Diagnostic Value of Contrast-Enhanced Sonography for Differentiation of Breast Lesions
A Meta-analysis

Xuelei Ma, MD, Rongjun Liu, MS, Chenjing Zhu, MD, Jing Zhang, MD, Wenwu Ling, MD

Objectives—The purpose of this study was to systematically review and evaluate the diagnostic accuracy of contrast-enhanced sonography in the differential diagnosis of benign and malignant breast lesions.

Methods—The scientific literature databases PubMed and Embase were comprehensively searched for relevant studies before January 2015. Data were pooled to yield the summary sensitivity, specificity, and diagnostic odds ratio using meta-analysis software.

Results—A total of 29 studies with 2296 lesions were included in the analysis. The pooled sensitivity and specificity were 0.88 (95% confidence interval [CI], 0.86–0.90; inconsistency index \( I^2 = 77.9\% \)) and 0.80 (95% CI, 0.78–0.83; \( I^2 = 84.0\% \)), respectively. The pooled diagnostic odds ratio was 30.35 (95% CI, 15.75–58.48; \( I^2 = 82.1\% \)), and the area under the summary receiver operating characteristic curve was 0.9115 (SE, 0.0243).

Conclusions—The comprehensive results suggest that contrast-enhanced sonography could be a potentially effective method for differential diagnosis of benign and malignant breast lesions.

Key Words—breast cancer; breast ultrasound; contrast-enhanced sonography; diagnosis; meta-analysis

Breast cancer is the leading cause of death in women with cancer, accounting for 23% of the total new cancer cases and 14% of the total cancer deaths, according to the Global Cancer Statistics in 2011.1 Due to the advances in many alternative medical treatment and diagnostic methods, the survival rate has had a slight increase in recent years.2 Detecting disease early has been proven as an effective strategy to reduce the breast cancer mortality rate.3 Currently, breast sonography is a routine application in clinical practice for cancer screening, as it is noninvasive, relatively inexpensive, widely available, and convenient. However, sonography cannot show the tumor microvascular architecture, and benign proliferative changes and fibroadenomas cannot be clearly differentiated from normal breast tissues on sonography, so breast sonography has shown relatively high sensitivity (≥90%) but low specificity (39.4%).4 In reality, the difference between contrast-enhanced sonography and conventional sonography in terms of sensitivity has been reported as 88.9% versus 55.6%.5 Core biopsy is usually used as the reference standard in the evaluation of breast lesions, but it is an invasive operation.6 Therefore, an effective noninvasive imaging method that can be used for differentiating suspicious breast cancer lesions is an urgent need in clinical settings.
Contrast-enhanced sonography has been developed to improve the diagnostic accuracy of sonography for differentiation of malignant lesions in the liver, kidney, pancreas, ovaries, and other organs. Contrast agents are injected intravenously into the systemic circulation. Microbubbles emit a nonlinear harmonic signal when insonated by low transmit power, while blood and surrounding tissues provide a weak signal; therefore, contrast-enhanced sonography could be used to evaluate tumor vascularity and tumor blood flow clearly. Early studies also suggested that first-generation contrast agents such as Levovist (Schering AG, Berlin, Germany) could improve the diagnostic accuracy of sonography. Over the past few years, progress in contrast agents was made, and second-generation contrast agents such as SonoVue (Bracco SpA, Milan, Italy) have been widely approved. Studies have shown that the diagnostic performance of contrast-enhanced sonography varies because of different research designs, sample sizes, contrast agents, and contrast modes, with the sensitivity ranging from 50% to 100% and the specificity from 37% to 100%. In addition, the performance of different types of contrast agents and contrast modes has not been evaluated thoroughly. Therefore, in this study, we assessed the performance of contrast-enhanced sonography in the differential diagnosis of benign and malignant breast lesions comprehensively, and we report the pooled performance of the different types of contrast agents and contrast modes.

Materials and Methods

Literature Search Strategy

Relevant studies published before January 2015 were identified through a comprehensive search of PubMed and Embase. Key words and medical subject headings were designed as follows: "breast, contrast-enhanced (or contrast enhanced, contrast agent)," "neoplasm (or carcinoma, tumor, cancer, mass, lesion)," and "ultrasound (or ultrasoundography, sonography)." We also performed a manual search by searching references of related articles to expand our included studies.

