

# The role of CA125 in diagnosis and follow-up of the patients with ovarian cancer

## Abstract

Ovarian cancer represents one of the most important health problems all over the world, being responsible for a high number of deaths annually. Serum level of cancer antigen 125 is one of the most often used methods for screening, monitoring the response to treatment, the eventual relapse and disease progression in these patients. This is a review of the most important studies conducted on these themes in order to assess an improvement in the management of this aggressive malignancy.

**Keywords:** ovarian cancer, CA125, debulking surgery, chemotherapy

## Ovarian cancer - the magnitude of the problem

Ovarian cancer still represents one of the most aggressive gynecologic malignancies which affect an important number of women worldwide every year and is the leading cause of death related to gynecologic cancer in United States of America<sup>(1)</sup>. While patients diagnosed in an early stage of the disease (FIGO stage I) treated by surgery and adjuvant chemotherapy report a 5 year overall survival of almost 95%, this value encounters a significant decrease up to 25% when it comes to advanced stages (FIGO stage IIIC-IV)<sup>(2,3,4)</sup>. Due to these significant differences in terms of survival, attention was focused in creating an efficient protocol of diagnostic and follow-up of these patients in order to provide an earlier diagnosis of this pathology, in a less advanced stage of the disease, when a curative treatment can still be feasible<sup>(5)</sup>. In order to discover the most specific marker for early detection of ovarian tumors, several epitopes derived from MUC1 gene have been proposed: cancer antigen (CA)549, CA15-3, CA125, or mucin cancer associated antigen. However, it seems that the most appropriate tumor marker for ovarian cancer remains CA125<sup>(6)</sup>.

## CA125 as tumor marker

CA125 is a high molecular glycoprotein of 200kDa which was first described by Bast et al.<sup>(7)</sup>; it contains 25% carbohydrates, and circulates in serum connected to another glycoprotein with molecular mass of 1000 kDa. Initially, CA125 was detected through a monoclonal antibody which recognizes a single transmembranar domain mucinous protein, MUC 16<sup>(8,9)</sup>.

The normal serum values of CA125 range between 0-35 IU/ml, the cut-off value of 35 IU/ml being established based on the values encountered in healthy subjects, in order to include 99% of them<sup>(10)</sup>. In adults CA125 is expressed by coelomic and Mullerian epithelial

tissues<sup>(11,12)</sup>. The serum levels of CA125 are influenced by the coffee consume, smoking, age at menarche, age at menopause or association of hormonal therapies. A higher serum value can be encountered in physiological conditions like menstruation (up to 100 IU/ml), pregnancy or benign diseases: endometriosis (CA125 levels being lower than 100 IU/ml in almost 88% of cases), hepatic disorders (in 40-80% of cases), inflammatory pelvic disease (up to 33% of cases), uterine fibromas, acute peritonitis (up to 75% of cases), acute pancreatitis (38% of cases), pericarditis or cardiac failure<sup>(13)</sup>. In this last condition, CA125 can also have a prognostic value especially when dosed in association with atrial natriuretic peptide. In these cases measures must be done in correlation with age, sex and race (CA125 levels being decreased in men, women in post-menopausal period, Africans and Asian people). Presence of inflammation and increased levels of cytokines usually produce an increase of the CA125 levels<sup>(14,15,16)</sup>.

A special category associated with increased CA125 serum levels are the ovarian tumors. The most important pathology associated with an increased level of CA125 is epithelial ovarian cancer. However this isn't the only ovarian disorder in which a high level of CA125 is seen. Other ovarian pathologies include benign ovarian tumors (ovarian fibroma, Brenner tumor, granulosa cell tumors); in these cases a pleural effusion can also be encountered giving birth to Meigs or pseudo-Meigs syndrome<sup>(17,18)</sup>. Other situations which comprise high levels of CA125 and pleural effusions with normal ovarian function are pulmonary cancer, mediastinal teratoma, non-Hodgkin lymphoma or conjunctive tissues disorders. Although ovarian cancer is not the only malignancy associated with high levels of serum CA125, it seems that in other neoplasia lower levels are encountered. The most important malignancies associated with increased levels of CA125 are other gynecological cancers: endometrial cancer, cervical

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cancer and breast tumors, gastro-intestinal cancers: gastro-oesophagian and colo-rectal tumors, hepatic, pancreatic and biliary tree tumors or lymphomas<sup>(19,20)</sup>.

### The role of serum CA125 dosage in epithelial ovarian cancer

When it comes to detection of early ovarian cancer, CA125 can be used as a screening test in association with trans-vaginal ultrasonography in cases at risk<sup>(21)</sup>.

In order to differentiate a malignant ovarian tumor from a benign condition, Risk of Ovarian Malignancy Algorithm score can be used. The superiority of this score is based on the association between dosage of CA125<sup>(22,23)</sup>.

