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FULL PAPER

Shear-wave elastography quantitative assessment of the male breast: added value to distinguish benign and malignant palpable masses

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Objective: To evaluate the ability of shear-wave elastography (SWE) to distinguish between benign and malignant palpable masses of the adult male breast.

Methods: Clinical examination, mammography, B-mode and Doppler ultrasound findings and SWE quantitative parameters were compared in 50 benign lesions (including 40 gynaecomastias) and 15 malignant lesions (invasive ductal carcinomas) from 65 patients who were consecutively addressed for specialized advice at our comprehensive cancer centre. Mean elasticity (EI mean), maximum elasticity (EI max), EI mean of the surrounding fatty tissue and lesion to fat ratio (EI ratio) were reported for each patient.

Results: Malignant masses displayed significantly higher EI mean ($p < 0.0001$), EI max ($p < 0.0001$) and EI ratio ($p < 0.0001$) compared to benign masses without overlap of values between the two groups. By adding SWE to clinical examination, mammography and

ultrasound, all the lesions would have been retrospectively correctly diagnosed as benign or malignant. One false positive could have been downstaged, 14/65 undetermined masses could have been correctly reclassified as 4 malignant and 10 benign lesions, for which biopsies could have consequently been avoided.

Conclusion: Evaluation of male breast palpable masses by SWE demonstrates that malignant masses are significantly stiffer lesions and may improve diagnostic management when clinical examination, mammography and conventional ultrasound are doubtful.

Advances in knowledge: Quantitative SWE is feasible in male breast and could be of great interest to help classify doubtful lesions after classical clinical and radiological evaluations, probably because of different anatomy and different tumours epidemiology compared with female breast.

INTRODUCTION

Male breast lumps are mostly due to gynaecomastia (80%). Other benign etiologies such as adipomastia, lipoma, haemangioma, inflammatory conditions, fibroadenoma, intraductal papilloma, or pseudoangiomatous stromal hyperplasia, abscess and hematoma are also implicated.^{1,2} The challenge is to detect the very small number of malignant causes, which account for 0.5–2% of all adult male breast lumps³ with an incidence of about 1 male per 100,000 per year,⁴ to avoid unnecessary core needle biopsies, patient anxiety and extra costs.

To address this question, several studies proposed investigative procedures for detecting a palpable male breast lump that take into account age, clinical data, mammography and conventional ultrasonography with Doppler.¹ However, there is no consensus as seen for female breast

lesions. Indeed, clinical examination of the male breast and mammography provide key elements to distinguish benign from malignant palpable lumps. Breast cancer can clinically appear as firm painless mass, with a subareolar eccentric location, skin retraction, bloody nipple discharge, nipple ulceration and axillary lymphadenopathy. Mammography of breast cancer classically displays a dense irregular spiculated mass associated with secondary signs such as skin thickening, nipple retraction or even inversion and pectoral retraction.⁵ Consequently, specificity and negative predictive value of clinical examination and mammography are excellent, approaching 99%.^{3,6} However, some authors have argued that ultrasonography should only be secondarily used in case of clinically and mammographically undetermined mass. Other authors have found this diagnostic management controversial as cancer and gynaecomastia can coexist (21–55% of cases)⁷ and as positive predictive

value of a first-line mammography remains limited.^{6,8} Consequently, the added value of each imaging modality and their place in diagnosis management remains unclear.

Elastography is a sonographic method to estimate the stiffness in tissue. The technique was primarily developed based on the observation that malignant tumours are stiffer than benign tumours. Two variations of the techniques have been developed: strain elastography and ShearWave™ Elastography (SWE, SuperSonic Imagine Aix-en-Provence, France), the latter being highly reproducible and the least operator-dependent of the two.⁹ SWE measures the speed of propagation of a shear wave that travels quicker in stiff tissue than in soft tissue, and therefore can be used to estimate the stiffness of a tissue. In addition to qualitative estimation (with a colour scale), SWE provides a precise quantification of stiffness, which is not possible with strain elastography.

