Benefit of Shear-wave Elastography in the differential diagnosis of breast lesion: a diagnostic meta-analysis

Jie Luo, Yong Cao, Weiqi Nian, Xiaohua Zeng, Hui Zhang, Yeli Yue, Feng Yu

Department of Breast Disease Surgery, Chongqing University Cancer Hospital, Chongqing Cancer Institute, Chongqing Cancer Hospital, Chongqing, China

Abstract

Aims: The purpose of this diagnostic meta-analysis was to explore the benefit of shear wave elastography (SWE) combinedly used with conventional ultrasound (US) in the diagnosis of the benign and malignant breast lesion. Material and methods: After a literature search on MEDLINE, Cochrane library, and Embase we included 14 studies with a total 1951 patients and 2060 breast lesions for further analyses. Summary descriptive statistics such as pooled sensitivity, specificity, and summary receiver operating characteristics curve were generated via a bivariate random effect model. Summary indicators such as area under curve (AUC) and confident region were used to compare the performance of conventional US and combination of conventional US and shear wave imaging (SWI) or two-dimensional and three-dimensional SWI. Results: As indicated by the results, the pooled sensitivity, specificity, and diagnostic odds ratio for combined usage of SWE and the conventional US were 0.877 (95%CI: 0.855-0.896) and 0.849 (95%CI: 0.826-0.869) and 40.164 (95%CI:31.135- 51.811). The AUC for combined use and the conventional US only were 0.928 and 0.899, suggesting a promise of integrating SWE in the routine of breast lesion examination. Also, the summary AUC for 2D and 3D SWE were 0.917 and 0.952 respectively. No significant difference was found between 2D and 3D SWE. No obvious publication bias was identified after employing Deeks’ regression test for asymmetry. Conclusion: Our analysis concluded that SWE improved the differential diagnosis of the breast lesion.

Keywords: Ultrasonography; Shear wave elastography (SWE); breast lesion; meta-analysis; diagnosis

Introduction

Breast cancer is associated with high morbidity and, by far, is the most commonly-seen cancer in females. Breast physical examination, mammography, and ultrasonography (US) has been widely used for diagnosis of breast tumors. However, a lack of clear quantitative evidence from the above methods hinders the reproducibility of measurements.

In the last decades, different sonographic methods have been used in the diagnosis of malignant breast lesions by determining the relationship between their structures and tissue elasticity. Sonoelastography, a technique using ultrasound to evaluate elasticity (tissue stiffness) by calculating the ratio of applied stress and the resultant tissue deformation to quantitatively image Young’s E modulus [1,2], renders advantages over biopsy especially when fibrosis is diffuse. Due to its low cost, real-time capacities, and portability, elastography was highly regarded as a valuable adjunct to replace or reproduce the palpation performed by clinicians. There are two major elastographic approaches: static (strain) and transient (Vibration; shear wave) elastography, in which static elastography employs constant stress to the tissue and the resulting strain are often represented as a colored map (elastogram). Elastographic scores (ES) and strain ratio (SR), two diagnostic indicators for static elastography (SE), are subjective semi-quantitative measurements which are associated with interobserver variability. In
contrast to SE, shear wave elastography (SWE) applies a time-varying approach to generate transverse shear waves propagating at a speed that is directly related to the medium shear modulus [3-5]. Measurement of the shear wave produces real-time quantitative estimates of tissue elasticity which is highly reproducible compared to SE. Currently, there are three technical approaches for SWE: 1) One-dimensional transient elastography (1D-SWE); 2) Point shear wave elastography (pSWE, former acoustic radiation force impulse elastography), and 3) Two-dimensional shear wave elastography (2D-SWE) such as virtual touch imaging quantification (VTIQ). As indicated by evidence from several meta-analyses aimed at comparing SWE and conventional ultrasound, SWE provides good sensitivity and specificity (>80%) during differential diagnosis of benign and malignant breast lesion [6-9].

Our primary purpose was to systematically review recent literature on the added value of SWE in differentiating benign and malignant tumors beyond conventional ultrasound. Furthermore, we also compared the diagnosis accuracy among the subtypes of SWE.

