Int J Clin Exp Med 2020;13(11):8700-8706
www.ijcem.com /ISSN:1940-5901/IJCEM0115528

*Original Article*

# Relationship between clinicopathological features of ovarian cancer with CA125, 199 and FIGO staging

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Received June 3, 2020; Accepted August 25, 2020; Epub November 15, 2020; Published November 30, 2020

**Abstract:** Objective: To explore the expression of CA125 and CA199 in epithelial ovarian cancer and the influencing factors on clinical prognosis. Methods: A total of 140 patients diagnosed with epithelial ovarian cancer in our hospital were enrolled in this study. All patients were either followed up for 5 years or died; CA125 and CA199 expressions were detected by chemiluminescence immunoassay and divided into 4 intervals including: q1, q2, q3, q4. Differences in survival rate in each of the 4 intervals were compared. Logistic regression analysis was performed to assess prognostic factors in patients with epithelial ovarian cancer. Results: CA125 and CA199 were expressed differently with regard to FIGO staging, age, residual lesion, pathological type and histological differentiation ($P<0.05$). The 5-year survival rates of patients with epithelial ovarian cancer were 48.4%, 32.3%, 21.0%, 11.5%, respectively, which were significantly different from the median survival time in q1, q2, q3 and q4 ($P<0.05$). Logistic regression analysis found that FIGO staging, age, CA125, CA199, and postoperative residual lesions were independent risk factors for epithelial ovarian cancer ($P<0.05$). Compared with q1, the prognostic OR values for death in q2, q3 and q4 were 1.624 (1.445-1.825), 2.447 (1.785-3.355) and 4.121 (2.624-6.472), respectively. Conclusion: The CA125 and CA199 levels were significantly correlated with the clinicopathological features of epithelial ovarian cancer, and may be used as independent risk factors for the prognosis of epithelial ovarian cancer before surgery.

**Keywords:** Epithelial ovarian cancer, CA125, CA199, prognosis

## Introduction

Ovarian cancer is a common malignant tumor seen in the Department of Gynecology, and it has a high mortality rate. The incidence of ovarian cancer is second only to endometrial and cervical cancers. The recurrence and metastasis have a significant impact the prognosis of patients with ovarian cancer [1]. Serum CA125 and CA199 could be used as tumor markers in the early detection of ovarian cancer. However, ovarian cancer, as the leading gynecological malignancy, has a high probability of metastasis, and is usually diagnosed at advanced stages [2]. The sites of metastasis are mainly lymph nodes, extra-lymph node tissues and various organs, which seriously affect the prognosis of patients [3].

The recurrence rate of ovarian cancer is 35%-72%. Therefore, a timely and sensitive detection method is extremely important for the benefits of patients [4]. At present, the primary diagnostic methods are imaging examinations such as CT and B-ultrasound. CA125 serum tumor marker test is the main pathological examination. Serum CA125 is extremely sensitive to ovarian cancer. Postoperative changes in CA125 levels are highly correlated with cancer recurrence [5].

At present, no studies have fully explained the pathogenesis of ovarian cancer, so there is no effective treatment. As stress levels are on the increase in women, the annual incidence of ovarian cancer has increased significantly, seriously affecting women's health [6]. CA125 is a transmembrane glycoprotein with a high molecular weight, and its baseline level has a significant correlation with the prognosis of ovarian cancer. CA199 is a mucous glycoprotein commonly used to detect gastrointestinal tumors, but in recent years, some researchers have applied it in the diagnosis of ovarian cancer [7]. In this study, 140 patients with epithelial ovarian cancer were selected to analyze

the correlation between serum levels of CA125 and CA199 and clinical prognosis, aiming to provide effective predictors for prognosis of epithelial ovarian cancer.