Several studies have already demonstrated stiffness measurement contribution in female breast imaging. Indeed, stiffness increases in malignant tumours compared to benign tumours.^{10–12} SWE improves the specificity of breast ultrasound mass assessment especially for Breast Imaging Reporting and Data System (BI-RADS) 3 and 4a¹¹ and decreases the false-positive rates in BI-RADS 4a category. Quantitative maximum stiffness in breast cancers significantly correlates to histopathological severity despite overlap.¹³ Additional details with SWE could distinguish triple negative breast cancers from the other types of tumours.¹⁴ Furthermore, SWE could be useful to monitor breast cancer in neoadjuvant chemotherapy setting.^{15,16}

While SWE has been extensively used in the female breast cancers, to our knowledge, no study has ever investigated SWE in the male breast, especially to distinguish benign and malignant. The aim of this study was to evaluate the performance of quantitative SWE of palpable male breast masses to identify features that would distinguish benign and malignant tumours and to evaluate its added value.

METHODS AND MATERIALS

This monocentric study was approved by our institutional review board. Informed consent was waived for each patient.

From January 2011 to December 2015, 65 consecutive adult male patients (average 62.1 years, range 26–87) were recruited for the study. All patients were addressed by a first-line radiological centre for specialized advice and complementary examination at our regional Comprehensive cancer centre for unilateral (8) or bilateral (57, one of the two being suspicious) palpable masses. None of the patients had a personal history of breast cancer, chemotherapy or radiation therapy for any other cancer. Mammography was performed for all the patients at our centre prior to a radiology consultation.

Ultrasound imaging acquisitions

Ultrasound imaging protocol was standardized and remained unchanged during the whole study. Clinical and mammography findings were recorded prior to being referred to our centre. All patients had a clinical examination and, if needed, additional

mammography was performed. Subsequently, ultrasound was performed by three radiologists (SF, GHL, MAS) with a minimum of 10 years of experience in breast imaging and breast ultrasound, respectively, on an Aixplorer scanner (SuperSonic Imagine, Aix en Provence, France) with the same linear transducer for greyscale, Doppler and SWE analyses (4–15 MHz). The three radiologists applied the same validated SWE technique.¹¹ Without manual compression, they carefully focused on the lesion and used the “Q-Box” quantification tool that enables measurement of stiffness of the tissue in kilopascals (kPa) in a region of interest (ROI). For each patient, a first 2 mm² circular ROI was placed over the stiffest part of the tumour and a second 2 mm² ROI over healthy breast fat tissue. Accordingly, the following quantitative measures were performed: mean elasticity (El mean), maximum elasticity (El max), mean elasticity value of the surrounding healthy fat (El surr mean) and the lesion to fat elasticity ratio (E ratio) defined as the ratio between El mean and El surr mean. One measurement per tumour was performed and stored on the picture archiving and communication system (PACS, Agfa, Netherlands). In addition, conventional and Doppler ultrasound images in at least two orthogonal planes were also collected. Therefore, clinical examination, mammography and breast ultrasound with conventional B-mode, Doppler and SWE were available for each patient.

Data analysis

Six months later (in order not to be biased by memory), two breast radiologists (GHL and SF) - blinded to pathological results or patients' follow-up - reviewed ultrasound images on PACS, using BI-RADS lexicon complemented with a common lexicon for the shape of gynaecomastia (dendritic, diffuse, nodular, oval, irregular). Using conventional B-mode imaging, size, shape, margins, echo pattern and posterior features were reported and vascularity was reported using Doppler imaging.

Finally, 2 months after this retrospective reading (in order not to be biased by memory) - blinded to previous analyses, pathological analysis or follow-up - the same two radiologists consensually reviewed: (i) mammography alone, (ii) mammography + conventional B-mode and Doppler ultrasound, (iii) mammography + conventional B-mode and Doppler ultrasound + SWE. For each of these three analyses, they had to classify the lesion as: benign (equivalent of American College of Radiology (ACR) BI-RADS 1–2), malignant (equivalent of ACR BI-RADS 5) or undetermined (equivalent of ACR BI-RADS 3–4). Concerning the third analysis that combined all the imaging modalities, patients were retrospectively upstaged if one of the SWE value was above the statistically determined thresholds. Patients were downgraded if an undetermined lesion did not exhibit SWE values above these thresholds.

