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CA 125 in the Diagnosis of Pelvic Masses

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Abstract—*CA 125 was measured preoperatively in 184 female patients presenting with pelvic masses. Ovarian tumors were diagnosed in 151 cases (91 carcinomas, eight borderline, 52 benign) and non-ovarian tumors in 33 (19 malignant, 14 benign). The sensitivity of CA 125 in identifying the malignant and borderline ovarian tumors was 86%, the specificity 78%; and the positive and negative predictive values 82% and 83%, respectively. Increased antigen values (>35 U/ml) were observed in 63% of the non-ovarian malignant tumors. Considering only the diagnosis of malignancy in pelvic masses (ovarian plus non-ovarian malignant tumors) the specificity improved to 89% and the positive predictive value to 93%; the sensitivity and the negative predictive value decreased to 82% and 74%, respectively. CA 125 in the normal range (≤35 U/ml) was observed both in ovarian and non-ovarian carcinomas. Therefore, preoperative CA 125 values in the normal range should be interpreted with caution. However, increased preoperative CA 125 levels in patients with pelvic masses are highly suggestive of a malignant tumor and CA 125 should be an adjunct to the preoperative diagnostic armamentarium.*

INTRODUCTION

FEMALE PATIENTS presenting with pelvic masses often represent a diagnostic problem and, previously, the differential diagnosis was left to be answered by an explorative laparoscopy or laparotomy. Ultrasound scanning or computerized tomography may be helpful in the preoperative diagnosis [1] but the question of malignancy often remains unsolved. Therefore, improved non-invasive diagnostic methods are desirable and may be of considerable help to the physician facing a pelvic mass.

Application of tumor markers in patients presenting with pelvic masses may improve the preoperative diagnostic precision. So far, no ideal tumor marker has been described for this purpose. The ovarian cancer-associated antigen CA 125 seems to be useful in monitoring the tumor response to treatment in patients with ovarian cancer [2–5]. However, the current literature has concentrated on measurements of the antigen after the primary operation and little attention has been paid to the diagnostic value of CA 125. The purpose of the present investigation was to determine whether preoperative measurements of CA 125 in patients presenting with pelvic masses might give information concerning the nature of the mass.

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MATERIALS AND METHODS

CA 125 was measured in serum from 184 female patients referred to hospitals with a pelvic mass. An explorative laparotomy was in all cases performed to reveal the nature of the tumor and the operative findings settled the extent of surgery. The blood samples were drawn prior to the operation and serum was stored at −80°C until analysis.

CA 125 was measured by a radioimmunoassay (Abbott CA 125-RIA) or by an enzymeimmunoassay (Abbott CA 125-EIA). Both analyses are two-site immunometric assays and the murine monoclonal antibody OC125 is used both as tracer and on the solid phase. The assays were performed according to the manufacturer's instructions and the CA 125 concentration was read from a point to point standard curve. All measurements were performed in duplicate and values above 35 U/ml were considered abnormal [2, 6].

The assay variation was determined from serum samples with varying content of CA 125. The samples were measured once at each assay and the coefficient of variation varied according to the antigen level (Table 1).

RESULTS

Figure 1 demonstrates the correlation between serum values of CA 125 and the diagnoses. Ovarian carcinoma was diagnosed in 91 (50%) patients. Eight (4%) patients had borderline ovarian tumors and 52 (28%) presented with benign ovarian tumors. Non-ovarian malignant and benign tumors

Table 1. *Interassay variations*

n	CA 125, RIA* Range (U/ml)	CV (%)‡	*n*	CA 125, EIA† Range (U/ml)	CV (%)‡
7	9–16	17.4	43	19–57	11.4
16	102–122	4.1	16	154–189	5.3
16	184–290	7.8	9	225–258	4.2

*RIA: radioimmunoassay.
†EIA: enzymeimmunoassay.
‡CV%: coefficient of variation in per cent.

