

Preoperative CA-125 Values as a Predictive Factor for the Postoperative Outcome in Primary Serous Ovarian Cancer

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Abstract. *Background/Aim:* The purpose of the study was to examine the preoperative CA-125 values as a predictive factor for postoperative outcome in primary serous ovarian cancer (POC) for complete tumor resection (CTR) and evaluate the preoperative CA-125 levels with other vital clinical dynamics such as ascites, lymph node involvement, diffuse peritoneal carcinomatosis, grading and staging. *Patients and Methods:* A cohort of 277 POC-patients aged 18-75 years, who had undergone primary cytoreductive surgery at the Department of Gynecology & Oncological Surgery, Charité, Campus Virchow Klinikum (CVK) between 2000 und 2009 was analyzed in correlation with the preoperative CA-125 values. *Results:* The median preoperative CA-125 value in high-grade serous POC patients was 636 U/ml (204- 2312 U/ml) compared to 284 U/ml (148.5-1,378 U/ml) in low-grade serous POC patients ($p=0.016$). For the survival analyses both the cut-off values 252 and 475 U/ml, with highest sum from sensitivity (79.1% and 65.9%, respectively) and specificity (41.9% and 55.1%, respectively), were used to compare the relationship between preoperative CA-125 levels and (CTR), progression-free (PFS) and overall survival (OS). There was no significant difference between PFS and OS in three different groups of patients (preoperative CA-125 levels <252 U/ml, CA 125 levels between 252-475 U/ml and >475 U/ml). *Conclusion:* Preoperative CA-125 is a poor, but statistically significant predictive factor for CTR after PCS. Preoperative CA-125 can predict neither the progression-free nor overall survival for POC patients.

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Epithelial ovarian cancer (EOC) is the seventh most common cancer worldwide, with 238,700 new cases and 151,900 deaths in 2012 (1). It remains the major cause of death from gynecologic malignancies and represents the fifth leading cause of all cancer-deaths among women (2).

CA-125 is a repeating peptide epitope of mucin (MUC) 16 (3-4), which promotes cancer cell proliferation and inhibits anti-cancer immune responses (5-6). This and published evidence pointing to an altered expression of the protein in ovarian cancers (7) have spurred the interest on CA-125 as a biomarker for serous ovarian cancer (8). Numerous research studies have investigated the role of preoperative CA-125 value as predictor for postoperative outcome: some of them reviewed only patients with epithelial ovarian cancer (2, 9), or the predictive value of preoperative CA-125 together with preoperative computed tomography scan (CT) in patient groups with advanced ovarian, fallopian tube and peritoneal cancer disease (10). However, the predictive value of CA-125 levels has been inconclusive (11), therefore research has also focused on another tumor marker like Human epididymal protein 4 (HE4) in serum plasma in order to predict the surgical outcome in Primary ovarian cancer (POC) patients (12).

The objective aim of our retrospective study was to examine the predictive value of preoperative CA-125 for optimal cytoreduction and postoperative overall survival after primary cytoreductive surgery (PCS) and evaluate the preoperative CA-125 levels with other vital clinical dynamics such as ascites, lymph node involvement, diffuse peritoneal carcinomatosis, grading and staging.

Materials and Methods

The database from the Tumor Bank Ovarian Cancer (www.toc-network.de) was utilized to identify patients with the required specific case history. This database, essentially, a prospective documentation tool includes clinical data, disease history, tumor spread, presence of ascites, and presence and location of residual tumor mass intra-operatively obtained through an interview with the

surgeon immediately post-operatively. The study had in place the requisite informed consent before collection of the clinical data and the ethics committee approval from Charité local Ethics Committee (EK207/2003). Cancer staging in the study was based on The International Federation of Gynecology and Obstetrics (FIGO) classification prior to 2014 to match the database (13). The optimal surgery was defined as no macroscopic tumor residual after PCS.

We included all serous POC-patients aged 18-75 years, which underwent PCS at the department of Gynecology with oncological surgery, Charité, Campus Virchow Klinikum (CVK) between 2000 and 2009. The design had an exclusion criterion of patients with non-epithelial ovarian cancer, other histologies than serous, patients with no preoperative CA-125 evaluations, women who had undergone interval surgery, and those who were treated for another malignant disease in the last 5 years of the study period.

The statistical analysis has been performed at the Charité Medical University Berlin. All analyses have been performed by IBM SPSS Statistics 22.0 (SPSS, Chicago, IL, USA).

Descriptive statistic tests were used to characterize the patient cohort and Kolmogorov-Smirnov test to characterize the distribution of preoperative CA-125 levels.

With Receiving operating characteristic (ROC) analysis sensitivity and specificity were calculated to define the optimal cut-off value of the preoperative CA-125 levels for predicting Complete tumor resection (CTR).