Diagnosis and pathological analysis

The final diagnosis was obtained for each patient by histopathology on ultrasound-guided core needle biopsy (25/65) by a specialized pathologist with more than 20 years of experience in breast tumours. If a lesion did not exhibit any suspicious criterion on all the breast imaging modalities, biopsy was not performed and patient was clinically and radiologically followed-up for at

least 2 years (40/65). Stability for at least 1 year was considered as benign. No patient was excluded due to insufficient follow-up. When required, ultrasound-guided core biopsies with an automated biopsy gun (Bard® Monopty®, 14G) were performed by the three radiologists. At least three samples inside the mass were obtained for each patient.

Statistical analysis

Statistical analyses were performed with GraphPad Prism Software v. 7 (GraphPad software, San Diego, California). For continuous variables, Gaussian distribution was tested with a Shapiro-Wilk normality test. Student *t*-test or Mann-Hitney test was used to compare patients with benign lesions and those with malignant lesions. For categorical or nominal variables, χ^2 test or Fisher's exact test was used. The receiver operating characteristic curve analysis for quantitative SWE parameters were built to evaluate their efficacy to distinguish benign from malignant lesions and were expressed as area under curve (AUC) with 95% confidence interval (CI). A *p*-value less than 0.05 was deemed significant. Data are expressed as mean $\pm$ SD.

RESULTS

Among the 65 consecutive patients who were assessed for a clinically palpable mass at our comprehensive cancer centre, 15 were diagnosed as invasive carcinoma of no special type and 50 benign lesions including: 40 gynaecomastias, 2 cystic haemangiomas, 4 inflammatory changes, 2 lipomas or angiolipomas, 1 papilloma and 1 neurofibroma.

On average, the age of patients with benign lesions was 62.4 ± 16 years old (26; 87) vs 61.5 ± 14.2 years old (36; 85) for malignant lesions, without significant difference.

Analyses of conventional ultrasound images showed similar sizes for malignant and benign lesions [20.6 ± 7.7 (7; 60) mm and 20.2 ± 6.8 mm (4; 32), respectively, $p = 0.38$], significantly different shapes with predominant irregular shapes (66.7%) for malignant lesions and dendritic shapes (70%) for benign lesions ($\chi^2 = 39.12$, $p < 0.0001$) and different margin patterns with more well-circumscribed margins for benign lesions (1/15, 6.7%) than for malignant lesions (12/50, 24%) ($\chi^2 = 11.73$, $p = 0.0084$). There was no significant difference concerning echogenicity ($\chi^2 = 3.545$, $p = 0.1699$), posterior features ($\chi^2 = 3.618$, $p = 0.1638$) or vascularity pattern ($\chi^2 = 0.944$, $p > 0.9999$) (Table 1).

SWE analysis demonstrated a significant increase of EI mean in malignant lesions (159.5 ± 51.54) than in benign lesions (11.12 ± 4.89) ($p < 0.0001$). There was a significant increase in EI max ($211 \pm \text{kPa}$ vs $12.73 \pm 6.7 \text{ kPa}$, $p < 0.0001$) and EI ratio (14.08 ± 11.93 vs 0.99 ± 0.46 , $p < 0.0001$) (Table 1). The ability of the SWE quantitative parameters to distinguish benign vs malignant palpable masses was analysed using the receiver operating characteristic curve analysis. These two groups could be perfectly distinguished by EI mean, EI max and EI ratio [for each of them AUC = 1, 95% CI (1–1), $p < 0.0001$]. A sensitivity (Se) of 100% and a specificity (Sp) of 100% for diagnosing a malignant breast tumour could be obtained using an EI mean threshold between 50 and 104 kPa, an EI max threshold between 118 and 132 kPa

and an EI ratio threshold of 3.5 (Figure 1). As our aim was not to miss any malignant lesion, we proposed the lowest value of each significant SWE quantitative parameter as a threshold for the evaluation of the added benefit of SWE to mammography and ultrasound, *i.e.* EI mean = 50 kPa, EI max = 119 kPa, EI ratio = 3.5.

