

Received: 2020.04.11  
Accepted: 2020.07.01  
Available online: 2020.07.14  
Published: 2020.09.10

# Prognostic Significance of CA125 Dynamic Change for Progression Free Survival in Patients with Epithelial Ovarian Carcinoma

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

**BCEF** Zemin Li  
**CD** Han Yin  
**AG** Mulan Ren  
**ACG** Yang Shen

Department of Obstetrics and Gynaecology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, P.R. China

**Corresponding Author:** Yang Shen, e-mail: shenyang0924@sina.cn

**Source of support:** This study was supported by National Natural Science Foundation of China (No. 81673130)

**Background:** This study aimed to investigate the value of CA125 dynamic change in PFS prediction for patients with epithelial ovarian carcinoma (EOC).





**Material/Methods:** Data analysis was performed using SPSS 24.0 statistical software with progression-free survival (PFS) as an outcome measure. Kaplan-Meier method was used to analyze the relationship between PFS and preoperative and postoperative NLR, PLR and CA125 levels, CA125 half-life, CA125-negative time, age, FIGO stage, histopathology, differentiation, vessel carcinoma embolus, and ascites. The survival curves were compared by the log-rank test. Based on the results of single-factor analysis, the Cox model was used for multifactor analysis to analyze independent risk factors affecting the PFS of epithelial ovarian carcinoma.

**Results:** A total of 117 patients with EOC were selected from January 2012 to January 2019 to carry out a retrospective study. Univariate analyses showed that PFS of the patients with EOC was associated with differentiation, vessel carcinoma embolus, FIGO stage, CA125 half-life, CA125-negative time, and preoperative NLR ( $P < 0.05$ ). Multivariate analysis by the Cox model showed that vessel carcinoma embolus, CA125 half-life, differentiation, and preoperative NLR are the independent risk factors for PFS in patients with EOC.

**Conclusions:** The serum CA125 dynamic as reflected by CA125 half-life is the most important independent prognostic factor in patients with EOC. The simplicity of CA125 monitoring and its correlation with EOC patient survival can identify patients with poor prognosis through monitoring CA125 half-life, which can provide a reference value for use in clinical practice.

**MeSH Keywords:** **CA-125 Antigen • Disease-Free Survival • Ovarian Neoplasms**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/925051>

 2387  2  2  39



## Background

Among gynecologic malignancies, ovarian carcinoma had the highest rate of morbidity, and about 75% of these patients have advanced to the late stage by time of diagnosis (FIGO IIb-IV) [1]. Among them, EOC is the most common, occurring primarily in women aged 50–60 years and accounting for 85–90% of ovarian carcinoma cases. The main treatment options for ovarian carcinoma are tumor cytoreductive surgery and post-operative adjuvant chemotherapy. After satisfactory tumor cytoreductive surgery and chemotherapy, the complete remission rate can be more than 70%, but the recurrence rate is as high as 80% [2]. Although the relapsed patients may achieve clinical remission after re-treatment, the overall prognosis is still poor and the 5-year survival rate generally does not exceed 30% [3]. Study results show that a longer remission period of ovarian carcinoma recurrence is associated with longer survival time [4]. Therefore, it would be useful to be able to predict and evaluate the prognosis early and correctly in patients with clinically complete remission (CCR) after standard treatment, which would assist clinically stratified treatment and ultimately improve prognosis.

In 1981, Bast et al. reported the identification of CA125 monoclonal antibodies produced by mice immunized with ovarian carcinoma cell lines [5]. Subsequently, radioimmunoassay was developed against the target antigen, CA125, and ovarian carcinoma patients showed elevated serum CA125 levels in 82% of cases, compared to 1% in healthy controls [6]. Also, many investigators have noted that elevated or decreased CA125 levels are associated with progression or regression of the disease, suggesting that CA125 is important for monitoring treatment response in patients with EOC. Serum CA125 has important clinical value in monitoring chemotherapy response and predicting recurrence [7].

