Biomedicine & Pharmacotherapy 75 (2015) 88–92

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Clinical value of relative quantification ultrasound elastography in characterizing breast tumors

Alfonso Fausto[a], Domenico Rubello[b,*], Alice Carboni[c], Paola Mastellari[b], Sotirios Chondrogiannis[b], Luca Volterrani[a,b,c]

[a] Department of Diagnostic Imaging, Azienda Ospedaliera Universitaria Senese, Policlinico Universitario 'Santa Maria alle Scotte', Viale Bracci 16, 53100 Siena, Italy
[b] Department of Radiology, Nuclear Medicine, Medical Physics, Head Service of Nuclear Medicine, PET/CT Centre, 'Santa Maria della Misericordia Hospital', Via Tre Martiri 8, 45100 Rovigo, Italy
[c] Department of Medical, Surgical and Neuro Sciences, Diagnostic Imaging, University of Siena, Strada delle Scotte 2, 53100 Siena, Italy

ARTICLE INFO

Article history:
Received 17 July 2015
Accepted 14 August 2015

Keywords:
Breast neoplasm
Tissue characterization
Ultrasound
Elastography
Strain ratio

ABSTRACT

Objectives: To evaluate ultrasound elastography (USE) using strain ratio (SR), a relative quantification approach for breast lesions characterization.
Methods: One hundred forty-seven consecutive patients with a total of 156 breast lesions underwent USE. Technical accuracy was assessed automatically. For SR evaluation a rounded ROI was depicted inside fat (F), glandular tissue (G) and inside the lesion (L), preferably at the same depth. *R*1, mean value of the G and F ratio, stands for in background tissue composition elasticity. *R*2; mean value of L/F stands for in lesion elasticity, both evaluated in arbitrary unit (au). Two-years follow-up and pathology results were standard of reference. Mann–Whitney test, ROC analysis and Chi-square with Yates correction were used.
Results: With the exception of 27 cysts, 17 malignant and 112 benign lesions were found. *R*1 values were 1.6 ± 0.7 au and 1.2 ± 0.9 au ($p = 0.015$ NS); *R*2 values were 6.1 ± 2.5 au and 1.9 ± 1.3 au ($p < 0.001$) for malignant and benign lesions, respectively. A threshold of 3.3 au showed a sensitivity and specificity of 88% and 87%, respectively with an AUC of 93%. Fifteen false positive and two false negative were detected.
Conclusion: Relative quantification of ultrasound elastography allows to find high levels of diagnostic accuracy in characterizing breast tumors above all in downgrading BI-RADS 3 and 4 lesions.

1. Introduction

Ultrasound elastography has been proved to be an important diagnostic tool to rise lesion characterization, improving specificity of conventional ultrasound (US) routinely applied in dense breast [1].

The 5th edition of the BI-RADS classification has introduced the elasticity assessment for lesion characterization as a validation that this technique is noteworthy independently of the different methods utilized [2].

A semi-quantitative assessment approach was proposed in order to obtain a more objective and less operator dependent free-hand technique with an improvement of the accuracy [3,4]; nevertheless a lack of standardization seems to be evident in literature due to the different cut-off levels considered by various Authors [5,6].

Recently some Authors have hypothesized that the stiffness of the surrounding tissue of malignant breast lesions could be higher than the surrounding tissue of benign lesions [7].

Aim of this study is to evaluate the diagnostic performance of a semi-quantitative assessment of free-hand ultrasound elastography (USE) in characterizing breast lesion and background tissue composition and analyse discordances between BI-RADS classification (4th edition) and USE.

2. Patients and methods

From May 2012 to October 2013, after institutional review board approval and oral informed consent collection, 147 consecutive outpatients (52 ± 14 years) with a total of 156 lesions referring to first level breast imaging office of University Hospital of XXXX were considered for our study. Inclusion criterion was the presence of at least one breast lesion, known or recently detected.

* Corresponding author at: Department of Nuclear Medicine, PET/CT Oncologic Centre, Radiology, Diagnostic and Interventional Senology, Interventional Radiology, NeuroRadiology, Medical Physics, Laboratory, Tumoral Biomarkers, Pathology, Microbiology Santa Maria della Misericordia Hospital, Rovigo, Via Tre Martiri 140, 45100 Rovigo, Italy. Fax: +39 425 39 4434.
E-mail address: domenico.rubello@libero.it (D. Rubello).

http://dx.doi.org/10.1016/j.biopha.2015.08.029
0753-3322/

Exclusion criterion was the lack of pathological confirmation or two years follow-up.