Following the application of these quantitative SWE thresholds, we were able to correctly classify all the lesions as benign or malignant, without any indeterminacy.

The results were similar for mammography, and mammography + conventional ultrasound with Doppler: there was one false positive, 10 and 14 undetermined lesions, respectively, and 54 and 50 correctly diagnosed lesions, respectively. Among the 10 undetermined lesions on mammography: 3 were breast cancers and 7 benign lesions. Similarly, among the 14 undetermined lesions after mammography and conventional ultrasound: 4 were breast cancers and 10 benign lesions. All these undetermined lesions were retrospectively diagnosed by SWE quantitative assessment associated with other imaging modalities. The false positive was an inflammatory change. Due to their indeterminate nature, all these cases were biopsied. Comparisons between mammography and mammography + conventional ultrasound with Doppler did not show significant differences ($\chi^2 = 1.050$, $p = 0.9021$). However, comparison of the ability to distinguish benign and malignant masses between mammography + conventional ultrasound with Doppler vs mammography + conventional ultrasound with Doppler + SWE led to significant differences ($\chi^2 = 17.54$, $p = 0.0075$) as well as the comparison between mammography vs mammography + conventional Ultrasound with Doppler + SWE showed significant differences ($\chi^2 = 16.96$, $p = 0.0002$) (Figure 2). Figures 3 and 4 illustrate the added value of SWE quantitative parameters to distinguish benign from malignant lesions.

DISCUSSION

We observed statistically significant differences for each quantitative SWE parameter between malignant and benign male breast masses. For breast cancers, EI mean = 159.5 kPa, EI max = 211 kPa and EI ratio = 14.1, whereas for benign masses, it was 11.12 kPa, 15.92 kPa and 1.1, respectively. AUC for all three was 1 with a sensibility and a specificity of 100%. Hence, quantitative SWE parameters could perfectly distinguish benign and malignant lesions without false-negative or -positive results.

While mammography, or mammography and conventional ultrasound, could not determine 10 and 14 lesions, respectively (as well as one false positive), quantitative SWE enabled to correctly classify all the tumours retrospectively. If SWE quantitative criteria had been applied to the equivalent ACR BI-RADS 3 and 4, seven biopsies for mammography alone, and 10 biopsies for the combination mammography + ultrasound with Doppler, could have been avoided. The sole false-positive mass by mammography + ultrasound with Doppler would have been downstaged, in accordance with previous studies.¹¹

Table 1. Conventional ultrasound (B-mode and Doppler) and elastographic findings of adult male patients with palpable mass of the breast

	Cancer (N = 15)	Benign lesions (N = 50)	
Conventional ultrasound			
Size	20.6 (4–32)	20.2 (7–60)	$p = 0.38^a$
Shape			
Dendritic	0 (0%)	35 (70%)	$***p < 0.0001^b$
Diffuse	0 (0%)	0 (0%)	
Irregular	10 (66.7%)	1 (2%)	
Oval	5 (33.3%)	14 (28%)	
Margin			
Circumscribed	1 (6.7%)	12 (24%)	$**p = 0.0084^b$
Indistinct	9 (60%)	36 (72%)	
Spiculated	1 (6.7%)	0 (0%)	
Lobulated	4 (26.6%)	2 (4%)	
Echogenicity			
Hypoechoogenic	15 (100%)	40 (80%)	$p = 0.1699^b$
Hyperechoogenic	0 (0%)	5 (10%)	
Isoechoogenic	0 (0%)	5 (10%)	
Peripheral Halo			
Absent	3 (20%)	48 (98%)	$***p < 0.0001^c$
Present	12 (80%)	2 (4%)	
Posterior features			
Absent	13 (86.7%)	48 (96%)	$p = 0.1638^b$
Enhancement	1 (6.7%)	2 (4%)	
Shadowing	1 (6.7%)	0 (0%)	
Vascularity			
Absent	0 (0%)	3 (6%)	$p > 0.9999^c$
Intern	15 (100%)	47 (94%)	
SWE			
El mean	159.5 (105–288)	11.12 (2–49)	$***p < 0.0001^d$
El max	211 (133–300)	15.92 (4–117)	$***p < 0.0001^d$
El ratio	14.1 (4–50)	1.1 (0–3)	$***p < 0.0001^d$

