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● *Original Contribution*

DIAGNOSTIC PERFORMANCE OF CONTRAST-ENHANCED ULTRASOUND FOR OVARIAN CANCER: A META-ANALYSIS

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Abstract—This meta-analysis is the first study aimed at assessing the overall diagnostic performance of contrast-enhanced ultrasound for ovarian cancer. PubMed, Embase and Medline databases were systematically searched for relevant articles published up to June 2014. Data were pooled to yield summary sensitivity, specificity, diagnostic odds ratio and receiver operating characteristic curves using Meta-Disc Version 1.4 software. Ten independent studies with 579 ovarian tumors were enrolled in this meta-analysis. The pooled sensitivity, specificity and diagnostic odds ratio statistics were 0.89 (0.83–0.94), 0.91 (0.88–0.93) and 91.70 (41.41–203.05), respectively, and the area under the summary receiver operating characteristic curve was 0.9619 (standard error: 0.0125), all indicating that contrast-enhanced ultrasound has high diagnostic accuracy in differentiation of malignant from benign ovarian tumors. (E-mail: Wuyingxiongxiong@163.com) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast-enhanced ultrasound, Diagnosis, Ovarian cancer, Meta-analysis.**

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy (Siegel et al. 2012), partly because it is detected late, with greater than 70% of patients presenting at an advanced stage (Cohen et al. 2014). Five-year survival for all stages is 47%, and for advanced stages, <30% (Carter and Downs 2011). Early detection is one of the most important strategies for improving patient prognosis (Suh et al. 2012). In the early stage, ovarian cancer is usually asymptomatic, and moreover, only a small number of the relatively common ovarian masses detected by imaging techniques are malignant, which makes it crucial to differentiate benign from malignant ovarian masses. Transvaginal sonography usually is the initial diagnostic modality of choice for assessment of most adnexal masses; however, some masses, especially early-stage ovarian cancer, remain difficult to classify by conventional transvaginal sonography, even in experienced hands (Veyer et al. 2010; Wang et al. 2011; Xiang et al. 2013). Solid tumors and their metastases persist and grow through angiogenesis, which is characterized by a neovascular network with irregularly branching vessels derived from pre-existing normal venules that contain numerous arteriolar–venous malformations without an intact basement membrane (Feldmann et al. 1999). Thus, imaging of vessels in tumors may help to assess the risk of ovarian cancer. However, radiologic assessment of tumor vascularity is not yet well established. The lack of screening tests for diagnosis of early-stage ovarian cancer is an important determinant of the mortality rate of this disease (Enakpene et al. 2009).

Contrast-enhanced ultrasound (CEUS), with the use of contrast agents consisting of gas microbubbles that are administered intravenously and remain intravascular, has been used to evaluate many tumors in the liver, kidneys, pancreas, breasts and other organs (Jakobsen et al. 2005), improving the characterization of tumor angiogenesis and perfusion. In addition, the kinetics of contrast agents in tumors can be evaluated objectively by quantifying time–intensity curve (TIC) parameters. A few studies have investigated the use of contrast-enhanced sonography in the differential diagnosis of malignant versus benign ovarian masses. Diagnostic accuracy in these published studies varied widely, with the sensitivity ranging from 74% to 100% and the specificity ranging from 42% to 98% (D'Arcy et al. 2004; Fleischer et al. 2009;

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Huchon et al. 2012; Kupesic and Kurjak 2000; Marret et al. 2004; Orden et al. 2003; Testa et al. 2007, 2009; Veyer et al. 2010; Xiang et al. 2013), probably as a result of advances in technology, the heterogeneity of patient populations and so on. The overall accuracy of CEUS in the diagnosis of ovarian cancer has never been systematically assessed. The purpose of this study was to perform a systematic review and meta-analysis of published information to assess the overall diagnostic performance of CEUS in ovarian cancer.