However, the specificity of serum CA125 is poor. As the incidence of epithelial ovarian cancer increases and patients tend to be younger, fertility-preserving surgery and treatment methods are becoming more common, and finding more sensitive and specific prognostic indicators is becoming more and more important [8,9]. In patients with ovarian carcinoma, tumor burden can be significantly reduced by tumor cytoreductive surgery, and the decrease in serum CA125 is associated with fewer tumor cells. If epithelial ovarian cancer tissue is cleared, CA125 will turn negative. It is expected that the dynamic monitoring of CA125 during treatment will be of great value in the evaluation of treatment effects and prognosis. Serum CA125 dynamic changes are associated with decreased CA125 levels during treatment, and a rapid decline predicts a favorable prognosis, which can be expressed as the half-life and CA125-negative time [10]. Several multivariate analyses showed that the half-life and lowest concentration of CA125 during neoadjuvant

chemotherapy were independent prognostic factors in EOC patients [11–14]. Other research suggests that serum CA125 concentrations are a strong independent predictor of the first 2 platinum-based chemotherapy cycles after suboptimal late ovarian cancer cytoreductive surgery [15]. Finally, research showed that the baseline CA125 serum level before the onset of first-line chemotherapy and maintenance chemotherapy after cytoreductive surgery were independent risk factor of recurrence and survival [15].

Although the prognostic significance of elevated CA125 levels before, during, and after comprehensive treatment of patients with EOC is clear, there is limited understanding of serum CA125 dynamic changes. Due to the complex dynamics of CA125, mainly due to factors such as surgical trauma and residual tumor burden of CA125-secreting cells, there is less concern about dynamic changes in CA125. Some studies reported that perioperative CA125 levels are associated with the size of residual lesions after tumor cell depletion [16–18]. Others have observed that use of CA125 improves accuracy in predicting residual disease [19,20]. Therefore, the clinical value of serum CA125 dynamics in the treatment of EOC patients needs further research. Based on this background, the present study was designed to investigate and evaluate the value of CA125 dynamics change in PFS in patients with EOC.

## Material and Methods

### Patients

Clinical data of patients with EOC who underwent treatment at Zhongda Hospital, Southeast University, and Jiangsu Cancer Hospital, Nanjing Medical University, were retrospectively collected from January 2012 to January 2019. All patients were diagnosed as having EOC by surgical pathology.

Case inclusion criteria were: 1) initial cytoreductive surgery; 2) satisfactory cytoreductive surgery, residual tumor maximum diameter <1 cm; 3) postoperative platinum-based combined first-line chemotherapy regimen; 4) patients who were evaluated for tumor progression after clinical complete remission (CCR) after treatment; 5) complete clinical and pathological data. Case exclusion criteria were: 1) incomplete clinical and pathological data; 2) evidence of acute/chronic infection or severe bleeding before surgery; 3) with hematological malignancies; 4) perioperative death due to surgical complications.

### Follow-up and data collection

The patient or family members were followed up by regular telephone calls, and the patient's condition, treatment status, and current living status were recorded. The patient's

previous medical examination, diagnosis, and treatment were reviewed through the hospital's electronic medical record system. The starting point of follow-up was the patient's first admission time. From the follow-up date to January 2019, patients who failed to follow-up were excluded. Demographic and clinical data were retrospectively collected from personal medical records.

The data collected included: preoperative and perioperative CA125 levels, the first normal CA125 value and time (if CA125 did not fall to normal within 3 months after the start of chemotherapy, we used the lowest value within 3 months). At the same time, the information on the patient's age, pathological type, FIGO stage, degree of differentiation, presence or absence of ascites, perioperative blood routine examination report, and vascular tumor thrombus were collected. All these patients were pathologically diagnosed or confirmed according to the WHO classification guidelines by expert pathologists. Multidisciplinary assessments were performed by gynecologic oncologists, surgeons, and pathologists based on the 2014 revised FIGO staging criteria. During the treatment or review follow-up, disease progression was confirmed by clinical imaging or pathology, and the time of disease progression and the cause of disease progression were recorded in detail.

