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Diagnostic Accuracy of Four Levels of Manual Compression Applied in Supersonic Shear Wave Elastography of the Breast

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Should manual compression be applied in Shear Wave Elastography of the breast?

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Should manual compression be applied in Shear Wave Elastography of the breast?

ABSTRACT

Purpose: to investigate whether manual pressure should be applied in Supersonic shear wave elastography (SSWE) of the breast and to assess the impact of compression on SSWE results.

Materials and methods: International review Board was obtained for this prospective study.

SSWE was performed on 60 breast masses (26 benign and 34 malignant) in 54 patients between April to September 2013. Stiffness values were compared between benign and malignant masses in the absence of and during increasing degrees of compression. Accuracy of SSWE was assessed using Receiving Operating Characteristics (ROC) analysis.

Reproducibility was assessed using Intraclass Correlation Coefficient (ICC).

Results: Without compression, we observed no significant difference in stiffness ($P>0.99$) between benign and malignant lesions, and SSWE demonstrated low accuracy (AUC=0.64). When compression was applied, stiffness increased according to the degree of compression ($P<0.001$). For a given level of compression, malignant masses were stiffer than benign lesions ($P<0.001$) and SSWE demonstrated good performance (AUC= 0.71 to 0.84) with high inter-observer agreement.

Conclusion: Avoiding compression is not appropriate in SSWE for breast lesion characterization. On the contrary, application of compression yields high diagnostic performance with good inter-observer agreement.

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3 **KEYWORDS**
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7 Shear wave elastography; compression; breast lesion characterization; variability.
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INTRODUCTION

Elastography is a recent imaging technique, which assesses tissue stiffness and improves characterization of breast lesions^{1,2}. Strain elastography, which evaluates stiffness by measuring the relative deformation of tissue with repeated manual compression, is a semi quantitative method. Theory states that, unlike strain techniques, Shear Wave Elastography (SWE) is an entirely automated process that does not require any manual compression to assess tissue stiffness³. In Supersonic Shear Wave Elastography (SSWE), compression waves are generated and focused automatically by the US transducer in order to shear the tissue. Stiffness quantification is obtained by measuring the speed of the resulting shear waves. On the basis of this automated acquisition process, the technique is considered to be: 1) truly quantitative, which means it would be able to measure the 'absolute' stiffness of a tissue whereas strain techniques would only provide 'relative' stiffness assessment and 2) independent of the operator and therefore highly reproducible³⁻⁵. In order to benefit from these advantages, manual compression should theoretically not be applied in SSWE of the breast⁶⁻⁸. On the basis of this theory, early publications using SSWE stated in their materials & methods that they applied 'no compression'^{5,6,9-11}. However, in clinical practice, a mild compression is naturally used to generate the B mode image, and there is usually at least the weight of the transducer against the skin. A more marked compression is also sometimes necessary in some situations to generate an analyzable image on B-mode US. In addition, it has been observed that without compression, some cancers can appear to be surprisingly 'soft' using SSWE¹². As a result, investigators recognized elsewhere the need to apply a 'light' or 'slight' compression when acquiring SSWE images¹³⁻¹⁵. However, to our knowledge, there has been no formal evaluation as to whether manual compression should be applied or not in breast SSWE. Furthermore, the consequences of manual compression on the reproducibility

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3 of SSWE quantitative results have also not been investigated. However, it is crucial to clarify
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5 this point for it can have a major impact on the use and interpretation of SSWE. In this
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7 context, the objectives of our study were to investigate whether manual compression should
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9 be applied on the breast when acquiring SSWE images in the clinical setting. We also aimed
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11 to assess the impact of manual compression on quantitative SSWE results and inter-observer
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13 reproducibility.
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MATERIALS AND METHODS

1) Population and inclusion criteria

A local ethics committee approved this prospective study, requiring patient information and non-refusal, but waiving informed consent.