## Materials and methods

### *Baseline data*

A total of 140 patients diagnosed with epithelial ovarian cancer in our hospital from July 2014 to July 2019 were enrolled. The patients, were aged 40 to 58 years, with an average of (47.37 ± 3.43) years, and were followed up for at least 5 years. According to the pathological type, patients were divided into different groups with: 55 cases of mucinous carcinoma and 85 cases of serous carcinoma. Through FIOG evaluation, we found 17 patients in stage I, 34 in stage II, 66 in stage III, and 23 in stage IV. There were 40 patients with low differentiation, 42 patients with moderate differentiation, and 58 patients with high differentiation. All patients were given tumor eradication or radical surgery after admission as well as platinum chemotherapy after surgery. There were 38 patients with residual lesions >2 cm after surgery and 102 patients with residual lesions ≤2 cm. Inclusion criteria: patients who were diagnosed with epithelial ovarian cancer for the first time and did not receive any radiotherapy or chemotherapy before surgery. Exclusion criteria: patients with complicated diseases of the heart, liver, lung, kidney and other important organs, malignant tumors in other body parts; patients with autoimmune diseases and blood clotting dysfunction. This study was approved by the Ethics Committee of our hospital. The research subjects and their families were informed and signed a fully-informed consent form.

## Detection method

Three mL of fasting venous blood was collected from all patients, and centrifuged at 3000 r/min for 10 min. Lectrochemiluminescence immunoassay was performed to detect CA125 and CA199 levels. The subjects fasted 4-6 h before the examination and had blood glucose levels at 4.4-9.3 mmol/L. After intravenous injection, patients were instructed to drink 500 mL of water and lie flat for 50-70 min in the dark. It was necessary to drinking water again before PET/CT imaging. Radiochemical purity >95%, and the dose administered to the subjects was 3.70-4.44 MBq (0.10-0.12 mCi/KG). Three imaging physicians analyzed the PET images, CT images and PET/CT fusion images, and the diagnosis results were based on mutual consensus reached by two of them. The diagnosis results of PET/CT focused on the patients themselves and the lesions. The lesions were examined at 9 sites: local pelvic recurrence, peritoneal metastasis, abdominal lymph node metastasis, pelvic lymph node metastasis, distant lymph node metastasis, tissue metastasis, and liver, spleen, lung, bone or soft tissue metastasis. The diagnostic criteria for tumor recurrence or metastasis are increased 18F-FDG concentrations in all monitored regions on PET image, and there are obvious lesions on the CT image. The region of interest is used to determine $SUV_{Max}$ and the positive criteria is $SUV_{Max} \geq 2.5$.

### *Interquartile range*

The quantitative values of serum CA125 and CA199 levels were sequenced from smallest to largest. The range is: (140 + 1) × 1/4 = 35.25 = q1, (140 + 1) × 2/4 = 70.5 = q2, (140 + 1) × 0.75 = 105.75 = q3; 140 values of CA125 and CA199 levels were divided into 4 intervals by q1, q2, q3 and q4 which were rounded up, where q1 = 1-35, q2 = 36-70, q3 = 71-105, q4 = 106-140.

### *Evaluation method*

The expression of CA125 and CA199 were observed in patients with different pathological features, and the 5-year survival rates in the interquartile ranges were recorded. The risk factors that affected the survival rate of ovarian cancer patients were assessed.

### *Statistical analysis*

SPSS 13.0 was used for data analysis. Kruskal-Wallis H test was used for measurement data. Log-rank test was used for comparison of survival rate. Logistic regression analysis was used for prognostic factors. $P<0.05$ was considered statistically significant.

## Results

### *Diagnosis of tumor recurrence and metastasis by CT and PET-CT*

Among the 140 patients, 68 were diagnosed with tumor recurrence and metastasis, 32 we-

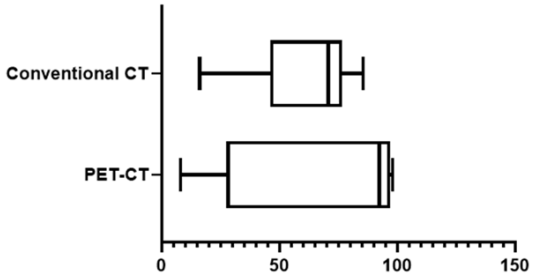


**Figure 1.** The detection rate of different CT examination methods. PET-CT results showed 98 cases of tumor recurrence and metastasis, 34 cases of missed diagnosis, 8 cases of false positive, sensitivity 92.1%, specificity 92.6% and accuracy rate 96.8%, which were significantly higher than results of CT, including 68 cases of tumor recurrence and metastasis, 56 missed cases, 16 cases of false positive, sensitivity 73.7%, specificity 73.5% and accuracy rate 85.5% ($P$<0.05).

re confirmed by pathology, and 40 were diagnosed in follow-up by CA125 and CA199 levels combined with imaging methods (**Figure 1**).

