JBUON 2021; 26(5): 1802-1808
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Application value of Doppler ultrasound combined with CA125 and CA19.9 in the early diagnosis of epithelial ovarian cancer

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Summary

Purpose: *An early diagnosis is of great significance in improving the survival rate of patients. At present, the application values of different diagnostic methods in ovarian cancer are different, and the clinical diagnosis alone is not ideal. Therefore, this study explored the application value of Doppler ultrasound combined with CA125 and CA19.9 in the early diagnosis of epithelial ovarian cancer.*

Methods: *A total of 58 patients with ovarian diseases were divided into an observation group (epithelial ovarian cancer group, n=29) and a control group (benign ovarian tumour group, n=29). Doppler ultrasound results and serum CA125 and CA19.9 detection results of the two groups were collected to analyse and compare the application value of ultrasound and different kinds of tumour markers in the early diagnosis of epithelial ovarian cancer.*

Results: *The results of Doppler ultrasound showed that the resistance index of blood flow in the observation group was lower than that in the control group, and the ultrasound score was higher than that in the control group (p<0.05). The levels of serum tumour markers CA125 and CA19.9 in the observation group were significantly higher than those in the control group (p<0.05). The results of the repeated measurement data of variance showed that there were significant differences in the ultrasound score, blood flow resistance index and CA125 and CA19.9 levels in different stages of ovarian cancer (p<0.05). There was no difference in the ultrasonographic score between stage I and the partum stage, while the stage of menstruation and implantation showed a gradually increasing trend (p<0.05). The blood flow resistance index and CA125 and CA19.9 levels increased gradually with the stage (p<0.05). The sensitivity (93.1%), specificity (96.55%), positive predictive value (96.43%), negative predictive value (93.33%) and diagnosis rate (94.83%) of Doppler ultrasonography combined with CA125 and CA19.9 in the diagnosis of epithelial ovarian cancer were higher than those of the single indicator detection method or the two combined diagnostic detection methods.*

Conclusion: *Doppler ultrasound combined with CA125 and CA19.9 has high sensitivity, high specificity and high coincidence rate and can improve the early clinical diagnosis of epithelial ovarian cancer.*

Key words: *epithelial ovarian cancer, Doppler ultrasound, tumour markers, early diagnosis, clinical application*

Introduction

Ovarian cancer refers to malignant tumour within the ovary. According to its different histological sources, ovarian cancer can be divided into epithelial tumours, germ cell tumours, sex hormone stromal tumours, metastatic tumours and so on [1,2]. Epithelial ovarian cancer is the most common type of ovarian cancer. Early-stage disease has no obvious clinical symptoms. Later, with tumour invasion, patients will gradually experience abdominal pain, abdominal distension, a low-grade

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Received: 25/05/2021; Accepted: 19/07/2021

fever, weight loss and other clinical symptoms. If patients are not hospitalized in time for effective treatment, there will be spread and metastasis of tumour cells, and other organs in the viscera will be damaged, which can endanger the life of patients [3]. Therefore, to improve the clinical efficacy and survival of patients with epithelial ovarian cancer, early detection and diagnosis should be improved to ensure that patients with this malignancy can receive effective treatment as soon as possible. However, as far as the clinical diagnosis is concerned, the misdiagnosis and missed diagnosis rates of early epithelial ovarian cancer are high, and most patients have developed an advanced stage before they are diagnosed with ovarian cancer [4,5]. Therefore, to further improve the clinical diagnosis rate of patients with early epithelial ovarian cancer, this study aimed to use Doppler ultrasound combined with carbohydrate antigen 125 (CA125) and carbohydrate antigen 19.9 (CA19.9) diagnostic methods to treat patients with this malignancy and to further explore and analyse the application value of this combined diagnosis method.

