Comparison of Clinical Characteristics and Ultrasound Features of Ovarian Clear Cell Carcinoma and Ovarian High-Grade Serous Carcinoma

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Research Article

Comparison of clinical characteristics and ultrasound features of ovarian clear cell carcinoma and ovarian high-grade serous carcinoma

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Abstract

Purpose To investigate clinical and ultrasound features for differentiating ovarian clear cell carcinoma (OCCC) from ovarian high-grade serous carcinoma (HGSC).

Methods Forty-five patients with OCCC and 72 patients with HGSC were retrospectively studied. Patient clinical characteristics and ultrasound features of tumors were evaluated. The differences, including laterality, menopausal status, Federation of Gynecology and Obstetrics (FIGO) stage between OCCC and HGSC patients were compared by Fisher's exact test. The ultrasound features of tumors, including laterality, shape, configuration, color score, peritoneal implantation, and ascites, were evaluated and compared between the two groups.

Results The average age at diagnosis in the OCCC group was 57.6±11.1 (range, 30–76) years, and 35.56% of patients were premenopausal. However, the average age at diagnosis was 63.4±12.2 (range, 42-81) years and 33.33% of patients were premenopausal in the HGSC group. There was a statistically significant difference in unilaterality (P< 0.001), clear boundaries (P<0.05), round or oval shape (P <0.05), and color score (P<0.05). Compared to HGSC patients, fewer OCCC patients had peritoneal implantation and ascites. There was a statistically significant difference in the mean size of papillary projections in OCCC and HGSC (P<0.05). The mean size of the papillary projections was significantly larger in OCCC than in HGSC.

Conclusions OCCC commonly appeared as a large, round or oval mass with a clear

boundary; the papillary projections of OCCC are larger and round. In contrast, HGSC was typically a large, irregular tumor with solid masses or mixed cystic-solid masses with small papillary projections.

Keywords Ovary, Clear cell carcinoma, High-grade serous carcinoma, Ultrasound

Ovarian clear cell carcinoma (OCCC) is a rare subtype of epithelial ovarian cancer (EOC) and comprises approximately 5-10% of ovarian carcinomas. OCCC is different from ovarian high-grade serous carcinoma (HGSC), which is the most common subtype of EOC[1–3]. There are many differences in clinical behavior between OCCC and HGSC. Patients with OCCC are younger than patients with HGSC[4, 5]. The incidence of venous thromboembolic events was significantly higher in patients with OCCC than in patients with HGSC[6, 7]. OCCC has a high frequency of hypercalcemia[8, 9]. In general, the therapeutic strategy for OCCC is different from that for HGSC. Therefore, discriminations between these tumors are critical. Ultrasound is a useful tool for describing characteristics in the preoperative diagnosis of an ovarian lesion.

Methods

Study subjects

This retrospective study was approved by the institutional review board of the Beijing Friendship Hospital of Capital Medical University. The inclusion criteria were as follows. 1) The medical records of patients with OCCC and HGSC who underwent surgical treatment at the Beijing Friendship Hospital of Capital Medical University between January 2005 and May 2017 were reviewed. 2) All the patients underwent a preoperative ultrasound examination by an experienced ultrasound examiner between January 2005 and May 2017, and complete preoperative ultrasound images and ultrasound reports were retrospectively available. A total of 45 patients with 46 pure ovarian clear cell carcinoma (OCCC) confirmed by surgery and histopathology were identified. We excluded 5 patients with OCCC mixed with other types of EOC. The mean age of the patients was 57.6±11.1 years (range, 30–76 years). In

comparison, a total of 72 patients with 98 primary HGSC were randomly selected from the same databases during the same period as the control group. The mean age of the patients was 63.4±12.2 years (range, 42–81 years). The operation was performed within two weeks after the completion of ultrasound examinations in both groups. Then, the cancers were confirmed by pathologists at Beijing Friendship Hospital of Capital Medical University. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2013 staging system.

Data collection

Data were collected from all enrolled patients and were compared between the two groups. Assessments included basic characteristics, such as menopausal status, whether with endometriosis, and FIGO stage (postsurgical stage).