The calculation formula [10] for the half-life of CA125 is  $(t_2-t_1)/2\log(c_1/c_2)$ , in which  $c_1$  is the level of CA125 before surgery,  $c_2$  is the first normal level after surgery (if the normal value is not restored within 3 months postoperatively, the lowest value after surgery is taken), and  $t_1$  and  $t_2$  are the corresponding time-points. CA125-negative time refers to the time required for postoperative serum CA125 level to fall to normal.

### Statistical analysis

All data were analyzed using IBM SPSS Statistics (Version 24.0; IBM Corp., Armonk, NY, USA). Differences between clinical characteristics and response rates were analyzed with the  $\chi^2$  test or one-way analysis of variance (ANOVA). The critical value of preoperative NLR and preoperative PLR was determined by the ROC curve. Survival analysis was performed by Kaplan-Meier method, and prognostic factor analysis was performed using the Cox regression model.  $p < 0.05$  was considered statistically significant.

## Results

### Clinicopathological characteristics

Clinicopathological characteristics are listed in Table 1. A total of 195 patients with complete clinical data and follow-up records were included in the inclusion criteria. PFS refers to

the time from the initial treatment to the time of tumor progression. We included 117 patients with PFS (1.3 to 59.7 days) in the study. The half-life of CA125 was calculated according to the calculation formula provided by Buller [10]. Using ROC curve analysis, when  $NLR=2.96$ , the Youden index was at most 0.41, and the critical point of NLR was determined to be 2.96. The sensitivity of evaluating ovarian cancer patients without disease progression was 64.1%, and the specificity was 76.9%. The area under the curve (AUC) was 0.667. The same method calculated that when the critical point of PLR was 221, the Youden index of 0.547 was the largest, and the sensitivity of evaluating ovarian cancer patients without disease progression was 70.1%, the specificity was 84.6%, and the AUC was 0.777 (Figure 1).

### Prognostic factors analyses

Univariate analyses showed that PFS of the patients with EOC was associated with differentiation, vessel carcinoma embolus, FIGO stage, CA125 half-life, CA125-negative time, and preoperative NLR ( $P < 0.05$ ) (Table 1). According to the results of univariate analysis, the survival curves of the 2 exposure levels of each risk factor were performed by Kaplan-Meier method (Figure 2). If the survival curves existed, the Cox survival analysis could not be applied. The results showed that the relevant factors could be included in the Cox survival analysis. Multivariate analysis by the Cox model showed that vessel carcinoma embolus, CA125 half-life, differentiation, and preoperative NLR were the independent risk factors for PFS in patients with EOC (Table 2). The serum CA125 dynamic as reflected by CA125 half-life is the most important independent prognostic factor in patients with EOC. The relative risk of disease progression in EOC patients with a serum CA125 half-life  $>20$  days was 1.766 times that of EOC patients  $\leq 20$  days.

### Discussion

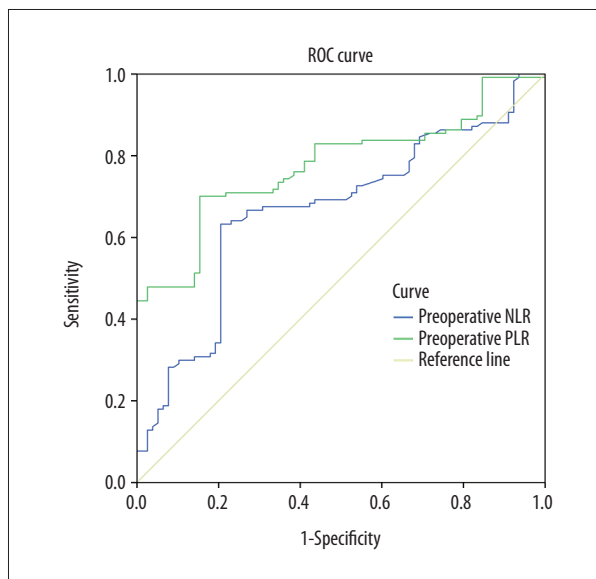
EOC is the second most common gynecological cancer in the world. Globally, there were approximately 230 000 new cases in 2012 and the death toll was 150 000 [21]. Primary cytoreductive surgery and platinum-based adjuvant chemotherapy are still the criterion standard treatment for EOC patients [22]. However, most of these patients were diagnosed in the advanced stage, and half of the patients relapsed within 16 months, with a 5-year overall survival rate of less than 50% [23–26]. The International Federation of Obstetrics and Gynecology (FIGO) has identified some survival predictors for EOC patients, including age at diagnosis, stage, histological grade, residual tumor, ascites, functional status score (PS), and CA125 levels [27–29]. However, biomarkers that are effective for individualized prediction of treatment outcomes and prognosis are still urgently needed [24].

