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CA-125 in Gynecological Malignancies

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Abstract—*CA-125 is an antigenic determinant that can be demonstrated in the majority of epithelial ovarian carcinomas. It can be measured in the serum with a radioimmunoassay by means of a monoclonal antibody. The tumor marker has a low specificity but high sensitivity for ovarian cancer, especially for serous cystadenocarcinoma. In our investigation we were interested in particular in the correlation between CA-125 and the histological findings at second-look operation. In 22 patients, second-look was performed after 6 cycles of chemotherapy; in 16 patients active tumor was demonstrated. In 6 patients with negative CA-125 values, residual tumor less than 1 cm was demonstrated. In order to verify a complete remission, a second-look operation has to be performed. No false-positive CA-125 levels were found. In all patients with elevated CA-125 serum values, residual tumor was histologically confirmed at second look.*

INTRODUCTION

ALONG with clinical investigation, blood chemistry and radiometric methods, especially computed tomography, tumor markers are of increasing importance in oncology. For several malignancies, for example gastrointestinal tumors, and also for gestational trophoblastic neoplasia, excellent tumor markers are already available.

During the last couple of years, several reports on CEA and TPA in gynecological tumors have been published [1–3]. The results do not justify the use of these 2 markers as a routine aid in clinical situations. A reliable tumor marker would, however, be of considerable interest for the control of primary therapy and for follow-up.

CA-125 is an antigenic determinant first described by Bast [4] on the surface of epithelial ovarian carcinoma cells. Serum levels can be measured with a radioimmunoassay by means of a monoclonal antibody (OC-125). In many clinical investigations, high sensitivity but relatively low specificity for epithelial ovarian carcinomas has been demonstrated. In our longitudinal study, the relevance of CA-125 for therapy control, evaluation of therapeutic success and for follow-up is investigated.

PATIENTS AND METHODS

From January, 1984, until August, 1985, serum levels of CA-125 were measured in 287 patients by solid phase radioimmunoassay using a commercial kit (Centocor CA-125) described elsewhere [5]. The upper normal serum level was 65 U/ml with a critical range from 35 U/ml to 65 U/ml.

In healthy and pregnant women, patients with benign ovarian tumors and in women with cancer of the breast, cervix, endometrium and Fallopian tube 1–3 determinations of CA-125 were performed. In all patients with ovarian cancer, 56 under primary therapy and 76 in follow-up, CA-125 serum levels were measured in 1–3-monthly intervals.

In women with primary ovarian cancer, an explorative laparotomy and, if possible, total abdominal hysterectomy, bilateral adnexectomy, resection of the omentum majus and a partial pelvic and para-aortal lymphonodectomy was performed. Post-operative chemotherapy, beginning within 2 weeks after laparotomy, consisted of 50 mg/m^2 cisplatinum, 50 mg/m^2 adriamycin and 500 mg/m^2 cyclophosphamide. Depending on the clinical status of the disease, second-look was performed after 6–8 cycles of chemotherapy.

RESULTS

Table 1 gives a survey of all patients examined. In 1 of 50 healthy women, the CA-125 serum level was above 65 U/ml without any evidence of disease. In 9 of 30 pregnant women (30%) elevated levels were seen. In 39 patients with breast, cervical and endometrial cancer, elevated levels were found in 10–15.4%. Also, in 21.9% of benign ovarian tumors, CA-125 serum levels were above 65 U/ml. None of the 4 patients with cancer of the Fallopian tube showed pathological CA-125 values at initial surgery.

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Table 1. Frequency of elevated CA-125 serum levels in healthy women and patients with different gynecological tumors

	Total	Number of patients with CA-125 > 65 U/ml		> 35 U/ml	
		n	%	*n*	%
Healthy women	50	1	2	2	4
Pregnant women	30	9	30.0	10	33.0
Breast cancer	16	2	12.5	2	12.5
Cervical cancer	13	2	15.4	3	23.1
Endometrium cancer	10	1	10.0	2	20.0
Cancer of the fallopian tube	4	0		1	
Benign ovarian tumors	32	7	21.9	7	21.9
Ovarian cancer	90	79	87.8	82	91.1

Table 2. Frequency of elevated CA-125 serum levels and histological type of ovarian tumor

Histology	Total	Number of patients with CA-125 > 65 U/ml		> 35 U/ml	
		n	%	*n*	%
Serous cystadenocarcinoma	70	66	94.3	69	98.6
Primary	42	39	92.9	41	97.6
Recurrence	28	27	96.4	28	100
Mucinous cystadenocarcinoma	2	2		2	
Endometrioid carcinoma	4	2		2	
Undifferentiated carcinoma	9	7	77.8	7	77.8
Mixed Müllerian tumor	3	0		0	
Endodermal sinus tumor	2	2		2	

Table 3. Details of patients with ovarian carcinoma and CA-125 determinations

	Number of patients	CA-125 > 65 U/ml
Primary therapy	56	48
Second-look	25	22
Without second-look	31	26
Follow-up	76	34
Remission	42	1
Recurrence	34	33
Total number	132	82

In contrast, in 87.8% of patients with primary ovarian cancer or recurrence after successful primary therapy, CA-125 values were elevated in a range from 75 U/ml to 10,000 U/ml.