The correlation between preoperative CA-125 levels and clinical factors such as age, ascites, FIGO stage and CTR was investigated using non-parametric univariate tests such as Kendall-Tau b, Spearman Rho, Man-Whitney and Kruskal Wallis test.

Median and 95% confidence intervals (95%CI) of Progression free survival (PFS) and Overall survival (OS) were estimated according to the Kaplan-Meier method. PFS was defined as the length of time between the end of the last chemotherapy cycle to the occurrence of the relapse. OS was determined as the length of time between the date of first diagnosis and the date of death or end of follow-up. Log-rank test statistics for analysis of the equality of survival distribution were performed. Statistical significance was defined by $p < 0.05$ and two-sided tests were applied.

Results

The patient characteristics are presented in Table I. A total of 227 patients in a POC cohort were investigated and CA-125 measured before the primary cytoreductive surgery in all patients. The median age of the cohort at the first diagnosis was 59 years. One in four patients was younger than 50 or older than 65 years. A percentage of 96.9% of them had an advanced recurrent POC (FIGO III-IV). A high-grade serous POC had been diagnosed in 64.5% of cases, with 81.5% of the patients with ascites (44.1% with less than 500 ml and 37.4% with more than 500 ml). A percentage of 59.9% of the women had been operated with no macroscopic tumor residual and 85.5% of the operated women had undergone some type of lymph node dissection. A percentage of 55.5% of them have had pelvic and/or paraaortal lymph node metastasis at the time of operation. The median follow-up time was 44.4 months (range=0.1-158 months). The main CA-125 value was 1991.9; the median was 552 U/ml (the interquartile range=IQR: 164-

Table I. Characteristics of 227 primary serous ovarian cancer patients underwent primary cytoreductive surgery in Charité Berlin.

Characteristics	All patients n=227 (%)
Age at first diagnosis [years]	Median 59 (21-92)
CA-125	552 U/mL (11-38 387)
FIGO classification	
II	7 (3.1%)
III	178 (78.4%)
IV	42 (18.5%)
Grading	
1-2	80 (35.2%)
3	147 (64.8%)
Ascites	
No ascites	42 (18.5%)
<500 ml	100(44.1%)
>500 ml	85 (37.4%)
Residual tumour	
No residual	136 (59.9%)
<10 mm	64 (28.2%)
≥10 mm	27 (11.9%)
Lymph nodes status	
N0	68 (30%)
N1	126 (55.5%)
Nx	33 (14.5%)

2,004 U/ml). The median preoperative CA-125 value in high-grade serous POC patients was 636 U/ml (range=204-2,312 U/ml) compared to 284 U/ml (range=148.5-1,378 U/ml) in low-grade serous POC patients ($p=0.016$). Kolmogorov-Smirnov Test does not display normal distribution of CA-125 in the cohort (Figure 1-A) whereas, the logarithmic converted CA-125 values illustrate a normal, symmetric distribution curve (Figure 1-B).

The correlation between preoperative CA-125 levels and the outcomes of surgery (CTR). Since, the Area Under Curve (AUC) has a small surface, to predict the prognostic value of preoperative CA-125; it was prudent to set a cut-off value of preoperative CA-125, which predicts the CTR. Thus, the estimated optimal CA-125 preoperative cut-off value in our study was 252 U/ml and 475 U/ml with highest sum from sensitivity (79.1% and 65.9%, respectively) and specificity (41.9% and 55.1%, respectively) (together, namely 121), so that we could predict the chance for CTR for 79.1% of patients, who had CA-125 less than 252 U/ml before the primary cytoreductive surgery and for 65.9% of patients with preoperative CA-125 of less than 475 U/ml.

The correlation between preoperative CA-125 levels and PFS or OS. For the survival analyses both the cut off values 252 and 475 U/ml were used to compare the relationship

