EDUCATIONAL COMMENTARY – CA 125

Learning Outcomes

Upon completion of this exercise, participants will be able to:

- discuss the use of CA 125 levels in monitoring patients undergoing treatment for ovarian cancer and in the detection of recurrent disease.
- interpret CA 125 levels to assess treatment response, recurrence of disease, or prognosis.
- list sample handling and storage requirements for specimens to be analyzed for CA 125.

Cancer of the ovaries is the sixth most common cancer in women and is the cause of death in more than 14,000 women each year in the United States. The lifetime probability of developing the disease is approximately 1 in 59 to 1 in 70. Incidence increases dramatically with age and is relatively rare prior to age 50. Incidence also varies by race and ethnicity, and both incidence and mortality are highest for white women. One of the main risk factors for ovarian cancer is a positive family history. Mutations in the \textit{BRCA1} and \textit{BRCA2} genes are associated with a 50% to 60% lifetime risk of developing the cancer.

Although new chemotherapeutic agents have significantly improved the 5-year survival rate, the overall mortality of ovarian cancer has remained relatively unchanged, mainly because of a lack of success in early diagnosis. One reason for this lack of early detection is that the symptoms of ovarian cancer are fairly nonspecific. Symptoms include abdominal discomfort, urinary urgency, change in bowel habits, pelvic pain, loss of appetite, indigestion, gas, or nausea. Ovarian malignancies can arise from epithelial, sex-cord stromal, or germ cell tissues, or be metastatic tumors. Epithelial tumors are the most common and are divided into 5 histologic types: serous, mucinous, endometrioid, clear cell, and transitional carcinomas. Serous ovarian carcinomas represent the majority of all primary ovarian cancers and have a high mortality rate.

By definition, stage I ovarian cancer involves the ovaries only; stage II, the ovaries and other organs in the pelvis; stage III, organs in the upper abdomen including the large and small bowel, omentum, diaphragm, and other peritoneal surfaces; and stage IV denotes spread outside the peritoneal cavity. When diagnosed at stage I the survival rate is more than 90%, but unfortunately most ovarian cancer is not discovered until stage III or stage IV.

Screening Technologies

A primary strategy for prevention of mortality is early detection via screening of either the general population or high-risk groups. Available screening technologies include physical examination, transvaginal ultrasonography, and biomarkers including cancer antigen 125 (CA 125). To date, none of these screening tools has been shown to be effective.
Cancer antigen 125 is a large (200-1000 kDa) glycoprotein found on the surface of many ovarian cancer cells and in some normal tissues. The first commercial immunoassay for this molecule was introduced in 1983, and a second-generation assay (CA 125 II) was subsequently developed. Although most manufacturers of CA 125 assays quote similar reference ranges, the assays are not interchangeable. The most commonly used cutoff for CA 125 assays is 35 U/mL, which was determined from the distribution of values in healthy individuals. Values tend to decline with age and menopause. In postmenopausal women, a variation by race of 20% to 50% has been found, with concentrations higher in white women than in African and Asian women.

Elevated values occur in approximately 1% to 2% of normal healthy individuals, 5% of those with benign diseases, and 28% of women with non-gynecologic cancers including malignancies of lung, breast, and the gastrointestinal tract. Other conditions and diseases in which elevations of CA 125 occur include early pregnancy, menstruation, pelvic inflammatory disease, endometriosis, uterine fibroids, pancreatitis, hepatitis, and cirrhosis. In fact, only about 3% of women with elevated CA 125 levels have ovarian cancer, and conversely up to 20% of women with ovarian cancer never have elevated CA 125 levels. These statistics help explain the previously noted fact that the CA 125 assay has not been shown to be effective as a screening test. In 1994, a National Institutes of Health consensus statement did recommend annual or semiannual evaluation of CA 125 levels for women with an increased risk including those between 25 and 35 years of age who are carriers of the \textit{BRCA1} mutation. Several groups have recommended combined use of CA 125 with transvaginal ultrasound for early detection in hereditary syndromes. Nonetheless the general consensus is that use of CA 125 for ovarian cancer screening in the general population is not recommended.

While the assay is not recommended for screening purposes, several clinical groups have recommended determination of CA 125 levels as an aid in the following situations:

- The differential diagnosis of a suspicious pelvic mass
- Postoperative detection of recurrence
- Monitoring therapy
- Determining prognosis

In postmenopausal women presenting with ovarian masses, CA 125 is widely accepted as an adjunct in distinguishing benign from malignant disease. In these women, elevated concentrations of CA 125 (more than 95 U/mL) can discriminate malignant from benign pelvic masses with a positive predictive value of 95% to 96%.
Post-treatment Monitoring
The treatment for almost all cases of ovarian cancer is surgical removal of the ovaries, fallopian tubes, and uterus along with as much metastatic disease as possible, with subsequent chemotherapy. Rarely, for low-grade or early-stage cancer, chemotherapy or radiotherapy is performed instead of surgery.