Methods

Study participants

This study was approved by the ethics com[illegible] tee of Yantaishan Hospital. Signed wri[illegible] inform[illegible] consent was obtained from all partic[illegible]nts [illegible]fore th[illegible] study entry. A total of 58 patients [illegible] ovari[illegible] disease[illegible] treated in our hospital from March 2019 to March 2021 were selected as the research subjects. According to the Guidelines for the Diagnosis and Treatment of Ovarian Malignant Tumours (fourth edition) [6], the patients were divided into an observation group and a control group based on histopathologic examinations, with 29 patients in each group. The observation group included patients with malignant ovarian tumours (25-78 years), average age 51.5±13.7 years, and average body mass index (BMI) 21.4±4.7 kg/m^2. According to the FIGO staging criteria, 4 patients were classif[illegible]s stage I, 12 patients were classified as stage II[illegible] pa[illegible]s were classified as stage III, and 3 patie[illegible] were clas[illegible]d as stage IV. In the control group, the [illegible]ent age w[illegible] benign ovarian tumours ranged [illegible]m 28[illegible]7 years[illegible] verage 49.7±10.2 years and av[illegible]ge BMI of 2[illegible].3[illegible]g/m^2). According to pathologi[illegible]ypes, [illegible]atients[illegible]d serous cystadenomas, 3 had i[illegible]o[illegible]ystadenomas, 14 had fibromas, 4 had fo[illegible]ular [illegible]nas, an[illegible] had endometrium-like tum[illegible].

Inclusion an[illegible]xclu[illegible] criteria

Th[illegible]lusion crit[illegible] were as follows: 1) No other gyn[illegible]logic surgery; 2)[illegible]ge between 25 to 80 years; 3)[illegible]cording to the clinical symptoms and pathologic ex[illegible]inations, t[illegible] patients were identified as having an epi[illegible]al ovari[illegible] cancer or a benign ovarian tumour. Exclu[illegible]a: 1) patients who had a history of allergy to an[illegible] ultrasound contrast agent or any other con[illegible]ications for an ultrasound examination; 2) patients [illegible]mental disorders, intellectual disabilities or had [illegible]oordination reflexes that were too low; 3) patients who were pregnant, or who had severe heart, liver and/or [illegible]enal insufficiency and other malignant tumours; 4) pa-

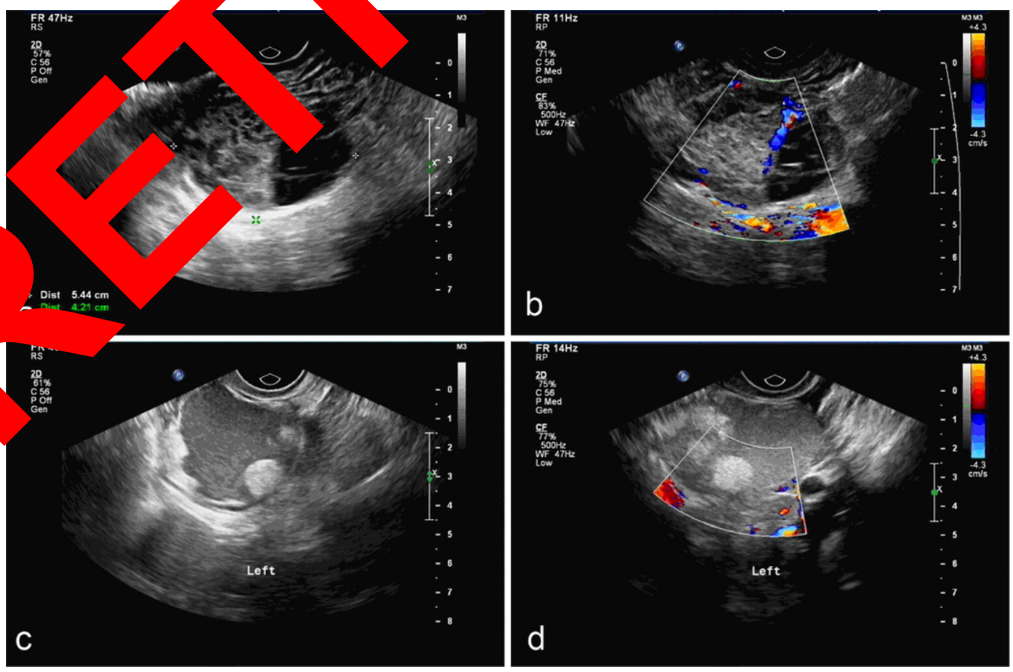

Figure 1. Ultrasound images of benign and malignant ovarian tumours. **A:** Ultrasound scanning image of an epithelial ovarian tumour. **B:** Image of a colour Doppler ultrasound to assess the blood flow of an epithelial ovarian tumour. **C:** Ultrasound scanning image of a benign tumour (fibroadenoma). **D:** Peripheral blood flow of a benign tumour.

tients who had received hormone therapy, radiotherapy and chemotherapy before this study, and 5) patients who had complications that affected the detection results of the tumour markers.

