

# Enzyme-Linked Immunosorbent Assay And Immunohistochemical Localisation Of Carcinoembryonic Antigen In Ovarian Neoplasia

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## Abstract

**Objective:** To evaluate the significance of including CEA in serum and tissues in the management protocol of patients with ovarian malignancies.

**Methods:** The study included 68 patients divided into three groups :Group A with 21 patients with malignant ovarian tumours; Group B with 3 patients with borderline ovarian tumours; Group C with 8 patients with benign ovarian tumours and Group D with 36 women without any apparent gynaecologic disorder (control group). Serum level of CEA was measured in all patients in group A, B and C prior to treatment and at least 12 weeks following therapy. Formalin - fixed and paraffin - embedded tissue blocks taken from 2 different sites of the studied lesions were prepared. Immunohistochemical staining for CEA was performed for the studied tissues.

**Results:** All the benign and borderline ovarian tumours had negative pre- and post-treatment serum levels of CEA (< 5 ng/ml) while 52.38% of malignant ovarian tumours had positive pre-treatment serum values. After treatment all the malignant ovarian tumours were seronegative for CEA. The mean pre-treatment serum CEA in malignant ovarian tumours (7.32 ng/ml) was significantly higher than that of the other groups, whereas the mean post-treatment serum values and the mean difference in serum levels showed no significant differences between the 3 groups. The mean difference between pre- and post-treatment serum CEA was significant only in malignant ovarian tumours. Up to 12.5% of the benign ovarian tumours, and 42.86% of the malignant ones had a positive reaction for CEA tissue stain. The mean values of serum CEA before treatment were significantly higher in positively stained malignant ovarian tumours ( $P < 0.0001$ ). The mean difference in serum CEA was significantly higher in positively stained malignant ovarian tumours ( $P < 0.0001$ ). The mean pre-treatment serum CEA and also the mean difference in serum levels showed significant progressive increase with the increase in degree of tissue stain of ovarian carcinomas.

In conclusion this study indicate that immunohistochemical identification of CEA in tumour tissue and monoclonal antibodies quantitative measurement of CEA in human serum may be a useful adjunct in the management protocol of patients with ovarian malignancies.

## INTRODUCTION

Ovarian masses fall into two broad categories, benign and malignant. The former are a nuisance but rarely dangerous, the latter are the most lethal of the common gynaecological malignancies. The surgical management of ovarian cancer is

complex and often involves gastrointestinal surgery. Differentiating between benign and malignant masses is of paramount importance<sup>(1)</sup> <sup>(2)</sup>.

There is an increasing need for a reliable cost-effective method for detecting ovarian cancer early. Most patients are

diagnosed with advanced-stage disease when the prognosis is poor, despite radical surgery and combined chemotherapy<sup>(2)</sup>.

In the US, ovarian cancer is the fifth leading cause of cancer death from gynaecologic malignancies. Ovarian cancer can be managed optimally with good results if detected early. However more than 70% of cases are diagnosed at an advanced stage, where 5 years survival approaches only 20%<sup>(3)</sup>. Unfortunately, despite advances in surgical technique and novel chemotherapeutic agents, survival rates have not improved significantly over past 25 years<sup>(4)</sup>.

The oncofoetal antigens comprise one particular group of markers produced by human neoplasms. These antigens have been detected in the sera of patients with gynaecological cancer. The practical use of such markers in the diagnosis and follow-up has been limited by the low sensitivity and specificity of their tests <sup>(5)</sup>. Carcinoembryonic antigen (CEA) is one of the first known tumour markers. Since then, many more have been described, but CEA, determined alone or in combination with others, is still one of the most used. CEA is not organ specific and abnormal values may be found in a wide range of carcinomas <sup>(6)</sup>.

In this work we try through the study of CEA in the serum and tissues to evaluate the significance of including this tumour marker in the management protocol of patients with ovarian malignancies.

## **PATIENTS AND METHODS**

The present study was conducted on patients treated at National Cancer Institute, Cairo university and the department of Obstetrics and Gynaecology, Al Hussain Hospital, Al Azhar university. The study included 68 patients. The patients were divided into the following groups