There is also a correlation with the histological type of ovarian carcinoma (see Table 2). Of the patients with serous cystadenocarcinoma, 94.3% had elevated serum levels. From the undifferentiated tumors, 77.8% did not lie in the normal range.

Table 3 shows details of the 132 patients with ovarian carcinoma. In 8 of 56 patients with primary ovarian cancer, CA-125 levels were in the normal range below 35 U/ml. These malignancies were histologically mainly mixed Müllerian tumors, undifferentiated and endometrioid carcinomas. In 2 cases, a serous cystadenocarcinoma was identified.

All but 1 of the 42 patients with complete remission after initial therapy had normal CA-125 serum levels. As the serum levels in this patient began to rise, all clinical and apparative examinations for metastases were negative. (11 months following the rise in serum CA-125 we have been able to identify liver metastases.) In only 1 of 34 women with recurrent ovarian cancer, CA-125 lay in the critical range between 35 and 65 U/ml. In all other patients, CA-125 lay clearly above 65 U/ml. In some of these patients, CA-125 levels rose 6–9 months before clinical manifestation of recurrence.

In 56 patients, serum levels of CA-125 were determined beginning at primary surgery. Forty-eight patients (85.7%) had elevated CA-125 levels at this time. Second-look laparotomy was not performed in 26 of the patients with initially elevated CA-125 levels; 13 women are still undergoing primary therapy (chemotherapy) and in 7 patients there was clinical evidence of progressive disease, so that a second-look operation could not be justified. In

Table 4. CA-125 levels and clinical status of disease in patients without second-look

Clinical status	Number of patients	CA-125 > 65 U/ml	CA-125 < 65 U/ml
Progressive disease	7	7	0
No change	5	5	0
Partial remission	6	6	0
Complete remission	8	0	8
Total	26	18	8

Table 5. CA-125 values and histological findings at second-look

	Second-look	CA-125 > 65 U/ml	CA-125 > 35 U/ml
Positive histology or cytology	16	10	12
Negative	6	0	0

another 6 patients with clinically complete remission, the second-look operation was not performed because of early stage or concurrent medical risk factors. In all cases, levels of CA-125 correlated well with the clinical status (Table 4).

Twenty-two of the 25 patients (88%) in whom a second-look operation was performed showed elevated CA-125 values initially. After tumor reduction at primary surgery and post-operative chemotherapy, second-look surgery was carried out. In 16 patients, residual tumor could be demonstrated. In 6 patients, no evidence of tumor or no positive peritoneal washings were found. CA-125 levels were above 65 U/ml in only 10 women, so there were false-negative values in 6 patients with histologically proven residual tumor at second-look (see Table 5). In all of these patients tumor size was less than 1 cm. The theory that this tumor might be regressive could not be confirmed. In 1 of the cases with a false-negative CA-125 level the tumor tissue was indeed regressive. In all others, vital tumor cells were detected.

In contrast to these results, no false-positive CA-125 levels were found. In all patients with elevated CA-125 serum values, residual tumor was histologically confirmed at second-look operation.

In addition, Fig. 1 shows CA-125 levels in patients without residual tumor at primary surgery and with a histologically-proven negative second-look ($n = 5$). After operation and chemotherapy, no tumor was detectable at second-look laparotomy. Further follow-up has shown recurrence-free patients up to date. CA-125 values correlated well with the course of disease.

Figure 2 shows the serum levels of CA-125 in patients with residual tumor of more than 2 cm at initial surgery. In all patients ($n = 8$), residual tumor was detected at second-look, and, in spite of further chemotherapy, the disease was progressive. CA-125 values increase after the initial decrease during first-line chemotherapy.

