Elastography as predictor of malignancy in male breast cancer

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Purpose

Gynecomastia and breast cancer are the two most frequent male breast diseases (1). The majority of lesions found in males are benign, with gynecomastia being the most common benign entity (2, 3). Gynecomastia, defined as benign proliferation of male breast glandular tissue, is usually caused by increased estrogen and decreased testosterone activities, or the use of various medications (4). Malignant lesions are rare, with breast cancer in men accounting for 0.5-1% of all breast cancer (1, 2, 3, 5) and 0.17% of all cancer in men (5, 6), but the incidence of breast cancer in men has increased by 26% over the past 25 years (2, 5).

Differentiating between benign and malignant masses is essential, because it alleviates patient anxiety and allows unnecessary procedures to be avoided (2). Unfortunately, on imagery gynecomastia can appear suspicious and mimic malignancy (2). Mammography has been traditionally used as the imaging modality of choice in the evaluation of male breasts. However, sonography is playing an increasingly important role in characterizing breast lesions and guiding percutaneous biopsies (3). In the literature for female breast disease, elastography has emerged as a promising technique for improving lesion differentiation, as benign lesions tend to be soft, while malignant lesions tend to be firmer (7, 8, 9). However, little is known about the use of elastography for male breast disease.

Our retrospective study aimed to determine the diagnostic accuracy of quantitative elastographic findings to differentiate male breast cancer from benign pathologies.
Methods and Materials

From January 2010 to December 2012, a retrospective review was performed for all male patients seen at our large tertiary referral centre with unilateral breast lumps. Clinical examination information, mammography and ultrasound with elastography reports were thus retrieved for 20 patients. Patients with suspicious lesions received core needle biopsies (14G) and other patients received clinical follow-up.

Ultrasound images were obtained on the Aixplorer ultrasound system (SuperSonic Imagine, Aix en Provence, France), which was installed in two of three ultrasound rooms within our breast imaging department. The probe used for the greyscale and shear wave elastography had a frequency range of 7.5 to 15 MHz. Shear wave elastography is a new method for obtaining elastography images based on the combination of a radiation force induced in a tissue by an ultrasonic beam and an ultrafast imaging sequence capable of capturing in real time the propagation of the resulting shear waves. Within a given region of interest (ROI), defined by an electronic cursor, values (kPa unit) for stiffness and ratio between lesion and surrounding tissue can be produced.

Two breast radiologists jointly reviewed ultrasound images (G.H., S.F. with 10 and 5 years of experience in breast radiology). We retrospectively analysed ultrasound images on the PACS system, using ultrasound features and elastography. We classified the lesions as masses or non-masses. For the purposes of the study, non-mass lesions were defined as lesions that showed focal heterogeneity, distinct from normal breast parenchyma. In contrast, masses were defined as space-occupying lesions. We used the ACR-BIRADS lexicon (10) and specified the size, shape (oval, round, lobulated or irregular), margins (circumscribed, microlobulated, indistinct, angular, speculated), lesion boundaries (abrupt interface or hyperechoic halo), echogenicity (hypoechoic, hyperechoic, complex) and posterior acoustic features (no change, enhancement or shadowing). We also used Doppler vascularity (positive if one or more vessels were present) and quantitative elastography. We recorded mean stiffness with the ROI placed in the stiffest area of the lesion identified on the colour maps and analyzed the ratio between the lesion and surrounding tissue. The kPa measure was inside the lesion for some masses and in the periphery of the lesion for others. Lesions were considered malignant if kPa was #70 and the ratio was #4.

Statistical analyses were performed with the use of statistical software (SPSS, Cary USA). We used the Wilcoxon test for quantitative data. P-value less than 0.05 were considered statically significant.
Results

All patients were men, between 26 - 80 years old (mean 58.2), with unilateral palpable breast lumps.

On elastography, six out of 20 patients (33.3%) had masses with intra- or peri-lesional hardness. The kPa values for these patients were between 105 and 203 (mean 144) and the ratio between 4.2 and 12 (mean 6). Biopsy confirmed the carcinoma diagnosis (3 IDC grade 3, 2 IDC grade 2+DCIS and 1 DCIS). On ultrasound, five out of six lesions had irregular shapes and one had an oval shape. The margins were angular for three, spiculated for one and microlobulated for one. All masses were hypoechoic with abrupt interface for two and hyperechogenic halo for three. There were no posterior acoustic features for five lesions and an enhancement for one. The Doppler vascularity was positive for all cancers. **Fig.1, 2**