Each patient over 40 years old, first underwent mammography using a dedicated indirect digital X-ray mammography unit (Performa, GE Healthcare, Milwaukee, USA) with standard medio-lateral oblique and cranio-caudal projections and additional mammograms or compression magnification image, when necessary.

After clinical evaluation, B-mode US imaging (LOGIQ E9, GE Healthcare, Milwaukee, USA) was performed in all subjects using a high resolution linear probe (ML6-15 MHz) and classified according to BI-RADS criteria (4th edition).

Both US and USE were performed by the same radiologist (XX, 8 years of experience in breast imaging and XX, senior resident). In particular, USE was assessed using rectangular region of interest (elasticity color-coded map) larger than lesion including both glandular and/or fatty tissue, when possible. Patient posture changed during the examination according to the lesion position maintaining the probe perpendicular to the ground. Any lesions displacement or irregular manual pressure application was carefully avoided. Visual USE evaluation was obtained on real-time images displayed on a double-screen with B-mode. Technical accuracy was evaluated by a quality bar indicator displayed during the examination. A movie of at least 5 s was recorded for semi-quantitative analysis in post-processing.

In all patients analysis was conducted using three small identical region of interest (ROI) of 2 mm in diameter for all patients. The first ROI was positioned inside fat tissue (displayed as a yellow circle); the second in glandular tissue (displayed as a green circle) and the last one inside the lesion (displayed as a red circle) preferably at the same depth as lesion using B-Mode image as reference for positioning the ROI's (Fig. 1).

Macrocalcifications were avoided while positioning ROIs and the presence of microcalcifications detected by X-ray mammography was recorded.

The strain ratio (SR) was obtained by the semi-quantitative analysis. Color-coded USE movie, B-mode movie and colored lines the SR graph were displayed at the same time, after positioning all ROIs. The graph obtained is a dynamic evaluation of SR with arbitrary units (au) on *y*-axis and time (s) on *x*-axis. For each ROI a corresponding colored line was displayed on the graph, representing the ratio between elasticity over the time, sampled every 2000 ms (Fig. 1).

The ratio between glandular and fat tissue represented the background tissue composition elasticity, *R*1 (green-colored line); ratio between lesion and fat tissue represented lesion elasticity, *R*2 (red-colored line); the SR reference depicted horizontally at 1 au (yellow-colored line) represented the tissue of reference. Considering the SR assessment of tissues, more horizontal were the lines depicted and less noisy was the analysis and much more homogeneous external pressure. Raw data were recorded after each analysis and stored in a database.

Moreover, we compared lesion final assessment using BI-RADS classification (4th edition) and *R*2 values to investigate on the contribution of SR in lesions characterization.

2.1. Standard of reference

Final lesion diagnosis was obtained by pathology using US guided core needle biopsy or a two years negative follow-up. Fine needle aspiration was used to prove or verify the presence of cystic lesions.

2.2. Statistical analysis

Non-parametric Mann–Whitney test was used to compare *R*1 and *R*2 values between benign and malignant tissues. Receiver operating characteristic curves (ROC) were calculated to reach the best cut-off point with Youden index evaluation. Finally, Chi-Square test with Yates correction was calculated using MedCalc and GraphPad Software available on the web (http://www.medcalc.org,http://www.graphpad.com, freeware version). For all tests, a $p < 0.05$ was considered statistically significant.