DISCUSSION

Our data confirm the observations of others, that CA-125 is a sensitive marker for epithelial ovarian carcinoma [6–8]. Taking 65 U/ml as the upper limit of the standard range, about 87% of the patients with this disease showed elevated values. There is an evident association with the histological type of ovarian tumor, the highest levels being found in serous cystadenocarcinomas [9]. Because of the small number of mucinous cystadenocarcinoma, endometrioid carcinoma, mixed Müllerian tumors and endodermal sinus tumors, we cannot draw conclusions about the frequency of elevated CA-125 levels in these cases. Elevated serum levels were found in mucinous cystadenocarcinomas as well, as has been described elsewhere [8]. Other tumor markers like TPA, CEA, HPL, HCG and AFP show, in general, a lower sensitivity for ovarian cancer [1, 3, 10, 11] than CA-125.

In contrast to this high sensitivity, CA-125 demonstrates a low specificity. Elevated levels can be found in other gynecological malignancies like cancer of the breast, cervix and endometrium; also in benign ovarian tumors and in pregnancy, CA-125 levels are elevated by 22.5 to 30% [12, 13, 14].

The conclusion is that this marker alone should be used mainly in the control of primary therapy and follow-up, but not as a screening method for ovarian cancer [6]; eventually the use of CA-125 in combination with other tests could be valuable as a

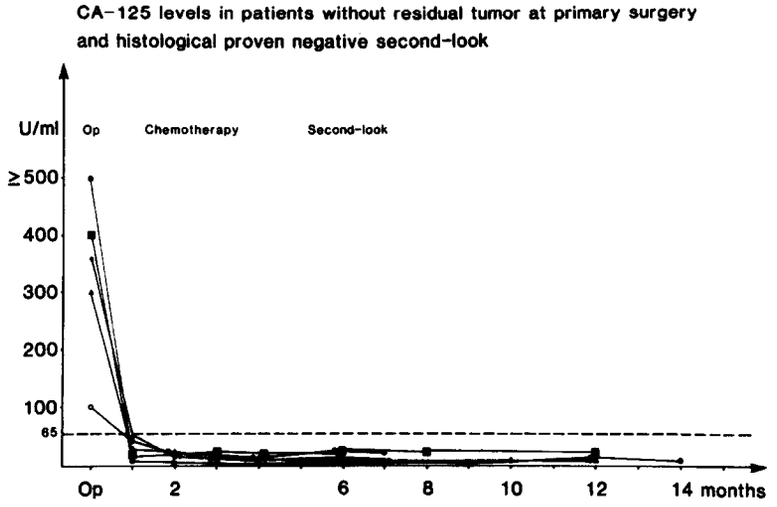

Figure 1.

screening test. The follow-up values correlate well with the clinical course of the disease [7, 8]. CA-125 was elevated in only 1 of 42 patients without any clinical evidence of disease. On the other hand, in 33 of 34 patients with progressive disease, CA-125 levels increased, in most cases several months before the clinical appearance of progression. Prospective studies are necessary to evaluate the effect of a second-line chemotherapy on CA-125 levels, when this coincides with already detectable or increasing CA-125 values [7].

Of special interest is the correlation between CA-125 and histological findings at second-look. In no patients were false-positive values found; that means in all of these patients residual tumor was seen at second-look. In 6 of 16 patients, there were false-negative CA-125 levels. In these cases, tumor size was less than 1 cm. Therapeutic consequences cannot be drawn from a negative tumor marker, since there might still be active tumor tissue [15, 16]. In order to confirm a complete remission after primary therapy, a second-look operation has to be performed. On the other hand, the question should be discussed, whether declining levels show response to chemotherapy and if the time interval to second-look can be reduced.

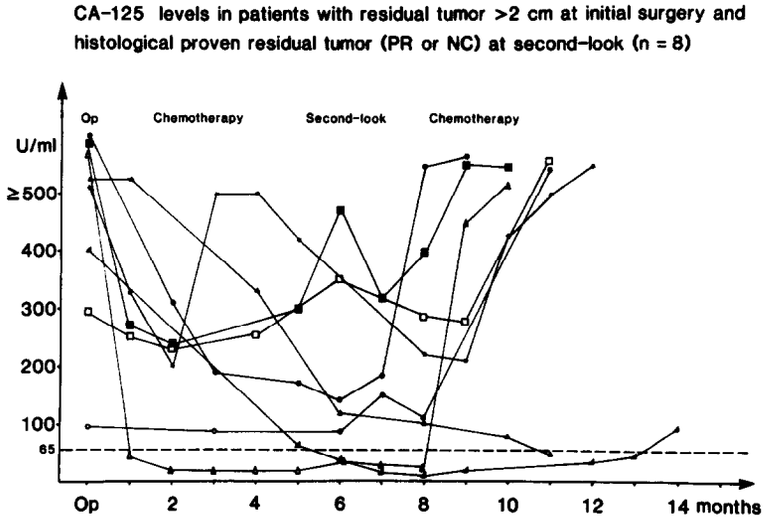

Figure 2.

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