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Original Article

The role of gray-scale ultrasound and elastography in differentiating benign from malignant axillary lymph nodes in patients with breast cancer

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Abstract
Introduction: Breast cancer is one of the most common cancers in women. Involvement of regional lymph nodes by breast cancer has shown to be a significant marker in the overall diagnosis of patients. In this study, we aimed to investigate the role of gray-scale ultrasound and elastography in discriminating benign from malignant axillary lymph nodes in patients with breast cancer.
Methods: In this analytical study, patients with breast cancer who were referred to sonography ward of a tertiary medical educational center and found to have suspicious lymph nodes were investigated. Formal properties were evaluated by grayscale ultrasound and tissue properties were assessed by elastography. Biopsies were performed on all cases and suspicious tissues were removed.
Results: This study was conducted on 50 patients with the mean age of 48.54±10.58 years. 52% of patients had a mass in their right breast and the most prevalent type of breast cancer was intra-ductal carcinoma. 60% of the lymph nodes were reported to be malignant. In 56% of the lymph nodes, grayscale ultrasound tests demonstrated unusual findings and the most common finding was the removal of fat from lymph node hilum. Moreover, elastography results indicated that 36% of the cases have grade 4 (blue) lesions.
Conclusion: This study indicated that grayscale ultrasound and elastography have high sensitivity and specificity in detecting metastatic lymph nodes. This finding was in line with the findings reported in many of the previous studies.

Introduction

The status of axillary lymph nodes is one the important prognostic factors in breast cancer.[1] The 5-year survival of patients with metastatic nodules has been reported to be 40% lower than that of the patients with normal lymph nodes.[2]

The biopsy of sentinel lymph nodes has replaced axillary lymph node dissection in patients with lower risks of metastasis to axillary lymph nodes as it has been found to decrease morbidity.[3,4] Sentinel lymph nodes indicate the overall status of the entire lymph nodes in the body. In the biopsies of sentinel lymph nodes, both positive and negative results have been reported.[4,5]

Non-invasive imaging methods are being used in the preoperative assessment of axillary sentinel lymph node status. The diagnostic accuracy of grayscale ultrasound in detecting axillary lymph node metastases is far higher than mammography, CT scan, MRI, and PET scan.[6-8] The factors which are assessed in the detection of metastases via grayscale ultrasound are size, form, hilum, and cortical thickening of lymph nodes.[9,10] However, ultrasonography of axillary lymph nodes has been reported to have a moderate sensitivity of 48.8%-87.1%.[11]

Sono-elastography is a diagnostic technique that is used to illustrate elastic properties of lesions. This technique is employed in the assessment of various organs including liver, thyroid, prostate, and pancreas.[12] This technique has advantages in the differential diagnosis of metastases in cervical and axillary lymph nodes.[12]

Considering the issues discussed above, this study was designed and implemented with the aim of exploring the diagnostic values of grayscale ultrasound and elastography in differentiating benign from malignant axillary lymph nodes in patients with known breast cancer.

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Methods

The whole process was explained to patients before entering the study and the patients received an informed consent. Patients who accepted the concept of study was entered to the study. All information of patients including the demographical data and US findings remained secret. Sample size was obtained by the basis of Wojcinski and colleagues' study[13] with Power and Sample Size Calculator with mean differences of 2.12 for mean long axis diameter and considering power of 90% and alpha error of 5% and final sample size was 50 patients.

This analytical study was done on all patients with a known history of breast cancer who were referred in 2017 to sonography ward of a tertiary medical educational center in North West of Iran to evaluate the lymph nodes in axillary region. The study was aimed to explore the diagnostic values of grayscale ultrasound and elastography in differentiating benign from malignant axillary lymph nodes in patients with known breast cancer. Patients with known breast cancer were entered to the study; while those with a history of surgery on axillary region as well as those who refused to participate in the study were excluded. Demographic information of patients as well as clinical and medical history of the patients were gathered using a checklist designed by the researchers.

Ultrasound and biopsy method

For all patients who were entered to the study, ultrasonography was done in order to investigate any lymph node at axillary regions using a Philips iU22 (Philips Healthcare Andover, MA). During the gray scale ultrasound investigation, a number of variables including short-axis diameter, long axis/short axis ratio, removal of fat from lymph node hilum, and cortical thickening of lymph nodes were assessed. Following that, elastography was performed and the lesions were scored from 1-4 based on their form and color (Table 1).[14,15] Then, based on their elasticity score, the tissues were classified into hard (scores of 3 and 4) and soft (scores 1 and 2) lesions.

