Review Article

Breast Ultrasound Elastography is the Most Mature and Well-documented Method for the Measurement of Tissue Stiffness: A Review

MH Rahman

Abstract:

Breast cancer is the most common malignancy and one of the leading causes of death in females worldwide. North America has one of the highest incidence breast cancer rates in the world, making breast cancer awareness a high priority. Only in the USA, 527 women are expected to be diagnosed with breast cancer while 110 women will die of it per day. Central to the importance of breast cancer diagnosis is the fact that almost one-third of the latter group could survive if their cancer is detected and treated early. In a worldwide context, this translates into nearly 400,000 lives that could be saved every year as a result of early detection. As such; developing technique that can help to detect and diagnose breast cancer at early stage can have a great impact on survival and quality of life of breast cancer patients.

Conventional breast cancer screening and detection techniques such as clinical breast examination and X- ray mammography are known to have low sensitivity. Breast magnetic resonance imaging (MRI) is more sensitive modality for breast cancer detection, however, MRI is costly and has been shown to have low specificity for breast cancer diagnosis. Dynamic contrast-enhanced MRI has been demonstrated to provide a good sensitivity and specificity for differentiation of benign versus malignant lesions, due to altered angiogenesis mechanisms in tumors. However, in addition to being costly, requires injection of exogenous contrast agents to provide such contrast. An alternate imaging technique for breast cancer detection employs tissue stiffness as contrast mechanism. The technique is founded on the fact that alterations in breast tissue stiffness are frequently associated with pathology. Ultrasound elastography is the most mature and well-documented method for the measurement of tissue stiffness. Elastography-based imaging technique has received substantial attention in recent years for non-invasive assessment of tissue mechanical properties. These techniques take advantage of changed soft tissue elasticity in various pathologies to yield qualitative and quantitative information that can be used for diagnostic purpose. Measurements are acquired in specialized imaging modes that can detect tissue stiffness in response to an applied mechanical force. Ultrasound-based methods are of particular interest due to its many inherent advantages, such as wide availability including at the bedside and relatively low cost. While ultrasound elastography has shown promising results for non-invasive assessment of breast stiffness is emerging.

Key words: Breast, Ultrasound elastography, Tissue stiffness, Cancer.

Introduction:

Ultrasound elastography is an imaging technique sensitive to tissue stiffness that was first described in the 1990s[1]. It has been further developed and refined in recent years to enable quantitative assessment of tissue stiffness. Elastography methods take advantage of the changed elasticity of soft tissue resulting from specific pathological or physiological process[2]. For instance, many solid tumors are known to stiffer mechanically from surrounding healthy tissue. Similarly, fibrosed tissue becomes stiffer than normal tissue. Elastography methods can hence be used to differentiate affected from normal tissue for diagnostic applications.

1. Dr. Hafizur Rahman MBBS, M.Phil (Nuclear Medicine), Chief Medical Officer & Professor, Institute of Nuclear Medicine and Allied Sciences, Faridpur.

Address of correspondence :
Dr. Hafizur Rahman MBBS, M.Phil (Nuclear Medicine), Chief Medical Officer & Professor, Institute of Nuclear Medicine and Allied Sciences, Faridpur. Mob: +88-01711235280,
E-mail: mhrn08@yahoo.com

Conventional ultrasound has the advantage of being an inexpensive, versatile, and widely available modality that can be used at the bedside, which also applies to ultrasound elastography. Ultrasound elastography has been explored for several clinical applications in recent years and has been introduced into clinical routine for specific applications such as breast lesion characterization. Elasticity imaging by ultrasound elastography provides complementary information to conventional ultrasound by adding stiffness as another measurable property to current ultrasound imaging technique.

Tissue stiffness of breast can be evaluated by ultrasound elastography methods. Currently two types of ultrasound elastography (USE) are available: strain elastography and shear wave elastography(SWE)[3]. Strain elastography is based on the comparison of echo signals acquired before and after compression of tissue. The results are displayed as an elastographic image, which shows the relative stiffness of tissue[4,5].

