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Combination of serum CA19-9 and CA125 levels and contrast-enhanced ultrasound parametric data facilitates to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer

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Abstract

Ovarian serous carcinoma (OSC) is semimalignant ovarian tumors that localized in the ovary at the initial presentation, and can be surgically resected in an excellent prognosis. In contrast, surgical treatment plus adjuvant chemotherapy for ovarian malignant epithelial cancer (OMEC) is the standard treatment stratagem that is painful with poor prognosis and cost quite expensively. Thus, the accurate preoperative differentiation of OSC from OMEC is important for determining the treatment methods and decreasing the cost for individual patients. This study aims to determine whether contrast enhanced ultrasound (CEUS) together with CA19-9/CA125 can improve the ability to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer. The positive rate of cancer antigen (CA) 199 and CA125 in ovarian malignant epithelial tumors was 68% and 94%, respectively, which was a higher incidence than in the serous carcinoma. The mean serum CA19-9 and CA125 concentration was significantly higher in the patients with ovarian malignant epithelial tumors (CA19-9, 514.0±104.8 U/mL; CA125, 440.0±154.8 U/mL) than that in the patients with ovarian serous carcinoma (CA19-9, 58.0±14.3 U/mL; CA125, 63.0±25.8 U/mL). The time to peak in ovarian serous carcinoma was significantly longer than in ovarian malignant epithelial tumors. However, the peak intensity, area under the curve, and washout time in ovarian serous carcinoma were significantly lower than in ovarian malignant epithelial tumors. The addition of CA19-9/CA125 increased the sensitivities from 79% CEUS only to 85% for CEUS plus CA19-9/CA125 data, and increased the specificities from 65% CEUS only to 91% for CEUS plus the CA19-9/CA125 information. Thus, the addition of the serum CA19-9/CA125 levels to parametric CEUS data was of significant diagnostic value for differentiating OSC from OMEC.

Abbreviations: AUC = area under the curve (AUC), CA = cancer antigen, CEUS = contrast-enhanced ultrasound, CI = confidence interval, MVD = microvessel density, OMEC = ovarian malignant epithelial cancer, OSC = ovarian serous carcinoma, PI = peak intensity, ROC = receiver operating characteristic, TTP = time to peak (TTP), WOT = washout time.

Keywords: cancer antigen, contrast enhanced ultrasound, diagnosis, malignant epithelial cancer, ovarian serous carcinoma

1. Introduction

Ovarian serous carcinoma (OSC) is semimalignant ovarian tumors, including cystadenoma, papillary cystadenoma, surface papilloma, adenofibroma, and cystadencofibroma.[1] These serous carcinomas tend to be localized in the ovary at the initial presentation, and can be surgically resected in an excellent prognosis.[2] And for the younger patients, unilateral oophorectomy may be a best choice for maintaining ovarian function.[3] In contrast, ovarian malignant epithelial cancer (OMEC) has multiple complex causes and strong invasiveness. Surgical treatment (abdominal hysterectomy, bilateral salpingo-oophorectomy) plus adjuvant chemotherapy for ovarian malignant epithelial cancer is the standard treatment stratagem that is painful and cost quite expensively.[4] Thus, the accurate preoperative differentiation of OSC from OMEC is important for determining the treatment methods and decreasing the cost for individual patients.

Contrast enhanced ultrasound (CEUS) has been widely used for making the preoperative diagnosis of ovarian cancer patients. Also CEUS is noninvasive that may benefit for patients to differentiate OSC from OMEC. Previous study demonstrated that the serum concentration of CA19-9 and CA125 was lower in the patients with OSC than that in the patients with OMEC.[5,6] Moreover, study also suggested that the addition of CA125 measurements to the CT results could improve the differentiation of borderline ovarian tumors from malignant epithelial ovarian tumors.[7]

To date, few studies have used the quantitative parameters of CEUS in an attempt to differentiate these lesions. And there have

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WZ and LW equally contributed to this work.

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been no studies that have assessed the additional diagnostic value of combination the CA19-9/CA125 level with CEUS for differentiating OSC from OMEC. This study aims to determine whether CEUS together with CA19-9/CA125 can improve the ability to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer.

