

# Contrast-enhanced ultrasound in the diagnosis of endometrial carcinoma: A meta-analysis

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**Abstract.** The present study evaluated the diagnostic value of contrast-enhanced ultrasound (CEUS) in endometrial carcinoma (EC). Articles published until 31 January 2017 were retrieved from PubMed, EMBASE, Elsevier, Springer and Google scholar, with the following inclusion criteria: i) The accuracy (sensitivity and specificity) of CEUS in the diagnosis of EC was evaluated; ii) a gold standard was adopted to treat and confirm EC, including surgery, histopathology and appropriate follow-up (as included in the meta-analysis); iii) the data allowed for construction of a 2x2 table of positives, false-positives, negatives and false-negatives. Pooled estimates of sensitivity, specificity, risk ratios and diagnostic odds ratios (DOR) were calculated in the present meta-analysis of the accuracy of CEUS in diagnosing EC. The summary receiver-operating characteristics (sROC) curve was also constructed. Among the 93 relevant articles, 7 studies were finally selected according to the inclusion criteria with a sample size of n=275. The pooled sensitivity of CEUS in the diagnosis of EC was 84% [95% confidence interval (CI), 0.78-0.88], while the pooled specificity was 90% (95% CI, 0.86-0.92). The positive likelihood ratio (+LR) of CEUS was 8.0 (95% CI, 5.9-10.8) and the negative likelihood ratio (-LR) was 0.18 (95% CI, 0.13-0.25). The DOR was 44 (95% CI, 26-77). The area under the sROC curve was 0.93 with specificity of 0.90 (0.86-0.92) and sensitivity of 0.84 (0.78-0.88) for the summary operating point. Moderate heterogeneity was observed for sensitivity, specificity and DOR with  $I^2$  values of 32.56, 34.68 and 41.2%, respectively. No significant publication bias was observed for the DOR of CEUS. In conclusion, the present meta-analysis indicates that CEUS is valuable in the diagnosis of EC. Additional clinical data and studies are still required to confirm these results and to further develop the diagnostic application of CEUS in EC.

## Introduction

Among gynecological diseases, endometrial cancer (EC) is the most common one and a threat to the health of women worldwide; it usually occurs in perimenopausal women around the age of 50 years (1,2). Over the years, the incidence rate of EC has displayed a rising trend worldwide; however, the 5-year survival rate has gradually decreased (3). Since most patients with EC are at stage I at the time-point of diagnosis, pre-operative assessment provides benefits regarding the therapeutic strategy selection for EC.

Diagnostic methods for EC usually include ultrasonography, hysteroscopy and curettage. However, the rates of misdiagnosis and missed diagnosis are remain high (4). Common diagnostic methods, including curettage scraping (5), hysteroscopy (6), magnetic resonance imaging (7), positron emission tomography/computed tomography (8) or traditional transvaginal ultrasound (9), all have their advantages, as well as a certain insufficiency. Recently, contrast-enhanced ultrasonography (CEUS), which has been applied in the discrimination of benign from malignant adnexal masses (10,11), has attracted the attention of researchers and clinicians due to its potential in the diagnosis of EC. During the past 10 years, CEUS, which uses a microbubble contrast agent, e.g., SonoVue or Levovist, has significantly improved the diagnostic accuracy of ultrasonography in examining gynecological diseases, including ovarian tumors (12). Application of CEUS to determine myometrial invasion and the cancer stage in EC has also been reported in recent years; however, relevant studies remain inadequate.

To the best of our knowledge, to date, no previous study has summarized the accuracy of CEUS in the diagnosis of EC. In the present study, a meta-analysis was therefore performed to determine the accuracy of CEUS in diagnosing EC.

## Materials and methods

**Protocol.** The present meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (13).

**Study selection criteria.** Prior to searching the literature, certain selection criteria were set for the studies to set standards for determining the diagnostic value of CEUS in EC. The selection criteria were as follows: i) The accuracy (sensitivity and specificity) of CEUS in the diagnosis of EC

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Table I. Summary of studies included in the present meta-analysis.

