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Original Research Article

Comparative evaluation of strain ratio on sonographic elastography and T2* values on 3 Tesla magnetic resonance imaging in differentiating malignant from benign axillary lymph nodes in breast cancer

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ABSTRACT

Background: The study aimed to assess whether strain ratio and T2* values can improve the sensitivity and specificity of differentiating metastatic from benign axillary lymph nodes in breast cancer patients taking histopathology as reference standard.
Methods: The study was done on 43 patients. A multi-echo transverse T2*W MR sequence was obtained with TE=0.9- 1.5 ms, TR=37.2 ms and flip angle=25°. Sonographic elastography was done using high frequency linear probe (L3-16 MHz). Manual selection of the region of interest was done on suspicious lymph nodes for calculation of T2* values and strain ratio. ROC curves were obtained for various T2* and strain ratio values in comparison to histopathological findings as gold standard.
Results: Correlation with histopathology was better with T2* values than strain ratio. The sensitivity and specificity were calculated using cut off values obtained from ROC curve (31.225 ms for T2* value and 1.85 for SR) and were 70.37%, 68.75% for strain ratio and 96.29%, 93.75% for T2* value respectively. The positive predictive value and negative predictive value were also assessed, values being higher for T2* than strain ratio. Comparison of areas under ROC curve was statistically significant with p=0.018.
Conclusions: T2* can be used as a potential biomarker for differentiating metastatic from benign axillary lymph nodes owing to its high sensitivity, specificity and relative ease of performance. Quantitative assessment of changes in T2* values may allow more objective analysis of signal changes with significant differences between benign and malignant lymph nodes, even in case of partial infiltration.

Keywords: Axillary lymph nodes, Sonographic elastography, Strain ratio, T2* value, ROC curve

INTRODUCTION

Breast cancer is the most common cancer and second leading cause of cancer related deaths in women with more than 200,000 new cases diagnosed every year.[1,2] The spread of breast cancer from local site to the surrounding lymphatics is a well-known transformation from the non-metastatic to the metastatic state. It is one of the important prognostic factors which affects the required medical and surgical management.[1] There is an association between the number of involved axillary lymph nodes and the probability of distant recurrence.[3] The presence of nodal metastases decreases 5-year survival by approximately 40% compared to node-negative patients.[4] Therefore, accurate detection of

axillary nodal metastases is critical for patients with breast cancer.[1]

There has been an evolution in the techniques used for evaluation of axillary lymph nodes from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) for grading of patients with clinically lymph node negative breast cancer. Although a less invasive method as compared to ALND, SLNB leads to diverse complications like lymphedema, seroma, localised swelling, pain, paraesthesia, decrease in arm strength, infectious neuropathy and shoulder stiffness in 20% of patients.[3] SLNB has the potential advantage of identifying the lymph nodes most probably involved with tumor, which permits application of techniques such as immunohistochemical analysis to the nodes likely to be of maximum yield.[5] Nonetheless, the diagnostic accuracy of the preoperative evaluation of the axillary lymph node (LN) status is far from perfect. Palpation of the axilla lacks sensitivity as only larger metastases are clinically evident. Mammography inadequately includes the axillary region and the prediction of the malignant or benign character of lymph nodes is not feasible on mammography. B-mode ultrasound is known to be fairly accurate technique for the assessment of the axilla with a sensitivity of 45-73% and a specificity of 44-100%, depending on the diverse B-mode criteria being investigated.[6] It is the primary non-invasive method for evaluating axillary lymph nodes.[7] Technical advances like sonoelastography, tissue harmonic imaging and increasing frequencies may permit a superior differentiation of benign and malignant masses.[6] Combined use of ultrasonography with fine-needle aspiration biopsy (FNAB) may have an added benefit for improving the presurgical staging of the axilla in breast cancer patients. Efforts have been made to evade complete axillary dissection by preoperative assessment with imaging techniques or intraoperative evaluation by axillary node sampling.[8]