Next, all of the patients underwent core needle biopsy guided by grayscale ultrasound and the samples were sent for pathological study. Dissection surgery performed for patients who had malignant lymph nodes at axillary regions. The data obtained from grayscale ultrasound, elastography, and pathology were all recorded on checklists.

Statistical analysis

Statistical analysis was performed by SPSS (SPSS Inc., Chicago, IL). Quantitative data was presented as mean ± SD. Paired *t* test was used to compare the CT and sonography quantitative values. Groups were matched first before analyses. Fisher's exact test was used to compare qualitative values. *P* value less than 0.05 was considered statistically significant. Diagnostic values consist of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) calculated by ROC analysis.

Results

In this study, 50 patients with known breast cancer who were referred for ultrasound investigation for axillary lymph nodes were studied. The mean age of the patients was 48.54 ± 10.58 years. 26 patients (52% of the total) had masses in their right breast and the major pathology of their breast mass was intraductal carcinoma.

Eight patients had metastasis in distal regions (Table 2). Considering all lymph nodes, the mean long axis diameter was 23.96 ± 11.05 mm and the mean short axis diameter was 16.43 ± 7.27 mm. In this study, the mean long axis diameter of suspicious lymph nodes was found to be 22.07 ± 9.86 mm and that of the normal lymph nodes was 14.04 ± 3.57 mm (P=0.001). Also, the mean short axis diameters of suspicious and normal lymph nodes were 15.78 ± 7.05 mm and 6 ± 3.49 mm, respectively, significantly different between two groups, analyzed by paired samples *t* test (P<0.001). Grayscale ultrasound exams suspicious findings were found at 28 patients (56%) and the most prevalent finding was removal of fat from lymph node hilum, which was observed in 17 patients (60.71%) (Table 2). The analysis of elastography results revealed that 26 patients (52%) had hard lesions (with elasticity scores of 3 or 4) while 24 patients (48%) had soft lesions (with elasticity scores of 1 or 2) (Table 3). Furthermore, it was observed

Table 1. Elastography scoring

Elasticity Score	Description
1	Absent or very small blue area
2	Small, scattered blue areas, total blue area < 45%
3	Large blue area, total blue area ≥ 45%
4	Blue area with or without a green rim

Table 2. Pathological description of study population

Variable		No.	%
Side	Right	26	52
	Left	24	48
Pathology	IDC	46	92
	ILC	3	6
	DCIS	1	2
Metastases site	Bone	4	8
	Liver	2	4
	Adrenal	1	2
	Lung	1	2
Needle Biopsy	Positive	30	60
	Negative	20	40

IDC: Invasive ductal carcinoma, ILC: Invasive lobar carcinoma, DCIS: Ductal carcinoma in situ that suspicious findings through ultrasonography and hard lesions detected through elastography in patients with positive pathology reports were significantly more than those in patients with normal pathology reports (Table 4). In this study, sensitivity, specificity, PPV, and NPV of both ultrasound and elastography techniques were also assessed (Table 5).

Discussion

The results of this study showed that there is significant relationship between the Gary scale ultrasonography findings such as removal of hilum fat, increase of the thickness of the cortex over 3.5 mm and increase in the ratio of largest to smallest diameter in lymph node with the presence of malignancy in the suspicious axillary lymph nodes. It was also observed that malignant lymph nodes compared with the reactive lymph nodes meaningfully showed more hard lesions (with elasticity scores of 3 or 4) in elastography.