2. Materials and methods

2.1. Study population

Around 183 patients with serous ovarian carcinoma (mean age, 54.8 years; range, 42–78 years) and 196 patients with ovarian malignant epithelial tumors (mean age, 50.9 years; range, 34–73 years) from February 2006 to December 2016 in the General Hospital of Daqing Oil Field were included in this retrospective analysis. Patients with ovarian serous carcinoma or ovarian malignant epithelial cancer were diagnosed by pathologist using the biopsy tissues. None of these patients had any contra-indications to surgery. The serum CA19-9 and CA125 level that analyzed in a gamma counter (Cobra II; Packard, Meriden, CT) were collected from medical record.

2.2. Contrast-enhanced ultrasound

The patients were routinely examined with according to the standard operating procedure. Contrast-enhanced sonography was conducted with iU22 ultrasonic inspection instrument (Royal Philips electronics NV, Eindhoven, the Netherlands) equipped with a 4 C1 curved linear array transducer with a frequency range of 1.0 to 4.0 MHz, in which the Qlab software was installed. Contrast-enhanced sonography was performed using a second-generation ultrasound contrast agent SonoVue (Bracco SpA, Milan, Italy). After informed consent for the contrast-enhanced sonographic examination was obtained, a 2.4-mL bolus of SonoVue was hand injected through a 20-gauge intravenous catheter in the antecubital vein, immediately followed by a 5-mL saline flush. Qlab software was used to analyze the microvessel image. The peak intensity (PI), area under the curve (AUC), time to peak (TTP), and washout time (WOT) were collected for analysis.

2.3. Statistical analysis

SPSS17.0 statistical software (SPSS Inc.; Chicago, IL) was used to analyze the continuous variables (mean and range) and categorical variables (percentages) by an unpaired t test and χ^2 test. Receiver operating characteristic curves were plotted to evaluate the diagnostic performance of contrast-enhanced ultrasound alone and combined contrast-enhanced ultrasound and CA19-9/CA125 in discriminating ovarian serous carcinoma from ovarian malignant epithelial tumors. Differences between ROC curves were compared by a univariate z score test. P value $<$ .05 was considered to be statistically significant.

3. Results

3.1. General features

The clinical and laboratory information for the patients with ovarian serous carcinoma and ovarian malignant epithelial tumors is shown in Table 1. The average age of these two type tumors was comparable. The average size of ovarian serous carcinoma was 13.6 cm, which was significantly higher than the average size of ovarian malignant epithelial tumors (9.2 cm). The positive rate of cancer antigen (CA) 19-9 and CA125 in ovarian malignant epithelial tumors was 68% and 94%, respectively, which was a higher incidence than in the serous carcinoma. The mean serum CA19-9 and CA125 concentration was significantly higher in the patients with ovarian malignant epithelial tumors (CA19-9, 514.0 ± 104.8 U/mL; CA125, 440.0 ± 154.8 U/mL) than that in the patients with ovarian serous carcinoma (CA19-9, 58.0 ± 14.3 U/mL; CA125, 63.0 ± 25.8 U/mL) (Fig. 1).

Table 1

Clinical and laboratory information on patients with ovarian serous carcinoma from ovarian malignant epithelial tumors.

Characteristic	Serous ovarian carcinoma (n = 183)	Malignant epithelial ovarian tumors (stage I, n = 196)	P
Age, mean (range)	54.8 (42–78)	50.9 (34–73)	.472
Size, cm, mean (range)	13.6 (3–32)	9.2 (8–24)	.002
CA19-9 positive (%)	36	68	.004
CA125 positive (%)	78	94	.023

3.2. CEUS evaluation for ovarian malignant epithelial tumors and ovarian serous carcinoma

The CEUS evaluation for ovarian malignant epithelial tumors and ovarian serous carcinoma are summarized in Table 2. The time to peak in ovarian serous carcinoma was significantly longer than in ovarian malignant epithelial tumors. However, the parameters including peak intensity, area under the curve and washout time in ovarian serous carcinoma was significantly lower than in ovarian malignant epithelial tumors.