*Detection of lesions*

Among the 140 patients with tumor metastasis and recurrence detected by PET-CT, 204 lesions were diagnosed, including local pelvic recurrence, peritoneal metastasis, abdominal lymph node metastasis, pelvic lymph node metastasis, distant lymph node metastasis, liver metastasis, and splenic metastasis, lung metastasis, abdominal wall soft tissue metastasis and false positives. CT confirmed 130 cases of tumor metastasis and recurrence, with peritoneal thickening as the primary sign which showed irregular shape, flocculent shadow, nodules and masses (**Figure 2**).

*The expression of CA125 and CA199 with regard to different clinicopathological features*

CA125 and CA199 were expressed differently in patients with epithelial ovarian cancer in terms of age, FIGO staging (I, II, III, IV), serous cancer, mucinous cancer, postoperative residual lesions (≤2 cm, >2 cm) and histological differentiation (high, moderate, low) ($P$<0.05, **Table 1**).

*CA125, CA199 expression and survival rate in interquartile ranges*

The median survival time of q1, q2, q3, q4 intervals was 57, 39, 18, and 10, respectively.

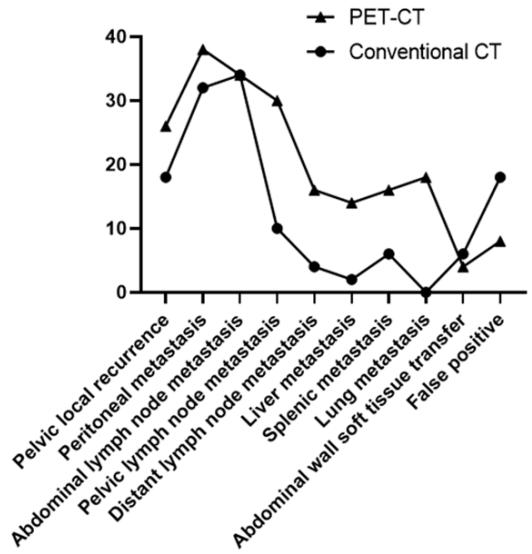


**Figure 2.** The detection of the lesions of the included patients. PET-CT found 26 cases of local pelvic recurrence, 38 cases of peritoneal metastases, 34 cases of abdominal lymph node metastases, 30 cases of pelvic lymph node metastases, 16 cases of distant lymph node metastases, 14 cases of liver metastases, 16 cases of spleen metastasis, 18 cases of lung metastasis, 4 cases of abdominal wall soft tissue metastasis and 8 cases of false positive; whereas in CT examination, the corresponding cases were 18, 32, 34, 10, 4, 2, 6, 0, 6 and 18, respectively.

The 5-year survival rate was 51.42, 37.14, 17.14 and 11.42, respectively, and the difference was statistically significant ($P$<0.05, **Table 2**; **Figure 3**).

*Variable assignment and logistic regression analysis*

Dependent variable Y = prognosis of epithelial ovarian cancer; Independent variable X = clinicopathological features. Variable assignments are shown in **Table 3**; FIGO staging, age, CA125, CA199, postoperative residual lesions were the independent risk factors for epithelial ovarian cancer ($P$<0.05, **Table 4**).

## Discussion

Ovarian cancer is the second most common gynecologic cancer, with a five-year survival rate of only about 30%. Ovarian cancer has the highest mortality rate among gynecological malignancies [8]. Although cytoreductive surgery and platinum, paclitaxel and other combined chemotherapy can improve the prognosis, the 2-year recurrence rate still exceeds

**Table 1.** Relationship between CA125 and CA199 and different clinicopathological features

| Pathological features | n | CA125/CA199 (U/mL) | Median value/(U/mL) | *P* |
|---|---|---|---|---|
| Age | | | | <0.05 |
| ≤54 years old | 71 | 3.7-18442.2 | 428.3 | |
| >54 years old | 69 | 5.9-20115.4 | 557.3 | |
| Pathological type | | | | <0.05 |
| Serous carcinoma | 85 | 5.7-20114.5 | 499.5 | |
| Mucinous carcinoma | 55 | 3.7-9799.2 | 384.6 | |
| FIGO | | | | <0.05 |
| I | 17 | 3.7-267.5 | 58.51 | |
| II | 34 | 15.6-1224.6 | 161.5 | |
| III | 66 | 37.7-18465.8 | 468.1 | |
| IV | 23 | 62.6-20124.4 | 963.5 | |
| Histological differentiation | | | | <0.05 |
| High differentiation | 58 | 8.4-20124.6 | 471.7 | |
| Moderate differentiation | 42 | 7.8-7227.2 | 351.5 | |
| Low differentiation | 40 | 3.9-5571.6 | 257.0 | |
| Postoperative residual lesions | | | | <0.05 |
| ≤2 cm | 102 | 3.9-6115.2 | 274.7 | |
| >2 cm | 38 | 88.6-20114.4 | 1276.5 | |

