DOI: 10.15386/cjmed-363

THE ADDED VALUE OF COLOR PARAMETERS IN ANALYZING ELASTOGRAPHIC IMAGES OF ULTRASOUND DETECTED BREAST FOCAL LESIONS

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Abstract

Aims. *The purpose of the study was to determine if the color quantitative analysis obtained on elastographic images of breast lesions could improve the benign-malignant differentiation, and also to identify some of the circumstances which would benefit most from such an analysis.*

Patients and methods. *The study design was a longitudinal prospective one, all data being acquired between May 2007 and September 2008. The US device used: Hitachi 8500 EUB machine with elastography option. For suspicious breast lesions histopathology was obtained by means of percutaneous biopsy or post-surgery. Studied color parameters (numeric values): average color (red, green, blue), color dispersion, average intensity, average hue, hue dispersion. Calculus modality: Image Processing Version 1.3, a program developed in collaboration with the Technical University of Cluj Napoca.*

Results. *Seventy-one (71) women were selected for the study. A hundred and six circumscribed breast lesions were detected by means of ultrasound in the studied group. Five color parameters were independently associated with the histological diagnosis (AvgBlue, AvgGreen and AvgRed; DispRed and DispIntensity) with AvgBlue parameter making the most important contribution (p<0.0001); the greater the values of AvgBlue (more than 92), the higher the chances of malignancy and the greater the values of AvgGreen (more than 88), the higher the chances for a benign lesion.*

Conclusion. *High numeric values for Avg Blue (more than 92) would increase the probability of malignancy and thus recommend a more aggressive diagnostic management (biopsy), while high numeric values for AvgGreen (more than 88) would reassure the examiner to proceed conservatively with short interval or routine follow-ups.*

Keywords: breast, ultrasound, elastography, color analysis.

Background and aims

Several elastography studies have shown that most of the breast neoplasms are 2 to 10 times stiffer than the neighboring, normal breast parenchyma [1-6].

The Hitachi US (ultrasound) elastography software enables radiologists and sonographers to obtain real time colored representation of a lesion relative elasticity

Manuscript received: 19.10.2014
Accepted: 09.12.2014
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(stiffness) by simply applying a slight probe compression perpendicular to the interest region. Thus the red and green tints were selected to depict areas with similar elasticity to surrounding tissues, while the blue tints were reserved for structures with increased stiffness [4,7,8].

In order to simplify and standardize the interpretation of elastographic images of breast focal lesions, two similar (Hitachi targeted) elasticity scores have been developed by a Japanese (Tsukuba score) and an Italian research group [4,9,10,11,12]. The most known and widely used is the Tsukuba elasticity score which grades on a scale from 1 to 5 the malignancy probability of breast nodules. Score 1 (green or mix of green and red) and 2 (mosaic: predominantly green with blue spots) correspond to typically benign (non-stiff) lesions, score 3 is intermediate (blue core, green periphery), while scores 4 (predominantly blue) and 5 (blue halo exceeding lesion margins) are indicative for highly suspicious or malignant (stiff) nodules. The particular three layered appearance, BGR (blue, green, red) is associated with cystic or fluid containing lesions [4,7,8].

Although the Tsukuba score is practical and easy to use in a clinical setting, it offers only qualitative, visual assessment of a lesion stiffness, in other words it subjectively appreciates how green (*soft*) or blue (*hard*) a nodule is. However, the daily practice revealed that some breast lesions present on elastography a highly heterogeneous appearance (mix of green and blue) which makes the eye-based cutoff between score 2 (benign) and 4 (suspicious) (Fig. 1 a, b) difficult. This is the reason why finding solutions for a more accurate, objective evaluation of problematic elastographic images of breast nodules, came into consideration.

Aims

The purpose of the study was to determine if Color quantitative analysis obtained on elastographic images of breast lesions can improve benign-malignant differentiation.

The secondary goal was to identify the circumstances which would benefit the most from such an analysis.

Patients and methods

The study design was a longitudinal prospective one, all data being acquired between May 2007 and September 2008. The target population was represented by patients referred to the Breast Unit Department of ER County Hospital of Cluj Napoca.

<u>Inclusion criteria:</u>

• mandatory strain sonoelastography (USE) assessment for each ultrasound detected lesion;

• a pathology report obtained either post biopsy or post surgery for BI-RADS 4 and 5 lesions;

• a minimum 2 years, unchanged follow-up report for BI-RADS 3 lesions (e.g. fibroadenoma-like);

• same Consultant Radiologist for each included case.