SWE, shear-wave elastography.

^aStudent *t*-test.

^b χ^2 test.

^cFisher test.

^dMann-Whitney test $**p < 0.005$, $***p < 0.001$.

This highlights the benefit of SWE in avoiding unnecessary biopsies for benign lesions, and thereby limiting patient anxiety and additional costs in complementary and invasive examinations. Furthermore, if mammography or conventional ultrasound with Doppler classify a male palpable mass as ACR BIR-RADS 5, then this result must be prioritized over whatever the results of SWE analysis and lead to a biopsy.

Similar to previous studies^{1,6,12–17} we question the added values of ultrasound alone for male breast. However, conventional ultrasound is mandatory prior to SWE. Therefore, based on our experience and our cohort of male patients, we believe that clinically suspicious palpable masses must first be examined by mammography. If the mammography are doubtful or strongly suggestive of malignancy, then, patients should undergo conventional ultrasound

Figure 1. Comparison of elastographic parameters (El max, El mean, El Ratio) between benign and malignant palpable masses in adult male patients. Stiffness is expressed in kiloPascal (kPa). Each point represents the value of a patient. **** $p < 0.0001$.

with Doppler examination associated with SWE assessment, in order to better describe undetermined lesions and to downstage false positives. The last step would be ultrasound-guided biopsy in case of persistent uncertainty or increased stiffness. However, one must note that mammography are analysed by radiologists with a

lot of experience in breast imaging, hence, there might be a bias regarding good results of mammography alone.

Figure 2. Comparison of diagnostic performances of the different imaging modalities, alone or combined. Grey indicates correctly classified lesions (true positive and true negative), white indicates undetermined lesions, black indicates ill classified lesions (false negative or false positive). χ^2 test, ** $p < 0.005$, *** $p < 0.001$. MG: mammography, Nb, Number; SWE, shear-wave elastography; US, ultrasound (B-mode and Doppler).

Regarding El mean, our values for breast cancers were comparable with those reported in previous studies on female breast: 146.6 kPa reported by Athanasiou et al¹² 153.3 kPa reported by Patterson et al¹⁸ a median of 133 kPa reported by Berg et al¹¹ an El ratio cut-off of 3.56, El mean of 42.5 kPa and El max of 46.7 kPa would be the most helpful to correctly distinguish BI-RADS category 3 and 4a masses. These ratios are similar to ours and, except for one benign palpable mass, they would have correctly classified our cases. However, the diagnostic performance of SWE in female breast lesions was not as efficient as for male breast. This better performance for male breast could be explained by different proportions of histological types of cancer. Infiltrating carcinoma of no special type actually accounts for 85% of male breast cancer,^{19,20} and was the sole malignant histological diagnosis of our series. Due to the rarity of male breast cancer, we did not encounter all the potential histological types of cancer, notably the rarer lobular carcinoma, papillary carcinoma, lymphoma, metastasis and ductal carcinoma *in situ* alone (which is reported in 5% of all breast cancers in males as opposed to 20% in females) that might have been misdiagnosed with SWE,⁷ and possibly less stiff than invasive ductal carcinoma. Mucinous carcinoma, a relatively soft cancer, as well as tubular and lobular neoplasms are an exception in male breast.^{21,22} Of note, no special types of carcinomas with low elasticity values have been described in female breast²³ until now and we did not observe them in male breasts (neither at our centre nor, to our

