International Journal of Radiology Sciences
Online ISSN: 2664-9829, Print ISSN: 2664-9810
Received: 03-03-2019; Accepted: 04-04-2019; Published: 22-01-2019
www.radiologyjournals.com
Volume 1; Issue 1; 2019; Page No. 10-14

Breast Shear Wave elastography and the war of differential diagnosis: are on the way to classify quantitatively breast pathology

Estela Fernández Cuadriello
Unidad de Patología Mamaria. Hospital Begoña, Avda. Pablo Iglesias, Gijón. Asturias, Spain

Abstract
Objectives: The fundamental purpose is to evaluate if elastography technique can predict the type of breast lesion conferring a numerical classification to different histopathological diagnosis. We also want to relate the BIRADS classification with the elastographic measurements in order to determine the point that increases the possibility of malignancy.
Material and Methods: From January to November of 2015, we study 116 patients with an age between 19 and 82 years. 117 lesions are evaluated consecutive with ultrasound, elastography and biopsy. Two index are measured, the hardness in kPa and the propagation speed of the waves in m/sec, in the most suspicious areas of the nodules. The minimum, maximum, average and standard deviation values are calculated. All cases are correlated with their histopathology.
Results: We found statistically significant differences ($p < 0.05$) for the kPas measure between the cancer group and the benign pathology group ($p < 0.0001$). With the measure kPas we could not predict the histopathological type of benign nodule, since there are no significant differences between patients with different diagnoses of benignity. The results for both the kPas and m/s measurements indicate statistically significant differences ($p < 0.05$) of the BIRADS 4C and BIRADS 5 compared to the rest.
Conclusion: The measures kPas and m/s allow to discern with a confidence level of 95% if a mammary nodule will be malignant or not, but it does not allow to differentiate between different types of benign nodules. They also allow us to discern with a 95% confidence level the patients with moderate or high probability of neoplasia (BIRADS 4C and BIRADS 5) of the rest.

Keywords: breast, cancer, ultrasound, elastography, shear wave

Introduction
Breast Shear-Wave elastography and the battle of differential diagnosis: are we on the way to quantitatively classify breast pathology?
Each year, around 26,000 women are diagnosed with breast cancer, the most diagnosed cancer among the female population, attending to an ever-increasing survival, directly related to advances in early diagnosis and increasingly better treatments. In addition, to the primary role that mammography plays in the diagnosis of breast cancer imaging, ultrasound (US) is a well known imaging modality with a high importance in the diagnosis of breast pathology. In order to increase the diagnostic accuracy of mammography, mainly in women with dense breasts and sintomatyc woman under 40, in recent years we have been attending to the improvement of US, that makes a considerable increase in the sensitivity of mammography, specifically with techniques such as elastography.
Ophir *et al*. [1] described this for first time in the early 90s. Elastography is an ultrasound technique that give us information about the consistency of a breast lesion concerning the soft tissues around, so we can know in real time the elastic properties of tissues at the same time that US is performed in B-mode and in a completely harmless way. With that the specificity values of technique are significantly increased, contributing also to a better and faster diagnosis of cancer. Also, this is a technique that improves the patient management with breast masses with low index of suspicion in B-mode US imaging [2].
The first study that demonstrated that the elastography was useful for differentiating solid lesions was performed by Garra *et al*. [3] in 1997, establishing the basis of its clinical applicability [4]. There are two elastography types: qualitative or by compression and quantitative or shear-wave. Qualitative technique studies deformation that a tissue experiments under a compression waves effect emitted by the US transducer through a smooth and homogenous compression on the area which we want to analyze, this deformation generated is detected by equipment and translated into a grey or color scale [5], which is we know as elastogram. The chromatic scales depends on comercial US groups, usually red colors indicate hardness tissues, therefore, suspicious, being blue colors a sign of benign behavior.
In grey scale, harder tissues appears darker than softer which are whiter, also considering that in this scale the size need to be analyzed, because the size of benign lesiones not change or decrease and those that increase in size are often malignant, possibly due to summation effect caused by the desmoplastic reaction. In fact, Krouskop showed that infiltrating ductal carcinomas were larger comparatively in elastographic image than with B-mode [4]. All time, we can see both images, B-mode and elastography mode, simultaneously, for a better interpretation, however, this is a operator-dependent technique with a non negligible interobserver variability.
On the other hand, in quantitative elastography the transducer generates a wave of longitudinal acoustic

pressure that, at the same time, displacing tissues and conditioning tangential shear waves to the longitudinal pulse originated and whose displacement speed can be measures in the region of interest (ROI) thanks to the lateral tracking pulses to the thrust wave (speed is measured in m/s). With this technique we can obtain objetive and measurable results, providing valuable structural data to the morphological properties of a ultrasound B mode study [6]. The point is that the equipment generates the pressure waves itself which makes more reproducible this type of elastography [7] (Fig 1).