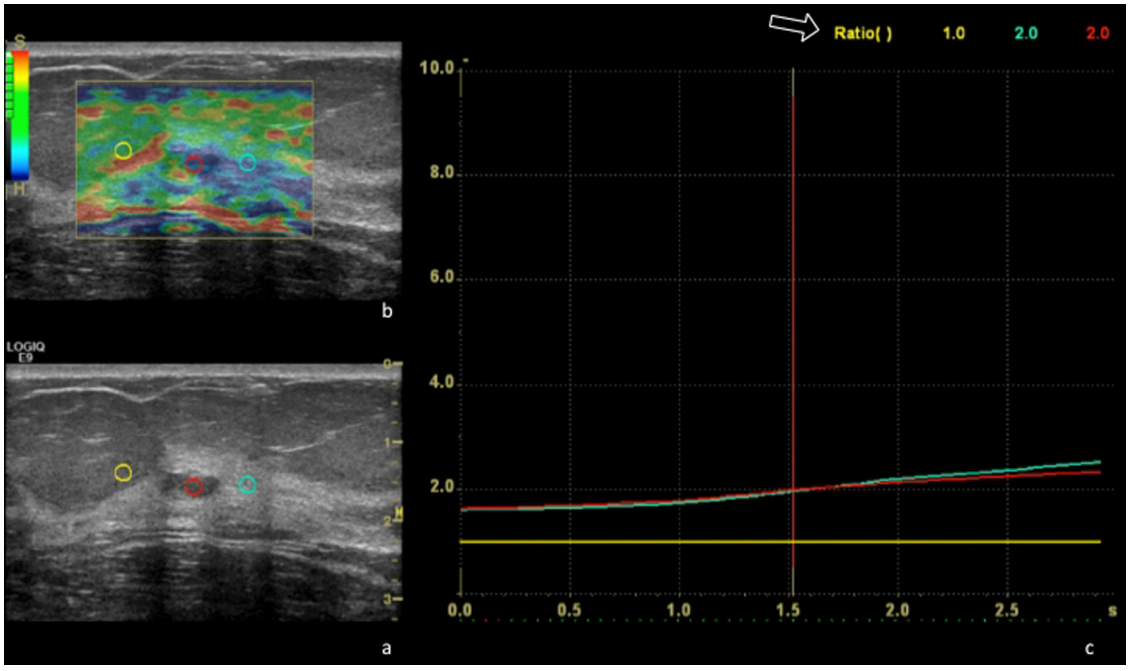

Fig. 1. (a) B-Mode image during free-hand elastography with three ROIs positioned in fat tissue (yellow circle), in glandular tissue (green circle) and inside the lesion (red circle) at the same depth. (b) Color-coded image of free-hand elastography evaluation. Technical accuracy depicted as a green bar positioned on the upper left side as well as the stiffness color bar scale. (c) Chart of the strain ratio analysis in which for each circle a line of the corresponding color is shown in arbitrary unit (au) during the time of the movie (s). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results

US revealed 21 cystic lesions and USE visual assessment 6 complicated cysts out of 156 lesions, confirmed by fine needle aspiration, in which the SR evaluation was avoided due to the well-known three-layer artefact [8]. A total of 129 lesions resulted for the analysis: 112 benign lesions and 17 malignant lesions. In 9 patients two lesions were studied.

Lesion size was 13 ± 9 mm (mean $\pm$ SD) and pathology revealed 17 malignant (13 IDC, 2 IDC + DCIS, 1 DCIS and 1 ILC) and 112 benign lesions (90 fibroadenomas, 7 lymph nodes, 5 fat necrosis, 5 sclerosing adenosis, 2 adenosis, 2 mastitis, 1 radial scar).

*R*1 values were 1.6 ± 0.7 au (mean $\pm$ SD) and 1.2 ± 0.9 au for malignant and benign lesions, respectively ($p = 0.015$ NS); *R*2 values were 6.1 ± 2.5 au (mean $\pm$ SD) and 1.9 ± 1.3 au for malignant and benign lesions, respectively ($p < 0.001$). A threshold of 3.3 au showed a sensitivity of 88%, a specificity of 87%, an area under the curve (AUC) of 94% and a Youden Index J of 0.779 (Fig. 2).

Considering the threshold just described, we found 15 false positive (12 fibroadenomas, 5 with micro or macrocalcifications; 2 sclerosing adenosis and 1 fat necrosis) and 2 false negative (1IDC + DCIS and 1 DCIS).

Thirty-one out of 135 lesions showed a BI-RADS lesion classification discordant to *R*2 value (1 IDC, 1 DCIS, 1 IDC + DCIS, 14 fibroadenomas, 3 sclerosing adenosis, 2 mastitis, 2 adenosis and 1 radial scar) or USE visual assessment (6 complicated cysts), ($p < 0.001$). BI-RADS showed a misleading classification in 1 malignant (IDC) and 13 benign lesions (2 adenosis, 2 mastitis, 1 fibroadenoma, 1 sclerosing adenosis, 1 radial scar and 6 complicated cysts); SR evaluation showed a misleading classification in 2 malignant (IDC + DCIS and DCIS) and 15 benign lesions (12 fibroadenomas, 2 sclerosing adenosis and 1 fat necrosis).