Materials and methods

Searching strategies

We searched articles from the Cochrane database, MEDLINE, and EMBASE published since Jan 2010 that examined diagnosis accuracy of SWE in differentiating benign and malignant breast lesions in May 2017. The search strategy included combinations of terms: “Shear wave elastography”, “Breast tumor”, “Breast lesion”, “Ultrasound”, “Accuracy”, “Sensitivity” and “Specificity”. The reference lists of retrieved articles were reviewed for screening potentially relevant studies.

Inclusion and exclusion criteria

Eligible studies should examine the performance of SWE in differentiating benign and malignant breast lesions. Two independent reviewers inspected titles and abstracts of the search results. Full texts of relevant studies were retrieved for further evaluation. To be included in the systematic review, studies had to meet the following inclusion criteria: 1) English-written; 2) Used SWE alone or in concert with conventional ultrasound to analyze quantitative characteristics of breast lesions; 3) At least 50 patients were included in the samples to guarantee enough sample size; 4) Data including true-positive (TP), true-negative (TN), false-positive (FP), false-negative (FN) were clearly reported; 5) Valid reference test such as histologic determination (biopsy or surgical specimen), clinical follow-up, or other imaging techniques were used; 6) Clearly states the specific SWE technology (i.e. 1D, 2D SWE or pSWE) that was employed. Reviews, case reports, and non-human studies were excluded. Different studies which analyzed the same samples of patients were also excluded. All studies had to be conducted with approval by an institutional review board (IRB) in which each patient provided informed consent.

Data extraction

The following information were collected from each included study: publication year, last name of first author, demographic characteristics of patients (e.g., sample size, mean age, comorbidity, and lesion diameter), detailed information on SWE technique (subtypes and parameters for set-up), area under receiver operating characteristic curve (AUC), diagnostic accuracy and specificity, overall numbers of TP, TN, FP and FN data, diameter of region of interest (ROI), percentage of malignant or symptomatic breast lesions, and percentage of diagnoses confirmed by reference tests. The quality of each study was assessed by two independent observers with expertise in ultrasonic analysis via using the Quality Assessment of Studies of Diagnostic Accuracy in Systematic Review (QUADAS-2 tool), which consisted of 4 key domains. These were patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of risk of bias or concerns regarding applicability.

Statistical Analyses

All statistical analyses were performed using the R version 3.3.2 with functional packages mada. If available, analyses were stratified according to the subtypes of SWE. To pool the diagnostic performance of included studies, we first extracted or reconstructed the 2 by 2 contingency table for each study. If more than one diagnostic performance on the same imaging modality was reported, the one with the highest diagnostic accuracy was included. Summary descriptive statistics including the sensitivity, specificity and false-positive rate of the primary studies and also their positive and negative likelihood ratios (LR+, LR−), and their diagnostic odds ratio (DOR) were calculated by using a bivariate generalized linear mixed modeling (a random effects model). Forest plots were presented to graphically demonstrate the above summary statistics. Summary receiver operating characteristic (SROC) curves with 95% confidence intervals (95% CIs) were constructed to quantitatively compare or summarize the results for diagnostic performance with varying diagnostic thresholds.

Publication bias was assessed by using Deeks’ funnel plot asymmetry test after constructing a funnel plot of the natural logarithm of diagnostic odds ratio (lnDOR) versus the inverse of the square root of the effective sample size (1/ESS1/2). A significant publication bias was defined with
a $p$-value less than 0.05 for the slope coefficient. Heterogeneity among the included studies was assessed by using the inconsistency index ($I^2$) statistics. $I^2$ values greater than 50% was considered to indicate substantial heterogeneity.

**Results**

**Search results**

As shown in figure 1, a total of 169 studies were found after initial search. Finally, 14 studies [10-23] were included in our diagnostic meta-analysis.

**Study characteristics**

Characteristics of the 14 selected studies were summarized in Table I. A total of 1951 patients and 2060 breast lesions were included as study targets. The studies were conducted across South Korea, United States, United Kingdom, Italy, China, and France. Four out of eight studies explicitly specified that the data collection was prospective and retrospective. Biopsy, surgical excision, and follow-up observation were used as a reference standard to confirm benign and malignant breast lesions. The average age of the patients was above 40 years old and the mean size of the lesion was heterogeneous among the studies. Most of the studies aimed at comparing the diagnostic performance of SWE with conventional B-mode ultrasound. Subtypes of SWE such as combo-push SWE (CPSE), point SWE, 2D, and 3D SWE were employed. The majority of studies did not specify subtype of breast lesions, apart from 3 studies which clearly described their targets as breast non-mass lesion or papillary lesion. Diagnostic measures for shear wave imaging (SWI) in differentiating benign and malignant breast lesions were mean, maximum, ratio or standard deviation of elasticity value ($E_{\text{mean}}, E_{\text{max}}, E_{\text{ratio}}, \text{or } E_{\text{sd}}$).

