Clinical Characteristics and Prognosis of Ovarian Clear Cell Carcinoma: a Retrospective Study of 112 Patients in Beijing

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Research

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Abstract

Objectives

This retrospective study aimed to evaluate the clinical characteristics and prognosis of ovarian clear cell carcinoma (OCCC) and to further explore the monitoring value of cancer antigen 125 (CA-125).

Methods

The medical records of 112 OCCC patients who were treated in Peking Union Medical College Hospital (PUMCH) between 2014 and 2019 were collected and reviewed, and data such as age, Federation of Gynecology and Obstetrics (FIGO) stage, CA-125 level, treatment, recurrence, and death were extracted.

Outcomes

The median patient age was 50 (45, 57) years. Sixty (53.57%) patients were in stage I, 13 (11.61%) patients were in stage II, 22 (28.57%) patients were in stage III, and 7 (6.25%) patients were in stage IV. In total, 109 (97.32%) patients received adjuvant chemotherapy. The median chemotherapy cycles of CA-125 normalization was 2 (0, 3). The 1-year and 3-year progression-free survival (PFS) rates were 87.85% and 72.90%, respectively. The median PFS1 duration was 19 (11, 35) months, and the median overall survival (OS) duration was 24 (13, 40) months. Recurrence occurred in 32 patients, of whom 7 (21.88%) developed platinum-resistant recurrence. Fifty percent of relapsed patients had a CA-125 level<35 IU/ml at the time of relapse. Nine (28.13%) patients experienced a second recurrence. In the multivariate Cox regression analysis, the Chemotherapy cycles of CA-125 normalization remained nonsignificant for stage I (P=0.003, HR 4.287, 95% CI=1.632–11.258) and stage III (P=0.003, HR 4.287, 95% CI=1.632–11.258) disease. Multivariate Cox regression showed that platinum resistance was an independent factor for PFS2 (P=0.008, HR 11.562, 95% CI=1.873–71.353).

Conclusions

FIGO stage and chemotherapy resistance are independent risk factors for prognosis. CA-125 levels following treatment are a valid indicator for treatment monitoring. Regardless of chemosensitivity to CA-125, CA-125 normalization before chemotherapy cycle 2 may not be a distinct inflection point for PFS and OS.

Background

As a form of epithelial ovarian cancer (EOC), ovarian clear cell carcinoma (OCCC) shows distinctive epidemiological and clinical characteristics.1 In Asia, OCCC accounts for 11.6% (Korea)2 and 30% (Japan)3 of all EOCs, surpassing 6% in the United States4. In addition, its probability is on the rise, with an observed increase from 3.56% in 1979–1984 to 18.13% in 2005–2008 in Taiwan5 and from 23.4% in 2010 to 29.1% as of 2010 in Japan3. The clinical management of OCCC consists of cytoreductive surgery
followed by platinum- and taxane-based chemotherapy. Compared to other EOCs, due to the relative resistance of OCCC to platinum drugs, the efficacy of platinum-based chemotherapy is less than 40% for patients in stage III/IV. The clinical outcomes of patients with advanced OCCC are dismal. Regarding stage I/II disease, the one-year survival rate of patients with OCCC and other histotypes is no less than 80%, while for stage III/IV disease, the one-year and five-year survival rates of patients with OCCC are 60% and 22%, respectively, which are lower than those of patients with other histotypes (80% and 35%, respectively). For patients who experience recurrence, the 5-year post-recurrence survival rate is only 13.2%. Given the prevalence and poor prognosis of OCCC in Asia, we retrospectively analysed OCCC patients who visited Peking Union Medical College Hospital (PUMCH) between 2015 and 2019, aimed to describe the treatment methods, recurrence rate and survival rate of OCCC patients and to determine risk factors for the recurrence and survival of OCCC patients.

Methods

Patients and data collection

This retrospective single-centre study used essentially the same method as the two-academic-Institute study published in Oncotarget in 2016. We reviewed patients with OCCC (International Federation of Gynecology and Obstetrics [FIGO] stage I – IV) who received treatment at PUMCH (Beijing, China) between 2015 and 2019. We excluded OCCC patients who chose fertility-preserving surgery.

