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

Skerl, Katrin; Vinnicombe, Sarah; Thomson, Kim; McLean, Denis; Giannotti, Elisabetta; Evans, Andrew

Published in:
Academic Radiology

DOI:
10.1016/j.acra.2015.09.016

Publication date:
2016

Document Version
Peer reviewed version

Elsevier Editorial System(tm) for Academic Radiology
Manuscript Draft

Manuscript Number:

Title: Anisotropy of solid breast lesions in 2D Shear Wave Elastography is an indicator of malignancy

Article Type: Original Investigation

Corresponding Author: Ms. Katrin Skerl,

Corresponding Author's Institution: University of Dundee

First Author: Katrin Skerl

Order of Authors: Katrin Skerl; Sarah Vinnicombe, MRCP, FRCR; Kim Thomson, DCRR, PGDIP; Denis McLean, MB, ChB, FRCP; Elisabetta Giannotti, MD; Andrew Evans, MRCP, FRCR

Abstract: Rationale and Objectives: To investigate if anisotropy at 2D Shear Wave Elastography (SWE) suggests malignancy and whether it correlates with prognostic and predictive factors in breast cancer.
Materials and Methods: Study-group A of 244 solid breast lesions was imaged with SWE between April 2013 and May 2014. Each lesion was imaged in radial and anti-radial planes and the maximum elasticity Emax, mean elasticity Emean and standard deviation SD were recorded and correlated with benign/malignant status and if malignant, to conventional predictive and prognostic factors. The results were compared to a study-group B of 968 solid breast lesions, which were imaged in sagittal and axial plane between 2010 and 2013.
Results: Neither benign nor malignant lesion anisotropy is plane dependent. However, malignant lesions are more anisotropic than benign lesions ($p \leq 0.001$). Anisotropy correlates with increasing elasticity parameters, BIRADS categories, core biopsy result and tumour grade. Large cancers are significantly more anisotropic than small cancers ($p \leq 0.001$). 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

Katrin Skerl[1], Dipl. Ing., +44(0)1382 383625, k.skerl@dundee.ac.uk

Sarah Vinnicombe[1], MRCP, FRCR, s.vinnicombe@dundee.ac.uk

Kim Thomson[1] DCRR, PGDIP, kim.thomson@nhs.net

Denis McLean[1], MB, ChB, FRCP, denismclean@nhs.net

Elisabetta Giannotti[1 2], MD

Andrew Evans[1], MRCP, FRCR, a.z.evans@dundee.ac.uk

[1]Medical Research Institute; Ninewells Hospital & Medical School; Mailbox 4; Dundee DD1 9SY; Scotland, UK

[2]Department of Biomedical Sciences, Experimental and Clinical "Mario Serio" University of Florence, Viale Morgagni 50, 50134 Firenze (FI), Italy

Cover Letter

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

Rationale and Objectives: To investigate if anisotropy at 2D Shear Wave Elastography (SWE) suggests malignancy and whether it correlates with prognostic and predictive factors in breast cancer.

Materials and Methods: Study-group A of 244 solid breast lesions was imaged with SWE between April 2013 and May 2014. Each lesion was imaged in radial and anti-radial planes and the maximum elasticity E_{max}, mean elasticity E_{mean} and standard deviation SD were recorded and correlated with benign/malignant status and if malignant, to conventional predictive and prognostic factors. The results were compared to a study-group B of 968 solid breast lesions, which were imaged in sagittal and axial plane between 2010 and 2013.

Results: Neither benign nor malignant lesion anisotropy is plane dependent. However, malignant lesions are more anisotropic than benign lesions ($p \leq 0.001$). Anisotropy correlates with increasing elasticity parameters, BIRADS categories, core biopsy result and tumour grade. Large cancers are significantly more anisotropic than small cancers ($p \leq 0.001$). The optimal anisotropy cut-off threshold for benign/malignant differentiation of 150 kPa^2 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.

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

$$E=3\varrho c^2 \quad (1)$$

where c is the propagation speed of the shear wave and ϱ 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_{max} – maximum elasticity

E_{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_{max} of 80 kPa for the optimal benign/malignant differentiation [2]. Evans et al. recommend a cut-off threshold for the mean elasticity, E_{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_{max}, E_{mean} and standard deviation (SD) were measured. To evaluate the anisotropic behaviour of the lesions the two measurements of E_{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

$$AD = antiradial - radial \quad (2)$$

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

$$AF=(antiradial-radial)^2 \quad (3)$$

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

$$AF=(sagittal-axial)^2 \quad (4)$$

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% ($p \leq 0.05$).

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_{max} and E_{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_{max} or E_{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_{max}, E_{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_{max} of 80 kPa, E_{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 (≥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_{max} and E_{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 ($p \leq 0.001$ 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 ($p \leq 0.001$), 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 ($p \leq 0.05$). 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 ($p \leq 0.001$).

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 $p \leq 0.05$; not significant in group B, $p \leq 0.1$) and BIRADS 4a lesions are significantly less anisotropic than BIRADS 4b lesions ($p \leq 0.05$ 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 ($p \leq 0.001$).

