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# Measurement of the Ovarian Cancer-associated Antigen CA 125 Prior to Second Look Operation

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**Abstract**—*CA 125 was measured in serum samples from 81 patients with a diagnosis of epithelial ovarian cancer. The samples were drawn prior to second look laparotomy performed in patients with complete or partial clinical remission after finishing cytostatic or radiation treatment. The positive and negative predictive value of the CA 125 measurements was 100% and 64%, respectively; the sensitivity and specificity were found to be 44% and 100%, respectively. At the second look operation no evidence of disease was observed in 40 patients, microscopic tumor was found in 10, and macroscopic tumor in 31 patients. All 81 patients had a gynecologic examination under anesthesia prior to the second look operation. Measurement of CA 125 was found superior to this examination with respect to positive and negative predictive value as well as to sensitivity and specificity. It is concluded that CA 125 values above 35 U/ml without exception announced residual tumor. Therefore, in cases with elevated CA 125 values, gynecologic examination under anesthesia or explorative laparotomy gave no further information concerning the result of treatment. CA 125 levels below 35 U/ml were without predictive value owing to a high number of false negative results.*

## INTRODUCTION

THE MANAGEMENT of ovarian cancer often includes a second look operation to evaluate the effect of treatment. Non-invasive methods like ultrasound scanning or computerized tomography often fail to detect residual tumor and these methods cannot replace an explorative laparotomy including microscopic examination of biopsy specimens, scrapings and liquid from peritoneal lavage. However, second look operation is not an ideal method to evaluate the effect of treatment as the 2-year recurrence-free survival of the patients demonstrating no evidence of disease at the time of operation is only 61% [1]. Furthermore, exploratory laparotomy is inconvenient to the patients and potentially hazardous. Therefore, reliable, non-invasive methods to detect residual tumor would be an advance.

The application of tumor markers may improve the detection of residual tumor and to some extent reduce the number of second look operations. So far, no ideal tumor marker has been described in ovarian cancer. The cancer antigen 125 (CA 125) has been demonstrated in elevated amounts in serum prior to the primary operation [2]. However, the influence of cytostatic and radiation treatment on the production and release of CA 125 is unknown and the correlation between CA 125 levels and the results of the second look operation deserves further elucidation.

In the present investigation CA 125 was measured in serum samples drawn prior to the second look operation. The purpose was to investigate if measurements of CA 125 could predict the effect of treatment evaluated by explorative laparotomy.

## MATERIALS AND METHODS

CA 125 was measured in serum from 81 patients with a diagnosis of epithelial ovarian cancer. The histopathologic diagnoses included 45 serous, 21 endometroid, 12 undifferentiated, two mixed and one malignant Brenner tumor. At the primary operation four cases were classified as FIGO stage I, 10 as stage II, 61 as stage III and six as stage IV.

The patients were treated according to the Danish Ovarian Cancer Study (DACOVA) protocols. Cases classified as stage I and II were treated with whole abdominal radiation exclusively or pelvic radiation and cyclophosphamide. Stage III and IV

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patients received one of two different chemotherapeutic regimens: cyclophosphamide and cisplatinum or cyclophosphamide, cisplatinum and doxorubicin. A gynecologic examination under anesthesia was performed at the end of the treatment period. The results of treatment are described elsewhere [1, 3].

The second look operation was performed in patients with complete or partial tumor remission at gynecologic examination under anesthesia. The operation was made as an exploratory laparotomy including microscopic examination of biopsies from surgical areas, scrapings from abdominal diaphragm and liquid from peritoneal lavage.

The blood samples for CA 125 measurements were drawn prior to second look and the results of the measurements were unknown to the physicians who performed the gynecologic examination and the second look operation.

CA 125 in serum was measured by radio- or enzyme immuno-assays (Abbott CA 125-RIA and Abbott CA 125-EIA monoclonal, respectively). Both are two-site solid phase immunoassays and the monoclonal, murine antibody OC125 serves both as detector and solid phase antibody. The assays are commercially available and the instructions given by the manufacturer were followed. All measurements were performed in duplicate. The serum samples were stored at −80°C until the analysis. Values above 35 units of CA 125 per ml of serum were considered to announce residual tumor [4].

## RESULTS

The 81 patients were grouped according to the findings at second look.

Residual tumor tissue was diagnosed in 41 patients. Thirty-one cases had macroscopic tumor and in 10 patients tumor could only be demonstrated by microscopic examination (Table 1).

Elevated serum levels of CA 125 (>35 U/ml) were proven in 18 (44%) of these 41 patients. Seventeen of the positive samples derived from patients with macroscopic tumor and one from a patient with microscopic tumor.

