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Preoperative CA-125 Value as a Predictive Factor for Postoperative Outcome in First Relapse of Platinum-sensitive Serous Ovarian Cancer

ASYA PARASHKEVOVA[1], JALID SEHOULI[2], ROLF RICHTER[2], DESISLAVA DIMITROVA[2], ELENA IOANA BRAICU[1,2] and MUSTAFA ZELAL MUALLEM[2]

[1]Ovarian Cancer Tumor Bank, and [2]Department of Gynecology, Virchow Campus Clinic, Charité Medical University, Berlin, Germany

Abstract. *Aim: The purpose of the study was to evaluate whether preoperative cancer antigen 125 (CA-125) levels predict outcome of secondary cytoreductive surgery (SCS) in patients with serous recurrent ovarian cancer and whether this could be used as a prognostic factor for progression-free (PFS) and overall (OS) survival. Patients and Methods: A cohort of 111 patients with first recurrence of platinum-sensitive serous ovarian cancer, who had undergone SCS at the Department of Gynecology and Oncological Surgery, Charité, Campus Virchow Clinic was analyzed in correlation with the preoperative CA-125 value. Results: The median preoperative CA-125 level was 164 U/ml. Complete tumor resection was achieved in 58.6% of the patients. PFS and OS for patients with preoperative CA-125 of less than 164.5 U/ml was significantly better than those with preoperative CA-125 ≥164.5 U/ml (p=0.025 and p<0.001, respectively). Conclusion: Preoperative CA-125 is not a statistically significant predictive factor for complete tumor resection after SCS. Preoperative CA-125 <164.5 U/ml can predict significantly better PFS and OS for patients with first recurrence of platinum-sensitive ovarian cancer.*

Epithelial ovarian cancer (EOC) is characterized by an aggressive course and high probability of disease recurrence. Due to lack of early symptoms, EOC is diagnosed mostly at an already advanced stage (1). In recent years, progression-free (PFS) and overall (OS) survival have been extended due to improved surgical skills of gynecological oncologists, better understanding of tumor biology, and implementation of new chemotherapeutic agents (2-7).

The majority of patients with EOC experience relapse even after successful therapy (8-10). The first recurrence is treated with surgery, followed by second-line chemotherapy or with chemotherapy alone (10).

Some studies attempted to define criteria for predicting surgical outcome. The Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP OVAR) I trial in patients with recurrent ovarian cancer was performed to test the hypothesis that certain criteria could be used for selecting patients who might benefit from surgery in recurrent ovarian cancer (ROC) (11). After retrospective analysis of 267 patients with ROC, the study described the following statistically significant results: patients with complete tumor resection (CTR) had significantly longer survival compared with those who underwent surgery leaving any postoperative residuals; favorable variables associated with complete resection were performance status 0, International Federation of Gynecology and Obstetrics (FIGO) stage I/II, no tumor present after primary surgery, and absence of ascites. The DESKTOP OVAR II trial confirmed the study hypothesis and introduced the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score: 1: complete resection at first surgery, 2: good performance status, 3: absence of ascites, as a predictive score for successful surgery. The study included 516 patients with first or second relapse of serous ovarian cancer. In total, 51% of these patients were classified as score-positive patients (when all three criteria were met). CTR was achieved In 76% of AGO score-positive patients. This score was the first prospectively validated instrument to predict positive surgical outcome in ROC (2).

The prospective DESKTOP III trial study showed that patients with platinum-sensitive first relapse of ovarian cancer and positive AGO score benefited from secondary cytoreductive surgery (SCS); these patients had a clinically

Correspondence to: Dr. med. Dr. (syr.) Mustafa Zelal Muallem, Charité University Medicine Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450664373, Fax: +49 30450564900, e-mail: Mustafa-Zelal.Muallem@charite.de

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meaningful increased PFS and time to start of first subsequent therapy, with acceptable treatment burden. This gives physicians a valuable option in the decision regarding surgical therapy for patients with first relapse in EOC (12).