- Group [A] : 21 patients with malignant ovarian tumours, including mucinous cystadenocarcinoma (9 cases) ; serous cystadenocarcinoma (7 cases), undifferentiated carcinoma (3 cases) and squamous cell carcinoma (2 cases).
  - Group : **3 patients with borderline ovarian tumours, two of them were borderline mucinous tumour and the third was of the serous type.**
  - Group [C] : 8 patients with benign ovarian tumours, four were mucinous cystadenomas and the other four were serous cystadenomas.
  - Group [D] : 36 women without any apparent gynaecologic disorder. They were age matched with the tumour patients - serum samples were taken from them were subjected to CEA measurement and considered as control.
- All the cases in group A and B, were subjected to the following :
1. Careful history, clinical examination and investigations
  2. Clinical staging for malignant lesions in group A according to the International Federation of Gynaecology and Obstetrics (FIGO) staging systems (7). Staging of ovarian cancer showed 8 patients with stage I, 9 patients with stage II, 3 patients with stage III and one patient with stage IV.
  3. Serum samples were collected from the patients in groups A, B and C prior to treatment and at least 12 weeks following surgery or completion of radio or chemotherapy. All the patients were clinically free of tumor at the time of the post-treatment sample proven by a second look laparoscopy.
  4. Serum CEA was assayed in all the serum samples using a monoclonal antibody based immunoassay commercially available kit from Abbott Laboratories (North Chicago, Illinois, USA,) which provides a quantitative measurement of CEA in human serum. It is a solid phase enzyme-linked immunosorbent assay based on sandwich principle. A positive result for CEA in serum was taken as 5 ng/ml or more.
  5. Sugical specimens from ovarian tumours (taken from two different sites) were fixed in 10% formalin and embedded in paraffin. Formalin fixed, paraffin - embedded tissue blocks with hematoxylin-eosin stained slides had been prepared for all cases without special processing for diagnosis confirmation and for selection of blocks for study. Serial sections not more than 5 um thick were deparaffinized in xylene and dehydrated in a series of graded concentrations of alcohol. The slides were incubated in methanol with 0.3% hydrogen peroxide to eliminate endogenous

peroxidase activity. After incubation with polyclonal rabbit primary antibody (Dako, Carpinteria, CA) for 60 minutes and with polyclonal enzyme (Dako Carpinteria, CA) for another 60 minutes at room temperature, the specimens were stained by the DAB(diaminobenzidine) working colour reagent and incubated for 5-10 minutes and counterstained with haematoxylin for 30-60 seconds.

According to Charpin et al (1982) (8). - a grading system was utilized quantify the staining positivity as follows :

- (0) - Denoting negative reaction i.e. showing no difference from the control sections.
- (+1) - Means that up to 25% of the cells were positive.
- (+2) - Means that >25 - 50% of the cells were positive
- (+3) - Means that >50 - 75% of the cells were positive.
- (+4) - Means that >75% of the cells were positive.

The patients with malignant ovarian tumours were treated with surgery alone or combined with radiation therapy or chemotherapy depending upon primary type, histologic differentiation and stage of disease. Those with non malignant lesions were treated only surgically.

## STATISTICAL ANALYSIS

Statistical analysis was carried out using an IBM - AT computer and SAS program (SAS, 1988). One way analysis of variance ( procedure GLM of SAS ) followed by Duncan's multiple range test were used to test the significance between the different variables studied. Paired t-test ( procedure Means of SAS ) was run to test the significance of the difference in serum CEA levels in relation to the variables studied in the current investigations, while student's t - test ( procedure test of SAS ) was employed to test the significance of change in serum CEA levels between negatively and positively stained lesions in relation to the different variables investigated. Cross tabulation and chi - square test ( procedure frequency of SAS ) were used to obtain and compare the percentage distribution of the studied cases according to their serum CEA levels and reactions to CEA immunostaining in relation to the studied variables. The probability level 0.05 ( p = 0.05 ) was used to test the significance of the previous tests. Sensitivity, specificity, positive predictive value and

negative predictive value were calculated using 2x2 table.

## RESULTS

All the benign and borderline ovarian tumours had negative pre- and post-treatment serum levels of CEA (< 5 ng/ml) while 52.38% of malignant ovarian tumours had positive pre-treatment serum values (> = 5 ng/ml). After treatment all the malignant ovarian tumours were sero-negative for CEA. The sensitivity, specificity, positive predictive value and negative predictive value of CEA were 34%, 67%, 52% and 50% respectively.

The mean pre-treatment serum CEA in malignant ovarian tumours (7.32 ng/ml) was significantly higher than that of the other groups, whereas the mean post-treatment serum values and the mean difference in serum levels showed no significant differences between the 3 types of ovarian tumours (Table 1).

**Figure 1**

Table 1: Serum CEA before and after treatment in different types of ovarian tumours.

Type of Tumor	No.	Serum CEA											
		Before Treatment			After Treatment			Difference					
		Mean	S.D	dt	Mean	S.D	dt	Mean	S.D	dt	S.E	T	P
Benign	8	1.13	0.615	b	0.9	0.582	a	0.23	0.763	a	0.27	0.853	N.S
Borderline	3	1.929	1.341	b	0.9	0.145	a	1.028	1.195	a	0.69	1.49	N.S
Malignant	21	7.32	6.854	a	0.754	0.519	a	6.566	6.686	a	1.459	4.5	0.0002
Control group	25	1.024	0.865	b	-	-	-	-	-	-	-	-	-

SD : Standard deviation; dt : Duncan's multiple range t-test

SE : Standard error T : Paired t-test, N.S : Not significant

The mean difference between pre-treatment and post-treatment serum CEA was significant only in malignant ovarian tumours (Table 1). On comparing this mean difference with those of benign and borderline tumours it was found insignificant because of the large standard deviation (S.D) of the malignant group (reflecting wide range of variability) which affects the significance of results.