Twenty-three of the 41 patients (56%) had serum levels below the cut-off level (false negative values). In 16 of these 23 patients the marker was measured monthly during the treatment prior to second look. In four of the patients the antigen content increased more than 50% during the last 3–4 months of therapy without exceeding the cut-off level. In the remaining 12 patients stable or decreasing CA 125 levels were registered.

All 40 patients with no evidence of disease had CA 125 levels equal to or below 35 U/ml and false positive antigen values were not observed.

Based on these results the positive and negative predictive value of CA 125 measurements prior to the second look operation were 100% and 64%, respectively; the sensitivity was 44% and the specificity 100%.

All 81 patients had a gynecologic examination under anesthesia prior to the second look operation and palpable tumor was diagnosed in 23. At the second look operation macroscopic tumor was demonstrated in 16 (70%), microscopic tumor in one (4%) and no evidence of disease in six (26%) of the patients in this group.

In 58 patients no tumor was found at the gynecologic examination; 15 (26%) had macroscopic disease at second look, nine (15%) had microscopic tumor and 34 (59%) had no tumor tissue. Based on these findings the positive and negative predictive values of the gynecologic examination prior to second look were 74% and 59%, respectively; the sensitivity was 42% and the specificity 85%.

## DISCUSSION

A second look laparotomy is generally considered necessary to evaluate the effect of cytostatic and radiation treatment in ovarian cancer. Operation is superior to non-invasive methods and although not highly predictive for long-term prognoses [1] it is so far the best method for evaluation of the response.

In the present investigation CA 125 measurements in serum samples drawn prior to the second look were correlated to the results of the operation. A correlation presupposes that the results of the CA 125 analyses are reproducible (results submitted for publication) and the exploratory laparotomy is exhaustive and homogeneously performed [3].

Berek *et al.* [5] and Schilthuis *et al.* [6] demonstrated a positive predictive value of the CA 125 analysis of 100% and 86%, based on 55 and 60 patients, respectively. These results correspond well

*Table* 1. *The findings at second look in relation to CA* 125

| | Result of second look | | |
|---|---|---|---|
| | Macroscopic tumor | Microscopic tumor | No evidence of disease |
| Patients | 31 | 10 | 40 |
| CA 125 U/ml, range | 0–4830 | 0–50 | 0–35 |
| Patients with CA 125 > 35 U/ml | 17 (55%) | 1 (10%) | 0 (0%) |

with those of the present investigation which demonstrated a positive predictive value of 100%.

The investigations cited [5, 6] showed a sensitivity of 39% and 31% compared to 44% in the present series.

Finally, Berek *et al.* [5] demonstrated false negative CA 125 values in 61% of the patients who had residual tumor compared to 56% in our series.

Ninety per cent of our patients who had microscopic tumor had false negative CA 125 values. The false negative results were not limited to cases with microscopic tumor or to certain histologic classes and the results cannot be explained exclusively by low assay sensitivity or by lack of producing or releasing the marker by certain tumor types. However, in the present study CA 125 was not measured before the primary operation and possibly tumors without production of CA 125 have been included and may account for some of the false negative results. In a preceding study [7] CA 125 levels were measured preoperatively and the antigen was ≤35 U/ml in 7% (3/41) of the patients with malignant ovarian tumors.

The CA 125 serum level depends, from a theoretical point of view, on production, release and disappearance of the marker. The mechanism by which cytostatic treatment or radiation influence these phases is unknown but false negative CA 125 levels prior to second look may be due to interference with the CA 125 producing cells. Comparative serologic and immunohistochemic studies of tumor cells before and during treatment may further elucidate this problem.

In four patients with false negative antigen levels preceding monthly measurements of CA 125 demonstrated increasing antigen levels within normal values (≤35 U/ml). This finding indicates that attention should be paid also to increasing CA 125 levels not exceeding 35 U/ml during cytostatic therapy as this finding may be of importance in predicting residual tumor at the second look operation.

The effect of treatment was evaluated prior to second look by a gynecologic examination under anesthesia. Measurement of CA 125 improved both the positive and negative predictive values of the examination as well as the sensitivity and specificity and should be considered as a valuable adjunct to the preoperative gynecologic examination which often fails to detect minor amounts of tumor masses.

## CONCLUSION

In the present study CA 125 values above 35 U/ml announced residual tumor at the second look operation which in all cases confirmed the presence of persistent tumor. There were no false positive CA 125 results. CA 125 levels below 35 U/ml were without predictive value owing to the high percentage of false negative results and they cannot be applied in the decision on operation.

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