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Original Scientific Paper

ULTRASOUND AND SHEAR WAVE ELASTOGRAPHY FOR DISTINGUISHING BENIGN AND MALIGNANT AXILLARY LYMPH NODES IN BREAST CANCER PATIENTS

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SUMMARY – This study aimed to assess the diagnostic efficacy of ultrasound (US) and shear wave elastography (SWE) in distinguishing benign and malignant axillary lymph nodes in patients with breast cancer. A total of 121 axillary lymph nodes from 61 breast cancer patients (mean age, 52.4±14.6 years) were enrolled between May 2019 and August 2020. Lymph nodes were histopathologically diagnosed through core needle biopsy or surgical excision. B-mode US features (short axis diameter, short-to-long axis diameter ratio, presence of echogenic hilum, presence of asymmetric cortical thickening, cortex thickness) were assessed and SWE measurements (maximum shear wave velocity (SWV_{max}), minimum SWV (SWV_{min}), median SWV (SWV_{median}), mean SWV (SWV_{mean})) were performed. There were 45 (37.2%) benign and 76 (62.8%) malignant lymph nodes. The short axis diameter, short-to-long axis diameter ratio, and mean cortical thickness of malignant lymph nodes were significantly higher compared to benign lymph nodes ($p<0.001$ all). SWV_{mean}, SWV_{median}, SWV_{max}, and SWV_{min} of malignant lymph nodes were significantly higher than those of benign lymph nodes ($p<0.001$ for all). Both US and SWE were useful in discriminating between benign and malignant axillary lymph nodes.

Key words: *Breast cancer; Lymph nodes; Elastography; Ultrasonography*

Introduction

Breast cancer stands as the most prevalent form of cancer among women and remains the leading cause of cancer-related fatalities[1]. The Breast Imaging-Reporting and Data System (BI-RADS), created by the American College of Radiology, serves as a cornerstone for radiological evaluation of breast lesions. This system provides a standardized language and reporting scheme for lesion evaluation. Lesions with a high risk of malignancy are classified into BI-RADS category 4 and category 5[2].

Axillary lymph node involvement stands as the most important prognostic factor in breast cancer. Nodal involvement affects staging and subsequently alters treatment approach. The presence of nodal metastasis reduces the five-year survival rate by approximately 40% compared to patients without nodal metastasis[3]. Due to the reduced morbidity associated with axillary lymph node dissection, sentinel lymph node biopsy is preferred in patients with low risk of axillary nodal metastasis. The status of the sentinel lymph node

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serves as an indicator of the overall axillary lymph node involvement. However, false-negative results are possible with sentinel lymph node biopsy[4,5].

Noninvasive radiological imaging techniques are commonly used to assess axillary lymph node involvement in the preoperative period. Ultrasound (US) has higher diagnostic accuracy in detecting axillary lymph node metastasis compared to other imaging modalities[6-8]. US assessment includes long and short axis diameter of lymph node, presence of echogenic hilum, and measuring cortical thickening[9-12]. However, axillary US alone may not be sufficient as a standalone examination modality and can determine benign and malignant lymph node diagnoses with moderate sensitivity[13].

Elastography is a US-based imaging modality that measures tissue stiffness. It has been developed and widely used in recent years to provide quantitative evaluation of tissue stiffness[14]. Several studies have shown that malignant lesions in organs such as the breast, thyroid and parathyroid glands, lymph nodes, and prostate are stiffer than benign lesions[15-18]. Metastatic axillary lymph nodes are stiffer compared to benign inflammatory lymph nodes[19,20]. In this study, we aimed to investigate diagnostic value of US and elastography in differentiating benign and malignant axillary lymph nodes in patients with breast cancer.

Materials and Methods

This prospective study was approved by the Ondokuz Mayis University Clinical Research Ethics Committee, protocol number B.30.2.ODM.0.20.08/686. Written and verbal consent was obtained from all participating patients.

Study design, US and SWE examinations

Between May 2019 and August 2020, a total of 121 lymph nodes from 61 patients (mean age: 52.4±14.6 years) were examined.

The US and shear wave elastography (SWE) evaluations were conducted by a radiologist (I.K.B., 17 years of experience in breast radiology) and senior radiology resident (C.K.). The US and SWE evaluations were performed using Siemens ACUSON S2000 (Siemens Medical Solutions, Mountain View, CA, USA) equipped with 9 MHz and 18 MHz linear probes.

During B-mode US evaluation, the following features of the lymph nodes were assessed: long and short axes of lymph nodes, and short axis to long axis diameter ratio, presence of echogenic hilum, presence of asymmetric cortical thickening in lymph nodes with echogenic hilum, and cortex thickness of the lymph node. In lymph nodes without echogenic hilum, the short axis of the lymph node was considered as cortical thickness.

