

Research Paper

# Reduction of CA125 Levels During Neoadjuvant Chemotherapy Can Predict Cyto-reduction to No Visible Residual Disease in Patients with Advanced Epithelial Ovarian Cancer, Primary Carcinoma of Fallopian tube and Peritoneal Carcinoma

Jing Zeng, Jie Yin, Xiao Song, Ying Jin, Yan Li, and Lingya Pan 

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences &amp; Peking Union Medical College, Beijing, China

 Corresponding author: Dr. Lingya Pan. Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Shuaifu Park #1, East City District, Beijing, China 100730 Email: panly@pumch.cn.© Ivyspring International Publisher. Reproduction is permitted for personal, noncommercial use, provided that the article is in whole, unmodified, and properly cited. See <http://ivyspring.com/terms> for terms and conditions.

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## Abstract

**Background and aims.** To determine whether reduction of CA125 levels is a predictive factor for cyto-reduction to no visible residual disease (NVRD) and chemotherapeutic sensitivity in advanced epithelial ovarian carcinoma (EOC), primary carcinoma of fallopian tube and peritoneal carcinoma patients who received neoadjuvant chemotherapy followed by interval debulking surgery (NAC-IDS).

**Methods.** This was a single-team-based study of advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma patients diagnosed between 1996 and 2015 at Peking Union Medical College Hospital. Patients were treated with NAC-IDS by one gynecologic oncologist. Demographic data, CA125 levels, radiographic data, and chemotherapy and surgical-pathologic information were obtained. Univariate and multivariate analyses were performed to evaluate variables associated with optimal cyto-reduction to NVRD and chemotherapy-sensitivity.

**Results.** One hundred and eighteen patients met the study inclusion criteria. Thirty-seven (31.4%) patients underwent resection to NVRD. The median serum CA125 level at presentation and before IDS was 1814.5 U/ml and 205.9 U/ml, respectively. In the univariate analysis, histology, a preoperative CA125 of  $\leq 200$  U/ml and a  $>80\%$  reduction of CA125 between presentation and IDS were significantly associated with the likelihood of NVRD ( $P=0.014$ ,  $0.000$ ,  $0.000$ , respectively). Multivariate analysis revealed that, of the various CA125 parameters tested, preoperative CA125  $\leq 200$  U/ml was the only independent predictor of NVRD (odds ratio 3.667, 95% confidence interval 1.337–10.057;  $P=0.012$ ). Preoperative CA125  $\leq 200$  U/ml was also significantly associated with chemotherapy-sensitive disease in the univariate analysis ( $P=0.037$ ).

**Conclusions.** EOC patients who received NAC-IDS and had a preoperative CA125 level of  $\leq 200$  U/ml were highly likely to be cyto-reduced to NVRD and to exhibit chemotherapeutic sensitivity.

Key words: epithelial ovarian cancer, CA125, interval debulking surgery, neoadjuvant chemotherapy.

## Introduction

Ovarian cancer is the leading cause of death from all gynecological malignancies [1]. The standard

treatment for advanced epithelial ovarian cancer (EOC), primary carcinoma of fallopian tube and

peritoneal carcinoma is primary debulking surgery (PDS) followed by platinum- and taxane-based chemotherapy [2-4]. Following the recent publication of two randomized controlled phase III trials investigating neoadjuvant chemotherapy (NAC) in advanced EOC [5, 6], some gynecologists have recommended NAC followed by interval debulking surgery (NAC-IDS) as an alternative treatment for advanced EOC. The two trials (EORTC-GCG/NCIC-CTG and CHORUS) found that progression-free survival and overall survival were similar in the PDS and NAC-IDS arms, implying non-inferiority of NAC-IDS compared with PDS. One study (CHORUS) also showed that surgical morbidity and mortality were significantly reduced in the NAC-IDS arm.

To the best of our knowledge, the clinical characteristics that determine the optimal timing of IDS in patients with advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma are not clearly defined. Computed tomography (CT) scans and preoperative CA125 levels are the most common methods of predicting cytoreductive outcome [7]. However, CT is limited by its low sensitivity and lack of reproducibility, suggesting that CA125 levels might have better predictive value [8, 9]. One study concluded that advanced EOC patients with preoperative CA125 levels <100 U/ml were more likely to achieve no gross residual disease after treatment with NAC-IDS [10]. Another study reported that a CA125 level of <75 U/ml was an independent predictive factor for complete IDS [11].

