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ROLE OF SHEAR WAVE ELASTOGRAPHY IN THE ASSESSMENT OF BENIGN AND METASTATIC AXILLARY LYMPH NODES IN BREAST MALIGNANCY

Radio-Diagnosis

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ABSTRACT

Background – Axillary assessment is a routine part of examination in patients with breast malignancy, to detect or rule out axillary lymph nodal metastases, and decide upon the clinical staging. This study included shear wave elastography (SWE) of axillary lymph nodes along with routine conventional ultrasound. **Aim** - To examine diagnostic performance of SWE for evaluation of status of axillary lymph nodes (ALN) in comparison with conventional ultrasound (US). **Materials And Methods –** A total of 50 patients were enrolled. Conventional US, quantitative SWE (four color patterns) and qualitative SWE were performed on suspicious ALNs. The diagnostic performances of the three methods were compared. **Results –** There were 28 metastatic nodes and 22 benign nodes in the 50 axillary lymph nodes. Metastatic ALNs exhibited higher scores in both qualitative and quantitative SWE. The highest diagnostic performance was achieved with qualitative SWE and among combination tests, with AUC of 0.884, was achieved with both conventional US and qualitative SWE. **Conclusion** - The qualitative SWE classification of ALNs proposed in our study exhibited better diagnostic performance than quantitative SWE parameters and conventional US, especially for differentiating metastatic ALNs from benign reactive ALNs. Qualitative SWE provided better sensitivity complementing quantitative SWE that provided better specificity.

KEYWORDS

Axillary lymph node, Shear wave elastography, Breast malignancy

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year [1]. Lymph node involvement is one of the most important prognostic factors in breast cancer and is important in determining the management of a breast cancer diagnosis [2]. Axillary lymph nodes are involved in majority of cases with breast cancer, that puts the case in stage II that reflects increased severity of the spread of cancer and poor prognosis. The status of axillary lymph nodes is one of the most important prognostic factors for evaluating breast cancer, and it is also mandatory for proper treatment planning [3]. In routine clinical practice, conventional ultrasound of bilateral axilla is done for pre-operative assessment of ALNs. its criteria for metastatic ALNs were based on morphologic characteristics, such as round shape, ratio of long axis to short axis (L/T) of <2, cortical thickening of more than 3mm or absence of hilum [4], with resemblance to sonographic appearance of reactive ALNs.

Elastography is a new and emerging sonographic technique that utilizes the principle of elasticity of tissue. As metastatic or malignant lesions are hard due to high cellularity, their reduced elasticity is picked up by ultrasonographic elastography. Such principle has been used in assessment of superficial, lymph nodes, thyroid lesions, and breast lesions. Shear Wave Elastography (SWE) is new and improved version of ultrasonographic elastography where waves are generated by the transducer and traverses through the targeted lesion.

Based on the qualitative SWE classification of breast lesions from the study of Cong [5], the proposed qualitative classification method was used for diagnosis of ALNs.

In this study, we aimed to evaluate the diagnostic performance of qualitative SWE classifications for ALNs, in comparison with that of conventional US, quantitative SWE parameters and combinations of US and SWE parameters.

MATERIALS and METHODS

Patients

The study was conducted in the Department of Radiodiagnosis in SMS Medical College and Hospital, Jaipur, Rajasthan after acquiring adequate approval from concerned Ethics Approval Committee. All patients were enrolled after their informed written consent. 50 female patients with breast malignancy and axillary lymphadenopathy were included. They were examined by conventional ultrasound and SWE to evaluate ALNs. The mean age was 47.08 years (age range 26 – 38 years). Some patients were excluded considering the following conditions: a) who underwent neoadjuvant chemotherapy or radiotherapy before biopsy b) malignancy other than breast c) axillary lymph nodes deeper than 30 mm and d) sub-standard elastographic images.

US examination

All patients underwent conventional US and SWE by Canon Aplio a ultrasonography machine equipped with a linear 4-15 MHz transducer. Conventional US involved assessment and recording of the following morphological data: length of longest (L) and shortest (S) axes, L/S ratio, cortical thickness and presence or absence of hilum. SWE was performed along the maximum longitudinal plane of lymph node. Care was taken to keep the transducer lightly placed on the axillary skin with adequate amount of gel. The probe was kept still with minimal possible breathing movement of the patient. Images without vertical stripe artefacts with homogenous surrounding fat met the diagnostic standard. Qualitative and quantitative SWE was performed.