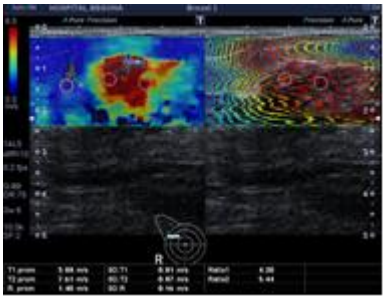

Fig 1: Echoelastography image. Left map reflects measurement in m/sec and in the right map we can see a propagation map in a hard lession. Is a lesion with a predominantly red color, compatible with a malignant tumor. Biopsy showed a grade 3 CDI.

Although the FDA has already approved two parameters to quantify the hardness of the lesions studied with quantitative elastography, m/s and kPa, we need to deepen into parameters that improve the specificity of this technique. Several studies have already shown that quantitative parameters obtained through Young's modulus of elasticity (kPa) improve the diagnosis on breast ultrasound, however, there are not many studies yet about the quantification of tissue in m/sec [8], a factor we approached in this study.
However, although this technique has been included in the BIRADS for some years, the morphological criteria in ultrasound continue to be the ones that show the greatest specificity, so it is necessary to carry out more research in order to incorporate some new concepts that support and confirm the validity alone of this selective technique. Also, with this study we want to take a further step and investigate the quantitative concepts of elastography in order to deepen and approach a more accurate ultrasound diagnosis.

Objetives

The objective of this study is to evaluate whether this ultrasound technique is statistically significant and predict the malignant or benign nature of the nodules based on the values obtained, conferring greater importance to the kPa unit. Also we want to demonstrate if we can predict the type of breast node and give the different histopathological diagnoses on the basis of a numerical classification of kPas values. In the second point, we want to associate BIRADS classification with the elastographic measures in order to determine the point that increases the possibility of malignancy, with particular interest on the category BIRADS 3 and BIRADS 4 and its subcategories (a, b and c).

Material and Methods

Patients and lesions: 116 patients with an age between 19 and 82 years are studied from January to November of 2015. 117 lesions were evaluated consecutively with ultrasound, elastography and biopsy.
Ultrasound exam and biopsy: the breast ultrasound is performed with an Aplio 500 (Canon Medical Systems) equipped with a 10 MHz probe, performed by a radiologist with 9 years of experience in breast ultrasound. At the time of test, the mammogram had been previously assessed, performing a B-mode ultrasound first, then SWE images of the lesion under study were obtained and biopsy was performed.
Two indices are measured, the hardness in kPa and the speed of propagation of the waves in m/sec in the most suspicious areas of the lesions. The minimum, maximum, median and standard deviation values are calculated. All cases were correlated with histopathological findings.
The statistical analysis programs SPSS 22.0 and GraphPad 7 were used.
A descriptive and frequency study was performed including minimum, maximum, average and standard deviation values.

Results

The t-Student test was applied to know if this technique is statistically significant and we can predict the malignant or benign nature of the nodules based on elastography values, so we classified the patients into two groups, neoplasia and non-neoplasia, as well as individual t-Student tests are applied for the values of kPas and m/sec in each group of patients based on the histopathological diagnosis against the group of neoplasia.
As Table 1 shows, there is a statistically significant difference ($p < 0.05$) for the kPas measurement between the group of patients diagnosed with cancer and the group of patients with non-malignant pathology ($p < 0.0001$). We also see significance ($p < 0.05$) when we compare the kPas values on patients with neoplasia versus patients with benign pathology: fibrocystic mastopathy ($p = 0.044$), stromal fibrosis ($p = 0.0002$), fibroadenoma ($p = 0.0001$), usual ductal hyperplasia ($p = 0.164$) and focal sclerosis-adenosis ($p = 0.0022$), but not against ductal ectasia ($p = 0.1432$) and papilloma ($p = 0.099$) groups.
This analysis was not carried out for the cyst, atipical duct hyperplasia and hamartoma diagnoses because it did not contain patients, and phyllodes with a single patient.