Chemotherapeutic sensitivity is a common concern in patients with advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma, however, clinical biomarkers to predict sensitivity to chemotherapy have not been established [12]. One study showed that a >80% change of CA125 between presentation and surgery was significantly associated with sensitivity to platinum-based chemotherapy, although it was not an independent predictor [10]. As more studies focus on the power of both absolute and changes in CA125 levels to predict survival, the relationship between CA125 and chemotherapeutic sensitivity needs to be clinically validated in EOC, primary carcinoma of fallopian tube and peritoneal carcinoma.

The primary purpose of this study was to evaluate the ability of CA125 changes to predict cytoreduction to no visible residual disease (NVRD) in advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma patients who received NAC-IDS. We also sought to identify an appropriate preoperative CA125 level that could predict cytoreduction to NVRD in our study population. Our

secondary aim was to analyze whether CA125 changes during NAC could predict chemotherapeutic sensitivity in these patients.

## Material and methods

This study was approved by the Ethics Committee of Peking Union Medical College Hospital, China.

### Study population

We identified 118 consecutive patients with International Federation of Gynecology and Obstetrics (FIGO) stage III and IV EOC, primary carcinoma of fallopian tube and peritoneal carcinoma who were treated with NAC-IDS by a single gynecologic oncologist and gynecological oncology team in Peking Union Medical College Hospital between January 1996 and April 2015. Patients with borderline malignancy of the ovary were excluded. Demographic data, CA125 levels, radiographic data, and chemotherapy and surgical-pathologic information were obtained from the patients' individual medical records.

Patients were administered between 1 and 7 cycles of NAC according to the gynecologic oncologist's decision. Two main chemotherapy regimens were employed: (1) paclitaxel (175 mg/m<sup>2</sup> intravenous injection [IV]) and a platinum-based drug (cisplatin at 70 mg/m<sup>2</sup> intraperitoneal injection [IP] or carboplatin at area under the curve of 4-6 IV) and (2) PAF-C (cisplatin 100 mg IP, cytosine arabinoside 300 mg IP, fluorouracil 750 mg IP, and cyclophosphamide 400 mg IV administered on days 1 and 2). Serum CA125 levels were measured with a commercially available radioimmunoassay. The same assay was used throughout the study period.

In early medical records, the residual tumor mass was recorded as one of four sizes; not visible, <2 cm, >2 cm, and large mass. Therefore, we could not determine whether the patients with <2 cm residual disease were optimally cytoreduced. However, the concept of optimal cytoreduction fluctuates, and debulking to NVRD has a survival advantage over optimally debulking to ≤1 cm of macroscopic disease [13]. Therefore, we divided the patients into two groups of NVRD and visible residual disease (VRD) for the statistical analyses.

Disease recurrence was defined as a rising CA125 level or the appearance of new lesions by CT scan. Chemotherapy-sensitive recurrence was defined as recurrence at least 6 months after postoperative chemotherapy; chemotherapy-resistant recurrence was defined as recurrence less than 6 months after postoperative chemotherapy, and chemotherapy-refractory disease was defined as

disease that progressed or was stable during initial chemotherapy.

### Statistical analysis

CA125 continuous variables were converted to categorical variables using the median value as the cutoff. Categorical variables were compared between groups by the Pearson chi-squared test or Fisher's exact test, as appropriate for the category size. A logistic regression model comparing the two groups of patients was used to evaluate independent predictive factors and to estimate their covariate-adjusted odds. All statistical tests were two-tailed with the significance level set at  $P < 0.05$ . Data analysis was performed using SPSS Version 20.0 software (IBM Inc., Chicago, IL).