4. Discussion

B-mode imaging offers lesion characterization based on its acoustic properties, which are interpreted according to current BI-RADS descriptors and consequently classified into the appropriate category [9]. Low PPVs are especially associated with BI-RADS 4a and 4b leading to increase numbers of false positive results across these categories and unnecessary biopsies [10]. The phenomenon could be in part related to modest inter-observer agreement on US descriptors such as lesion margins, posterior acoustic features and echo pattern [11]. Elastography was introduced in addition to US providing insight into lesion mechanical properties to improve B-mode specificity while maintaining overall sensitivity levels [1,12].

Breast elastography can be performed using two different methods: USE and shear-wave elastography (SWE). In the latter, the acoustic radiation force impulse technology (ARFI) and the supersonic shear-wave imaging (SSI) can be included considering the SSI an implementation of ARFI technology [13,6]. Recently, the comparison of the two methods has demonstrated no differences between USE and SWE. [14].

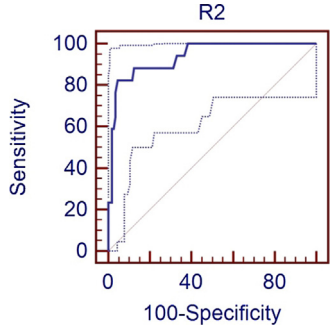

Fig. 2. Receiver operating characteristic curves for *R*2 values with an AUC of 0.937% (IC 95% 0.881–0.972). A sensitivity of 88% and a specificity of 87% were obtained with a threshold higher of 3.3 au.

USE or compression elastography is based on external force application to the breast and the shape-deforming effect measurement, thus providing a value of lesion stiffness compared to the surrounding tissues. Initially USE was based only on a qualitative assessment of breast tissue elasticity encoded in color map superimposed on B-mode images. The standard of reference for stiffness measurement of breast lesions was applied by Samani et al. studying ex vivo samples of all different benign and malignant breast lesions in which kPa values were obtained [15].

In a second time was proposed a semi-quantitative approach using the SR allowing to obtain numerical values which are more objective and less operator dependent. [6,7].

In our study we obtain dynamic SR evaluation using three small ROIs with a steady diameter of 2 mm for all patients and preferably at the same depth. Our choice was justified firstly by the possibility of a pressure gradient decay inside the USE box. Secondly to avoid partial volume effect after positioning the ROI into the lesion and the tissue of reference. Thirdly, the same dimensional ROIs used for all patients seems to give a more homogeneous evaluation of the sample. Finally, we measured both fat and glandular tissue because we could not be sure to find both reference tissues at the same lesion depth in all patients.

Considering the points just described, this is the first study to our knowledge in which this method has been applied, trying to be more 'objective' during elastography evaluation.

The ratio between glandular and fat tissue, the *R*1 value, represents the background tissue composition in which breast lesions are embedded. In our study, the *R*1 values were 1.6 ± 0.7 au and 1.2 ± 0.9 au for malignant and benign lesions, respectively, with no statistical difference. Zhou et al. have reported different results measuring the elasticity of the surrounding tissue probably related to a partial volume effect of the ROIs manually drawn along the lesion boundaries [7]. Furthermore, it could be questionable to compare different lesions with ROIs different in size, too.

Alhabshi et al. performed a semi-quantitative assessment using a square ROIs of 10 mm, fat tissue as standard of reference and the width and strain ratio measurement of the lesions during USE [16]. However, for lesions smaller than 10 mm (number not reported in the publication) a partial-volume effect of the surrounding tissue cannot be excluded with a consequent impact on the threshold. In fact, we experienced 4 malignant and 43 benign lesions smaller then 10 mm in size. No lesions were found smaller then 2 mm.

In our study *R*2 values were statistically different between benign and malignant lesions. A threshold of 3.3 au demonstrated a diagnostic performance of 94% with a specificity of 87%.

Alhabshi et al. reported a threshold of 5.6 to distinguish benign and malignant breast lesions at USE. The higher result in comparison to our is probably related to the choice of the Authors to position the lesion ROI in the area of maximal stiffness. As we described before, we decided to position the ROIs at the same depth starting from the reference tissues position and subsequently the lesion ROI, without considering the color-scale strain pattern. To our knowledge no other Authors have reported a stiffness threshold using a ROC analysis. The specificity obtained using our method is similar to that one described in the meta-analysis carried by Sadigh et al. [17], a higher value then Alhabshi et al. [16].