Ultrasound examination

All 117 patients underwent presurgical ultrasound examinations of the pelvis with transvaginal ultrasound (supplemented with a transabdominal scan, if necessary). Standard ultrasonographic examinations were performed using a Logiq E9 or Voluson E8 system (GE Healthcare Ultrasound, Milwaukee, WI, USA). The frequency of the vaginal probes ranged from 5.0 to 9.0 MHz and that of the abdominal probes ranged from 3.5 to 5.0 MHz. Continuous multisection and multiangle scans were performed to image the pelvic mass. The following lesion parameters were evaluated: 1) the maximum diameter of lesions; 2) uni- or bilaterality; 3) shape of lesions; 4) the presence of ascites; 5) peritoneal metastasis; and 6) mass configuration (which was evaluated as (a) mainly cystic, less than one-third solid components; (b) mixed cystic-solid, one-third to two-thirds solid components; and (c) solid, more than two-thirds solid components). 7) The vascularization of the tumors on color Doppler was described according to standards established by D. Timmerman et al. no detectable blood flow (color score=1), minimal blood flow (color score=2), moderate blood flow (color score=3), or abundant blood flow (color score=4)[10, 11]. 8) the presence of papillary projections. 9) the size of papillary projections.

Statistical analyses

Statistical analyses were performed with SPSS 19.0 for Windows (SPSS, Inc.,Chicago, IL,USA). The differences between OCCC and HGSC in regard to laterality, shape, mass configuration, color score, ascites, peritoneal metastasis, menopausal status and clinical stage were compared using Fisher's exact test. A P-value less than 0.05 was considered statistically significant.

Results

The maximum diameter of OCCC ranged from 4.8 to 17.6 cm, and those of HGSC ranged from 4.2 to 16.8 cm. Forty-six tumors were found in 45 patients with OCCC; bilateral tumors were found in one patient, and unilateral tumors were found in forty-five patients. Ninety-eight tumors were found in 72 patients with HGSC; bilateral tumors were found in twenty-six patients, and unilateral tumors were found in forty-six patients. The clinical features of OCCC and HGSC are compared in **Table 1**. There was a statistically significant difference in the laterality, clinical stage, and FIGO stage(postsurgical stage) between OCCC and HGSC (P <0.05). No statistically significant differences were found in menopause status between the two groups (P=0.805).

The ultrasound features of OCCC and HGSC are compared in **Table 2**. The mass was round or oval in 32 of 46 (69.6%) OCCC patients compared to 20 of 98 (20.4%) HGSC patients (P<0.001). A clear boundary was found in 87.0% (40/46) of OCCC versus 26.5% (26/98) of HGSC (P<0.001). Among all patients, 13.3% (6/45) and 38.9% (28/72) had ascites in OCCC and HGSC, respectively (p= 0.003). A total of 4.4% (2/45) and 18.1% (13/72) had peritoneal metastasis in OCCC and HGSC, respectively (p= 0.032). There was a statistically significant difference between the two groups in the color score (P=0.025). There were no significant differences between the OCCC and HGSC groups in the mass configuration (P=0.072) and ovarian size(P=0.077). The size of the papillary projections in the OCCC group was 5.40±0.7 cm, while the size of the HGSC group was 2.06±0.4 cm(P<0.001)**(Figs1、 2、 3)**.

Discussion

The clinical characteristics of CCC and HGSC have been widely explored. OCCC

presents more often in younger and premenopausal women than ovarian HGSC[4, 12]. The average age at diagnosis in the OCCC group was 57.6 ± 11.1 years, and 35.56% of the patients were premenopausal. However, the average age at diagnosis was 63.4 ± 12.2 years and 33.33% of the patients were premenopausal in the HGSC group. Many researchers have found that OCCC presents more often in the early stages of disease. However, HGSC are more likely to present as advanced-stage disease[13, 14]. Our results indicate that 77.78% of OCCC was in the early stage compared with 29.17% of HGSC. There are some reasons why OCCC is diagnosed at an early stage. One of the reasons is that growing tumors are more likely to be confined to the ovary for a longer period of time before spreading, allowing them to be diagnosed at an earlier stage. Another reason may be the higher frequency of symptoms and signs in patients with early-stage OCCC, which leads to early detection. However, advanced stage OCCC has a worse prognosis than HGSC, because OCCC is less sensitive to platinum-based chemotherapy than HGSC[15, 16]. Endometriosis was most frequently associated with OCCC. Several studies confirmed that endometriosis is significantly associated with an increased risk of OCCC. It has been reported that approximately one-third of OCCC arises from endometriosis. In contrast, only 7% of ovarian HGSC patients have a history of ovarian endometriosis [4, 5, 17−19]. However, Fei-Chun Ku et al. found that a history of endometriosis was not associated with invasive ovarian HGSC[12].