**Table 1.** Clinicopathological characteristics and Univariate analyses of the factors for progression-free survival.

Clinicopathological characteristics	Cases	Mean PFS (95% CI)	$\chi^2$	P
Age (y)			0.947	0.331
<55	54	21.44 (17.79~25.08)		
≥55	63	19.62 (16.37~22.87)		
Histopathology			1.101	0.294
Serous carcinoma	86	21.33 (18.41~24.25)		
Others	31	18.58 (14.02~23.15)		
Differentiation			8.643	0.003
Well	67	23.79 (12.93~19.71)		
Poor, others	50	16.32 (12.93~19.71)		
Ascites			0.475	0.491
Yes	60	19.76 (16.44~23.10)		
No	57	21.48 (17.81~25.13)		
Vessel carcinoma embolus			10.930	0.001
Yes	59	16.62 (13.59~19.66)		
No	58	24.65 (21.02~28.28)		
FIGO stage			9.782	0.002
I-II	45	25.74 (21.55~29.93)		
III-IV	72	17.39 (14.59~20.19)		
Preoperative serum CA125 (U/mL)			1.113	0.291
≤500	69	21.88 (18.70~25.06)		
>500	48	18.76 (14.89~22.64)		
Postoperative CA125 decline			3.741	0.154
0.0~49.9%	6	15.88 (15.57~16.20)		
50.0~75.0%	48	18.64 (14.77~22.51)		
>75.0%	63	22.55 (19.10~25.99)		
CA125 half-life (d)			8.302	0.004
≤20	63	23.95 (20.56~27.35)		
>20	54	16.68 (13.38~19.99)		
CA125 negative time (w)			8.506	0.004
≤8	60	24.15 (20.58~27.72)		
>8	57	16.87 (13.74~19.99)		
Preoperative NLR			21.445	0.000
≤2.96	66	25.43 (22.18~28.69)		
>2.96	51	14.34 (11.33~17.37)		

**Table 1 continued.** Clinicopathological characteristics and Univariate analyses of the factors for progression-free survival.

Clinicopathological characteristics	Cases	Mean PFS (95% CI)	$\chi^2$	P
Postoperative NLR change			1.282	0.257
Increase	54	19.16 (15.70~22.61)		
Decrease	63	21.84 (18.36~25.32)		
Preoperative PLR			2.674	0.102
$\leq 221$	35	17.17 (12.59~21.75)		
$> 221$	82	22.07 (19.18~24.95)		
Postoperative PLR change			0.890	0.345
Increase	61	18.82 (15.49~22.16)		
Decrease	56	22.53 (18.93~26.14)		