Tabla 1: Resultados del análisis estadístico *t*-Student para la medida kPas.

	Neoplasia	No Neoplasia	MFQ	Ectasia	Stromal Fibrosis	FAD	Papilloma	Usual ductal hyperplasia	Sclerosis Adenosis
Patients	5	111	10	2	22	56	5	5	9
Minimum	21,8	7,2	12,2	8,4	10,9	8,8	19,6	7,2	8,3
25th percentile	26,7	13,9	15,9	8,4	14,4	14,0	24,5	9,6	11,5
Median	57,6	20,0	22,0	18,6	22,3	19,3	31,1	15,1	13,8
75th percentile	67,9	26,5	29,4	28,9	24,5	25,6	34,6	25,2	24,6

Maximum	77,9	55,4	34,4	28,9	55,4	34,3	35,1	25,7	34,2
Average	49,30	21	22,86	18,6	22,00	20,07	29,84	16,95	17,41
Standar deviation	22,50	8,21	7,79	14,5	9,87	6,74	6,18	8,05	8,54
P value		<0,0001	0,0044	0,1432	0,0002	<0,0001	0,099	0,0164	0,0022
Significant difference (p<0,05)		Yes	Yes	No	Yes	Yes	No	Yes	Yes

Table 2: Results of the t-Student statistical analysis for the m/s measurement

	Neoplasia kPas	**No Neoplasia kPas**	**Neoplasia m/s**	**No Neoplasia m/s**
Average	49,35	21,03	3,97	2,47
95% interval confidence				
Inferior limit	21,35	19,49	2,82	2,41
Superior limit	77,34	22,58	5,13	2,53
Standar deviation	22,54	8,21	0,93	0,50
Median	57,55	20,00	4,14	2,43
Variance	506,13	67,37	0,87	0,25
Minimum	21,8	7,2	2,7	1,1
Maximum	77,9	55,4	5,2	5,2

By contrast, with kPas measures we cannot predict the histopathological type of benign breast nodule, since there are no statistically significant differences between patients with different diagnoses of benignity.

Parallels were obtained when the t-Student test was applied for the elastographic measurement m/s. Thus, there is also a statistically significant difference ($p < 0.05$) for this parameter between the group of patients diagnosed with neoplasia and the group of patients with non-malignant pathologies ($p < 0.0001$). The results of this analysis are shown in Table 2. It can be observed that, analogously to what happened with the kPas measure, there is significance ($p < 0.05$) when comparing the m/s values of patients with neoplasia compared to patients with fibrocystic mastopathy ($p = 0.0019$), stromal fibrosis ($p = 0.0001$), ADF ($p < 0.0001$), usual ductal hyperplasia ($p = 0.0083$) and sclerosis-adenosis ($p = 0.0008$), but not against patients with ducal ectasy ($p = 0.0981$) or papilloma ($p = 0.0781$).

Table 3: Results of the t-Student statistical analysis for the kPas and m/s measurements including the upper and lower limits.

	Neoplasia	**No Neoplasia**	**MFQ**	**Ectasia**	**Stromal Fibrosis**	**FAD**	**Papilloma**	**Usual ductal hyperplasia**	**Sclerosis Adenosis**
Patients	5	111	10	2	22	56	5	5	9
Minimum	2,7	1,6	2,0	1,7	1,9	1,7	2,4	1,6	1,7
25th percentile	3,1	2,1	2,3	1,4	2,2	2,1	2,8	1,8	1,9
Median	4,1	2,5	2,3	2,4	2,6	2,5	3,1	2,2	2,2
75th percentile	4,7	2,9	3,0	3,1	2,8	2,9	3,3	2,8	2,7
Maximum	5,2	4,2	3,3	3,1	4,2	3,4	3,3	2,9	3,3
Average	3,972	2,54	2,63	2,37	2,57	2,51	3,05	2,28	2,29
Standar deviation	0,931	0,49	0,44	0,99	0,53	0,43	0,36	0,56	0,51
P value		<0,0001	0,0019	0,0981	0,0001	<0,0001	0,0718	0,0083	0,0008
Significant difference (p<0,05)		Yes	Yes	No	Yes	Yes	No	Yes	Yes

Also we have found that with m/s it is not possible to predict the type of non-malignant breast nodule, since there are no statistically significant differences between patients with different diagnoses.