In our clinical practice, we found that ultrasound features differ between OCCC and HGSC. Therefore, we investigated the characteristic features of OCCC and evaluated the use of ultrasound for distinguishing CCC from HGSC. Although ultrasound examinations cannot clearly diagnose the specific histological type of ovarian tumor, some imaging features were more common and more suggestive of particular histologic types.

The sonographic features of OCCC included a well-demarcated hypoechoic mass with smooth and clear margins in 86.96% of patients (40/46); however, HGSC were mostly masses with unclear boundaries (73.47%, 72/98). There was a statistically significant difference between the two groups. It is rare to encounter bilateral

involvement among patients with OCCC. Several studies have indicated that patients with OCCC are more likely to present with a unilateral pelvic mass; in contrast, patients with HGSC are more likely to present with a bilateral mass[20, 21]. Our results indicate that significant differences were found in unilaterality (97.78% vs 63.89%) between ovarian OCCC and HGSC. In general, OCCC tumors do not have rich blood flow. Minimal Doppler flow signals were detected in 60.87% (28/46) of tumors, while 39.13% (18/46) of tumors showed moderate or abundant flow signals. In contrast, abundant blood flow is common in HGSC tumors. Compared to HGSC patients, fewer OCCC patients had peritoneal implantation and ascites. There was also a statistically significant difference between the two groups in terms of presence of peritoneal metastasis and ascites. OCCC commonly appears as a large, round or oval mass ; the configuration includes solid, both solid and cystic, or mainly cystic with solid nodules or papillary projections. In contrast, HGSC is typically a large, irregularly shaped tumor with solid masses or mixed cystic-solid masses with small papillary projections .

Mural nodules and papillary projections play an important role in distinguishing OCCC from HGSC. Papillary projections are defined as pathology that involves the folding of the proliferating neoplastic epithelium growing over a central fibrovascular stromal core. Papillary projections are mainly located against the inner wall of cysts or rarely on the septa[22, 23]. Histopathologically, mural nodules or papillary projections had a loose structure with fewer tumor cells[24, 25]. Approximately 54.35% (25/46) of OCCC contained papillary projections, compared to only 41.84% (41/98) of HGSC. Many researchers have found that papillary projections of HGSC are smaller and irregular, while those of OCCC are larger and round. In our study, there was a statistically significant difference in the mean size of papillary projections between CCC and HGSC (P<0.05). The mean size of the papillary projections was significantly larger in CCC than in HGSC (5.40 ± 0.7 cm vs 2.06 ± 0.4 cm). F Pozzati et al[4]. confirmed that papillary projections are particularly common in OCCC (41.7%) arising from endometriosis. Mural nodules and papillary processes are effective methods for distinguishing the two groups of lesions.

Our study had several limitations. The main limitation was the number of OCCC; therefore, larger samples are necessary to confirm the value of these imaging features for diagnosing OCCC. Second, this was a retrospective study that may lack a desirable study design, and there may have been some selection bias in the patients included in the analyses. Third, the interreader variability was not evaluated.

In our study, we found that there are many differences between OCCC and HGSC. The combination of clinical examinations and different imaging features is conducive to the differential diagnosis of these two tumors, which is helpful for providing valuable imaging information in clinical practice.

Abbreviations

OCCC：ovarian clear cell carcinoma；HGSC：ovarian high-grade serous carcinoma

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Author contributions

LW: Design of the study, data collection, and writing the manuscript. QLX: Design of the study and revising the manuscript. WXJ: Data analysis.