From April to September 2013, consecutive patients with breast lesions undergoing ultrasound were included in this study. Inclusion criteria were as follows: 1) patient with BI-RADS 3, 4 or 5 breast lesions according to the fifth edition of BI-RADS lexicon¹⁶ 2) visibility of the lesion under ultrasound and 3) patient was verbally informed and given a refusal form. Exclusion criteria were: prior personal history of breast cancer, patient under the age of 18, patient refusal to participate in the study. A radiologist (XX, with 10 years and 4 years of experience in breast US and breast SWE respectively) performed all ultrasound examinations. In a subgroup of 18 patients, a second radiologist (XX, with 1 year and 6 months of experience in breast US and breast SWE respectively) repeated the SSWE acquisitions to evaluate reproducibility. When the second operator was available, patients who did not refuse were consecutively enrolled in this reproducibility study. Histology of breast masses was obtained by core needle biopsy. In cases where biopsy was not performed (for BI-RADS 3 probably benign lesions), two-years US follow-up was obtained. Stability at two years was considered to confirm the benign character of the lesion.

2) Image acquisition and manual compression

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3 Examinations were performed using the Aixplorer® ultrasound system (SuperSonic Imagine,
4 Aix en Provence, France) using a clinical superficial probe (SL 15-4).

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7 First, stiffness of all lesions was measured without any pressure applied on the breast (*no*
8 *compression*). Attention was paid that a layer of gel remained visible between the probe and
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10 the skin to ensure that any physical contact between the transducer and the breast was
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15 avoided.

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17 We subsequently repeated stiffness measurements with increasing degrees of pressure applied
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19 on the breast: first, the transducer was laid on the skin without any additional pressure, the
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21 operator holding the transducer cable (*mild compression*). Then the weight of the operator's
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23 hand was added to the transducer but no deliberate pressure was applied. The forearm and the
24
25 wrist rested on the patient's chest wall (*moderate compression*). Finally, the operator
26
27 applied a deliberate pressure on the breast with the probe (*marked compression*).

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30 In all situations, attention was paid to obtain a satisfactory ultrasound B-mode image.
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34 35 3) SSWE analysis 36 37 38 39

40 On each image, the tissue stiffness of each pixel on the SSWE image was displayed as a semi-
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42 transparent color map ranging from dark blue to red (corresponding to the default settings: 0–
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44 180 kPa). The color map was set to include the mass and the surrounding breast tissue. A ROI
45
46 was placed to include the whole mass and surrounding breast tissue, including the stiffest part
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48 of the lesion as previously described¹⁷. Maximum (E_{max}) and mean elasticity (E_{mean}) values
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50 within the ROI were collected.
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56 4) Reproducibility 57 58 59 60

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3 Two radiologists, independently repeated stiffness measurements for all degrees of
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5 compression in a subgroup of 18 breast lesions. Tissue compression was performed according
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7 to the predefined method of compression as detailed above in the section on “*Image*
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9 *acquisition and manual compression*”.

10 11 12 13 14 15 5) Statistical analysis

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20 Results for maximum diameter and elasticity values (E_{max} and E_{mean}) and average
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22 difference of stiffness values between the two operators are given as mean \pm 95% Confidence
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24 Interval (CI).

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27 Differences in stiffness between benign and malignant lesions were assessed using a two-way
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29 ANOVA with Bonferroni correction for multiple comparisons. Area Under the Curve (AUC)
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31 of Receiving Operator Characteristic (ROC) curves was calculated to evaluate the
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33 performances of SSWE for the differentiation of benign from malignant lesions for each
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35 degree of compression.

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38 For the reproducibility study, an Intraclass Correlation Coefficient (ICC) was calculated to
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40 assess the inter-observer agreement, as previously described¹⁸. A Bland and Altman plot was
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42 drawn and a Wilcoxon matched-pairs signed rank test was used to assess systematic bias
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44 between the two operators.

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47 The P values calculated were two-sided, and $P < 0.05$ was considered a statistically significant
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49 difference. Statistical analysis was performed using GraphPad® Software, (version 5.04, San
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51 Diego CA, USA).

RESULTS

1) Study population

Sixty breast masses (26 benign and 34 malignant) in 54 patients (53 women and one man), average age 56 years (range 23-90), were included in this study. Histology was obtained for all malignant and for 22 benign lesions. Histology was not available for 4 probably benign lesions, which were followed for two years, and remained stable in size and appearance. All malignant lesions were surgically excised. Histopathological analysis of the 34 malignant lesions showed 30 invasive ductal carcinomas (88%), 3 invasive lobular carcinomas (9%) and 1 mucinous carcinoma (3%). Pathological analysis of the 22 biopsied benign lesions showed 10 fibroadenomas (45%), 3 collagenous stroma (14%), 2 papillomas (9%), 1 gynecomastia (5%) and 3 cystic changes (14%).