Evaluation of Conventional US

The scores of conventional US were calculated based on the 4 criteria: short-axis diameter (<7.0mm, score 0; _7.0mm, score 1), long-to-short-axis diameter ratio (<2.0, score 0; _2.0, score 1), hilum (present, score 0; absent, score 1), and cortical thickening (<3.0mm, score 0; _3.0mm, score 1) (4, 6).

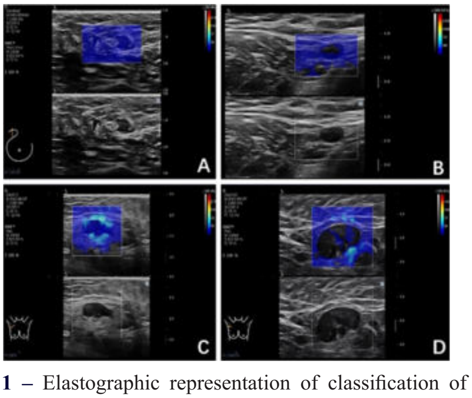

Figure 1 – Elastographic representation of classification of color patterns in qualitative shear wave elastography. [10]

(A) Color Pattern 1: Homogenous - Marginal sinus echo, homogenous; Intra-lymph node echo, complete filling;

(B) Color Pattern 2: Not homogenous - Marginal sinus echo, homogenous; Intra-lymph node echo, defect filling;
(C) Color pattern 3: Heterogenous - Marginal sinus, heterogenous; Intra-lymph node echo, complete filling;
(D) Color Pattern 4: Heterogenous - Margin sinus echo, heterogenous; Intra-lymph node echo, defect filling.

Qualitative SWE assessment

The SWE images of ALNs were classified into four color patterns through the qualitative assessment, similar to a qualitative classification used in the diagnosis of breast lesions(5, 6): Color Pattern 1: homogeneous pattern (**Figure 1A**); Color Pattern 2: filling defect within lymph node (**Figure 1B**); Color Pattern 3: homogeneous within lymph node with a localized colored area at the margin (**Figure 1C**); Color Pattern 4: filling defect within lymph node with a localized colored area at the margin (**Figure 1D**). The classifications were based on the presence of "black hole" signs (6) or a localized colored area, manifested as increased stiffness in color elastic map.[7]

Figure 2 (1) - Left axillary lymph node in a 51-year-old female with malignant mass in left breast. Conventional USG revealed **(A)** SAD = 17.9 mm and L:S ratio of 1.79, **(B)** cortical thickness of 6.1 mm, **(C)** preserved fatty hilum and hilar vascularity. Conventional USG score – 2/4 – signified metastatic axillary node.

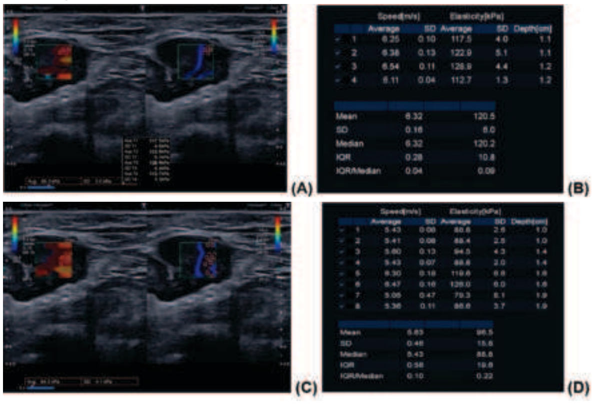

Figure 2 (2) – (A – D) Qualitative and quantitative shear wave elastography of the same patient revealed color pattern 4 – heterogenous (Margin echo – heterogeneous and intra-lymph node echo - defect filling) and values E_{max}, E_{min}, E_{mean}, and SD suggestive of metastatic axillary node.

