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Role of Strain Elastography in the Evaluation of Borderline Axillary Lymph Nodes in Breast Cancer Patients

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Abstract

Background: Detection of malignant infiltration in axillary lymph node remains a significant predictive factor in breast cancer with a significant impact on prognosis and staging. Elastography new ultrasound method developed that measures the stiffness of tissue can diagnose early malignant change in the cortex of lymph node and can help to decrease the use of invasive procedures.

Aim of the study: Analyzing strain elastography findings in borderline axillary lymph nodes in breast cancer patients.

Patients and method: This is a prospective cohort study conducted in the Breast Center/Shar Hospital / Sulaymaniyah City/ Iraq, in a period of one year between October 2022 and October 2023. Forty-two patients 2 males and 40 females with newly diagnosed breast cancer were included in the study, we examined the patients with conventional ultrasound and elastography with a 7.5-12MHz superficial linear transducer using Samsung HS60 and Samsung V7 ultrasound machines. After determining whether borderline axillary LNs were present ultrasound elastography was performed for the borderline lymph node, and each case was properly described and reported. After gray-scale ultrasonography, Elastography (real-time Elastography) was conducted. In our study, we used a 5-point scoring system. To determine the strain ratio, a circular region of interest (ROI) was positioned in the axillary fat, and the second ROI was set at the same level and of the same size over the stiffest part of the lymph node being studied. The final reference was the histopathological result of the core needle biopsy of the examined lymph node.

Results: A total of 42 patients were studied, the age range was between 33- 77 years old. 54.8% (n=23) of our patients were negative for malignant cells, whereas 45.2% (n=19) were positive. The strain ratio (SR) of the negative results for malignant cells (1.8 ± 0.9) was much lower than the positive results (4.7 ± 1.4). Two-thirds (65.2%, n=15) of the negative results had SR less than 2.1 and the rest 34.8% (n=8) were ≥ 2.1. On the contrary, the positive results, (94.7%, n=18) were ≥ 2.1, and only 5.3% (n=1) was below 2.1, with a statistically highly significant difference (P<0.001). Regarding elasticity score, more than half (56.5%, n=13) of the patients with negative results for malignant cells have score 2, about one-third (34.8%, n=8) have score 3, and 4.3% (n=1) have score 4, also, score 1 was 4.3% (n=1). Paradoxically, the majority of the positives (52.6%, n=10) have score 3, followed by score 4 (21.1%, n=4) then score 2 (15.8%, n=3) then score 5 (10.5%, n=2). With a significant difference (P=0.027).

Conclusion: The strain ratio and elasticity score of malignant borderline axillary lymph node is much higher than that of benign lymph node, making this new ultrasound method superior to B-mode in the detection of early malignant infiltration to the cortex of axillary lymph node. These two non-invasive methods (B-mode ultrasound and elastography) can be used together to increase diagnostic accuracy. 65.2%, (n=15) of the negative results had SR less than 2.1 whereas 94.7% (n=18) of malignant cases had a strain ratio ≥ 2.1. Regarding elasticity score 60% of benign cases had scores 2 and 1, whereas 84% of malignant cases had scores 3,4, and 5.

Keywords: Borderline or unspecified axillary lymph node, Elastography, Strain elastography, Strain ratio, Elasticity score.

Introduction: The status of axillary lymph nodes remains a crucial determinant in the prognosis of early-stage breast cancer, influencing disease staging and guiding appropriate surgical and systemic treatment decisions. However, evaluating borderline or unspecified axillary lymph nodes presents a significant diagnostic challenge (1). These nodes, characterized by normal size and preserved echogenic hilum but with eccentric cortical thickening, focal bulge, or irregularities, cannot be definitively classified as benign or malignant using conventional B-mode ultrasound (2). This diagnostic uncertainty often leads to therapeutic dilemmas, as unnecessary aggressive interventions on axillary lymph nodes can result in complications such as lymphedema, infection, fluid collection, motion limitation, and numbness. While imaging criteria can identify benign and malignant axillary lymph nodes, there is a lack of data on borderline or unspecified axillary lymph nodes (BALNs) that do not fully meet the criteria for either category. Real-time elastography (RTE) has emerged as a novel ultrasound technique that offers a non-invasive method to differentiate malignant from benign, borderline axillary lymph nodes (3).

RTE examines the stiffness or hardness of tissue based on the principle that external pressure will deform softer tissue more quickly than hard or stiff tissue. This tissue deformity assessment by external pressure has been applied to differentiate benign from malignant BALNs (4). To understand the context of this diagnostic challenge, it is essential to review the anatomy and structure of lymph nodes. Lymph nodes are complex structures consisting of a capsule, subcapsular sinus, cortex, and medulla. The cortex, in particular, plays a crucial role in the immune response and is the initial site of tumoral infiltration in cases of metastasis (5).