Another detailed consideration should be made on discordances between BIRADS characteristic features and USE lesion results. Six out of 31 discordant lesions appeared solid on B-Mode with BIRADS 2 or 3 classification in which USE revealed a three-layer artefact confirmed at US-guided aspiration. The liquid obtained

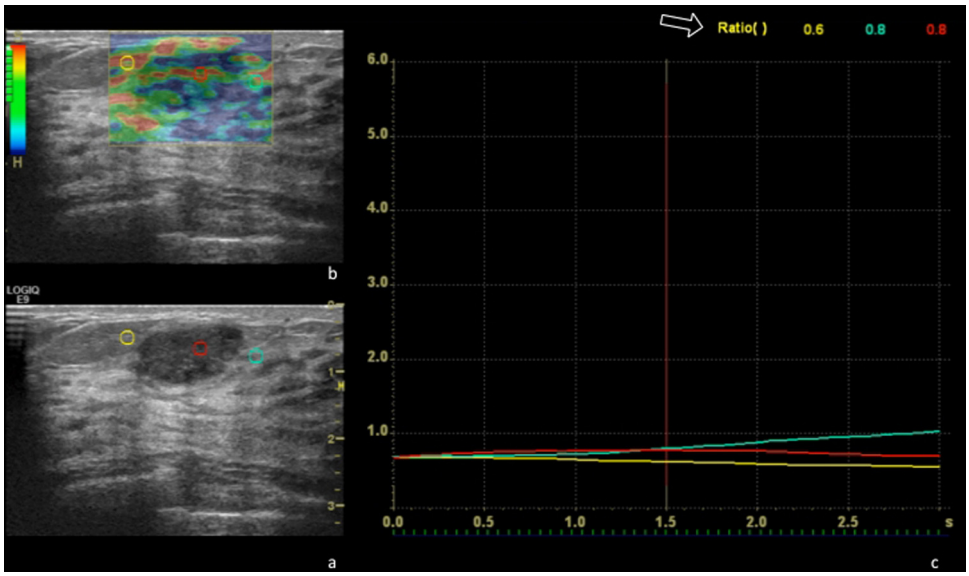

Fig. 3. (a) B-Mode image shows, during free-hand elastography with three ROIs positioned as described (see Fig. 1), a hypoechoic lesion of 16 mm with irregular borders at the conjunction of the external quadrants of the right breast classified BI-RADS 4b. (b) Color-coded image of free-hand elastography shows a scattered green pattern. (c) The chart shows the strain ratio analysis with a *R*2 mean value of 0.8 au (arrow) of the lesion studied (red line). Pathology revealed a IDC low grade with and extensive intraductal component. The discordant result between BI-RADS classification and elastography strain ratio analysis shows the limitation of *R*2 value in characterizing breast cancers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

resulted protein-based and acellulated in all cases at cytology. The remaining 25 discordances were 3 malignant and 22 benign lesions. Two false negative at *R*2 had a BIRADS 4b classification (Fig. 3). Pathology revealed in both cases a DICS partial or total component. Only one malignant lesion demonstrated BIRADS 2 classification and *R*2 value of 7.1 au being an IDC of 6 mm (Fig. 4). Twenty-two out of 31 were benign lesions in which 15 were false positive at *R*2 (see Section 3). However, five fibroadenomas have a proved macro or micro calcification component giving an expected poor elasticity pattern as reported in literature. [1,18]. Moreover the remaining 2 sclerosing adenosis and 1 fat necrosis could be explained with an increased stiffness due to the evolution toward sclerosis that can cause controversial US images and generate high SR values [19]. Seven benign discordant lesions had BIRADS 4a or 4b classification with an *R*2 value under the threshold. Two mastitis, 2 adenosis, 1 sclerosing adenosis, 1 fibroadenoma and 1 radial scar presented a suspicious pattern at B-mode as well reported in literature [19,6] for the architectural distortion frequently associated with radial scar, mastitis and other fibrotic changes of the glandular tissue.

