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ORIGINAL ARTICLE

# Analyzing the Role of CA125 in the Care of Patients with Epithelial Ovarian Cancer

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## ABSTRACT

**Background:** Ovarian cancer is the most lethal gynecological malignancy, often diagnosed at advanced stages due to asymptomatic presentation. The CA125 tumor marker plays a crucial role in the diagnosis and management of this disease. **Aim:** To evaluate the impact of CA125 levels on clinical stage, surgical outcomes, and survival in patients with epithelial ovarian cancer. **Methods**: A prospective multicenter observational study was conducted from January 2016 to June 2019 in regional cancer centers. Patients with confirmed epithelial ovarian cancer were enrolled, and data regarding CA125 levels, treatment modalities, and clinical outcomes were collected and analyzed using SPSS. Survival analyses were performed using Kaplan-Meier estimation and the log-rank test. Multivariate analysis was conducted through logistic regression. **Results:** Among 121 patients, CA125 levels were tested in 77.7%, with elevated levels detected in 68.6%. Higher CA125 levels significantly correlated with advanced disease stages ($p<0.0001$). Elevated initial CA125 levels were associated with a twofold increased risk of inoperability (OR 2.3; $p=0.004$). Additionally, patients receiving palliative treatment predominantly exhibited high CA125 values (90.0%). Median overall survival was significantly lower in patients with elevated baseline CA125 levels ($p=0.041$). **Conclusion**: CA125 is a crucial biomarker in the management of epithelial ovarian cancer, significantly impacting diagnosis, treatment strategies, and prognosis. Its strong association with disease stage and surgical outcomes underscores its importance in clinical decision-making. Regular monitoring of CA125 levels can enhance early detection and inform treatment response, ultimately improving patient outcomes.

**Keywords**: ovarian cancer, prognosis, CA125.

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## 1. INTRODUCTION

Ovarian cancer is a significant public health issue that, despite its low incidence, remains the deadliest gynecological cancer. It is the fifth leading cause of cancer death among women in developed countries and the seventh worldwide. This is largely because the disease is often asymptomatic, with 75% of cases diagnosed at an advanced stage [1-3]. Numerous reports have emphasized the diagnostic value of CA125 in ovarian cancer and have advocated for increased use of serum CA125 in primary care as a means of enhancing ovarian cancer detection. CA125 levels above 35 U/mL are considered abnormal and are associated with 90% of ovarian

carcinomas, as well as a poor prognosis. A preoperative CA125 level above 500 IU/mL for primary surgery has been correlated in the literature with a risk of suboptimal surgical outcomes. Serum CA125 levels are routinely monitored in ovarian cancer patients, and an increase from an individualized nadir concentration serves as a prognostic indicator of cancer recurrence. Additionally, CA125 levels are useful indicators of response to chemotherapy, relapse, and disease progression. In this article, we discuss the role of CA125 in the management of ovarian cancer, particularly in evaluating treatment response and prognosis.

**Aim**: Evaluate the impact of CA125 levels on clinical stage, surgical outcomes, and survival in patients with epithelial ovarian cancer

**Research Hypothesis**: Higher levels of the CA125 tumor marker are associated with advanced stages of epithelial ovarian cancer and correlate with poorer patient outcomes.

## 2. METHODS

Prospective multicenter observational study of the contribution of the tumor marker CA125 in the management of epithelial ovarian cancers. Patients treated in the medical oncology departments of the regional cancer centers for epithelial ovarian cancer were listed prospectively (January 2016–June 2019). The patients were recruited from common consultations: the medical oncology department of Constantine University Hospital, Setif Cancer Control Center, Batna Anti-Cancer Center, Annaba Anti-Cancer Center, and Oum El Bouaghi medical oncology unit. This study population represents a multicenter hospital series (exhaustive sample).

Inclusion criteria for this study were a histologically proven malignant tumor of the epithelial lining of the ovary, all stages (according to the FIGO classification 2014). Non-inclusion criteria for this study were concurrent cancers (in organs other than the ovaries), ovarian cancer occurring during pregnancy, and a tumor with low malignant potential ("borderline").