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 ($p \leq 0.001$ in both groups). Furthermore B5b lesions are more anisotropic than B5a lesions ($p > 0.1$ in group A, $p \leq 0.001$ 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 ($p \leq 0.001$ 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 $kPa^2/100$ in group A and 24 vs. 23 $kPa^2/100$ in group B. Lesions with ER+/- had an AF of 22 vs. 27 $kPa^2/100$ in group A and 24 vs. 22 $kPa^2/100$ in group B. Lesions with PR+/- had an AF of 24 vs. 21 $kPa^2/100$ in group A and 24 vs. 22 $kPa^2/100$ in group B.

Furthermore no correlation could be found with lymph node involvement (23 vs. 22 $kPa^2/100$ in group A; 25 vs. 23 $kPa^2/100$ in group B for lymph node positive/negative) nor vascular invasion (18 vs. 24 $kPa^2/100$ in group A; 26 vs. 23 $kPa^2/100$ 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 kPa^2. A threshold of AF=150 kPa^2 resulted in the best sensitivity with a reasonable specificity; if specificity is more important, a threshold of AF=250 kPa^2 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

[1] Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Transactions On Ultrasonics, Ferroelectrics, And Frequency Control. 2004;51(4):396–409.

[2] Berg WA, Cosgrove DO, Doré CJ, Schäfer FKW, Svensson WE, Hooley RJ, et al. Shear-wave elastography improves the specificity of breast US: the BE1 multinational study of 939 masses. Radiology. 2012;262(2):435–449.

[3] Fleury EdFC, Fleury JCV, Piato S, Roveda J Decio. New elastographic classification of breast lesions during and after compression. Diagnostic And Interventional Radiology (Ankara, Turkey). 2009;15(2):96–103.

[4] Evans A, Whelehan P, Thomson K, Brauer K, Jordan L, Purdie C, et al. Differentiating benign from malignant solid breast masses: value of shear wave elastography according to lesion stiffness combined with greyscale ultrasound according to BI-RADS classification. British Journal Of Cancer. 2012;107(2):224–229.

[5] Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, et al. Quantitative shear wave ultrasound elastography: initial experience in solid breast masses. Breast Cancer Research: BCR. 2010;12(6):R104–R104.

[6] Ciurea AI, Bolboaca SD, Ciortea CA, Botar-Jid C, Dudea SM. The influence of technical factors on sonoelastographic assessment of solid breast nodules. Ultraschall In Der Medizin (Stuttgart, Germany: 1980). 2011;32 Suppl 1:S27–S34.

[7] Thomson JZ, Evans AJ, Pinder SE, Burrell HC, Wilson AR, Ellis IO. Growth pattern of ductal carcinoma in situ (DCIS): a retrospective analysis based on mammographic findings. British Journal Of Cancer. 2001;85(2):225–227.

[8] Conklin MW, Eickhoff JC, Riching KM, Pehlke CA, Eliceiri KW, Provenzano PP, et al. Aligned collagen is a prognostic signature for survival in human breast carcinoma. The American Journal Of Pathology. 2011;178(3):1221–1232.

[9] Skerl K, Thompson K, Vinnicombe S, Whelehan P, Evans A. Anisotropy in solid breast lesions at shear wave elastography: relationship to the radial plane and implications for benign/malignant differentiation; 2013. Oral

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

[10] Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, et al. Invasive breast cancer: relationship between shear-wave elastographic findings and histologic prognostic factors. Radiology. 2012;263(3):673–677.

[11] Evans A, Rauchhaus P, Whelehan P, Thomson K, Purdie CA, Jordan LB, et al. Does shear wave ultrasound independently predict axillary lymph node metastasis in women with invasive breast cancer? Breast Cancer Research And Treatment. 2014;143(1):153–157.

[12] Vinnicombe SJ, Whelehan P, Thomson K, McLean D, Purdie CA, Jordan LB, et al. What are the characteristics of breast cancers misclassified as benign by quantitative ultrasound shear wave elastography? European Radiology. 2014;24(4):921–926.

[13] Evans A, Armstrong S, Whelehan P, Thomson K, Rauchhaus P, Purdie C, et al. Can shear-wave elastography predict response to neoadjuvant chemotherapy in women with invasive breast cancer? British Journal Of Cancer. 2013;109(11):2798–2802.

[14] National Research Ethics Service: Approval for Medical Devices Research: Guidance for Researchers, Manufacturers. Research Ethics Committees and NHS R&D Offices; 2008. Version 2 London: National Patient Safety Agency; available at www.hra.nhs.uk; accesed 08-05-2014.

[15] Guidelines for pathology reporting in breast disease. NHSBSP; 2005. Version 2 London: National Patient Safety Agency.

[16] Skerl K, Thompson K, Vinnicombe S, Whelehan P, Evans A. Influence of region of interest(ROI) size on the performance of shear wave elastography in solid breast masses; 2013. Poster presented at 12th International Tissue Elasticity Conference (ITEC), October 1–4, Lingfield, United Kingdom; DOI: 10.13140/2.1.1468.5760.