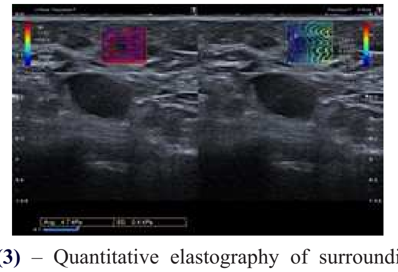

Figure 2 (3) – Quantitative elastography of surrounding fat for estimation of fat tissue stiffness, 4.7kPa, was used to calculate Eratio, ratio of lesion stiffness to that of the surrounding fat. E_{ratio} = 2.01 suggested metastatic nature. The histopathology revealed metastatic axillary lymph node.

Quantitative SWE

Multiple small measurement areas of diameter 1 mm were placed over the hardest intra- or peri-lesional area. Three assessments were done of quantitative SWE whose mean was taken for the final record. Calculation of elasticity of the surrounding axillary fat was also done. The following parameters were then determined: maximum stiffness (Emax, kPa), mean stiffness (Emean, kPa), minimum stiffness (Emin, kPa), ratio of lesion stiffness to that of the surrounding fat (Eratio), and SD (kPa).

Afet receiver operating characteristic (ROC) analyses, optimal cutoff values of qualitative and quantitative SWE parameters to differentiate between metastatic and benign ALNs were obtained.

Combination Tests

For the combination tests, the scores and values of the conventional US and respective SWE were added and assessed. The ALNs were regarded as benign if the value of the SWE parameter was equal to or less than its optimal cutoff value, and those as metastatic ALNs if the SWE parameter was higher than its optimal cutoff value.

Pathology

Examined axillary lymph nodes were subjected to pathological evaluation to determine their benign or metastatic cellular composition. They were examined using a single H&E-stained section after either core needle biopsy of ALNs, SLNB, ALND and/or SLNB. Metastases were defined as the presence of a tumor deposit > 0.2mm in diameter in the lymph node.[7]

Statistical Analyses

Statistical analyses were performed using SPSS version 26 (SPSS, Chicago II, USA).

RESULTS

Pathological Results

Of the 50 ALNs, 28 were metastatic and 22 were benign. ALN diameters ranged from 3.6 mm to 65 mm. The mean length of longest and shortest axes were 17 mm (3.6 - 65 mm) and 9.3 mm (2.5 - 31 mm). The mean size of metastatic ALNs was not significantly larger than that of benign ALNs (p>0.05)

Diagnostic performance of conventional US features

The average scores of benign and malignant lymph nodes by conventional US were points respectively, without a significant difference ($p<0.05$) **(Table 1)**. The optimal cut-off value of this scoring standard was 1.5 points, with 0.544 AUC value, 60.7% sensitivity,50 % specificity, 62.2% NPV and 52.3% PPV. Compared with pathology results, the kappa value of the scoring standard of conventional US was 0.144.

Table 1 – Depiction of range of values among different parameters of quantitative SWE in benign and metastatic ALNs

Parameter	Benign ALNs	Metastatic ALNs
E_{mean}	17.0 ± 6.39 kPa	48.38 ± 20.04 kPa
E_{min}	13.18 ± 5.99 kPa	38.56 ± 17.75 kPa
E_{max}	22.10 ± 6.20 kPa	58.06 ± 23.39 kPa
E_{ratio}	1.66 ± 0.94	5.12 ± 2.20
SD	1.44 ± 1.08 kPa	5.01 ± 2.53 kPa

Diagnostic performance of quantitative SWE features

The mean value of Emean, Emin, Emax, SD, and Eratio was significantly higher in metastatic lymph nodes than in benign lymph nodes **(Table 1)**. The optimal cut-off values of E_{mean}, E_{min}, E_{max}, E_{ratio} and SD were 29.1 kPa, 21.80 kPa, 32.4 kPa, 2.65 and 1.95 kPa respectively, and the corresponding kappa values were 0.798, 0.720, 0.586, 0.672, and 0.759, respectively. The AUC values have been summarized in **Table 2**. Among all the quantitative SWE parameters, the AUC value of Emean was the highest.

Table 2 – Comparative table depicting various parameters of diagnostic performance for conventional ultrasound, qualitative and quantitative SWE of ALNs.