Inclusion and Exclusion Criteria

Articles assessing the performance of contrast-enhanced sonography in differentiating malignant from benign breast lesions were included according to the following criteria: (1) clinical studies focused on the diagnostic value of contrast-enhanced sonography in breast cancer; (2) the reference standard for lesion diagnosis was histopathologic findings; (3) studies offered sufficient data to construct a 2 × 2 table corresponding to true-positive, true-negative, false-positive, and false-negative rates; (4) the sample size must have been more than 10 patients; and (5) duplicate results needed to be eliminated.

Letters, reviews, editorials, and case reports were excluded. When 2 articles involving the same author(s) or from the same medical center had similar (but not the same) data and patient design, the article with the larger sample size was selected. Eligible studies were reviewed by 2 authors, who independently followed the above criteria. Disagreements were resolved by consulting a third author, and an agreement would be reached through discussion.

Data Extraction

The following data were extracted independently by 2 researchers: the first author’s name, publication year, geographic location, organizations, mean age of the patients, probe frequency, mechanical index, contrast agent, and contrast mode. True-positive, true-negative, false-positive, and false-negative rates were also collected directly or calculated according to the sensitivity, specificity, positive predictive value, and negative predictive value in every selected study. We also e-mailed the authors of the studies for additional information and the data needed.

Statistical Analysis

A summary of the sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio (OR) with corresponding 95% confidence intervals (CIs) was yielded by the true-positive, false-positive, false-negative, and true-negative rates from all studies, which could indicate the diagnostic performance of contrast-enhanced sonography for differentiation between malignant and benign breast lesions. In addition, we constructed a summary receiver operating characteristic curve by the Moses-Shapiro-Littenberg method to summarize the true-positive and false-positive rates from different studies. The inconsistency index ($I^2$ and $\chi^2$ test were used to detect heterogeneity among all studies. An $I^2$ value of greater than 50% was considered significant for heterogeneity. When heterogeneity existed, a random-effect model was used for our meta-analysis. The Deeks funnel plot asymmetry test was conducted to investigate publication bias. All of the above statistical analyses were performed in Stata version 12.0 software (StataCorp, College Station, TX) and MetaDiSc version 1.4 software.

Quality Assessment

To assess the quality of the studies included in this meta-analysis, Quality Assessment of Diagnostic Accuracy Studies
version 2 (QUADAS-2) was used as a systematic review assessment method, the form of which comprised of 4 domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter did not apply for the flow and timing domains) were analyzed and rated as low risk, high risk, and unclear risk. The QUADAS-2 was performed in Review Manager 5.2 (Cochrane Informatics and Knowledge Management Department, Copenhagen, Denmark).

Results

Study Selection
The initial search yielded a total of 440 publications after duplicates were removed. Then another 369 were excluded through the titles and abstracts. Full texts and data integrity were reviewed, and 42 articles were further excluded. All of the included studies did obtain informed consent from every participant, and each study was approved by an Ethics Committee or Institutional Review Board. Finally, 29 studies were considered eligible for our research. There were 3 authors who had published 2 articles. However, after careful review, we found that the patient samples in the articles with the same authors were studied at different times or examined by different ultrasound machines. Therefore, all 6 of these studies were considered eligible. The full screening and selection process is shown in Figure 1.

Characteristics of the Eligible Studies
The studies were published from 1996 to 2015. A total of 2234 patients and 2296 lesions were assessed. The number of lesions examined in the studies ranged from 15 to 498, and the mean number was 79. Types of contrast agents mentioned in the researches were Levovist, SonoVue, Optison (GE Healthcare, Chalfont St Giles, England), Sonazoid (Daichi Sankyo Co, Ltd), and Definity (Lantheus Medical Imaging, North Billerica, MA). Levovist was the first-generation contrast agent, and others were second-generation contrast agents. Types of contrast modes were power/color Doppler mode and harmonic mode. All of the characteristics extracted from the eligible studies are presented in Table 1.

Differentiation of Benign and Malignant Breast Lesions
The pooled sensitivity and specificity of the eligible studies were 0.88 (95% CI, 0.86–0.90; $I^2 = 77.9\%$) and 0.80 (95% CI, 0.78–0.83; $I^2 = 84.0\%$), respectively (Figure 2). The pooled positive and negative LRs for contrast-enhanced sonography were 4.20 (95% CI, 2.96–5.95; $I^2 = 87.9\%$) and 0.17 (95% CI, 0.11–0.25; $I^2 = 81.3\%$). The pooled diagnostic OR for contrast-enhanced sonography was 30.35 (95% CI, 15.75–58.48; $I^2 = 82.1\%$). The summary receiver operating characteristic curve for the value of contrast-enhanced sonography in the diagnosis of breast lesions is illustrated in Figure 3. The overall area under the curve (AUC) was 0.9115 (SE, 0.0243).

