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● *Original Contribution*

PREDICTING PROGNOSTIC FACTORS OF BREAST CANCER USING SHEAR WAVE ELASTOGRAPHY

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Abstract—The purpose of the study described here was to investigate the correlation between histologic factors, including immunohistochemical factors, related to the prognosis of breast cancer and shear wave elastography (SWE) measurements. One hundred twenty-two breast cancers from 116 women were subjected to sonoelastography. Of the SWE features, mean and maximum elasticity and SWE ratio were extracted. The SWE ratio was calculated as the ratio of the stiffness of a portion of the lesion to that of a similar region of interest in fatty tissue. High ratios indicate stiffer lesions. The Mann-Whitney *U*-test, Kruskal-Wallis test and receiver operating characteristic (ROC) curve were used for statistical analysis. Estrogen receptor negativity, progesterone receptor negativity, p53 positivity, Ki-67 positivity, high nuclear grade, high histologic grade and large tumor (invasive) size were associated with a significantly high SWE ratio ($p < 0.05$). ROC curve analysis yielded SWE ratio cutoff values of 2.74–3.69 for significant immunohistochemical factors and 4.21 for the basal-like subtype by maximizing specificity while ensuring more than 80% sensitivity. Breast cancers with aggressive histologic features had high SWE ratios. Shear wave elastography may provide useful information for determining prognosis. (E-mail: hhkim@amc.seoul.kr) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Breast cancer, Breast ultrasound, Shear wave elastography.**

INTRODUCTION

Breast cancer is a heterogeneous disease consisting of several histologic subtypes with different clinical outcomes. Accurate prognoses are necessary not only to predict the natural history of the disease, but also to establish the appropriate treatment. The strongest prognostic factors are related to tumor stage and include lymph node involvement, tumor size and histologic grade (Carter et al. 1989; Elston and Ellis 1991). Although these factors are strongly correlated with prognosis, they are unable to accurately predict response to therapy or relapse in patients with breast cancer.

Many studies have reported that a breast cancer patient's survival depends not only on the stage of the disease, but also on immunohistochemical factors. Gene expression studies using DNA micro-arrays have identified distinct molecular subtypes that are associated with different clinical outcomes (Calza et al. 2006; Carey et al. 2006; Sorlie et al. 2001). Furthermore, it has been found that the various breast cancer subtypes differ remarkably in their response to treatment, as reviewed by Brenton et al. (2005). Expression of estrogen receptor (ER) and progesterone receptor (PR) determines the responsiveness of tumors to hormone therapy and is currently used to select patients for such treatments (Yaghan et al. 1998). Human epidermal growth factor receptor 2 (HER2) status may predict sensitivity to certain cytotoxic drugs or anti-estrogens, and its over-expression clearly indicates a poorer prognosis (Borg et al. 1990; Lovekin et al. 1991). Human epidermal growth factor receptor 1 (HER1) regulates cell growth, adhesion, motility and apoptosis processes, and its over-expression correlates with a higher tumor grade (Da Silva et al. 2007; Tzaida et al. 2007). Cytokeratin 5/6 (CK5/6), the cytokeratin expressed by the basal cells of the glandular tissue of the breast, is considered a poor prognostic factor in triple-negative breast cancers (Choccalingam et al. 2012). The tumor suppressor gene

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p53 has critical functions in control of the cell cycle and apoptosis, and its increased expression is associated with a poor prognosis (Bergh 1999; Cattoretti et al. 1988). The Ki-67 protein, known as a general proliferation marker, has proven to be a powerful negative prognostic factor for node-negative patients (Scholzen and Gerdes 2000). These biologic markers correlate with the differentiation, invasiveness and metastatic capacity of breast tumor cells (Bergh 1999; Lovekin et al. 1991; Scholzen and Gerdes 2000).