Axillary lymph nodes are classified into five groups: anterior (pectoral), posterior (subscapular), lateral (humeral), central, and apical. These nodes drain lymph from the upper limb, breast, and trunk above the umbilicus (6). Understanding this anatomical arrangement is crucial for accurate assessment and staging in breast cancer patients. Ultrasound is the primary diagnostic method for examining axillary lymph nodes, typically using a probe with a frequency of 7.5 MHz or higher. Normal axillary lymph nodes on ultrasound appear oval-shaped with a preserved echogenic fatty hilum and cortical thickness less than 3 mm. However, early malignant changes can be subtle, presenting as focal cortical changes, eccentric cortical thickening, or focal bulges while maintaining a standard overall shape and size. The limitations of conventional ultrasound in accurately characterizing these borderline nodes have led to the exploration of advanced imaging techniques, such as elastography. Elastography, first conceptualized in the 1950s and practically applied in the 1980s, has evolved significantly over the past few decades. Ultrasound elastography (USE) is a tissue imaging technique that detects variations in tissue stiffness, providing an additional quantifiable characteristic to enhance traditional ultrasound imaging (7-10).

There are several methods of ultrasound elastography, broadly categorized into strain imaging and shear wave imaging. Strain elastography (SE), the focus of this study, can be further subdivided based on the excitation method: manual compression by the operator or internal physiologic motion (11). The induced tissue displacement is measured, and the results are displayed as a color-coded elastogram overlaid on the B-mode image. Strain elastography offers several advantages in the assessment of axillary lymph nodes. It can evaluate the rigidity of both the cortex and medulla of lymph nodes, potentially identifying early localized malignant infiltration. The technique is non-invasive, real-time, and can be performed as an adjunct to conventional ultrasound examination, potentially improving diagnostic accuracy without additional patient discomfort or radiation exposure. The application of strain elastography in evaluating borderline axillary lymph nodes holds promise for addressing the current diagnostic challenges (12, 13).

Providing additional information about tissue stiffness may help differentiate between benign and malignant nodes in cases where conventional ultrasound findings are equivocal. This could reduce unnecessary biopsies or surgical interventions while ensuring that truly malignant nodes are not overlooked (14). However, the role of strain elastography in this specific clinical scenario is the evaluation of borderline axillary lymph nodes in breast cancer patients that require further investigation. While the technique has shown promise in various applications, including breast lesion characterization and assessment of cervical lymph nodes, its specific utility and diagnostic performance in borderline axillary lymph nodes need to be established (15). This study aims to evaluate the role of strain elastography in assessing borderline axillary lymph nodes in breast cancer patients. By comparing strain elastography findings with histopathological results, we seek to determine the technique's sensitivity, specificity, and overall diagnostic accuracy in this challenging subset of lymph nodes. Additionally, we aim to identify any elastographic features or patterns that may be particularly indicative of malignancy in borderline nodes.

Materials and Methods :This prospective study was conducted at the Breast Cancer Center, Shar Hospital, Sulaymaniyah, Iraq, from October 2022 to October 2023. The study included 42 patients with newly diagnosed breast cancer who had borderline axillary lymph nodes, as confirmed by conventional ultrasound imaging. The study was approved by the Scientific Board

Committee of the Iraqi Board of Diagnostic Radiology, and verbal consent was obtained from all participating subjects after explaining the details and benefits of the research.

1.1. Study Design and Timing

Three board-certified breast radiologists conducted the study with 5 to 10 years of experience in the breast center. After determining the presence of borderline axillary lymph nodes, ultrasound elastography was performed on the borderline lymph nodes, and each case was adequately described and reported.

1.2. Patients

The study population comprised 42 patients, including 40 females and two males, aged 33 to 77. After explaining the details and benefits of the research, verbal consent was obtained from all patients.

1.3. Inclusion Criteria

Patients with proven breast cancer who were sent for ultrasound assessment of axillary regions and had borderline axillary lymph nodes (defined as a lymph node with standard size, short axis of 10mm or less, oval shape, preserved echogenic hilum, but with focal cortical thickness, irregularity, bulge, or diffuse increase in cortical thickness) were included in the study. These patients underwent elastography and a core needle biopsy of the examined lymph node.

1.4. Exclusion Criteria

Patients were excluded from the study if:

- Histopathological data was not obtained
- Axillary lymph nodes had all malignant features on B-mode ultrasound
- Axillary lymph nodes had all benign features on B-mode ultrasound

1.5. Equipment

At the Breast Center, Shar Hospital, Sulaymaniyah City, Iraq, patients were examined using conventional ultrasound and elastography with a 7.5-12MHz superficial linear transducer on Samsung HS60 and Samsung V7 ultrasound machines (Figure 1).