We extracted and evaluated the following information from medical records: demographic and pathological characteristics, immunohistochemistry indicators (Napsin A, HNF1B), stage at diagnosis, surgery, subsequent systemic chemotherapy, recurrence and disease status at last contact. Serum cancer antigen 125 (CA-125) levels were measured using a radioimmunoassay kit (Roche F170 Modular system). The commonly accepted normal upper limit for CA-125 is 35 U/ml. Serum CA-125 levels were measured at the time of the first attack, preoperation and post-operation, at each cycle of chemotherapy, and at each contact during the follow-up period. The need for informed consent was waived because of the retrospective nature of the study. The study protocol was approved by the Ethics Committee of PUMCH.

Main outcome indicators

Progression-free survival 1 (PFS1) and overall survival (OS) were defined as the time intervals from the date of the primary surgery to the date of first recurrence and death or last contact, respectively. Progression-free survival 2 (PFS2) was defined as the time interval from the date of the second surgery or chemotherapy to the date of second recurrence and death or last contact. Patients were considered to have platinum-resistant disease if the interval time was less than 6 months from the completion of the last platinum-based chemotherapy to disease recurrence, and the patients were considered to have platinum-sensitive disease if the time exceeded 6 months.

Statistical analysis
Statistical analysis was performed using SAS V9.3. The distributions of clinicopathologic events were evaluated using the chi-square test or Fisher’s exact test. The Wilcoxon rank-sum test or the Kruskal-Wallis H test was used to determine the distribution of continuous variables between groups. The survival curves were compared by employing the log-rank test. A Cox proportional hazards model was used to evaluate the independent factors affecting survival. A $P$ value < 0.05 was considered significant.

Outcomes

1. Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. The median patient age was 50 (45, 57) years. Fifty-four (48.21%) patients had a CA-125 level at diagnosis less than 35 IU/ml. Sixteen (14.29%) patients received primary chemotherapy, and 109 (97.32%) patients received chemotherapy. The median chemotherapy cycles of CA-125 normalization was 2 (0, 3). The median follow-up time of 112 patients was 23 months (12.50, 39.50). Napsin A and HNF1B were negative in 9% of patients. The 1-year and 3-year PFS rates were 87.85% and 72.90%, respectively. The median PFS duration was 19 months (11, 35), and the median OS duration was 24 (13 40) months. Pretreatment CA-125 levels, chemotherapy cycles of CA-125 levels normalization, number of chemotherapy cycles, disease status at the last follow-up, 1-year PFS rate, 3-year PFS rate, 3-year OS rate, and PFS were significantly different according to different FIGO stages.

2. Characteristics of patients who experienced recurrence

Table 2 lists the characteristics of 32 patients who experienced recurrence, of whom 7 (21.88%) had platinum-resistant recurrence. Fifty percent of patients who experienced recurrence had a CA-125 level < 35 U/ml at the time of recurrence. Twenty-one (65.63%) patients underwent a second cytoreductive operation, and 9 (28.13%) patients experienced a second recurrence. The median PFS2 values for stages I, II, III, and IV were 7.00 (3.00, 24.00), 3.00 (2.50, 7.00), 8.50 (3.00, 15.00), and 14.00 (8.00, 36.00), respectively.

3. Survival analysis

Log-rank tests showed that the median PFS1 durations of stage I and stage II-IV disease were significantly different (57 months vs 21 months, $P = 0.0003$). The median PFS1 durations were also significantly different (17 months vs 54 months, $P = 0.0019$) between patients who received > 6 and ≤ 6 chemotherapy cycles (supplemental material-Figures 1, 2). Univariate Cox analysis showed that FIGO stage ($P = 0.001$, HR: 3.57, 95% CI = 1.72–7.41), number of chemotherapy cycles ($P = 0.004$, HR: 3.23, 95% CI = 1.47–7.08) and chemotherapy cycles of CA-125 normalization ($P = 0.004$, HR: 3.98, 95% CI = 1.57–7.08) were positive predictors of PFS1. After adjusting for FIGO stage and age, these variables were not significant. In the multivariate Cox regression analysis, chemotherapy cycles of CA-125 normalization remained nonsignificant in patients in stage I ($P = 0.319$, HR 2.26, 95% CI = 0.45–11.27) and stage III ($P = 0.965$, HR 1.03, 95% CI = 0.27–3.89). (supplemental material-Table 4)
Log-rank tests also showed a statistically significant difference in the median PFS2 durations between platinum-resistant relapsed patients and non-platinum-resistant relapsed patients (8 months vs 19 months, $P = 0.0020$) (supplemental material-Figure 3). Multivariate Cox regression showed that platinum resistance was an independent factor for PFS2 ($P = 0.008$, HR 11.562, 95% CI = 1.873–71.353) (supplemental material-Table 5).