[17] Barnes C, Speroni L, Quinn KP, Montevil M, Saetzler K, Bode-Animashaun G, et al. From single cells to tissues: interactions between the matrix and human breast cells in real time. Plos One. 2014;9(4):e93325–e93325.

[18] Provenzano PP, Eliceiri KW, Campbell JM, Inman DR, White JG, Keely PJ. Collagen reorganization at the tumor-stromal interface facilitates local invasion. BMC Medicine. 2006;4(1):38–38.

[19] Partridge SC, Ziadloo A, Murthy R, White SW, Peacock S, Eby PR, et al. Diffusion tensor MRI: preliminary anisotropy measures and mapping of breast tumors. Journal Of Magnetic Resonance Imaging: JMRI. 2010;31(2):339–347.

[20] Partridge SC, Murthy RS, Ziadloo A, White SW, Allison KH, Lehman CD. Diffusion tensor magnetic resonance imaging of the normal breast. Magnetic Resonance Imaging. 2010;28(3):320–328.

[21] Baltzer PAT, Schäfer A, Dietzel M, Grässel D, Gajda M, Camara O, et al. Diffusion tensor magnetic resonance imaging of the breast: a pilot study. European Radiology. 2011;21(1):1–10.

[22] Tagliafico A, Rescinito G, Monetti F, Villa A, Chiesa F, Fisci E, et al. Diffusion tensor magnetic resonance imaging of the normal breast: reproducibility of DTI-derived fractional anisotropy and apparent diffusion coefficient at 3.0 T. La Radiologia Medica. 2012;117(6):992–1003.

[23] Sinkus R, Tanter M, Catheline S, Lorenzen J, Kuhl C, Sondermann E, et al. Imaging anisotropic and viscous properties of breast tissue by magnetic resonance-elastography. Magnetic Resonance In Medicine: Official Journal Of The Society Of Magnetic Resonance In Medicine / Society Of Magnetic Resonance In Medicine. 2005;53(2):372–387.

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_{max} and E_{mean} in group A. AD does not correlate with malignancy but AF. However, the diagnostic performance of AF is inferior to that of E_{max} or E_{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_{max}, E_{mean}, SD). There is no further correlation of AF with malignancy in soft or hard lesions.

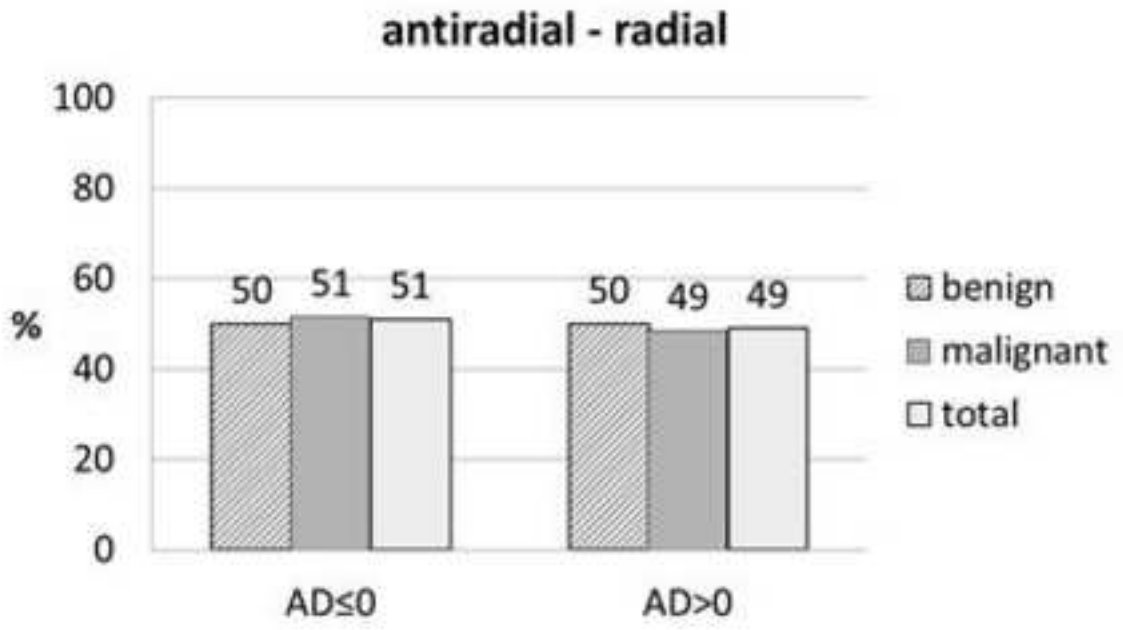
Figure 5: BIRADS 3 and 4a lesions are less anisotropic on SWE than BIRADS 4b, 4c or 5 lesions. Malignant BIRADS 3 or 4a lesions are more anisotropic than benign BIRADS 3 or 4a lesions.

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.