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Availability of data and materials

Please contact the first author for data requests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Friendship Hospital affiliated to Capital Medical University. Written informed consent was obtained from

patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table 1 Comparison of clinical features between OCCC and HGSC

Clinical features	OCCC (n=45)	HGSC (n=72)	χ^2	P value
Laterality			17.916	<0.001
Unilateral	44	46		
Bilateral	1	26		
Menopausal status			0.061	0.805
Premenopause	16	24		
Postmenopause	29	48		
FIGO stage(postsurgical stage)			26.223	<0.001
Ⅰ/Ⅱ	35	21		
Ⅲ/Ⅳ	10	51		
Endometriosis			20.059	<0.001
Absent	29	69		
Present	16	3		

Table 2 Comparison of ultrasound features between OCCC and HGSC

ultrasound features	OCCC (n=46)	HGSC (n=98)	χ^2	P value
Boundary of the tumor			46.042	<0.001
Clear	40	26		
Unclear	6	72		
Shape			32.789	<0.001
Round/oval	32	20		
Irregular	14	78		
Ovarian Size(cm)			3.130	0.077
<10	26	70		
>10	20	28		
Papillary projections			1.970	0.160
Present	25	41		
Absent	21	57		
Configuration			5.265	0.072
Solid	15	52		
Cystic	12	18		
Cystic-solid	19	28		
Color score			5.051	0.025
Score1-2	28	40		
Score3-4	18	58		
Peritoneal metastasis^			4.590	0.032
Absent	43	59		
Present	2	13		
Ascites^			8.770	0.003
Absent	39	44		
Present	6	28		

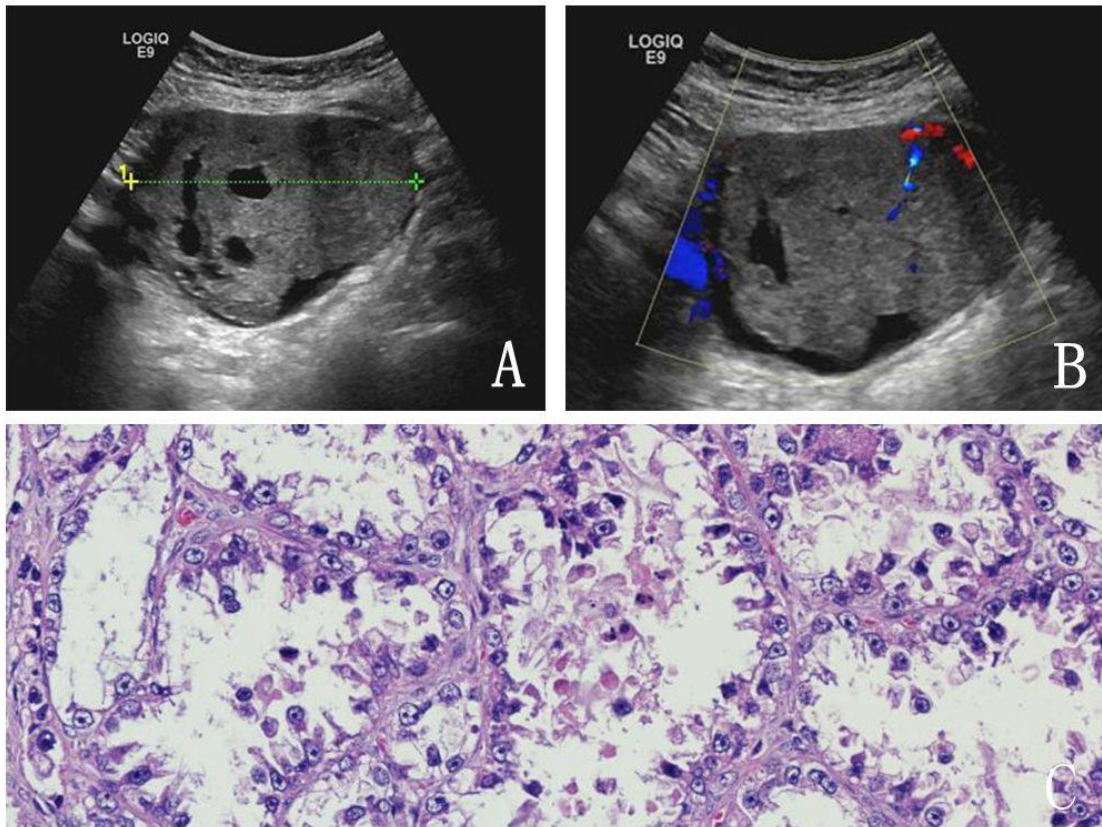**^ numbers for 45 patients with OCCC and 72 patients with HGSC.**