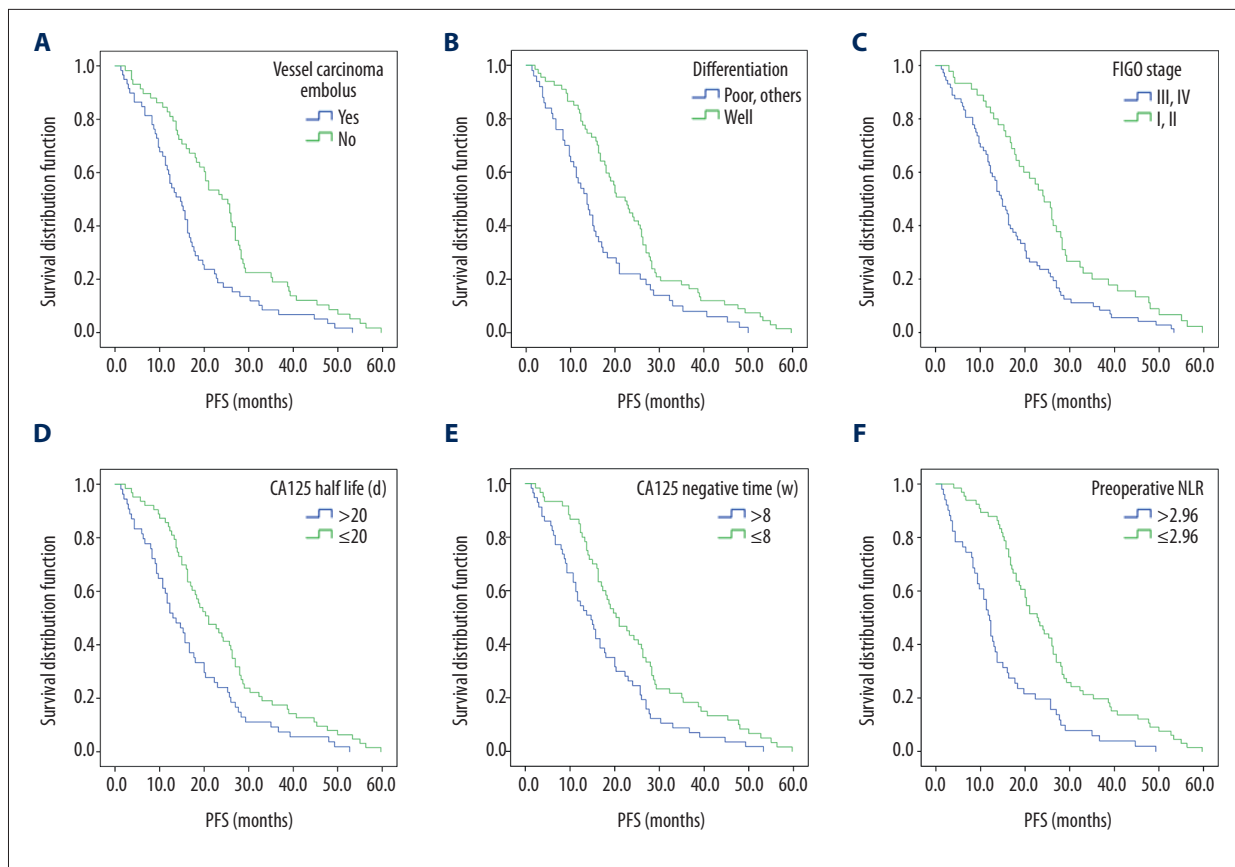
**Figure 1.** The ROC curve of preoperative NLR and PLR optimal cut-off points.

CA125 is currently the most widely used tumor marker for the diagnosis of EOC [7,30–32]. It is a glycoprotein with a molecular weight of 200 000, encoded by the MUC16 gene. It originates from the fetal body cavity epithelial tissue and is widely distributed in mesothelial cells (including peritoneum, pleura, pericardium), Miller tube epithelium (including fallopian tubes, endometrium, and endocervix), and tumors (including ovarian epithelial cancer, fallopian tube cancer, endometrial cancer, cervical cancer, and mesothelioma). CA125 rarely exists in normal clinical tissues, but serum CA125 levels are elevated in patients with EOC.

CA125 is widely used in the diagnosis and follow-up of ovarian carcinoma due to its low cost and simple operation. Clinically, routine measurement of serum CA125 levels is used to monitor