<u>Exclusion criteria:</u>

• absence of sonoelastography acquisitions from the imaging investigation;

• simple breast cysts (transonic circumscribed lesions with stratified BGR aspect on USE);

• non-circumscribed or diffuse breast lesions;

• no 2 years follow up reports or pathology for non-specific or suspicious lesions;

• sonoelastographic acquisitions performed by other radiologists in the Department;

• sonoelastographic acquisitions which did not meet the quality criteria stated in the examination protocol.

<u>Examinations and devices:</u>

The standard radio-imaging examinations (mammography, conventional ultrasound, MRI) were performed according to the ACR (*American College of Radiology*) recommendations, considering the age of patient and case particular features. Each detected lesion was classified into a BI-RADS category from 1 to 5 [13].

Selected focal breast lesions detected on conventional ultrasound underwent elastographic evaluation using a Hitachi 8500 EUB machine. The elastography examination protocol was designed in accordance with Hitachi guidelines for obtaining superior qualitative images [7,8].

<u>Elastography examination protocol and</u>

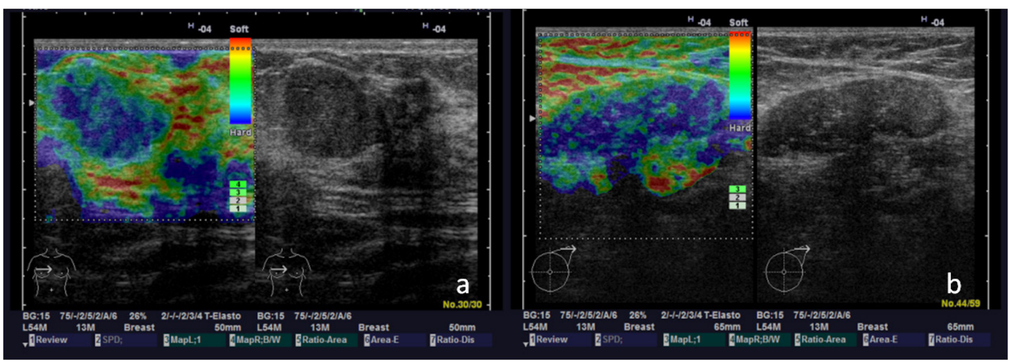


Figure 1. Markedly heterogeneous elastography appearances of breast nodular lesions: a Benign nodule - fibroadenoma. b Malignant nodule - metastatic invasive ductal carcinoma . The mix of green and blue colors are very similar for the two images; the question raised was which elasticity score to give to each of them: 2 - non-suspicious?, or 4 - suspicious?

interpretation modalities

Step I: conventional ultrasound evaluation using a 13 MHz linear transducer

Step II: elastographic assessment

• The transducer was placed perpendicular to the region of interest without an additional stabilizer

• The elastography box was set large and the lesion under evaluation was kept centered within the box

• The superior and inferior demarcation lines for the elastography box were set under the skin line, respectively immediately above the plane of the pectoralis muscle

• Slight compression was applied with a frequency of 3 to 4 as indicated by the vibration scale visible on the US screen

• The *Color Gain* was set to 26%

• The *Density* was set to 2

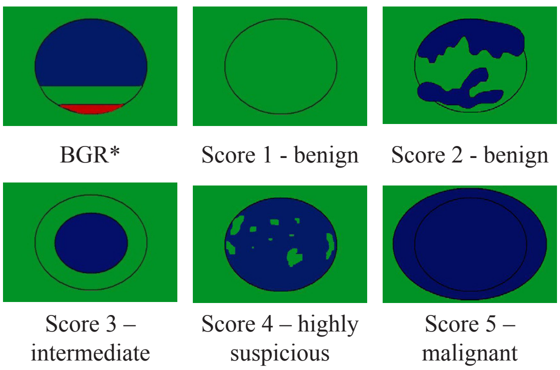
• The *Frame Rate* was set to *High*

• Minimum 6 acquisitions per lesion were obtained in perpendicular planes

• At least one *avi* file was acquired for each lesion

Step III: qualitative assessment based on the Tsukuba elasticity score (Scheme 1)

The following scheme represents a graphic adaptation after Tsukuba and Italian elasticity scores for breast focal lesions [4,9,10,11,12]:



Scheme 1. *The stratified BGR pattern or its variants are characteristic for cystic or fluid containing lesions (necrotic and hypercellular nodules included).