Several studies have been conducted to evaluate the relationship between ultrasonography of lymph nodes and their pathology reports which showed variable results. In a

Table 3. Ultrasound and elastography findings in patients

	Variable			No.	%
Sonography	Abnormality in sonography finding		Normal	22	44
			Abnormal	28	56
	Suspicious finding in lymph nodes	Removal of fat	Absent	11	39.28
			Present	17	60.72
		Increase the thickness of the cortex over 3.5 mm	Absent	16	57.14
			Present	12	42.86
		Ratio of largest to smallest diameter in lymph node	≤50%	3	10.71
			>50%	25	89.29
Elastography	Elasticity score		1 (Red)	10	20
			2 (yellow)	14	28
			3 (green)	8	16
			4 (blue)	18	36

Table 4. Ultrasound and elastography findings in patients with benign and malignant pathology

	Variable		Positive patology		Negative patology		*P* value[a]
			No.	%	No.	%	
Sonography	Abnormality in sonography finding	Normal	4	18.2	18	81.8	<0.000
		Abnormal	26	92.5	2	7.1	
	Removal of fat in the lymph nodes	Absent	14	42.4	19	57.6	<0.000
		Present	16	94.1	1	5.9	
	Increase the thickness of the cortex over 3.5 mm	Absent	19	50	19	50	0.010
		Present	11	91.7	1	8.3	
	Ratio of largest to smallest diameter in lymph node	≤50%	6	24	19	76	<0.000
		>50%	24	96	1	4	
Elastography	elasticity score	1 (Blue)	2	20	8	80	0.004
		2 (Yellow)	7	50	7	50	
		3 (Green)	5	62.5	3	37.5	
		4(Red)	16	88.9	2	1.11	

[a] Fisher's exact test was used to compare values.

Table 5. Sensitivity, specificity, PPV and NPV in Ultrasound and elastography findings

	Varible	Sensitivity	Specificity	PPV	NPV
Sonography	Abnormality in sonography Finding (overal)	86.66	90	92.5	81.81
	Removal of fat in the lymph nodes	53.33	95	94.11	57.57
	Increase the thickness of the cortex over 3.5 mm	36.66	95	91.66	50
	Ratio of largest to smallest diameter in lymph node	80	95	96	76
Elastography	elasticity score (hard to soft)	70	75	80.76	62.5

PPV: Positive predictive value, NPV: Negative predictive value.

study by Wojcinski et al it was reported that patients with normal lymph nodes and those with metastatic lymph nodes are not significantly different considering long-axis diameter of lymph nodes while their short-axis diameters were found to be 7.2 mm and 9.2 mm, respectively, suggesting a statistically significant difference between the two groups (*P*=0.013).[13] In normal and metastatic patients, the cortical thickening of lymph nodes was 1.4 mm and 4.2 mm (*P*<0.001), cortex/medulla ratios were 0.39 and 1.22 (*P*<0.001), and the long axis/short axis ratios were 0.5 and 0.7 (*P*=0.002), respectively. Park et al investigated normal and metastatic patients and observed that the mean long axis diameters were 1.5 cm and 2.3 cm (*P*<0.001), the mean short axis diameters were 0.7 cm and 1.2 cm (*P*<0.001), and the long axis/short axis ratios were 2.1 and 2 (*P*<0.15), respectively. Moreover, cortical thickening was observed in 31% of the normal and 52% of the metastatic patients (*P*>0.05). Also, removal of fat from lymph node hilum was reported in 9% of the normal and 32% of the metastatic cases (*P*>0.05).[16] In another study, Zhao et al analyzed two groups of normal and metastatic patients and observed removal of fat from lymph node hilum in 14.7% and 70.4% of the groups (*P*<0.05), cortical thickening of more than 3 mm in 23.5% and 81.8% of the groups (*P*<0.05), and increases of more than 2 in long axis/short axis ratios of 20.5% and 54.4% of the patients, respectively (*P*<0.05).[17] In Fidan and colleagues' study, ultrasound was found to be helpful in differentiating between normal and metastatic lymph nodes.[18] In line with the previous studies, the present study also indicated that through the analysis of various factors such as removal of fat from the lymph node hilum, cortical thickening in lymph nodes, and the increases in long axis/short axis ratio, ultrasonography can differentiate between benign and malignant lymph nodes with a high probability. The meaningfulness of these factors in ultrasonography has been confirmed in the majority of previous studies.

