicator for nodal metastatic prediction in their study.

On combining the ultrasound imaging findings, a respective ultrasound sensitivity and specificity of 92.3% and 64.7% were achieved in our study. Comparable sensitivity and a lower specificity were achieved in our study as compared to a study performed by Xu et al. **[2]**, who reported a sensitivity of 92% and a specificity of 73%.

On the other hand, strain elastography is a feasible method to visualize the elasticity distributionof LNs. It might be capable of detecting elasticity differencesbetween metastatic and benign LNs. Hence, the thought of being able to yield additional information about axillary LN status and improve the positive predictive value (PPV) **[13]**.

Based on combining both semi-quantitative and qualitative analysis in our study, the achieved sensitivity and specificity were 86.3% and 65.45%, whereas the overall accuracy was 71.4%. Our results were higher than those reported by Choi et al. **[14]**, who achieved a sensitivity, specificity, andaccuracy of 82.8%, 56.3%, and 67.2%. Conversely, Xu et al. **[2]** achieved better specificity (76%) and diagnostic accuracy (81%) in their study. This may be attributed to the different techniques used in calculating the strain ratio, as in our study, we chose the thickest portion of the node on the gray-scale sonogram as the region of interest (ROI), similar to that reportedby Choi et al. **[14]**. Conversely, Xu et al. **[2]** evaluated the strain ratio indices on the deepest blue portion of the nodes.

When comparing the grey scale US to SE, the accuracy of SE was lower than that of grey-scale ultrasound. According to Park et al. **[1]**, in the examination of suspicious axillary lymph nodes in patients with breast cancer, SE has no significant advantage over conventional ultrasound. However, according to Xu et al. **[2]**, grey-scale ultrasound had a higher sensitivity than SE (92% vs 78%, $p=0.039$), while SE had a higher specificity (93% vs 73%, $p=0.012$).

The main limitations of this study are the lack of standardized technique and standardized interpretation of elastography images. This led to an evident discrepancy between the results of different research. We believe that in clinical practice, in-depth knowledge of the patient's clinical background is of utmost importance as it will greatly impact the way of interpretation.

Conclusions:

We concluded from this study that strain elastography can't be employed independently in the evaluation of axillary lymph nodes. It can be utilized as a complementary imaging tool to ultrasound examination into the evaluation of unilateral axillary lymphadenopathy. In the absence of known breast malignancy, and guided by the patient's clinical data, it can increase our confidence in the diagnosis and eliminate the necessity for interventional procedure.

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هل من الممكن تحسين تشخيص اعتلال العقد اللمفاوية الإبطى أحادى الجانب باستخدام التصوير الإلستوجرافى الإنفعالى ؟

قد يكون التقييم الفورى لإعتلال العقد اللمفاوية الإبطى الأحادى أمراً صعباً. على الرغم من أن السبب الأكثر شيوعاً هو الاضطرابات الحميدة، فقد يكون أول علامة على الإصابة بسرطان الثدى. الموجات فوق الصوتية هى طريقة غير جائرة وتلعب دوراً هاماً فى تقييم العقد الليمفاوية الابطية خاصة فى مرضى سرطان الثدى فيما قبل الجراحة. تعتبر التصوير الإلستوجرافى الإنفعالى أداة مكملة للموجات فوق الصوتية حيث يمكن تقدير صلابة الأنسجة بواسطتها. اعتماداً على المفهوم الراسخ إن الآفات الخبيثة تكون فى الغالب أكثر صلابة من الأنسجة الطبيعية.

هدفنا فى هذه الدراسة هو تقييم الأداء التشخيصى للتصوير الإلستوجرافى الإنفعالى فى تقييم اعتلال العقد اللمفاوية الإبطى الأحادى وقد أكدت الدراسة أنه لا يمكن اعتباره بديلاً عن الموجات فوق الصوتية التقليدية لكن بإمكانه تحسين موثوقية الموجات فوق الصوتية التقليدية فى بعض الحالات مما يؤدى إلى تجنب الإجراءات التدخلية الغير ضرورية والإكتفاء بمتابعة قصيرة المدى.