**Discussion**

This study is one of the largest retrospective series of OCCC patients in which data were collected from patients at diagnosis to second recurrence. We mainly described the stage composition, recurrence status, and PFS of OCCC patients and found that FIGO stage and chemotherapy resistance are independent risk factors for prognosis. We also aimed to explain the limitations associated with CA-125 in the staging and recurrence monitoring of OCCC. The limitations of CA-125 in patients with FIGO stage I and those who experience recurrence are highlighted.

Among the 112 patients included, 53.57% were in stage I and 28.57% were in stage III, which is similar to the results of a national study performed in South Korea$^2$ but quite different from other single-centre studies$^6$ $^7$. All patients underwent staging or cytoreductive surgery. Except for one patient who refused chemotherapy after surgery, all the other patients received platinum chemotherapy drugs. Approximately $1/4$ of patients in stage III/IV receive advanced chemotherapy, although we found that advanced chemotherapy is not beneficial to prognosis. It is worth noting that the one-year PFS rate of patients with stage I, II and III disease was approximately 90%, and the three-year PFS rate varied greatly, with 86.44% for patients in stage I, 66.67% for patients in stage II, and 66.67% for patients in stage III 56.67%. These three indicators were slightly higher than the national research data of South Korea. Staging has been confirmed as a risk factor for the prognosis of OCCC in many studies, so I will not repeat it here. OCCC patients with platinum-resistant recurrence had a shorter PFS duration than those with platinum-sensitive recurrence (8 months vs 19 months). The median survival duration with single-agent chemotherapy and bevacizumab does not exceed 16 months$^{12}$. Most other chemotherapy regimens are almost ineffective.$^{11}$ A recent study summarized the biological rationale and available clinical data on immunotherapy in platinum-resistant ovarian cancer and discussed the challenges and future areas of research in the field$^{13}$.

In contrast to other studies$^{10}$ $^{14}$, we found that the monitoring of CA-125 is of limited significance and has no predictive significance for prognosis.$^{10}$ $^{14}$ We previously published a study in which OCCC patients who visited PUMCH between 1993 and 2013 were analysed and found that CA-125 levels following treatment were a valid indicator for treatment monitoring$^{10}$. Although the same method was used, in the current study, we obtained a negative result, that is, the normalization of CA-125 levels before 2 cycles of chemotherapy does not affect PFS or OS. This may be because the samples we collected are different. In addition, we found that 61.11% of stage I patients had CA-125 levels in the normal range when they first became ill. During treatment, there was no difference in the number of courses of chemotherapy or
prognosis between these patients and other stage I patients, and 72.73% of these patients had normal CA-125 levels after surgery or 1 course of chemotherapy. Therefore, we believe that for patients who are not sensitive to the CA-125 test the first time, ultrasound, CT or MRI should be considered first. Importantly, an examination can reduce the disease burden on patients. In contrast to stage I patients, 76.67% of stage III patients had CA-125 levels greater than 35 IU/ml. We believe these patients are more suitable for CA-125 monitoring. Moreover, 50% of patients who experienced recurrence had CA-125 levels in the normal range, which further showed that monitoring CA-125 levels is of limited significance and may delay the discovery of recurrence.