Shear wave elastography (SWE) is a highly reproducible technique that provides quantitative measurements of lesion stiffness during a breast ultrasound examination, based on an estimate of the speed of a shear wave (Tanter et al. 2008). Shear waves are transversely oriented waves that penetrate tissue and can be generated by an acoustic radiation force generated by the ultrasound transducer. The speed information can be provided as a color map of tissue elasticity that is super-imposed on a real-time gray-scale ultrasound image. Generally, breast cancer tissue is harder than the adjacent normal breast tissue. Shear waves travel faster in hard tissue than in soft tissue, and therefore, cancers usually have a higher stiffness expressed in kilopascals. Several published studies have reported that elastography can improve the accuracy of ultrasound, thereby helping to differentiate between benign and malignant breast lesions (Berg et al. 2012; Moon et al. 2009; Tozaki and Fukuma 2011). Reliability of SWE in the same participant population has been reported (Cosgrove et al. 2012). Several studies have investigated the correlation between other imaging studies such as mammography, magnetic resonance imaging, positron emission tomography-computed tomography and contrast-enhanced ultrasound, and some of the histologic and biologic characteristics (Koo et al. 2012; Lee et al. 2008; Mussurakis et al. 1997; Sanli et al. 2012; Shin et al. 2011; Wan et al. 2012). Gray-scale ultrasound correlation with an immunohistochemical assessment of invasive breast cancer was studied by Au-Yong et al. (2009). Evans et al. (2012) introduced the relationship between SWE and histologic prognostic factors such as histologic grade, tumor size (Bosch et al. 2003), lymph node involvement, tumor type and vascular invasion. However, to our knowledge, no published study has compared SWE and the expression of prognostically significant immunohistochemical factors such as ER, PR, HER2, HER1, CK5/6, p53 and Ki-67 in breast cancer. Therefore, our purpose in this study was to investigate the correlation between SWE measurements and histologic factors, including immunohistochemical factors, related to the prognosis of breast cancer.

METHODS

Patients

The institutional review board of our hospital approved this retrospective study and waived informed consent. The following inclusion criteria were developed based on information in our institutional consecutive database of breast ultrasound and medical records for the period comprising January 2012 and February 2012: (i) women with an ultrasound-visible breast mass who underwent elastography imaging using the Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France); (ii) histopathologically proven breast cancers for which information on histologic factors was available. Forty-seven women who underwent radiotherapy or neoadjuvant chemotherapy before elastography imaging or surgery were excluded. Therefore, 122 breast cancers from 116 women (age range: 27−77 y, mean age: 48.1 y) were included in the final study.

Ultrasound examination

Conventional ultrasound and elastography images were obtained using the Aixplorer ultrasound system with a 4- to 15-MHz linear transducer by one of five board-certified radiologists who specialize in breast imaging and had 1 to 10 y of experience interpreting images from a minimum of 1000 breast ultrasound examinations in the prior year. Each reader had experience with more than 100 cases of ultrasound breast elastography. At least two orthogonal gray-scale images and elastographic images were obtained of each solid lesion. For elastography, the same depth, focus position and gain setting were used as for conventional images. Elastographic images were generated without pressure, and the image was allowed to build up over about 10 s. SWE imaging was performed by setting the region of interest (ROI) so that it included the lesion and the surrounding normal tissue. Within the ROI, elastography values were obtained by placing a 3-mm round electronic cursor over the stiffest part of the lesion, including the immediate adjacent stiff tissue or halo. The maximum, mean and standard deviation of the stiffness were obtained within these areas. A second ROI of the same size was placed in the breast fatty tissue. This allowed calculation of the ratio of mean elasticity in the lesion to that in fat, called the *SWE ratio* (Figs. 1 and 2).

Histopathologic analysis

All patients in the study group underwent surgery for the breast mass and sentinel lymph node biopsy and/or axillary lymph node dissection. All breast lesions were histologically verified. The cancers were typed histologically according to the World Health Organization classification (Bocker 2002). Tumor size, nuclear and