Anisotropy of solid breast lesions in 2D shear wave elastography is an indicator of malignancy

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Results: Neither benign nor malignant lesion anisotropy is plane dependent. However, malignant lesions are more anisotropic than benign lesions ($p<0.001$). Anisotropy correlates with increasing elasticity parameters, BIRADS categories, core biopsy result and tumour grade. Large cancers are significantly more anisotropic than small cancers ($p<0.001$). The optimal anisotropy cut-off threshold for benign/malignant differentiation of 150 kPa2 achieves the best sensitivity (74%) with a reasonable specificity (63%).

Conclusions: Anisotropy may be useful during benign/malignant differentiation of solid breast masses using SWE. Anisotropy also correlates with some prognostic factors in breast cancer.
Anisotropy of solid breast lesions in 2D Shear Wave
Elastography is an indicator of malignancy

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Dear Sir or Madam,

Please consider the attached paper for publication.

Thank you very much in advance!

Kind regards,

Katrin Skerl
Acknowledgement

This project is part of a PhD studentship which is funded by SuperSonic Imagine and the Engineering and Physical Science and Research Council (EPSRC).
Anisotropy of solid breast lesions in 2D Shear Wave Elastography is an indicator of malignancy

Abstract

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Conclusions: Anisotropy may be useful during benign/malignant differentiation of solid breast masses using SWE. Anisotropy also correlates with some prognostic factors in breast cancer.

Keywords: Elastography, breast, breast cancer, ultrasound, Shear Wave Elastography

Introduction

Supersonic Shear Wave Elastography (SWE) is an ultrasound imaging modality which visualizes the elasticity of tissue. It was introduced by Bercoff et al. in 2004 [1] and has been in clinical use since 2009 [2]. During examinations the propagation speed of the shear wave is measured and the elasticity, represented as Young’s Modulus E, is calculated as

\[ E = 3\varrho c^2 \]

where \( c \) is the propagation speed of the shear wave and \( \varrho \) is the density of the tissue. Thus SWE is a quantitative measurement method. The elasticity is visualised as a colour map overlaying the grey-scale B-mode ultrasound image of the lesion. As the shear wave is induced by applying an acoustic radiation force, there is no need to move the transducer. A good inter-observer reproducibility can be achieved [2]. Furthermore, Berg et al. have shown that analysing the

Abbreviations

AD – anistropic difference (difference of the measurements in each plane)
AF – anisotropy factor (square of AD)
AUC – area under the curve (statistic measurement to evaluate the diagnostic performance of a method)
E – Young’s Modulus (measurement unit of tissue Elasticity)
\( E_{\text{max}} \) – maximum elasticity
\( E_{\text{mean}} \) – mean elasticity
ROC – receiver operator characteristics (statistical tool to evaluate the diagnostic performance of a method)
ROI – region of interest
SD – standard deviation
SWE – Shear Wave Elastography (used elastography technique in the paper)
quantitative elasticity of a lesion with SWE is useful for the differentiation of benign and malignant lesions [2] as malignant tissue is generally stiffer than benign tissue [3]. Berg et al. recommended the use of a cut-off threshold for the maximum elasticity, $E_{\text{max}}$ of 80 kPa for the optimal benign/malignant differentiation [2]. Evans et al. recommend a cut-off threshold for the mean elasticity, $E_{\text{mean}}$ of 50 kPa [4].

Evans et al. obtain four SWE images per lesion; each two in two orthogonal planes [5]. Observation of anisotropy during routine SWE evaluation of breast lesions prompted this study. Although Ciurea et al. observed anisotropy in solid breast lesions in 2011 [6], to our knowledge there have been no publications on the evaluation of the anisotropy of solid breast lesions on SWE to date.

Anisotropy is found in normal breast tissue and breast lesions. Ductal carcinoma in situ (DCIS) is known to grow faster in the radial than anti-radial plane [7]. Furthermore collagen alignment has been shown to be prognostic in invasive breast cancer [8]. This suggests that detection of anisotropy in SWE could potentially help characterise lesions with ultrasound.

The aim of this study was to observe the frequency and directional characteristics of anisotropy at SWE in benign and malignant lesions and correlate anisotropy with prognostic and predictive factors in breast cancer.

