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● *Review*

META-ANALYSIS: CONTRAST-ENHANCED ULTRASOUND VERSUS CONVENTIONAL ULTRASOUND FOR DIFFERENTIATION OF BENIGN AND MALIGNANT BREAST LESIONS

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Abstract—This meta-analysis aimed to compare the diagnostic performance of contrast-enhanced ultrasound (CEUS), conventional ultrasound (US) combined with CEUS (US + CEUS) and US for distinguishing breast lesions. From thorough literature research, studies that compared the diagnostic performance of CEUS versus US or US + CEUS versus US, using pathology results as the gold standard, were included. A total of 10 studies were included, of which 9 compared the diagnostic performance of CEUS and US, and 5 studies compared US + CEUS and US. In those comparing CEUS versus US, the pooled sensitivity was 0.93 (95% CI: 0.91–0.95) versus 0.87 (95% CI: 0.85–0.90) and pooled specificity was 0.86 (95% CI: 0.84–0.88) versus 0.72 (95% CI: 0.69–0.75). In studies comparing US + CEUS versus US, the pooled sensitivity was 0.94 (95% CI: 0.92–0.96) versus 0.87 (95% CI: 0.84–0.90) and pooled specificity was 0.86 (95% CI: 0.82–0.89) versus 0.80 (95% CI: 0.76–0.84). In terms of diagnosing breast malignancy, areas under the curve of the summary receiver operating characteristic (of both CEUS ($p = 0.003$) and US + CEUS ($p = 0.000$) were statistically higher than that of US. Both CEUS alone and US + CEUS had better diagnostic performance than US in differentiation of breast lesions, and US + CEUS also had low negative likelihood ratio. (E-mail: xiangfx@hotmail.com)

Key Words: **Breast, Ultrasonography, Contrast, Diagnosis, Meta-analysis.**

INTRODUCTION

Globally, breast cancer is the most common cancer and the leading cause of cancer death among women (Torre et al. 2015). High-frequency ultrasonography has become the first-line imaging modality in evaluation of breast lesions because of its widespread availability, non-invasiveness and low cost. However, conventional ultrasound (US) faces some limitations in differentiating benignity from malignancy because of overlapping sonographic findings in some cases (Zhi et al. 2007). Unlike conventional US, the newly emerging contrast-enhanced ultrasound (CEUS) helps evaluate blood distribution and perfusion of tumors, thus offering more valuable information for lesion differentiation (Harvey et al. 2015; Ishii et al. 2017; Lekht et al. 2016).

However, the capability of CEUS to diagnose breast cancer accurately remains unclear. A meta-analysis of 16 studies found that the pooled sensitivity and specificity of CEUS alone in diagnosing breast cancers were 0.86 and 0.79 (Hu et al. 2015), which were similar to the sensitivity (0.82–0.95) and specificity (0.71–0.79) of conventional US reported in several studies (Du et al. 2012; Liu et al. 2008; Xiao et al. 2016). This difference was ascribed to CEUS's capability to delineate the morphologic features of breast masses, which conventional US does not

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possess. Therefore, to make full use of the sonographic information offered by each technique, conventional US and CEUS (US + CEUS) were combined. Although several studies found improved sensitivity (US + CEUS: 0.88–0.97 versus US: 0.82–0.89) and specificity (US + CEUS: 0.82–0.93 versus US: 0.78–0.79) (Du et al. 2012; Wang et al. 2011; Xiao et al. 2016), no improvement was found in other studies (Fujimitsu et al. 2016; Sorelli et al. 2010).

Until now, no meta-analysis has compared the diagnostic performance of CEUS and US or US + CEUS and US in differentiating breast cancers. Here we systematically reviewed the literature *via* a meta-analysis to compare the diagnostic performance of these ultrasound techniques on benign and malignant breast lesions, using pathologic results as the reference standard.

METHODS

Our meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). We included studies of patients suspected of having one breast mass or more, using (i) US and CEUS or (ii) US and US + CEUS as diagnostic methods, histopatholog or cytologic results for comparison and reporting true positive (TP), false positive (FP), true negative (TN) and false negative (FN) and the study type was diagnostic test.

Search strategy

We searched online all published studies without language restrictions from the earliest available date of indexing to August 31, 2016, in the PubMed, EMBASE and Cochrane Library databases. We also searched the most comprehensive Chinese academic databases in medicine: China National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database. The references of retrieved articles were also searched manually. The search strategy included the following terms: ("contrast enhanced ultrasound" OR "contrast enhanced ultrasonography" OR "CEUS") in combination with ("breast") and ("ultrasound" OR "ultrasonography" OR "sonography"). The search strategy for Chinese papers was similar to that used for English papers (S1 File).

Study selection

All published studies that compared the diagnostic accuracy of CEUS, US + CEUS and US for breast lesions were identified. Study selection was performed independently by two researchers. If disagreements occurred, a third reviewer made the adjudication. First, the titles and abstracts were screened to determine the potential usefulness of the articles, followed by full-text screening according to the following criteria (i) patients suspected of having breast mass, (ii) studies obtained informed consent from each study participant and approved by an ethics committee or institutional review board, (ii) index tests: both US and CEUS or both US and US + CEUS were used for diagnostic purposes, (iv) studies compared the performance of CEUS and US or US + CEUS and US for differentiating benign from malignant breast masses, (v) studies of harmonic-mode CEUS, (vi) reference standard was either histopathology or cytology and (vii) TP results and FN results or TN results and FP results were available or could be derived adequately. Exclusion criteria were (i) case reports or case series, review articles, letters, comments; (ii) studies of contrast-enhanced power or color Doppler sonography; (iii) duplicate publications in different databases and studies, using the same study population from the same institution; (iv) fewer than 15 cases confirmed by reference standard; and (v) postsurgical studies.

Data extraction

Two authors independently extracted the data from eligible studies and discrepancies were resolved by discussion. Adjudication by a third investigator was performed when disagreements occurred. Extracted information included (i) first author name, (ii) year of publication, (iii) age, (iv) number of patients, (v) number of masses, (vi) total number of malignant masses, (vii) mass long axis and (viii) reference standard. The diagnostic accuracy data on each index test and number of TP, TN, FP and FN findings for each index test were recorded or calculated. Sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR–) were extracted or calculated as follows: sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), LR + = sensitivity/(1– specificity) and LR– = (1– sensitivity)/ specificity. If more than one CEUS criterion was used in one individual report, the data from the one with the highest Youden index or area under the curve (AUC) were extracted or calculated.

To ensure the consistency of patients and methods in the included studies, we extracted, pooled and compared the diagnostic accuracy of US and CEUS from the literature that compared these two techniques (group 1). Studies comparing US and US + CEUS were classified into another group (group 2).

Quality assessment

All included studies were assessed for methodologic quality by two authors independently, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting 2011). If the two readers disagreed, a third reader adjudicated. None of the readers was involved in any of the included studies. The QUADAS-2 checklist consists of four domains: patient selection, index test, reference standard and flow/timing. Based on several questions, each of the four domains was assessed for risk of bias, but only