Figure

Click here to download high resolution image



Figure

Click here to download high resolution image

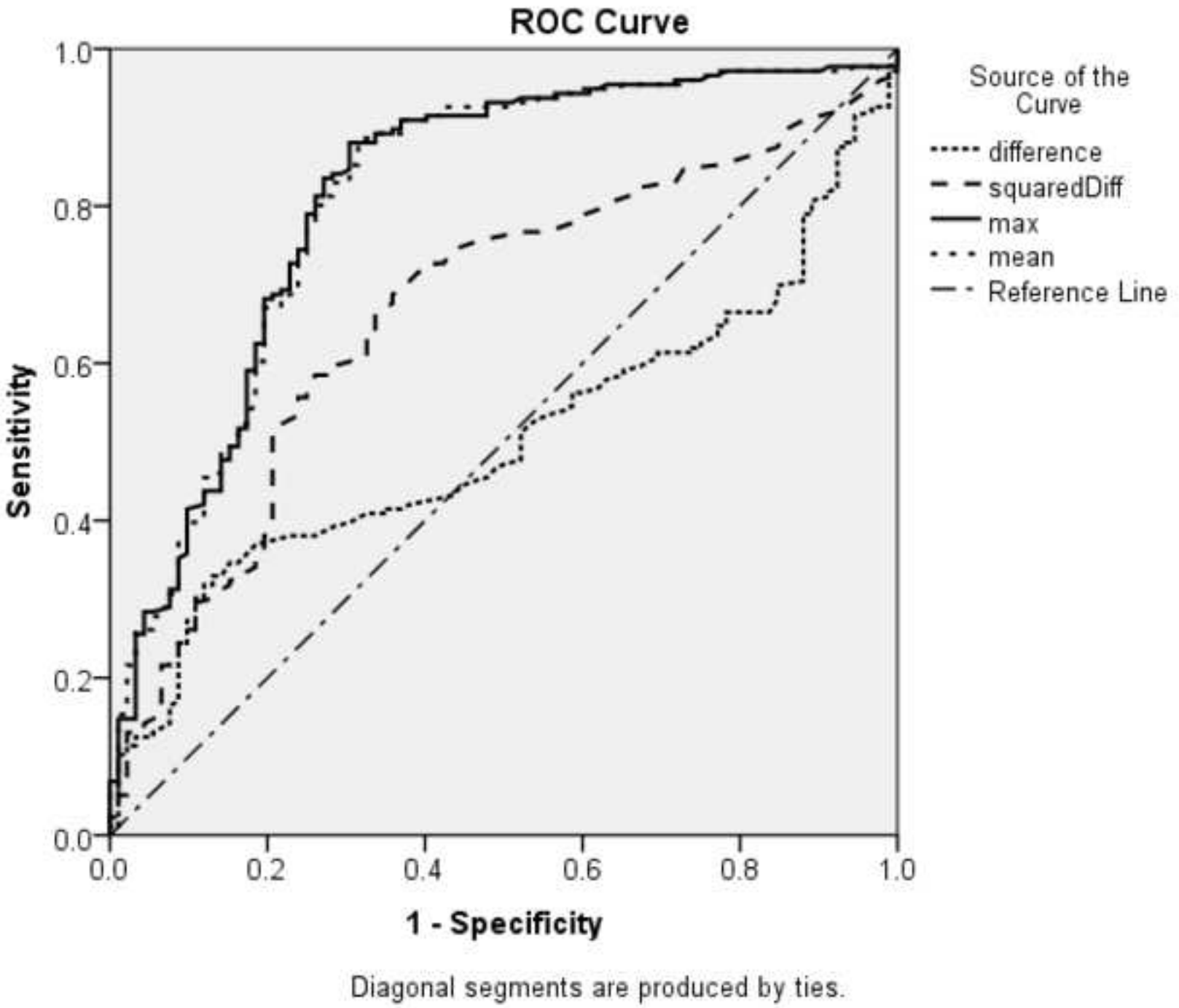
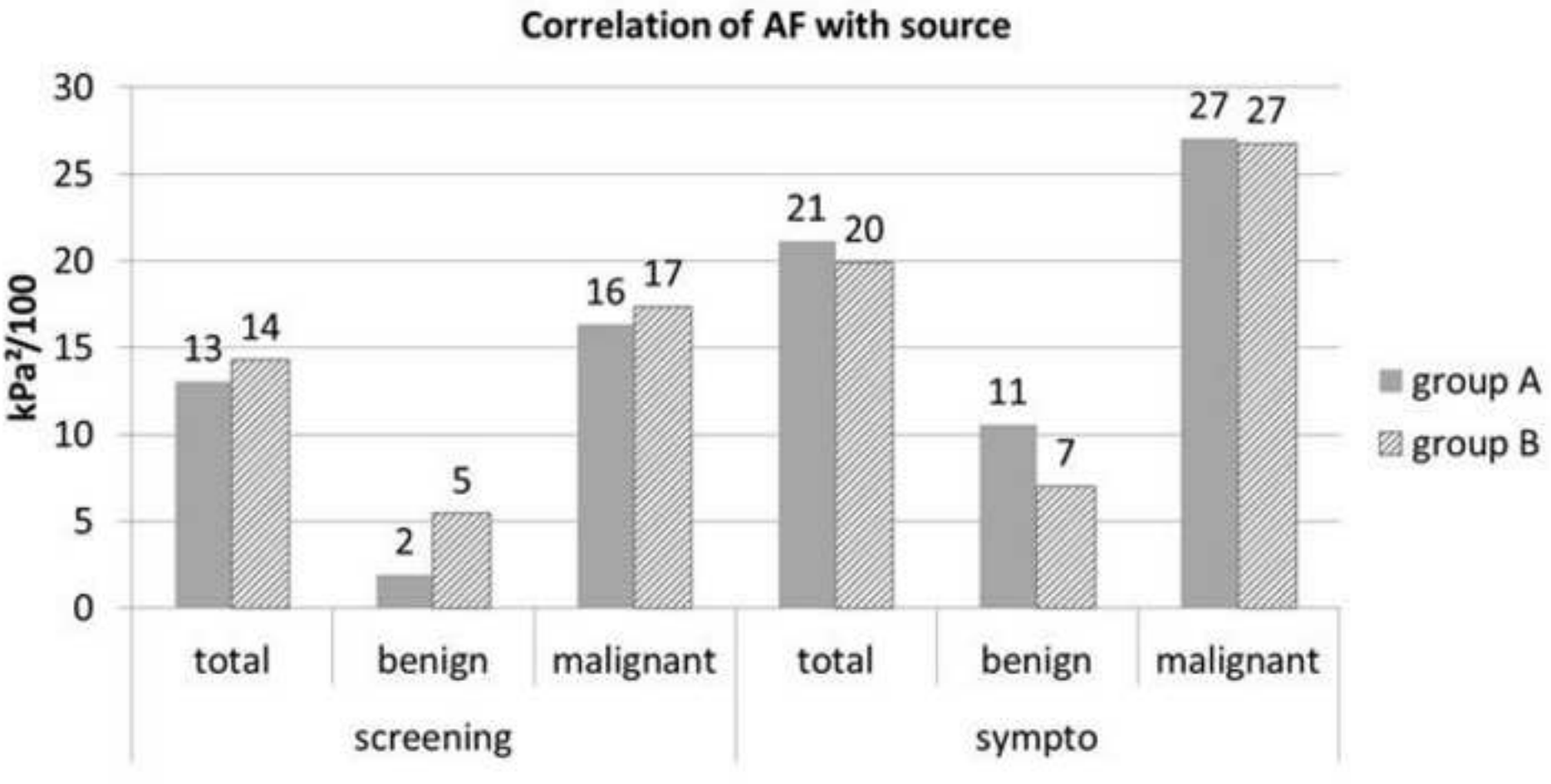
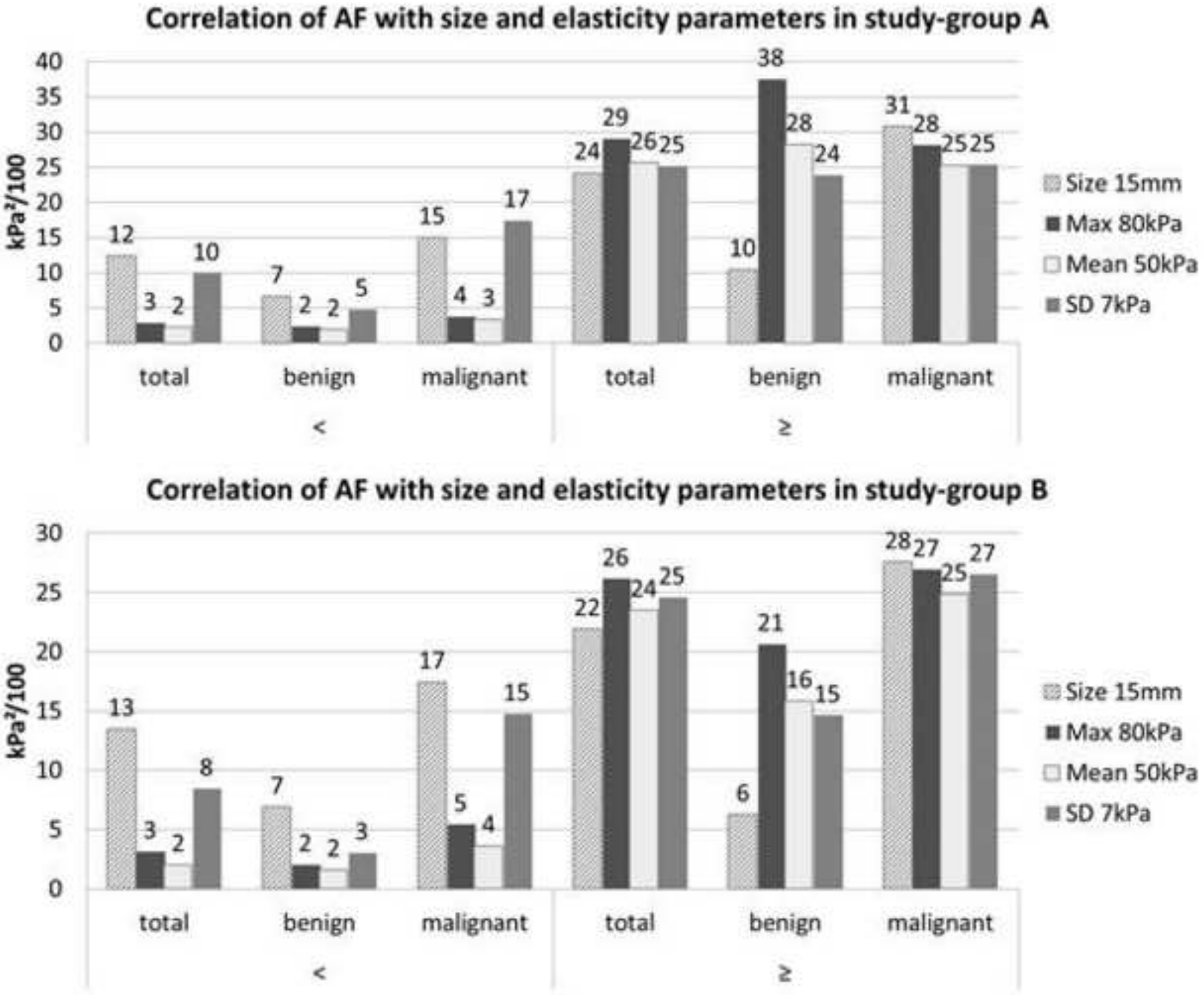