Parameters	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy(%)	Kappa
Conventional US	1.5	0.544	60.7	50	52.30	62.20	58	0.144
Qualitative SWE	1.5	0.957	92.5	95.5	91	96	94	0.879
Quantitative SWE	4.5	0.931	82.1	100	86.6	85.71	86	0.717
E_{min} (kPa)	21.80	0.925	85.7	95.5	90.5	82.14	86	0.720
E_{max} (kPa)	32.45	0.913	89.3	95.5	68.18	89.28	80	0.586
E_{mean} (kPa)	29.1	0.932	85.7	95.5	90.9	89.2	90	0.798
E_{ratio}	2.65	0.913	89.3	95.4	77.27	89.25	84	0.672
SD (kPa)	1.95	0.917	89.3	90.9	90.9	85.7	88	0.759

Combination 1*	4.5	0.884	85.7	86.4	88.9	82.6	86	0.717
Combination 2*	5.5	0.769	46.4	95.5	92.8	58.3	68	0.390

Combination 1*: combination of conventional US and qualitative SWE parameters.
Combination 2*: Combination of conventional US and quantitative SWE parameters.
kappa value of different assessment compared with pathology, a kappa value in the range of 0.21–0.40 be considered "fair" agreement kappa = 0.41-0.60 be considered "moderate" agreement, kappa = 0.61-0.80 be considered "substantial" agreement, kappa > 0.81 be considered "almost perfect" agreement.

Diagnostic performance of qualitative SWE features

The benign ALNs presented as Color Pattern 1, while metastatic ALNs usually presented as Color Pattern 2 to 4. There were significant differences in qualitative SWE patterns between metastatic and benign ALNs ($p < 0.05$). The AUC value of qualitative SWE patterns was 0.957, significantly higher than that of conventional US ($p<0.05$) and all quantitative SWE parameters ($p<0.05$) **(Figure 3).** The optimal cutoff value of qualitative SWE as a diagnostic standard of metastatic lymph nodes was Color Pattern 2, with 92.5% sensitivity, 95.5% specificity, 96% NPV and 91% PPV **(Table 2).** Compared with pathology, the kappa value of qualitative SWE assessment for lymph node was 0.879 (**Table 2).**

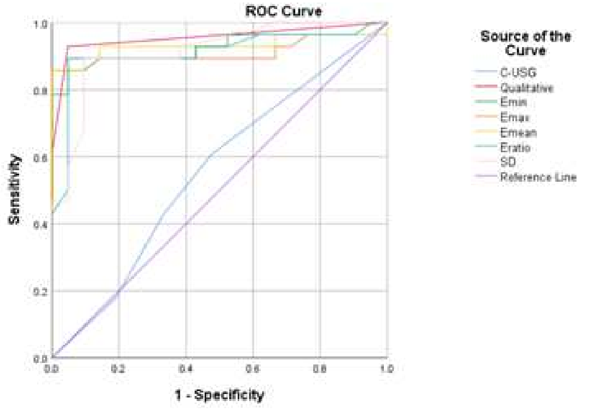

Figure 3 - Comparative ROC curves of conventional ultrasound, qualitative SWE and various parameters of quantitative SWE

Diagnostic Performance of Combining SWE Parameters with Conventional US

The diagnostic performance of combining SWE parameters and conventional US are summarized in **Table 2. T**he AUC value of the combination of conventional US and qualitative SWE classification was 0.717, higher than that of the combination of conventional US and quantitative SWE (0.390), and E_{mean} (0.798) but lower than qualitative SWE classification (0.879) alone. Moreover, the combination of conventional US and qualitative SWE classification obtained a higher sensitivity (85.7%); meanwhile, the combination of conventional US and quantitative SWE classification obtained a higher specificity (95.5%) among combination tests, higher than conventional US alone with sensitivity and specificity of 60.7% and 50% respectively.

DISCUSSION

Superficial lesions including superficial lymph nodes are easily assessed with ultrasound elastography. Earlier, strain elastography has been used which only provided qualitative information with high operator dependence. Meanwhile, SWE can provide qualitative and quantitative information on tissue elasticity. However, inter-operator and intra-operator variation are present in elastography assessment. Standardisation (images without vertical stripe artifacts while presenting the surrounding fat as homogenous) of SWE images is significantly important for accurate diagnosis that requires time and expertise. Current studies [8,9] have confirmed the significance of quantitative SWE parameters in evaluation of axillary lymph node status. In our study, the diagnostic performances of qualitative SWE and quantitative SWE parameters were higher than that of conventional US. And all SWE parameters including qualitative SWE patterns and quantitative SWE parameters were statistically significantly different between metastatic and benign ALNs. The optimal cutoff value of Emean, Emin, Emax, and Eratio in our study was similar to those in some previous studies. In order to reflect the elasticity for the hardest area of the ALN and reduce the containing of surrounding fatty tissue as much as possible, the sample area diameter was set at minimum i.e. 1mm in our study.