**Primary analyses**

The pooled diagnostic accuracy of combined conventional US and SWI (named as the SWE group) without consideration of the subtypes of the SWI technique were visualized as a forest plot (fig 2). After meta-analysis the pooled sensitivity and specificity of the SWE group was 0.877 (95%CI: 0.855-0.896) and 0.849 (95%CI: 0.826-0.869), respectively. The pooled diagnostic OR (DOR), LR+, and LR- were 40.164 (95%CI:31.135-51.811), 5.805 (95%CI: 5.024-6.707), and 0.145 (95%CI:0.122-0.171), respectively. Chi-squared test of equality was used to inspect heterogeneity of sensitivity and specificity across the 14 studies. As shown by the results, heterogeneity existed in sensitivity ($p<0.001$) and specificity ($p=0.001$) in our selected studies. In addition, a random effects model following the approach of Der Simonian and Laird $I^2$ statistics were applied to summarize DOR. We also found no significant heterogeneity in DOR ($I^2=2.989\%, p=0.417$) among the included studies. To generate summary ROC, we employed a bivariate normal model for the logit-transformed pairs of sensitivities and false positive rates (fig 3, summary AUC=0.928).

**Subgroup analysis**

3D SWE has come into use as a new technique in recent years and was hypothesized to provide more de-
<table>
<thead>
<tr>
<th>Study, country</th>
<th>Study design</th>
<th>Study reference standard</th>
<th>IY</th>
<th>N</th>
<th>Age* (years)</th>
<th>SWE</th>
<th>Lesion size* (mm)</th>
<th>NL</th>
<th>Malignant lesion (%)</th>
<th>Diagnostic measure</th>
<th>Lesion type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi 2017 [10], South Korea</td>
<td>R</td>
<td>Biopsy Surgical excision</td>
<td>2014</td>
<td>199</td>
<td>51.7 (13.3)</td>
<td>2D/3D + B mode</td>
<td>16.6 (10.2)</td>
<td>205</td>
<td>51.2</td>
<td>Emax</td>
<td>Emean</td>
</tr>
<tr>
<td>Yang 2017 [11], China</td>
<td>R</td>
<td>Biopsy Surgical excision</td>
<td>2016</td>
<td>218</td>
<td>45.3 (14.6)</td>
<td>2D + B mode</td>
<td>15.7 (9.0)</td>
<td>225</td>
<td>20.9</td>
<td>Esd</td>
<td>Emean</td>
</tr>
<tr>
<td>Bayat 2017 [12], USA</td>
<td>P</td>
<td>Biopsy Follow-up</td>
<td>2014</td>
<td>223</td>
<td>59.9 (14.9)</td>
<td>CPSE</td>
<td>18.3 (2.45)</td>
<td>227</td>
<td>48.4</td>
<td>Emx</td>
<td>Emean</td>
</tr>
<tr>
<td>Chen 2016 [13], China</td>
<td>R</td>
<td>Biopsy Surgical excision</td>
<td>2016</td>
<td>198</td>
<td>49.1 (11.1)</td>
<td>3D + B mode</td>
<td>19.5 (7.14)</td>
<td>198</td>
<td>63.1</td>
<td>Esd</td>
<td>Emean</td>
</tr>
<tr>
<td>Youk 2013, [14], South Korea</td>
<td>/</td>
<td>Biopsy Surgical excision</td>
<td>2012</td>
<td>123</td>
<td>46.7 (11.2)</td>
<td>pSWE + B mode</td>
<td>13.0 (7.7)</td>
<td>130</td>
<td>37.7</td>
<td>Esd</td>
<td>Emean</td>
</tr>
<tr>
<td>Evans 2010 [15], UK</td>
<td>R</td>
<td>Biopsy</td>
<td>/</td>
<td>52</td>
<td>53</td>
<td>2D + B mode</td>
<td>12</td>
<td>53</td>
<td>56.6</td>
<td>Emean</td>
<td>Solid breast mass</td>
</tr>
<tr>