Figure (1): Samsung HS60 U/S machine (Left) Samsung v7 ultrasound machine, linear probe ((Right)

Technique and Procedure :Axillary lymph nodes detectable on conventional ultrasound imaging were examined, and each underwent elastography. The evaluation of axillary lymph nodes by grayscale ultrasound involved the utilization of five standard criteria: longitudinal and transverse diameter (short and long diameter), longitudinal-to-transverse diameter ratio, cortical thickness, hilum status, and vascular pattern. In the context of elastography, the proportion of the firm region within each lymph node was determined using visual judgment. The lymph nodes were evaluated synchronously utilizing a combination of ultrasound (US) and elastography. The final reference was the histopathologic result of the core needle biopsy of the examined lymph node. After gray-scale ultrasonography, elastography (real-time elastography) was conducted. A 5-point scoring system was used by Alam et al. in 2008 (20) to classify the qualitative US elastogram based on the blue portion in the cortex of the lymph nodes:

1. Nearly all of the cortex is green
2. Less than 50% of the cortex is blue
3. More than 50% of the cortex is blue
4. Nearly all of the cortex or more than 90% of the cortex is blue
5. The blue portion occupies almost all of the cortex and extends beyond the expected edges of the cortex with a green ring on the edge of the node

The histogram technique and assessment involved applying gentle compression and decompression using the ultrasonic transducer. The pressure index was increased and maintained for 2 or 3 seconds, producing a quality graph with continuous high peaks until a consistent image was achieved. The image was frozen for color analysis and strain ratio measurement. The dimensions of the region of interest (ROI) box were modified by the size of the chosen lymph node, ensuring that an adequate amount of surrounding reference fatty tissue was included (the reference area was to be at least one-third of the examined lymph node). The color spectrum spanned from red (representing the softest portion) to blue (representing the most challenging portion), and the color assessment was done by comparison with the color map. To determine the strain ratio, a circular ROI was positioned in the axillary fat, and another ROI of the same size was placed at the same level over the most rigid section (bluest part) of the lymph node being studied. The ROIs were positioned at the same plane to calculate the strain ratio accurately.

1.6. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, USA, version 27). The data were expressed as numbers (%) for categorical data and mean (standard deviation) for numerical data. The chi-square test was used for categorical variables, and an independent sample t-test and Mann Whitney-U test were used for parametric and non-parametric variables, respectively. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall test accuracy were calculated. A receiver operating characteristic (ROC) curve analysis was performed to measure the strain ratio. A p-value ≤ 0.05 was considered statistically significant.

2. Results

Figure (1) presents the demographic characteristics of patients segmented by age and gender. The data indicates that most patients are over 50 years old, with a notable gender distribution showing more males than females across all age groups (Figure 1).

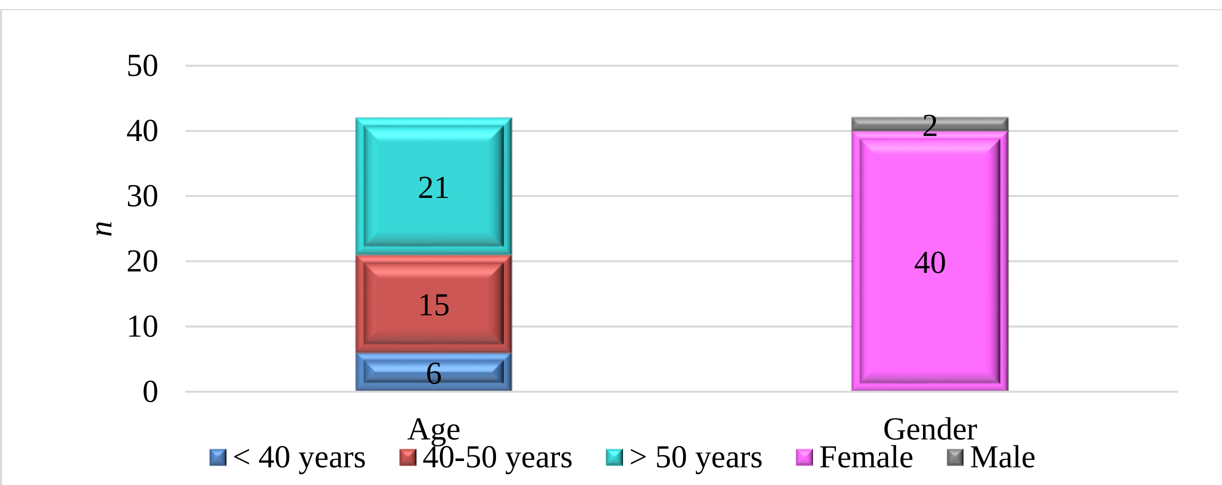

Figure (2). demographic characteristics of the patients.

Figure (2) presents the clinical characteristics of breast cancer patients evaluated through strain elastography. It categorizes data based on axis ratio, cortex thickness, and cytological impression.

The results indicate a distribution of lymph nodes with axis ratios less than 0.5 and greater than or equal to 0.5, alongside cortex thickness measurements of less than 3 mm and greater than or equal to 3 mm, highlighting the relationship between these factors and diagnostic outcomes.