We verified the value of Napsin A and HNF1B in the diagnosis of OCCC by calculating the false positive rate. In 2013, Skirnisdottir I\textsuperscript{15} proposed that the positivity of Napsin A is helpful for the diagnosis of OCCC. In 2020, Fatemeh Nili\textsuperscript{16} reported that the sensitivity of Napsin A in the diagnosis of OCCC was 85%. However, we found that 39.62% of patients were still negative for Napsin A. Only 15% of patients were negative for HNF1B, which is consistent with Wenbin Huang's findings\textsuperscript{17}. We combined the two indicators and found that the false positive rate was 9%. It is also worth noting that patients who were in remission had a shorter follow-up time than patients who relapsed (22.50 vs 33.00), (not shown in the table due to space reasons). There is no doubt that disease monitoring has been gradually relaxed in these patients. We believe that clinicians should provide patients with continuous follow-up to detect disease recurrence in advance and intervene as soon as possible.

The patients included in the current study were from economically developed areas in China, and they had satisfactory economic and medical conditions, which suggests that in poor areas in China, the accessibility of treatment and prognosis may be worse. Due to the habit of case writing, clinicians are accustomed to recording key CA-125 values, such as preoperative CA-125 values and chemotherapy cycles of CA-125 normalization. CA-125 values that do not exhibit major changes, such as those after each chemotherapy procedure, cannot be obtained and are thus not conducive to our discussion of the monitoring value of CA-125.

**Conclusion**

FIGO stage and chemotherapy resistance are independent risk factors for prognosis. CA-125 levels following treatment are a valid indicator for treatment monitoring. Regardless of chemosensitivity to CA-125, CA-125 normalization before chemotherapy cycle 2 may not be a distinct inflection point for PFS and OS.

**Abbreviations**

OCCC: ovarian clear cell carcinoma;

CA-125: cancer antigen 125;

FIGO: International Federation of Obstetrics and Gynecology;
HR: hazard ratio;  PFS: progression-free survival;  OS: overall survival

Declarations

Funding Statement

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Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of PUMCH.

Author Contributions

Huimei Zhou designed the study, performed the data analyses and wrote the manuscript. Qian Liu performed the data analyses and revised the manuscript. Jiaxin Yang designed the study, performed the data analyses, revised the manuscript and approved the final version of the manuscript. Xiaohua Shi, Dongyan Cao, Tao Wang and Keng Shen collected and reviewed the data and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Tables
Table 1
Patient characteristics

| Characteristic                                      | Stage I  (N = 60) | Stage II (N = 13) | Stage III (N = 32) | Stage IV (N = 7) | All (N = 112) | Statistics | P-value |
|----------------------------------------------------|-------------------|-------------------|--------------------|------------------|---------------|------------|---------|
| Age at diagnosis, years, median (range)            | 49 (42.50, 56)    | 52.50 (45.50, 56.50) | 49.50 (46.50, 57.50) | 59 (47, 64) | 50 (45, 57) | 3.47*      | 0.3245  |
| Pretreatment CA-125 level, IU/ml                   |                   |                   |                    |                  |               | 22.23#     | <0.0001 |
| <35, n (%)                                         | 36 (66.67)        | 3 (25.00)         | 5 (16.67)          | 2 (33.33)        | 46 (45.10) |            |         |
| ≥35, n (%)                                         | 18 (33.33)        | 9 (75.00)         | 25 (83.33)         | 4 (66.67)        | 56 (54.90) |            |         |
| Primary chemotherapy                               |                   |                   |                    |                  |               | 7.23#      | 0.0648  |
| No, n (%)                                          | 54 (90)           | 13 (100.0)        | 24 (75)            | 5 (71.43)        | 96 (85.71) |            |         |
| Yes, n (%)                                         | 6 (10)            | 0 (0)             | 8 (25)             | 2 (28.57)        | 16 (14.29) |            |         |
| Chemotherapy cycles of CA-125 normalization, median (range, cycles) | 1 (0, 2) | 2 (2, 3) | 2 (2, 4) | 1.50 (0, 3) | 2 (0, 3) | 14.67* | 0.0021 |
| Received chemotherapy                              |                   |                   |                    |                  |               | 1.71*      | 0.6355  |
| Yes, n (%)                                         | 59 (98.33)        | 12 (92.31)        | 31 (96.88)         | 7 (100.0)        | 109 (97.32) |            |         |
| No, n (%)                                          | 1 (1.67)          | 1 (7.69)          | 1 (3.13)           | 0 (0.00)         | 3 (2.68)    |            |         |
| Number of chemotherapy cycles, median (range)      | 6 (3.50, 6)       | 5 (5.6)           | 6 (5.50, 8)        | 5 (5, 8)         | 6 (4, 6)    | 11.23*     | 0.0105  |
| Napsin A +, n (%)                                  | 16 (61.54)        | 5 (55.56)         | 10 (62.50)         | 1 (50)           | 32 (60.38)  | 0.22#      | 0.9739  |