Table 3 shows the upper and lower limits for the kPas and m/s measurements in the two groups compared, not neoplasia and neoplasia, for a 95% confidence interval.

To determine the cut-off point from which to classify a nodule as malignant, the upper limit of the non-neoplasm group interval can be taken, since they had lower values, both for kPas and for m/s, or the lower limit of the interval from the neoplasia group. Depending on whether one or the other is chosen, it is expected that the sensitivity and specificity values vary. In addition, in the case of kPas, there is a circumstance that the upper limit of the interval of the non-neoplasm group is greater than the lower limit of the interval of the neoplasm group, creating a "gray zone" where the technique would not have diagnostic capacity. This does not happen, however, with the measure m/s.

Tables 4 and 5 show how the use of a lower cut-off point in Kpas and m/s leads to an improvement in sensitivity, that is, the ability to diagnose patients with disease, but implies a decrease in specificity, what invariably implies diagnose healthy patients as sick, raising the number of false positives.

Tables 4 and 5: Sensitivity and specificity values depending on the cutoff point used (used kPas on the left and m/s on the right).

	Histological diagnosis		
		Sick	Healthy
Kpas= 22, 58	Positive	4	44
	Negative	1	67
	Sensitivi4ty	80 %	
	Specifity	60,4 %	
Kpas= 21,36	Positive	5	50
	Negative	0	61
	Sensitivi4ty	100 %	
	Specifity	55 %	

For our second objective "to know from which measurement we can increase the probability of malignancy, with a focus on the equivalent of BIRADS 3 and BIRADS 4 with its subcategories (BIRADS 4a, 4b and 4c)" a t-Student analysis was carried out for the kPas and m/s values of the

BIRADS groups with the highest probability of malignancy; BIRADS 5 and BIRADS 4c compared to the rest.

	Histological diagnosis		
		Sick	Healthy
m/s= 2,53	Positive	5	55
	Negative	0	56
	Sensitivity	100 %	
	Specifity	49,5 %	
m/s= 2,82	Positive	4	33
	Negative	1	78
	Sensitivity	80 %	
	Specifity	70 %	

The results also show statistically significant differences ($p < 0.05$) for the kPas measurement between the BIRADS 5 group versus the BIRADS 2 ($p < 0.0001$), BIRADS 3 ($p < 0.0001$) and BIRADS 4a ($p = 0.0003$), but not against BIRADS 1 ($p = 0.1031$), BIRADS 4b ($p = 0.1272$) or BIRADS 4c ($p = 0.8148$).

Similarly, there is significance ($p < 0.05$) for the measurement kPas between the BIRADS 4c group versus the BIRADS 2 ($p < 0.0001$), BIRADS 3 ($p < 0.0001$) and BIRADS 4a ($p = 0, 0142$), but neither against BIRADS 1 ($p = 0.1427$) nor BIRADS 4b ($p = 0.1726$).

The results of the t-Student analysis for the kPas measurement among the rest of the BIRADS 3 and BIRADS 4 groups were: BIRADS 3 vs BIRADS 4a ($p = 0.0021$), BIRADS 3 vs BIRADS 4b ($p = 0.8544$) and BIRADS 4a vs BIRADS 4b ($p = 0.5458$).

The same trend was observed when performing the t-Student statistical analysis for the m/s measurement (Table 6). Thus, there is also a statistically significant difference ($p<0.05$) for this measure between the BIRADS 5 group versus the BIRADS 2 ($p < 0.0001$), BIRADS 3 ($p < 0.0001$) and BIRADS 4a ($p = 0.0002$), but not against BIRADS 1 ($p = 0.0571$), BIRADS 4b ($p = 0.0763$) or BIRADS 4c ($p = 0.6552$). For that reason, there is significance ($p < 0.05$) for this measure between the BIRADS 4c group versus the BIRADS 2 ($p = 0.0023$), BIRADS 3 ($p = 0.0003$) and BIRADS 4A ($p = 0, 0396$), but not against BIRADS 1 ($p = 0.124$) or BIRADS 4b ($p = 0.1552$).