In contrast, SWE, including the acoustic radiation force impulse imaging and the supersonic shear-wave imaging, can provide a quantitative assessment of stiffness by measuring the propagation speed of shear waves generated by acoustic radiation force[6]. In recent years, USE has been used for the clinical diagnosis and evaluation of breast tumors. It has been shown that breast cancer is characterized by increasing stiffness, and malignant breast lesions exhibited high stiffness not only in the lesion but also in the surrounding tissue, whereas benign lesions demonstrated low stiffness in both lesion and the surrounding area[7,8]. The content of collagen fiber of malignant lesions was significantly higher than that of benign lesions[9].

Shear-wave elastography is a recently developed ultrasound technique that can visualize and measure tissue elasticity. In breast ultrasound, SWE has been shown to be useful for differentiating benign breast lesions from malignant lesions, and it has been suggested that SWE enhances the diagnostic performance of ultrasound, potentially improving the specificity of conventional ultrasound using the breast imaging reporting and data system criteria. More recently, not only has SWE been proven useful for the diagnosis of breast cancer, but has also been shown to provide valuable information that can be used as a preoperative predictor of the prognosis or response to chemotherapy.

Prediction of Breast Cancer Prognosis and Response to Chemotherapy:

Breast cancer is considered to be a group of heterogeneous diseases, in terms of morphology, clinical course, and response to treatment. To characterize breast cancer and predict its prognosis accurately SWE is the mainstay of successful treatment. Clinicopathological features such as histological type, tumor size, histological grade, the presence of lymph node metastasis, and lympho-vascular invasion have been well established as prognostic factors of breast cancer. Shear wave elastography is a large invasive size; high nuclear grade, high histological grade, and lympho-vascular invasion were reported to be associated with increased stiffness of invasive breast cancer[10-13]. Estrogen receptor negativity, progesterone receptor negativity, p53 positivity and Ki-67 positivity were significantly associated with a higher ratio, and triple-negative and HER2-positive tumors showed greater stiffness than estrogen receptor-positive tumors[12,13]. Some aggressive tumors, such as high-grade cancers and triple-negative tumors, are likely to be assessed as BI-RADS category 3 in B-mode ultrasound, but SWE may provide additional information for diagnosing those benign-looking malignancies[12]. Predicting the axillary lymph node status in patients with newly diagnosed breast cancer is an integral component of breast cancer management, including the staging, treatment plan, prognosis[13]. Ultrasound has been performed for the noninvasive preoperative evaluation of the axillary nodal basin because it is widely available and easily incorporated into the standard workup for breast cancer patients[14]. Ultrasonographic criteria based on size or morphologic characteristics have shown variable diagnostic performance for metastatic lymph nodes[15]. SWE for sentinel axillary lymph node in patients with breast cancer[16,17], greater axillary lymph node stiffness was correlated with the risk of metastasis, and the high specificity of lymph node cortical stiffness can be complementary to B-mode ultrasound for decision-making regarding fine-needle aspiration biopsy.

Neoadjuvant chemotherapy (NAC) has been applied as an established treatment strategy for tumor down-staging in patients with breast cancer who would not be optimally treated by immediate surgery[18]. A complex pathologic response after NAC may be a predictor of a low risk of subsequent recurrence and longer disease-free survival[19,20]. However, the response to NAC can be quite variable. The early and accurate predictor of responsive and resistant to NAC is crucial to avoid futile chemotherapy and guide more effective treatment strategies, such as modifying the chemotherapy regimen optimizing the timing of surgery in nonresponsive patients. A clinical examination combined with conventional imaging modalities has not yet become sensitive or specific enough to predict pathologic response to NAC. Considering that tumor stiffness is related to the collagen content in the stoma, stomal stiffness measured by SWE may be useful as an imaging biomarker for stomal structural abnormalities and the response to NAC[21]. Tumor elasticity measured by SWE before NAC had a significant relationship with a subsequent reduction in the cellularity of the primary tumor response to NAC[22]. During NAC, the relative change in tumor elasticity showed a significant correlation with the response to NAC, and the second NAC cycle was recommended as the optimal time point for performing SWE evaluations to reduce the change of unnecessary cytotoxic exposure or to perform surgery in patients with NAC resistance[23].