*: Kruskal-Wallis H test; #: chi-square test
| Characteristic                          | Stage I (N = 60) | Stage II (N = 13) | Stage III (N = 32) | Stage IV (N = 7) | All (N = 112) | Statistics  | P-value  |
|----------------------------------------|------------------|-------------------|--------------------|------------------|--------------|------------|----------|
| - , n (%)                              | 10 (38.46)       | 4 (44.44)         | 6 (37.50)          | 1 (50)           | 21 (39.62)   | 0.52#      | 0.9138   |
| HNF1B                                  |                  |                   |                    |                  |              |            |          |
| + , n (%)                              | 15 (83.33)       | 4 (80)            | 13 (86.67)         | 2 (100)          | 34 (85)      |            |          |
| - , n (%)                              | 3 (16.67)        | 1 (20)            | 2 (13.33)          | 0 (0)            | 6 (15)       |            |          |
| Napsin A and HNF1B                     |                  |                   |                    |                  |              | 4.97#      | 0.5473   |
| ++, n (%)                              | 10 (62.50)       | 3 (75.00)         | 7 (58.33)          | 0 (0.00)         | 20 (60.61)   |            |          |
| +-, n (%)                              | 5 (31.25)        | 0 (0.00)          | 4 (33.33)          | 1 (100.0)        | 10 (30.30)   |            |          |
| -, n (%)                               | 1 (6.25)         | 1 (25.00)         | 1 (8.33)           | 0 (0.00)         | 3 (9.09)     |            |          |
| Disease status at the last follow-up   |                  |                   |                    |                  |              | 32.22#     | < 0.0010 |
| Alive with disease, n (%)              | 7 (11.67)        | 4 (30.77)         | 16 (50)            | 2 (28.57)        | 29 (25.89)   |            |          |
| Alive, n (%)                           | 51 (85)          | 8 (61.54)         | 13 (40.63)         | 2 (28.57)        | 74 (66.07)   |            |          |
| Dead, n (%)                            | 2 (3.33)         | 1 (7.69)          | 3 (9.38)           | 3 (42.86)        | 9 (8.04)     |            |          |
| Follow-up time (months), median (range)| 27.50 (14, 41)   | 20 (11, 35)       | 18.50 (7.50, 38.50)| 19 (13, 51)      | 23 (12.50, 39.50) | 2.76*   | 0.4304   |
| 1-year PFS rate, n (%)                 | 53 (89.83)       | 11 (91.67)        | 27 (90)            | 3 (50)           | 94 (87.85)   | 8.56#      | 0.0357   |
| 3-year PFS rate, n (%)                 | 51 (c)           | 8 (66.67)         | 17 (56.67)         | 2 (33.33)        | 78 (72.90)   | 14.47#     | 0.0023   |
| 1-year OS rate, n (%)                  | 58 (98.31)       | 12 (100.0)        | 29 (96.67)         | 5 (83.33)        | 104 (97.20)  | 4.87#      | 0.1812   |
| 3-year OS rate, n (%)                  | 57 (96.61)       | 12 (100.0)        | 28 (93.33)         | 3 (50)           | 100 (93.46)  | 20.33#     | 0.0010   |

*: Kruskal-Wallis H test; #: chi-square test
| Characteristic  | Stage I  | Stage II | Stage III | Stage IV | All     | Statistics | P-value |
|----------------|----------|----------|-----------|----------|---------|------------|---------|
|                | (N = 60) | (N = 13) | (N = 32)  | (N = 7)  | (N = 112)|            |         |
| PFS, median (range) | 26 (11, 38) | 23 (12, 32.50) | 14 (8, 20) | 12 (10, 16) | 19 (11, 35) | 8.06*  | 0.0449 |
| OS, median (range)  | 26 (14, 41) | 23 (13.50, 37) | 19.50 (9, 40) | 19 (13, 51) | 24 (13, 40) | 1.24*  | 0.7443 |