Doppler ultrasound diagnosis

Examination methods: 1) The subjects in the two groups were examined by colour Doppler ultrasound (Siemens (China) Co., Ltd., Beijing, model Acuson S2000) through the abdomen and vagina. 2) Transabdominal ultrasound examination: To help the patient keep a supine position the probe frequency was adjusted to 3.5-5 MHZ, and the observation of the uterus and double annex area, tumour location, size, shape and internal echo source, relationship with the adjacent organs, presence of ascites, presence of enlargement of iliac blood vessels and lymph nodes, and the measurement of the blood flow resistance index (PI) and peak flow velocity (PSV) were obtained. 3) Transvaginal ultrasound: when the results of transabdominal ultrasound were not satisfactory or if the patient made a request, the patient was asked to empty her bladder and take a lithotomy position for a transvaginal ultrasound. The probe frequency was 5-7.5 MHz, the probe was put into a disposable contraceptive condom, and the coupling agent was evenly coated. The location, shape, edge, thickness of the ovarian mass, the size of papillary process of tumor sac wall or parenchyma, echo and posterior acoustic attenuation of the patient were examined. The morphology of the blood vessels inside and around the tumour was observed with colour Doppler flow imaging, and the blood flow distribution was analysed. The modified Ala[illegible]trasound scoring system was used to score the tumour and more than 3 blood cycle maps were collected, as shown in Figure 1. By using the images obtained [illegible] examination methods, two experienced attending physicians made a comprehensive assessment and diagnosis of the patient's condition. The diagnostic indicators of ovarian cancer were defined as blood flow resistance index ≤0.5 and an [illegible]czar ultrasound score ≥7 points.

Detection of tumour markers CA125 and CA19.9

1) Blood sample collection: Fasting samples of 4 ml of venous blood from the subjects were collected in the morning for the test [illegible]es, the collected blood samples were injected in the blood collection vessel coated with [illegible] and blood samples were sent for analysis in a timely manner. 2) Detection method: After centrifugation at 4000 r/min for 10 min (Thermo Field, Micro21), the serum that was separated was taken and stored at -80℃ for further analysis. After that, the serum to be tested was placed in an automatic chemiluminescence immunoanalyser (Siemens Co., Ltd., Beijing, China, model ADVIA CENAUR) to detect the levels of CA125 and CA19.9, and the values of these two indexes in the two groups of subjects were recorded and analysed statistically. 3) Diagnostic mode: CA125 was defined as normal when the serum levels were <35 KU/L; if the serum CA125 were ≥ 35 KU/L, the test result was considered positive. The CA19.9 was considered normal when the serum level was <37 KU/L. If the serum level of CA19.9 was ≥37 KU/L, the test result was considered positive.

According to the results of Doppler ultrasound examination, ovarian tumour location, size, texture, shape and internal echo source, relationship with the adjacent organs, presence of ascites and presence of iliac blood vessels and lymph node enlargement were recorded and analysed in the two groups of patients with ultrasound blood flow peak velocity (PSV), vascular resistance (PI) and ultrasonic score results. The serum tumour markers CA125 and CA19.9 were recorded and compared between the two groups. The differences in the ultrasonographic examination index and the levels of tumour markers CA125 and CA19.9 in different stages of epithelial ovarian cancer were analysed. The early diagnostic values of Doppler ultrasonography, CA125, CA19.9, Doppler ultrasonography+CA125, Doppler ultrasonography+CA19.9, CA125+CA19.9, Doppler ultrasonography+CA125+CA19.9, Doppler ultrasonography+CA125+CA19.9, Doppler ultrasonography +CA125+CA19.9, and Doppler ultrasonography +CA125+CA19.9 in the differential diagnosis of epithelial ovarian cancer and benign tumours were compared.

Statistical analysis

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for the statistical analyses of the research data. Measurement data were expressed as mean±standard deviation. Independent samples were used for comparisons between the two groups. Enumeration data were expressed as percentages. The comparisons between multiple groups were performed using a one-way ANOVA followed by *post hoc* test (least significant difference). Percentages (%) were used to express the enumeration data, and the x^2 was used for data analysis. P values <0.05 were considered statistically significant.

Results

Comparison of ultrasound Doppler imaging between benign and malignant ovarian tumours

There was no significant difference in the tumour diameter between benign and malignant ovarian tumours when measured by Doppler ultrasound ($p > 0.05$), but there were significant differences in morphology, location, texture, nipple, ascites, blood flow when evaluated by the Doppler ultrasound and the haemodynamics ($p < 0.05$), as shown in Table 1.