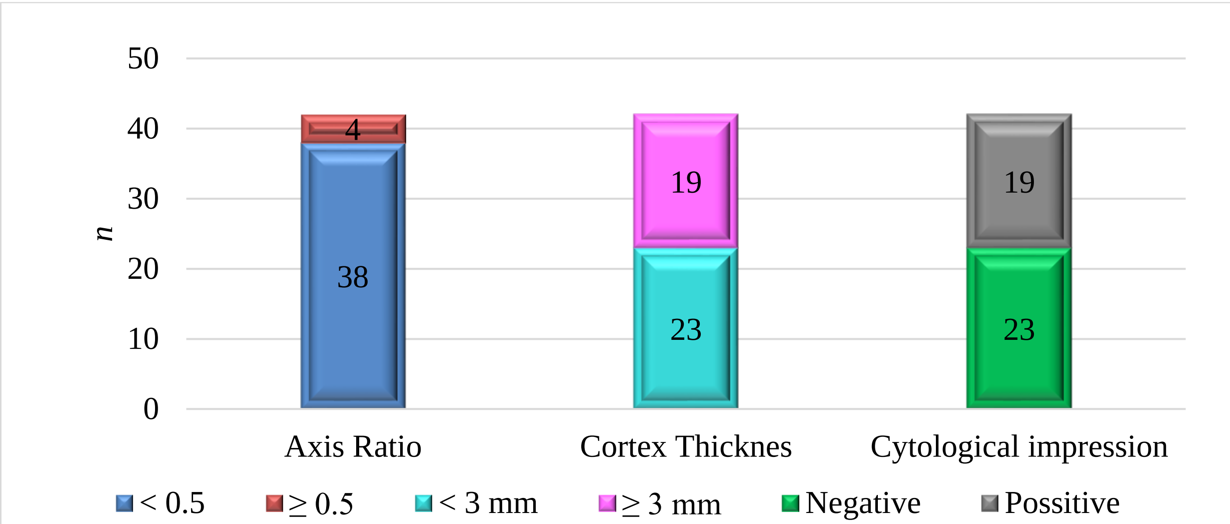

Figure (3). clinical characteristics of the patients.

Figure 3 presents the elastography features of axillary lymph nodes in breast cancer patients, comparing malignant and non-malignant cases. For axis ratio, 95.7% of benign cases had a ratio below 0.5, while 84.2% of malignant cases did. Cortex thickness showed that the mean for negative results was 2.9 mm, significantly lower than 3.4 mm for positive results (P=0.034). Regarding strain ratio, negative results averaged 1.8, while positive results averaged 4.7, with a highly significant difference (P<0.001). Regarding elasticity scores, most negative results scored 2, while most positive cases scored 3. The differences in elasticity scores were statistically significant (P=0.027).