Computed tomography (CT) can precisely identify the level of axillary involvement in cases of enlarged lymph nodes and can assess extracapsular node extension. Conventional CT, however, lacks accuracy in predicting axillary metastasis and has low negative predictive value since it uses nodal size alone as a criterion for differentiation of benign from malignant nodes. Whereas high-resolution sonography is valuable only for superficial lesions, CT is an objective noninvasive technique for direct visualization of the axilla.[9] MRI is an essential tool in the armamentarium of the oncologic imager owing to its better soft-tissue contrast and resolution. It portends prognosis, guides therapy and evaluates response to treatment by providing staging information.[10]

The study aimed to evaluate sensitivity and specificity of strain ratio on sonographic elastography and value of T2* from a 3 Tesla (3T) clinical MRI system in differentiating metastatic from benign lymph nodes in patients with breast cancer.

METHODS

This was a diagnostic cross-sectional study. The study was conducted at Max's super speciality hospital, Saket, New Delhi from December 2016 till November 2017.

Forty-three consecutive patients of suspected or proven breast cancer from the outpatient department and wards of Max's super speciality hospital, Saket were included in the study. Sample size was calculated on the basis of sensitivity and specificity (which have been reported as 94.6% and 98.5% respectively) of T2* values in a research article published in PLOS ONE journal by Li et al[1] with cut off value of T2* as 37.5 ms. With 10% error on either side in estimation of sensitivity with 95% confidence interval, the sample size comes to 43 using the following formula:

$$n= Z_{\alpha/2}^2 \times S_N (1- S_N)/ L^2 \times \text{Prevalence}$$

Where, n=Sample size
$Z_{\alpha/2}$ =1.96
S_N=Sensitivity
L = 0.10

Prevalence=56/121=46.28 (calculated on the basis of sensitivity in the research article by Li et al).[1]

The sample size calculated on the basis of specificity was less. So, we have taken larger of the two values as sample size.

Pregnant patients, patients with an implanted device, claustrophobia or any other contraindication for MRI were excluded from the study group.

MRI for all subjects was performed on 3.0 T MR scanner (G.E. Discovery) with a 8-channel breast coil. Patients were placed in prone position with their arms extended, head first in the scanner. In addition to the conventional MRI sequences (transverse T2-weighted images and T1-weighted images), a multi-echo transverse T2*W imaging sequence was obtained from the upper thorax to axilla with the following parameters: TE=0.9- 1.5 ms, TR=37.2 ms, flip angle=25°. For all sequences, field of view (FOV) was 360×360 mm^2, matrix 384 × 384 and slice thickness 3 mm with 1mm gap. Manual selection of the region of interest (ROI) was done on every slice of the suspicious lymph node, excluding cross sections of fatty centre. T2* values were automatically calculated by the commercial workstation.

Sonographic elastography was done on Samsung RS 80 using high frequency linear probe (L3-16 MHz). Patient was positioned supine with ipsilateral arm elevated so as to expose the axilla. After identification of most suspicious node on conventional ultrasound, strain

elastography was applied using freehand compression technique. The measurement of strain ratio was done on a representative static image including coupled B-mode and elastographic images. The region of interest for the axillary lymph node was manually drawn in the thickened cortex or in the whole lymph node including the cortex and hilum. The ultrasound scanner automatically calculated the strain ratio (SR) using E-strain technique (Figure 1 and 2). ROC curves were obtained for various values of T2* and strain ratio in comparison to the histopathological findings (ultrasound guided FNAC/biopsy or post excision biopsy results) as gold standard. The area under ROC curve was compared using Student T test in view of n=43 and the optimal cut off value of these two parameters was established. Sensitivity, specificity, positive predictive value and negative predictive value of T2* and strain ratio in differentiating malignant from benign axillary lymph nodes were calculated at the cut off values. The two modalities were compared to determine the better one.