Patient data were collected in a manner that ensured their anonymity and the confidentiality of personal information. This study was conducted in accordance with the Declaration of Helsinki, thereby adhering to the ethical standards applicable to clinical research. The databases were entered, coded, and analyzed using SPSS statistical software version 25. An overall description of the population was made using the tools of descriptive analysis (frequency and mean) with tabular and graphical presentations. To measure the strength of association between two binary variables, we used the relative risk and the odds ratios. For the survival analysis, median survival and relative survival rates were estimated using the Kaplan-Meier method within the subgroups of individuals defined by the different variables studied. The impact of the treatment scenario on survival was studied by constructing Kaplan-Meier survival curves. Differences in survival were compared using the log-rank test.

Our results are statistically accurate to the 95% confidence interval, accepting a first-order risk $\alpha = 5\%$; a p-value less than 0.05 was considered statistically significant. Hazard ratio calculations were done by logistic regression according to the COX model.

## 3. RESULTS

One hundred twenty-one cases of epithelial ovarian cancer have been studied; the plasma level of the tumor marker CA125 before the start of treatment was available in 77.7% of the patients, and it was elevated in 68.6% of the cases. The levels ranged from 11.16 to 11988.00 IU/ml with a mean value of 836.39 IU/ml and a standard deviation of 1541.30 IU/ml, the most frequent value being 600 IU/ml. The level of the marker was higher in advanced disease (p<0.0001) (Table 1).

**Table 1.** Distribution of the CA125 level according to the stage of the disease.

| CA125 | stage | | Total % | p-value |
|---|---|---|---|---|
| | Early % | Advanced % | | |
| **High** | 40.6 | 78.7 | 68.6 | <0.0001 |
| **Normal** | 15.6 | 6.7 | 9.1 | |
| **Not dosed** | 43.8 | 14.6 | 22.3 | |

**Relationship between CA125 level and surgical management:**

*Time to surgery*

There was no difference in CA 125 levels between patients who had initial, interval, or closure surgery (p=0.688) (Table 2).

**Table 2.** Characteristics of the population according to the time of surgery, percentages calculated among the operated patients.

| Parameters studied | | Surgery time | | | p-value |
|---|---|---|---|---|---|
| | | Initial % | interval % | closure % | |
| CA 125 initial value | High | 51.2 | 63.6 | 50.0 | 0.688 |
| | Normal | 9.3 | 18.2 | 16.7 | |
| | Not dosed | 39.5 | 18.2 | 33.3 | |

*Operability*

The marker level was elevated in 53.0% of operated patients and 87.3% of non-operated patients (p=0.0002). In the logistic regression model we used in multivariate analysis (including patient age, initial CA125 level, and stage of disease), the risk factor retained was the initial CA125 level. A high initial CA125 level was associated with a twofold higher risk of not undergoing surgery, with an odds ratio of 2.3 (CI95%: 1.16-4.56) (p=0.004). For a normal level of the marker, the odds ratio was 1.06 (CI95%: 0.27-30.96) (p= 0.37).

*Tumor residue*

For the CA 125 level, we found a p=0.143. However, if we exclude the cases where the assay was not done, we find that the difference is statistically significant with a p=0.020 (Table 3).

**Table 3.** Tumor residue by initial CA125 level.

| | | CA125 high | CA125 normal | Chi-squared test | Fisher's exact test |
|---|---|---|---|---|---|
| **Tumor residue** | R0 | 74.2% | 25.8% | 0.020 | 0.029 |
| | R1 | 96.3% | 3.7% | | |

R0: no residual tumor. R1: presence of residual tumor.

**Relationship between CA125 level and systemic treatment modality**

The majority of patients (90.0%) who received palliative treatment had a high initial CA125 value. The same was true when chemotherapy was induction (70.8%). This difference in the distribution of the cohort according to the different modalities (induction, adjuvant, palliative) according to the initial CA125 value is statistically highly significant (p<0.0001) (Table 4).

**Table 4.** Level of CA125 according to systemic treatment modality.

| Studied parameters | | Systemic treatment modality | | | p-value Chi-squared test |
|---|---|---|---|---|---|
| | | induction % | adjuvant % | palliative % | |
| initial CA 125 | High | 70.8 | 47.6 | 90.0 | <0.0001 |
| | Normal | 4.2 | 11.9 | 4.0 | |
| | Not dosed | 25.0 | 40.5 | 6.0 | |

**Relationship between CA125 level and patient survival:**

*Progression-free survival according to initial CA125 level*

The median survival was 12.00 months (95% CI=9.060-14.940) when CA125 was elevated at baseline, and survival rates differed according to whether the marker was elevated, normal, or not. The median survival was 12.00 months (95% CI=9.060-14.940) when CA125 was initially elevated, and survival rates differed between elevated, normal, and not dosed markers (p=0.004) (Figure 1).