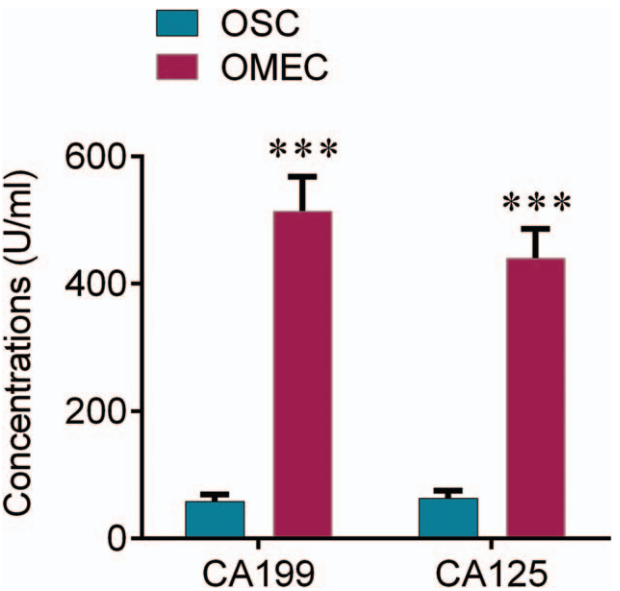

Figure 1. CA19-9 and CA125 serum concentrations in patients with stage I ovarian malignant epithelial cancer (OMEC) and ovarian serous carcinoma (OSC). The mean serum CA19-9 and CA125 concentration was significantly higher in the patients with ovarian malignant epithelial tumors (CA19-9, 514.0 ± 104.8 U/mL; CA125, 440.0 ± 154.8 U/mL) than that in the patients with ovarian serous carcinoma (CA19-9, 58.0 ± 14.3 U/mL; CA125, 63.0 ± 25.8 U/mL). *** $P < .001$. OMEC = ovarian malignant epithelial cancer, OSC = ovarian serous carcinoma.

Table 2

Comparisons of quantitative parameters of CEUS between ovarian serous carcinoma and ovarian malignant epithelial cancer.

Characteristic	Ovarian serous carcinoma	Ovarian malignant epithelial cancer	*P*
Time to peak, seconds	38.02 ± 4.31	25.45 ± 5.31	.023
Peak intensity, dB	47.42 ± 5.76	78.76 ± 13.23	.001
Area under the curve, dB s	604.67 ± 67.86	1340.50 ± 131.20	.0004
Washout time, seconds	42.76 ± 8.52	94.54 ± 20.31	.008

CEUS = contrast enhanced ultrasound.

Table 3

Accuracy of CEUS and combined CEUS data and serum CA-125/CA19-9 concentration for differentiating ovarian serous carcinoma from ovarian malignant epithelial cancer.

Condition	Sensitivity (95% CI)	Specificity (95% CI)
CEUS	79 (65–89)	65 (50–79)
CEUS+CA125/CA19-9	89 (87–95)*	95 (89–98)*
CEUS+CA125	84 (78–88)	72(65–86)
CEUS+CA19-9	81 (76–90)	73 (73–90)

CEUS = contrast enhanced ultrasound.
* $P < .05$ vs. CEUS group.

3.3. Differentiating ovarian malignant epithelial tumors from ovarian serous carcinoma

In differentiating ovarian malignant epithelial tumors from ovarian serous carcinoma, the AUCs with and without the use of the serum CA19-9/CA125 concentrations were 0.78 (95% confidence interval [CI]: 0.63–0.86) and 0.95 (95% CI: 0.88–0.97), respectively ($P = .013$) (Fig. 2). From the ROC curve, we found that the cut-off CA19-9/CA125 concentration for differentiating ovarian malignant epithelial tumors from ovarian serous carcinoma was 186 U/mL. The sensitivity, specificity and positive and negative predictive values for differentiating ovarian malignant epithelial tumors from ovarian serous carcinoma, using the cutoff points of the ROC curves, are shown in Table 3. The sensitivities were 79% for CEUS only and 89% for CEUS plus CA19-9/CA125 data. The specificities were 65% for using the CEUS only, and 95% for using the CEUS plus the CA19-9/CA125 information (Table 3). We also found that the sensitivities were 84% for CEUS plus CA125, and 81% for CEUS plus CA19-9. The specificities were 72% for CEUS plus CA125, and 73% for using the CEUS plus CA19-9 information (Table 3). Although there was slightly increase in the sensitivities and specificities for CEUS along with CA19-9 or CA125, it was not statistically significant (Table 3). Thus, the inclusion of the CA19-9/CA125 concentration simultaneously rose the sensitivity and specificity, indicated that more ovarian malignant epithelial tumors were correctly diagnosed.