## Result

### Study population and clinicopathological characteristics

We identified 118 consecutive patients for analysis in this study. Patient characteristics are listed in Table 1. The median age was 55 years (range 36–76 years). One hundred patients (84.7%) had stage IIIc disease and 18 (15.3%) had stage IV disease. One hundred and one patients (85.6%) had papillary serous histology. Thirty-seven patients (31.4%) achieved cytoreduction to NVRD. Seventy-six patients (64.4%) received paclitaxel and platinum-based NAC, and 33 patients (28.0%) received PAF-C. Of the remaining 9 patients, 3 received single-agent cisplatin and 6 received one of the following treatments: single-agent paclitaxel, paclitaxel and topotecan, paclitaxel and fluorouracil, cisplatin and docetaxel, cisplatin and cyclophosphamide, pemetrexed and nedaplatin. One hundred and fifteen patients (97.5%) received between 1 and 3 cycles of NAC, of whom 42 (35.6%) received 1 cycle, 50 (42.4%) received 2 cycles, and 23 (19.5%) received 3 cycles. Only 3 (2.5%) patients received more than 4 cycles.

The median CA125 levels at diagnosis, after the first cycle of NAC, and before IDS were 1814.5 U/ml (range 56.6–56541.0 U/ml), 844.0 U/ml (18.5–25000.0 U/ml), and 205.9 U/ml (9.3–10971.0 U/ml), respectively. The median reduction of CA125 level after the first NAC and between presentation and IDS was 32.4% (range –324.9%–98.9%) and 80.9% (–152.0%–99.5%), respectively (–342.9% and –152.0% means the CA125 levels increased by 342.9% and 152.0%). CA125 levels were not obtained from 7 patients (5.9%) after the first cycle of NAC and they were excluded from the CA125 analysis thereafter.

**Table 1: Patient Characteristics.**

Characteristic	Total, n(%)/median(range)
Age(years)	55(36-76)
Primary site of disease	
Ovary	107(90.7)
Paritoneum	3(2.5)
Fallopian tube	8(6.8)
FIGO Stage	
III	100(84.7)
IV	18(15.3)
Tumor Grade	
G1	4(3.4)
G2	11(9.3)
G3	98(83.1)
UnKnown	5(4.2)
Histology	
Serous	101(85.6)
Endometrioid	3(2.5)
Clear cell	6(5.1)
Mucinous	1(0.9)
Others	7(5.9)
Neoadjuvant chemotherapy	
TC/TP	76(64.4)
PAF-C	33(28.0)
Others	9(7.6)
Cycles of neoadjuvant chemotherapy	
1	42(35.6)
2	50(42.4)
3	23(19.5)
≥4	3(2.5)
CA125U/ml presentation	1814.5(56.6-56541.0)
CA125U/ml≤1800U/ml presentation	
Yes	60(50.8)
No	58(49.2)
CA125U/ml after the 1st NAC	844.0(18.5-25000.0)
CA125U/ml≤850U/ml after the 1st NAC	
Yes	57(48.3)
No	54(45.8)
UnKnown	7(5.9)
Reduction CA125U/ml after the 1st NAC(%)	32.4(-324.9-98.9)**
Reduction CA125U/ml>30% after the 1st NAC	
Yes	59(50.0)
No	52(44.1)
UnKnown	7(5.9)
CA125U/ml preoperatively	205.9(9.3-10971.0)
CA125≤200U/ml preoperatively	
Yes	58(49.2)
No	60(50.8)
Reduction CA125U/ml presentation to preop (%)	80.9(-152.0-99.5)**
Reduction CA125U/ml>80% presentation to preop	
Yes	61(51.7)
No	57(48.3)
Residual disease	
No visible residual	37(31.4)
Residual disease≤2cm	62(52.5)
Residual disease>2cm	19(16.1)
Chemotherapeutic sensitive disease*	
Chemotherapeutic sensitive	43(53.1)
Chemotherapeutic resistant or refractory	38(46.9)

\*Some patients did not measure; \*\*–342.9% and –152.0% means the CA125 levels increased by 342.9% and 152.0%.

### Reduction of CA125 as a predictor of NVRD

Table 2 shows clinicopathological factors and the ability of reductions in serum CA125 levels to predict cytoreduction to NVRD. By univariate analysis, the factors significantly associated with cytoreduction to

NVRD were histology, a preoperative CA125 of  $\leq 200$  U/ml and a  $>80\%$  reduction of CA125 between presentation and surgery. When these three variables were entered unto the multivariable model, only a preoperative CA125 of  $\leq 200$  U/ml was an independent predictor (odds ratio 3.667, 95% confidence interval 1.337-10.057;  $P=0.012$ ).