tumor response in chemotherapy. Studies have shown that longer patient survival is associated with decreased CA125 levels [33]. In patients with ovarian carcinoma, tumor burden can be significantly reduced by tumor cytoreductive surgery, and the decrease in serum CA125 level is consistent with the decrease in the number of tumor cells. If epithelial ovarian cancer tissue is cleared, CA125 turns negative. The dynamic monitoring of CA125 during treatment is expected to be of great value in the evaluation of treatment effects and prognosis. A study investigated the relationship between perioperative changes in serum CA125 levels and PFS, and results showed that decrease of serum CA125 levels  $\geq 80\%$  after surgery is an independent prognostic factor for PFS [34]. Markman et al. [35] studied 101 patients with advanced EOC to investigate the correlation between CA125 and prognosis, finding that the patients with a reduction of serum CA125  $> 50\%$  after 2 cycles of chemotherapy had a more favorable prognosis. Another study showed that in both the postoperative intravenous chemotherapy group and the postoperative intraperitoneal chemotherapy group, the CA125 value above 35 U/mL after the first-line chemotherapy indicated that the condition was not controlled [36]. A study of patients with advanced EOC who achieved CCR after treatment confirmed that CA125 was related to prognosis [37]. Groups with CA125 greater than 10 U/mL had significantly shorter PFS than those with less than 10 U/mL [15]. Rocconi et al. [38] found that after 3 cycles of chemotherapy, patients with CA125 levels that did not fall to normal values had a significantly worse prognosis than patients with normal values. Nyvang et al. [39] reported that serum CA125 level after 3 chemotherapy cycles is the most important prognostic predictor for patients with EOC.

CA125 is secreted by ovarian carcinoma cells, and its level is related to tumor size. After the cancerous tissue is removed, CA125 should be negative. Therefore, the dynamic detection of CA125 can determine treatment efficacy and monitor



**Figure 2.** Kaplan-Meier curves depicting PFS according to vessel carcinoma embolus (A), differentiation (B), FIGO stage (C), CA125 half-life (D), CA125-negative time (E), and preoperative NLR (F).

**Table 2.** Multivariate Cox hazard model analysis of factors associated with progression-free survival in patients with epithelial ovarian carcinoma.

Factors	B	Wald	HR (95% CI)	P
Vessel carcinoma embolus	0.544	7.368	1.722 (1.163–2.550)	0.007
Differentiation	0.760	14.185	2.139 (1.440–3.178)	0.000
CA125 half-life	0.569	7.981	1.766 (1.190–2.620)	0.005
Preoperative NLR	0.635	9.469	1.887 (1.259–2.828)	0.002

disease progression. Serum CA125 dynamic is a rate of decrease of CA125 levels during treatment, and a rapid decline predicts a favorable prognosis, which can be expressed as the half-life [10]. In this study, we investigated the connection between PFS in patients with EOC and preoperative CA125 values, postoperative CA125 changes, CA125 half-life, CA125-negative time, CA125 level, and CA125 half-life. CA125-negative time was associated with better PFS in patients with EOC ( $P<0.05$ ). Multivariate analysis of the Cox hazard model of factors of progression-free survival in patients with EOC showed that CA125 half-life was the independent risk factor. The relative risk of disease progression in ovarian cancer patients with a CA125

half-life of  $>20$  days is 1.766 times that of ovarian cancer patients with a CA125 half-life of  $\leq 20$  days. The best correlation between CA125 half-life and survival was obtained using the formula provided by Buller et al. [10], who found that a long half-life of CA125 predicted a lack of disease progression and a response to chemotherapy. Van der Burg et al. [11] found that patients with a CA125 half-life of  $>20$  days had a 3.2-fold higher rate of progression compared to those with a CA125 half-life of fewer than 20 days ( $p=0.01$ ) and had a significantly shorter median PFS (11 months vs. 43 months).

## Conclusions

EOC patients often have no specific symptoms and signs in the early stage, so most of them have reached the advanced stage when diagnosed. Although the treatment of EOC has been gradually standardized, the recurrence rate of advanced-stage patients is still high. Therefore, evaluating the curative effect and finding signs of recurrence as soon as possible are important parts of the treatment process. This study assessed the value of serum CA125 dynamic changes in evaluating the PFS of EOC patients. The results show that the dynamic change in serum

CA125, reflected by the half-life of CA125, is the most important independent prognostic factor in EOC patients. Dynamic monitoring of CA125 levels can predict recurrence, allows timely adjustment of the individualized treatment plan, and could ultimately improve the prognosis of EOC patients. It is simple, inexpensive, and is suitable for clinical use.

## Conflict of interest

None.