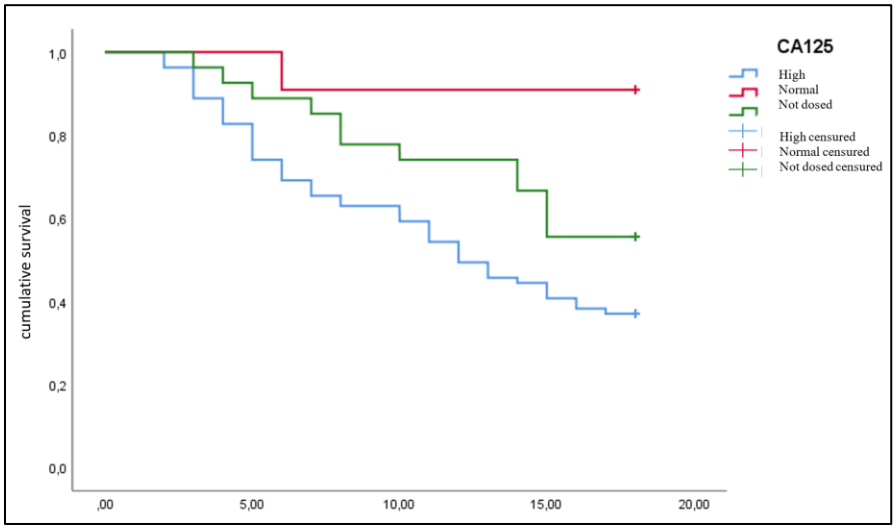


**Figure 1.** Progression-free survival according to initial CA125 level.

*Overall survival according to initial CA125 level*

From the results of the univariate analysis of OS according to baseline CA125 level, we found that the OS rate was lower (56.6%) when the tumor marker was initially high. This difference in OS was statistically significant, with a p-value of 0.041 (Figure 2).

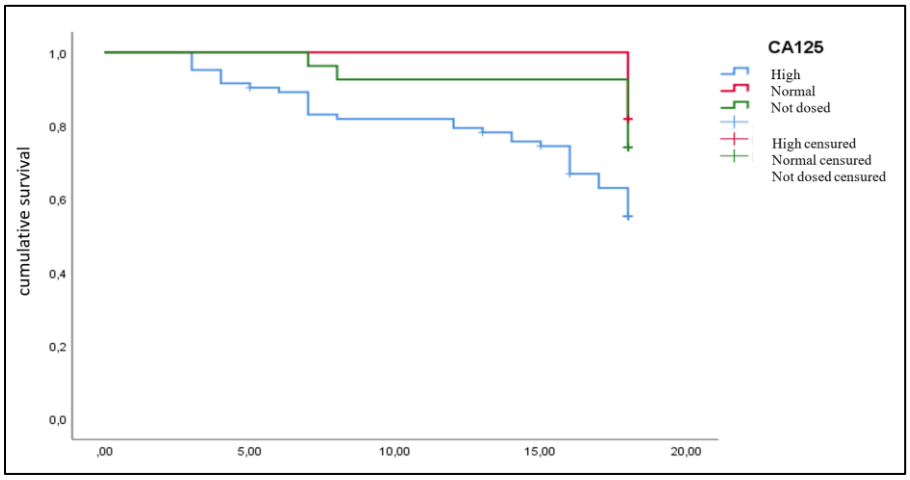


**Figure 2**. Kaplan-Meier curve (overall survival) according to initial CA125 level.

## 4. DISCUSSION

The most widely used tumor marker in ovarian carcinoma, often considered the gold standard, is CA125. It is increased in 90% of epithelial ovarian cancers. CA125 is currently the most sensitive and widely used marker in the management of epithelial ovarian cancer at different stages of the disease. The assay is used at the time of disease diagnosis to assess sensitivity to chemotherapy and for the diagnosis of recurrence. It therefore has diagnostic, prognostic, and therapeutic evaluation value [4,5]. The plasma level of the tumor marker CA125 before the start of treatment was available in 77.7% of our cohort and was high in 68.6% of cases.