**Table 2.** The 5-year survival rate and the interquartile range of CA125 and CA199

| Interval | n | CA125/ CA199 (U/mL) | Median value/(U/mL) | Median survival/month | 5-year survival rate |
|---|---|---|---|---|---|
| q1 | 35 | 3.7-157.6 | 55.2 | 57 | 18 (51.42) |
| q2 | 35 | 161.5-425.7 | 351.6 | 39 | 13 (37.14) |
| q3 | 35 | 435.8-811.4 | 611.4 | 18 | 6 (17.14) |
| q4 | 34 | 816.5-20114.4 | 1367.7 | 10 | 4 (11.42) |

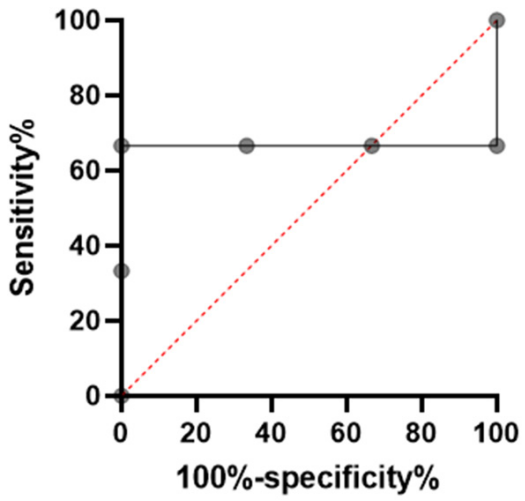


**Figure 3.** The 5-year survival rate of the enrolled patients.

70% [9, 10]. Data shows that as many as 114,000 women die of ovarian cancer worldwide each year. Epigenetics is used to describe inheritance through mechanisms other than the DNA sequence of genes, which is characterized by reversibility, position effects, and high frequency mutations [11, 12]. Epigenetic modification is not only related to the development of cells and tissues, but also plays a crucial role in cancer progression. Some studies have found that the lack of p16INK4a expression or decreased p16INK4a expression is involved in the occurrence of ovarian cancer and is an unfavorable prognostic factor of ovarian cancer. Endothelial protein C receptor (EPCR) is a new type of protein receptor discovered in recent years. It can participate in coagulation and anticoagulation functions *in vivo* by binding with activated protein C (aPC) [13, 14]. Studies have found that the increased expression of plasma endothelial protein C receptor (sEPCR) in various solid tumors may affect the inflammatory responses in tumor patients. However, the exact relationship between the physiological function of sEPCR and immune-related complications are still unclear [4, 15].

Epithelial ovarian cancer is a common gynecological malignancy, and 76% of female patients have intra-abdominal metastasis, intracranial metastasis, or thoracic metastasis at the time of diagnosis. Ovarian cancer is mostly confirmed by imaging and serum indicators CA125 and CEA in the past. In recent years, some scholars have combined them with CA199 to confirm the diagnosis and have achieved good results [16, 17]. Effective treatment can be selected according to FIGO staging and classi-

**Table 3.** Variable assignment

| Clinical indicators | Variable | Assignment |
|---|---|---|
| Prognosis | Y | Survival = 0, Death = 1 |
| CA125/CA1299 | X1 | q1 = 0, q2 = 1, q3 = 2, q4 = 3 |
| Age | X2 | ≤54 years old = 0, >54 years old = 1 |
| Pathological type | X3 | Mucinous cancer = 1, serous cancer = 1 |
| FIGO staging | X4 | Stage I-II = 0, III-IV = 1 |
| Histological differentiation | X5 | Medium and Low differentiation = 0, high differentiation = 1 |
| Postoperative lesions | X6 | ≤2 cm = 0, >2 cm = 1 |