METHODS

Literature search

PubMed, Embase and Medline databases were systematically searched for relevant articles on the diagnosis of ovarian masses using CEUS up to June 2014. Key words and medical subject headings were designed as follows: ovarian or adnexal; neoplasm or carcinoma or tumor or cancer or mass or lesion; contrast enhanced or contrast media or contrast agent; and ultrasound or ultrasonography or sonography.

Selection criteria

Inclusion criteria were as follows. (i) The study must relate to CEUS in differentiating between benign and malignant ovarian masses. (ii) The study must have been performed on human subjects. (iii) The study must be in the English language. (iv) The reference standard must be histopathologic findings or clinical diagnosis. (v) Sufficient data must be available in the fourfold (2×2) tables, corresponding to true positive (TP), true negative (TN), false positive (FP) and false negative (FN). (vi) The data or subsets of the data must not have been published more than once. (vii) The study population must be >10 patients.

Reviews, editorials, letters and case reports were excluded because of the limited data provided. When there were two articles by the same author(s) or from the same medical center with the same date, the article with the larger sample size was selected. Studies in which data were incomplete were excluded. Study selection was conducted by two researchers independently (Y.W. and H.P.). Disagreement was resolved by a third researcher (X.Z.) through discussion.

Extraction of data

The data recorded for each article included First author, publication year, country of study, mean age of patients, sonographic diagnostic criteria, contrast agent, number of lesions and TP, TN, FP and FN results. Data were extracted by two researchers independently (Y.W. and H.P.). Disagreement was resolved by a third researcher (X.Z.) through discussion.

Quality assessment

Methodologic quality was assessed independently by two researchers (Y.W. and H.P.) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS). QUADAS criteria include 14 assessment items for systematic reviews of diagnostic accuracy studies. Each of 14 items was scored yes (score 1), no (score –1) or unclear (score 0). Study quality was defined as high when the QUADAS score was ≥ 11 (Whiting et al. 2003). Any disagreement between the two researchers was resolved by a third researcher (X.Z.) through discussion.

Statistical analysis

Between-study heterogeneity was estimated with Cochran's Q statistic and the inconsistency index (I^2) (Higgins et al. 2003). For a significant Q-test with $p < 0.1$ (Higgins and Thompson 2002) or $I^2 > 50\%$, considered as significant heterogeneity, the random-effect model was used; otherwise, the fixed-effect model was used. Diagnostic threshold effect was evaluated with receiver operating characteristic (ROC) space and the Spearman correlation coefficient between sensitivity and specificity. Representation of a typical "shoulder arm" pattern in a ROC space and a strong positive correlation between the log of sensitivity and log of 1 – specificity would suggest the presence of a threshold effect (Hu et al. 2014).

The pooled statistics of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–) and diagnostic odds ratio (DOR) were calculated with corresponding 95% confidence intervals (CIs) in a fixed-effect model or random-effect model, as were their forest plots were. Summary ROC (SROC) curves with the area under the curve (AUC) and the Q^* index (the point on the SROC curve where sensitivity and specificity are equal) were obtained to summarize the overall diagnostic performance of CEUS in ovarian cancer. AUC values

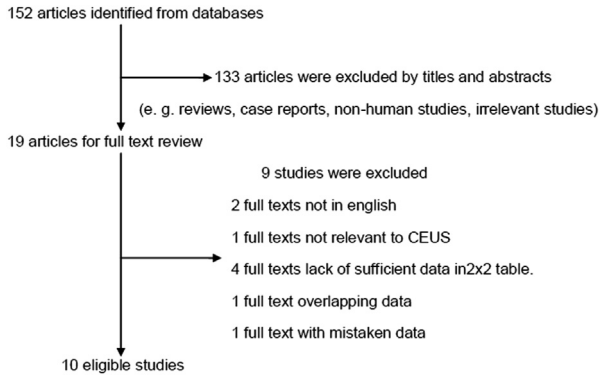

Fig. 1. Flowchart of literature search and study selection. Ten studies were included in this meta-analysis. CEUS = contrast-enhanced ultrasound.