Step IV: quantitative assessment based on the numeric values of Color and Hue parameters

Methodology of quantitative elastographic assessment

The calculation method used a software (Image Processing Version 1.3) developed in collaboration with the *Technical University of Cluj Napoca*.

The analyzed parameters were as follows: numeric values of average blue, red and green colors; numeric values of color dispersion (for red, green and blue), numeric values of average hue and its dispersion, numeric values of average intensity and intensity dispersion per lesion (AvgBlue, AvgGreen, AvgRed, AvgHue, DispHue, DispBlue, DispRed, DispGreen, AvgIntensity).

The following procedures were undertaken in order to obtain these numeric values:

• selection of the most probable dual US image (elastography – grayscale) of the target lesion. The selection was realized upon a consensual decision of 2 experienced breast radiologists, both with at least 6 months experience in small parts strain sonoelastography;

• thorough graphic delineation of the target lesion depicted on the grayscale image, using a freeform ROI (region of interest), action automatically followed by an over imposed identical contour on the elastography image;

• accessing the *Elasto Measurments* option from the program tool bar which automatically displayed the average values for color and hue parameters;

• the use of *Write results* option from the tool bar automatically generated an Excel worksheet with each parameter labeled and valued.

The following figure (Fig. 2) illustrates an example of how this particular quantitative analysis would look on a computer monitor:

Statistical analysis

The statistical analysis was performed using commercially available software (MedCalc for Windows, version 9.5.0.0., MedCalc Software, Mariakerke, Belgium). Continuous variables were presented as mean values and standard deviation or median values and confidence interval (CI) and categorical variables as percentages. In case the variables were not normally distributed a logarithmic transformation was performed. The distribution of hue values for each analyzed class was studied with the box-plots diagrams. Univariate analysis was performed in order to establish factors in direct relationship with the diagnosis of malignancy. For this purpose, the difference of means was tested with Anova analysis of variance. Through backward stepwise multiple regression analysis independent elastography measurements for the malignant diagnosis were identified. The backward method first enters all variables into the model and next it removes the non-significant variables sequentially.

The accuracy of the new elastography score for the assessment of tumor diagnosis was evaluated by calculating sensitivity (Se%), specificity (Sp%) and ROC curves ("Receiver-Operating Characteristic curve"). Optimal cutoff values were chosen to maximize the sum of Se% and Sp%. A p value of 0.05 or less was considered to indicate a significant difference regarding anthropometric and elastography parameters, the multiple regression test and ROC curve analysis.

Results

According to the inclusion and exclusion criteria a number of 71 women were finally selected for the study. A hundred and six circumscribed breast lesions were detected by means of ultrasound in the studied group. Each lesion was assessed as a separate case, being classified