Elastography examination was performed using the Virtual Touch Tissue Imaging Quantification (VTIQ) function of the device. A sufficient amount of gel was applied to the area where the lymph node would be examined to prevent compression by the operator. After activating the VTIQ function of the device, the region of interest (ROI) box was placed to cover the entire lymph node and a small portion of the surrounding tissue, and a shear wave velocity (SWV) map was generated. In this map, the stiff areas of the lymph node were color-coded in red, whereas the soft areas were color-coded in green. The SWV measurement range was set at 0-10 meters *per* second (m/s). Shear wave quality maps were also generated for each evaluation, and SWV measurements were performed from the green areas representing high-quality SWV measurements. Within the cortex of the examined lymph node on the SWV maps, 5-7 small ROIs measuring 2×2 mm were placed, and SWV measurements were noted. The ROIs were positioned in the color-coded areas representing the stiffest parts of the cortex on the SWV map. Subsequently, a single 2×2 mm ROI was placed in the neighboring fatty tissue, selected as a reference at the same level, and measurement was taken (Fig. 1). The maximum SWV (SWV_{max}), minimum SWV (SWV_{min}), median SWV (SWV_{median}), mean SWV (SWV_{mean}) of the lymph nodes, and the ratio of SWV_{mean} to the SWV of the reference fatty tissue (SWV_{ratio}) were used on statistical analysis.

To assess the interobserver validity of the SWE examination, the measurements of 50 randomly selected lymph nodes were repeated by a second observer (I.K.B.).

Histopathologic examination

Pathologic diagnosis was established through either core needle biopsy (tru-cut biopsy) or surgical excision of the measured lymph nodes. Core needle

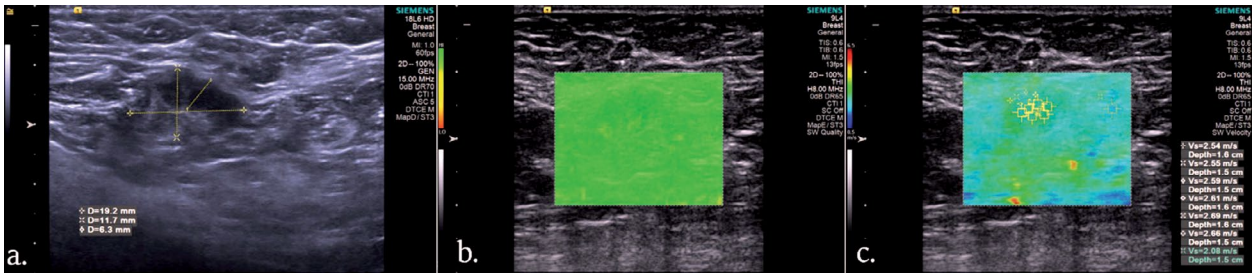

Fig. 1. Ultrasound examination of the right axillary region in a 67-year-old female patient: (a) a lymph node 19.2x11.7 mm characterized by an asymmetrically thick cortex and an echogenic hilum; (b) the shear wave elastography (SWE) quality map revealed the region of interest (ROI) box interior in a homogeneous green color, indicating a high-quality measurement; (c) during the SWE examination, the lymph node showed a mean shear wave velocity (SWV) value of 2.61 m/s, with maximum SWV value measured at 2.69 m/s. The histopathologic examination results were indicative of a malignant lymph node.

biopsies were performed using a 14-18 gauge automatic biopsy needle (22 mm; Geotek, Maxicore, Ankara, Turkey). Surgical excisions were carried out by the general surgery professional from our hospital, experienced in breast surgery. Pathologic examination of the specimens was performed by experienced pathologists in our center.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Data yielded by descriptive statistics were expressed as mean and standard deviation, and median and range as appropriate. Pearson χ^2-test was utilized for comparison of categorical variables. Independent samples t-test and Mann-Whitney U test were used to compare independent continuous variables. Diagnostic performance of SWE examination in differentiating malignant and benign lymph nodes was evaluated using receiver operating characteristics (ROC) curve. Pearson correlation was used to assess inter-observer variability. The level of statistical significance was set at $p<0.05$.