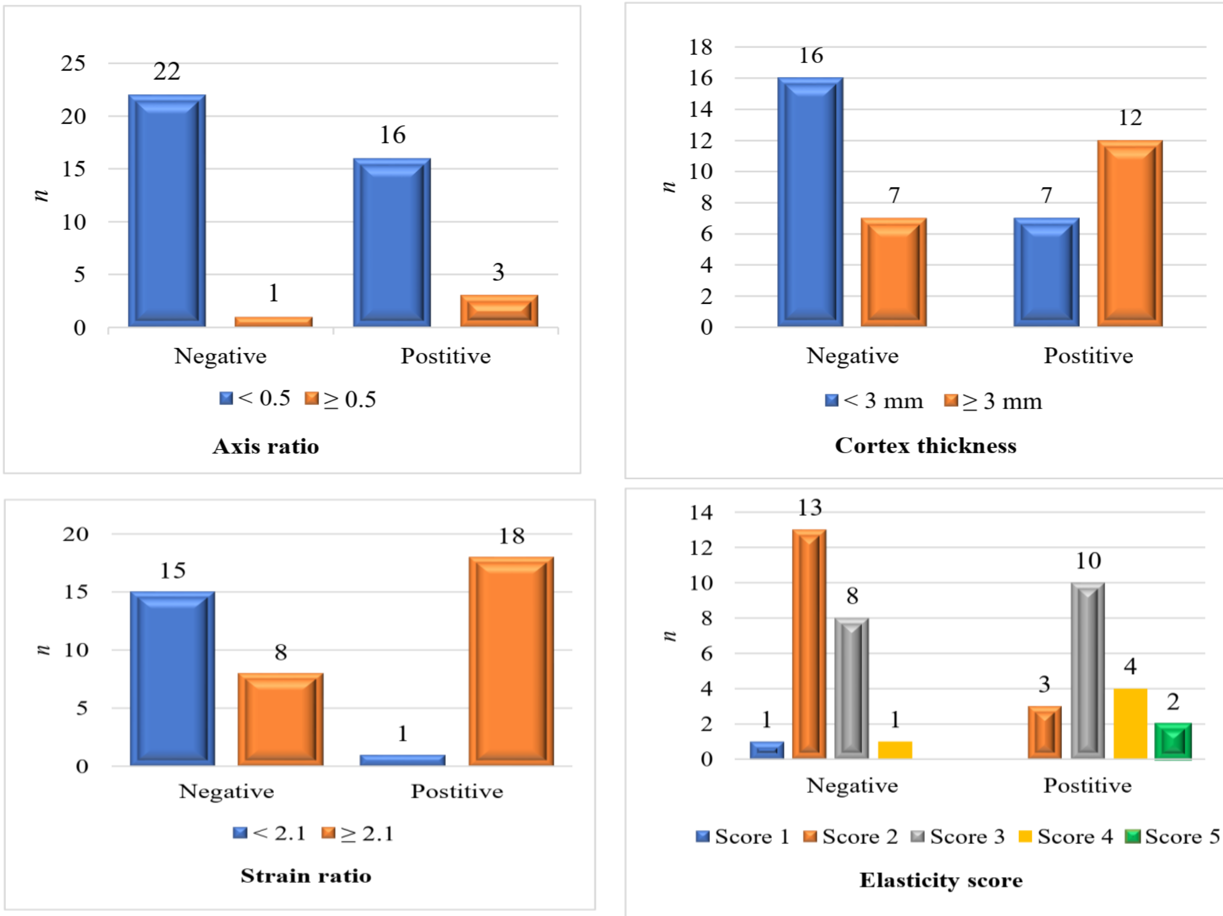

Figure (4). Mode and elastography features of the malignant and no malignant axillary lymph nodes.

Table (1): The table presents the validity measures of elasticity score (ES) and strain ratio (SR) in evaluating axillary lymph nodes in breast cancer patients. For SR < 2.1, the test shows perfect sensitivity (100%) and negative predictive value (100%), with high specificity (92.2%) and accuracy (94.5%). When SR ≥ 2.1, specificity increases to 95%, but sensitivity drops to 66.7%. For elasticity scores, ES 1, 2 & 3 combined demonstrate balanced performance with high sensitivity (92.3%), specificity (86.4%), and accuracy (88.7%). ES 4 & 5 show perfect specificity (100%) and positive predictive value (100%) but lower sensitivity (83.3%).

Table (1). Validity Of Elasticity Score And Strain Ratio.

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
SR < 2.1	100 %	93.3 %	50 %	100 %	87.5 %
SR ≥ 2.1	94.4 %	75 %	89.5 %	85.7 %	88.5 %
ES 1, 2 &3	92.3 %	86.4 %	80.0 %	95.0 %	88.6 %
ES 4 & 5	83.3 %	100. 0 %	100.0 %	50.0 %	85.7 %

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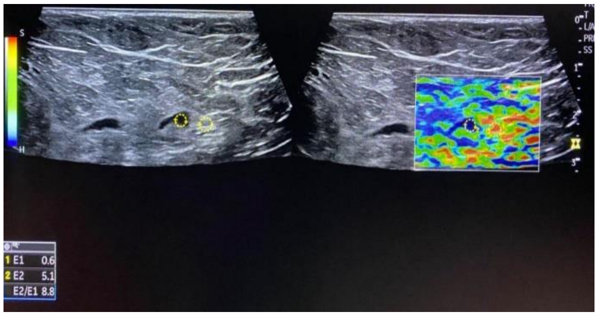
Figure (4) illustrates a range of elastography scores and strain ratios in axillary lymph nodes of breast cancer patients, along with their corresponding histopathological findings. The results suggest that higher elastography scores and strain ratios correlate with malignant findings, while lower scores are more often associated with benign results. However, there are exceptions, highlighting the importance of combining elastography with other diagnostic methods for accurate assessment of axillary lymph nodes in breast cancer patients.



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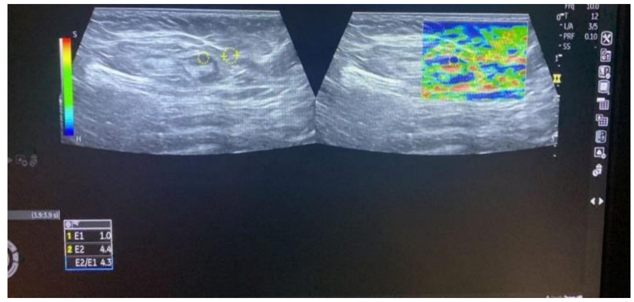

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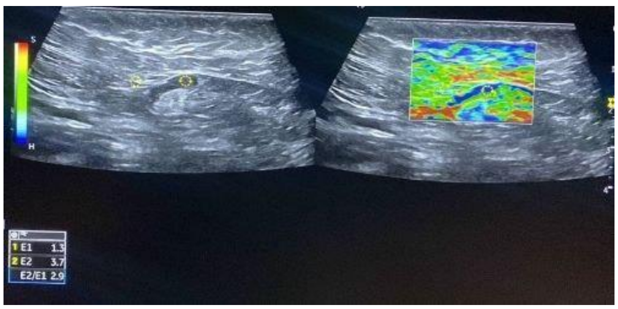