Limitations of our study are related to the small variability in histological types of benign lesions. Moreover, the inter and intra-observer variability was not studied and the positioning of the ROI remained subjective. Last but not least, the inclusion criterion

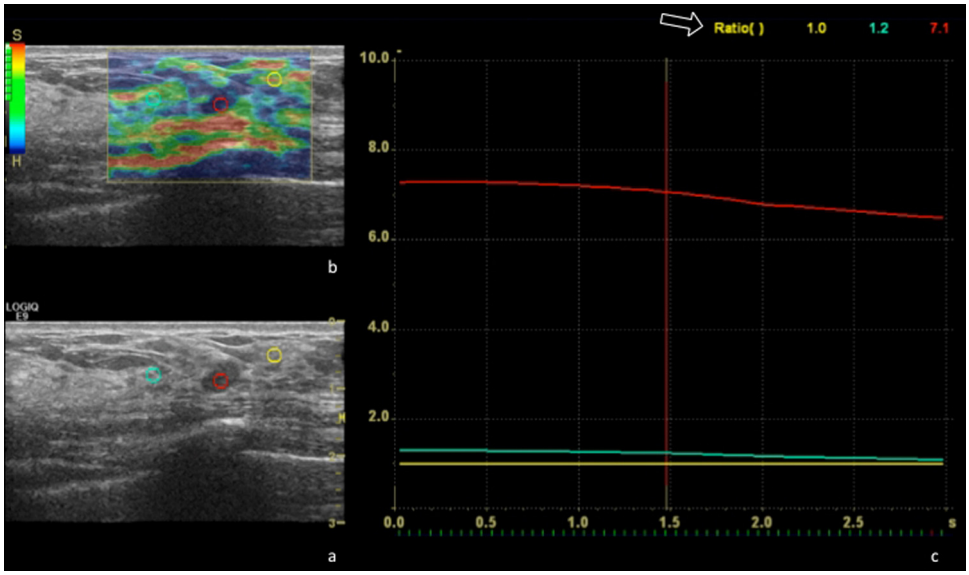

Fig. 4. (a) B-Mode image shows, during free-hand elastography with three ROIs positioned as described (see Fig. 1), a hypoechoic lesion of 6 mm with regular borders at the conjunction of the external quadrants of the left breast classified BI-RADS 2. (b) Color-coded image of free-hand elastography shows a scattered blue pattern. (c) The chart shows the strain ratio analysis with a *R*2 mean value of 7.1 au (arrow) of the lesion studied (red line). Pathology revealed an IDC. The discordant result between BI-RADS classification and elastography strain ratio analysis shows the importance of *R*2 value in characterizing breast lesions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

could be considered an intrinsic limitation of this study because we have not considered all the additional lesions detected at MR imaging only, without a US correlation. All those lesions firstly blinded at US before breast MR of the breast were not included and studied in our paper but they are well known in literature [20,21].

5. Conclusions

Our clinical results on 129 breast lesions showed a high level of specificity with a standardized method and demonstrated the absence of statistical difference in stiffness of the surrounding tissue. Moreover the significant presence of discordances with BI-RADS descriptors confirmed the importance of USE analysis with the SR. The application of this technique could reduce useless biopsies.

The vertical red line represent the time in which the mean valued of the lesion SR is found. Numerical values are depicted for each ROI (arrow). Pathology revealed a fibroadenoma.

Conflict of interest

The authors have no conflicts to declare.