Table 6: Results of the t-Student statistical analysis for the m/s measurement of the BIRADS 5 group compared to the rest.

	BIRADS 1	BIRADS 2	BIRADS 3	BIRADS 4a	BIRADS 4b	BIRADS 4c	BIRADS 5
Patients	3	92	148	37	3	2	4
Minimum	1,9	1,1	1,6	1,7	2,2	2,9	2,7
25th percentile	1,9	2,1	2,1	2,2	2,2	2,9	2,9
Median	2,3	2,4	2,4	2,7	2,4	3,5	3,9
75th percentile	2,7	2,8	2,7	3,1	2,8	4,1	5,0
Maximum	2,7	3,6	3,5	4,2	2,8	4,1	5,2
Average	2,31	2,42	2,41	2,63	2,48	3,50	3,93
Standar deviation	0,39	0,47	0,40	0,54	0,33	0,91	1,07
P value	0,0671	<0,0001	0,0001	0,0002	0,0763	0,652	
Significant difference (p<0,05)	No	Yes	Yes	Yes	No	No	

The results of the t-Student analysis for the m/s measurement among the rest of BIRADS 3 and BIRADS 4 groups were: BIRADS 3 vs BIRADS 4ª ($p = 0.0055$), BIRADS 3 vs BIRADS 4b ($p = 0, 7793$) and BIRADS 4a vs BIRADS 4b ($p = 0.6252$).

The results obtained, both for the measurement kPas and for m/s, indicate that there is a statistically significant difference ($p < 0.05$) of the two groups with the highest probability of malignancy BIRADS 4c and BIRADS 5 compared to the rest.

Conclusions

The measures kPas and m/s allow to discern with a level of confidence of 95% if a breast nodule will be malignant or not, as already described in the literature, but it does not allow to differentiate between the different types of benign breast nodules, while the view that I wanted to give to the study is the first in the line of qualitatively classifying the different histologies.

The use of a cut-off point kPas= 22.58 means that this measure has a sensitivity of 80% and a specificity of 60.4% to differentiate malignant nodules. If a cut-off point kPas= 21.36 is used, a sensitivity of 100% and a specificity of 55% are obtained.

The use of a cut-off point m/s= 2.53 makes this measure have a sensitivity of 100% and a specificity of 49.5% to differentiate malignant nodules. If a cut-off point m/s= 2.82 is used, a sensitivity of 80% and a specificity of 70% are obtained.

The kPas and m/s measures allow the classified patients with moderate or high probability of neoplasia (BIRADS 4c and BIRADS 5) to be discerned with a 95% confidence level from the rest, but not between patients belonging to these two groups or those belonging to groups BIRADS 1 to BIRADS 4B with each other.

Therefore, as this study demonstrates ecoelastography technique in a complement to the B-mode ultrasound, it is extremely useful in the day-to-day of the breast radiologist, contributing to a better and safer diagnosis which implies a better management of the patients from the beginning, in many cases decreasing the number of biopsies and, ultimately, the patient's anxiety.

Limitations of the study

In general, for a statistical analysis to be valid it is recommended that the different experimental groups consist of at least 20 people. This is not the case in several study groups according to their classification of pathological diagnosis: neoplasia (n = 5), fibrocystic mastopathy (n = 10), ductal ectasia (n = 2), papilloma (n = 5), hyperplasia usual ductal (n = 5) and sclerosis-adenosis (n = 9). The same occurs when patients were classified according to the BIRADS estimate: BIRADS 1 (n = 3), BIRADS 4b (n = 3), BIRADS 4c (n = 2) and BIRADS 5 (n = 4), so that statistical results obtained with these groups have to be assessed always with this limitation in mind. Since no statistically significant differences ($p<0.05$) were obtained between the groups with a non-malignant diagnosis, these

being formed by a number of patients below 20 are less relevant, however, it is that in the main group for comparison (neoplasia) the sample size is low (n = 5).
So, we recommend to continue working in this way with a greater number of patients in the malignant pathology group. This will give greater validity to the results obtained, which can confirm the current ones or modify them, allowing also to adjust the sensitivity and specificity values obtained in this study.

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