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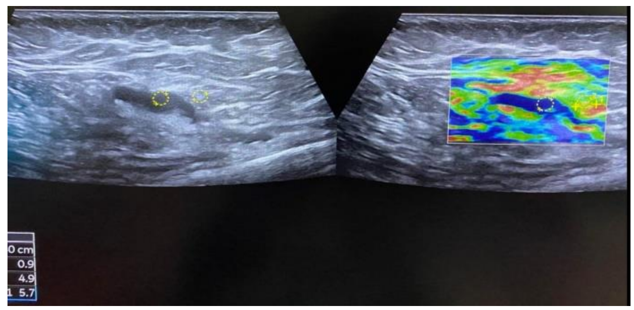
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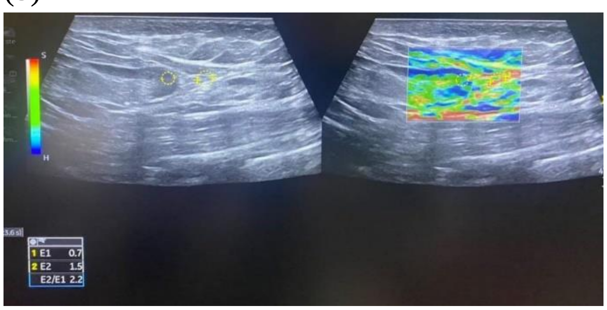

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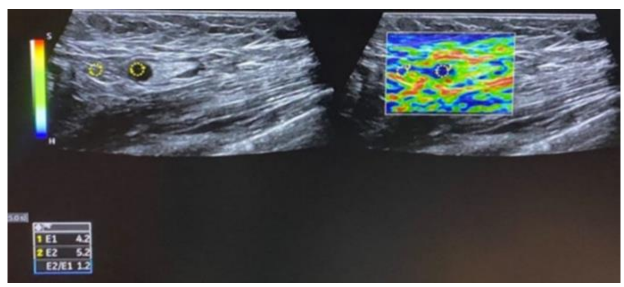


(6)

Figure (5). Elastography and Histopathological Findings in Axillary Lymph Nodes of Females with Breast Cancer

(1) 57-year-old female with breast cancer, Elastography score: 5, Strain ratio: 4.4, Core needle biopsy: Positive for malignancy, Post-operative histopathology: Confirmed malignant infiltrations

(2) Age not specified (possibly 54 years old), Elastography score: 3, Strain ratio: 5.7, Core needle biopsy: Positive for malignancy, Post-operative histopathology: Confirmed malignancy

(3) 48-year-old female with breast cancer, Elastography score: 1, Strain ratio: 2.9, Histopathology: Benign lymphoid tissue, negative for malignant cells

(4) 75-year-old female with right breast carcinoma, Elastography score: 5, Strain ratio: 6.4, Core needle biopsy: Positive for malignancy, Post-operative histopathology: Confirmed malignancy
(5) 60-year-old female with breast cancer, Elastography score: 2, Strain ratio: 3.3, Core needle biopsy and post-operative histopathology: Benign reactive lymph node, no malignant cells found
(6) 58-year-old female with left breast carcinoma, Elastography score: 3, Strain ratio: 1.3, Core needle biopsy and post-operative histopathology: Negative for malignancy

The elastoscore and strain ratio indicate malignancy in the ipsilateral borderline axillary lymph node. These findings were confirmed by ultrasound-guided core needle biopsy and postoperative lymph node dissection, which both tested positive for malignancy (Figure 5).

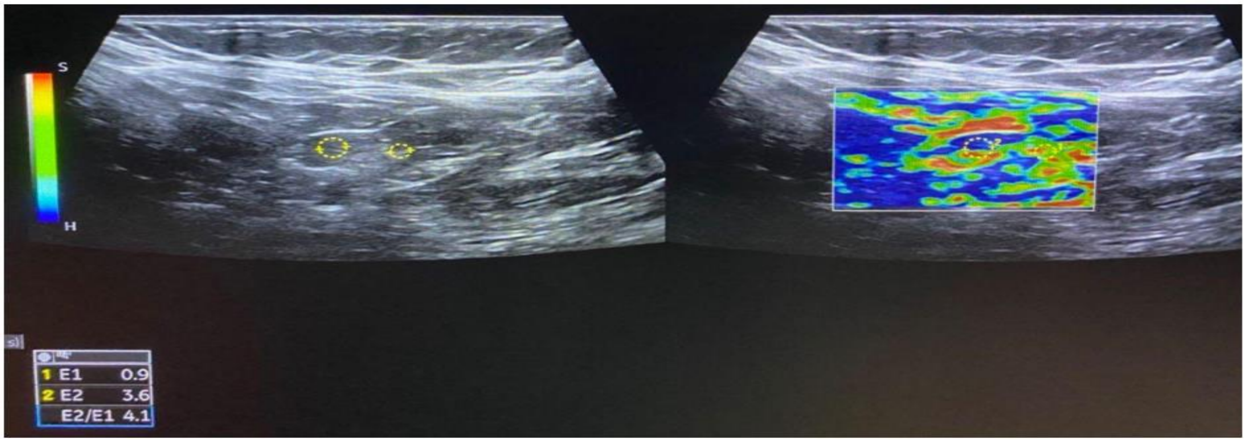
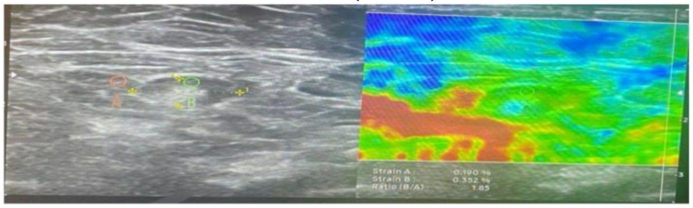


