CA 125 is a widely used marker of ovarian cancer which is currently employed in the routine clinical setting for post-operative screening of patients with ovarian cancer and for monitoring treatment regimens. The low sensitivity and specificity of this marker limit its use as a general screening tool for the detection of early ovarian cancer. However, preoperative levels of CA 125 in post-menopausal women may aid in the differentiation of benign and malignant pelvic masses. Longitudinal testing with CA 125 during initial therapy can also help to detect recurrent disease. New tumour markers associated with ovarian cancer should be compared with CA 125.

Assays for CA 125

The first generation assays for the quantitative detection of CA 125 levels in serum were immunoradiometric assays that employed Oc125 as both the capture and detector antibody. CA 125 assays have since been modified and most of the assays available today are based upon one capture antibody located in domain B (e.g. M11, or similar) and one antibody that recognises domain A (e.g. Oc125) for detection. This modified assay is known as CA 125II. Although the majority of manufacturers use a similar cut-off value, measured concentrations of CA 125 may vary due to the assay methods employed and the reagent specificities. An alternative CA 125 assay, which is more robust and more sensitive than the second generation assays, uses Ov197 or OvK95 as the capture antibody and Ov185 (an M11-like monoclonal antibody) as the detecting antibody [Figure 2]. Generally heterologous double determinant assays (CA 125II or the OvK95/Ov185 monoclonal assay from CanAg Diagnostics) are more robust and sensitive than single determinant assays.

Ovarian cancer is one of the most common causes of death from gynaecological cancer among women in Western countries. Epithelial ovarian cancer is responsible for 85-90% of all primary ovarian tumours. Because of the asymptomatic nature of the disease, ovarian cancer is usually not detected in the early stages and therefore many women present with advanced disease and systemic metastases. Approximately 70-80% of patients present with late stage disease and consequently have a poor prognosis [1]. Ovarian cancer has become a major challenge in clinical oncology due to the poor response to therapy and the presence of extensive disease at the time of first diagnosis.

Mass screening programs utilising pelvic or vaginal ultrasound are an attractive method of detecting early disease and thus reducing the mortality rate. However, ultrasound methods are neither sensitive nor specific enough to detect the early stages of ovarian cancer which limits their utility. In post-menopausal women, measurement of CA 125 levels may aid the differential diagnosis of benign and malignant pelvic masses. In addition, measurement of CA 125 during initial chemotherapy can give an indication of a patient’s likely response to therapy.

The current recommended strategy for treating ovarian cancer in the primary setting is aggressive cytoreductive surgery. However, in most cases, patients have advanced stage disease and complete surgical removal is not possible. When surgery is successful, serial determination of CA 125 in asymptomatic patients can aid early detection of recurrences.

Antigenic domains of CA 125

CA 125 was originally identified as an antigenic determinant found on a high molecular weight glycoprotein (ranging from 200 to 2000 kDa) recognised by the Oc125 monoclonal antibody. Recently CA 125 has been cloned using a partial cDNA sequence for the peptide core of the molecule identified. Molecular cloning revealed that the glycoprotein CA 125 has a number of features typically associated with mucin proteins (156 amino acid tandem repeat region) and consequently CA 125 was designated MUC16 [2, 3]. A proposed structure of CA 125 is shown in Figure 1.

Data from the ISOBM (International Society of Oncodevelopmental Biology and Medicine) TD Workshop studying the characteristics and epitope specificity of 26 monoclonal antibodies against CA 125 and related antigens, identified only three antigenic domains in CA 125 [4], suggesting that the antigenic domains are located within the 156 amino acid tandem repeat region. The CA 125 antigen contains two main, but not related, antigenic domains, as well as one unique but related domain. The grouping of the antibodies into the three antigenic domains is shown in Figure 2. The three antigenic domains are located in the protein core of the CA 125 antigen; one antigenic domain (domain A) is defined by the Oc125 monoclonal antibody (Fujirebio Diagnostics, Inc.), the second domain (domain B) is defined by the M11 monoclonal antibody (Fujirebio Diagnostics, Inc.) and the third domain (domain C), which is related to domain A, is defined by the Ov197 antibody (CanAg Diagnostics AB).

Low levels of CA 125 can be detected in serum from apparently healthy males and females. However, a number of factors are known to influence serum CA 125 levels in healthy women: age (pre-menopausal women have higher serum CA 125 levels than post-menopausal women); menstrual cycle (some women have fluctuating serum CA 125 levels throughout the menstrual cycle); pregnancy (CA 125 levels increase during pregnancy) and race (significantly higher CA 125 levels are found in healthy Caucasian women compared to Asian or African women). These factors should be taken into account when interpreting CA 125 test results.

CA 125 in benign diseases and non-ovarian cancer

Benign gynaecological disorders may be associated with increased CA 125 serum levels and these disorders include endometriosis, fibromas, uterine myomas, salpingitis and pelvic inflammatory diseases. Serum CA 125 levels are also increased in several non-gynaecological benign diseases, for example, liver cirrhosis, active and chronic hepatitis, acute and chronic pancreatitis and lung diseases. Elevated levels of CA 125 are also observed in most types of adenocarcinomas, particularly advanced breast, colorectal, pancreas, lung, endometrium and cervical cancer. Such diseases should be excluded as the source of the elevated CA 125 levels when using this marker to monitor ovarian cancer.