Author, year	Country	Study type	Mean age (years)	Cases (n)	Modality	Contrast agent	(Refs.)
Wang, 2012	China	Retro	56	37	Color Doppler CEUS	SonoVue	(15)
Zhou <i>et al</i> , 2015	China	Prosp	50	68	2D and 3D CEUS	SonoVue	(16)
Song <i>et al</i> , 2009	China	Prosp	None	35	CEUS	SonoVue	(17)
Ding <i>et al</i> , 2013	China	Retro	55	40	Color Doppler CEUS	SonoVue	(18)
Liu <i>et al</i> , 2011	China	Retro	56	37	Color Doppler CEUS	SonoVue	(19)
Sun <i>et al</i> , 2008	China	Retro	55	30	Color Doppler CEUS	SonoVue	(20)
Zhang <i>et al</i> , 2011	China	Retro	None	28	Color Doppler CEUS	SonoVue	(21)

Prosp, prospective study; retro, retrospective study; CEUS, contrast-enhanced ultrasound; 2D, 2-dimensional.

was evaluated; ii) a gold standard was adopted to treat and confirm EC, including surgery, histopathology and appropriate follow-up and iii) the data allowed for construction of a 2x2 table for true-positives, false-positives, true-negatives and false-negatives.

**Literature search.** Articles published until 31 January 2017 were retrieved from PubMed, EMBASE, Elsevier, Springer and Google scholar. The search terms were a combination of the following key words: 'Ultrasonic angiography', 'endometrial carcinoma', 'contrast enhanced ultrasonography', 'sensitivity', 'specificity', 'positive predictive value' and 'negative predictive value'. A manual search was also performed through searching the reference lists of relevant articles to expand the number of included studies. In the case of insufficient data provided in a study, the authors were contacted. Only studies in English and Chinese language, which met the selection criteria, were included.

**Data collection and extraction.** Two independent observers reviewed abstracts to examine whether they qualified for inclusion according to the pre-defined criteria. Selected papers were then retrieved, evaluated for their eligibility, and relevant data were extracted by the two observers independently. A third observer was consulted when disagreements occurred. The following items were extracted according to a fixed protocol: Author, year of publication, country, study type, original study population, ultrasound modality and contrast agents. Diagnostic 2x2 contingency tables were constructed from the selected papers.

**Statistical analysis.** Pooled estimates of sensitivity, specificity, likelihood ratios [positive likelihood ratios,  $+LR = \text{sensitivity} / (1 - \text{specificity})$ ; negative likelihood ratios,  $-LR = \text{specificity} / (1 - \text{sensitivity})$ ] and diagnostic odds ratios (DORs) were calculated in the present meta-analysis of the accuracy of CEUS in diagnosing EC. The fixed-effects model and the random-effects model were used and heterogeneity result was also recorded. The summary receiver operating characteristics (sROC) curve was also constructed. Confidence intervals were calculated using the F distribution method (14). Forrest plots were drawn to illustrate the distribution of the data-points in each study in association with the summary pooled estimate. The heterogeneity of

Table II. Parameters for the analysis of CEUS accuracy in the diagnosis of EC.

Parameter	Estimate	95% CI
Sensitivity	0.84	(0.78-0.88)
Specificity	0.90	(0.86-0.92)
Positive likelihood ratio	8.0	(5.9-10.8)
Negative likelihood ratio	0.18	(0.13-0.25)
Diagnostic odds ratio	44	(26-77)

CEUS, contrast-enhanced ultrasound; EC, endometrial carcinoma; CI, confidence interval

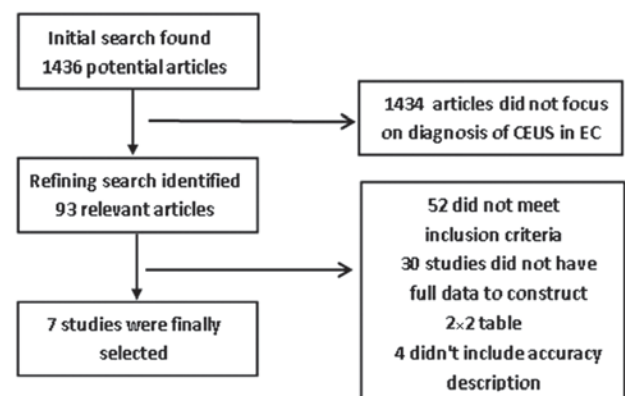


Figure 1. Search results. CEUS, contrast-enhanced ultrasound; EC, endometrial carcinoma.

the sensitivities and specificities were tested by applying the likelihood ratio test. Heterogeneity of the pooled studies was tested by using sROC curves as previously described (14). sROC curves were used to calculate the area under the curve (AUC). Publication bias was assessed using Deek's funnel plot asymmetry test, through  $P > 0.05$  suggesting no significant publication bias and with Review Manager 5.3 (Cochrane Collaboration, London, UK). All statistical analyses were performed using STATA 12.0 (STATA, College Station, TX, USA) except for the assessment of publication bias with Review Manager 5.3.