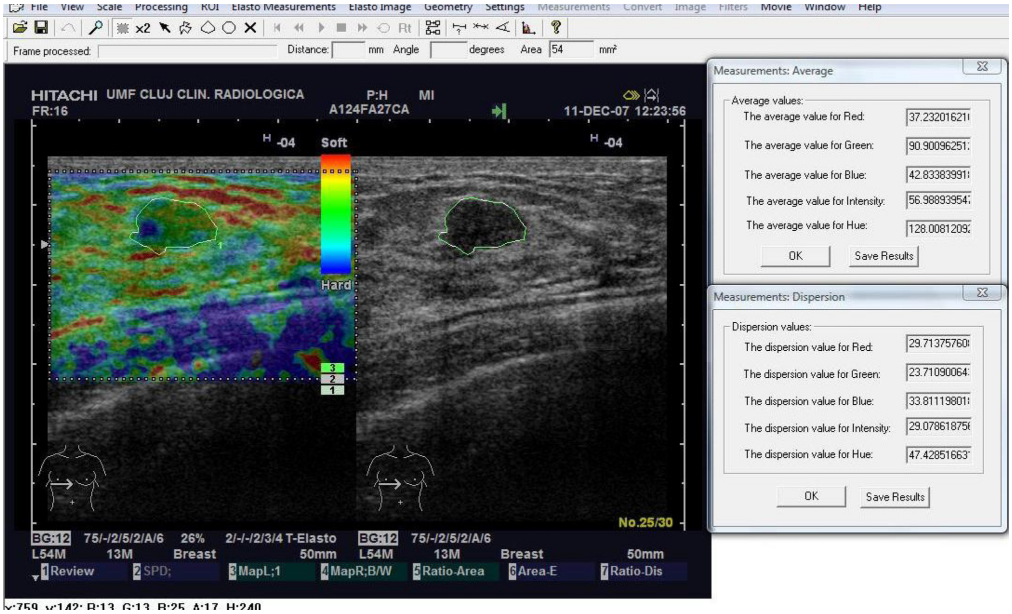


Figure 2: Dual US image (elastography-grayscale) of a benign breast nodule (fibroadenoma). Illustration of the calculation method for color and hue parameters using a dedicated software (Image Processing Version 1.3).

into a BI-RADS category, receiving a Tsukuba score and a quantitative evaluation of its USE appearance based on color and hue parameters.

Patients with malignant tumours were significantly older, with an average age of 54 years, with all lesions classified as BI-RADS 4 and 5 and with elastography scores raging between 2 and 6 (in our study the score 6 is the equivalent of the BGR pattern). The details are presented in table I.

According to table II, there were significant differences regarding all parameters computed by the software, except the average intensity values, when comparing benign with malignant lesions.

In order to identify the parameters with clinical significance that independently associated with the histological diagnosis, we performed a multivariate analysis.

According to table III, five parameters were independently associated with the histological diagnosis (AvgBlue, AvgGreen and AvgRed; DispRed and DispIntensity). Taken together, the regression model obtained is able to predict the presence of malignant lesions with an accuracy of 94% (AUROC) with **AvgBlue parameter** making the most important contribution (p<0.0001). The odds ratio (O.R.) for the independent variables gives the *relative* amount by which the odds of a malignant tumor increase (O.R. greater than 1) or decrease (O.R. less than 1) when the value of the independent variable is increased by 1 unit. **Thus, the greater the values of AvgBlue (more than 92), the higher the chances of malignancy and the greater the values of AvgGreen (more than 88), the higher the chances for a benign lesion.**

The regression model obtained has a very good diagnostic value for the diagnosis of malignant lesions, with an AUROC of 0.95 (95% CI 0.88—0.98), a sensitivity of 83%(95% CI 69.2 - 92.3) and a specificity of 93% (95% CI 83.3 - 98.0).

Table I. Summary statistics table regarding BI-RADS classification and elastography scores in the patients according to histology grading.

	Benign n=59	Malignant n=47	p
Age (mean±SD)	35.03±**12.60**	54.27±**9.31**	<0.0001
BI_RADS			
2 (N, %)	7 (12%%)	0	
3(N, %)	13 (22%)	0	
4a(N, %)	28 (47%)	1 (2%)	<0.0001
4b(N, %)	10 (17%)	2 (4%)	
4c(N, %)	1 (2%)	5 (8%)	
5(N, %)	0	39 (82%)	
Elastography score			
1	13 (22%)	0	
2	28 (47%)	6 (12%)	
3	11 (19%)	3 (6%)	<0.0001
4	5 (8%)	7 (15%)	
5	1 (2%)	30(64%)	
6*	1 (2%)	1 (2%)	

*Score 6 is equivalent to the BGR/stratified pattern corresponding to fluid containing lesions such as necrotic carcinomas or cytosteatonecrosis (CNS).

Tabel II. The numeric values for different average values computed by the automatic software, obtained according to pathology type (benign or malignant).

	benign				malignant				p
	Mean	SD	Min	Max	Mean	SD	Min	Max	
AvgBlue	61.40	24.80	14.98	141.99	92.91	20.28	52.59	139.12	<0.001
AvgGreen	88.56	16.72	50.21	135.45	58.52	20.29	29.48	106.77	<0.001
AvgIntensity	63.08	12.61	36.41	102.26	60.30	13.21	43.23	93.54	0.27
AvgHue	144.41	33.39	74.85	219.50	205.19	28.21	125.34	240.09	<0.001
AvgRed	39.27	15.00	18.01	82.27	29.48	12.63	12.39	67.06	0.001
DispBlue	33.05	5.23	17.46	42.22	24.60	9.39	12.46	66.54	<0.001
DispGreen	25.92	6.91	14.10	43.11	29.69	6.22	18.25	52.78	0.004
DispHue	45.59	11.77	20.26	76.47	34.23	16.04	9.85	70.04	<0.001
DispIntensity	28.49	3.78	19.85	37.27	24.68	7.09	14.29	59.10	0.001
DispRed	26.51	5.62	13.63	36.60	19.74	7.85	11.19	57.98	<0.001

Discussion

The practical questions arising with the use of this computerized program for analyzing elastographic images of breast lesions would be:

• First of all, is it efficient to apply this procedure in all cases?