Mean maximum diameter was 18 (± 4) mm for malignant lesions and 17 (± 5) mm for benign lesions

2) Effect of compression

Table 1 shows mean \pm 95% CI stiffness values (E_{max} and E_{mean}) of the 26 benign and 34 malignant lesions for each degree of compression. Without compression, stiffness values of malignant masses were low. We observed no significant difference in stiffness between benign and malignant masses. On the contrary, malignant masses were significantly stiffer than benign masses for all other degrees of compression. Without compression, the accuracy of SSWE was low, whereas it was good when compression was applied. The quantitative thresholds associated with best likelihood ratios were: 95, 186 and 286 kPa for E_{max} and 42,

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3 66 and 102 kPa for Emean for each degree of compression, respectively. It is important to
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5 note that with a marked degree of compression, we measured high stiffness values even in
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7 benign lesions: 188 (± 33) kPa for Emax and 93 (± 21) kPa for Emean.
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10 Figure 1, representing the stiffness curves according to degrees of compression, shows that
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12 stiffness of breast lesions increased with compression ($P < 0.0001$ for Emax and Emean).
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14 Stiffness curves according to the degree of compression were different between benign and
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16 malignant lesions ($P < 0.0001$).
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18 Figure 2 shows examples of SSWE color maps of one benign and one malignant mass for the
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20 different degrees of compression.
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23 24 25 26 3) Inter-observer reproducibility 27

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30 Inter-observer reproducibility was studied in a subgroup of 18 masses (9 benign and 9
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32 malignant) in 18 patients. When compression was applied, agreement between the two
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34 operators for the overall quantitative values was substantial for Emax (ICC= 0.75) and almost
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36 perfect for Emean (ICC= 0.85). Regarding each degree of compression separately, ICC was
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38 0.61 and 0.79 for mild, 0.75 and 0.80 for moderate and 0.74 and 0.83 for marked compression
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40 for Emax and Emean respectively. The Bland and Altman plot (Figure 3) and Wilcoxon
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42 matched-paired signed rank test showed that, when compression was applied, there was a
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44 systematic bias between the two operators with one obtaining values consistently higher than
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46 the other (Table 2).
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56 **DISCUSSION** 57 58 59 60

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3 Our study is the first to show that at least mild compression should be applied when
4 performing SSWE of the breast in the clinical setting. We also showed that compression had
5 an impact on the measured stiffness values obtained, depending on the degree of compression
6 applied to the breast. However, when the amount of compression applied was defined
7 beforehand, as was the case in our study, we showed that inter-observer agreement remained
8 high. We believe our results are crucial for the understanding of this relatively new technique
9 and for its optimal use in routine clinical practice.
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19 When no manual compression was applied, we measured low stiffness values even in cancers.
20 Similar observations have been reported in other studies using shear wave techniques^{12,19}.
21 Good quality shear waves might be difficult to generate in some situations, in particular in the
22 case of very hard and attenuating tissues, such as invasive breast cancers^{20,21}. We hypothesize
23 that this phenomenon would be emphasized in the absence of compression of the breast,
24 which is supported by Shiina et al., who recommended in the '*appropriate measurement*
25 *conditions*' paragraph of their recent guidelines, to '*apply a minimal compression (e.g. <0.3*
26 *mm in a typical 3cm thick breast) during imaging*'²².
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37 It has been previously described in the literature that tissues become stiffer when compressed
38 ^{12,23–26}. In our study, both malignant and benign lesions displayed higher stiffness values when
39 compression was more marked. As a result, the optimal threshold for the differentiation of
40 breast lesions was variable according to the degree of compression. This suggests, that in the
41 clinical setting, it may not be possible to define a single reference threshold, which may
42 explain the important variability of the thresholds reported in literature^{6,10,27–29}. We also
43 observed variability in stiffness measurements that depended on the operator, which is in line
44 with a previous study showing that measurements taken by two different operators on the
45 same lesion could yield significantly different results²⁸. From these observations, a number of
46 conclusions may be drawn: 1) given the variability associated with compression, quantitative
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3 results should be interpreted very cautiously; 2) as compression in clinical practice is
4 subjective, SSWE is not completely independent of the operator, which highlights the
5 importance of training and quality control; and 3) it would be of great interest to develop an
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10 'absolute' quantitative technique for stiffness measurement which would integrate manual
11 compression and would therefore be suitable for clinical practice, as the one proposed by
12 Bernal et al. in a recent feasibility study³⁰.