Results of ultrasound and CA125 and CA19.9 in the diagnosis of benign and malignant ovarian tumours

The results of Doppler ultrasonography showed that the blood flow resistance index of the observation group was lower than that of the control group, the ultrasonography score of the observation group was higher than that of the control group, and the difference between the groups was statistically significant ($p<0.05$). Serum tumour

markers CA125 and CA19.9 in the observation group were significantly higher than those in the control group, and the differences were statistically significant (p<0.05), as shown in Table 2.

Analysis of the ratio of ultrasound parameters and tumour markers in different stages of ovarian cancer

The results of the repeated measurement analysis of variance showed that there were significant differences in the ultrasound score, blood flow resistance index, and CA125 and CA19.9 levels in different stages of ovarian cancer (p<0.05). The results showed that (1) there was no significant difference in the ultrasound score between stage I and stage II (p>0.05), and the ultrasound scores of stage II, stage III and stage IV increased gradually with increasing stage (p<0.05); (2) the blood flow resistance index and CA125 and CA19.9 levels increased gradually with increasing stage (p<0.05), as shown in Table 3.

Comparison of the different diagnostic methods in the early diagnosis of epithelial ovarian cancer

The sensitivity, specificity, positive predictive value and negative predictive value of Doppler ultrasonography combined with CA125 and CA19.9 in the diagnosis of epithelial ovarian cancer were 93.1%, 96.55%, 96.43% and 93.33% ctively, and the clinical diagnosis rate s 94.8 The sensitivity, specificity, positi redictive lue, negative predictive value a d dia sis rate the combined diagnostic m ods wer gni antly higher than those of e sin inde tection method or the two co in diagnostic methods, and the differen s we atistic y significant (p<0.05), as sh n in Tabl

Table 1. Analysis of Doppler ultrasound imaging results of beni alignant tu s in the two groups

Imaging and haemodynamic characteristics	*Optimum*	*Malign*	x^2	*p value*
Form			18.196	0.000
Rule	20			
Irregular	9	25		
Diameter (cm)			0.276	0.599
<5	13	15		
≥5	16	14		
Position			5.695	0.017
Unilateral		12		
Bilateral	8	17		
Quality			6.658	0.036
Ridged bumps	13	6		
Substantiality	10	8		
Mixedness	6	15		
Papillary proc of cyst l condition			8.385	0.004
Yes	10	21		
No	19	8		
Asc			5.613	0.018
es	9	18		
	20	11		
Blood			12.176	0.000
Blood in the tumour	11	24		
No blood flow in the tumour	18	5		

Table 2. Analysis of ultrasound indexes and tumour markers CA125 and CA19.9 in the two groups

Group	*n*	*CA125 (U/ml)*	*CA19.9 (U/ml)*	*Ultrasound score (points)*	*Blood flow resistance index (U/ml)*
Observation group	29	124.83±18.21	166.84±30.01	9.55±1.94	0.44±0.11
Control group	29	15.11±3.25	21.89±3.92	4.99±1.12	0.72±0.23
t	-	31.945	25.792	10.962	5.914
p	-	0.001	0.001	0.001	0.001

Table 3. Analysis of ultrasound indexes and tumour markers in different stages of ovarian cancer

Group	*n*	*CA125 (U/ml)*	*CA19.9 (U/ml)*	*Ultrasound score (points)*	*Blood flow resistance index (U/ml)*
Stage I	4	98.43±10.72	123.21±12.89	4.81±0.98	0.23±0.08
Stage II	12	109.34±14.87	136.98±8.93	5.76±1.12	0.53±0.14
Stage III	10	137.82±21.98	189.76±12.32	7.39±2.73	0.65±0.26
Stage IV	3	156.38±9.24	203.34±14.59	9.77±2.85	0.83±0.27
F		198.384	149.419	68.974	58.432
p		0.000	0.009	0.013	0.027

Table 4. Early diagnostic value of different diagnostic methods in epithelial ovarian cancer

Evaluating indicator	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Diagnostic rate*
	%	%	%	%	%
Doppler ultrasound	72.41	93.10	91	84	82.76
CA125	68.97	89.66	8	74.2	79.43
CA19.9	65.52	86.21	82.61	71.43	75.86
Doppler ultrasound+CA125	76.12	91.22	89.76	75.27	84.29
Doppler ultrasound+CA19.9	73.75	90.46	87.49	74.63	86.35
CA125+CA19.9	73.21	94.21	93	80.46	81.84
Doppler ultrasound+CA125+CA19.9	93.10	96.55	96	93.33	94.83