Subgroup Analysis
When we grouped the studies by contrast agent type, the pooled sensitivity, specificity, and diagnostic OR of the first-generation contrast agent group were lower than the values of the second-generation group. When we grouped the studies by contrast mode, the pooled sensitivity, specificity, and diagnostic OR of the power/color Doppler group were lower than the values of the harmonic mode group. Results of the above subgroup analyses in our meta-analysis are shown in Table 2.

Assessment of Publication Bias
The evaluation of publication bias in the eligible studies was performed by the Deeks funnel plot asymmetry test (Figure 4). Results showed that there was no significant publication bias for the diagnostic OR of contrast-enhanced sonography in the differentiation of benign and malignant breast lesions ($P = .12$).
Table 1. Characteristics of the Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Patients, n</th>
<th>Lesions, n</th>
<th>Mean Age, y</th>
<th>Frequency, MHz</th>
<th>MI</th>
<th>Contrast Mode</th>
<th>Contrast Agent</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
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<td>1996</td>
<td>34</td>
<td>34</td>
<td>49</td>
<td>7</td>
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<td>Levovist</td>
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<td>0</td>
<td>0</td>
<td>16</td>
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<td>Levovist</td>
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<td>SonoVue</td>
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<td>28</td>
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</table>

FN indicates false-negative; FP, false-positive; MI, mechanical index; 3D, 3-dimensional; TN, true-negative; TP, true-positive; 2D, 2-dimensional; and UC, unclear.

Figure 2. A. Forest plot of sensitivity of contrast-enhanced sonography for diagnosis of breast cancer. B. Forest plot of specificity of contrast-enhanced sonography for diagnosis of breast cancer.
Quality Assessment
Based on the updated QUADAS-2, the quality assessment of the included studies is outlined in Figure 5. Overall, the quality of the studies was satisfactory.

Discussion
In the 29 studies, diagnoses were made on the basis of contrast-enhanced sonography. For benign lesions, the patterns included strong or weak homogeneous enhancement and no enhancement of the entire lesion. In contrast, heterogeneous enhancement with or without clear defects, rapid wash-out from the lesion in comparison with the surrounding mammary tissues, and enhancement extending outward beyond the expected border of the lesion were the patterns for malignant lesions.

Our meta-analysis systematically evaluated the diagnostic performance of contrast-enhanced sonography for differential diagnosis between benign and malignant breast lesions. The pooled sensitivity and specificity were 0.88 and 0.80, respectively; the pooled positive and negative LR were 4.20 and 0.17; and the diagnostic accuracy as quantified by the AUC was 0.9115. These results suggest that contrast-enhanced sonography could be a considerable tool for distinguishing benign from malignant breast lesions.

Our results were consistent with a previous meta-analysis of the same topic published in 2015 by Hu et al. However, that meta-analysis only included 16 studies with 957 breast lesions published from 1996 to 2012. It was not a comprehensive meta-analysis, as 6 studies published during that period were missing. In addition, it did not perform a subgroup analysis according to sonographic modes, which is very important for evaluating the performance of contrast-enhanced sonography. After October 2012, more studies related to the topic were published. Most of the studies in the past 2 years used second-generation contrast agents, and the microbubbles were more stable and durable. The second-generation contrast agents can achieve high-quality perfusion imaging and influence the final sensitivity and specificity.

Table 2. Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Studies,n</th>
<th>Groups, n</th>
<th>Lesions, n</th>
<th>Sensitivity (95% CI; I², %)</th>
<th>Specificity (95% CI; I², %)</th>
<th>Diagnostic OR (95% CI; I², %)</th>
<th>AUC (SE)</th>
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<tr>
<td>All studies</td>
<td>29</td>
<td>31</td>
<td>2296</td>
<td>0.88 (0.86–0.90; 77.9)</td>
<td>0.80 (0.78–0.83; 84.0)</td>
<td>30.35 (15.75–58.48; 82.1)</td>
<td>0.9115 (0.0243)</td>
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<tr>
<td>First-generation</td>
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<td>11</td>
<td>582</td>
<td>0.86 (0.82–0.89; 88.8)</td>
<td>0.77 (0.72–0.82; 83.2)</td>
<td>26.34 (7.52–92.23; 84.3)</td>
<td>0.8062 (0.1078)</td>
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<td>18</td>
<td>1661</td>
<td>0.90 (0.88–0.92; 44.7)</td>
<td>0.85 (0.82–0.87; 73.9)</td>
<td>4719 (28.54–78.03; 45.4)</td>
<td>0.9388 (0.0122)</td>
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<td>Power/color Doppler</td>
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<td>15</td>
<td>758</td>
<td>0.85 (0.82–0.89; 86.0)</td>
<td>0.69 (0.65–0.74; 87.9)</td>
<td>18.69 (6.61–52.90; 83.4)</td>
<td>0.8785 (0.0670)</td>
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<td>15</td>
<td>1495</td>
<td>0.90 (0.87–0.92; 54.2)</td>
<td>0.87 (0.84–0.89; 30.4)</td>
<td>51.56 (30.63–86.84; 43.4)</td>
<td>0.9361 (0.0133)</td>
</tr>
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</table>