Results

Demographic characteristics and histopathologic results of the study population

Pathologic diagnoses were established through percutaneous biopsy (n=61), axillary dissection (n=43) or sentinel lymph node biopsy (n=17). Among the examined lymph nodes, 45 (37.2%) were diagnosed as

Table 1. Comparison of B-mode ultrasound features between benign and malignant lymph nodes

Variable		All lymph nodes	Benign lymph nodes	Malignant lymph nodes	p value
Short diameter (mm)		9.48±3.96	7.12±2.34	10.88±4.06	<0.001
Diameter ratio		0.58±0.17	0.49±0.15	0.63±0.16	<0.001
Cortex diameter		6.65±4.18	4.48±1.41	8.52±4.15	<0.001
Echogenic hilum:	Present	87 (71.9%)	44 (50.6%)	43 (49.4%)	<0.001
	Absent	34 (28.1%)	1 (2.9%)	33 (97.1%)	
Asymmetric cortical thickening:	Present	73 (83.9%)	31 (42.5%)	42 (57.5%)	<0.001
	Absent	14 (16.1%)	13 (92.9%)	1 (7.1%)	

benign and 76 (62.8%) were diagnosed as malignant. Of these, 57 (47.1%) were located in the right axilla and 64 (52.9%) in the left axilla. Malignancy rates were 59.6% for the right axilla and 65.6% for the left axilla, with no significant relationship between location and malignancy (p=0.497).

Among the lymph nodes diagnosed with core needle biopsy, 45 (73.8%) were malignant, whereas among those diagnosed with surgery 31 (51.7%) were malignant. Malignancy was significantly more common in lymph nodes diagnosed with core needle biopsy (p=0.012).

B-mode US features of lymph nodes

Table 1 shows comparison of B-mode US characteristics between benign and malignant lymph nodes. Malignant lymph nodes exhibited a significantly larger mean short-axis diameter (10.88±4.06 mm) than benign lymph nodes (7.12±2.34 mm, p<0.001). A short-axis cutoff value of 8.25 mm showed sensitivity of 72.4%, specificity of 77.8%, and accuracy of 74.4% (area under the curve, AUC=0.785, p<0.001).

The short axis to long axis ratio of malignant lymph nodes (0.63±0.16) was significantly higher than that of benign lymph nodes (0.49±0.15, p<0.001), with a cutoff value of 0.51 yielding sensitivity of 73.7%, specificity of 66.7%, and accuracy of 70.25% (AUC=0.743, p<0.001).

The mean cortex thickness of malignant lymph nodes (8.52±4.15 mm) was significantly higher than that of benign lymph nodes (4.48±1.41 mm, p<0.001). A cutoff value of 4.5 mm resulted in sensitivity of 89.5%, specificity of 80.0%, and accuracy of 86.0% (AUC=0.913, p<0.001).

Lymph nodes with echogenic hilum had a lower probability of malignancy (49.4%) compared to those without echogenic hilum (97.1%), showing a significant difference (p<0.001). Similarly, asymmetric cortical thickening was more frequent in malignant lymph nodes (p<0.001).

Shear-wave elastography characteristics of lymph nodes

Table 2 illustrates comparison of SWV values between benign and malignant lymph nodes. Malignant lymph nodes showed significantly higher SWV_{mean} (3.22±0.65 m/s), SWV_{median} (3.26±0.7 m/s), SWV_{min} (2.94±0.56 m/s), SWV_{max} (3.53±0.77 m/s), and SWV_{ratio} (1.66±0.47 m/s) compared to benign lymph nodes (p<0.001 for all).

Assessment of the reliability of shear-wave elastography measurements

There was a very strong correlation between the SWV_{mean}, SWV_{median}, and SWV_{max} values observed by the observers (Pearson correlation: r=0.986, p<0.001; r=0.981, p<0.001, and r=0.967, p<0.001, respectively).

Diagnostic performance of shear-wave elastography in distinguishing malignant and benign lymph nodes

Table 3 displays diagnostic efficacy of SWE measurements in distinguishing between malignant and benign lymph nodes. When employing a SWV_{mean} cutoff value of 2.447 m/s, diagnostic parameters were as follows: sensitivity 92.1%, specificity 88.9%, positive predictive value 93.3%, negative predictive value 87.0%, and accuracy 90.9% (AUC=0.960, p<0.001).