Figure (6). The elastography results of a 71-year-old male patient with breast carcinoma

The following Elastoscores demonstrate a progression from benign to malignant findings: As the Elastoscore increases from 1 to 5, the lymph node's blue coloration increases. Lower Elastoscores (1 and 2) correspond to benign histopathology, while higher scores (3, 4, and 5) correspond to malignant findings. The extent of blue coloration correlates with the likelihood of malignancy, with more blue indicating a higher probability of cancer involvement (Figure 6).



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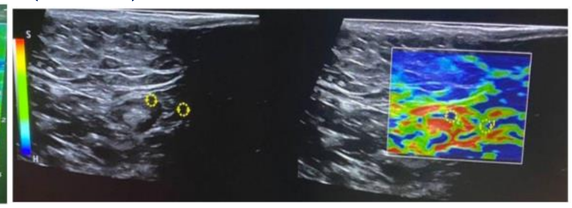

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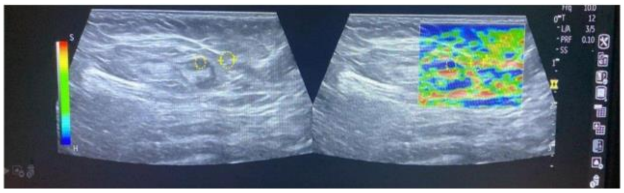

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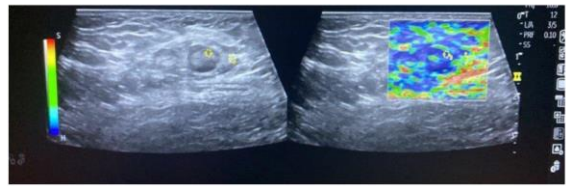

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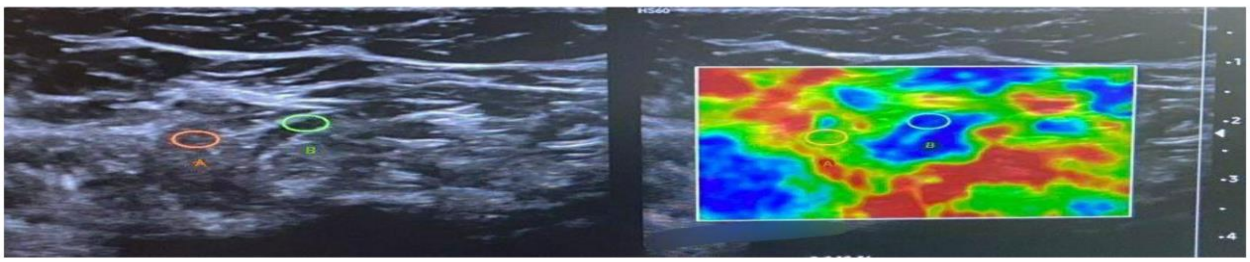

(5)

Figure (7). Different Elastoscores for lymph nodes (LNs) in breast cancer patients. Each figure corresponds to a different Elastoscore, ranging from 1 to 5, demonstrating the correlation between the elastography imaging and histopathological findings.

(1) The cortex of the lymph node appears utterly green in the elastography image. This corresponds to a benign lymph node, confirmed by histopathology showing normal lymphoid tissue without malignant cells. (2) Less than 50% of the cortex is blue. Histopathology of this lymph node was negative for malignancy. (3) more than 50% of the cortex is blue, with scattered green portions. Histopathology of this lymph node was positive for malignancy. (4) Nearly all of the cortex or more than 90% of the cortex is blue. Histopathology confirmed malignancy in this lymph node. (5) Nearly all lymph nodes are blue, extending beyond the expected edge. A green ring surrounds the outside edge of the node. Histopathology confirmed malignancy in this lymph node.