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17 Despite the inter-observer variability, the inter-observer agreement remained high in our
18 study. This indicates that the operators obtained results in the same relative order of
19 magnitude even though there was a significant difference in the absolute measurements.
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21 Unlike the study of Cosgrove et al, who showed high reproducibility for the retrospective
22 reading of images acquired by a single operator⁵, our study showed high agreement on
23 measurements performed prospectively by two independent operators, which is consistent
24 with the results obtained by Evans et al²⁸.

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33 There are limitations to this study. First, the method we defined for standardization of
34 compression may be improved and more optimal methods might be developed. Nevertheless,
35 we have shown that his technique is accurate for differentiating benign from malignant breast
36 lesions, has a high inter-observer agreement, and can readily be implemented in the clinic.

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42 Barr et al. assessed compression by calculating the percentage decrease of the distance
43 between the skin and a fixed structure in the breast¹². However, as stated by the strain
44 elastography theory, tissue deformation varies depending on tissue stiffness and does not
45 necessarily correlate with the amount of pressure applied. Second, our population is relatively
46 small with a high proportion of malignant masses, which does not reflect the ratio
47 encountered in clinical routine in most centers. However, we believe that our population,
48 which is to our knowledge the largest among studies dealing with compression in SWE, is
49 sufficient to support our conclusions. In addition, we only assessed reproducibility in a sub-
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3 group of patient. Nevertheless, the number of patients in this sub-group is larger than in the
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5 only other study that addressed reproducibility of SWE prospectively²⁸. Third, we did not
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7 study the effect of compression in devices from other manufacturers, and can therefore not
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9 generalize our results to all SWE techniques.
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12 In conclusion, we showed that avoiding manual compression is not appropriate in SSWE for
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14 breast lesion characterization. Application of compression yields high diagnostic performance
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16 but is associated with variability of the quantitative measurements of stiffness. This
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18 underlines the importance of interpreting any threshold value with caution. However, when
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20 manual compression is defined beforehand, high inter-observer agreement can be achieved to
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22 differentiate benign from malignant breast lesions.
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FIGURES CAPTIONS

Figure 1: Mean \pm 95% Confidence Interval of maximum (E_{max}) (A) mean (E_{mean}) (B) stiffness according to the degree of compression in benign and malignant lesions and in normal breast. Stiffness increased with compression for benign and malignant lesions as for normal breast tissue ($p < 0.0001$). Without compression, no difference was observed between benign and malignant lesions ($P > 0.99$) whereas a significant difference was observed for all other degrees of compression ($P < 0.001$ for E_{max} and $P < 0.01$ for E_{mean}).

Figure 2: Supersonic Shear Wave Elastography (SSWE) color maps of a benign (A) and a malignant (B) mass on B-mode (1), and for the different compression levels, respectively none (2), mild (3), moderate (4) and marked (5). At no compression (A2 and B2) both benign

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3 (37 kPa and 13 for maximum (E_{max}) and mean (E_{mean}) stiffness respectively) and malignant
4 lesions (21 and 10 kPa for E_{max} and E_{mean} respectively) demonstrated low elasticity values.
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6 For mild (3) and moderate (4) compression, higher stiffness values were observed in the
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8 malignant (B3: 118 and 75 kPa; B4: 207 and 100 kPa) than in the benign mass (A3: 46 and 33
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10 kPa; A4: 116 and 77 kPa). For marked compression, stiffness increased in the malignant
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12 lesion (B5: 300 and 123 kPa) but high stiffness values were also obtained in the benign mass
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14 (A5: 245 and 146 kPa).
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23 Figure 3: Bland and Altman plots representing the difference between the two operators'
24 measurements according to their average value for maximum (E_{max}) (A) and mean (E_{mean})
25 (B) stiffness when compression was applied. As the majority of points are located above 0, it
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27 shows that one operator obtained higher stiffness values than the other. The systematic bias
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29 between the two operators (represented as the dotted grey line) was: 27 (\pm 56) kPa (p=0.002)
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31 for E_{max} and 14 (\pm 22) kPa (P<0.001) for E_{mean}.
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TABLES