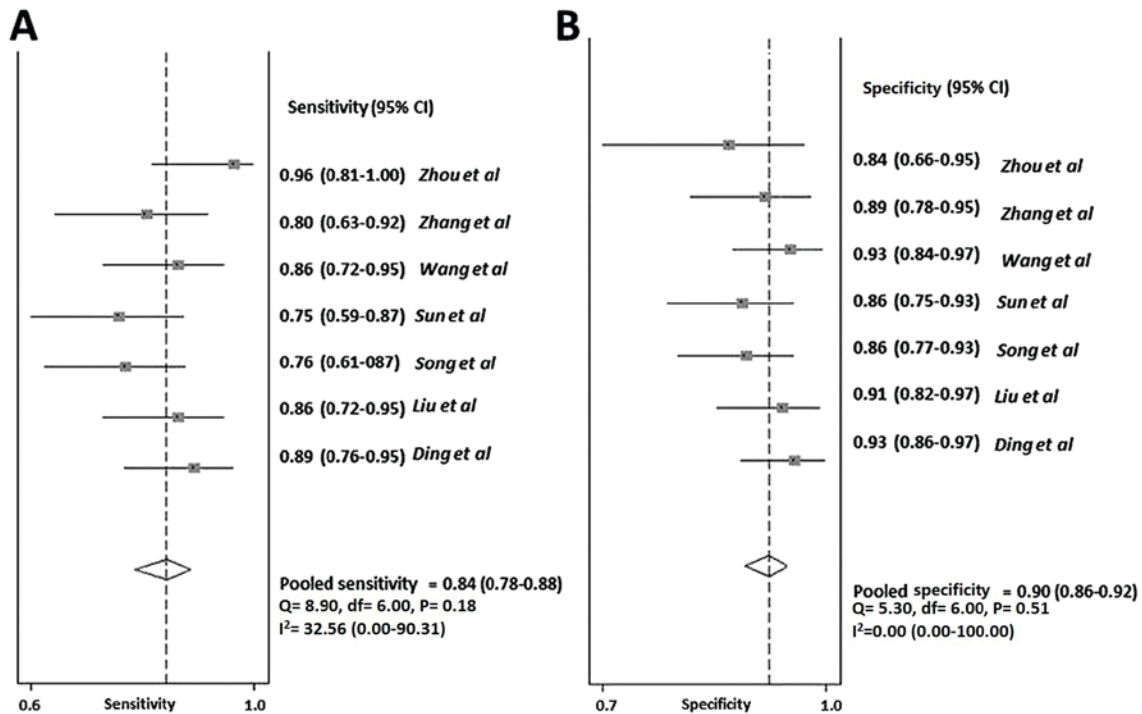


Figure 2. (A) Forest plot of study-specific estimates of sensitivity (ratio with 95% confidence interval) of CEUS in the diagnosis of EC; (B) Forest plot of study-specific estimates of specificity (ratio with 95% confidence interval) of CEUS in the diagnosis of EC, every plot represents a related study, global results (pooled sensitivity/specificity) are presented at the bottom. The horizontal bars are the CI 95% ranges, and the squares within the bars are the estimate values. CEUS, contrast-enhanced ultrasound; EC, endometrial carcinoma; CI, confidence interval.

## Results

**Study collection and characteristics.** The initial search identified 1,436 references, of which 93 relevant studies were selected and reviewed. After reviewing their abstracts, 52 studies were excluded. And after evaluation of the full-text articles, another 30 references were excluded. Among the 11 remaining studies, 4 did not meet the inclusion criteria due to insufficient sensitivity, specificity, accuracy or correlation values. Thus, 7 studies with a total sample size of n=275 were finally included in the present meta-analysis and their data were extracted (15-21). All selected studies are in accordance with the inclusion criteria. A flow chart depicting the selection process is presented in Fig. 1.