Discussion

Epithelial ovarian cancer is one of the most common malignant tumours in the ovari, and its incidence has been increasing in recent years. Studies have pointed out that the survival of ovarian cancer has important significance for the prognosis of patients, because the 5-year survival rate of stage I patients can be as high as 90%, but the 5-year survival rate of patients with stage IV is only less than 25%; therefore, an early diagnosis in the treatment of ovarian cancer and improvement of the prognosis of patients is crucial [8,9]. At the present stage, serological indicators are an important tool for the clinical diagnosis of ovarian cancer, and there are many kinds of tumour markers and many influencing factors in the detection process. The diagnostic rate obtained by a single examination method is not high, so the specificity in early clinical diagnosis is not ideal [10,11].

In this study, Doppler ultrasonography combined with the serum tumour markers CA125 and CA19.9 were used for the early diagnosis of epithelial ovarian cancer. In this combination diagnosis, CA125 is the most commonly used tumour marker for epithelial ovarian cancer, and it is mainly derived from the coelomic epithelium during embryonic development. Normal ovaries do not contain this substance [12]. Therefore, if this substance is detected in the body and the detection value of this index shows an obvious upward trend, it is necessary to be concerned that the ovaries of the subject may be affected. CA19.9 is an oligosaccharide tumour-associated antigen. Although it is widely used in gastrointestinal cancer examination, it can also achieve good application effects in ovarian cancer, especially in the diagnosis of mucinous adenocarcinomas [13]. In an ultrasound examination, the Alaczar ultrasound score and blood flow resistance index are mainly used for evaluation and diagnosis. Because transabdominal and transvaginal ultrasound can both reconstruct the images obtained of the subject's uterus, the size and location of the tumour can be preliminarily evaluated and diagnosed according to the images. A Doppler ultrasound to determine the uterine blood flow dynamics and to check for the generation of new blood vessels in the malignant tumour was performed, so that the transfer of tumour cells, the diffusion of the cells, and the patient's uterine blood flow resistance index were determined for the diagnosis. The haemodynamic examination resulted in the assessment of the uterine tumour lesions [14,15]. The lower the blood flow resistance index, the more severe the malignant transformation of the tumour.

The results of this study showed that, compared with the control group, the detection val-

ues of CA125 and CA19.9 in the observation group were significantly higher, the ultrasound score was higher, the detection value of blood flow resistance index was lower, the number of patients with ovarian cancer diagnosed by CA125, CA19.9 and colour Doppler ultrasound was greater, and the number of ovarian cancer cases diagnosed by the combined diagnostics was greater. Compared with patients with stage III-IV disease, patients with stage I-II disease had lower CA125 and CA19.9 values, and ultrasound scores and had greater blood flow resistance indexes. Compared with patients with single diagnostic markers such as CA125, CA19.9 and colour ultrasonography, the diagnostic rate, sensitivity, specificity, positive prediction and negative prediction of the combined diagnostic method were significantly higher. This shows that the combined examination method can achieve a better application effect and a higher diagnosis rate. Combined with Nameki et al research [16], it is believed that although the single application of each diagnostic method can also achieve a good diagnostic effect, the effect is limited, and the diagnostic rate can still be improved. Therefore, CA125, CA19.9 and colour ultrasound can be properly combined to maximize the advantages of each diagnostic method a improve the sensitivity and diagnosis rate. I he study of Javadi et al [17], 53 patients with e epithelial ovarian cancer were compa with 1 patients with benign ovarian lesions which showed that the detection value of CA125, CA19.9, ultrasound score and blood flow resistance index of patients with ovarian cancer were higher, and there were significant differences in CA125, CA19.9, ultrasound score and blood flow resistance index among patients with ovarian cancer of different pathologic stages. These methods can effectively detect whether there are tumours in the subjects. Compared with CA125, CA19.9 and c Doppler ultrasound alone, the accuracy, s sitiv specificity, positive predictive and ative pre tive value of combining these three d ostic me ods are higher, which is cons ent wit e re ts of this study and can be d as a bette od for the early diagnosis o varia ancer.

Conclusion

The appli CA125 and CA19.9 combined with c Doppler rasound in the clinical examin ion and diagno s of patients with early ep elial ovari n cancer can improve the clinical dia osis rate d allow patients to receive timely effe treat nt.

flict of interests

The authors declare no conflict of interests.

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