Limitations of Breast Ultrasound Elastography:

With a growing clinical interest in developing new USE applications, or refining existing ones, it is essential to understand current technical limitations that hinder reproducibility of measurements. Several technical confounders are known to affect USE. A number of these can be traced back to general sonography limitations such as shadowing, reverberation, and clutter artifacts, or the operator-dependent nature of

free-hand ultrasound system. Tissue attenuation decreases ultrasound signal as a function of depth, limiting accurate assessment of deeper tissue or organs. Fluid or subcutaneous fat also attenuates propagation of the external stimulus applied at the skin surface, which can invalidate measurements in the setting of obesity or abdominal ascites. System setting and parameters can also produce biased results if not standardized across patient groups and time points in longitudinal applications. Measurements are highly subjective since the magnitude of the applied stress is difficult to control with operator dependent manual compression and the inherent variability of physiologic motion when used as a stimulus. Selection of the RIO is also operator dependent and can introduce variability. Elastogram color coding and scoring are not standardized. Occasionally a malignant lesion may appear soft in SWE. The surrounding tissue should then be carefully studied to help identity the stiffest part of the lesion. The increased shear wave speed in the surrounding tissues is relevant to help characterize the lesion as malignant. It is difficult to characterize heterogeneous lesions with mixed benign and malignant features. Some benign lesions may also be stiff. Masses in the posterior breast are difficult to assess because deep tissues may not be displaced by compression forces applied at the breast surface.

Conclusions:

Breast elastography is now an adjunct tool in breast ultasonography. It is easily performed in clinical practice, adding only a short amount of time to breast ultrasound. To ensure the best possible performance of elastography in the diagnosis of breast cancer, the technique should be optimized to acquire high-quality images, and practitioners should properly interpret the acquired data and images. Evaluation of breast lesion is the best validated applications of USE and has been widely adopted for non-invasive detection and staging of cancer as well as treatment response. There is encouraging data that USE may also be used to assess malignancy of breast and lymph nodes. It is a recently developed ultrasound technique that can visualize and measure tissue elasticity, has been shown to be useful for differentiating benign breast lesions from malignant breast lesions and also been shown to provide valuable information that can be used as a preoperative predictor of the prognosis or response to chemotherapy.

References :

1. Gennisson JL, Deffieux T, Fink M, Tanter M. Ultrasound elastography: principles and techniques. Diagnostic and interventional Imaging 2013; 94:487-95.

2. Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part I: basic principles and terminology. Ultrasound in medicine & biology 2015; 41:1126-47.

3. Hooley RJ, Scoutt LM, Philpotts LE. Breast ultrasonography: state of the art. Radiology 2013; 268:642-59.

4. Itoh A, Uneo E, Tohon E, Kamma H, Takahashi H, Shiina T, et al. Breast disease: clinical application of US elastography for diagnosis. Radiology 2006; 239:341-50.

5. Balleyguier C, Ciolovan L, Ammari S, Canale S, Sethom S, AI Rouhbane R, et al. Breast elastography: the technical process and its applications. Diagn Interv Imaging 2013; 94:503-13.

6. Bercoff J, Tanter M, Fink M. Supersonic Shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans Ultrasound Ferroelectr Freq Control 2004; 51:396-409.

7. Yi A, Cho N, Chang JM, Koo HR, La Yun B, Moon WK. Sonoelastography for 1,786 non-palpable breast massess: diagnostic value in the decision to biopsy. Eur Radiol. 2012; 22(5):1033-40.