**Table 4.** Logistic regression analysis

| Factors | β | SE | OR | 95% CI | Wald $X^2$ | *P* |
|---|---|---|---|---|---|---|
| CA125/CA199 | | | | | | |
| Q2 | 0.474 | 0.199 | 1.613 | 1.434-1.814 | 9.15 | 0.000 |
| Q3 | 0.884 | 0.275 | 2.436 | 1.774-3.344 | 18.35 | 0.000 |
| Q4 | 1.415 | 0.351 | 4.110 | 2.613-6.461 | 62.36 | 0.000 |
| >54 years old | 0.512 | 0.242 | 1.676 | 1.351-2.089 | 6.14 | 0.015 |
| Serous carcinoma/mucinous carcinoma | 0.473 | 0.315 | 1.612 | 1.383-1.889 | 2.15 | 0.123 |
| III-IV | 0.583 | 0.217 | 1.811 | 1.444-2.261 | 8.15 | 0.003 |
| High differentiation | 0.412 | 0.301 | 1.515 | 1.222-1.893 | 3.32 | 0.065 |
| Postoperative lesion >2 cm | 0.562 | 0.230 | 1.763 | 1.377-2.256 | 12.43 | 0.000 |

fication to improve the survival rate of patients. CA125 level is normally lower than 35 U/mL, CA125 belongs to IgG series and contains 5797 base pairs. Studies have found that the expression of CA125 in serum of patients with ovarian cancer was significantly increased, and CA125 appeared earlier than the clinical symptoms, so this marker can be used for the clinical prognosis and treatment of ovarian cancer [18-21]. Studies have found that CA125 and CA199 were significantly correlated with different clinicopathological characteristics of patients, and the serum levels of CA125 and CA199 in patients aged >54 years were significantly higher than those aged ≤54 years. Due to the high expression of CA199 in mucinous carcinoma and the high expression of CA125 in serous carcinoma, the high expressions of the two serum levels were significantly correlated with the development and occurrence of serous and mucinous carcinoma [22-24]. This study showed that the diagnostic efficiency of PET/CT, CT was 92.1% and 73.7% ($P<0.05$). The specificity of PET/CT and CT was 92.6% and 73.5% ($P<0.05$).

Studies have shown that patients with non-serous ovarian cancer have abnormal expression of CA125 before the onset of symptoms, while those with serous ovarian cancer do not have such a situation, confirming that non-serous and serous cancers are developed and expressed through different mechanisms. The expression of CA125 and CA199 being increased with the increase of FIGO staging, indicates that there was a significant correlation between the two serum indicators and the degree of tumor deterioration. In this study, we found that the levels of CA125 and CA199 in patients with postoperative lesions >2 cm were significantly higher than those with lesions ≤2 cm, confirming that there is a significant correlation between the two indicators and clinical prognosis. On basis of serum levels of CA125 and CA199, 4 interquartile ranges (q1, q2, q3, q4) were created. This study found that the 5-year survival rates of patients with epithelial ovarian cancer were 48.4%, 32.3%, 21.0%, and 11.5%, respectively, while the median survival time of interquartile ranges were 58, 40, 19, and 11 months, respectively; confirming that 5-year survival rate and median survival time can decrease with the increase of CA125 and CA199 levels, and they showed a negative linear relationship. The risk of death in patients with epithelial ovarian cancer is independent of

postoperative lesion residue, FIGO staging and age, confirming that CA125 and CA199 are independent risks for prognosis of epithelial ovarian cancer and age, and FIGO staging and residual size of postoperative lesions are all independent risk factors for clinical prognosis.

In summary, both CA125 and CA199 are significantly overexpressed in epithelial ovarian cancer. There is a significant correlation between the two indicators and clinicopathological features, and with the increase of the expression of the two indicators, the prognosis of patients is decreased significantly. CA125 and CA199 can be used as prognostic indicators for epithelial ovarian cancer.

However, this study has some limitations. The number of included cases is small, and there are certain limitations of clinical medication. Future research should be performed to explore the new drugs that target E3 ligase, VEGF/VEGFR pathway, PD-1/PD-L1 pathway, IL-6/IL-6R pathway, and macrophage migration inhibitory factors.

## Acknowledgements

This research received no specific financial support from any funding agency in the public, commercial, or not-for-profit sectors.

## Disclosure of conflict of interest

None.

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