Figure
Click here to download high resolution image



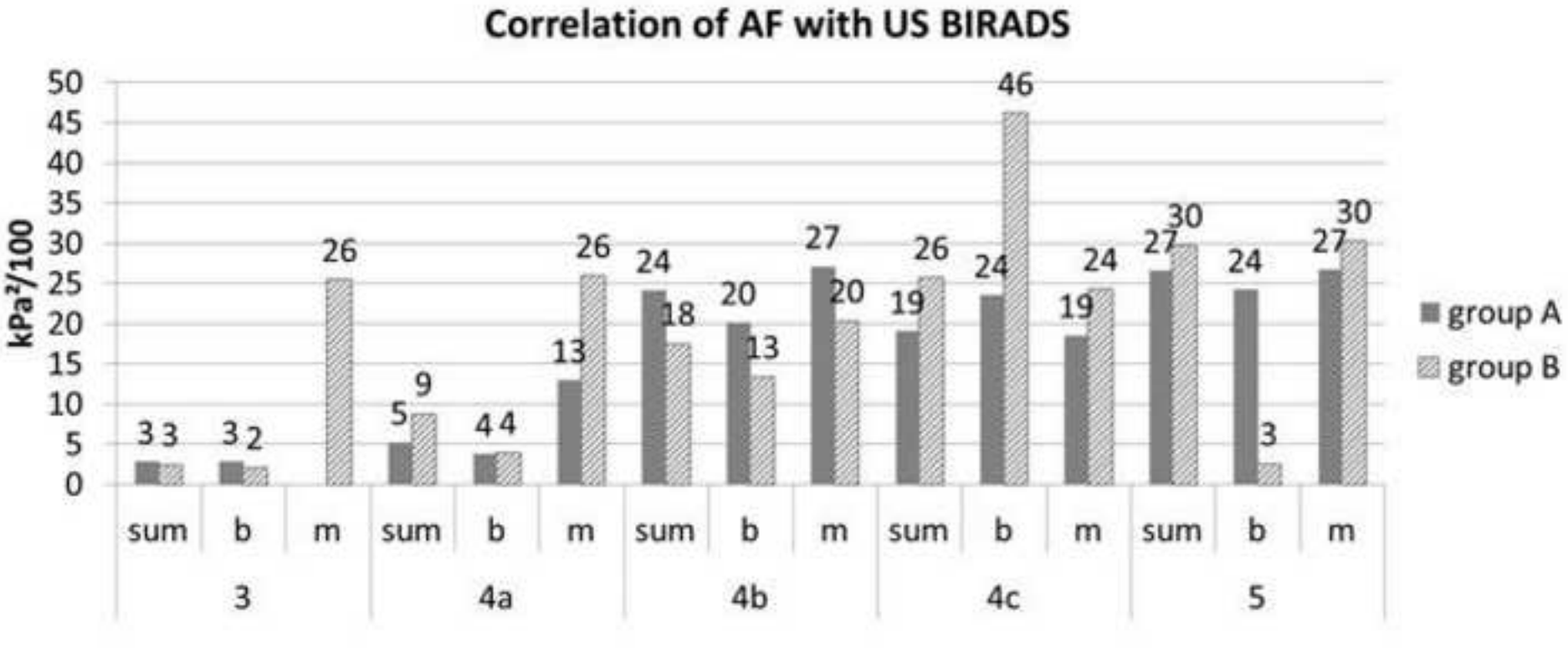
Figure

Click here to download high resolution image



Figure