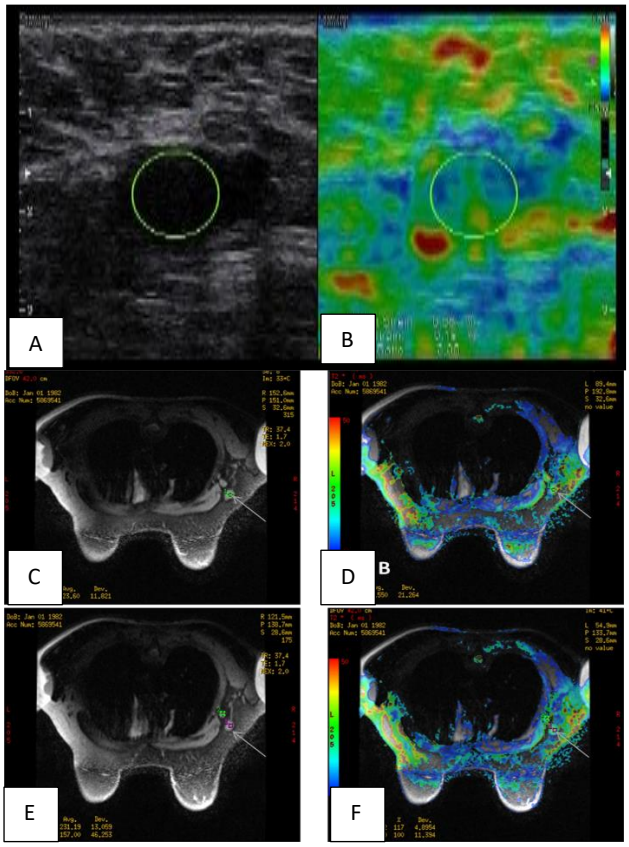

Figure 1: 35-year-old female with biopsy proven breast cancer.

Figure 1 (A and B): B mode US (left) and sonographicelastographic image (right) showing calculation of strain ratio using E-strain technique. The color scale is depicted on the right side of the elastographic image with red representing soft area and blue representing hard area. The circle represents the ROI drawn in the lymph node being examined. The strain ratio was found to be 2.05.

Figure 1 (C-F): C and F are T2*W images and B and F are corresponding T2* maps with color coding represented as scale on the left side of the T2* maps, blue representing the lowest T2* value and red representing the highest T2* value. The lymph node being evaluated is indicated by an arrow. The T2* value was calculated as average of the values obtained on every slice of lymph node and found to be 34.88 ms.

On histopathology, the lymph node was found to be malignant. The T2* value and strain ratio correlated with histopathological diagnosis.

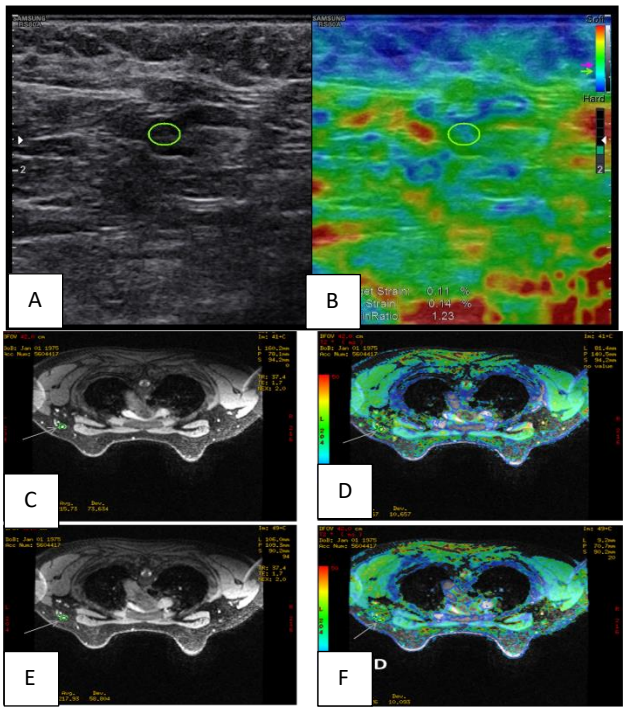

Figure 2: 42-year-old female with biopsy proven breast cancer

Figure 2 (A and B): B mode US (left) and sonographic elastographic image (right) showing calculation of strain ratio using E-strain technique. The color scale is depicted on the right side of the elastographic image with red representing soft area and blue representing hard area. The circle represents the ROI drawn in the lymph node being examined. The strain ratio was found to be 1.23.