One established clinical parameter of ovarian cancer is the cancer antigen 125 (CA-125). It promotes cancer cell proliferation and inhibits anticancer immune responses (13-15). CA-125 is implemented in the diagnosis of primary EOC and ROC. Moore *et al*. described the Risk of Ovarian Malignancy Algorithm (ROMA Index), CA-125/HE4 Index, which helped to detect EOC depending on pre-/postmenopausal status of the patients with high sensitivity and moderate specificity for both pre- and postmenopausal women (16).

The main objective of our study was to evaluate if the preoperatively measured CA-125 level predicted the outcome of SCS in patients with serous ROC and whether it could be used as prognostic factor for PFS and OS.

Materials and Methods

A total of 111 patients with first recurrence of platinum-sensitive serous ovarian cancer were included in this retrospective study. The patients were recruited from the Ovarian Cancer Tumor Bank (www.toc-network.de). 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 postoperatively. All participants gave their inform consent. The study was approved from Charité Medical University local Ethics Committee (EK207/2003). The clinical data were extracted from patient's records.

The optimal surgical outcome after SCS was defined as no macroscopic tumor residual (R0) or CTR.

All patients included in the study had platinum- sensitive disease (recurrence after more than 6 months from the end of platinum-based chemotherapy) and received a platinum-based chemotherapy 6-8 weeks after SCS. Cancer staging in the study was based on the FIGO classification prior to 2014 to match the database (17). The CA-125 level was measured preoperative in U/ml in blood serum using Elecsys® CA-125 II (Roche diagnostics, Basel, Switzerland).

Patients with platinum-resistant recurrence were excluded from the analysis, as were patients with histology other than serous papillary, patients without preoperative CA-125 evaluation and those who had been treated for second malignancy in the 5 years before first diagnosis of EOC.

At the end of treatment, patients were regularly evaluated for evidence of new recurrence by clinical examination, transvaginal and transabdominal sonography, and CA-125 (if the preoperative value was elevated). A computerized tomography (CT)/ magnetic resonance imaging (MRI) examination was performed if the above examinations revealed pathological findings. No treatment decisions were taken based only on raised CA-125 level.

The statistical analysis was performed at Charité Medical University Berlin using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistic tests were used to characterize the patient cohort and Kolmogorov–Simirnov test to characterize the distribution of preoperative CA-125 levels.

Table I. *Characteristics of 111 patients with first platinum-sensitive relapse of serous epithelial ovarian cancer underwent secondary cytoreductive surgery (SCS) in Charité Medical University, Berlin, Germany.*

Characteristic	Value
Age at first relapse, years	
Median (range)	55 (28-85)
CA-125, U/ml	
Median (range)	164 (5-29000)
FIGO classification at first diagnosis, n (%)*	
II	4 (3.6%)
III	89 (80.2%)
IV	16 (14.4%)
Grading, n (%)	
Low	31 (27.9%)
High	78 (70.3%)
Ascites, n (%)	
None	64 (57.7%)
<500 ml	37 (33.3%)
≥500 ml	10 (9%)
Residual tumor, n (%)	
R0	65 (58.6%)
R1	46 (41.4%)
Lymph node status, n (%)	
N0	16 (14.4%)
N1	51 (45.9%)
Nx	44 (39.6%)

CA-125: Cancer Antigen-125 (<35 U/ml); FIGO: International Federation of Gynecology and Obstetrics (17).

With receiving operating characteristics analysis, sensitivity and specificity were calculated to define the optimal cut-off value of preoperative CA-125 for predicting CTR.

The correlation between preoperative CA-125 levels and clinical factors such as age, ascites, grading, FIGO stage and CTR was investigated using non-parametric univariate tests such as Kendall's Tau-b, Spearman's Rho, Wilcoxon–Mann–Whitney test and Kruskal–Wallis test and again with a multivariate analysis.