We acknowledge that the absence of CA125 measurements in 22.3% of patients referred to oncology services after surgery is a notable limitation. However, the findings still provide valuable insights into the clinical outcomes of those for whom data is available. Promoting multidisciplinary collaboration before treatment will help ensure that tumor marker assessments are systematically

conducted, thereby minimizing gaps in essential data. In our study, CA125 levels varied between 11.16 and 11,988.00 IU/ml, with a mean value of 836.39 IU/ml and a standard deviation of 1,541.30 IU/ml; the most frequently reported value was 600 IU/ml. In the study by Kuehn [6], plasma levels of CA125 before treatment were available for 86 patients (63.23%), ranging from 0 to 10,000 IU/ml, with a mean value of 981.2 IU/ml and a standard deviation of 1,633.2 IU/ml. Additionally, according to results reported by Benjelloun Andaloussi [7], this assay was performed in all patients (100%), and in 93.82% of cases, levels were elevated (> 35 IU/ml)."

CA125 was elevated in 40.6% of early-stage disease and 78.7% of advanced disease (p<0.0001). This result is consistent with data from the literature, which reports that serum CA125 is elevated in 50% of early-stage and 80% of advanced-stage epithelial ovarian cancer [8-9,11].

**Tumor residue**

In our cohort, 48 patients (57.8%) had no tumor residue at the end of surgery. In univariate analysis, the predictive factors for suboptimal resection that were identified were stage of disease and initial CA125 level. For the CA 125 level, a p=0.143 was found. However, when analyzed excluding cases where the test was not performed, the difference was found to be statistically significant with a p=0.02. A meta-analysis of 14 studies evaluated the initial CA125 level as a predictor of suboptimal. A high CA125 level (>500 U/ml) increased the risk of suboptimal cytoreduction [12]. Suboptimal cytoreduction (OR: 3.69; 95% CI, 2.02- 6.73) but low sensitivity (68.9%) and specificity (63.2%). M. Timmermans et al. report in a retrospective study (January 2008-December 2015),

in a series of 1232 patients treated for OCE whose data were captured from the Dutch cancer registry, the preoperative CA125 values for the cancer registry of the Netherlands, the preoperative CA125 values for patients with no macroscopic residual disease after cytoreductive surgery was significantly lower than that of patients with residual disease of 1 cm (p = 0.001) or more than 1 cm (p = 0.003) [13]. A meta-analysis was published in 2010 [14], including data from 14 studies in addition to 154 patients with ovarian cancer, a total of 2192 patients were included in the analysis, the analysis, the optimal cytoreduction rate was 53.7% with a median CA125 level of 580 IU/ml. A CA125 level > 500 IU/ml was associated with a higher risk of non-optimal surgery: OR = 3.69 (95% CI: 2.02 to 6.73)

Since 2010-2011 and the meta-analysis by Kang et al., numerous retrospective studies have been published with the aim of correlating the evolution of CA125/HE4 levels. We note that all these studies are based on retrospective data and study populations with limited numbers.

**Survival**

The progression-free survival rate in the overall study population was 46.2%, with a median of 15.00 months. Significant (univariate) differences in progression-free survival in the overall population included FIGO stage, initial treatment modality, surgical status, and initial tumor marker CA125 level. The overall survival rate in our cohort was 62.8%. Subject to the length of follow-up, the factors for which we found a significant difference in terms of OS in univariate analysis were histological type (p=0.017), disease stage (p=0.042), and initial CA125 level (p=0.041). Research into prognostic factors for ovarian cancers is based on retrospective studies, with recognized factors including young age, stage of disease, histological grade, CA125 level, and microscopic residual disease after surgery [15-23]. Our results support these data.

## 5. CONCLUSION

CA125 is a crucial biomarker in the management of epithelial ovarian cancer, significantly impacting diagnosis, treatment strategies, and prognosis. Its strong association with disease stage and surgical outcomes underscores its importance in clinical decision-making. Regular monitoring of CA125 levels can enhance early detection and inform treatment response, ultimately improving patient outcomes.

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