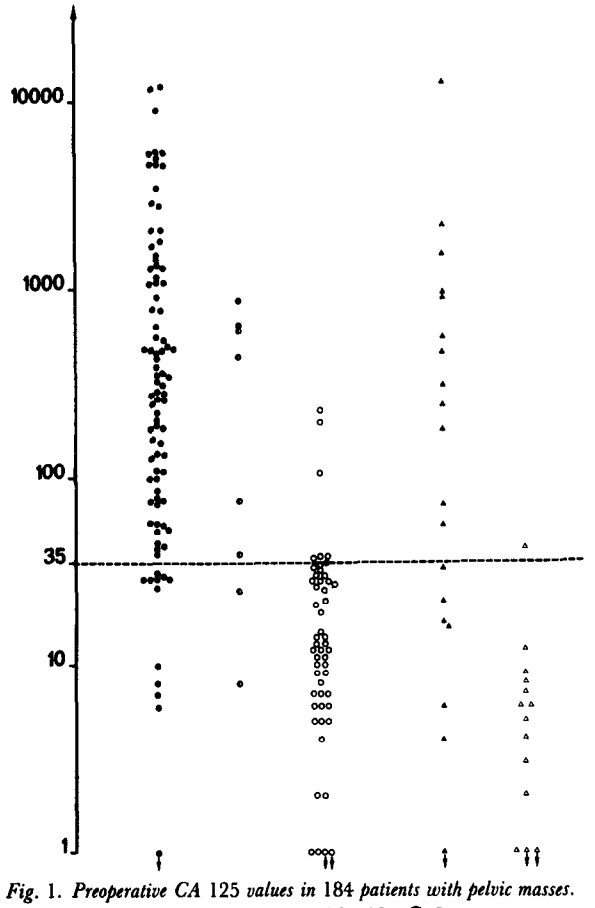

Fig. 1. *Preoperative CA* 125 *values in* 184 *patients with pelvic masses. The ordinate represents the serum values of CA* 125. ● *Ovarian carcinoma* (n = 91); ◐ *borderline ovarian tumor* (n = 8); ○ *benign ovarian tumor* (n = 52); ▲ *non-ovarian malignant tumor* (n = 19); △ *non-ovarian benign tumor* (n = 14).

were demonstrated in 19 (10%) and 14 (8%) cases, respectively.

The measurements demonstrated increased CA 125 levels (>35 U/ml) in 104 patients and 80 had levels in the normal range. In the group of malignant and borderline ovarian tumors (Table 2) increased CA 125 values were found in 87% (79/91) and 75% (6/8), respectively. Among the benign ovarian tumors normal values of CA 125 were found in 88% (46/52). False positive values were demonstrated in two serous adenomas (38 and 104 U/ml), one mucinous adenoma (37 U/ml), two granulosa-theca cell tumors (38 and 196 U/ml) which appeared clinically and histologically benign and one endometriosis (225 U/ml).

Table 2. *CA* 125 *in* 151 *patients with ovarian tumors*

	CA 125 (U/ml) ≤35	>35
Carcinomas (n = 91)		
FIGO stage:		
I	7	11
II	2	4
III	3	49
IV	0	15
Serous carcinoma	0	37
Endometroid carcinoma	4	15
Undifferentiated carcinoma	1	14
Mucinous carcinoma	5	4
Mixed carcinoma	0	6
Clear cell carcinoma	2	2
Brenner tumor	0	1
Borderline tumors (n = 8)	2	6
Benign tumors (n = 52)		
Adenoma	23	3
Cyst	19	0
Fibroma	3	0
Granulosa-theca cell tumor	1	2
Ovarian endometriosis	0	1

Comment: The number of increased CA 125 values in the group of carcinomas and borderline tumors was significantly higher compared with the benign tumors (chi-square test with Yates correction: $P < 0.001$).

Non-ovarian diseases were diagnosed in 33 patients of whom 19 had malignant and 14 benign tumors (Table 3). In the 19 malignant cases, increased CA 125 values were observed in 12 (63%) of the samples. Nine of the 12 positive values were demonstrated in patients with low differentiated tumors of unknown origin.

In the group of 14 benign non-ovarian tumors (Table 3), one (7%) false positive antigen value (42 U/ml) was found in a patient who had a fibromyoma of the uterus.

Based on these results the sensitivity and specificity of CA 125 in identifying malignant and borderline ovarian tumors were 86% and 78%, respectively. The positive and negative predictive value was alike (82% and 83%, respectively).

The CA 125 measurements were correlated to FIGO stage and histopathologic diagnosis in the 91 ovarian carcinomas (Table 2). In FIGO stage I and II the percentages of false negative antigen levels were 39% and 33%, respectively. In stage III it was 6%, only, and in stage IV no false negative values occurred.

The correlation between CA 125 and the histopathologic diagnosis (Table 2) demonstrated elevated antigen levels in all tumor types. However, false negative CA 125 values were more common in the mucinous (5/9), clear cell (2/4) and endometroid (4/19) tumors than in the other tumor types.

Table 3. *CA* 125 *in* 33 *patients with non-ovarian tumors*

	CA 125 (U/ml) ≤35	>35
Malignant tumors (n = 19)		
Undifferentiated cancer	2	9
Gastro-intestinal cancer	2	1
Endometrium cancer	2	1
Fallopian cancer	1	1
Benign tumors (n = 14)		
Fibromyoma	10	1
Cyst	2	0
Benign nephroma	1	0

Comment: The number of increased CA 125 values in the group of malignant tumors was significantly higher compared with the benign tumors (chi-square test with Yates correction; $0.001 < P < 0.01$).

