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

Wei Liu
Capital Medical University Affiliated Beijing Friendship Hospital  https://orcid.org/0000-0002-3428-9258

Lin-Xue Qian (✉ 18310238439@163.com)
Beijing Friendship Hospital Captial Medical University

Xue-Jing wei
Capital Medical University Affiliated Beijing Friendship Hospital

Research Article

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

Posted Date: November 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1037923/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Comparison of clinical characteristics and ultrasound features of ovarian clear cell carcinoma and ovarian high-grade serous carcinoma

Wei Liu¹, Lin-Xue Qian¹, Xue-Jing Wei²

¹Department of Ultrasound, Beijing Friendship Hospital, Capital Medical University, 100050 Beijing, China
²Department of Pathology, Beijing Friendship Hospital, Capital Medical University, 100050 Beijing, China

Address correspondence to: Lin-Xue Qian.
E-mail: qianlinxue2002@163.com

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\[^1\text{–}3\]. 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 $63.4 \pm 12.2$ 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) (Figs 1, 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\cite{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\cite{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\cite{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 \cite{4,5,17-19}. However, Fei-Chun Ku et al. found that a history of endometriosis was not associated with invasive ovarian HGSC\cite{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

**Acknowledgements**

Not applicable.

**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.

**Funding**

This study was funded by the Beijing Municipal Administration of Hospitals’ Mission Plan under Grant No. [SML 20150101].

**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.

References
1. Ma FH, Qiang JW, Zhang GF, Li HM, Cai SQ, Rao YM (2016) Magnetic resonance imaging for distinguishing ovarian clear cell carcinoma from high-grade serous carcinoma. J Ovarian Res. Jul 4;9(1):40.
2. Sahin H, Sari ME, Cuylan ZF, Haberal AN, Sirvan L, Coban G, Yalcin I, GÜngör T, Celik H, Meydanli MM, Ayhan A. (2018) Is the presence of endometriosis associated with a survival benefit in pure ovarian clear cell carcinoma? Arch Gynecol Obstet. Apr;297(4):1005-1013.
3. Prat J (2012) Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virch Arch 460:237–249
4. Pozzati F, Moro F, Pasciuto T, Gallo C, Ciccarone F, Franchi D, Mancari R, Giunchi S, Timmerman D, Landolfo C, Epstein E, Chiappa V, Fischerova D, Fruscio R, Zannoni GF, Valentin L, Scambia G, Testa AC. (2018) Imaging in gynecological disease (14): clinical and ultrasound characteristics of ovarian clear cell carcinoma. Ultrasound Obstet Gynecol. Dec;52(6):792-800.
5. Kucukgoz Gulec U, Paydas S, Guzel AB, Vardar MA, Khatib G, Gumurdulu D. (2015) The clinical characteristics and outcomes of cases with pure ovarian clear cell, mixed type and high-grade serous adenocarcinoma. Arch Gynecol Obstet.Oct;292(4):923-9.
6. Ye S, Yang J, Cao D, Bai H, Huang H, Wu M, Chen J, You Y, Lang J, Shen K. (2015) Characteristic and prognostic implication of venous thromboembolism in ovarian clear cell carcinoma: a 12-year retrospective study. PLoS One. Mar 20;10(3):e0121818.
7. Matsuura Y, Robertson G, Marsden DE, Kim SN, Gebski V, Hacker NF. (2007) Thromboembolic complications in patients with clear cell carcinoma of the ovary. Gynecol Oncol.Feb;104(2):406-10.
8. Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, Suzuki M, Sato I, Taguchi K. (2000) Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. June 1;88(11):2584-9.
9. Behbakht K, Randall TC, Benjamin I, Morgan MA, King S, Rubin SC. (1998) Clinical characteristics of clear cell carcinoma of the ovary. Gynecol Oncol Aug:70:255–8.
10. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. (2000) Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol. Oct;16(5):500–5.

11. Chen H, Liu Y, Shen LF, Jiang MJ, Yang ZF, Fang GP. (2016) Ovarian thecoma-fibroma groups: clinical and sonographic features with pathological comparison. J Ovarian Res. 2016 Nov 22;9(1):81.

12. Ku FC, Wu RC, Yang LY, Tang YH, Chang WY, Yang JE, Wang CC, Jung SM, Lin CT, Chang TC, Chao A, Lai CH. (2018) Clear cell carcinomas of the ovary have poorer outcomes compared with serous carcinomas: Results from a single-center Taiwanese study. J Formos Med Assoc. Feb;117(2):117-125.