8. Zhou J, Zhan W, Dong Y, Yang Z, Zhou C. Stiffness of the surrounding tissue of breast lesions evaluated by ultrasound elastography. Eur Radiol. 2014; 24(7):1659-67.

9. Wang ZI, Sun L, Li Y, Li N. Relationship between elasticity and collagen fiber content in breast disease: a preliminary report. Ultasonics. 2015; 57:44-9.

10. Youk JH, Gweon HM, Son EJ, Kim JA, Jeong J. Shear-wave elastography of invasive breast cancer: correlation between quantitave mean elasticity value and immunohistochemical profile. Breast Cancer Res Treat. 2013; 138:119-26.

11. Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, et al. Invasive breast cancer: relationship between shear-wave elastographic findings and histologic prognostic factors. Radiology 2012; 263:673-77.

12. Choi WJ, Kim HH, Cha JH, Shin HJ, Kim H, Chae EY, et al. Predicting prognostic factors of breast cancer using shear wave elastography. Ultrasound Med Biol. 2014; 40:269-74.

13. Chang JM, Park IA, Lee SH, Kim WH, Bae MS, Koo HR, et al. Stiffness of tumours measured by shear-wave elastography correlated with subtypes of breast cancer. Eur Radiol. 2013; 23:2450-58.

14. Humphery KL, Saksena MA, Freer PE, Smith BL, Rafferty EA. To do or not to do: axillary nodal evaluation after ACOSOG Z0011 Trial. Radiographics 2014; 34:1807-16.

15. Moorman AM, Bourez RL, de Leeuw DM, Kouwenhoven EA. Preoperative ultrasonographic evaluation of axillary lymph nodes in breast cancer patients: for which group still of additional value and in which group cause for specialattention? Ultrasound Med Biol. 2015; 41:2842-48.

16. Alvarez S, Anorbe E, Alcota P, Lopez F, Alonso I, Cortes J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a review. AJR Am J Roentgenol. 2006; 186:1342-48.

17. Tourasse C, Denier JF, Awada A, Gratadour AC, Nessah-Bousquet K, Gay J. Elastography in the assessment of sentinel lymph nodesprior to dissection. Eur J Radiol. 2012; 81:3154-59.

18. Kilic F, Velidedeoglu M, Ozturk T, Kandemiril SG, Dikici AS, Er.ME, et al. Ex vivo assessment of sentinel lymph nodes in breast cancer using shear wave elastography. J ultrasound Med. 2016; 35:271-77.

19. Ma. Y, Zhang S, Zang L, Li J, Li J, Kang Y, et al. Combination of shear wave elastography and Ki-67 index as a novel predictive modality for the pathological response to neoadjuvant chemotherapy in patients with invasive breast cancer. Eur J Cancer 2016; 69:86-101.

20. Ma Y, Zhang S, Zang L, Li J, Li J, Kang Y, et al. Comparison of strain and shear-wave ultrasonic elastography in predicting the pathological response to neoadjuvant chemotherapy in breast cancers. Eur Radiol. 2017; 27:2282-91.

21. Jing H, Cheng W, Li ZY, Ying L, Wang QC, Wu T, et al. Early evaluation of relative changes in tumor stiffness by shear wave elastography predicts the response to neoadjuvant chemotherapy in patients with breast cancer. J Ultrasound Med. 2016; 35:1619-27.

22. Evans A, Armstrong S, Whelehan P, Thomson K, Rauchhaus P, Purdie C, et al. Can shear-wave elastography predict response to neoadjuvant chemotherapy in women with invasive breast cancer? Br J Cancer 2013; 109:2798-2802.

23. Athanasiou A, Latorre-Ossa H, Criton A, Tardivon A, Gennissom JL, Tanter M. Feasibility of imaging and treatment monitoring of breast lesions with three-dimensional shear wave elastography. Ultraschall Med. 2017; 38:51-59.