Compression degrees	E _{max} (kPa)				E _{mean} (kPa)			
	Benign (n=26)	Malignant (n=34)	<i>P</i>	<i>AUC</i>	Benign (n=26)	Malignant (n=34)	<i>P</i>	<i>AUC</i>
none	40 (±12)	55 (±13)	>0.99	0.64	14 (±3)	15 (±2)	>0.99	0.53
mild	100 (±33)	185 (±31)	***	0.77	37 (±11)	65 (±13)	**	0.77
moderate	144 (±38)	240 (±24)	***	0.77	66 (±17)	96 (±13)	**	0.71
marked	188 (±33)	271 (±19)	***	0.84	93 (±21)	125 (±14)	**	0.70

Table 1: Mean ± 95% Confidence Interval of maximum (E_{max}) and mean (E_{mean}) elasticity values and according to degree of compression for benign and malignant lesions. The difference between benign and malignant lesions was extremely significant ($P < 0.001$ ***) for E_{max} and very significant ($P < 0.01$ ***) for E_{mean} at mild, moderate and marked compression but not for none. At no compression, accuracy of shear wave elastography was poor as shown by low Area Under the Curves for both E_{max} and E_{mean}.

Compression degrees	E _{max}		E _{mean}	
	<i>Systematic bias (kpa)</i>	<i>P value</i>	<i>Systematic bias (kpa)</i>	<i>P value</i>
<i>All</i>	27 (±56)	0.002**	14 (±22)	< 0.001***
<i>mild</i>	46 (±25)	0.005**	10 (±9)	0.045*
<i>moderate</i>	12 (±27)	0.48	16 (±10)	0.007**
<i>marked</i>	25 (±24)	0.33	17 (±12)	0.01*

Table 2: Systematic bias according to degree of compression. When compression was applied, we observed a systematic bias between the two operators, with one measuring values consistently higher than the other. Considering each degree of compression, this difference was not significant for E_{max} for moderate and marked degrees of compression.

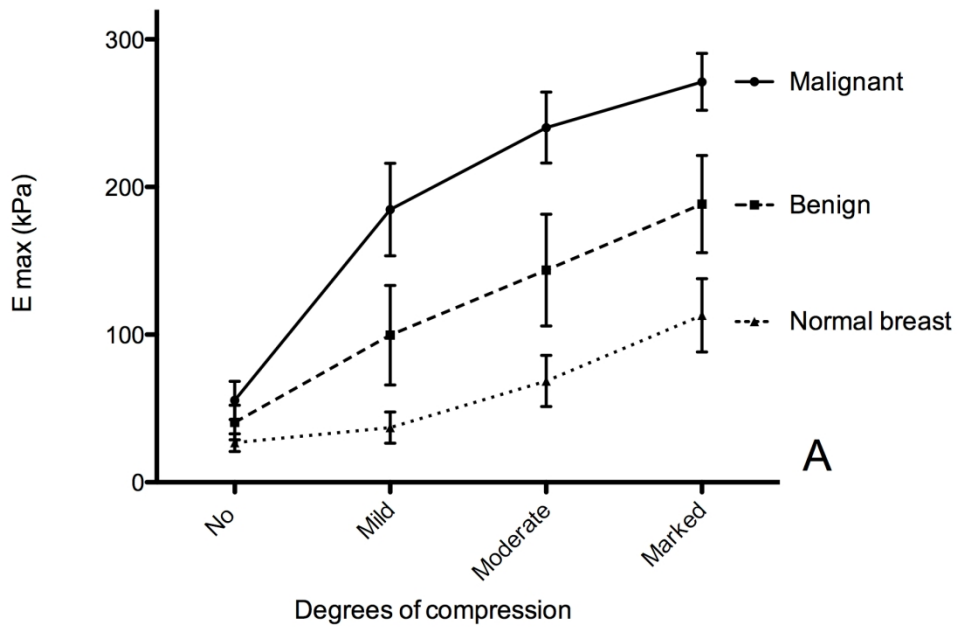


Figure 1: Mean \pm 95% Confidence Interval of maximum (Emax) (A) mean (Emean) (B) stiffness according to the degree of compression in benign and malignant lesions and in normal breast. Stiffness increased with compression for benign and malignant lesions as for normal breast tissue ($p < 0.0001$). Without compression, no difference was observed between benign and malignant lesions ($P > 0.99$) whereas a significant difference was observed for all other degrees of compression ($P < 0.001$ for Emax and $P < 0.01$ for Emean).