**Materials and methods**

**Study-groups**

Study-group A comprised 244 solid lesions visible on ultrasound (78 benign, 166 malignant) in 243 patients (age range 17-92, mean 58) scanned in our clinic between April 2013 and May 2014. For each lesion four images were obtained; first two in the radial plane and then two in the anti-radial plane. As preliminary data from a sub-group of the study-group A (174 of the 244 lesions in study-group A) suggested that anisotropy in solid breast lesions is not plane dependent [9], another
study-group B of 968 solid breast lesions (306 benign, 662 malignant) in 949 patients (age 17-95, mean 57) was also evaluated. For this group, images had been obtained in two orthogonal planes unrelated to the radial plane. The lesions of the study-group B were evaluated between 2010 and April 2013. Some of the 968 lesions in study-group B were evaluated in previous studies investigating the diagnostic performance of SWE (53 lesions [5], 165 lesions [4]), its correlation with prognostic factors (101 lesions [10]), lymph node involvement (396 lesions [11]) and tissue subtypes (302 lesions [12]) and whether SWE stiffness suggests response to neoadjuvant chemotherapy (40 lesions [13]). However, anisotropy was not measured on any of the SWE examinations in any of the previous studies.

Only patients who underwent core biopsy or surgical excision were included. Women with BIRADS 3 lesions younger than 25 years old did not undergo biopsy or short term follow up in our institution. Further exclusion criteria did not apply. Ethical approval by the National Research Ethics Service guidance was not necessary for this retrospective study [14]. Written informed consent for research purposes was available according to standard procedure in our clinic.

**Ultrasound device**

All examinations were performed using the ultrasound device Aixplorer (SuperSonic Imagine, Aix en Provence, France). The probe that was used to acquire the greyscale and SWE images had a frequency range of 4 to 15 MHz, which gives at -6 dB an axial resolution of 0.3 to 0.5 mm and a lateral resolution of 0.3 to 0.6 mm.

**Image evaluation**

All images were obtained by observers with 5-20 years’ experience in breast ultrasound and at least 3 months experience in the performance of SWE. All four images in the two orthogonal planes were evaluated using a region of interest (ROI) size of 2 mm positioned at the stiffest point of $E_{mean}$ in
the lesion or the surrounding tissue. Artefacts and areas without measured elasticity (black on the
colour-map) were excluded. Each image plane was centred at the approximated centre of the lesion.
The elasticity parameters $E_{\text{max}}$, $E_{\text{mean}}$ and standard deviation (SD) were measured. To evaluate the
anisotropic behaviour of the lesions the two measurements of $E_{\text{mean}}$ for each plane were averaged.
To estimate the plane dependence the anisotropic difference (AD) of the estimations per plane in
study-group A was calculated as

$$AD = \text{antiradial} - \text{radial}$$

(2)

To evaluate the general plane independent anisotropy of the lesion the anisotropy factor (AF) was
calculated as the squared anisotropic difference:

$$AF = (\text{antiradial} - \text{radial})^2$$

(3)

Study-group B was imaged randomly in sagittal and axial plane. Therefore a plane dependency
could not be evaluated but the anisotropy factor:

$$AF = (\text{sagittal} - \text{axial})^2$$

(4)

The results of these calculations were compared to the histological features. Furthermore the
diagnostic performance of the anisotropic difference and the anisotropy factor were calculated. The
gold standard was histology from core biopsy or surgery.

BIRADS classification of the grey scale images was performed by an experienced breast radiologist
blinded to the SWE and histological findings.

Core biopsy results were classified as recommended by the NHSBSP in [15], which is: Category B1
- unsatisfactory or normal tissue; category B2 - benign tissue; category B3 - tissue of uncertain
malignant potential; category B4 - suspicious tissue; category B5a - malignant tissue in situ;
category B5b - invasive tissue; category B5c - not assessable.
Statistics

The Receiver Operator Characteristic (ROC) analysis and statistical analysis using the T-test was performed using IBM SPSS (IBM, Armonk, New York, USA).

The performance of the different thresholds was compared with web-based software using Chi-square test. The null hypothesis was rejected at a level of 5% (p≤0.05).

Results

Evaluation of the study-groups

The 244 lesions of group A comprised 78 benign lesions and 166 malignant lesions. Three hundred and six of the 968 lesions in group B were benign and 662 lesions, malignant. The distribution of histology of each group is shown in Table 1; the distribution off screen detected and symptomatic lesions is shown in Table 2. The ultrasound imaging and histological features are also shown in Table 2.