Other scores which take into consideration CA125 values and which can increase the predictive value in order to diagnose ovarian cancer are: Risk of Malignancy Index<sup>(24,25)</sup> which provides a correlation between CA125, menopausal status and ultrasonography (in a study conducted on 467 patients, a cut-off value of 150 this indicator had a sensibility of 84% and a specificity of 97% in order to diagnose early ovarian cancer), which offers a correlation between CA125 and other indicators established through mass spectrometry such as  $\beta$ 2 microglobuline, transferine, transtretine and apolipoproteine<sup>(23)</sup>.

A study conducted in Nara Medical University from Japan demonstrated that a slight increase of CA125 levels in serum is seen many years before ovarian cancer is diagnosed, especially in non-serous sub-types. Oppositely, in serous ovarian cancer normal seric levels of CA125 can be found even in cases which are already symptomatic<sup>(24-26)</sup>.

Another utility of dosage of CA125 is monitoring the treatment response in cases already diagnosed with ovarian cancer. In these cases repeated dosages can be useful. Gynecologic Cancer Intergroup defines the response to treatment as a 50% decrease of the pre-treatment CA125 levels for at least 28 days. The pre-treatment value should be at least double than normal, measured 2 weeks before treatment. Due to the fact that the medium half-life is 5-7 days post-procedural measurements should be done 2 weeks after treatment, then every 2 weeks. Usually CA125 encounters a rapid decrease during the first week after surgery followed of normalization of the values three weeks after surgery<sup>(27,28,29,30)</sup>.

A prospective study realized in India included 50 patients and established a strong positive correlation between serum CA125 levels measured pre-operatively and the histologic expression of this marker, with a sensibility rate of 100% and a specificity rate of 86%. The positive predictive value was 74% while the negative one reached 100%. Unfortunately, high serum values of CA125 associated with high tissue expression was encountered in benign conditions as endometric cysts too. On the other hand, an inverse situation with high levels of CA125 associated with negative tissue expression was also seen. This fact was explained by the

destruction of the tissue markers during the procession procedures in order to obtain the histopathological specimen<sup>(31)</sup>.

There are also cases in which a low level of serum CA125 is in fact associated with a high tissue expression of this tumor marker. The explication consists in the fact that some tumors are incapable of secreting the antigen in circulation. Another possible explication is the presence of a modified molecules of CA125 which are hard to be detected in serum or which have a lower half life. However, both measurements (serum levels and tissue levels) are important in order to predict best the existing tumor volume<sup>(32)</sup>.

Medeiros et al. conducted a study on 2374 patients diagnosed with ovarian tumors and obtained a sensibility of 80% and a specificity of 75% of serum levels of CA125 when compared with the tissue expression and which is in fact the gold standard in diagnosis and follow-up of ovarian malignancies<sup>(33)</sup>.

Studies went even further and tried to establish which histopathological sub-types of the ovarian cancer correlate best with the tissue expression of CA125. They concluded that a higher tissue expression is seen in the serous subtype when compared with the other sub-groups (mucinous, endometrioid or other histology) ( $p < 0.00001$ ). The same study concluded that patients diagnosed in an advanced stage of the disease who present negative tissue expression of CA125 reported a significantly poorer overall survival when compared to those with positive tissue expression ( $p = 0.0003$ ). When it comes to more advanced ovarian cancer, a high level of CA125 is much often seen. For example in patients diagnosed in FIGO stages II, III and IV, CA125 is increased in 80%, 93%, and 97% of cases respectively while in early ovarian cancer increased values can be seen in 43% of patients (stage I)<sup>(34,35)</sup>.

A multinational retrospective study conducted in 2011 evaluated the prognostic value of CA125 seric levels higher than 50U/ml in cases with low malignancy ovarian tumors. This study included 940 patients diagnosed with ovarian malignant tumors in 6 gynecological centers, between 1985 and 2008. They showed that higher levels of CA125 were encountered more frequently in serous tumors when compared to mucinous tumors and in more advanced FIGO stages (II, III, IV) when compared to FIGO stage I. Five years disease free survival was 89% and 95% respectively in patients with increased preoperative levels of CA125 respectively normal preoperative levels ( $p < 0.05$ ). The same study showed a 5 year overall survival of 95% in cases with increased preoperative CA125 levels and 90% in cases with normal preoperative levels. ( $p < 0.05$ )<sup>(36)</sup>.

Cramer et al. also demonstrated in a study which included 805 patients that higher pre-treatment levels of serum CA125 are associated with an overall poor survival. They also concluded that higher levels of CA125 are strongly correlated with an advanced FIGO stage, histopathological findings and the presence of ascites at the moment of surgery<sup>(37)</sup>.

Numerous studies have demonstrated the utility of CA125 dosage for monitoring the evolution of patients with epithelial ovarian cancer<sup>(6,7,11,38,39)</sup>. Most studies are based on the observation that an augmentation of CA125 level is seen 3 months before clinical detection<sup>(40)</sup>.