Table 2. Comparison of SWV values of benign and malignant lymph nodes

SWV measurement (m/s)	Whole lymph nodes	Benign lymph nodes	Malignant lymph nodes	p value
SWV_{mean}	2.82±0.77	2.13±0.34	3.22±0.65	<0.001
SWV_{median}	2.84±0.80	2.13±0.33	3.26±0.7	<0.001
$SWV_{minimum}$	2.58±0.67	1.98±0.35	2.94±0.56	<0.001
SWV_{max}	3.07±0.88	2.3±0.38	3.53±0.77	<0.001
SWV_{ratio}	1.48±0.46	1.16±0.20	1.66±0.47	<0.001

Data are presented as mean and standard deviations; SWV = shear wave velocity

Table 3. Diagnostic performance of SWV parameters in differentiating benign and malignant axillary lymph nodes

Parameter	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
SWV_{mean}	2.447	0.960	92.1%	88.9%	93.3%	87.0%	90.9%
SWV_{median}	2.460	0.959	92.1%	91.1%	94.6%	87.2%	91.7%
$SWV_{minimum}$	2.415	0.938	86.8%	91.1%	94.3%	80.4%	88.4%
SWV_{max}	2.620	0.960	93.4%	86.7%	92.2%	88.6%	90.9%
SWV_{ratio}	1.238	0.858	82.9%	73.3%	84.0%	71.7%	81.8%

SWV = shear wave velocity; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value

In the assessment of diagnostic performance of SWV_{max} in discriminating malignant from benign lymph nodes, an optimal cutoff value of 2.620 m/s yielded sensitivity of 93.4%, specificity of 86.7%, positive predictive value of 92.2%, negative predictive value of 88.6%, and accuracy of 90.9% (AUC=0.960, p<0.001) based on ROC curve analysis. Similarly, for SWV_{median} with a cutoff value of 2.460 m/s, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were found to be 92.1%, 91.1%, 94.6%, 87.2%, and 91.7%, respectively (AUC=0.959, p<0.001).

Discussion

Differentiation of benign and malignant lymph nodes often proves challenging with conventional imaging methods, including US, contrast enhanced US, and magnetic resonance imaging. Histopathologic examination remains necessary for a definitive diagnosis. This study investigated the potential contribution of SWE, in conjunction with grayscale US findings, to enhance differentiation of malignant and benign lymph nodes.

In a cohort of 65 axillary lymph nodes in breast cancer patients, US examination demonstrated 69% sensitivity and 100% specificity[21]. In contrast, Bonnema *et al*. report lower sensitivity (36%) and high specificity (95%) in their study of 150 axillary lymph nodes[22]. Another study by Holwitt *et al*. with 256 patients found 79% sensitivity and 81% specificity[23].

Various threshold values for maximum short-axis diameter of lymph nodes, such as 5 mm, 8 mm, and 10 mm, have been proposed in previous studies for distinguishing between malignant and benign nodes[24,25]. However, there is still no consensus on which threshold value should be used. In this study, the mean short-axis diameter in malignant lymph nodes was 10.88±4.06 mm, compared to 7.12±2.34 mm in benign lesions. ROC curve analysis revealed 72.4% sensitivity, 77.8% specificity, and 74.4% accuracy for a threshold value of 8.25 mm (AUC=0.785, p<0.001). Seo *et al*. examined 54 axillary lymph nodes and found the mean short-axis length to be 5.49±1.55 mm for benign lymph nodes and 11.09±4.50 mm for malignant lymph nodes. In this study, a threshold value of 7.55 mm was determined for the short-axis diameter, resulting in 79% sensitivity and 95% specificity[26]. Similarly, in a study conducted by Choi *et al*. with 425 breast cancer patients, the mean short-axis diameter was 5.75±1.87 mm for benign lymph nodes and 7.77±4.14 mm for malignant lymph nodes. When a threshold value of 7.1 mm was used, 41% sensitivity and 84% specificity were obtained[9].

Regarding the short-to-long axis ratio, our study identified a ratio of 0.51 as having the highest sensitivity, specificity, and accuracy in distinguishing between malignant and benign lymph nodes. This aligns with the findings reported by Choi *et al*. and Yang *et al*.[9,27].

Deurloo *et al*. determined optimal threshold value for cortical thickness of lymph nodes as 2.3 mm in patients with breast cancer, achieving sensitivity of 95% and specificity of 44%[28]. In the study by Choi *et al*., a threshold value of 3 mm for cortical thickness resulted in 68% sensitivity and 72% specificity in distinguishing metastatic disease[9].

In our study, 73 out of 87 selected lymph nodes with an echogenic hilum exhibited asymmetric cortical thickening (83.9%). Among these nodes, 42 (57.8%)

were identified as malignant and 31 (42.5%) as benign. In contrast, among the lymph nodes without asymmetric cortical thickening, 13 (92.9%) were benign and one (7.1%) was malignant (p<0.001). Seo *et al*. observed asymmetric cortical thickening in 20% of benign and 26.9% of malignant lymph nodes in their study of 54 axillary lymph nodes[26]. In our study, combining evaluation of lymph nodes without an echogenic hilum and those with observed asymmetric cortical thickening resulted in 88% sensitivity and 75% specificity in differentiating between malignant and benign lymph nodes. The study by Choi *et al*. on 313 axillary lymph nodes found asymmetric cortical thickening in 42.2% of malignant and 28.3% of benign nodes, with sensitivity of 55% and specificity of 70%[9].