On elastography, 14 out of 20 patients (66.6%) had mass or non-mass lesions with smoothness criteria: kPa values between 3.3 and 49 (mean 17.5), and ratio between 0.24 and 3 (mean 1.5). Three out of 14 patients had suspicious or indeterminate masses according to ultrasound and were referred for biopsy. Pathological results showed that all three had benign pathologies: kystic hemangiomia for two, and inflammatory changes for one. The elastographic features were identical for each mass with smoothness criteria: kPa values between 20 and 49 (mean 34.6) and ratio between 1.4 and 3 (mean 2). On sonography, two of these masses had an oval shape, one with circumscribed and one with microlobulated margins. The third mass had irregular shape with angular margins. The echogenicity was different for each lesion, one hypoechoic, one isoechoic and one hyperechoic. For lesion boundaries, two masses had abrupt interfaces and one hyperechogenic halo. All masses had no posterior acoustic features. The Doppler vascularity was positive for two lesions and negative for the other. **Fig.3, 4**

Eleven out of these 14 patients had lesions with benign aspects suggestive of gynecomastia. Clinical follow-up was proposed for these patients with mean time of 14.5 months (3 to 24).The elastographic mode data were homogeneous with smoothness criteria for all lesions. kPa values ranged from 3.3 to 25 (mean 12.8) and the ratio from 0.24 to 2.6 (mean 1.4). On sonography, four patients had mass lesions and seven had non-mass dendritic lesions. All masses were hypoechoic with oval shape, abrupt interface and no posterior acoustic features. The margins were circumscribed for three and indistinct for one. The Doppler vascularity was positive for all lesions. **Fig.5, 6**

We did not have any false positives using the elastography criteria. kPa values and ratio were statistically different between the cancerous lesions (six patients) and benign lesions (14 patients)(p<0.001 for both), indicating perfect sensitivity and specificity of 100%.
Fig. 1: 81-year-old man with palpable mass in left breast. Transverse ultrasound image of the left nipple region shows the irregular nonparallel hypoechoic mass with speculated margins and hyperechoic halo.

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Fig. 2: 81-year-old man with palpable mass in left breast. Ultrasound and elastography images shows typical peri-tumoral stiffness. Mean 203 kPa. Biopsy confirmed invasive cancer.

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Fig. 3: 75-year-old man with palpable mass in right breast. Sonography image shows oval shape hypoechoic mass with microlobulated margins and positive Doppler.

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Fig. 4: 75-year-old man with palpable mass in right breast. Ultrasound, elastography images show benign elastography features. Biopsy confirmed kystic hemangioma.

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Fig. 5: 40-year-old man with palpable mass in left breast. Transverse ultrasound image of the left nipple region shows the subareolar, fanshaped, hypoechoic nodule.

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**Fig. 6:** 40-year-old man with palpable mass in left breast. Ultrasound and elastography images show benign elastography features (mean 21 kPa). Follow-up confirmed gynecomastia.

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Conclusion

The aim of our study was to determine the utility of elastographic findings to differentiate male breast cancer from benign pathologies. To our knowledge, this is the first series concerning elastographic features of male breast diseases in the literature.

kPa and ratio elastographic values were clearly different between the group of patients with confirmed carcinoma (6 patients) and those with benign pathologies (14 patients). This is similar to reports in the literature from female breast lesions (7). The elastography mode is particularly successful in identifying lesions that were morphologically indeterminate or suspicious on sonography, but they all had smoothness criteria on elastography indicating the benign nature.

We did not encounter any difficulties for gynecomastia diagnosis with clinical aspects and mammographic and sonographic data. Elastographic features helped us to achieve our diagnosis with smoothness criteria.

In the cancer group, it's interesting to note that the patient with the lowest stiffness value was the patient with DCIS (kPa 102) and the two highest values came from patients with DCI grade 2 + DCIS (mean kPa: 188). The kPa values for the three patients with DCI grade 3 were intermediate between 102 and 188.

In terms of grade, we noticed that three out of five (60%) DCI were high grade, in contrast to Yang et al.'s series (6) where they found 12 % Grade 3 (1 out 8 patients). We also recorded 3 DCIS (50%) out of the patients with cancer, which is comparable with rates reported in the literature between 35 and 50% (1, 5, 6).

The limitations of this study are the retrospective design and the small number of patients limiting statistical analyses, but this is explained by the low frequency of the disease. The statistical difference observed for the kPa and ratio values between the patients with cancer and those with gynecomastia, was large and highly significant, but should be tested in a larger series of patients. Another limitation is the absence of a histological gold standard for the gynecomastia population, but it is not recommended to perform invasive procedures such as needle core biopsies in this pathology (1). We decided to clinically follow-up our patients, but the current median follow-up is only 14.5 months. Although we did not observe any false negatives during this study, the possibility that lesions will be revealed in the future is not ruled out, indicating that these diagnostic accuracy rates require confirmation.

Incorporation of elastographic specific features with clinical, mammographic and sonographic data should help us to distinguish benign to malignant breast male pathologies, guide the therapeutic approach and facilitate prognostic assessment and patient outcome in case of cancers.
References