<td>Park 2017 [16], South Korea</td>
<td>R</td>
<td>Follow-up Surgical excision</td>
<td>2015</td>
<td>147</td>
<td>47</td>
<td>2D + B mode</td>
<td>20</td>
<td>152</td>
<td>52</td>
<td>Emean</td>
<td>Non-mass</td>
</tr>
<tr>
<td>Chung 2016 [23], South Korea</td>
<td>R</td>
<td>Biopsy Surgical excision</td>
<td>2013</td>
<td>71</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>79</td>
<td>7.6</td>
<td>Emax/min</td>
<td>Papillary</td>
</tr>
<tr>
<td>Wang 2017 [24], China</td>
<td>/</td>
<td>Biopsy Surgical excision</td>
<td>2009</td>
<td>63</td>
<td>40.1 (21.2)</td>
<td>2D + B mode</td>
<td>/</td>
<td>67</td>
<td>49.3</td>
<td>Emax/min</td>
<td>Non-mass</td>
</tr>
<tr>
<td>Choi 2016 [21], South Korea</td>
<td>R</td>
<td>Biopsy</td>
<td>2013</td>
<td>113</td>
<td>48.4 (10)</td>
<td>2D + color Doppler</td>
<td>27.5 (15.7)</td>
<td>116</td>
<td>63.8</td>
<td>Emax</td>
<td>Non-mass</td>
</tr>
<tr>
<td>Skerl 2015[17], UK</td>
<td>R</td>
<td>Biopsy Surgical excision</td>
<td>2012</td>
<td>206</td>
<td>57.9</td>
<td>2D + B mode</td>
<td>16</td>
<td>210</td>
<td>66.7</td>
<td>Emean</td>
<td>Solid breast mass</td>
</tr>
<tr>
<td>Tang 2015 [20], China</td>
<td>P</td>
<td>Biopsy/ follow-up</td>
<td>2014</td>
<td>98</td>
<td>56.3 (12.2)</td>
<td>2D + color Doppler</td>
<td>22.5 (14.7)</td>
<td>133</td>
<td>19.5</td>
<td>SWV</td>
<td>/</td>
</tr>
<tr>
<td>Chang 2011 [19], South Korea</td>
<td>P</td>
<td>Biopsy Surgical excision</td>
<td>2010</td>
<td>158</td>
<td>48.1</td>
<td>2D+ B mode</td>
<td>/</td>
<td>182</td>
<td>48.9</td>
<td>Emean</td>
<td>/</td>
</tr>
<tr>
<td>Feldmann 2015 [18], France</td>
<td>P</td>
<td>Biopsy</td>
<td>2011</td>
<td>82</td>
<td>51</td>
<td>2D+Bmode</td>
<td>17 (6)</td>
<td>83</td>
<td>45.8</td>
<td>Emean</td>
<td>/</td>
</tr>
</tbody>
</table>

IY – Inclusion year; N – number of patients; NL – number of lesions; * – Expressed in mean (median) years; R – Retrospective; P – Prospective; SWE – shear wave elastography; 2D – Two-dimensional SWE; 3D – three-dimensional SWE; CPSE – Comb-push Ultrasound ShearElastography; pSWE – Point shear wave elastography; Emax/min – maximum/minimum of elasticity value; Emean – mean elasticity value; Esd – standard deviation of elasticity value; Eratio – ratio of elasticity values
tailed and comprehensive information on the data of tissue elasticity compared to 2D SWE. In our subgroup analysis, we were interested in comparing the diagnostic performance of 2D and 3D SWE in differentiating benign and malignant breast lesions. Similarly, we used bivariate diagnostic random-effects meta-analysis to estimate pooled diagnostic accuracy. SROC for 2D (n=11) and 3D SWE (n=2) were shown in fig 4. The pooled sensitivity for 2D and 3D SWE were 0.865 (95%CI: 0.790-0.916) and 0.959 (95% CI: 0.877-0.987). Summary AUC for 2D and 3D SWE were 0.917 and 0.952, respectively. As seen in the overlapped confident region between 2D and 3D SWE, no significant difference in diagnostic performance was found between 2D and 3D SWE.