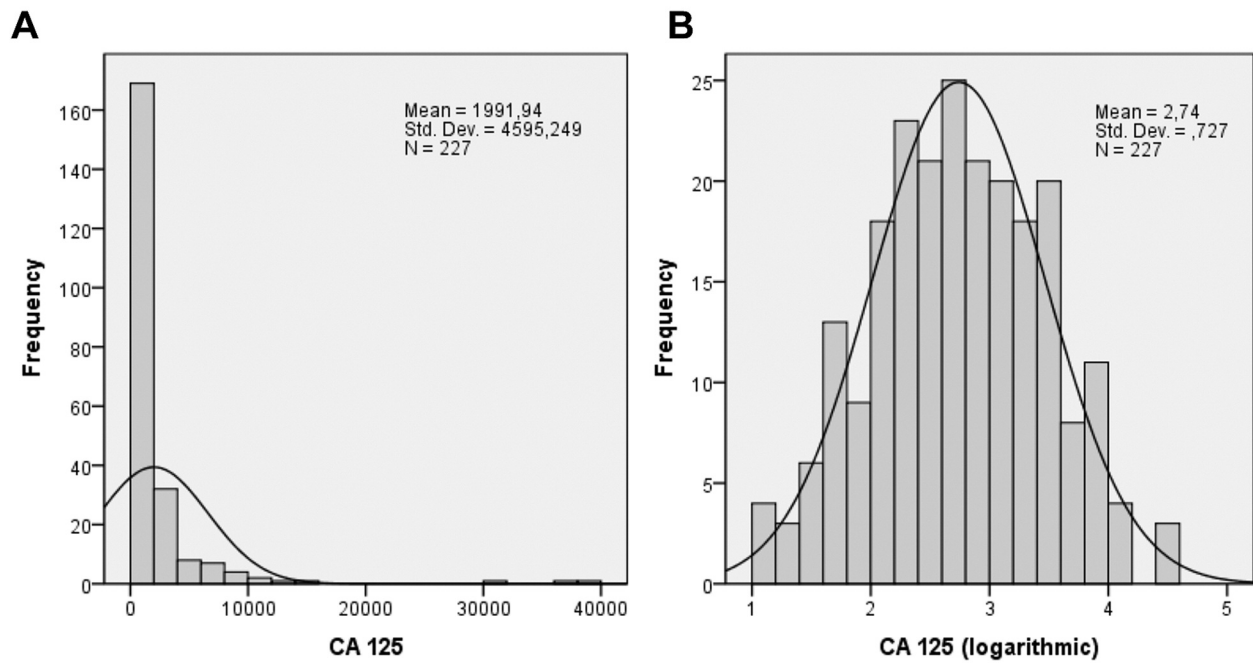


Figure 1. The distribution of CA-125 values in our collective. A: Kolmogorov-Smirnov Test with normal distribution. B: Logarithmic converted CA-125 values with symmetric curve of distribution.

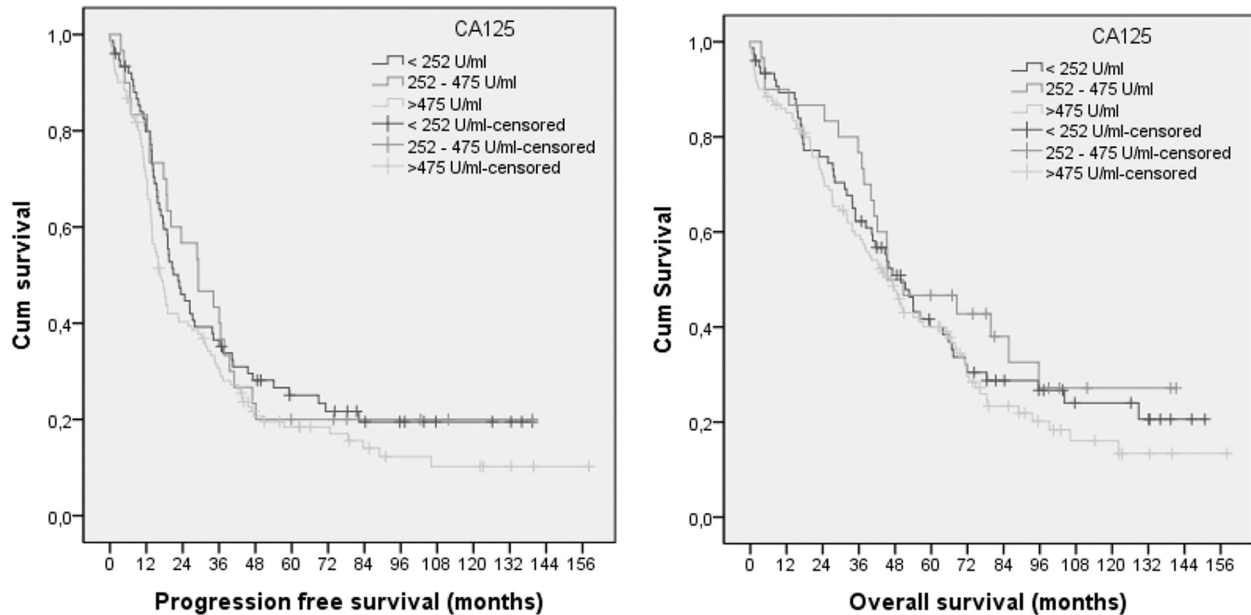


Figure 2. Progression-free and overall survival in the 3 groups of primary serous ovarian cancer patients according to preoperative CA-125 values.

between preoperative CA-125 levels and PFS or OS. There was no significant difference between PFS and OS in three different groups of patients (preoperative CA-125 levels <252 U/ml, CA-125 levels between 252-475 U/ml and >475 U/ml) (Figure 2).