Under the conditions of images with adequate quality, a portion of metastatic lymph nodes presented as filling defect in color elastic map suggested metastatic ALNs, but they were misdiagnosed as benign ALNs considering the quantitative parameters of them were still below the optimal cutoff values. In these cases, quantitative parameters were not sensitive to assess ALNs status properly.

Cancer cells usually invade the edge of the ALNs through the afferent lymphatic vessel at early metastasis. And the increasing density of tumor cells would result in elasticity changes and a localized colored area at the marginal sinus. Thereafter, the cells would spread to the medullary sinus and the whole lymph node, leading to the significant increase of lymph node stiffness. Gradually, cancer cells dominate the lymph node and infiltrate the envelope leading to adhesion to the surrounding tissues. As for the presence of filling defect within the metastatic lymph node, one possible explanation is that low shear wave amplitude within the metastatic lymph nodes was caused by attenuation of the energy of the shear wave at the margin of metastatic lymph node [10].

Based on the results of our study, color patterns 2-4 were predominant patterns in metastatic lymph nodes. Qualitative SWE provided highest diagnostic accuracy with highest AUC value, % sensitivity and % specificity. Few cases that were not picked up by qualitative SWE were estimated to have micro-metastases. Furthermore, combined assessment of qualitative SWE and conventional ultrasound revealed less accurate results than qualitative SWE alone. Some cases that had been misdiagnosed as benign axillary lymph nodes by conventional ultrasound revealed color pattern 2-3 in qualitative SWE assessment. Other lymph nodes that had been misdiagnosed as metastatic by conventional ultrasound score due to increased cortical thickness and L/S ratio. However, they all presented color pattern 1 in qualitative SWE assessment, pointing to the possibility of benign reactive lymph nodes. Reactive lymph nodes usually manifest as lymphadenectasis and cortical thickening, similar to the metastatic lymph nodes in conventional US images. But the fact is that there are no elasticity changes in neither peri- nor intra-lymph nodes. Consequently, they were classified into Color Pattern 1 by qualitative SWE classification. Therefore, the combination of conventional US and qualitative SWE classification could improve the diagnostic accuracy of benign reactive lymph nodes [7].

CONCLUSION

Axillary assessment in patients with breast malignancy is essential to diagnose axillary lymphadenopathy and differentiate between benign and metastatic axillary lymph nodes to provide accurate clinical staging. Conventional ultrasound of axillary lymph nodes is limited to a few morphological criteria namely size, long axis to short axis ratio, cortical thickness and presence/ absence of fatty hila; that can be possibly raised in benign reactive nodes. Addition of SWE adds the dimension of detection of elasticity in targeted tissue, hence increasing diagnostic accuracy for detection of malignant cells in metastatic lymph nodes due to their hardness or reduced tissue elasticity. Qualitative SWE color pattern classification provides highest diagnostic accuracy, sensitivity and pattern of elastic changes. Quantitative SWE provides assessment with quantitative parameters of the suspicious axillary lymph nodes, higher values among all parameters in metastatic ALNs with highest specificity and positive predictive value. Among combination tests, combination of conventional ultrasound with qualitative SWE provides higher diagnostic accuracy and sensitivity. Combination of conventional ultrasound and quantitative SWE provides higher specificity among combination tests.

Future Aspects :

Shear Wave Elastography (SWE) has multiple applications in various sectors of medicine and surgery. In this article we explored its use in oncologic assessment of superficial axillary lymph nodes to assist accurate staging and patient management. Streamlining its usage in patients will be the way forward to unfold further benefits.

Morphological pattern of elasticity changes in metastatic lymph nodes

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detected by qualitative SWE classification can help direct accurate ALN tissue sampling.

Limitations :
Inter-observer and intra-observer variations in results of elastographic assessment is initially an inevitable limitation which can be improved upon with practice and regulation. US Elastography requires specialised ultrasonographic machines which are available in limited and higher centres.

Conflicts Of Interest – There are no conflicts of interest

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