Figure 2 (C- F): C and E are T2*W images and D and F are corresponding T2* maps with colour coding represented as scale on the left side of the T2* maps, blue representing the lowest T2* value and red representing the highest T2* value. The lymph node being evaluated is indicated by an arrow. The T2* value was calculated as average of the values obtained on every slice of lymph node and found to be 29.88 ms.

On histopathology, the lymph node was found to be benign. The T2* value and strain ratio correlated with histopathological diagnosis.

RESULTS

In our study, out of total 43 lymph nodes evaluated, 16 were benign (37.21%) and 27 were malignant (62.79%) on histopathology.

Eight cases were in age group of 30 to 39, 19 cases were in age group of 40 to 49 and 8 cases were in age group of 50 to 59 and 60 to 70 years each. Thus, majority of the cases were between 40-49 years of age amounting to 44.2% of the cases.

ROC (receiver operating characteristic**)** curves were obtained for various values of T2* and strain ratio in comparison to the histopathological findings as gold standard (Figure 3).

Accuracy of a test is measured by the area under the ROC curve which depends on how well the test separates the group being tested into those with and without the disease in question. The area under ROC curve for T2* values was 0.954 and that for strain ratio was 0.748 reflecting higher accuracy of T2* value than strain ratio for differentiating malignant from benign axillary lymph nodes in patients with breast cancer. The areas under ROC curves for T2* and strain ratio were compared using T- test and the results were found to be statistically significant with p=0.018.

The cut off values for T2* and strain ratio were calculated from the ROC curve. The optimal cut off value which maximises the sum of sensitivity and specificity was determined. The cut off value for T2* was 31.225 ms and that for strain ratio was 1.85.

The sonographic elastography detected 19 malignant lymph nodes out of total 27 (proven malignant on histopathology) taking value of SR>1.85 as cut off. Eleven lymph nodes were identified as benign out of total 16 (benign on histopathology) with SR less than or equal to 1.85 (Figure 4).

The MRI detected 26 malignant lymph nodes out of total 27 (proven malignant on histopathology) taking value of T2*>31.225 ms as cut off. Fifteen lymph nodes were identified as benign out of total 16 (benign on histopathology) with T2* value less than or equal to 31.225 ms (Figure 5).

The sensitivity and specificity of strain ratio on sonographic elastography with cut off value of SR>1.85 were calculated and found to be 70.37% and 68.75% respectively. The positive predictive value (PPV) and negative predictive value (NPV) were also assessed, PPV being 79.16% and NPV 57.89%. The sensitivity and specificity of T2* value on 3T MRI with cut off value of T2* >31.225 ms were found to be 96.29% and 93.75% respectively. The positive predictive value (PPV) and negative predictive value (NPV) were also calculated, PPV being 96.29% and NPV 93.75% (Table 1).

Thus T2* value on 3T MRI showed higher sensitivity, specificity, PPV and NPV as compared to strain ratio on sonographic elastography in differentiating malignant from benign axillary lymph nodes in patients with breast cancer. Also, higher area under ROC curve of T2* value reflects higher accuracy of T2* value than strain ratio for differentiating malignant from benign axillary lymph nodes in patients with breast cancer.

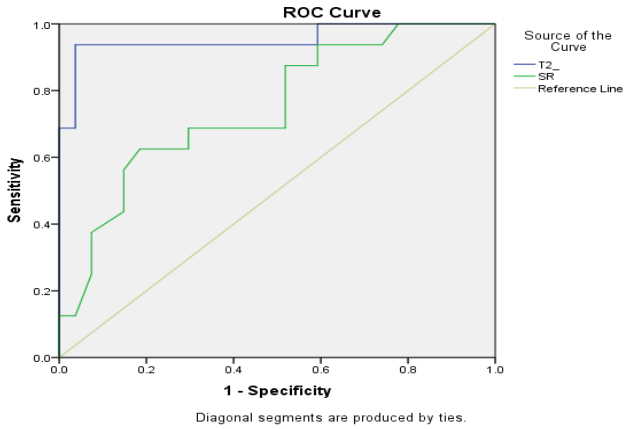

Figure 3: ROC curves for strain ratio values and T2* values of the lymph nodes evaluated in the study (T2_should be read as T2* in the ROC curve).