*: Kruskal-Wallis H test; #: chi-square test
Table 2
Characteristics of patients who experienced recurrence

| Characteristic                  | Stage I (N = 11) | Stage II (N = 4) | Stage III (N = 14) | Stage IV (N = 3) | All (N = 32) | Statistics | P-value |
|--------------------------------|------------------|------------------|--------------------|------------------|--------------|------------|---------|
| Platinum resistance            |                  |                  |                    |                  |              |            |         |
| Yes, n (%)                     | 4 (36.36)        | 1 (25.00)        | 1 (7.14)           | 1 (33.33)        | 7 (21.88)    | 3.38#      | 0.3363  |
| No, n (%)                      | 7 (63.64)        | 3 (75.00)        | 13 (92.86)         | 2 (66.67)        | 25 (78.13)   |            |         |
| CA-125 level at recurrence     |                  |                  |                    |                  |              |            |         |
| <35, n (%)                     | 7 (63.64)        | 1 (25.00)        | 6 (42.86)          | 2 (66.67)        | 16 (50.00)   | 2.44#      | 0.4867  |
| ≥35, n (%)                     | 4 (36.36)        | 3 (75.00)        | 8 (57.14)          | 1 (33.33)        | 16 (50.00)   |            |         |
| Second cytoreductive operation |                  |                  |                    |                  |              |            |         |
| Yes, n (%)                     | 10 (90.91)       | 2 (50.00)        | 7 (50.00)          | 2 (66.67)        | 21 (65.63)   | 5.07#      | 0.167   |
| No, n (%)                      | 1 (9.09)         | 2 (50.00)        | 7 (50.00)          | 1 (33.33)        | 11 (34.38)   |            |         |
| Second recurrence              |                  |                  |                    |                  |              |            |         |
| Yes, n (%)                     | 1 (9.09)         | 0 (0.00)         | 7 (50.00)          | 1 (33.33)        | 9 (28.13)    | 6.89#      | 0.0755  |
| No, n (%)                      | 10 (90.91)       | 4 (100.0)        | 7 (50.00)          | 2 (66.67)        | 23 (71.88)   |            |         |
| PFS2                           | 7.00 (3.00, 24.00)| 3.00 (2.50, 7.00)| 8.50 (3.00, 15.00)| 14.00 (8.00, 36.00)| 8.00 (3.00, 14.50)| 3.26*      | 0.3531  |

*: Kruskal-Wallis H test; #: chi-square test
| Parameter                                                      | Univariate |          | Multivariate* |          |
|---------------------------------------------------------------|------------|----------|---------------|----------|
|                                                               | HR         | P-value  | HR            | P-value  |
| FIGO stage (II-IV vs I)                                       | 3.57 (1.72, 7.41) | 0.001    | ---           | ---      |
| Age at diagnosis (> 50 vs ≤ 50)                               | 0.88 (0.44, 1.76) | 0.717    | ---           | ---      |
| CA-125 level at diagnosis (≥ 35 vs < 35)                      | 2.56 (0.76, 8.7)  | 0.131    | 1.23 (0.6, 2.51) | 0.567 |
| Primary chemotherapy (Yes vs No)                             | 1.04 (0.41, 2.6)  | 0.941    | 0.6 (0.22, 1.65) | 0.319 |
| Number of chemotherapy cycles (> 6 vs ≤ 6)                   | 3.23 (1.47, 7.08) | 0.004    | 2.1 (0.91, 4.84) | 0.080 |
| chemotherapy cycles of CA-125 normalization (>1 vs ≤ 1)       | 3.98 (1.57, 10.09) | 0.004    | 2.71 (0.99, 7.38) | 0.052 |

* Multivariate Cox regression adjusted for FIGO stage and age; HR: hazard ratio

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- supplementalmaterial3figures.docx