Discussion :The identification of malignant ALN plays a vital role in determining the outlook of breast cancer. It impacts the stage of the disease and assists in the selection of appropriate surgical approaches. The presence of unspecified (ALN) is frequently observed during the surveillance of patients with a breast cancer diagnosis. Moreover, its presence can be detected in non-malignant conditions. B-mode ultrasound aids in identifying malignant lymph nodes by observing specific malignant characteristics, such as a significant increase in cortical thickness, transformation from an oval shape to a round shape with a long-to-short axis ratio of less than 2, loss of hilar echogenicity, complete or partial loss of the hilum, and the presence of peripheral blood flow as detected by Doppler ultrasound. However, none of these characteristics are observed in borderline ALN cases. The level of suspicion for malignancy has decreased. Nevertheless, the potential for nodal metastasis cannot be completely ruled out. Additional methods are required to exclude the presence of malignant infiltration. These techniques may involve invasive procedures such as fine-needle aspiration cytology (FNAC), sentinel ALN biopsy, or excisional biopsy (15).

In such scenarios, using innovative ultrasound techniques like elastography proves highly beneficial. Elastography represents a non-invasive approach. Our investigation employed strain elastography to identify malignant lymph nodes within borderline axillary lymph nodes. These lymph nodes exhibit normal size, preserved echogenic hilum, and a round shape but display eccentric or focal thickness. The cortical thickness of the lymph nodes examined in our study ranged from 2.2mm to 4mm, with the maximum thickness observed being 4mm, while the thickness of the hilar fat remained intact. Following the implementation of strain elastography on the specific lymph node, we compared the obtained strain ratio (SR) and elastoscore with the histopathological findings. To determine the histopathological result of the ALN, we conducted a core needle biopsy on the lymph node and continued monitoring until the post-operative histopathological outcome was acquired (16,17).

Our cohort was formed based on stringent selection criteria, intentionally excluding highly suspicious lymph nodes. Instead, we focused on relatively small ALN that exhibited alterations in cortical thickness and subtle changes in shape, without consideration of the specific type of breast cancer. Within our research, encompassing a sample size of 42 patients, the diagnosis derived from elastography results and histopathological analysis revealed that the majority of our patients (54.8%) exhibited a benign condition. This outcome aligns with the discoveries of a separate investigation conducted in Baghdad by Muhi et al. in 2022 (18).

In histopathologically confirmed metastatic ALN, most short/long axis ratios were above 0.5. Conversely, in benign ALN cases, the predominant proportion of axis ratios was < 0.5. However, the observed difference was not deemed statistically significant. These findings align with the results reported by Muhi et al. in 2022 (18). The average cortical thickness in benign cases was significantly lower than that in malignant ALN. The majority of benign cases exhibited cortical thicknesses below 3, whereas the majority of malignant cases had cortical thicknesses ≥ 3. These findings are consistent with the research conducted by Ahmed et al. in 2021 (19).

Remarkably, the average strain ratio observed in malignant cells was notably higher compared to the ratio observed in benign cells. These findings align with the research conducted by Alam et al. in 2008 (20). Our study employed a five-point elasticity score, which exhibited a satisfactory predictive value. This approach closely resembles the methodology used in a study conducted by Alam et al. in 2008 (20). Notably, the average elasticity score was significantly higher in malignant cases than in benign cases, corroborating the findings of Choi et al. in 2012 (21). According to the results obtained, we determined that utilizing a cut-off value of strain ratio below 2.1 yielded higher sensitivity (100%) and specificity (93.3%) compared to employing a strain ratio of ≥ 2.1, which demonstrated specificity and sensitivity values of 75% and 94.4%, respectively.

In another study, the strain ratio (SR) of 2.6 was found to be a practical tool in accurately identifying axillary lymph node (ALN) metastasis, with a sensitivity of approximately 88.9% and a specificity of 83.3%. Equally important, the study also identified a strain ratio of 2.1, which demonstrated a sensitivity of 100% and a specificity of 66.7% (21). Within this investigation, it was observed that the elasticity scores of 1, 2, and 3 exhibited higher sensitivity (92.3%) but lower specificity (86.4%) compared to the scores of 4 and 5, which demonstrated sensitivity of 83.3% and specificity of 100%. A separate study conducted by Barr et al. in 2015 reported that an elasticity scores greater than 3 displayed a specificity of 83.33% and a sensitivity of 88.89% (22).

Conclusion: In conclusion, strain elastography demonstrates significant potential as a valuable tool in evaluating borderline axillary lymph nodes in breast cancer patients. The study findings reveal that elasticity scores and strain ratios correlate strongly with malignancy, offering high sensitivity and specificity in distinguishing between benign and malignant lymph nodes. Notably, strain ratios below 2.1 showed perfect sensitivity and negative predictive value, while elasticity scores of 4 and 5 exhibited perfect specificity and positive predictive value. Combining elastography with conventional ultrasound features, such as cortex thickness and axis ratio, enhances diagnostic accuracy. However, exceptions exist, emphasizing the importance of integrating elastography with other diagnostic methods for comprehensive assessment. This non-invasive technique could potentially reduce unnecessary biopsies and improve preoperative staging of axillary lymph nodes in breast cancer patients. Further research is warranted to standardize elastography criteria and validate its role in clinical decision-making.

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