162x108mm (300 x 300 DPI)

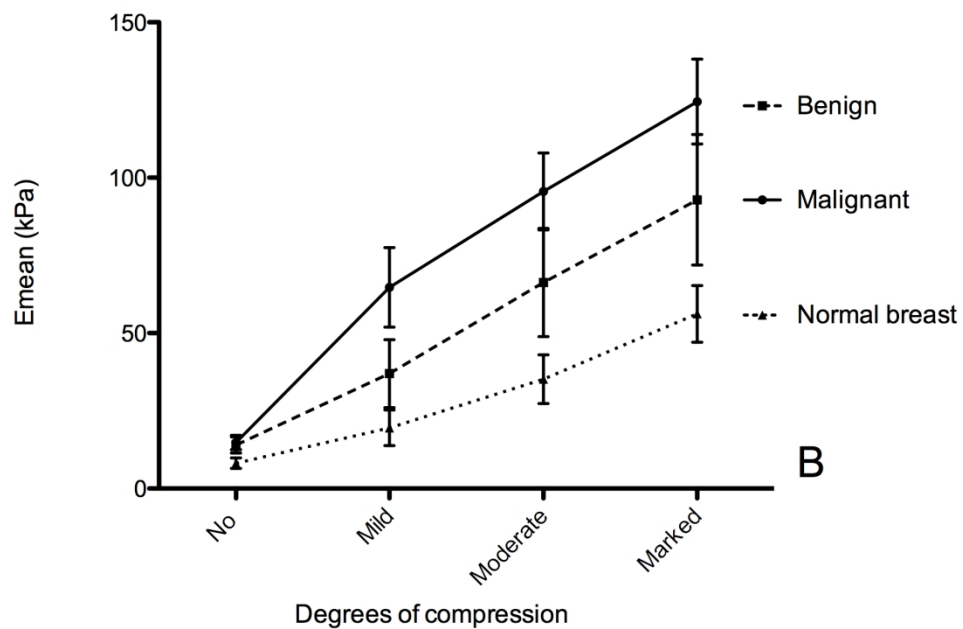


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165x110mm (300 x 300 DPI)

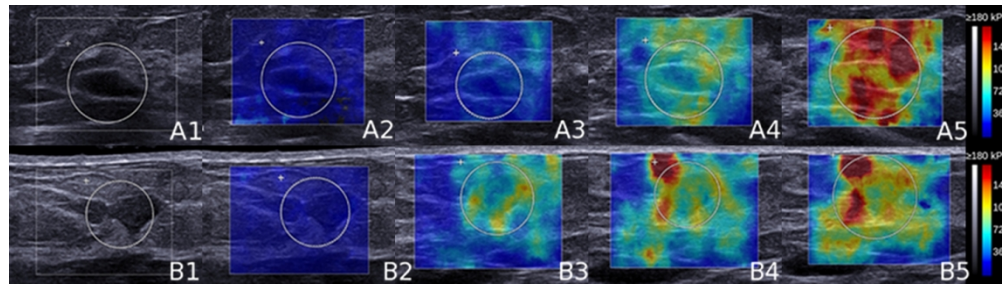


Figure 2: Supersonic Shear Wave Elastography (SSWE) color maps of a benign (A) and a malignant (B) mass on B-mode (1), and for the different compression levels, respectively none (2), mild (3), moderate (4) and marked (5). At no compression (A2 and B2) both benign (37 kPa and 13 for maximum (E_{max}) and mean (E_{mean}) stiffness respectively) and malignant lesions (21 and 10 kPa for E_{max} and E_{mean} respectively) demonstrated low elasticity values. For mild (3) and moderate (4) compression, higher stiffness values were observed in the malignant (B3: 118 and 75 kPa; B4: 207 and 100 kPa) than in the benign mass (A3: 46 and 33 kPa; A4: 116 and 77 kPa). For marked compression, stiffness increased in the malignant lesion (B5: 300 and 123 kPa) but high stiffness values were also obtained in the benign mass (A5: 245 and 146 kPa).