The presence of an echogenic hilum in a lymph node is a significant indicator of benign status. Previous studies have shown that echogenic hilum is observed in 84%-92% of benign lymph nodes compared to 4%-51.5% of malignant lymph nodes[24,29,30]. In our study, among the 87 lymph nodes with echogenic hilum, 43 (49.4%) were malignant, whereas among the 34 lymph nodes without echogenic hilum, 33 (97.1%) were malignant (p<0.001).In the study by Choi *et al*., the absence of an echogenic hilum alone showed a sensitivity of 24% and specificity of 95% in distinguishing between benign and malignant lymph nodes[9]. Seo *et al*. report that only 5% of benign lymph nodes lacked an echogenic hilum, while 61.8% of malignant lymph nodes did not show an echogenic hilum[26].

In our study, the SWV_{mean}, SWV_{median}, SWV_{max}, and SWV_{min} values of malignant lymph nodes were significantly higher than those of benign lymph nodes. Azizi *et al*., in their study involving 236 patients and 270 cervical lymph node measurements using VTIQ functional SWE found that maximum SWV values were significantly higher in malignant lymph nodes (3.96±0.96 m/s) compared to benign lymph nodes (2.71±0.65 m/s). They determined an optimal cutoff value of maximum SWV as 2.93 m/s, yielding a sensitivity of 92% and specificity of 75%[31]. In our study, the optimal cutoff value of maximum SWV was determined to be 2.62 m/s, aligning with these findings.

Our study had several limitations. Firstly, a limited number of cases were included (n=61), but the number of lymph nodes subjected to measurement and histopathologic confirmation in our study is comparable to those reported in the literature (n=121). Interobserver agreement statistics could only be conducted on randomly selected 50 lymph nodes and could not be evaluated for all lymph nodes.

Conclusion

Our findings suggest that VTIQ function of SWE can significantly contribute to distinguishing between benign and malignant axillary lymph nodes. B-mode US findings also provide valuable information for detecting metastatic disease. The integration of SWE with grayscale US examination is believed to improve diagnostic accuracy in distinguishing benign and malignant axillary lymph nodes. This implies a potential reduction in the necessity of invasive procedures such as biopsy or surgery for patients.

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Sažetak

ULTRAZVUK I ELASTOGRAFIJA S POSMIČNIM VALOM ZA RAZLIKOVANJE DOBROĆUDNIH I ZLOĆUDNIH LIMFNIH ČVOROVA U BOLESNICA S RAKOM DOJKE

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Ovo istraživanje imalo je za cilj procijeniti dijagnostičku učinkovitost ultrazvuka (UZ) i elastografije s posmičnim valom (*shear wave elastography*, SWE) u razlikovanju dobroćudnih od zloćudnih aksilarnih limfnih čvorova u bolesnica s rakom dojke. Ukupno 121 aksilarnih limfnih čvorova od 61 bolesnice s rakom dojke (srednja dob, 52,4±14,6 godina) uključeno je između svibnja 2019. i kolovoza 2020. Limfni čvorovi histopatološki su dijagnosticirani biopsijom *core* iglom ili kirurškom ekscizijom. Procijenjena su UZ obilježja B-moda (promjer kratke osi, omjer promjera kratke i duge osi, prisutnost ehogenog hiluma, prisutnost asimetričnog kortikalnog zadebljanja, debljina korteksa) i mjerenja SWE (maksimalna brzina smicanja vala (SWV_{max}), minimalna SWV (SWV_{min}), medijan SWV (SWV_{median}), srednji SWV (SWV_{mean})). Bilo je 45 (37,2%) dobroćudnih i 76 (62,8%) zloćudnih limfnih čvorova. Promjer kratke osi, omjer promjera kratke i duge osi i srednja kortikalna debljina zloćudnih limfnih čvorova bili su značajno veći u usporedbi s dobroćudnim limfnim čvorovima ($p<0,001$ svi). SWV_{mean}, SWV_{median}, SWV_{max} i SWV_{min} zloćudnih limfnih čvorova bili su značajno viši od onih dobroćudnih limfnih čvorova ($p<0,001$ svi). I US i SWE bili su korisni za razlikovanje dobroćudnih od zloćudnih aksilarnih limfnih čvorova.

Ključne riječi: *Rak dojke; Limfni čvorovi; Elastografija; Ultrazvuk*