Median and 95% confidence intervals (95% CI) for PFS and 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 second relapse. OS was determined as the length of time between SCS for the first relapse and the date of death or end of follow-up. Statistical significance was defined by $p<0.05$ and two-sided tests were applied.

Results

A total of 111 patients in an ROC cohort were investigated and CA-125 measured before SCS in all patients. The median age of patients at the time of SCS was 55 years. The patients characteristics are presented in Table I. Overall, 96.2% of patients were diagnosed with advanced stage at the time of first diagnosis of EOC. Only 3.6% of the patients in this cohort had an early stage (FIGO II) at the time of first diagnosis.

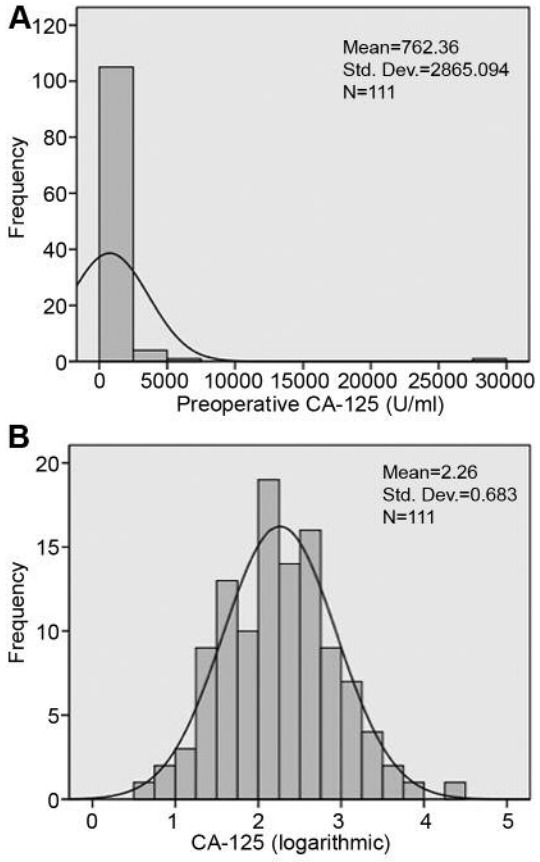

Figure 1. *Distribution of preoperative cancer antigen (CA)-125 in our collective. A: Kolmogorov–Smirnov test presents a non-normal distribution. B: Values were approximately normal (Gaussian) distributed after logarithmic conversion.*

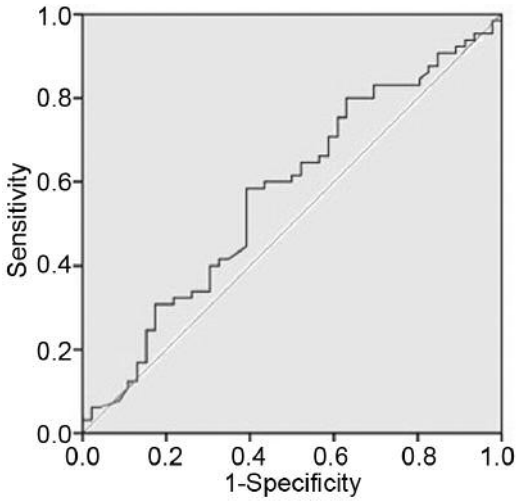

Figure 2. *Receiver operating characteristic curve analysis. Representation of area under the curve=0.572 (p=0.195).*

Most patients with ROC had no ascites at the time of SCS (57.7%), whereas 9% had 500 ml ascites or more. Of all cases with ROC, 67.4% underwent lymph node dissection in the frame of their SCS and the final histological study showed affected lymph nodes in 45.9% of the total cohort (76.1% of patients with lymph node dissection as a part of SCS). CTR was achieved in 58.6% of the patients; in the remaining patients, different volumes of residual tumor could not be resected.

