Clinical Radiology xxx (2018) 1–7

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Correlation between elastic parameters and collagen fibre features in breast lesions

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ARTICLE INFORMATION

Article history:
Received 24 August 2017
Accepted 31 January 2018

AIM: To correlate elastic parameters with collagen fibre shape and arrangement features in breast lesions.

MATERIALS AND METHODS: Shear-wave elastography (SWE) was used to measure the stiffness of breast lesions in 54 patients before surgical removal. The value of stiffness was expressed as the mean and maximum elasticity (Emean and Emax). Lesions were sliced and stained with picric acid–sirius red to display the extracellular matrix (ECM) collagen fibre. The categories of the collagen fibres were based on the shape and arrangement features, i.e., category 0, wavy collagen fibres similar to normal breast tissue; category 1, taut parallel collagen fibres around tumour nests; category 2, straightened and aligned collagen fibres tending to be perpendicular to the tumour boundary; category 3, collagen fibre in a honeycomb arrangement. Bivariate correlation analysis was used to analyse the relationship between elastic parameters and collagen fibre category.

RESULTS: For all 54 lesions, the correlation coefficient between Emean and category was 0.693 ($p < 0.001$), and between Emax and category was 0.794 ($p < 0.001$). For 36 malignant lesions, the correlation coefficient between Emean and category was 0.658 ($p < 0.001$), and between Emax and category was 0.771 ($p < 0.001$).

CONCLUSION: Emean and Emax of breast lesions evaluated by SWE were positively correlated with ECM collagen fibre shape and arrangement category. Changes of ECM collagen fibre shape and arrangement may account for the stiffness variations of breast lesions.

Introduction

Recently, several studies have reported that shear-wave elastography (SWE) showed good performance in assessing benign and malignant breast lesions.[1–8] In general, SWE demonstrated that malignant breast lesions exhibit increased stiffness compared with benign lesions.

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https://doi.org/10.1016/j.crad.2018.01.019
0009-9260/

Researchers suggested that malignant lesions are harder than benign ones because of the presence of desmoplastic extracellular matrix (ECM), with collagen being a major component.[9] Collagen fibres are the major structural ECM component in breast gland tissue. Collagen type I and collagen type III are principal components of normal mammary stroma. Increased collagen type I has been found to facilitate breast tumour formation, invasion, and metastasis.[10,11] Jodele *et al.* demonstrated there were changes in the ECM during cancer progression, such as upregulated collagen expression, deposition, and structural changes.[12] Previous studies of SWE and breast tissue stroma focused on the relationship between quantity of collagen or fibrosis and elastic parameters; however, collagen fibre shape and arrangement features were not taken into consideration. Several studies have revealed that differences in collagen features contribute to variations in tissue stiffness.[13–15] Further evidence is required to validate the clinical reliability of SWE as a clinical technique. The focus of the present study was the relationship between collagen fibre shape and arrangement features and the elastic parameters of breast lesions as evaluated using SWE.

Materials and methods

Patients

From March 2015 to December 2015, 54 consecutive patients in whom breast lesions were found on ultrasound screening or palpation underwent SWE prior to surgical resection. The age of the patients ranged from 31 to 82 years (mean ± SD, 52.1 ± 10.8 years). Patients were excluded if they were pregnant or lactating, had breast implants, had a scar adjacent to the lesion in question, were receiving radiotherapy or chemotherapy, or had already undergone needle biopsy prior to ultrasound screening. This study was approved by the local ethics committee and written informed consent was obtained from all patients upon enrolment.

Ultrasound and SWE examinations

Breast ultrasound and SWE examinations were performed by two radiologists, both with more than 10 years of experience each in breast ultrasound, using an Aixplorer Ultrasound System (SuperSonic Imagine, Aix-en-Provence, France) with a 4–15 MHz linear-array transducer. Conventional ultrasound was used to evaluate the breast lesions and then SWE examination was performed to measure the stiffness of the lesion. The probe was applied as lightly as possible to avoid too much pressure and was maintained as steadily as possible for at least 10–20 seconds during elastic image acquisition. Participants were asked to hold their breath to prevent motion artefacts if needed. The sampling area was set to the largest area possible to avoid interference from skin and muscle unless these tissues were involved in the lesion. Then, a semi-transparent colour map of tissue stiffness was overlaid on the ultrasound image, with a scale of 0–180 kPa. Regions of interest (ROIs) were chosen to measure elasticity and to include the largest possible portion of a lesion on conventional ultrasound images. Care was taken to adjust the ROI to include any halo or abnormal marginal foci of inelasticity, while minimising the inclusion of any normal tissue. To enable a comparison with histopathology data, the maximum imaging section of the lesion was obtained to measure the stiffness of the lesion. Conventional ultrasound was used to obtain the maximum imaging section of the lesion, and then start the SWE check, freeze, and measure. The above process was repeated for three times, and the final value of Emean or Emax was the average value of these three repetitions.

Collagen staining and category

To match the SWE imaging plane, the surgically excised specimens of maximum lesion section were sliced under ultrasound guidance for histopathological analysis. The sliced lesions specimens were divided into four quadrants by two perpendicular lines, fixed in 10% formaldehyde at room temperature, and then embedded in paraffin. Each slide from each quadrant contained the dominating tumour and peritumoural tissue. Picric acid–sirius red was used to stain the ECM collagen fibres. A Nikon E200 optical microscope equipped with a polarised filter was used to observe the collagen fibres at 100× magnification. The pathological category of each lesion was determined based on other sections stained with haematoxylin and eosin.

In the present study, collagen fibre shape and arrangement features in breast lesions were classified into four categories: category 0, 1, and 2 were developed based on previous studies[16–19]: categories 1 and 2 were developed from tumour-associated collagen signatures (TACS) reported by Provenzano *et al.*,[18,19] whereas category 3 was developed by the present authors. The definitions are described according to the following descriptions: category 0: wavy collagen fibres similar to collagen fibres in normal breast tissue[16,17]; category 1: taut parallel collagen fibres around tumour nests; category 2: straightened and aligned collagen fibres tending to be perpendicular to the tumour boundary; category 3: collagen fibres connected as in honeycomb.

Two researchers, one pathologist, and one majored in breast histopathology for 5 years, analysed and categorised the ECM collagen fibres in each section blinded to each other and to the SWE results. Discrepancies regarding category allocations were resolved in consensus to agree and assign a final category.

Statistical analysis

All statistical analyses were performed with SPSS 13.0, standard version (SPSS, Chicago, IL, USA). Quantitative data are displayed as mean ± SD. An independent samples *t*-test was used to compare the values of Emean and Emax between benign and malignant groups. One-way analysis of variance (ANOVA) was used to compare the values of Emean and Emax between multiple groups. The chi-squared test was used to compare the rate between the two groups.

Please cite this article in press as: Shi X-Q, et al., Correlation between elastic parameters and collagen fibre features in breast lesions, Clinical Radiology (2018), https://doi.org/10.1016/j.crad.2018.01.019