

## Prognostic Value of Ca 125 Levels during Primary Therapy

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**Abstract.** *Aim: The prognosis of patients with ovarian cancer depends on stage, histological type, age, presence of ascites, performance status and debulking surgery. Complete cytoreductive surgery is the most important prognostic factor. We investigated the suitability of Ca 125 as a prognostic factor in patients with ovarian cancer at various. Patients and Methods: In a retrospective analysis, the Ca 125 level in 197 patients with epithelial ovarian cancer was determined and evaluated the results statistically. Our patients were diagnosed, treated and followed up for an average of three years at Rostock University Hospital, Germany from 1990 till 2000. Data were analyzed using the Kaplan-Meier curves, Log-rank test, Cox regression and Pearson correlation coefficient. An ELISA was used for the determination of Ca 125. Results: The baseline level of 60 patients, the postoperative level of 86 patients and the level of 76 patients after treatment were available. Thirty-three out of 197 patients received a Ca 125 determination during all the above mentioned events. In 20% of the cases, the level of Ca 125 was normal prior to surgery (<35 U/l). The level was not strongly correlated with FIGO-stage (Pearson correlation coefficient  $r_{\text{prior to surgery}}=0.444$ ,  $p<0.001$ ;  $r_{\text{after surgery}}=0.476$ ,  $p<0.01$ ;  $r_{\text{after treatment}}=0.244$ ,  $p<0.05$ ). Patients with a Ca 125 level above 100 U/l had a significantly lower three-year survival rate ( $p<0.05$ ). The number of patients with a normal Ca 125 level increased after surgery (26.7%) and after primary treatment (69.7%). Patients with a Ca 125 >100 U/l after treatment died significantly sooner. Thirty-three patients showed a decrease in their Ca 125 level after each part of their treatment (baseline/after surgery  $p<0.001$ ; baseline/after treatment  $p<0.05$ ). The level of Ca 125 after the entire treatment has yet to show significance as a prognostic factor for survival ( $p<0.001$ ). Conclusion: The level*

*of Ca 125 in ovarian cancer correlated with overall survival. A significant difference between patients with Ca 125 >100 U/l after treatment and a normal Ca 125 was observed. The tumor marker Ca 125 is a prognostic factor. Levels around 100 U/l are indicative of a bad prognosis.*

For ovarian cancer patients who complete chemotherapy and achieve complete clinical remission, the primary objective of treatment is to prevent recurrences. However, despite radical therapeutic strategies, the majority of ovarian cancer patients will suffer from intraabdominal relapse within a few years following surgery. Various diagnostic tools, including ultrasound or computer tomography, are available to detect an ovarian cancer progression or recurrence. These procedures are expensive, have limited sensitivity and specificity, and are difficult to compare. Ca 125 is an established tumor marker for ovarian cancer, though in mucinous carcinoma Ca 72-4 or Ca 19-9 is superior (1). Tumor marker determination is a simple, reproducible technique.

Ca 125 is a large glycoprotein. It occurs as a differentiation antigen in fetal tissue from derivatives of coelomepithelium and tissue of serous adenocarcinoma. The cut-off for Ca 125 was defined as lower than 35 U/l. Ca 125 is the most important parameter for patients with ovarian cancer (2, 3). The serum level of Ca 125 correlates with the tumor burden. However, not every increase signifies a progression of disease. Diseases like adnexitis, hepatitis, pancreatitis, cirrhosis of the liver, auto immune diseases or early pregnancy also lead to elevated Ca 125. We assume that Ca 125 estimations in the serum are meaningful only if preoperatively elevated values are present.

### Patients and Methods

In our study, 197 patients with ovarian cancer under medical treatment from 1990-2000 at Rostock University Hospital were included. The patient selection took place according to the clinical admission. The outcome was observed for a minimum of 36 months, on average 48 months. The tumor marker was examined before and after surgery and after primary treatment. The predictive value of Ca 125 was examined at three specific dates. An

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Table I. Patient data (n=197).