Click here to download high resolution image



Figure

Click here to download high resolution image

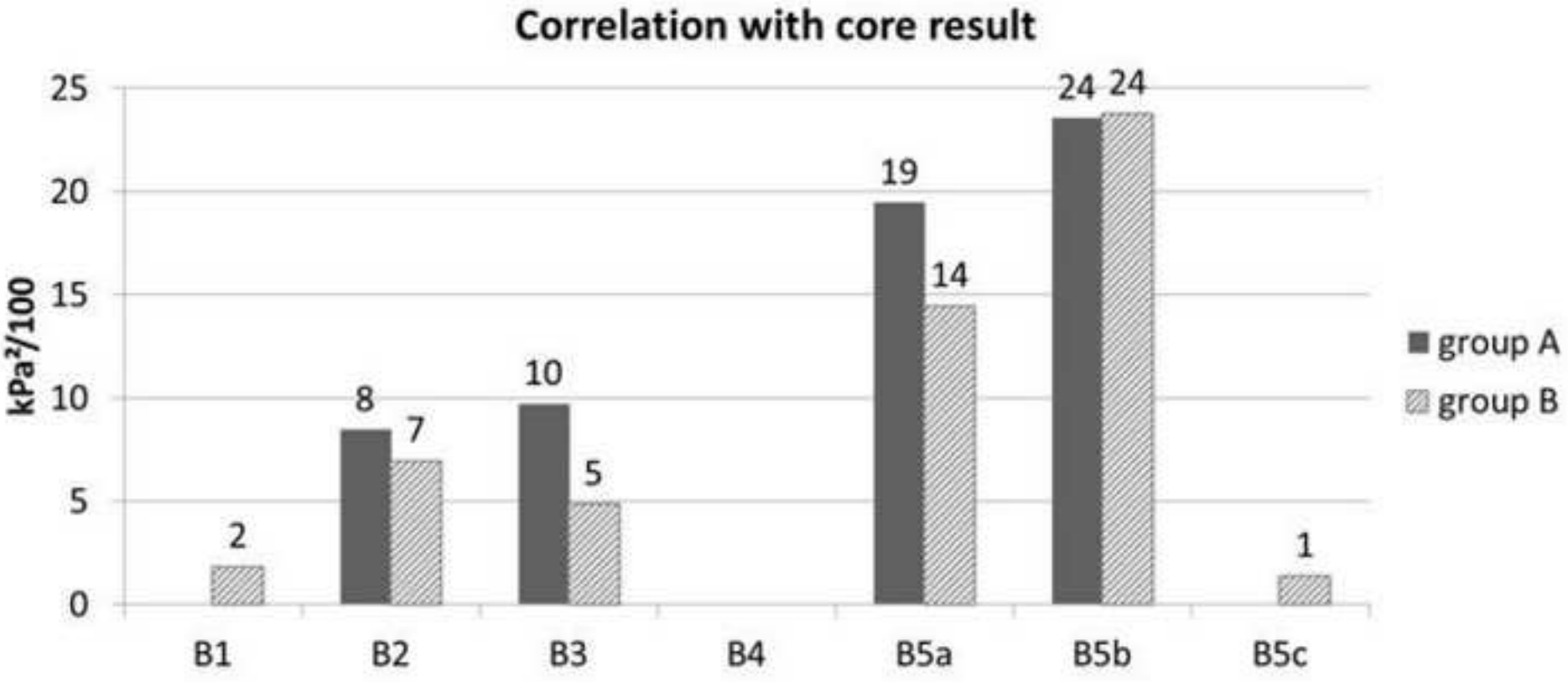
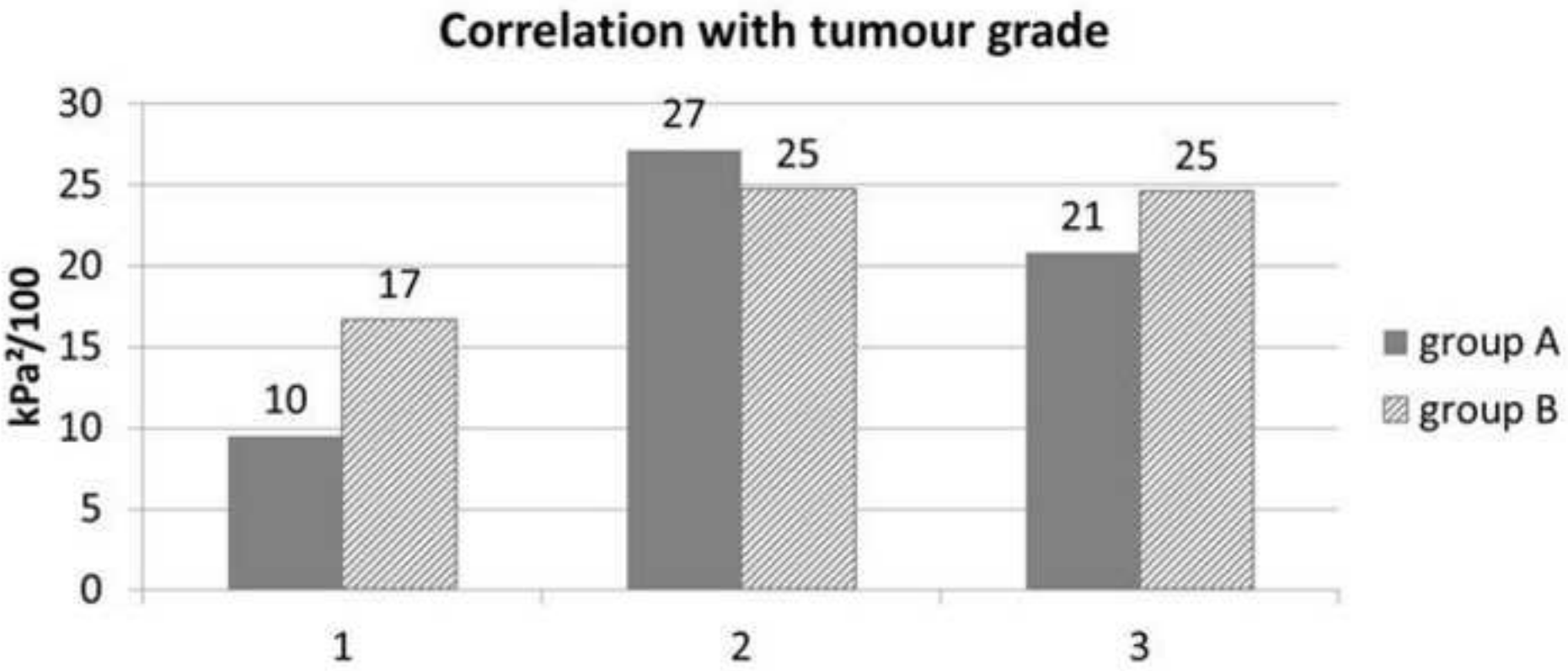