• If not, which images or situations would benefit the most from such an analysis?

• And last, but not the least, what are the pitfalls and limitations?

In order to be readily used in a clinical setting all calculations should be realized at the same time with the patient examination. Currently there are necessary at least 5 to 10 minutes post image-acquisition to complete the process and theincreased processing times could interfere negatively with daily practice. Furthermore, quantitative analysis of elastographic images of typically benign or malignant lesions on conventional US would be futile. On the other hand there are lesions which appear indeterminate on conventional ultrasound. In such cases if the elastography appearance is highly heterogeneous, the exclusively visual assessment of the predominant color or hue can be difficult. The mosaic pattern could be due to a peculiar intrinsic structure or to an *imperfect* acquisition performed by a less experienced sonoelastographer (less than 6 months training with elastography). These are the situations where a quantitative analysis of the elastographic images could shift the examiner opinion towards a *most likely benign* (score 2 for a higher Avg Green value) or *most likely malignant* (score 4 for a higher Avg Blue value) (Figs. 4, 5)

Nevertheless there are situations when the quantitative analysis may prove to be falsely positive or falsely negative. For example old, calcified or hyalinized fibroadenomas (Fig. 6), sclerosing adenosis, some forms of cytosteatonecrosis or complicated cysts (Fig. 7) may demonstrate suspicious appearances both on conventional US and elastography (qualitative and quantitative altogether). Some particular breast cancers like the in situ ductal carcinoma (DCIS), mucinous, medullary or necrotic ones may appear as pseudo-benign lesions on conventional and elastographic US evaluation (quantitative analysis included) [14, 15].

Another limitation of this analysis derives from the breast structure which can be predominantly adipose, intermediate, or mostly glandular [13]. The elasticity of a lesion is related to the neighboring, normal breast

Tabel III. Logistic regression analysis using the backward analysis of parameters independently associated with the histological diagnosis.

Variable	Coefficient	Std. Error	Odds Ratio	95% CI	P*
AvgBlue	0.12	0.03	1.13	1.06 to 1.20	0.00006
AvgGreen	-0.07	0.02	0.92	0.88 to 0.97	0.004
AvgRed	-0.14	0.05	0.86	0.78 to 0.95	0.003
DispIntensity	-0.33	0.14	0.71	0.54 to 0.95	0.02
DispRed	0.48	0.16	1.62	1.18 to 2.22	0.002
Constant	-1.72				
AUROC	0.94 (0.88-0.98)				
Variables not included in the model					
AvgHue					
DispBlue					
DispGreen					
DispHue					

*using ANOVA test.

parenchyma. Thus, a benign lesion may appear stiff if surrounded by a largely adipose tissue or may demonstrate a non-suspicious aspect if encompassed by a predominant glandular tissue. That is why for further studies it would be ideal to quantify color parameters according to breast structure also.

However, it is known that any imaging diagnosis, including breast assessment should always be a correlative evaluation which must integrate information obtained from the entire set of investigations (clinical, paraclinical and radio-imaging altogether).

Conclusions

Quantitative analysis of USE images of breast focal lesions using color parameters (e.g. numeric values for AvgBlue and AvgGreen) may be useful in selected circumstances as follows:

Nodules or focal mass with non-specific features on conventional US (BI-RADS 3 or 4) demonstrating an extremely heterogeneous appearance on elastography,