Characteristic	Rostock 1990-2000	Literature
Median age in years (range)	60 (19-86)	50 (13-83)
FIGO		
I and II	65 (33%)	35.1%
III and IV	132 (67%)	64.9%
Histological type		
Serous	131 (66.5%)	55.8 (40-50%)
Mucinous	27 (13.7%)	9.7 (10-15%)
Endometrioid	6 (3.0%)	4.9 (10-15%)
Clear cell	5 (2.5%)	3.9 (2-6%)
Undifferentiated	11 (5.6%)	25.7 (Ref. 6) / 5-10% (Ref. 7)
Complete surgical tumor reduction	68 (34.5%)	-
3-year/5-year survival	51% / 39.9%	41% / 35% (Ref. 8)

ELISA was used for determination. The serum samples were frozen at -80°C. Blood was taken up to two weeks before surgery, one to six weeks after surgery and one to four weeks after primary treatment (last cycle of chemotherapy).

The detailed patient characteristics are listed in Table I. The stage distribution was typical of ovarian cancer and therapeutic procedures with surgery and chemotherapy were comparable with established standards. Tumor debulking was the main goal. Patients had a higher incidence of serous adenocarcinoma compared to that found in the literature.

## Results

A detectable level of Ca 125 was found in 60 cases prior to surgery, in 86 cases after surgery and in 76 cases after primary treatment. An increase in normal Ca 125 was observed between measurements prior to and after surgery and after primary treatment.

At each measurement, the level of Ca 125 correlated only slightly with the tumor stage.

Pearson's correlation coefficient:  $r_{\text{prior to surgery}}=0.444$ ,  $p<0.001$ ;  $r_{\text{after surgery}}=0.476$ ,  $p<0.001$ ;  $r_{\text{after treatment}}=0.244$ ,  $p<0.05$ .

Serial measurements of Ca 125 correlated with three-year survival (Figure 1A-C). Normal levels of Ca 125 after adjuvant therapy were found in 69.7% of the patients. Of these patients, 63% were alive after three years. Median survival time was not available. Patients with a Ca 125 level higher than 100 U/l died sooner (Table III).

We identified 33 patients with consistently elevated values of Ca 125 (preoperative, postoperative, after chemotherapy).

Table II. Ca 125 results during primary therapy. (Number of patients/%)

Ca 125 [U/l]	Prior to surgery	After surgery	After treatment
≤35 (normal)	12 / 20.0%	23 / 26.7%	53 / 69.7%
36-100 (↑)	8 / 13.3%	18 / 20.9%	10 / 13.2%
101-1000 (↑↑)	28 / 46.7%	33 / 38.4%	10 / 13.2%
>1000 (↑↑↑)	12 / 20.0%	12 / 14.0%	3 / 3.9%
Total	60 / 100.0%	86 / 100.0%	76 / 100.0%

Table III. Outcome of 76 patients dependent on Ca 125 value after adjuvant therapy.

Ca 125 [U/l]	Three-year survival (%)	Median survival (months)
≤35 (normal)	63.5	-
36-100 (↑)	33.7	26.0
101-1000 (↑↑)	0	11.0
>1000 (↑↑↑)	0	5.9

In these patients we also saw an increase in the occurrence of normal Ca 125 levels after each therapy (normal value in 14% prior to surgery and 85.7% after treatment). Three patients with normal Ca 125 level prior to surgery had serous carcinoma, one had mucinous and one undifferentiated type.

We investigated whether the determination of the Ca 125 level at any of the specific measurement dates had a prognostic value for the proportional survival rate using Cox regression. After primary therapy, we found that a high Ca 125 level was significant ( $p<0.001$ ). Ca 125 was also important as a prognostic factor after surgery ( $p<0.05$ ). Measurement before surgery did not have a predictive value ( $p=0.06$ ). All patients with a Ca 125 level higher than 35 U/l died within five years of follow-up.