References

[1] A. Itoh, E. Ueno, E. Tohno, H. Kamma, H. Takahashi, T. Shiina, et al., Breast disease: clinical application of US elastography for diagnosis, Radiology 239 (2006) 341–350.
[2] ACR BI-RADS Atlas 5th ed. http://www.acr.org (05.02.14).
[3] H. Zhi, X.Y. Xiao, H.Y. Yang, B. Ou, Y.L. Wen, B.M. Luo, Ultrasonic elastography in breast cancer diagnosis: strain ratio vs 5-point scale, Acad. Radiol. 17 (2010) 1227–1233.
[4] H. Yerli, T. Yilmaz, T. Kaskati, H. Gulay, Qualitative and semiquantitative evaluations of solid breast lesions by sonoelastography, J. Ultrasound Med. 30 (2011) 179–186.
[5] R.J. Hooley, L.M. Scoutt, L.E. Philpotts, Breast ultrasonography: state of the art, Radiology 268 (2013) 642–659.
[6] P. Ricci, E. Maggini, E. Mancuso, P. Lodise, V. Cantisani, Catalano, Clinical application of breast elastography: state of the art, Eur. J. Radiol. 83 (2014) 429–437.
[7] J. Zhou, W. Zhan, Y. Dong, Z. Yang, C. Zhou, Stiffness of the surrounding tissue of breast lesions evaluated by ultrasound elastography, Eur. Radiol. 24 (2014) 1659–1667.
[8] G. Scaperrotta, C. Ferranti, C. Costa, L. Mariani, M. Marchesini, L. Suman, et al., Role of sonoelastography in non-palpable breast lesions, Eur. Radiol. 18 (2008) 2381–2389.
[9] V. Ianculescu, L.M. Ciolovan, A. Dunant, P. Vielh, C. Mazouni, S. Delaloge, et al., Added value of Virtual Touch IQ shear wave elastography in the ultrasound assessment of breast lesions, Eur. J. Radiol. 83 (2014) 773–777.
[10] A. Athanasiou, A. Tardivon, M. Tanter, B. Sigal-Zafrani, J. Bercoff, T. Deffieux, et al., Breast lesions: quantitative elastography with supersonic shear imaging-preliminary results, Radiology 256 (2010) 297–303.
[11] E. Lazarus, M.B. Mainiero, B. Schepps, S.L. Koelliker, L.S. Livingston, BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value, Radiology 239 (2006) 385–391.
[12] F.K.W. Schaefer, I. Heer, P.J. Schaefer, C. Mundhenke, S. Osterholz, B.M. Order, et al., Breast ultrasound elastography—results of 193 breast lesions in a prospective study with histopathologic correlation, Eur. J. Radiol. 77 (2011) 450–456.
[13] C. Balleyguier, S. Canale, W. Ben Hassen, P. Vielh, E.H. Bayou, M.C. Mathieu, et al., Breast elasticity: principles, technique, results: an update and overview of commercially available software, Eur. J. Radiol. 82 (2013) 427–434.
[14] J.H. Youk, E.J. Son, H.M. Gweon, H. Kim, Y.J. Park, J.A. Kim, Comparison of strain and shear wave elastography for the differentiation of benign from malignant breast lesions, combined with B-mode ultrasonography: qualitative and quantitative assessments, Ultrasound Med. Biol. 40 (2014) 2336–2344.
[15] A. Samani, J. Zubovits, D. Plewes, Elastic moduli of normal and pathological human breast tissues: an inversion-technique-based investigation of 169 samples, Phys. Med. Biol. 52 (2007) 1565–1576.
[16] S.M. Alhabshi, K. Rahmat, N. Abdul Halim, S.M. Alhabshi, K. Rahmat, N. Abdul Halim, et al., Semi-quantitative and qualitative assessment of breast ultrasound elastography in differentiating between malignant and benign lesions, Ultrasound Med. Biol. 39 (2013) 568–578.
[17] G. Sadigh, R.C. Carlos, C.H. Neal, B.A. Dwamena, Accuracy of quantitative ultrasound elastography for differentiation of malignant and benign breast abnormalities: a meta-analysis, Breast Cancer Res. Treat. 134 (2012) 923–931.
[18] A. Thomas, F. Degenhardt, A. Farrokh, S. Wojcinski, T. Slowinski, T. Fischer, Significant differentiation of focal breast lesions: calculation of strain ratio in breast sonoelastography, Acad. Radiol. 17 (2010) 558–563.
[19] A. Stachs, S. Hartmann, J. Stubert, M. Dieterich, A. Martin, G. Kundt, et al., Differentiating between malignant and benign breast masses: factors limiting sonoelastographic strain ratio, Ultraschall Med. 34 (2013) 131–136.
[20] D.M. Plecha, R.M. Pham, N. Klein, A. Coffey, A. Sattar, H. Marshall, Addition of shear-wave elastography during second-look MR imaging-directed breast US: effect on lesion detection and biopsy targeting, Radiology 272 (2014) 657–664.
[21] E.P. Pons, F.M. Azcón, M.C. Casas, S.M. Meca, J.L. Espona, Real-time MRI navigated US: role in diagnosis and guided biopsy of incidental breast lesions and axillary lymph nodes detected on breast MRI but not on second look US, Eur. J. Radiol. 83 (2014) 942–950.