Elastographic features of triple negative breast carcinoma

**Poster No.:** C-0481  
**Congress:** ECR 2014  
**Type:** Scientific Exhibit  
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**Keywords:** Breast, Elastography, Diagnostic procedure, Cancer  
**DOI:** 10.1594/ecr2014/C-0481

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Aims and objectives

Breast cancer is a heterogeneous disease, with lot of different groups (1), but new approach was suggested in 2001 and is based on tumor's molecular characteristics. Tumors are divided in hormone receptor (HR)-positive (+) and HR-negative tumors (-). HR+ tumors are divides in luminal A and luminal B subtype (gene expression similar to luminal epithelial mammary cells) and HR- tumors are clustered in three distinct molecular subgroups: basal like (gene expression similar to basal/myoepithelial mammary cells); human epidermal growth factor receptor 2 (HER 2) positive (tumors with characteristics of HER2 gene amplification) and normal-like breast cancer (expression patterns related to normal mammary stromal cells) (2).

Triple-negative breast cancer (TNBC) is a distinctive sub-group of breast cancers that do not express estrogen receptors (ER), progesterone receptors (PR) or HER 2 (1). This phenotype of breast cancer demonstrates poor prognosis because of aggressive tumor biology, mutation of the TP53 gene and a high degree of correlation with suppressed BRCA1 function. This subtype, which comprises 15% of all breast cancers (3), currently lacks effective targeted therapies. TNBC are typically characterized by large, high-grade tumors that have relatively high rates of recurrence and distant metastasis, and poor prognosis (4-6). Markers for cytokeratin 5/6 and epidermal growth factor receptor divide TNBC into 'basal-like' (BBC) and 'normal-like' sub-types. BBC is a particularly aggressive sub-type defined by genes expressed by epithelial cells in the basal layer of the adult mammary gland. (7).

There have been some studies that tried to find some imaging features of TNBC. TNBC most often present as mass with circumscribed margins without calcifications on mammography and hypoechogenic oval/round masses with posterior acoustic enhancement on ultrasound. On MRI they present as mass type of enhancement with sharp margins and rim type of enhancement, most often with persistent type of curve (7-9).

Elastography depicts strain, which allows qualitative estimation of the stiffness of a lesion, independent of morphologic features. Breast cancers tend to be stiff, whereas many benign masses tend to be soft (10). Shear-wave (SW) elastography (SWE; SuperSonic Imagine, Aix-en-Provence, France) is a highly reproducible technique (11), which allows measurement of the propagation speed of SWs within the tissue to locally quantify its stiffness in kilopascals or meters per second. A variety of features can be measured with SW elastography, including quantitative elasticity, size ratios relative to B-mode imaging, shape at SW elastography, and homogeneity of elasticity (12).

There have been few studies that evaluated elastographic imaging of TNBC but none of them gave us some features that we can say are specific for TNBC (14-16), especially because it will be interesting to see will TNBC have benign or malignant elastographic features. Aim of this study is to evaluate elastographic features of TNBC, find some useful
discriminators from other carcinomas and to compare it to the non TNBC (ER+ and HER 2+).
Methods and materials

We reviewed reports and images of 26 TNBC. Only ER, PR and HER-2 negative tumors which were admitted to elastographic examination were included in this study and they make an examined group.

As a control group, 32 tumors that are ER or HER 2 positive were randomly selected in the same period of time.

Elastography was performed by well experienced radiologists (Aixplorer, Supersonic Imagine, Aix en Provance, France). Images were reviewed by two radiologists using Berg criterions of elastographic imaging (12).

Shear-wave (SW) elastographic evaluation mean (El mean), maximum (El max) and minimum (El min) elasticity of the stiffest portion of mass and surrounding tissue (El mean surr); lesion to fat elasticity ratio (E ratio); SW elastographic lesion color (red, orange, yellow, green, blue, black), lesion shape (regular/irregular) and SW elastographic homogeneity (homogenous, moderately homogenous, heterogeneous) of all tumors in examined and control group was performed (Figure 1).

To compare features of elastographic images and values between patients with triple negative breast cancer and control group we used chi squared test, student T test and Mann Whitney test.

The receiver operating characteristic (ROC) curve analysis was expressed as area under curve (AUC) with its 95% confidence intervals (CI) and used to determine the efficacy of analyzed elastographic values to discriminate between TN and non TN groups. Diagnostic efficacy for elastographic values values was assessed through sensitivity and specificity at cut-off point.