## Discussion

In this study, we analyzed retrospective data from 197 patients, treated over a total of 11 years for ovarian cancer. This disease is heterogeneous: we did not find Ca 125 present in all patients. Severe interventions of the marker Ca 125 were not observed (e.g. time between blood taking and analysis, daily rhythm, nicotine, disorder of liver or kidney function) (3).

A Ca 125 around 100 U/l was associated with a lower three-year survival rate.

Another interesting group of investigated patients were those with persistently elevated Ca 125 levels. Measurements

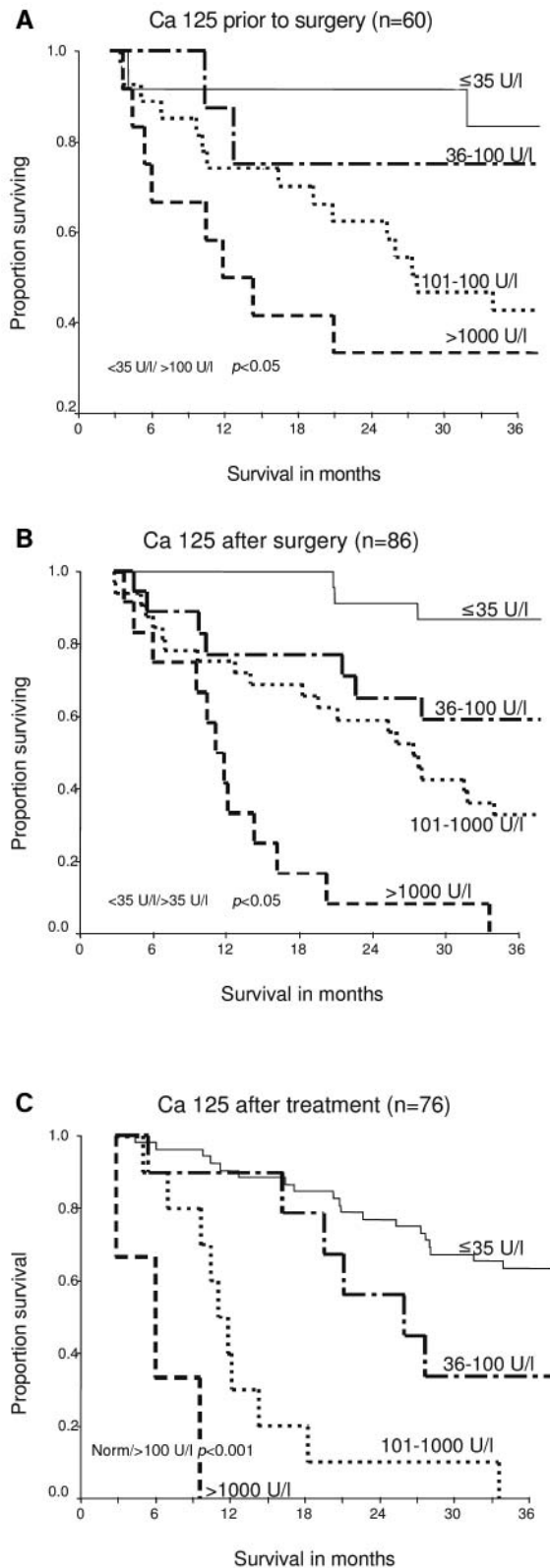


Figure 1. Kaplan-Meier curves for overall survival analyzed according to Ca 125 level (A) prior to surgery, (B) after surgery and (C) after primary treatment (Normal  $>100$  u/l  $p < 0.01$ ).

of Ca 125 are included in clinical trials as a response marker. New guidelines have been established to evaluate the response to treatment in ovarian cancer (4, 5). Our results prove that it is meaningful to determine the marker Ca 125 before the beginning of the therapy, in order to select follow up investigations. Further statements are possible to the prognosis.

### Conclusion

The tumor marker Ca 125 should be measured before surgery in order to detect patients with a Ca 125-sensitive carcinoma; there is no prognostic relevance at that time. After surgery and adjuvant therapy, the Ca 125-level is of significant prognostic relevance before therapy as well as after chemotherapy. This is consistent with the American Consensus Conference 1999.

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