Plane dependency

To investigate any correlation of the anisotropy of solid breast lesions with the anatomic structure of the breast, the AD of study-group A was evaluated. Fig. 1 shows the distribution of lesions stiffer in the radial plane (AD<0) and lesions stiffer in the anti-radial plane (AD>0).

No plane dependency of anisotropy could be found in any of the lesions whether benign or malignant. This result was confirmed by ROC analysis (Fig. 2) with an area under the curve (AUC) of 0.49 for benign/malignant differentiation.
Anisotropy threshold

The anisotropic factor (AF) was calculated. The AF is plane independent and indicates the degree of anisotropy. In Fig. 2 the ROC analysis for the correlation of AF with benign/malignant-differentiation is shown. For comparison the ROC of the elasticity parameters $E_{\text{max}}$ and $E_{\text{mean}}$ are also shown.

With an AUC of 0.67, the AF suggests malignancy. However, the diagnostic performance of the AF is not as good as $E_{\text{max}}$ or $E_{\text{mean}}$ (AUC for both 0.81). Calculation of the Youden’s index gives an optimal cut-off threshold of AF=200 kPa$^2$. In Table 3 the diagnostic performance for different thresholds of AF around the calculated Youden’s Index is shown.

A threshold of 150 kPa$^2$ yielded the best sensitivity with a reasonably good specificity. This result was confirmed analysing group B. The overall diagnostic performance of thresholds of AF=200 kPa$^2$ and AF=250 kPa$^2$ was identical in group A. However, in group B a cut-off value of AF=250 kPa$^2$ yielded the best overall performance. ROC analysis was in agreement with these thresholds.

Correlation with source of referral

To evaluate the correlation of anisotropy and the source of the referral, groups A and B were subdivided into screen detected or symptomatic lesions, and further subdivided into benign and malignant lesions. The AF of each subgroup was averaged and evaluated.

Fig. 3 shows the averaged AF for all sub-groups in groups A and B.

In group A all sub-groups of symptomatic lesions are significantly more anisotropic than screen detected lesions ($p \leq 0.005$ for total and malignant, $p \leq 0.05$ for benign lesions). In study-group B the
results are similar for the sub-groups of all (total) and malignant lesions. However, symptomatic benign lesions are not significantly more anisotropic than screen detected lesions (p=0.4).

**Correlation with Ultrasound Imaging and elasticity characteristics**

The dependence of anisotropy on the size of the lesion (ultrasound diameter) and the elasticity parameters (\(E_{\text{max}}\), \(E_{\text{mean}}\) and SD) was evaluated. Therefore the lesions of group A and B dichotomised according to a threshold for each parameter, identified from the literature \([2, 5, 16]\) as follows: that is an ultrasound diameter of 15 mm, \(E_{\text{max}}\) of 80 kPa, \(E_{\text{mean}}\) of 50 kPa and a SD of 7 kPa. Furthermore the sub-groups were divided into all (total), benign and malignant lesions. The results are shown in Fig. 4.

Overall, large lesions (\(\geq 15\) mm) are significantly more anisotropic than small lesions (<15 mm) (p\(\leq 0.001\)). In particular, large malignant lesions are significantly more anisotropic than small cancers (p\(\leq 0.001\)). However, this correlation is not significant for benign lesions and may even be independent of lesion size when the results in group B are considered.

A very strong correlation between anisotropy and the elasticity parameters \(E_{\text{max}}\) and \(E_{\text{mean}}\) was found (p\(\leq 0.001\) for all sub-groups in groups A and B). However, in the sub-groups below and above the threshold the AF of benign and malignant lesions are similar. In group A, benign lesions with high elasticity were even more anisotropic than malignant lesions of high elasticity. However, this was not observed in group B.
Anisotropy also correlates with the elasticity parameter SD (p≤0.001 for the sub-groups of all and benign lesions). The correlation with SD in the sub-group of malignant lesions was non significant in group A, but significant in group B (p≤0.001), which is probably due to a greater number of cases in group B. For the sub-groups with SD<7 kPa, malignant lesions are significantly more anisotropic than benign lesions (p≤0.05). However, all lesions of group A with SD≥7 kPa are in the same range and a difference of AF in benign and malignant lesions was seen only in group B (p≤0.001).

**Correlation with ultrasound BIRADS**

Groups A and B were divided into subgroups by ultrasound BIRADS categorisation. Furthermore the subgroups were divided into benign and malignant lesions. The averaged AF of each sub-group was correlated with ultrasound BIRADS categories (Fig. 5).