**Table 2:** Univariate and multivariate analyses of associated with optimal cytoreduction.

Variables	No visible residual disease(n=37)	Visible residual disease(n=81)	Univariate P value	Multivariate P value	Multivariate OR(95%CI)
Age(years)			0.824		
≤55	20	42			
>55	17	39			
FIGO Stage			0.844		
III	31	69			
IV	6	12			
Histology			0.014	0.256	3.491(0.403-30.216)
Serous	36	65			
None serous	1	16			
CA125U/ml≤1800U/ml presentation	Yes 18	42	0.747		
	No 19	39			
CA125U/ml≤850U/ml after the 1st NAC*	Yes 19	38	0.526		
	No 15	39			
Reduction CA125U/ml >30% after the 1st NAC*	Yes 17	42	0.685		
	No 17	35			
CA125≤200U/ml preoperatively	Yes 29	29	0.000	0.012	3.667(1.337-10.057)
	No 8	52			
Reduction CA125U/ml >80% presentation to preop	Yes 28	33	0.000	0.059	2.540(0.965-6.683)
	No 9	48			

### Reduction of CA125 as a predictor of platinum-based chemotherapy sensitivity

We further studied whether some clinicopathological factors and reductions in serum CA125 levels could predict sensitivity to platinum-based chemotherapy. At the time of analysis, 81 patients (68.6%) had relapsed. Forty-three patients (53.1%) had chemotherapy-sensitive recurrence and 38 (36.9%) had either chemotherapy-resistant recurrence or chemotherapy-refractory disease. As presented in Table 3, univariate analysis showed no significant association between sensitivity to chemotherapy and age, FIGO stage, pretreatment CA125 levels  $<1800$  U/ml, CA125  $<850$  U/ml after the first NAC cycle,  $>30\%$  reduction of CA125 after the first NAC cycle, and  $>80\%$  reduction of CA125 between presentation and surgery. In the univariate analysis, histology and CA125  $\leq 200$  U/ml preoperatively was two significant predictive factor for chemotherapy-sensitive disease

( $P=0.023$  and  $P=0.037$ , respectively). However, a preoperative CA125 of  $\leq 200$  U/ml was not an independent predictor for chemotherapy sensitivity in the multivariate analysis (odds ratio 2.086, 95% confidence interval 0.781-5.570;  $P=0.142$ ).

**Table 3:** Univariate analyses of associated with chemotherapeutic sensitive disease.

Variables	chemotherapeutic sensitive(n=43)	chemotherapeutic resistant or refractory (n=38)	Univariate P value	Multivariate P value	Multivariate OR(95%CI)
Age(years)			0.873		
≤55	23	21			
>55	20	17			
FIGO Stage			0.249		
III	38	30			
IV	5	8			
Histology			0.023	0.092	3.046(0.834-11.122)
Serous	39	27			
None serous	4	11			
CA125U/ml≤1800U/ml presentation	Y 17	22	0.099		
	N 26	16			
CA125U/ml≤850U/ml after the 1st NAC*	Y 25	16	0.145		
	N 15	19			
Reduction CA125U/ml >30% after the 1st NAC*	Y 20	19	0.711		
	N 20	16			
CA125≤200U/ml preoperatively	Y 21	10	0.037	0.142	2.086(0.781-5.570)
	N 22	28			
Reduction CA125U/ml >80% presentation to preop	Y 22	13	0.124		
	N 21	25			

\*Some patients did not measure.

### Discussion

In the current study, we evaluated the power of various parameters associated with CA125 to predict the likelihood of achieving cytoreduction to NVRD in patients with advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma treated with NAC. Our data suggest that a preoperative CA125 level of  $\leq 200$  U/ml and a  $>80\%$  reduction of CA125 level between presentation and IDS are useful predictors of cytoreduction to NVRD in EOC, primary carcinoma of fallopian tube and peritoneal carcinoma patients receiving NAC-IDS, but preoperative CA125

$\leq 200$  U/ml is the only independent predictor. Conversely, there were no significant differences between the NVRD and VRD groups in the CA125 level at presentation, CA125  $\leq 850$  U/ml after the first NAC cycle, or  $>30\%$  reduction of CA125 after the first NAC cycle.