The correlation between preoperative CA-125 values and the important clinical prognostic factors. Univariate analysis of the conventional key clinical prognostic factors for POC and its correlation to preoperative CA-125 showed no correlation between preoperative CA-125 and the patient's age. However,

a correlation was observed with advanced POC (FIGO III-IV) in comparison with early staged POC (FIGO I-II); with ascites >500 ml in comparison with no ascites or ascites <500 ml; with high-grade serous POC in comparison with low-grade serous POC and with CTR in comparison with residual tumor (p -value=0.579, 0.008, 0.000, 0.014 and 0.001 respectively). Interestingly, lymph node status was an important factor, which correlated significantly ($p=0.029$) with preoperative CA-125. The Kruskal-Wallis test for lymph node metastasis showed a significant correlation in patients with lymph nodes metastasis (N1) in comparison to those without any lymph node metastasis (N0), ($p=0.015$) and in patients who did not undergo lymph nodes dissection (when CTR is not possible) (Nx) in comparison with those without any lymph node metastasis (N0), ($p=0.039$).

Discussion

One of the statistically significant cut-off values using ROC analysis of preoperative CA-125 levels in the study has been 475 U/ml with best sensitivity (65.9%) and specificity (55.1%). The value matches with other similar studies that have reported that an optimal cytoreduction (defined here as with residual tumor less than 1 cm) could be predicted only in 50% of cases with FIGO III-staged epithelial POC using a cut off value of preoperative CA-125 of 500 U/ml. The study has also elucidated that the chance of an optimal cytoreduction decreases with higher values of preoperative CA-125 (14).

These results fall in tandem with studies of Mury *et al.* (15) that have analyzed the prognostic and predictive values of CA-125 serum concentrations before and after surgery as well as their correlation with clinicopathological variables in a collective of 231 patients with POC (with different histological subtypes). Despite of correlation with some surgical results, they could not determine a preoperative cutoff value for prediction of the surgical result. A prognostic relevance was only observed for postoperative CA-125 in stage III/IV patients.

The study also falls in line with the study of Memarzadeh *et al.* (9) in 99 patients with stage IIIC and IV epithelial POC aiming to test the utility of preoperative CA-125 to predict optimal primary tumor cytoreduction (defined here as largest volume of residual disease <1 cm in maximal dimension). Optimal cytoreduction was achieved in 73% of patients with a mean CA-125 level of 569 U/ml, while among patients with suboptimal cytoreduction the mean CA-125 level was 1520 U/ml ($p<0.007$). With a CA-125 level of 912 U/ml identified as the optimal cut-point to distinguish the two groups, the sensitivity of the test in predicting optimal cytoreduction has been just 58% (in tandem with 79.1% and 65.9%, respectively for our both cutoff values 252 and 475 U/ml in present study) and the specificity 54% leading us to

the conclusion that CA-125 level is a weak positive and negative predictor of optimal cytoreductive surgery in patients with advanced epithelial ovarian cancer.

Similar study by Chi *et al.* (16) have also concluded that preoperative CA-125 does not predict the primary cytoreductive outcome of patients with advanced ovarian, tubal, or peritoneal carcinoma. However, with a preoperative CA-125 >500 U/ml, extensive upper abdominal procedures were necessary in 50% of cases to achieve residual disease ≤ 1 cm. Interestingly, CTR was achieved only in 25% of their collective.

Harter *et al.* (17) reviewed prognostic factors for CTR after first- and second-line ovarian cancer. They could not find sufficient predictive markers (including the preoperative CA-125) for CTR.

In the European multi-centric project "Ovarian Cancer: Diagnosis of a silent killer" (OVCAD) (12), 275 consecutive patients with POC were enrolled and analyzed. The results showed that the combination of HE4 and CA-125 expression in plasma might predict the surgical outcome in EOC which may have a prognostic impact on PFS and OS. Plasma CA-125 and the risk index (HE4 and CA-125) were independent predictive factors for surgical outcome ($p=0.001$, OR=3.37, 95%CI=1.61-7.06 and $p<0.001$, OR=6.041, 95% CI=2.33-15.65, respectively).

Limiting factors of this study were the retrospective design, and the FIGO classifications provided were defined according to the old classification system. Nevertheless, our study has convincing advantages. The study cohort was restricted to patients with serous POC, thus only patients where preoperative CA-125 values assumed to be reflecting the peritoneal dissemination of cancer were included. In addition, the rather high number of patients in this collective, the high rate of CTR and the long median follow-up period add more value to our results.

In conclusion, preoperative CA-125 is poor, but statistically significant predictive factor for CTR after PCS. Preoperative CA-125 can predict neither the progression-free nor the overall survival for POC patients.

Conflicts of Interest

The Authors declare in financial or personal conflict of interest.

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