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The added value of contrast-enhanced ultrasound to conventional ultrasound in differentiating benign and malignant solid breast lesions: a systematic review and meta-analysis

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AIM: To investigate the added value of contrast-enhanced ultrasound (CEUS) to the conventional ultrasound (US) in the diagnosis of breast lesions.

MATERIALS AND METHODS: PubMed, EMBASE, and Web of Science were searched for relevant studies published between 24 May 2005, and 29 October 2017. Studies incorporating CEUS into the conventional US were included. The reference standard was set by means of histopathological findings. The quality assessment of diagnostic studies (QUADAS) instrument was used to assess the quality of the included studies. Meta-Disc version 1.4. was used to calculate the sensitivity, specificity, summary receiver-operating characteristic (sROC) curves, and area under the curve (AUC). Meta-regression with Stata 12.0 was used to compare the diagnostic accuracy of the two techniques.

RESULTS: Five studies, comprising 992 patients, were eligible for this meta-analysis. For conventional US, the pooled sensitivity and specificity for were 0.87 (95% confidence interval [CI]: 0.84–0.91) and 0.80 (95% CI: 0.76–0.84), respectively, the AUC was 0.9049. For CEUS-rerated US, the pooled sensitivity and specificity were 0.93 (95% CI: 0.90–0.95) and 0.87 (95% CI: 0.84–0.90). The AUC was 0.9482. Meta-regression showed the sensitivity of CEUS-rerated US did not differ from conventional US (p=0.29), while specificity showed significant difference (p<0.01). There was evidence of between-study heterogeneity regarding sensitivity and specificity for both assessments.

CONCLUSIONS: Adding CEUS to conventional US could improve the diagnostic performance in differentiating benign from malignant solid breast lesions, whilst retaining high sensitivity, especially in Breast Imaging-Reporting and Data System (BI-RADS) 3–5 lesions. A uniform

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standard to distinguish benign from malignant lesions might be needed for further clinical application.

Introduction

Ultrasound (US) is a main adjunctive method for screening breast lesions, especially in Asian people, who characteristically have dense breasts.[1] The American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) proposed standardised diagnostic criteria in 2003, which was updated in 2013. The ACR defines BI-RADS 3 lesions as "probably benign" with a low chance of malignancy (<2%), and BI-RADS 4 lesions as "probably malignant" with a 2–95% chance of malignancy.[2,3] The ACR BI-RADS has standardised the treatment process and improved the diagnosis efficiency of breast lesions worldwide[4]; however, the low specificity troubles clinicians.[5,6] It has been reported that most patients with BI-RADS 4 lesions undergo biopsy (69–95% in the USA,[7] 50–64% in the UK[8]), whereas the majority of the results are benign.

During the progression of solid tumours, tumour angiogenesis plays an important role in the formulation of the vascular network derived from pre-existing vessels.[9] This fact allows for the potential of tumour flow detection in differentiating benign from malignant solid breast lesions. Conventional colour Doppler imaging was proven to add value to US in diagnosing breast lesions; however, Doppler imaging was characterised by low sensitivity to small vessels, especially in vessels <200 mm.[10,11] Contrast-enhanced US (CEUS) could exhibit more sensitive imaging for the visualisation of the morphology and flow of microvessels.[12] Several studies have investigated the use of CEUS in the diagnosis of breast cancers,[13–15] and a previous meta-analysis also concluded that CEUS has good sensitivity and specificity in characterising breast lesions[16]; however, because BI-RADS occupies a pivotal position in the diagnosis of breast lesions, it is important to investigate the added value of CEUS to conventional US and to explore the potential of CEUS to modify the BI-RADS grade. In recent years, several studies have focused on the diagnostic performance of CEUS-rerated US and improved the diagnostic accuracy[17–19]; however, there were no direct comparisons of these two techniques, and the combination patterns were different. Therefore, it is necessary to give a summary of these articles and to provide more evidence for the clinical application of this method.

In recent years, meta-analysis of diagnostic test accuracy (DTA) was developed by the Cochrane Group to summarise and compare the accuracy of tests.[20,21] The present study was a systematic review and meta-analysis to summarise the features of the combination method and to compare the diagnostic performance of conventional US and the combination method.

Materials and methods

Institutional review board approval was not required for this type of study at the authors' institutions. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[22]

Search strategy

PubMed, EMBASE, and Web of Science were searched systematically for relevant studies published in English between 24 May 2005, and 29 October 2017, using the combinations of keywords as follows: "contrast-enhanced ultrasonography OR contrast enhanced ultrasound OR CEUS" and "breast neoplasms [MeSH] OR breast lesions OR breast cancer OR breast" and "BI-RADS OR BIRADS". The reference lists of all relevant articles were also searched to identify additional studies. Two reviewers searched the database to obtain the original data, and disagreements were resolved by discussion.

Eligibility criteria

Studies were included in this meta-analysis if they fulfilled the following criteria: (I) studies that investigated the diagnostic performance of conventional US and CEUS rerated BI-RADS; (II) studies that provided true-positive (TP), false-positive (FP), false-negative (FN), true-negative (TN) or key information for calculation; (III) breast lesions determined by histopathological examination obtained from surgery or biopsy. For multiple studies of the same or overlapping population source by the same researchers, only data from the largest publication were included.

Data extraction and quality assessment

The data of the eligible full-text articles studies were extracted by two investigators (X.D.L. and M.M.) independently, and discrepancies were resolved by discussion and consensus. The following data were collected: first author, publication year, number of patients, number of lesions, mean age, diameters of the lesions, ultrasound contrast, diagnostic method, BI-RADS grade, diagnose threshold, TP, FP, TN, FN, and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) score. For studies with several multivariable-adjusted estimates, those studies reflecting the greatest degree of control for potential confounders were extracted. The QUADAS-2 score tool was used to assess the quality of the included studies in this meta-analysis and was assessed by two independent investigators (M.M. and M.W.).[23] Each trial was scored as high, low, or unclear risk of

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