CA 125 and ovarian cancer screening

Routine screening for ovarian cancer has been widely discussed, but so far most expert groups have advised against population screening. It is important to emphasise that the relative low prevalence of ovarian cancer may limit the cost-effectiveness of a general population screening program.

Prospective screening studies have demonstrated that measuring CA 125 can detect ovarian cancers before symptoms arise. There is a strong correlation between the 5 year overall survival rate and early detection of the disease; 5 year survival is only 10% for stage 3 and 4 ovarian tumours and more than 90% when disease is confined to the ovary [5]. Using CA 125 to screen patients for ovarian cancer does have several limitations: low sensitivity for early disease (FIGO stage 1) and low specificity in
premenopausal women. Combining the measurement of CA 125 with the detection of other biomarkers or ultrasound examination increases the clinical utility of CA 125 as a screening test for ovarian cancer.

**Prognosis**

CA 125 levels have been shown to correlate well with tumour volume. CA 125 levels, both pre-operatively and post-operatively, may be of prognostic significance. It has been reported that CA 125 is elevated in approximately 50% of ovarian cancer patients with FIGO stage I, 70% of FIGO stage II, 90% of FIGO stage III and more than 95% of patients with FIGO stage IV disease [6]. Several studies have also reported that the CA 125 level itself has no independent prognostic significance. However, in patients with early disease (FIGO stage I ovarian cancer), CA 125 may be of great importance for guiding treatment. For those patients with a better prognosis (defined as CA 125 levels lower than 65 U/mL) less extensive surgery could be offered compared to patients with pre-operative CA 125 levels exceeding 65 U/mL [7].

**Monitoring treatment regimens**

Following diagnosis, the management of patients with ovarian cancer can be improved by measuring tumour marker levels during chemotherapy. The CA 125 concentration may play an important role in monitoring a patient’s response to treatment. Unfortunately, pre-operative CA 125 has no clear prognostic significance and, in addition, CA 125 levels that lie below the upper reference limit after combined chemotherapy cannot be taken to exclude the continuing presence of disease.

A multiple markers approach has been used to monitor patient response to chemotherapy and to detect any recurrence of disease as soon as possible. TPS (Tissue Polypeptide Specific antigen), a biomarker of cytokeratin 18, is a useful adjunct to CA 125. TPS and CA 125 have been used in combination, both before and after chemotherapy, to successfully establish response to therapy and to predict clinical outcome. The results from a prospective chemotherapy study have recently been reported [8]. This study involved 213 epithelial ovarian cancer patients with the following entrance criteria and patient characteristics: FIGO stages (I-IV) cancer, with all grades of differentiation and histological types (serous, mucinous, endometroid, clear cell and undifferentiated), undergoing combined chemotherapy. The tumour marker assays used in this study were CA 125 (cut-off 35 U/mL) and TPS (cut-off 80 U/L). The two-year overall survival was not significantly different in FIGO stage I/I patients (64 patients receiving 3 chemotherapy courses) when CA 125 and/or TPS levels were above or below the cut-off levels. However, in FIGO stage III/IV patients (149 patients), the 2-year survival rate was highly dependent on tumour marker levels. When CA 125 was above the cut-off value, the survival rate was only 26% after 3 chemotherapy courses. The survival rate increased to 69% when CA 125 was below the cut-off value. These differences between the subsets of patients were highly significant (p<0.0001). TPS gave similar information.

CA 125 and TPS assays were also used in combination for a final survival analysis. The optimal discrimination level was evaluated from ROC analysis (CA 125 cut-off 25 U/mL and TPS cut-off 100 U/L). Based upon the combined reference level, the 2 year survival was evaluated by univariate and multivariate analysis. The combined tumour marker levels in FIGO I/II stage patients were not correlated with survival after three courses of chemotherapy. The 2 year overall survival in FIGO stage III/IV patients, with both markers below the respective discrimination levels after completing three courses of chemotherapy, was 77% versus 17% in patients with elevated CA 125 and TPS levels (p<0.0001). Combining the post-treatment levels of both tumour markers increased the prognostic significance considerably.

**Conclusion**

Assays for CA 125 have an important and well established role in the management of ovarian cancer. CA 125 has proved to be an especially valuable marker to oncologists for both the detection of ovarian cancer and for monitoring disease progression. Combined measurement of CA 125 and TPS following three courses of chemotherapy provides prognostic information that may prompt physicians to change a therapeutic regime. However, there is no evidence at present that the initiation of treatment based on rising CA 125 levels results in improved outcome or better quality of life. Which patients might benefit from more aggressive treatment or salvage therapy will only be established by appropriate randomised trials. However, until the results of such trials are available, the combined measurement of CA 125 and TPS could undoubtedly benefit the quality of life of those patients currently receiving ineffective treatment.

**References**


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