Elastography, which is recently being used as a complementary modality for ultrasonography in differentiating between benign and malignant lymph nodes, has yielded in the positive results. For example, in Wojcinski and colleagues' study, elastography images revealed that 40% of the patients with malignant lymph nodes had turquoise lesions while 60% of them had blue lesions (hard tissue).[15] On the other hand, in patients with normal lymph nodes, elastography images did not show any instance of lesions with soft tissue. The color of lesions in 20.6% of the cases was blue (hard tissue), in 64.2% of the cases was turquoise, in 13.9% of the cases was green, and in 1.2% of the cases was yellow. In their study, only blue-colored lesions were reported to be significantly more among the patients with malignant lymph nodes compared to those with normal ones. In another study, Choi et al reported that the elasticity score of patients with malignant lymph nodes is higher than that of the patients with reactive lymph nodes.[19] In the studies conducted by Evans et al[20] and Zhao et al,[17] it was observed that an increase in tissue stiffness score (elasticity) increases the probability of developing malignancies and metastases. However, Park et al[16] reported that the elasticity score of lymph nodes cannot help differentiating between malignant and reactive lymph nodes. In line with the findings of the majority of the related studies, the present study also indicated that via analyzing the stiffness of lymph nodes and the changes in the color of lesions, elastography can differentiate between benign and malignant lymph nodes with a high sensitivity and specificity. Thus, it can be routinely used in breast cancer screening tests in order to detect metastatic lymph nodes.

In Wojcinski and colleagues' study,[15] the reported sensitivity and specificity were40% and 96.8% for cortical thickenings of more than 3 mm, 60% and 79.6% for elastography, and 73.3% and 77.5% for the combination of ultrasound criteria, respectively. In another study, Choi et al[19] reported sensitivity and specificity of 74.2% and 90.9% for short axis diameters, 64.5% and 39.4% for long axis/short axis ratios, 48.4% and 84.9% for the removal of fat from lymph node hilum, 25.8% and 97% for cortical thickening, 74.2% and 78.8% for ultrasound in general, 80.7% and 66.7% for elastography, and 87.1% and 54.6% for the combination of ultrasound and elastography, respectively. In Taylor and colleagues' study,[21] it was observed that sensitivity, specificity, PPV, and NPV are 76%, 78%, 80%, and 81% for ultrasound, 90%, 866%, 83%, and 93% for visual elastography, and 100%, 48%, 58%, and 100%, respectively, for elastography accompanied by scoring of lesions. Zhao et al[17] reported the sensitivity and specificity of 77.3% and 76.5% for 2-D ultrasound, 86.4% and 85.3% for elastography scoring, and 93.2% and 73.5% for the combination of ultrasound and elastography, respectively, in detecting metastases of the breast cancer to the lymph nodes. Fidan et al[18] reported sensitivity, specificity, PPV, and NPV of ultrasound in detecting malignant lymph nodes to be 91%, 77%, 87%, and 83%, respectively. The sensitivity and specificity of ultrasound and elastography obtained in the present study were similar to those reported in other related studies. Previous studies have mainly indicated relatively high levels of sensitivity and specificity for the use of these radiological methods in detecting metastatic lymph nodes. When elastography results are combined with B-mode ultrasound images, sensitivity increases considerably, but specificity decreases. Combining these two methods for detecting metastatic lymph nodes; may sometimes lead to false-positive detection of malignant lymph nodes, however in histopathological studies, metastatic involvements was not seen.

Conclusion

The results of our study indicate that use of elastography and ultrasonography can readily identify malignant metastasis of breast cancer to lymph nodes. Further study

Study Highlights

What is current knowledge?

- Sono-elastography has advantages in the differential diagnosis of metastases in cervical and axillary lymph nodes

What is new here?

- Grayscale ultrasound and elastography have high sensitivity and specificity in detecting metastatic lymph nodes. This finding was in line with the findings reported in many of the previous studies.

is needed in order to generalize the use of these methods, and to show if combination with other diagnostic methods may increase sensitivity and specificity.

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Author's Contribution

BM: data gathering, interpretation of imaging findings, manuscript preparation. ASBO: Study conception, overall supervision, interpretation of imaging findings. HHF: data acquisition, patient selection, study supervision. BS: Study concept, interpretation of imaging findings, systemic review of literature. JJ: Manuscript preparation, statistical analysis, patient selection. MMAA: manuscript preparation, final edit, systemic review of literature. SP: Manuscript preparation, statistical analysis, final edit, supervision over study. AZ: Manuscript preparation, statistical analysis, final edit, supervision over study.

Competing Interests

The authors do not have any conflict of interest to declare.

Ethical Approval

The protocol for the research project has been approved by the ethic committee at TUMS (Tabriz University of Medical Sciences) which is in compliance with the Helsinki Declaration and all participants gave informed consent before inclusion in the trial.

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