Statistical analysis was performed using the MedCalc software package (Mariakerke, Belgium). For all experiments, the # -level was set at 0.05.
Fig. 1: TNBC - elastographic image

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Results

RESULTS:

TNBC present on elastography mostly as a red lesions (42.3%), but also great number of tumors appear as orange (15.4%), blue and green lesion (19.2% each). They are most often presented as heterogeneous lesions (42.3%) with only 19.2% being purely homogenous but this finding isn't supported with significant statistical difference comparing to non TNBC tumors. They appear as regular shaped lesions on elastography with significant statistical difference (Table 1).

Table 1. Elastographic findings of patients with TNBC.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CONTROL</th>
<th>TRIPPLE NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER OF TUMORS</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>COLOR*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red</td>
<td>30 (93.7 %)</td>
<td>11 (42.3 %)</td>
</tr>
<tr>
<td>Orange</td>
<td>1 (3.1%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Yellow</td>
<td>1 (3.1%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Green</td>
<td>-</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Blue</td>
<td>-</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Black</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HOMOGENEITY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogenous</td>
<td>1 (3.1%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Moderately homogenous</td>
<td>9 (28.1 %)</td>
<td>10 (38.5%)</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>22 (68.7%)</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>SHAPE (regular/irregular)*</td>
<td>2(6.2%)/30 (93.7%)</td>
<td>15(57.7%)/11 (42.3%)</td>
</tr>
<tr>
<td>EL MAXa*</td>
<td>226.63 ± 54.1</td>
<td>166.85 ± 64.71</td>
</tr>
<tr>
<td>EL MEANa*</td>
<td>191.68 ±49.4</td>
<td>135.93 ± 47.26</td>
</tr>
<tr>
<td>EL MIN&lt;sup&gt;a*&lt;/sup&gt;</td>
<td>142.33 ± 44.66</td>
<td>102.69 ± 37.2</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>EL SURR. TISSUE MEAN&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.29 ± 16.6</td>
<td>23.02 ± 8.97</td>
</tr>
<tr>
<td>EL RATIO&lt;sup&gt;b*&lt;/sup&gt;</td>
<td>8.5 (6.15-12.85)</td>
<td>5.45 (4.8-7.1)</td>
</tr>
</tbody>
</table>

<sup>*</sup> p < 0.05, chi squared test, student T test, Mann Whitney

Values are shown as mean ± standard deviation

Values are shown as median with lower and upper quartile

TNBC are much less stiff comparing to non TNBC, as it is shown in the El mean, max and min values, also in E ratio. Mean stiffness of the surrounding tissue is similar to the stiffness of the surrounding tissue of non TNBC (Table 1).

Mean El max of TNBC was 166.85 ± 64.71 kPa, mean El mean was 135.93 ± 47.26 kPa and mean El min was 102.69 ± 37.2 kPa. In examined group median E ratio was 5.45 (4.8-7.1).

Best elastographic feature for differentiating TBNC from other types of cancers with greatest sensitivity and specificity for the cut off value was El min. For values El min <=125.76 kPa there was sensitivity 80.8% and specificity 68.7% for TNBC. Also other cut off values showed acceptable sensitivity and specificity: El max <= 150.7 kPa, El mean <=165.3 kPa and E ratio <=6 (Figure 2, 3 and 4).
Fig. 2: Discriminatory ability of EI max elastographic values between non-TNBC (control) and TNBC patients. Receiver operating characteristic (ROC) curves for EI max. Diagnostic efficacy for those values was assessed using the sensitivity and specificity at a cut-off point. ROC curve analyses, p values #0.05 are considered statistically significant. EI max, maximum elasticity of the stiffest portion of mass; TNBC, triple negative breast carcinoma.

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Fig. 3: Discriminatory ability of El min elastographic values between non-TNBC (control) and TNBC patients. Receiver operating characteristic (ROC) curves for El min. Diagnostic efficacy for those values was assessed using the sensitivity and specificity at a cut-off point. ROC curve analyses, p values $\leq 0.05$ are considered statistically significant. El min, minimum elasticity of the stiffest portion of mass; TNBC, triple negative breast carcinoma.