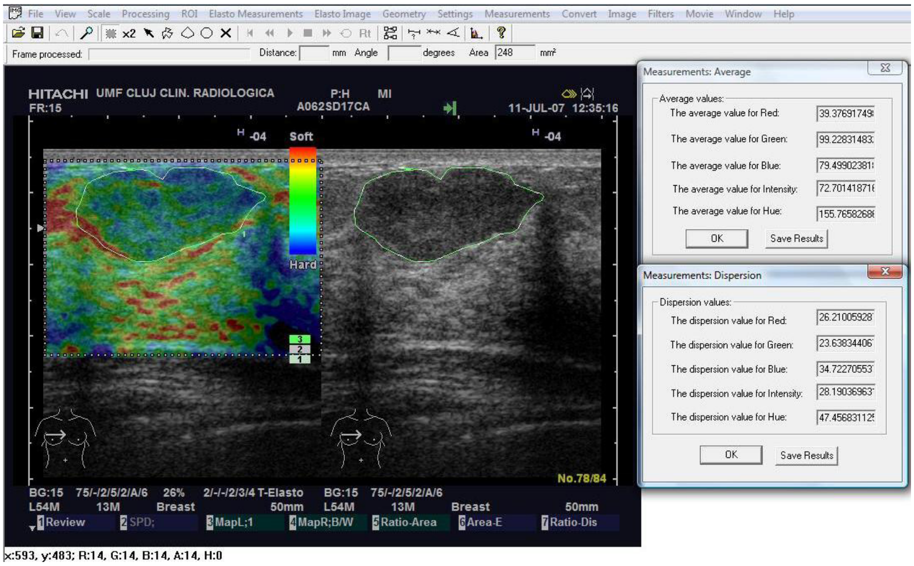


Figure. 4. Palpable nodule recently detected in a 17 years old patient. The slightly irregular contour determined the Consultant Radiologist to classify this lesion as BI-RADS 4b. The elastography revealed a mosaic pattern, with the apparent predominance of blue tints which would have corresponded to a suspicious Tsukuba score 4. The small values for Avg Blue (79 – less than 92) and higher value for Avg Green (99 –more than 88) pleaded in favor for score 2-non-suspicious. Post surgery pathology: breast adenoma.

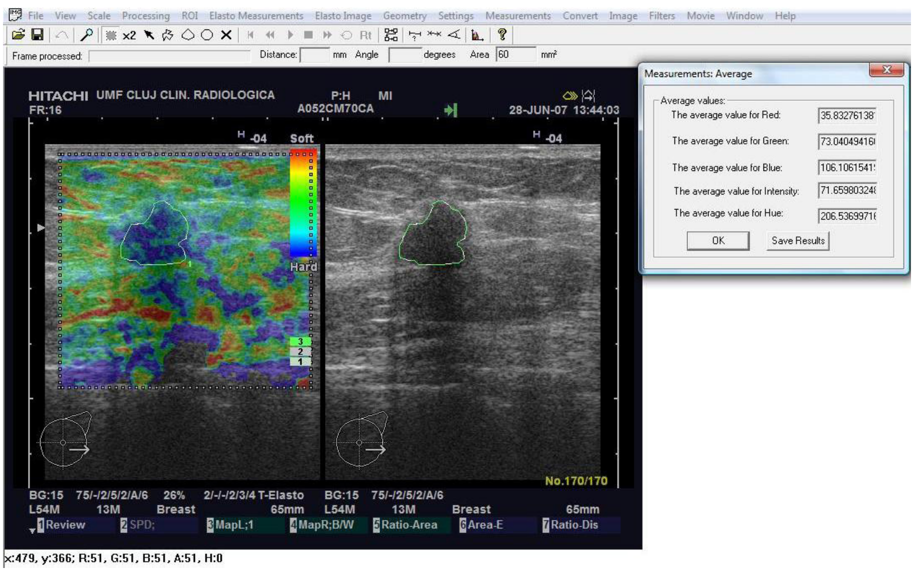


Figure 5. Non-palpable breast focal lesion displaying non-specific features on conventional ultrasound rising suspicion either for a mastopathic nodule (benign) or a carcinoma. The elastography heterogeneous appearance (blue-green) is doubtful between scores 2 and 4. The high numeric value for. Avg Blue (106 -more than 92) and the smaller value for Avg Green (73 - less than 88) pleaded for a score 4, suspicious lesion. Pathology report: invasive ductal carcinoma.