Fig.1　A 52-year-old woman with pelvic mass was found by physical examination. **A**　A heterogeneous solid mass with an irregular shape was detected in the right ovary by ultrasound examination; **B**　minimal blood flow signals were detected in the mass. **C**　pathological findings showed ovarian clear cell carcinoma.
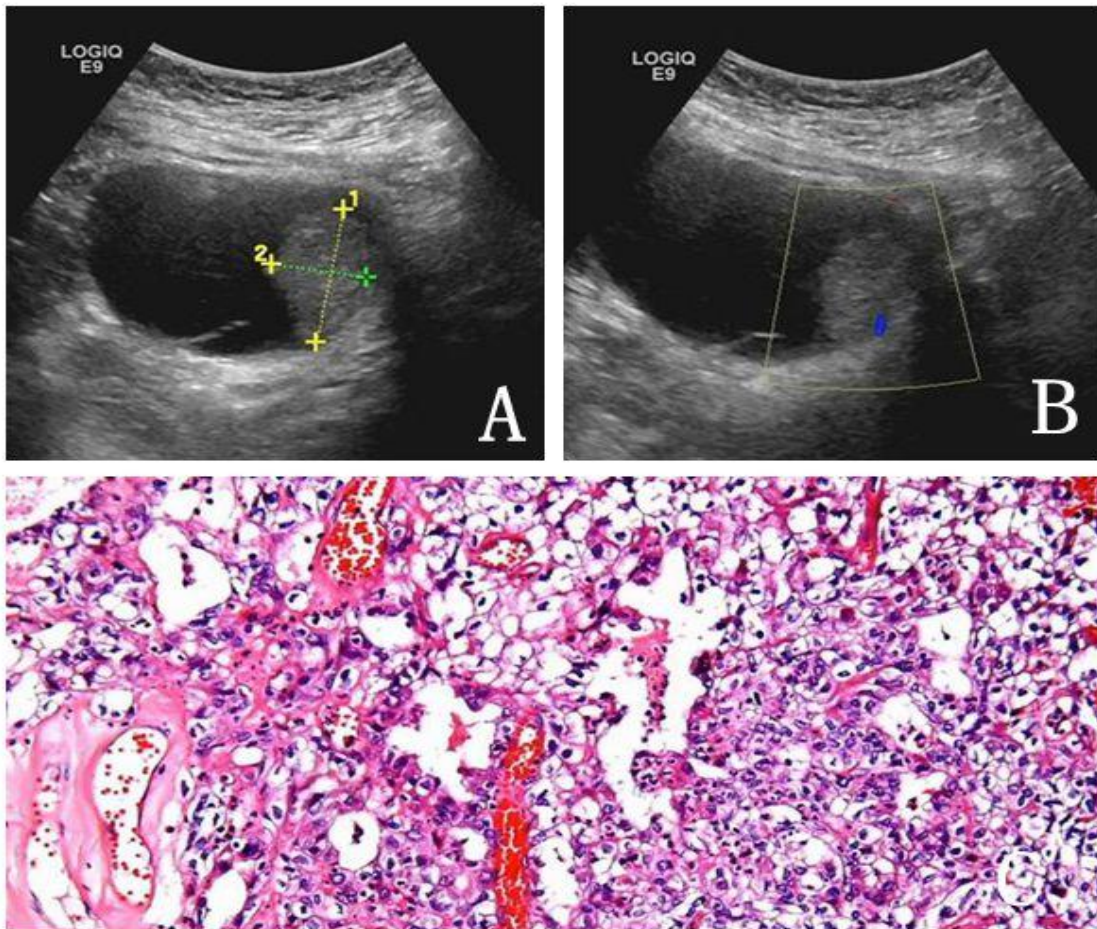
Fig.2 A 66-year-old woman with pelvic mass was found by physical examination. On ultrasound examination, **A** In the right ovary, a well-circumscribed cystic mass with papillary