As indicated in Table I, the 7 included studies were published between 2008 and 2015. Among the studies, three were prospective studies and five were retrospective. The number of cases varied between 28 and 68. All studies used certain types of CEUS, including regular CEUS, color Doppler CEUS and combination of 2-dimensional (2D) and 3D CEUS. The microbubble contrast agent used in all studies was SonoVue. In all of the studies, CE was pathologically confirmed in addition to the diagnosis by CEUS.

**Accuracy of CEUS in the diagnosis of EC.** For the analysis CEUS accuracy in the diagnosis of EC, heterogeneity results demonstrated that the data was homogeneous with P=0.461. Thus, a fixed model in STATA was utilized. Parameters for the analysis of CEUS accuracy in the diagnosis of EC are shown in Table II. As presented in Fig. 2A and B, the pooled sensitivity of CEUS in the diagnosis of EC was 84% [95%

confidence interval (CI), 0.78-0.88], while the pooled specificity was 90% (95% CI, 0.86-0.92). The positive likelihood ratio (+LR) of CEUS was 8.0 (95% CI, 5.9-10.8) and the negative likelihood ratio (-LR) was 0.18 (95% CI, 0.13-0.25). The DOR was 44 (95% CI, 26-77). The AUC under the sROC curve was 0.93 (Fig. 3). Moderate heterogeneity was observed for the sensitivity, specificity and DOR with I<sup>2</sup> values of 32.56, 34.68 and 41.2%, respectively.

**Assessment of bias.** The publication bias was examined using Deeks' funnel plot asymmetry test (Fig. 4). No significant publication bias was observed for the DOR of CEUS in the diagnosis of EC (P=0.58). The result of the risk of bias assessment performed with Review Manager 5.3 is presented in Fig. 5. The results demonstrated that no study exhibited a high risk of bias in patient selection, index test, reference standard, trial process or timing of the studies.

## Discussion

In recent years, CEUS has been proved to be efficient in the diagnosis of numerous diseases, e.g., liver cancer (22). In more recent years, the diagnostic value of CEUS in EC has gained the attention of researchers and clinicians. In China, an increasing number of clinicians choose to use CEUS to diagnose uterine lesions, including uterine fibroid (23). Sconfienza *et al* (24) studied the efficacy of CEUS in the diagnosis of uterine fibroids and demonstrated that CEUS was effective in determining the degree of vascular occlusion at the end of superselective uterine fibroid embolization procedures. Based on a study by Seitz and Strobel (25), CEUS was

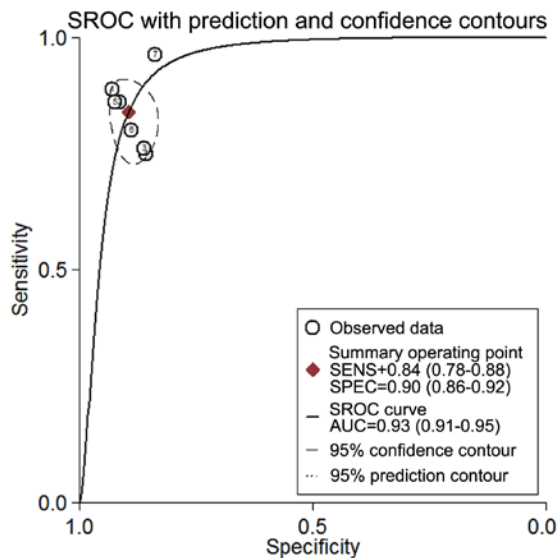


Figure 3. SROC curve of contrast-enhanced ultrasound in the diagnosis of endometrial carcinoma. Numbers represent the studies in Table I in the order that they are presented. SROC, summary receiver-operating characteristics; AUC, area under curve; SENS, sensitivity; SPEC, specificity.