## References:

1. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin*, 2018; 68(6): 394–424
2. Uzan J, Bonsang-Kitzis H, Rossi L et al: Prognostic impact of initial tumor load and intraperitoneal disease dissemination patterns in patients with advanced ovarian cancer undergoing complete cytoreductive surgery. *Eur J Surg Oncol*, 2019; 45(9): 1619–24
3. Torre LA, Trabert B, DeSantis CE et al: Ovarian cancer statistics, 2018. *Cancer J Clin*, 2018; 68(4): 284–96
4. Pignata S, Pisano C, Di Napoli M et al: Treatment of recurrent epithelial ovarian cancer. *Cancer*, 2019; 125(Suppl. 24): 4609–15
5. Bast RC, Feeney M, Lazarus H et al: Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest*, 1981; 68(5): 1331–37
6. Bast RC, Klug J, John ES et al: A radioimmunoassay using a monoclonal antibody to monitor the cause of epithelial ovarian cancer. *N Engl J Med*, 1983; 309: 383–87
7. Kessous R, Wissing MD, Piedimonte S et al: CA-125 reduction during neoadjuvant chemotherapy is associated with success of cytoreductive surgery and outcome of patients with advanced high-grade ovarian cancer. *Acta Obstet Gynecol Scand*, 2020; 99(7): 933–40
8. Balachandren N, Davies M: Fertility, ovarian reserve and cancer. *Maturitas*, 2017; 105: 64–68
9. Rosa VL, Garzon S, Gullo G et al: Fertility preservation in women affected by gynaecological cancer: The importance of an integrated gynaecological and psychological approach. *Eccancermedalscience*, 2020; 14: 1035
10. Buller RE, Berman ML, Bloss JD et al: CA 125 regression: A model for epithelial ovarian cancer response. *Am J Obstet Gynecol*, 1991; 165(2): 360–67
11. Me VDB, Lammes FB, van Putten WL, Stoter G: Ovarian cancer: The prognostic value of the serum half-life of CA125 during induction chemotherapy. *Gynecol Oncol*, 1988; 30(3): 307–12
12. Riedinger JM, Wafflart J, Ricolleau G et al: CA 125 half-life and CA 125 nadir during induction chemotherapy are independent predictors of epithelial ovarian cancer outcome: Results of a French multicentric study. *Ann Oncol*, 2006; 17(8): 1234–38
13. Crawford SM, Peace J: Does the nadir CA125 concentration predict a long-term outcome after chemotherapy for carcinoma of the ovary? *Ann Oncol*, 2005; 16(1): 47–50
14. Yoshikawa T, Takano M, Kita T et al: Normal serum CA125 half-life and normal serum nadir CA125 level in patients with ovarian cancers. *Eur J Gynaecol Oncol*, 2012; 33(3): 269–73
15. Markman M, Federico M, Liu PY et al: Significance of early changes in the serum CA-125 antigen level on overall survival in advanced ovarian cancer. *Gynecol Oncol*, 2006; 103(1): 195–98
16. Abu Hassan SO, Nielsen DL, Tuxen MK et al: Performance of seven criteria to assess CA125 increments among ovarian cancer patients monitored during first-line chemotherapy and the post-therapy follow-up period. *Future Sci OA*, 2017; 3(3): FSO216
17. Guo N, Peng Z: Does serum CA125 have clinical value for follow-up monitoring of postoperative patients with epithelial ovarian cancer? Results of a 12-year study. *J Ovarian Res*, 2017; 10(1): 14
18. Abu Hassaan SO: Monitoring ovarian cancer patients during chemotherapy and follow-up with the serum tumor marker CA125. *Dan Med J*, 2018; 65(4): B5463
19. Yedema CA, Kenemans P, Thomas CM et al: CA 125 serum levels in the early post-operative period do not reflect tumour reduction obtained by cytoreductive surgery. *Eur J Cancer*, 1993; 29(7): 966–71
20. Gadducci A, Landoni F, Maggino T et al: The relationship between post-operative decline of serum CA 125 levels and size of residual disease after initial surgery in patients with advanced ovarian cancer: A CTF study. *Gynecol Oncol*, 1996; 63(2): 234–37