Numerous studies conducted since 1975 have reported that 'optimal cytoreduction', as opposed to 'suboptimal cytoreduction', improves the prognosis for patients with advanced EOC; however, the appropriate cutoff level separating the two has remained controversial [14-16]. The definition of optimal cytoreduction in the 1970s was  $<2$  cm, but this was changed to  $>3$  cm by the Gynecologic Oncology Group in the 1980s [14, 17]. Since 1986, the most common definition of optimal cytoreduction has been  $\leq 1$  cm [18, 19]. However, studies performed over the past 10 years have suggested that NVRD should be the goal of "optimal cytoreduction" [13, 20, 21]. In our study, 84.9% of patients with advanced EOC, primary carcinoma of fallopian tube and peritoneal carcinoma who underwent NAC-IDS were optimally cytoreduced when the threshold was 2 cm, but using the definition of "optimal cytoreduction" in the setting of NAC as resection to NVRD, 31.4% of our patients reached this target.

CA125 levels are widely used to predict optimal cytoreduction in PDS; however, the accuracy of prediction and the ideal threshold remain controversial [22-24]. A few studies have reported the predictive value of changes in CA125 levels during NAC, but as the use of NAC to treat advanced EOC patients increases, the threshold CA125 level changes. Rodriguez et al. suggested that a preoperative CA125 of  $\leq 100$  U/ml may be useful in predicting optimal cytoreduction to no gross residual disease in patients treated with NAC [10]. Pelissier et al. reported that a CA125 level of  $<75$  U/ml after the third cycle of NAC is an independent predictor of complete IDS [11]. In these studies, surgery was performed by different gynecological oncologists, and the concept of "optimal cytoreduction" may have varied from operator to operator. Our data were collected by one operator at one center, suggesting minimal variation in surgical skill. We also analyzed various CA125 reduction parameters to determine which best predicted "optimal cytoreduction". Among the five parameters analyzed, the percentage change and the absolute level of CA125 after the first cycle of NAC were not associated with "optimal cytoreduction", suggesting that evaluation of CA125 levels after a single cycle may have little predictive value. However, we found that a preoperative CA125 of  $\leq 200$  U/ml was an independent predictor of optimal cytoreduction to NVRD in patients treated with NAC.

In our hospital, this standard has helped us to identify EOC patients who are likely to achieve cytoreduction to NVRD.

Drug resistance is a critical issue in the treatment of EOC. Many studies have reported biomarkers that predict chemotherapeutic sensitivity, and some have even been clinically accepted. Unfortunately, none of the biomarkers have been clinically validated for use in EOC [25]. In our study, we analyzed the relationship between five parameters of CA125 reduction and chemotherapeutic sensitivity and found that a preoperative CA125 of  $\leq 200$  U/ml was the only predictor of chemotherapy-sensitive disease in EOC patients with NAC-IDS, though, it was not the independent predictor. This suggests that preoperative CA125  $\leq 200$  U/ml may be useful in predicting chemotherapy-sensitive disease in patients treated with NAC, whereas patients with preoperative CA125 levels  $>200$  U/ml after NAC should be closely monitored for signs of drug resistance.

There were several limitations to our study. First, the retrospective nature of the study design makes selection bias inevitable. Second, we analyzed data from patients treated by only one operator to maintain consistency in the surgical procedure, but this also limits the representation of the results. Finally, the duration of our study is too long to control the effects of medical progress, such as changes in chemotherapy. Therefore, the results of our current study should be confirmed in a large, well-designed prospective study.

In summary, we observed that CA125 reduction can predict cytoreduction to NVRD in advanced EOC patients who received NAC-IDS. In our study, a CA125 level of  $\leq 200$  U/ml before IDS was not only an independent predictor of cytoreduction to NVRD but also a predictor of chemotherapeutic sensitivity among patients with EOC who received NAC-IDS.

## Competing Interest

The authors have declared that no competing interest exists.

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