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● *Original Contribution*

EX VIVO AND *IN VIVO* ASSESSMENT OF THE NON-LINEARITY OF ELASTICITY PROPERTIES OF BREAST TISSUES FOR QUANTITATIVE STRAIN ELASTOGRAPHY

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Abstract—The aim of this study was to reveal the background to the image variations in strain elastography (strain imaging [SI]) depending on the manner of manipulation (compression magnitude) during elasticity image (EI) acquisition. Thirty patients with 33 breast lesions who had undergone surgery followed by SI assessment *in vivo* were analyzed. An analytical approach to tissue elasticity based on the stress-elastic modulus (Young's modulus) relationship was adopted. Young's moduli were directly measured *ex vivo* in surgical specimens ranging from 2.60 kPa (fat) to 16.08 kPa (invasive carcinoma) under the weak-stress condition (<0.2–0.4 kPa, which corresponds to the appropriate "light touch" technique in SI investigation. The contrast (ratio) of lesion to fat in elasticity *ex vivo* gradually decreased as the stress applied increased (around 1.0 kPa) on the background of significant non-linearity of the breast tissue. Our results indicate that the differences in non-linearity in elasticity between the different tissues within the breast under minimal stress conditions are closely related to the variation in EI quality. The significance of the "pre-load compression" concept in tissue elasticity evaluation is recognized. Non-linearity of elasticity is an essential attribute of living subjects and could provide useful information having a considerable impact on clinical diagnosis in quantitative ultrasound elastography. (E-mail: umemoto@tmch.or.jp) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Elastic modulus (Young's modulus), Pre-load compression, Non-linearity, Stress, Strain, Elastography, Elasticity imaging, Strain imaging, Shear wave imaging, Breast cancer.**

INTRODUCTION

Previous studies on direct tissue elasticity measurements (Krouskop et al. 1998; Samani et al. 2007) reported that different tissues within the breast have specific elastic moduli (Young's moduli). With the goal of using this property in imaging diagnosis, various techniques for the measurement of ultrasound (US) tissue elasticity have been investigated and categorized mainly into two groups: strain imaging and shear wave imaging (Bamber et al. 2013; Shiina et al. 2013).

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Strain imaging (SI) is based on strain that is generated by manual compression and reflects the deference of tissue stiffness (Ophir et al. 1991; Shiina et al. 1996; Yamakawa and Shiina 2001). "Real-time tissue elastography (RTE)," developed and implemented on the EUB-8500 system (Hitachi Aloka Medical, Tokyo, Japan) in 2003 (Matsumura et al. 2002), enables real-time observation of tissue elasticity (tissue strain). Its clinical value was first assessed for breast diagnosis by Matsumura et al. (2004). Shear wave imaging (SWI) is based on the shear wave speed of tissue, which is related to tissue elasticity, and has recently been integrated into clinical practice (Chang et al. 2011, Tozaki et al. 2011).

In the clinical application of SI, the "Tsukuba elasticity score," which is used to evaluate the relative stiffness of tissue based on a color scale, greatly accelerated the standardization and general diagnostic use of SI

(Itoh et al. 2006). Various analyses after the latter report indicated that US diagnosis on the basis of conventional B-mode imaging combined with RTE improves specificity and accuracy, and today, the usefulness of US tissue elasticity imaging for breast diagnosis is well established (Cho et al. 2009; Japan Association of Breast and Thyroid Sonology [JABTS] 2008; Zhi et al. 2007).

Another two methods of interpreting strain images have been proposed: (i) evaluation of the ratio of lesion stiffness to fat, or the fat/lesion ratio (FLR) (Ueno et al. 2007; Waki et al. 2007), which has a sensitivity of 90% and specificity of 89% (Thomas et al. 2010) and high accuracy (Zhi et al. 2010); and (ii) evaluation of the change in size between the B-mode image and the strain image (Hall et al. 2003), which has a sensitivity of 99% and specificity of 88%–91% (Barr 2006, 2010; Barr et al. 2012; Destounis et al. 2013). Toda, RTE has been positively evaluated for clinical diagnosis in thyroid tumor (Fukunari 2005; Hong et al. 2009; JABTS 2012) and prostate cancer (Miyanaga et al. 2006; Tsutsumi et al. 2007).