21. Torre LA, Bray F, Siegel RL et al: Global cancer statistics, 2012. *Cancer J Clin*, 2015; 65(2): 87–108
22. Xiao Y, Xie S, Zhang N et al: Platinum-based neoadjuvant chemotherapy versus primary surgery in ovarian carcinoma International Federation of Gynecology and Obstetrics stages IIIc and IV: A systematic review and meta-analysis. *Gynecol Obstet Invest*, 2018; 83(3): 209–19
23. Markman M, Bundy BN, Alberts DS et al: Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*, 2001; 19(4): 1001–7
24. Feng Z, Wen H, Bi R et al: Preoperative neutrophil-to-lymphocyte ratio as a predictive and prognostic factor for high-grade serous ovarian cancer. *PLoS One*, 2016; 11(5): e0156101
25. Berek JS, Crum C, Friedlander M: Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*, 2015; 131(Suppl. 2): S111–22
26. Ledermann JA, Raja FA, Fotopoulou C et al: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2013; 24(Suppl. 6): vi24–32
27. Chang LC, Huang CF, Lai MS et al: Prognostic factors in epithelial ovarian cancer: A population-based study. *PLoS One*, 2018; 13(3): e0194993
28. Kaban A, Topuz S, Saip P et al: Prognostic factors in patients undergoing primary cytoreductive surgery for FIGO stage IIIc ovarian, tubal or peritoneal cancer. *J Obstet Gynaecol Can*, 2018; 40(4): 447–53
29. Dinca AL, Birla RD, Dinca VG et al: Prognostic factors in advanced ovarian cancer – a clinical trial. *Chirurgia (Bucur)*, 2020; 115(1): 50–62
30. Ducoulombier S, Golfier F, Colombari O et al: Modeling CA-125 during neoadjuvant chemotherapy for predicting optimal cytoreduction and relapse risk in ovarian cancer. *Anticancer Res*, 2017; 37(12): 6879–86
31. Parashkevova A, Sehouli J, Richter R et al: Preoperative CA-125 value as a predictive factor for postoperative outcome in first relapse of platinum-sensitive serous ovarian cancer. *Anticancer Res*, 2018; 38(8): 4865–70
32. Colombari O, Tod M, Leary A et al: Early modeled longitudinal CA-125 kinetics and survival of ovarian cancer patients: A GINECO AGO MRC CTU study. *Clin Cancer Res*, 2019; 25(17): 5342–50
33. Söletormos G, Duffy MJ, Hassan SOA et al: Clinical use of cancer biomarkers in epithelial ovarian cancer: Updated guidelines from the European Group on Tumor Markers. *Int J Gynecol Cancer*, 2016; 26(1): 43–51
34. Seung-Chul Y, Jong-Hyuck Y, Mi-Ok L et al: Significance of postoperative CA-125 decline after cytoreductive surgery in stage IIIc/IV ovarian cancer. *J Gynecol Oncol*, 2009; 19(3): 169–72

35. Markman, Liu PY, Rothenberg ML et al: Pretreatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol*, 2006; 24(9): 1454–58
36. Krivak TC, Chunqiao T, Scott RG et al: A Gynecologic Oncology Group Study of serum CA-125 levels in patients with stage III optimally debulked ovarian cancer treated with intraperitoneal compared to intravenous chemotherapy: An analysis of patients enrolled in GOG 172. *Gynecol Oncol*, 2009; 115(1): 81–85
37. Song MJ, Lee SH, Choi MR et al: Diagnostic value of CA125 as a predictor of recurrence in advanced ovarian cancer. *Eur J Gynaecol Oncol*, 2013; 34(2): 148–51
38. Rocconi RP, Matthews KS, Kemper MK et al: The timing of normalization of CA-125 levels during primary chemotherapy is predictive of survival in patients with epithelial ovarian cancer. *Gynecol Oncol*, 2009; 114(2): 242–45
39. Nyvang GB, Mogensen O, Bichel P, Jakobsen A: Combined prognostic importance of CA 125, histopathologic grade and DNA-index in advanced ovarian cancer. *Eur J Gynaecol Oncol*, 2000; 21(6): 569–72