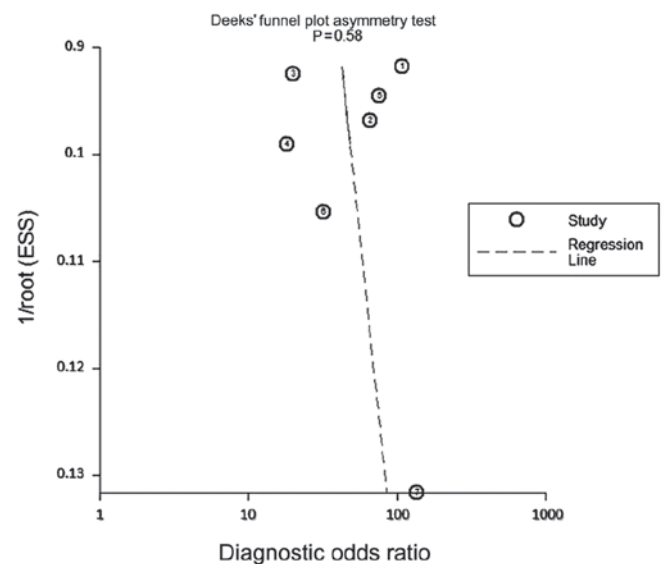


Figure 4. Deek's funnel plot asymmetry test for publication bias for the 7 studies included in the meta-analysis. Numbers represent the studies in Table I in the order that they are presented. ESS, effective sample size.

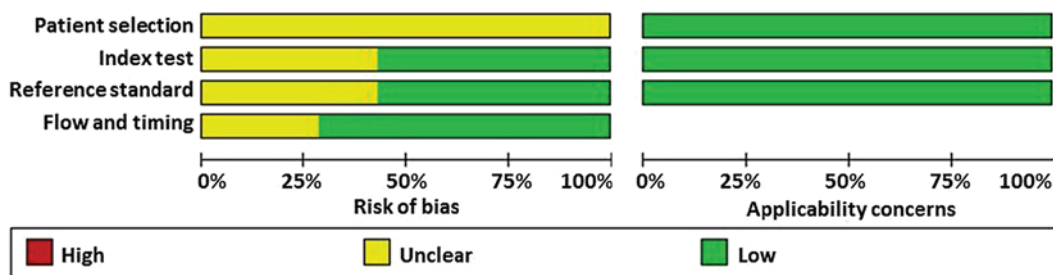


Figure 5. Publication bias assessed by Review Manager for the 7 studies included in the meta-analysis.

approved for diagnostic liver imaging in adults and children in the USA. However, compared with the application of CEUS in other fields, its use in the diagnosis of EC still requires further research.

In the present study, a meta-analysis was performed to summarize the accuracy of CEUS in diagnosing EC. Two reviewers were involved in the study to analyze the literature independently to reduce the bias of researchers. The meta-analysis also followed the PRISMA recommendations (13), which suggests that only studies containing at least four of the Quality Assessment of Diagnostic Accuracy Studies criteria (26) are included and in addition, all patients were confirmed by pathological analysis.

The present meta-analysis study provided a pooled sensitivity and specificity of 84% (95% CI, 0.78-0.88) and 90% (95% CI, 0.86-0.92), respectively, with a DOR of 44 (95% CI, 26-77) and an AUC of 0.93. Moderate heterogeneity was observed for the sensitivity, specificity and DOR. The present results suggest that CEUS has a high accuracy in the diagnosis of EC. Furthermore, the present meta-analysis indicated a high +LR of 8.0 (95% CI, 5.9-10.8) and a low -LR of 0.18 (95% CI, 0.13-0.25), suggesting that the diagnostic test performs well in correctly identifying the true disease state, which should also be confirmed by histopathological analysis. The publication

bias was examined using both Deeks' funnel plot asymmetry test and Review Manager 5.3, and no significant publication bias was observed.

Of note, the present study had several limitations. First, due to the limited number of cases and studies included, further evidences are still required. Furthermore, all studies that met the inclusion criteria for the meta-analysis were from China. This may be due to the application of CEUS having been widely adopted for diagnosing EC in China, but are not that common in other countries. Finally, the studies were limited by language, as the literature search only included those in English and Chinese.

In conclusion, the present meta-analysis indicates that CEUS is valuable in the diagnosis of EC. Additional clinical data and studies are still required to confirm the present results and to further develop the diagnostic application of CEUS in EC.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

JG conducted the analysis and wrote the manuscript; and JT collected and performed a preliminary analysis of references, revised the manuscript, and approved it for submission.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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