Conventional US versus combination of SWE and US

We were interested in the added value of SWI when combined with the conventional US. The combined diagnosis sensitivity and AUC for conventional US (n=9) alone were 0.965 (95%CI: 0.916-0.986) and 0.899. Compared to the results in our primary analyses, implementing the conventional US only during the diagnosis of breast lesions had a lower specificity and AUC than the combination of SWE and US (fig 5), suggesting an added value of SWE in the differential diagnosis.

Study quality

The study quality of each study was assessed by using the QUADAS-2 tool. Signaling questions are used to categorize the risk of bias as low, high, or unclear and were tailored to the questions for our systematic review. As shown in Table II, the included studies were generally of high quality.

Publication bias

Figure 6 displayed the Deeks’ effective sample size funnel plot on lnDOR and the regression test of asymmetry of the included studies. The regression test was not statistically significant (p=0.4562) suggesting symmetry in the data and a low likelihood of publication bias.

Discussions

An accurate diagnosis of the malignant lesion is extremely important in the early prevention of breast cancer. Traditional diagnostic methods such as biopsy and conventional US have shortcomings in terms of cost and
Benefit of Shear-wave Elastography in the differential diagnosis of breast lesion

reliability. SWE, as an adjunct for the conventional US, may improve the accuracy in differential diagnosis of benign and malignant breast tumors. In this study, we summarized the overall diagnostic performance of SWE beyond the conventional US based on recently available literature. Through a meta-analysis of the included studies with 1951 patients and 2060 breast lesions, we concluded that the sensitivity and specificity of combined use of conventional US and SWE were 0.877 and 0.849, respectively. The diagnostic performance in US and SWE group (AUC=0.928) was higher than conventional US group (AUC=0.899), suggesting a potential value of integrating SWE into the routine of breast lesion diagnosis. In addition, we performed a subgroup analysis on 2D and 3D SWE whose elasticity features were acquired by 2D and 3D techniques to compare their quantitative accuracy and we found there was no significant difference in improving diagnostic performance, although 3D SWE had a slightly higher AUC score than 2D SWE. By employing the QUADAS-2 tool and Deeks’ regression test of funnel asymmetry, we found that the included studies were generally of high quality and with no significant publication bias.

Several meta-analyses have reported similar results in the overall diagnosis performance of SWE in differentiating breast masses [6-9]. Their results also confirmed that SWE has a high sensitivity and specificity and demonstrated the potential of SWE in integrating into routine imaging protocols. Biopsy and surgical excision were regarded as a golden standard in the differentiated diagnosis of benign and malignant breast lesions, which provided information in a precise, quick, and relatively inexpensive manner. Meantime, they also caused discomforts which could be avoided by employing alternatives or adding an adjunct to the conventional methods that largely improve their diagnostic accuracy. SWE could quantitatively establish increased stiffness of malignant breast lesions, representing a promise of clinical usefulness. The recent development of ultrasound 3D shear wave technology further advances the diagnosis of malignant lesions. Unlike 2D modalities, 3D SWE evaluates images using individual planes (axial, sagittal, or coronal) [10]. Currently, few studies have reported the diagnostic performance of 3D SWE possibly due to the difficulty of integrating it with conventional 2D US.

Our study has several limitations: 1) We extracted optimistic diagnosis accuracy of SWE from the selected studies which provided multiple elasticity measures (i.e. Emean, Emax, and Esd) with different cut-off value. Despite the fact that the sensitivity and specificity derived from different shear wave values are of no significant heterogeneity, a potential inconsistency due to extracting data from different measures among the eligible studies may be caused; 2) We were unable to perform a subgroup analysis on different types of breast lesion even though 3 studies had specified their targets as papillary and non-mass-like lesions. Also, lesions with different BI-RADAS categories may influence the performance of SWI; 3) Only two 3D studies were found to be able to be included in our meta-analysis, which made the comparison between 2D and 3D SWE in differentiating malignant breast lesions less convincing. Multi-center prospective studies with a substantial study population or breast lesions using 3D SWE are required for further elucidation of the advantages of 3D SWI technique.
Conclusion

Our meta-analysis showed that SWE improved the differential diagnosis of breast lesions.

Acknowledgments: This study was supported by Chongqing Science and Technology Committee (Grant No.: cstc2016shmszx0327).

Conflict of interest: none

References