Through clinical experience, however, the image variations that depend on the manner of manipulation (compression magnitude) during US tissue elasticity imaging have been highlighted as a technical issue or limitation by Itoh et al. (2006) and Umemoto et al. (2009). We reported that image variations that depend on the compression magnitude in SI possibly derive from the non-linearity in tissue elasticity and also mentioned the importance of "pre-load compression" (Umemoto et al. 2009). With respect to SWI, Barr and Zhang (2012) recently evaluated the relationship between compression magnitude and SW speed propagation and reported the importance of "pre-compression" and a useful method for its assessment in clinical settings.

In terms of the non-linear properties of tissue elasticity, Krouskop et al. (1998) revealed that breast tissue elasticity possesses strong non-linearity by measuring the elasticity of tissue samples for different values of strain. However, for the case of SI, the stain distribution itself is evaluated for diagnosis; thus, it is better to use stress than strain for assessment of the optimal condition of compression. In practice, it is difficult to set the specified value of stress on the body surface with the present SI system in clinical examination. Therefore, we are currently investigating a more quantitative SI system that measure stress on the surface using a coupler (Matsumura et al. 2005). In addition, the range of pre-compression reported in the article by Krouskop et al. seems to be larger than the light pressure recommended for clinical examination by SI. It is important to discuss the fundamental relationship between initial pressure (stress) and elasticity with the range covering the small stress.

In this article, we quantitatively assess the fundamental relationship between initial pressure (stress) and elasticity with reference to a stress axis by directly measuring the loaded stress and strain of tissue samples (*ex vivo*). We also investigate the relation between image variations in SI (*in vivo*) and magnitude of compression (stress) for the purpose of estimating the optimal range of stress for proper SI. In the near future, the results described here are expected to be used to develop a more quantitative SI system, in which the compression magnitude is set by stress, for superior diagnostic performance by SI.

METHODS

Patients

Between May 2007 and March 2009, we studied 33 breast lesions (30 patients) that were (i) classified as Breast Imaging Reporting and Data System (BI-RADS) US category ≥3; (ii) referred for consideration of surgical treatment; and (iii) for which not to influence the post-operative pathologic diagnosis was not considered to be influenced by preparation of the sliced samples from the surgical specimens (lesion diameter ≥ 10 mm). The study protocol was approved by the Institutional Ethics Committee of the University of Tsukuba and the Human Subjects Institutional Review Board of Tsukuba Medical Center Hospital. Before enrollment, each patient gave written informed consent. The mean age of the examined patients—1 man and 29 women (14 pre-menopausal, 15 post-menopausal)— was 56.8 ± 13.6 years (range: 37–80). Pre-operative diagnoses for 33 breast lesions included 30 malignant lesions and 3 benign tumors diagnosed on the basis of US images and core needle biopsy results. The planned surgical procedures were excisional biopsy for 3 cases, lumpectomy for 19 cases and mastectomy for 11 cases. One patient who had bilateral malignant lesions underwent simultaneous bilateral surgery. Three patients who were pre-operatively diagnosed with a benign tumor had surgery at their request. Thus, all patients underwent surgery, and the final diagnoses, which were based on results of the pathologic examination of the resected breast tissue, as determined by established criteria (Tavassoli and Devilee 2003), completely correlated with the pre-operative diagnoses. None of the patients in this study had any adverse events.

Ultrasound examination

For all patients who gave written informed consent and were enrolled in this study, pre-operative US examinations including B-mode, color Doppler and RTE were performed with a clinical US scanner (EUB-8500 or HIVISION 900, Hitachi Aloka Medical) and a 6- to 14-MHz or 5- to 13-MHz linear probe (EUP-L65,