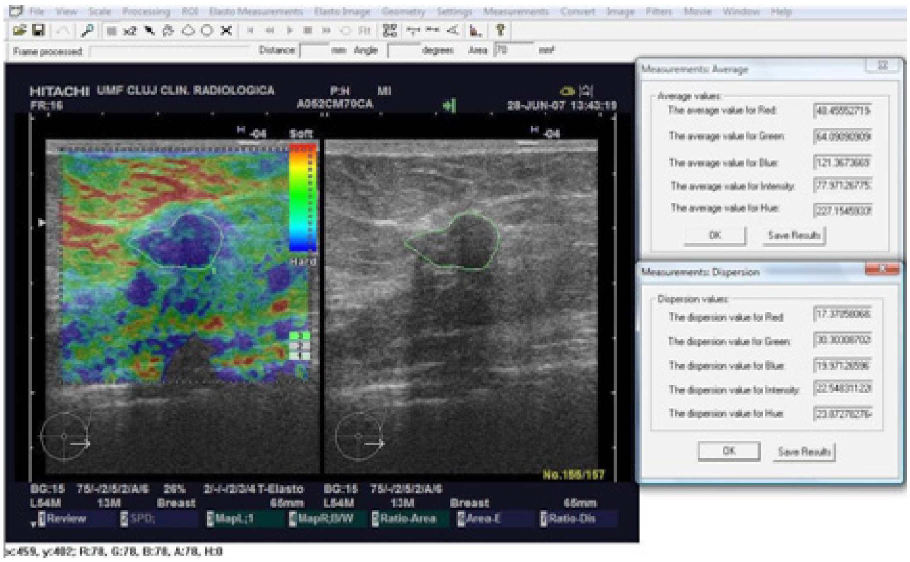


Figure 6. Small, slightly irregular nodule with mild posterior shadowing (BI-RADS 4b) with a mix blue-green appearance on USE. The high value for the AvgBlue parameter (121-more than 92) and lesser value for AvgGreen (64 –less than 88) reinforced the imaging diagnosis towards a suspicious nodule. Excision biopsy revealed an old hyalinized fibroadenoma.

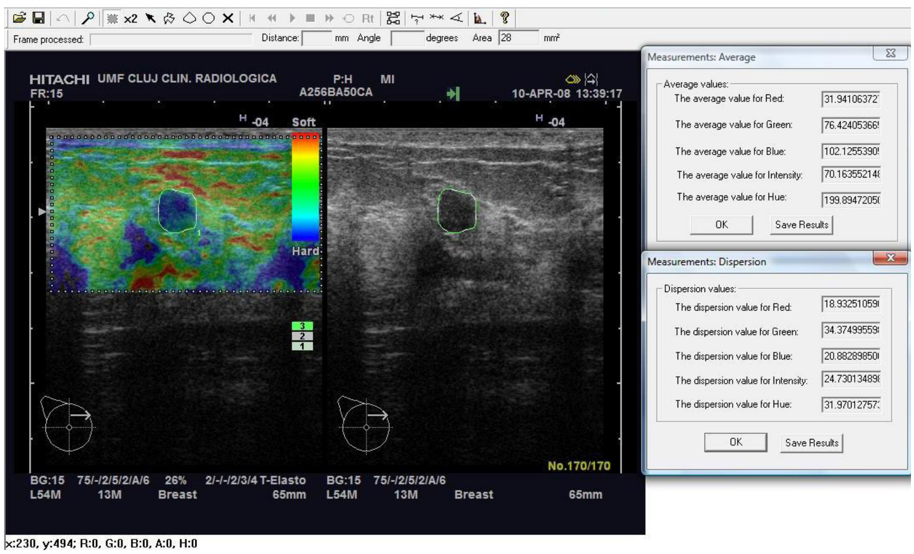


Figure 7. Small hypoechoic nodule detected in a 50 years old patient. The conventional US aspect is non-specific, well delineated, but with a rather "taller than wide" appearance (BI-RADS IVb). The predominance of blue color on USE evaluation is also worrisome as are the high values for Avg Blue (102 –more than 92) and low figures for Avg Green (73 –less than 88). Pathology result: viscous cyst (complicated cyst).

which makes the visual evaluation doubtful, especially in differentiating score 2 (benign) from 4 (highly suspicious)

whenever a less experienced sonoelastographer needs a complementary analysis to orient his/her opinion towards *most likely benign* or *most likely malignant* interpretation.

High numeric values for Avg Blue (more than 92) would increase the probability of malignancy and thus recommend a more aggressive diagnostic management (biopsy) while high numeric values for AvgGreen (more than 88) would reassure the examiner to proceed conservatively with short interval or routine follow-ups.

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