13. Joo HL, Shin YR, Rha SE, Park CS, Shim DJ, Kim K. (2018) Preoperative discrimination of tumour stage in clear cell carcinoma of the ovary using computed tomography and magnetic resonance imaging. Eur J Radiol. Dec;109:19-26.

14. Timmers PJ, Zwinderman AH, Teodorovic I, Vergote I, Trimbos JB. (2009) Clear cell carcinoma compared to serous carcinoma in early ovarian cancer: same prognosis in a large randomized trial. Int J Gynecol Cancer. Jan;19(1):88-93.

15. Hogen L, Thomas G, Bernardini M, Bassiouney D, Brar H, Gien LT, Rosen B, Le L, Vicus D. (2016) The effect of adjuvant radiation on survival in early stage clear cellovarian carcinoma. Gynecol Oncol. Nov;143(2):258-263.

16. Del Carmen MG, Birrer M, Schorge JO. (2012) Clear cell carcinoma of the ovary: a review of the literature. Gynecol Oncol. Sep;126(3):481-90.

17. Scarfone G, Bergamini A, Noli S, Villa A, Cipriani S, Taccagni G, Vigano' P, Candiani M, Parazzini F, Mangili G. (2014) Characteristics of clear cell ovarian cancer arising from endometriosis: a two center cohort study. Gynecol Oncol. Jun;133(3):480-4.

18. Boyraz G, Selcuk I, Yazıcıoğlu A, Tuncer ZS. Ovarian carcinoma associated with endometriosis. (2013) Eur J Obstet Gynecol Reprod Biol. Sep;170(1):211-3.

19. Munksgaard PS, Blaakaer J. (2012) The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. Gynecol Oncol. Jan;124(1):164-9.

20. Morioka S, Kawaguchi R, Yamada Y, Iwai K, Yoshimoto C, Kobayashi H. (2019) Magnetic resonance imaging findings for discriminating clear cell carcinoma and endometrioid carcinoma of the ovary. J Ovarian Res. Feb 25;12(1):20.

21. Moro F, Baima Poma C, Zannoni GF, Vidal Urbinati A, Pascuito T, Ludovisi M, Moruzzi MC, Carinelli S, Franchi D, Scambia G, Testa AC. (2017) Imaging in gynecological disease (12): clinical and ultrasound features of invasive and non-invasive malignant serous ovarian tumors. Ultrasound Obstet Gynecol. Dec;50(6):788-799.

22. Hassen K, Ghossain MA, Rousset P, Sciot C, Hugol D, Baddoura R, Vadrot D, Buy JN. (2011) Characterization of papillary projections in benign versus borderline and malignant ovarian masses on conventional and color Doppler ultrasound. AJR Am J Roentgenol. Jun;196(6):1444-9.
23. Mascilini F, Savelli L, Scifo MC, Exacoustos C, Timor-Tritsch IE, De Blasis I, Moruzzi MC, Pasciuto T, Scambia G, Valentino L, Testa AC. (2017) Ovarian masses with papillary projections diagnosed and removed during pregnancy: ultrasound features and histological diagnosis. Ultrasound Obstet Gynecol. Jul;50(1):116-123.

24. Li HM, Qiang JW, Xia GL, Zhao SH, Ma FH, Cai SQ, Feng F, Fu AY. (2015) MRI for differentiating ovarian endometrioid adenocarcinoma from high-grade serous adenocarcinoma. J Ovarian Res. Apr 30;8:26.

25. Landolfo C, Valentino L, Franchi D, Van Holsbeke C, Fruscio R, Froyman W, Sladkevicius P, Kaijser J, Ameye L, Bourne T, Savelli L, Coosemans A, Testa A, Timmerman D. Differences in ultrasound features of papillations in unilocular-solid adnexal cysts: a retrospective international multicenter study. Ultrasound Obstet Gynecol. 2018 Aug;52(2):269-278.
### Table 1  Comparison of clinical features between OCCC and HGSC

| Clinical features                      | OCCC (n=45) | HGSC (n=72) | χ²  | 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) | $\chi^2$ | 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   |
| Score 1-2                            | 28          | 40          |          |         |
| Score 3-4                            | 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.
A 52-year-old woman with pelvic mass was found by physical examination. 

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.