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**Fig. 4:** Discriminatory ability of El mean elastographic values between non-TNBC (control) and TNBC patients. Receiver operating characteristic (ROC) curves for El mean. Diagnostic efficacy for those values was assessed using the sensitivity and specificity at a cut-off point. ROC curve analyses, p values <0.05 are considered statistically significant. El mean, mean elasticity of the stiffest portion of mass; TNBC, triple negative breast carcinoma.

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Conclusion

The accuracy of shear-wave elastography in benign and malignant differentiation is likely to lead to a bigger number of benign lesions that can be accepted as benign without requiring percutaneous biopsy. Before this can be done it is important to explore which subgroups of breast cancer are associated with benign elastographic features.

In a previous preliminary study, a 50-kPa cut-off was derived from the initial 10 patients and then was prospectively applied to 53 further patients. Use of this cut-off resulted in a sensitivity of 97% and a specificity of 83%. The average El mean was 140 kPa. Higher histologic grade, large size, axillary lymph node involvement, tumor type (ductal, lobular, tubular, papillary) and vascular invasion all showed significant associations with higher mean stiffness values. However, since stiffness is a continuous variable, different cut-off values could be chosen. For example, if improved specificity was desired, a higher cut-off could be used but the cost would be a reduction in sensitivity (15).

Youk et al. demonstrated in their work that E ratio and four-color overlay pattern significantly differed between benign and malignant lesions (16).

Lee et al. showed that El max with a cut-off of 82.3 kPa had the highest area under the receiver operating characteristics curve value compared with other SWE parameters (sensitivity 88.9 %, specificity 77.5 %, accuracy 80.1 %) (17).

Interesting finding was also that there is a significant correlation between elasticity and fibrosis, a negative correlation with necrosis but no significant correlation with cellular tissue (18).

Although mucinous carcinoma had an elastographic features similar to that of usual invasive carcinoma, elastography may be useful for distinguishing mucinous carcinoma from benign fibroadenoma (20).

According to Chang et al. mean stiffness values for TNBC were 146.8 kPa ± 57.0 and 165.8 kPa ± 48.5 (El mean and El max values) and all breast cancers classified as BI-RADS category 3 on B-mode ultrasound were TN subtype (13). Also, according to others, palpability, larger size, lymphovascular invasion, higher histological grade and lymph node involvement were significantly associated with the mean elasticity value. For the immunohistochemical profiles and tumor subtypes, the estrogen receptor, progesterone receptor, Ki-67 and the TN tumor subtype were correlated with the mean elasticity value. After multivariate logistic regression analysis it was shown that the following variables were significantly associated with the mean elasticity value: palpable abnormality, histological grade, and lymphovascular invasion. No immunohistochemical profile of the cancers was independently correlated with the mean elasticity value (16).
Our results show that TNBC present on elastography mostly and with statistical significance as a red lesions (42.3%), but also great number of tumors appear as orange (15.4%), blue and green lesion (19.2% each). They are most often presented as heterogeneous lesions (42.3%) with only 19.2% being purely homogenous but this finding isn't supported with significant statistical difference comparing to non TNBC tumors. They appear as regular shaped lesions on elastography. We also have found that they are much less stiff comparing to non TNBC, as it is shown in the Ei mean, max and min values, also in E ratio. Mean stiffness of the surrounding tissue is similar to the stiffness of the surrounding tissue of non TNBC. Our Ei max for TNBC is $166.85 \pm 64.71$ kPa and E ratio is $5.45$ (4.8-7.1). When we calculated area under the receiver operating characteristics curve for this values, we got interesting findings. Best elastographic feature for differentiating TBNC from other types of cancers with greatest sensitivity and specificity for the cut off value was, surprisingly, Ei min. Use of $\leq 125.76$ kPa as a cut-off resulted in a sensitivity of 80.8% and a specificity of 68.7%. Also other cut off values showed acceptable sensitivity and specificity: Ei max $\leq 150.7$ kPa, Ei mean $\leq 165.3$ kPa and E ratio $\leq 6$. As we have seen, according to published studies, cut off values for differentiating between benign and malignant lesion had been for some publishers around 50 kPa and for others around 85 kPa. We can conclude that TNBC have some benign elastographic features (color and shape), they show decreased stiffness of the lesion, and lesion to fat stiffness ratio comparing to other types of breast cancer but also show increased stiffness comparing to benign lesions (Figure 7).
**Fig. 5:** Elastographic features of triple negative breast cancer

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