Figure 3. Example of a malignant palpable mass. A 36-year-old male without medical history presented with a rapidly growing central, right retro areolar mass for 15 days. (a) Mammographies (face and oblique) demonstrated an irregular high density 19 mm mass. Skin and nipple were not retracted. (b) Ultrasound analysis with Doppler demonstrated a hypoechogenic well-circumscribed round mass with abundant internal vascularity. There was no suspicious lymphadenopathy. (c) Shear-wave elastographic analysis with Q-Box showed a very stiff lesion with El max = 300 kPa, El mean = 287.6 kPa, El ratio = 49.85, which strongly oriented towards malignancy. An ultrasound-guided core needle micro biopsy was performed. Pathological analysis confirmed a breast cancer (Grade 3 invasive ductal carcinoma, not otherwise specified).

knowledge, in the literature). In addition, we did not find rare benign etiologies like pseudoangiomatous stromal hyperplasia or fibroadenoma (an exception in male breast) that could have had overlapping quantitative values.

Our study has limitations. First, this is a small series with selection bias. Patients were sent to our comprehensive cancer centre for a second or a third opinion by first-line radiological centre. Male breast masses that were easy to diagnose were, consequently, under represented. This could explain why the proportion of malignant palpable masses (23.1%) is much more than in other studies (about 1%).²⁴ In a larger cohort, the El mean, El max and El ratio values could have been confusing. Nevertheless, with 15 cases, our work presents the most important series of malignant male breast cancers analysed by SWE. Our study provides an original and, to our knowledge, first overview of SWE in male breast malignant tumours. Multicentre prospective studies need to be carried out to validate SWE in this indication in the global population.

Most of the mammography were not re-performed, again in order to limit radiations, but the breast radiologists at our centre always re-analyse them in medical consultations and ultrasound evaluation, and images are integrated on our PACS.

In our study, SWE was performed by three experts in breast imaging with at least 10 years of experience and only once for each patient. We did not estimate either inter- or intra-observer reproducibility. Consequently, even if this technique seems simple to apply, one must keep in mind the possibility of technical errors such as compression during scanning (notably for superficial tumours or against ribs), misplacement of the ROIs in the surrounding tissue or in the tumour etc. However, with the published guidelines¹¹ and following training, intra- and inter-observer reproducibility are excellent.²⁵ Moreover, considering the factors that improve the quality of ultrasound elastography,²⁶ namely breast thickness and shallower lesion depth, male breast SWE would provide high quality data.

Furthermore, benign diagnoses after clinical examination, mammography and ultrasound were not followed by a biopsy; in the clinical and radiological follow-up (of at least 18 months) none of the tumours have been altered.

We did not perform stiffness qualitative assessment although Barr et al showed improved elastography sensitivity.²⁷ Sensitivity and specificity of SWE in our series were 100% and consequently, colour scale would not have added sensitivity or specificity.

Figure 4. Example of a benign palpable mass in a 79-year-old male who presented with a clinically suspicious mass for 1 month, of the upper outer quadrant of the right breast. (a) Mammographies demonstrated an irregular spiculated dense mass without microcalcification. Skin was slightly retracted on face incidence. (b) Ultrasound showed an irregular centimetric hyperechogenic 11 mm mass with internal vessels. (c) SWE exhibited reassuring features with low EI mean, EI max and EI ratio (7.9 kPa, 11.7 kPa and 246, respectively). Ultrasound-guided microbiopsy was subsequently performed. Pathological analysis revealed inflammatory benign tissue; patient's follow-up over 24 months did not show any abnormality. SWE, shear- wave elastographic.

To conclude, this pilot study on SWE to distinguish benign and malignant palpable male breast masses has enabled to identify three quantitative SWE parameters (EI max, EI mean, EI ratio) for further prospective multicentre studies. We believe that, when faced with an undetermined mass after clinical examination, mammography and ultrasound, adding SWE would limit

false positive and avoid invasive, expensive and anxiety-provoking managements.

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