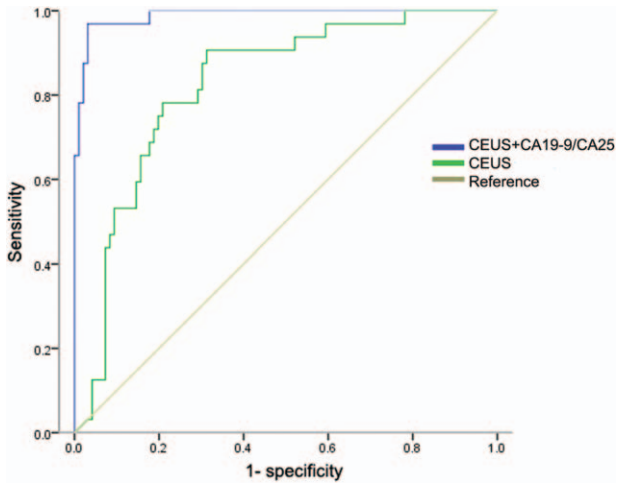

Figure 2. Receiver operating characteristic curve analyses showing addition of CA19-9/CA125 for differentiating ovarian malignant epithelial cancer (OMEC) and ovarian serous carcinoma (OSC). Areas under curve were 0.78 and 0.95 before and after addition of serum CA19-9/CA125, respectively ($P = .013$). OMEC = ovarian malignant epithelial cancer, OSC = ovarian serous carcinoma.

4. Discussion

CEUS has been extensively used to make the preoperative diagnosis of ovarian tumors. However, CEUS alone has lower diagnostic accuracy for differentiating benign from malignant ovarian lesions. To our knowledge, no previous studies have investigated whether the addition of the serum CA19-9 and CA125 concentration data to the parameters of CEUS increases the accuracy of differentiating OSC from OMEC. Our findings indicate that OMEC are characterized by significantly shorter time to peak and significantly higher peak enhancement intensity than OSC. Surgical removal remains the standard treatment for OMEC, and this decision should be estimated by basing largely on the results of diagnostic imaging studies. Although the final diagnosis of ovarian masses is based on histology, preoperative differentiation of benign and malignant lesions is essential for decisions on the timing and technical characteristics of the surgery.[8]

Increased vascularization is one of the futures of neoplastic lesions, so assessment of this parameter would facilitate differentiating the masses. Contrast enhancer can improve visualization of vascular structures, especially those of the microcirculation. However, CEUS alone, even in the hands of an expert examiner, is not sufficiently reliable for differentiating OSC from OMEC, especially those in the early stage. Parametric mapping method that allows for stricter cutoff criteria would be a more sensitive method than region of interest analysis for the detection of malignant tumors but was also less specific than standard region of interest analysis.[9] Previous study showed that analysis of peak intensities and time/intensity curves revealed significant differences between benign and malignant lesions.[8] The peak intensity and AUC in the malignant tumors were shown to be significantly higher than those in the benign tumors or tumor-like lesions, which were positively correlated significantly with the microvessel density (MVD) that reflected angiogenesis in ovarian masses.[10] And the accuracy of CEUS in differential diagnosis of benign and malignant ovarian tumors was relative satisfied.[11]

We here found that the addition of the serum CA19-9/CA125 concentration data to the CEUS parametric information increased the accuracy of differentiating OSC from OMEC. The parametric mapping method and stricter cutoff criteria may also increase the inter-observer agreement. The serum CA19-9 and CA125 levels were significantly increased in several tumors, including ovarian chocolate cysts, primary ovarian mucinous tumors and epithelial ovarian cancer.[12–14] However, the serum CA19-9 and CA125 levels alone cannot differentiate between benign and malignant tumors since they also increased in endometriosis, tubo-ovarian abscesses and fibromas.[15] We found that the addition of the serum CA19-9 and CA125

concentration to the parameters of CEUS increased the sensitivity and specificity of differentiating OSC from OMEC.

In summary, our findings demonstrate that evaluation of patients using a combination of the parametric CEUS data and CA19-9/CA125 concentration results in more reproducible and accurate differentiation of OSC from OMEC. Thus, the addition of the serum CA19-9/CA125 levels to parametric CEUS data was of significant diagnostic value for differentiating OSC from OMEC.

Author contributions

Conceptualization: Zhongqiu Xin.
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Investigation: Zhongqiu Xin.
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Software: Wei Zhang.
Validation: Zhongqiu Xin, Wei Zhang, Liying Wang.
Writing – original draft: Zhongqiu Xin, Wei Zhang.
Writing – review & editing: Zhongqiu Xin, Liying Wang.

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