The Food and Drug Administration (FDA) initially approved CA 125 assays for postoperative use in predicting discovery of tumor recurrence at a second-look operation, with pretreatment CA 125 concentrations used as a baseline level. At least one study has concluded that baseline CA 125 levels before initiation of maintenance chemotherapy predict the risk of subsequent relapse. Postoperative levels of more than 35 U/mL after debulking surgery and chemotherapy indicate that residual disease is likely and that maintenance chemotherapy will be required. Current recommendations for women with elevated preoperative CA 125 levels, instead of the somewhat controversial practice of second-look laparotomy, are postoperative monitoring with CA 125 testing along with a routine history and physical and rectovaginal pelvic examination. Current practice suggests following patients every 2 to 4 months for four years, and then less frequently. Negative values do not exclude disease presence but elevated, rising, or doubling CA 125 concentrations predict relapse.

Serial measurement to aid in monitoring response to therapy is a second FDA-indicated use for CA 125. There is general consensus in recommending measurement of CA 125 levels to monitor therapeutic response, primarily to chemotherapy. Declining concentrations correlate with treatment response, and rising levels may indicate tumor recurrence or failure to respond to therapy. Because of assay variability, small changes in values may not be significant. When pretreatment levels are at least twice the upper limit of the reference range, the Gynecologic Cancer Intergroup (GCIG) defines a response as a reduction of 50% or more in the pretreatment CA 125 level that is maintained for at least 28 days. Conversely, a doubling of values is associated with disease progression and treatment failure in more than 90% of cases. The initial sample should be collected within 2 weeks prior to treatment initiation and subsequent samples at 2 to 4 weeks during treatment and at intervals of 2 to 3 weeks during follow-up.

The prognostic significance of both pre- and post-operative CA 125 concentrations has been demonstrated in many ways. Declines in CA 125 concentrations during chemotherapy following primary surgery and chemotherapy have been observed to be independent prognostic factors, whereas persistent elevations indicate a poor prognosis. One study concluded that patients with preoperative concentrations greater than 65 U/mL had significantly lower 5-year survival rates and a 6-fold higher risk of death than patients with values less than 65 U/mL. In another study, patients with CA 125 concentrations higher than 450 U/mL had a median survival of 7 months compared with 23 months for patients with CA 125 concentrations lower than 55 U/mL. A third study demonstrated that patients with a decrease in CA 125
concentration of more than 50% had a 2-year survival rate twice as high as those with a decrease of less than 50%.

The half-life of the CA 125 marker also indicates prognosis after chemotherapy. A half-life of less than 20 days was associated with significantly improved survival as compared with a CA 125 half-life of more than 20 days. Normalization of CA 125 levels after 3 cycles of combination chemotherapy also correlates with improved survival.

**Laboratory Assays**
The first immunoassay for CA 125 used the OC125 antibody developed using a cell line derived from a patient with ovarian serous carcinoma. The second-generation CA 125 II assays incorporated M11 antibodies, which have non-overlapping epitopes. As previously stated, different CA 125 assays are not interchangeable although the same reference range may be used. If the testing methodology changes, patients who are serially monitored should have new baseline measurements established.

Serum, separated from the clot as soon as possible after collection and centrifugation, is the recommended specimen for most CA 125 assays. Plasma is an acceptable sample for some assays and is listed as an unacceptable sample for other assays. Typical CA 125 stability is 1 to 5 days refrigerated, 2 weeks to 3 months frozen at –20°C, and stable long-term when frozen at –70°C. Potential interference from hemolysis or the presence of human anti-mouse antibodies (HAMA) should be considered for all assays. Procedures for sample pretreatment with blocking agents to inhibit possible heterophilic interference have been developed and utilized.

**Summary**
Cancer antigen 125 is the only tumor marker routinely used as a marker associated with ovarian cancer. Testing for CA 125 is not recommended for ovarian cancer screening of the general population, but it is recommended for monitoring of treatment, monitoring for postoperative tumor recurrence, discrimination of pelvic masses, and prognosis. Another use of CA 125 testing is for screening/early detection in high-risk individuals.

**Suggested Reading**
Chan DW, Shih LM, Sokoll LJ, et al. *National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Ovarian Cancer (Draft).* Available online at:  

*Genetics of Breast and Ovarian Cancer.* Available online at the National Cancer Institutes’ Web page:  
EDUCATIONAL COMMENTARY – CA 125 (cont.)

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