DISCUSSION

General diagnostic tests for cancer seem an elusive goal. More specific analyses have, however, proved to be of crucial importance in minor subgroups of patients, e.g. markers for testicular cancer and trophoblastic tumors. The application of diagnostic tests faces a number of problems among which sensitivity, specificity and predictive values take the lead. These parameters depend to a considerable extent on the composition of the population investigated. The target population, therefore, should be representative of the patients in question allowing the conclusions to be applied in daily routine use. Neglect of these problems may result in poor practical value of a diagnostic test.

Female patients with a pelvic mass represent a diagnostic problem and if a more precise preoperative diagnosis could be obtained the referral of patients with malignant tumors to centers with experience in oncologic surgery would be facilitated. Furthermore, the extent of the operation could be better planned and the patient better informed. Patients with pelvic masses, therefore, are potential candidates for routine CA 125 analyses.

Current literature about CA 125 has paid little attention to the diagnostic value of the antigen in patients with pelvic masses. Einhorn *et al.* [7] measured CA 125 prior to the primary operation in 100 patients presenting with pelvic masses and demonstrated a sensitivity and specificity of CA 125 to predict malignant and borderline ovarian tumors of 78% and 89%, respectively. The positive and negative predictive value was 61% and 95%, respectively, and the former value was considerably lower compared to the positive predictive value (82%) in our study. However, malignant or borderline ovarian tumors were diagnosed in only 18% (18/100) of the patients included in Einhorn *et al.*'s study in contrast with 54% (99/184) in the present investigation and this finding may explain the observed difference between the positive predictive values.

O'Connell *et al.* [8] measured CA 125 preoperatively in 56 patients with pelvic masses, and ovarian carcinomas or borderline tumors were diagnosed in 24. The authors observed no false negative CA 125 values but the specificity was 41% and the positive predictive value was 56%, only. The majority (12/19 = 63%) of false positive CA 125 levels in the cited study was demonstrated in the group of non-ovarian malignant tumors which is in accordance with our findings. However, the percentage of false positive samples (19/56 = 34%) was higher than observed in the present study (19/184 = 10%) and this difference cannot easily be explained.

Increased CA 125 levels were observed in 12 patients with non-ovarian malignant tumors (Table 3) and the histopathologic evaluation demonstrated low differentiated tumors of unknown origin in nine of these cases. If some of these tumors originated from the ovary the positive predictive value, the sensitivity and specificity of the CA 125 assay to identify malignant and borderline ovarian tumors are underestimated.

Based on the results in Tables 2 and 3 the sensitivity of CA 125 to identify a malignant pelvic mass (ovarian plus non-ovarian malignant tumors) could be calculated at 82%, the specificity was 89%, and the positive and negative predictive value 93% and 74%, respectively. These findings indicate that increased CA 125 values in patients with pelvic masses are highly informative of malignancy.

In the group of malignant ovarian tumors false negative CA 125 values were observed in 13% of the samples. Antigen values below 35 U/ml were more common in FIGO stage I and II tumors compared with stage III and IV tumors. This finding is in accordance with Brioschi *et al.* [9] who demonstrated nine FIGO stage I tumors out of 13 false negative ovarian carcinomas, and probably the number of tumor cells in these cases is too small to provoke increased CA 125 levels. Maughan *et al.* [10] correlated serum values of CA 125 with the presence of antigen in tumor tissue from 41 patients with ovarian adenocarcinomas. The authors observed antigen reactivity in tumor tissue from 34 patients of whom 19 had increased and 15 had normal serum CA 125 levels. In the latter group the tumor size was significantly smaller compared with the patients with increased CA 125 values and Maughan *et al.* [10] concluded that the major determinant of serum CA 125 levels appeared to be the size of tumor rather than decreased CA 125 production. However, the type of tumor also seems to be important considering that the majority of false negative samples in the present study was observed in patients with mucinous and endome-

troid tumors (Table 2). This is in accordance with Koelma *et al.* [11] and Shishi *et al.* [12] who demonstrated CA 125 reactivity in tumor tissue from 57% (4/7) and 25% (3/12) of patients with mucinous ovarian carcinomas. Larger studies correlating the CA 125 reactivity in tumor tissue, serum values of CA 125, FIGO stage and histopathologic diagnosis may elucidate this problem further.

CONCLUSION

Increased CA 125 values are highly suggestive of malignancy in patients with a pelvic mass and it seems reasonable to include the analysis in the preoperative diagnostic examinations. CA 125 values in the normal range should be interpreted with caution and considered an adjunct to other investigations.

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