* A study by Forsberg et al, which used both Levovist and Optison as contrast agents, was excluded from the subgroup analysis of contrast agents.

Figure 3. Summary receiver operating characteristic (SROC) curve.

Figure 4. Deeks funnel plot of the publication bias summary for meta-analysis of the diagnostic odds ratio.
As contrast agents remain within the blood vessels and do not diffuse into the interstitial space, contrast-enhanced sonography can clearly show blood flow in breast lesions. Among our 29 eligible studies, 10 used Levovist, 14 used SonoVue, 2 used Optison, 1 used Sonazoid, 1 used Definity, and 1 used Levovist and Optison. In our study, the second-generation agent group had relatively finer diagnostic performance results compared with the first-generation group. This finding might have been a result of the different materials in the contrast agents. The first-generation contrast agents are covered by galactose and palmitic acids with microbubbles of air inside, whereas the second-generation agents contain inert gases inside, which increase their stability and duration. In addition, the flexible shells of the agents make it possible to use low acoustic power to get strong harmonics without destroying the bubbles.

Nowadays, contrast-enhanced sonography is performed with different contrast modes, including the power or color Doppler mode and the harmonic mode. Contrast-enhanced power or color Doppler sonography has relatively higher imaging discrimination than other conventional sonographic modes, but when combined with contrast agents, it is limited by the slow frame rate, and if the patient breathes or the ultrasound probe moves rapidly, motion artifacts will be enhanced. In addition, high acoustic power quickly destroys the microbubbles, so the stability and duration of the contrast will decrease. According to our results, contrast-enhanced power or color Doppler sonography had obviously low specificity, indicating that this mode might not be a good choice for detecting breast lesions. The contrast-enhanced harmonic mode, however, is a new technology, which can detect signal release when microbubbles are disrupted or resonated by ultrasonic beams. This technology detects signals from microbubbles with very slow flow without Doppler-related artifacts, and the images can be optimized by using a low mechanical index, allowing minimal bubble destruction and continuous real-time assessment of the microvascularization during uptake of the contrast medium. In our study, the diagnostic performance was significantly higher in the harmonic mode, suggesting that the use of this mode could increase diagnostic accuracy in breast cancer differentiation.

Substantial heterogeneity among the included studies was found. Subgroup analyses were conducted to investigate the potential sources of heterogeneity. Unfortunately, the heterogeneity could not be eliminated in the subgroup analyses. Potential sources could have come from data irregularities and different operators, machines, and contrast agents. To identify the potential sources, we created a Deeks funnel plot to assess publication bias in the...
included studies. However, no publication bias was detected; thus, publication bias could not be identified as a main source of heterogeneity.

Furthermore, this study had several potential limitations. First, we did not evaluate intraobserver and interobserver variability, which is an important issue because sonography is an operator-dependent procedure. Second, the breast lesions were classified as “benign” or “malignant” by quantitative or qualitative assessment for sonographic interpretations in different studies.53 However, we did not make a comparison between quantitative and qualitative assessment. Finally, the second-generation contrast agents can produce high-quality perfusion images and increase the performance of contrast-enhanced sonography, but nearly all of the studies using the second-generation contrast agents used the harmonic mode; thus, we could not explore which sonographic mode was more suitable for detecting breast lesions when using the advanced contrast agents because of a lack of data.

In conclusion, our study suggests that contrast-enhanced sonography is a promising and effective method for differential diagnosis of benign and malignant breast lesions. It may be a valuable supplement to fine-needle aspiration, which is still needed in cases of Breast Imaging Reporting and Data System category 3 and 4 lesions. In the subgroup analyses, the results suggested that the second-generation contrast agents might increase the diagnostic accuracy of contrast-enhanced sonography, and the harmonic mode might be more suitable for performing contrast-enhanced breast sonography. However, further studies are still required to confirm our findings.

References

Ma et al—Contrast-Enhanced Sonography for Differentiation of Breast Lesions