The median preoperative CA-125 level was 164 U/ml and the mean value was 762.36 U/ml (95% CI=223.43-1,301.28 U/ml). The mean follow-up period was 26.4 months. Kolmogorov–Smirnov test showed the preoperative CA-125 levels were not normally distributed in this cohort (Figure 1A). Logarithmic conversion of CA-125 values led to normalization (Gaussian) of their distribution (Figure 1B).

Correlation between preoperative CA-125 levels and the outcomes of SCS. Using receiver operating characteristics analysis, there was no prognostic power of preoperative CA-125 to predict CTR, which is the most important prognostic factor of ROC after SCS. Since, the area under curve (AUC) was small for the prognostic value of preoperative CA-125; it was prudent to set a cut-off value of preoperative CA-125 which would predict the CTR. Therefore the estimated optimal preoperative CA-125 cut-off value in our study was 164.5 U/ml, with highest sum of sensitivity (58.5%) and specificity (60.9%), allowing prediction of the chance for CTR as 58.5% for patients who had CA-125 less than 164.5 U/ml before SCS, with corresponding AUC of 0.572 (p=0.195), which means the distribution of false-positive and true-positive results could be accidental (Figure 2).

Correlation between preoperative CA-125 levels and PFS or OS. For the survival analyses, the cut-off value of 164.5 U/ml was used to compare the relationship of preoperative CA-125 level with PFS and OS using Kaplan–Meier curves. PFS and OS were significantly better for patients with preoperative CA-125 of less than 164.5 U/ml than those with preoperative CA-125 ≥164.5 U/ml (p=0.025 and p<0.001, respectively; Figure 3). Median PFS was 20 (95% CI=16.7-23.3) and 13 (95% CI=10.1-15.8) months, and median OS was 46.3 (95% CI=4-68.5) and 25 (95% CI=18.4-31.6) months after SCS with and without CTR, respectively.

Correlation between preoperative CA-125 values and the important clinical prognostic factors. Univariate analysis of the conventional clinical prognostic factors for ROC and its correlation to preoperative CA-125 showed higher values of preoperative CA-125 in patients with ascites compared to those without ascites, and in patients with advanced-stage

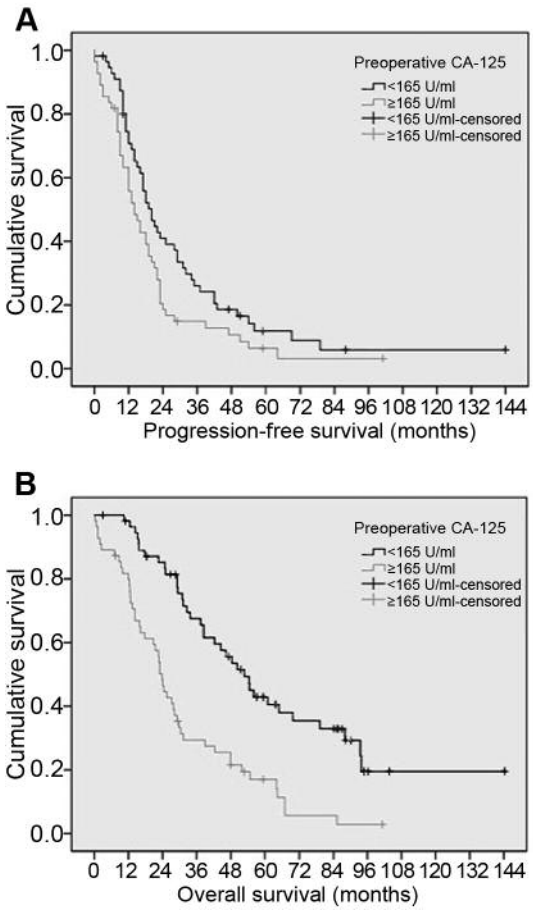

Figure 3. *Progression-free (A) and overall survival (B) in the two groups of patients with recurrent serous ovarian cancer according to preoperative cancer antigen (CA)-125 value.*

EOC at first diagnosis (FIGO III and IV) compared to patients with early-stage of EOC (FIGO I or II). These two correlations were weak to moderate. Wilcoxon–Mann–Whitney test indicated higher preoperative CA-125 values in patients with ≥500 ml ascites compared to those with <500 ml (p=0.033), and those without ascites (p=0.027).