In the postoperative period, once a good control of the disease is achieved, CA125 provides in association with clinical examination and imagistic studies the most important follow-up protocol in order to detect the recurrent disease. This protocol consists in patients' monitoring every 3 months for 2 years and every 6 months for the next 3 years; from the 6<sup>th</sup> postoperative year controls should be performed once a year. Although dosage of CA125 alone cannot exclude the presence of recurrent disease, sometimes increased values can be seen 2-6 months before any imagistic or clinic signs of recurrence. This phenomenon, also called biochemical recurrence can provide a correlation between CA125 levels and the recurrent tumor volume. Once the recurrence is diagnosed, CA125 dosage is useful in order to predict the further evolution. Patients presenting preoperative levels of CA125 higher than 65 kU/l, half life higher than 20 days, high level of CA125 during adjuvant chemotherapy or at the end of 3 cycles of adjuvant chemotherapy have a poor 5 year overall survival. However the benefit of early detection of an increased level of CA125 in order to restart a chemotherapeutical protocol is still to be discussed<sup>(11)</sup>.

Markman et al. conducted a study on 106 patients and concluded that although higher pre-treatment values of CA125 do not represent a poor prognostic factor themselves, a decrease over 50% of the pre-treatment values 8 weeks after initiation of therapy is associated with an improved survival. The same study concluded that patients presenting a CA125 level lower than 35U/ml at the same moment was also associated with an improved outcome<sup>(41)</sup>.

Similar results were also reported by Gadducci et al. and Ron and et al., both studies reporting an improved outcome whether normalization of CA125 is seen at the end of the second chemotherapy cycle<sup>(42,43)</sup>.

Davidson et al. demonstrated the presence of a strong correlation between the maximal cytoreductive effort at the moment of performing debulking surgery and a seric level of CA15 <50 u/ml four weeks after surgery, both parameters being associated with an improved survival<sup>(44)</sup>.

Contrary to these studies, other authors concluded that pre-chemotherapy values of CA125 represent themselves important prognostic factors in terms of survival<sup>(45,46,47)</sup>.

In a study conducted in 2010, 1422 patients considered to be in complete remission after surgery and the first cycle of chemotherapy were followed up by dosing CA125 serum levels at every 3 months. When they encountered double values when compared to the superior limit of the normal values, they were splinted in 2 study groups: in the first group chemotherapy was

re-introduced at that moment while in the second group no treatment was instituted, the patients continued to be followed up until the moment that symptoms reappeared. In this way, in the second group chemotherapy was introduced 5 months later. However, no difference in terms of survival was obtained between the 2 groups, the authors' conclusion being that an early chemotherapeutic treatment instituted in the moment of detection of increased CA125 levels is not capable to provide a benefit in terms of survival<sup>(48,49)</sup>.

Fleming et al. showed that there is a strong relationship between the moment of detection of an increased value of the tumor marker and the moment of secondary cytoreduction. They studied the impact of the interval between the moment in which the serum CA125 levels doubled and the moment in which the patient was submitted to surgery. An optimal cytoreduction was considered when residual tumor <0.5 cm was achieved<sup>(50)</sup>.

### Post-chemotherapy serums CA125 levels and follow-up

A study conducted in Korea in 2009 included patients diagnosed with early stages ovarian cancer who were in complete remission after surgery and chemotherapy. They tried to evaluate which is the most appropriate cut-off value of CA125 in order to predict evolution. A 12u/ml cut off value at the end of chemotherapeutic treatment was associated with a 5 year overall survival of 70% (the sensibility was 71.4% while the specificity was 82.1%). In multivariate analysis a serum CA125 >12 u/ml at the end of chemotherapy was also an independent prognostic factor. Five year disease free survival was 83.3% in cases with serum CA<12 u/ml and only 37.5% for cases with serum CA125>12 u/ml (p<0.001).

Another study conducted in Holland in 2010 tried to determine which is the prognostic value of the nadir level of CA125 for patients with all stages ovarian cancer who were found in complete remission at the moment of the study. The study included 331 patients with no clinical or radiological sign of disease, who reported a CA125 serum level<35 kU/l. They concluded that a nadir level of CA125< 5kU/l was significantly associated with an improved disease free survival and overall survival (p<0.001, p=0.003 respectively) and represented an independent prognostic factor; other significant prognostic factors were the histopathological type, FIGO stage and the volume of the residual tumor<sup>(51)</sup>.

### Conclusions

Although the outcomes of various studies are sometimes contradictory, CA125 remains one of the most important parameters in order to assure an appropriate follow-up in patients with ovarian cancer. It also represents a strong prognostic factor correlated with both disease free survival and overall survival in ovarian malignancies. However, future prospective longitudinal studies are still needed in order to provide the most efficient therapy protocol for this aggressive gynecologic malignancy. ■



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