A correlation of the averaged AF and ultrasound BIRADS categories was observed. Overall lesions categorised as BIRADS 3 are less anisotropic than BIRADS 4a lesions (significant in group A with p≤0.05; not significant in group B, p≤0.1) and BIRADS 4a lesions are significantly less anisotropic than BIRADS 4b lesions (p≤0.05 for both groups). The difference in the averaged AF of benign and malignant lesions is non significant in BIRADS 3 as the number of malignant cases was low (one case) and significant in BIRADS 4a lesions (p≤0.001).

**Correlation with core result**

Groups A and B were subdivided according to the core biopsy result. The averaged AF was then correlated with results of core biopsy (Fig. 6).

The AF correlates with the core result; in general a more anisotropic lesion is more likely to be malignant. Lesions with a core result of B1, B2 or B3 are significant less anisotropic than lesions
with a core result of B5a (p≤0.001 in both groups). Furthermore B5b lesions are more anisotropic than B5a lesions (p>0.1 in group A, p≤0.001 in group B).

**Correlation with tumour grade**

Malignant lesions in groups A and B were subdivided according to tumour grade and correlated with AF as shown in Fig. 7.

While the AF of lesions with a tumour grade of 2 and 3 are in the same range, lesions with a tumour grade of 1 are significantly less anisotropic (p≤0.001 in both groups).

**Correlation with other histological features**

The averaged AF was correlated with the HER2, PR and ER receptor status. There was no correlation found. Lesions with HER+/− had an AF of 21 vs. 23 kPa²/100 in group A and 24 vs. 23 kPa²/100 in group B. Lesions with ER+/− had an AF of 22 vs. 27 kPa²/100 in group A and 24 vs. 22 kPa²/100 in group B. Lesions with PR+/− had an AF of 24 vs. 21 kPa²/100 in group A and 24 vs. 22 kPa²/100 in group B.

Furthermore no correlation could be found with lymph node involvement (23 vs. 22 kPa²/100 in group A; 25 vs. 23 kPa²/100 in group B for lymph node positive/negative) nor vascular invasion (18 vs. 24 kPa²/100 in group A; 26 vs. 23 kPa²/100 in group B for vascular invasion positive/negative).

**Correlation with subtypes**

The benign and malignant lesions of groups A and B were divided into their subtypes. The averaged AF of each tissue subtype was calculated and is shown in Table 4. Mucinous and tubular carcinomas are less anisotropic than other malignant lesions while ductal carcinomas of no specific
type and lobular carcinomas are more anisotropic in both groups. A difference between group A and group B is visible which may be caused by the small numbers in each subgroup.

Discussion

We have shown that solid breast lesions are anisotropic at SWE assessment. Neither benign nor malignant lesions show consistent plane-dependent anisotropy; that is, elasticity may be greater in either radial or anti-radial plane regardless of the nature of the lesion. However, the degree of anisotropy represented by AF suggests malignancy. The optimal cut-off threshold for benign/malignant differentiation in group A, in whom elasticity was assessed in radial and anti-radial planes, was calculated to be 200 kPa². A threshold of AF=150 kPa² resulted in the best sensitivity with a reasonable specificity; if specificity is more important, a threshold of AF=250 kPa² is preferable. These results were confirmed by analysing group B, where images were acquired in sagittal and axial planes.

Breast tissue is anisotropic in structure as the fibroglandular tissue is oriented along the ducts leading radially to the nipple. For ductal elongation local collagen fibre alignment is necessitated which leads to local mechanical anisotropy in the mammary gland [17]. Provenzano et al. have shown that the orientation of collagen fibres changes during tumour growth: first regions of dense collagen develop in the tissue, then the collagen fibres are aligned parallel to the tumour boundary while during further tumour growth, collagen fibres become reorganized orthogonal to the tumour boundary to enable invasion [18].

The higher anisotropy in the elasticity of malignant breast lesions may therefore correlate with the degree of invasiveness. Furthermore, the stiffest plane could suggest the growing direction of the tumour. This would also explain the higher anisotropy in invasive lesions. It is possible that the observed anisotropy in in situ lesions may correlate with the invasive potential of the lesion.
The anisotropy of solid breast lesions can also be evaluated with diffusion tensor magnetic resonance imaging (DTI), which quantifies the directionality, if any, of diffusion of water molecules in response to motion-probing local magnetic field gradients. In normal breast tissue, water diffusion is anisotropic with a predominant vector towards the nipple (ie. along the radial plane). Previous studies have shown that evaluating the anisotropy may be helpful for benign/malignant differentiation [19 - 22]. They found malignant lesions more anisotropic than benign lesions [19, 21] which is in agreement with our results.