The multivariate analysis reported a higher risk for residual tumor in patients with diffuse peritoneal cancer compared to those without diffuse peritoneal dissemination (p<0.001).

Discussion

The role of SCS in ROC has not been defined by level-1 evidence. Such evidence may be provided by the final results of DESKTOP III trial. Until then, SCS should at least be considered as a valuable option in patients with a positive AGO score (12). The AGO score, developed within a retrospective analysis and validated in a prospective independent cohort, has gained attention in treatment of patients with ROC. Harter *et al*. concluded that the positive predictive value of the AGO score in patients with first relapse was 76% (2); the negative predictive value was only 38% and specificity was low at 53%.

The AGO score does not include CA-125 as one of its criteria for a positive score, therefore in this study, we tried to test the predictive value of preoperative CA-125 for postoperative outcome in SCS in term of CTR, PFS and OS independently from the AGO-Score; and we aimed to evaluate the correlation between preoperative CA-125 levels and important clinical prognostic factors.

In this study, a cut-off value of preoperative CA-125 with sub-optimal prognostic power was set at 164.5 U/ml. In the study of Mahner *et al*., a CTR was achieved in 33% of the patients (18). This rate was higher in our study at 58.6%. Muallem *et al*. from our Institute reported a CTR rate of 61% after SCS in all patients with ROC (19). This rate was increased to 67% by including only patients with a positive AGO-Score, which is identical to the CTR rate reported in the SCS arm of DESKTOP III trail for patients with a positive AGO-score. The rate of CTR registered by Harter *et al*. was 49.8% (11). In other studies, the CTR rate ranged between 9% and 82% (20-38). This difference could be due to the procedures having been performed in a tertiary center by highly experienced surgeons in our study.

Mahner *et al*. also investigated the prognostic value of CA-125 in the management of patients with ROC selected for SCS and included 36 patients in their study (18). They reported that preoperative CA-125 was elevated (>35 U/ml) at the time of ROC in 30 out of 36 patients (81%), with a median of 212 U/ml in comparison with our median preoperative CA-125 of 164 U/ml. They concluded that preoperative CA-125 had no prognostic relevance. The only independent prognostic factors of improved survival were the progression-free interval before SCS (p=0.047) and minimal residual disease after SCS (p=0.024). Harter *et al*. reviewed prognostic factors for CTR after primary cytoreductive surgery and SCS for EOC. They were unable to find sufficient predictive markers (including preoperative CA-125) for CTR in both groups (39). In our previous study on preoperative CA-125 value as a predictive factor for postoperative outcome in primary serous ovarian cancer, we concluded that preoperative CA-125 was a statistically significant predictive factor for CTR after primary cytoreductive surgery (40). However, preoperative CA-125 cannot predict PFS nor OS for patients with primary serous ovarian cancer. In contrast to this conclusion, the current study about ROC showed the preoperative CA-125 had no prognostic significance and was unable to predict the CTR. On the other hand, PFS and OS was better for patients with preoperative CA-125 of less than 164.5 U/ml (p=0.025 and p<0.001, respectively).

Limiting factors of this study were its retrospective design, and that 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 ROC, therefore only patients with preoperative CA-125 values, assumed to reflect 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 value to our findings.

In conclusion, preoperative CA-125 is a poor, not statistically significant predictive factor for CTR after SCS. Preoperative CA-125 <164.5 U/ml can predict significantly better PFS and OS for patients with first relapse of platinum-sensitive EOC.

Conflicts of Interest

There exists no financial or personal conflict of interest by any of the Authors to declare.

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