Figure
Click here to download high resolution image



Table

Subtype		study-group A number	%	study-group B number	%
Malignant	ductal carcinoma in situ	4	2	18	3
	ductal carcinoma of no specific type	110	68	482	76
	lobular carcinoma	34	21	78	12
	mucinous carcinoma	7	4	9	1
	tubular carcinoma	6	4	23	4
	papillary carcinoma	1	1	17	3
	Other	5	31	26	4
Benign	Fibroadenoma	43	69	148	55
	Fibrocystic changes	7	11	56	21
	Liponecrosis	3	5	15	6
	Papilloma	1	2	14	5
	Other	8	13	38	14

Table 1: Subtypes of solid breast lesions in the study-group A and study-group B

Table

Feature		study-group A number	%	study-group B number	%
Source	screening	75	31	339	35
	symptomatic	170	69	629	65
Imaging	US size <15mm	115	47	454	47
	US size ≥15mm	130	53	514	53
	US BIRADS 3	34	14	53	11
	US BIRADS 4a	25	10	68	15
	US BIRADS 4b	28	11	88	19
	US BIRADS 4c	70	29	109	23
	BIRADS 5	88	36	152	32
	Emax<80kPa	97	40	336	35
	Emax ≥80kPa	148	60	615	65
	Emean<50kPa	73	30	250	26
	Emean≥50kPa	172	70	717	74
	SD<7kPa	104	42	393	41
	SD≥7kPa	141	58	572	59
Histology	Core result B1	0	0	7	1
	Core result B2	70	29	261	27
	Core result B3	8	3	39	4
	Core result B5a	9	4	33	3
	Core result B5b	158	64	626	65
	Core result B5c	0	0	2	0
Characteristics of invasive cancers	HER2+	15	10	85	13
	ER+	136	83	522	81
	PR+	111	68	437	68
	Grade 1	15	9	71	11
	Grade 2	85	52	274	43
	Grade 3	65	39	289	46
	Lymph node positive	49	38	174	31
	Vascular invasion	40	31	156	28

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

	study-group A			study-group B		
Threshold	Se	Sp	DA	Se	Sp	DA
150	74	63	71	72	59	68
200	70	68	69	69	62	67
250	68	71	69	68	68	68

Table 3: Diagnostic performance of anisotropy factor (AF)

Table

Subtype		study-group A AF [kPa2/100]	study-group B AF [kPa2/100]
Benign	Fibroadenoma	5	4
	Fibrocystic changes	6	13
	Liponecrosis	42	4
	Papilloma	6	5
	Other	13	8
Malignant	ductal carcinoma in situ	26	7
	ductal carcinoma of no specific type	23	24
	lobular carcinoma	32	24
	mucinous carcinoma	5	11
	tubular carcinoma	7	15
	papillary carcinoma	2	32
	Other	17	22

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