Anisotropy was also evaluated by Sinkus et al. using magnetic resonance elastography (MRE) [23]. They found that anisotropy of solid breast lesions correlates with the degree of stiffness. However, only two solid breast lesions (one fibroadenoma, one invasive ductal carcinoma) were included into their study. Our results confirm and expand on their findings.

Our study does have some limitations. Groups A and B were subdivided and the AF was averaged for each subgroup. However, evaluating the mean can be misleading if outliers are present particularly in small subgroups.

SWE measurements were only made in two orthogonal planes. Therefore it is uncertain if the stiffest plane of the tumour was measured, which may distort the results.

Furthermore the elasticity is calculated by the ultrasound system using equation 1, which is a simplified equation and might hence influence the measurements. However, our aim was to investigate anisotropy observed during clinical practice.

A further limitation is that this study was a single centre study, retrospective study, though care was taken to minimise bias by blinding the observer to the final pathology of the lesions, and the observer carrying out the greyscale BIRADS classification was not the one measuring the anisotropy.

To our best knowledge this study is the first to investigate the significance of anisotropy of solid breast lesions on SWE. The elasticity parameters should be investigated in further planes to enable
the inclusion of the evaluation of the stiffest plane. Furthermore an investigation of the position of
the lesion within the entire breast may be of interest.

References


presentation at British Society of Breast Radiology Conference BSBR, November 10–12, Liverpool, United Kingdom; DOI: 10.1186/bcr3502.


Figure Captions

Figure 1: Neither benign nor malignant lesions’ stiffness is plane dependent. The distribution of lesions stiffer in the anti-radial plane (orthogonal to ducts) equals the distribution of lesions, which are stiffer in the radial plane (along ducts).

Figure 2: ROC curve of the plane dependent anisotropic difference (AD) and the plane independent anisotropy factor (AF) compared to the performance of $E_{\text{max}}$ and $E_{\text{mean}}$ in group A. AD does not correlate with malignancy but AF. However, the diagnostic performance of AF is inferior to that of $E_{\text{max}}$ or $E_{\text{mean}}$.

Figure 3: Symptomatic lesions’ stiffness is more anisotropic than screen detected lesions.

Figure 4: Larger lesions are more anisotropic on SWE than smaller lesions. Small benign lesions are less anisotropic than small cancers; large benign lesions are less anisotropic than large cancers. Furthermore, anisotropy on SWE correlates with stiffness ($E_{\text{max}}$, $E_{\text{mean}}$, SD). There is no further correlation of AF with malignancy in soft or hard lesions.

Figure 5: BIRADS 3 and 4a lesions are less anisotropic on SWE than BIRADS 4b, 4c or 5 lesions. Malignant BIRADS 3 or 4a lesions are more anisotropic than benign BIRADS 3 or 4a lesions.

Figure 6: Anisotropy on SWE correlates with the result of core biopsy. Invasive cancers (B5b) are more anisotropic than in-situ cancers (B5a).

Figure 7: Tumours with grade 1 are less anisotropic on SWE than tumours with grade 2 or 3.
Diagonal segments are produced by ties.
Correlation of AF with source

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Correlation of AF with US BIRADS

kPa/100

33 32 26 24 27 46
3 4a 4b 4c 5

Group A

Group B
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Table 1: Subtypes of solid breast lesions in the study-group A and study-group B
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</table>

Size, nodal status and vascular invasion were not available in those women treated initially with systematic therapy. HER status is missing in women with equivocal ELISA results who were not candidates for chemotherapy.

Table 2: Ultrasound assessment and histological features of the study-group A and the study-group B
<table>
<thead>
<tr>
<th>Threshold</th>
<th>study-group A</th>
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<th>study-group B</th>
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<td>DA</td>
<td>Se</td>
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Table 3: Diagnostic performance of anisotropy factor (AF)
<table>
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<th>Subtype</th>
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<th>study-group B AF [kPa²/100]</th>
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</thead>
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<td>5</td>
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<td>32</td>
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<tr>
<td>Other</td>
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<td>22</td>
</tr>
</tbody>
</table>

Table 4: Correlation of AF with tissue subtype of the lesions of study-group A and B