projections was seen, the size of which was 3.97×2.39cm. **B** minimal Doppler flow signals were detected in the papillary projections. **C** pathological findings showed ovarian clear cell carcinoma.
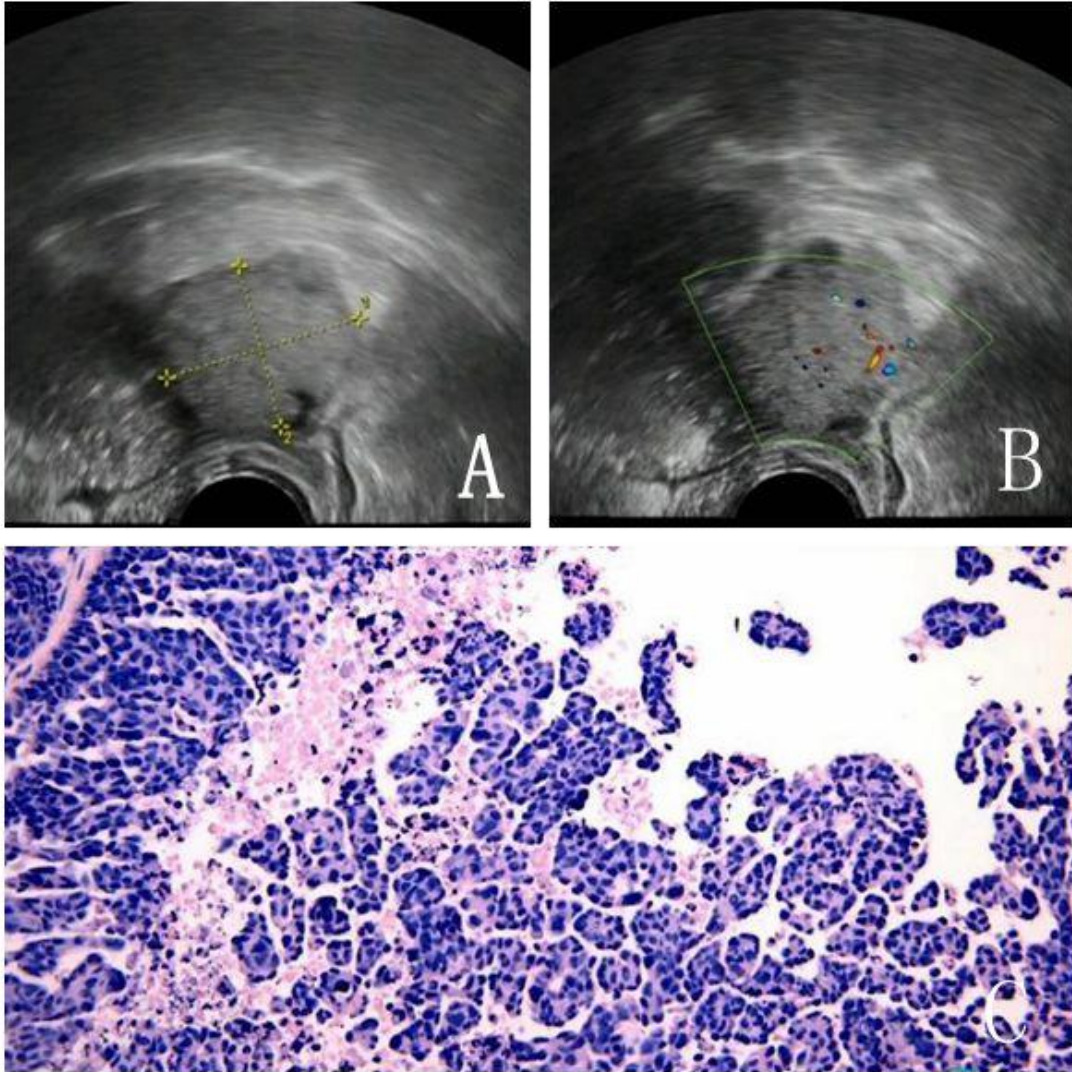
Fig.3 A 62-year-old woman with pelvic mass was found by ultrasound examination. **A** A well-circumscribed mass was detected in the left ovary by ultrasound examination; **B** minimal blood flow signals were detected in the mass. **C** pathological findings showed ovarian high-grade serous carcinoma.