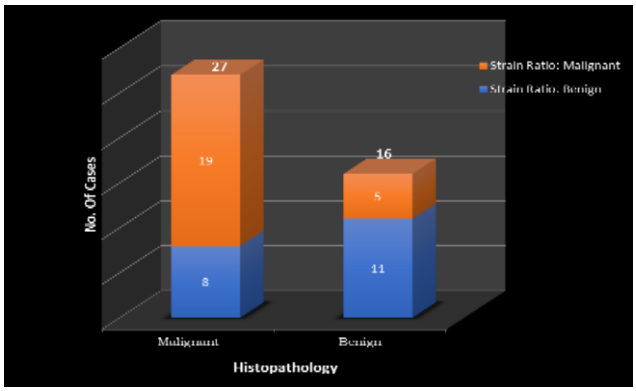

Figure 4: Bar diagram of comparison of strain ratio of lymph nodes on sonographic elastography and histopathological findings.

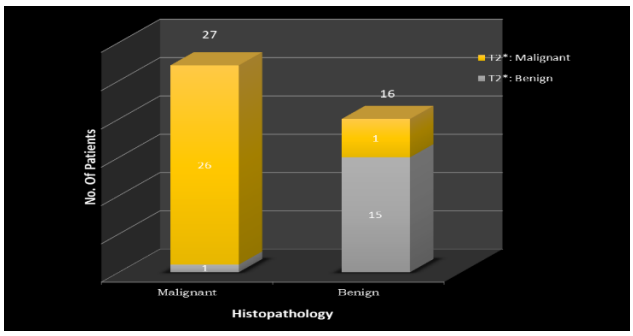

Figure 5: Bar diagram of comparison of T2* values of lymph nodes on 3T MRI and histopathological findings.

Table 1: Comparative evaluation of T2* value on 3T MRI and strain ratio on sonographic elastography.

Parameters	T2* value (%)	Strain ratio (%)
Sensitivity	96.29	70.37
Specificity	93.75	68.75
Positive predictive value	96.29	79.16
Negative predictive value	93.75	57.89
Area under ROC curve	0.954	0.748

DISCUSSION

Breast cancer is the most common malignancy in women. Various factors affecting prognosis of breast cancer are axillary lymph node status, tumor diameter, tumor type/grade, lymphatic and vascular invasion, proliferation markers, ethnicity and patient's age at diagnosis; the most important being the status of axillary lymph nodes in early-stage breast cancer. There is a correlation between the number of involved axillary lymph nodes and the likelihood of distant recurrence.[3]

Present study was performed to evaluate sensitivity and specificity of strain ratio on sonographic elastography and value of T2* from a 3T clinical MRI system in differentiating metastatic from benign lymph nodes in patients with breast cancer.

In our study, out of total 43 lymph nodes evaluated, 16 were benign and 27 were malignant on histopathology. Majority of the cases in the study group were between 40-49 years of age amounting to 44.2 percent of the total cases. The sonographic elastography detected 19 malignant lymph nodes out of total 27 (proven malignant on histopathology) taking value of SR>1.85 as cut off. Eleven lymph nodes were identified as benign out of total 16 (proven benign on histopathology) with SR less than or equal to 1.85. The sensitivity and specificity of strain ratio on sonographic elastography with cut off value of SR>1.85 were calculated and found to be 70.37% and 68.75% respectively in our study. The positive predictive value (PPV) and negative predictive value (NPV) were also assessed, PPV being 79.16% and NPV 57.89% respectively. The results of our study are fairly comparable to those of the previous study by Choi et al and Dudea et al provided a meticulous overview on the applications of real time sonoelastography in the diagnosis of superficial lymphadenopathy and concluded that more than 50% hardness on the node surface or SR > 1.5 is fair indicator of malignancy.[4,11] Similar observations were made by Lyshchik et al who also concluded that strain index greater than 1.5 is a good indicator of metastatic lymph nodes.[12] In our study also, SR>1.85 detected malignancy in 19 lymph nodes out of total 27 malignant nodes. The cut off value of SR>2.3 in previous studies by Zhang et al and Latif et al showed a higher specificity of strain ratio on sonographic elastography.[13,14] Our study took SR>1.85 as cut off for differentiating malignant from benign axillary lymph nodes in patients with breast cancer. An increase in the cut off value for strain ratio is likely to decrease sensitivity and increase specificity of strain ratio on sonographic elastography and vice versa.