127x35mm (300 x 300 DPI)

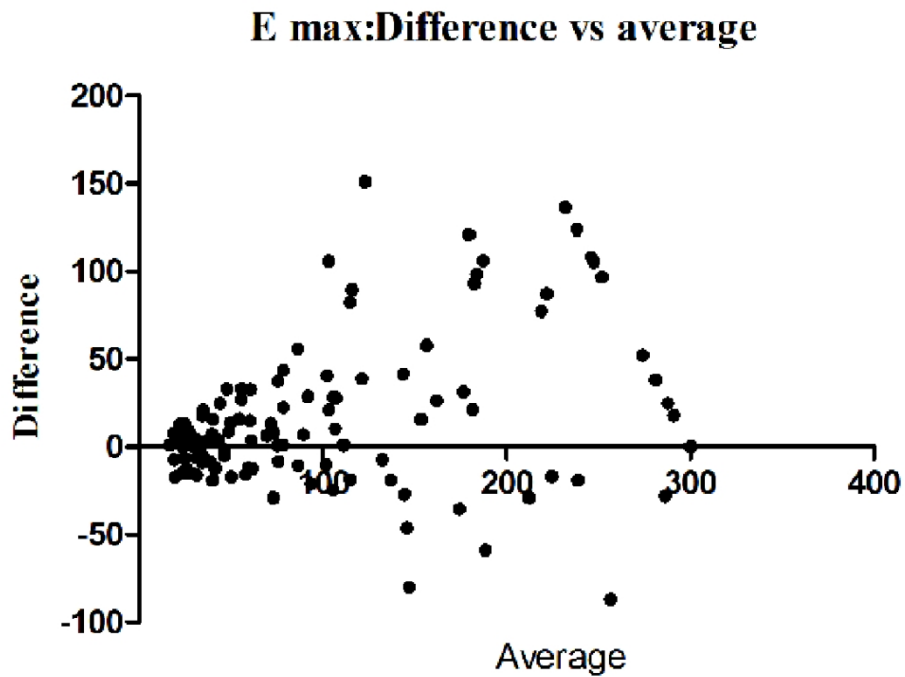


Figure 3: Bland and Altman plots representing the difference between the two operators' measurements according to their average value for maximum (E_{max}) (A) and mean (E_{mean}) (B) stiffness when compression was applied. As the majority of points are located above 0, it shows that one operator obtained higher stiffness values than the other. The systematic bias between the two operators (represented as the dotted grey line) was: 27 (± 56) kPa ($p=0.002$) for E_{max} and 14 (± 22) kPa ($P<0.001$) for E_{mean} .

101x74mm (300 x 300 DPI)

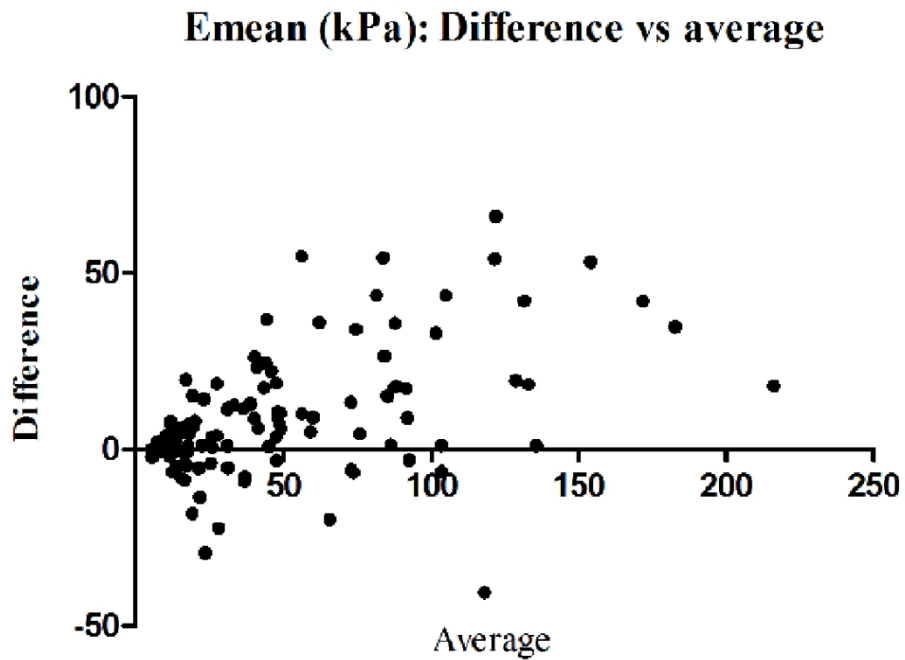


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101x72mm (300 x 300 DPI)