Our study calculated the strain ratio using E-strain technique. This technology requires only one ROI to be selected by the user unlike conventional ultrasound elastography and calculates the strain ratio between the selected target and surrounding fatty tissues. It increases consistency and reduces the chance of error by eliminating the step of manual selection of the surrounding fatty tissue region. This was in contrast to the previous studies where manual selection of ROI was done in the lymph node to be evaluated as well as in the reference tissue.

In our study, the MRI detected 26 malignant lymph nodes out of total 27 (proven malignant on histopathology) taking value of T2* >31.225 ms as cut off. Fifteen lymph nodes were identified as benign out of total 16 (proven benign on histopathology) with T2* value less than or equal to 31.225 ms. The cut off for T2* value was calculated from the ROC curve. T2* >31.225 ms indicated malignancy in our study and it was comparable to the cut off value of T2* in a study by Li et al (37.5 ms).[1] The sensitivity and specificity of T2* value on 3T MRI with cut off value of T2* >31.225 ms were calculated and found to be 96.29% and 93.75% respectively in our study. The positive predictive value (PPV) and negative predictive value (NPV) were also assessed, PPV being 96.29% and NPV 93.75%. The results agree well with the previous study done by Li et al which showed sensitivity of 94.6%, specificity of 98.5%, positive predictive value of 98.17 and negative predictive value of 95.54 with cut off value of 37.5 ms.[1] The AUC of T2* in differentiating benign from metastatic lymph nodes was 0.954 in our study which was quite similar to the AUC of T2* in a study by Li et al.[1] According to an in vivo study by Korteweg et al, the metastatic nodes were found to have a significantly longer T2* time compared to non-metastatic nodes.[15] These observations are similar to those of our study.

Limitations

The major limitation was selection of patients having breast cancer and undergoing SLNB or/and axillary lymphadenectomy, which could possibly be a source of bias. The other limitation was related to the method used for generating the ROI for evaluation. The ROIs were placed manually and T2* values were calculated over the entire lymph node. This has the probability of including cystic or calcified components in the measurements. Micro-metastases and isolated tumor cells were not considered in the study because of limited MRI resolution. Potential sources of variations in measurement

of strain ratio on sonographic elastography were related to technique execution and sources of metastases. Other factors which may influence strain ratio are ROI size, shape and distance from the transducer. There is no obvious explanation to measurement of strain ratio in a partially involved node.

CONCLUSION

From the observations, we conclude that:

T2* value on 3T MRI has higher sensitivity and specificity than strain ratio on sonographic elastography in differentiating malignant from benign axillary lymph nodes in patients with breast cancer taking histopathology as gold standard.

T2* values on 3T MRI have greater area under ROC curve (0.954) than strain ratio on sonographic elastography (0.748) reflecting higher accuracy of T2* value than strain ratio for differentiating malignant from benign axillary lymph nodes in patients with breast cancer.

Positive predictive value and negative predictive value of T2* on 3T MRI are superior to those of strain ratio on sonographic elastography.

Thus T2* can be used as a potential biomarker for differentiating metastatic from benign axillary lymph nodes in breast cancer patients owing to its high sensitivity, specificity and relative ease of performance. It has the advantage of being safe (no contrast media required), non-invasive, convenient and reliable imaging technique for differentiating metastatic from benign axillary lymph nodes in breast cancer patients. Moreover, quantitative assessment of changes in T2* from multi echo time (TE) images in lymph nodes may allow a more objective analysis of signal changes with significant differences between benign and malignant lymph nodes, even in the case of partial infiltration.

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