As shown in table 2 12.5% of the benign ovarian tumours, and 42.86% of the malignant ones had a positive reaction for CEA tissue stain, while all the borderline tumours showed a

negative reaction. Of all the positively stained ovarian tumours 90% were malignant. The mean values of serum CEA before treatment were significantly higher in positively stained malignant ovarian tumours (13.2 ng/ml) in comparison with the negative ones (2.9 ng/ml). The other 2 groups were not valid for such a comparison as they were almost devoid of positive cases.

**Figure 2**

Table 2: Serum CEA in different types of ovarian tumour's according to their reaction to tissue stain.

Type of Tumor	Reaction to CEA tissue stain	No. (%)	Serum CEA before treatment						Serum CEA after treatment					
			Mean	S.D	S.E	T	df	P Value	Mean	S.D	S.E	T	df	P Value
Benign	- ve	7 (87.50)	1.009	0.552	0.209				0.856	0.614	0.232			
	+ ve	1 (12.50)	1.976	-	-				1.207	-	-			
Borderline	- ve	3 (100.00)	1.929	1.341	0.774				0.900	0.145	0.084			
	+ ve	0 (00.00)	-	-	-				-	-	-			
Malignant	- ve	12 (57.14)	2.929	1.302	0.376				0.627	0.370	0.107			
	+ ve	9 (42.86)	13.174	6.902	2.301	5.065	19	0.0001	0.923	0.655	0.218	1.318	19	0.203

S.D : Standard deviation; df : Degree of freedom;

S.E : Standard error; t: Paired t-test; T : Student's t-test

**Figure 3**

Type of Tumor	Reaction to CEA tissue stain	No. ( % )	Difference in serum CEA							
			Mean	S.D	S.E	T	df	P Value	t	P
Benign	- ve	7 (87.50)	0.153	0.790	0.299				0.513	0.626
	+ ve	1 (12.50)	0.769	-	-				-	-
Borderline	- ve	3 (100.00)	1.028	1.195	0.69				1.490	0.275
	+ ve	0 (00.00)	-	-	-				-	-
Malignant	- ve	12 (57.14)	2.302	1.456	0.42				5.475	0.0002
	+ ve	9 (42.86)	12.25	6.724	2.241	5.012	19	0.0001	5.466	0.0006

The mean serum CEA levels after treatment were decreased in all types of ovarian tumours. This decline was most marked in malignant ovarian tumours but with no significant differences between these cases according to their reaction to

stain. The mean difference in serum CEA was significantly higher in positively stained malignant ovarian tumours in comparison with the negative ones.

The mean difference between pre- and post-treatment serum CEA was highly significant in the positively and negatively stained malignant tumours (Table 2). All the positively stained ovarian tumours (12.5% of this group) belonged to (+1) degree of reaction. Positive staining of malignant ovarian tumours was detected in 42.9% of the studied cases, most of them (33.3%) had a (+1) degree of reaction and only 9.5% showed a (+3) positive reaction.

Up to 83.3% of the negatively stained ovarian carcinomas had negative pre-treatment serum CEA levels and 16.7% showed positive serum values. Whereas all the positively stained ovarian carcinomas had positive pre-treatment levels of serum CEA, the post-treatment serum CEA was negative for all the studied cases of ovarian carcinomas.

The mean difference between pre-treatment and post-treatment serum CEA was highly significant in negatively stained tumours (degree 0) and in positively stained tumours with (+1) degree of reaction.

The mean pre-treatment serum CEA and also the mean difference in serum levels showed significant progressive increase with higher degree of tissue stain of ovarian carcinomas (Table 3). The sensitivity, specificity, positive predictive value and negative predictive value of combined serum and tissue CEA were, 88%, 58%, 48% and 92% respectively.

**Figure 4**

Table 3: Serum CEA in different degree of tissue stain of ovarian carcinomas.

Degree of Tissue stain		No. (%)	Serum CEA										
			Before Treatment			After Treatment			Difference				
			Mean	S.D	dt	Mean	S.D	dt	Mean	S.D	dt	S.E	T
- VE	0	12 (57.1)	2.9	1.3	c	0.63	0.37	a	2.30	1.46	c	0.42	5.48
+ VE	+ 1	7 (33.3)	9.9	2.7	b	0.84	0.73	a	9.16	2.68	b	1.01	9.05
	+ 3	2 (9.5)	24.3	4.3	a	1.20	0.18	a	23.08	4.14	a	2.9	7.88

dt : Duncan's multiple range t- test; T : Paired t-test; S.D : Standard deviation;

S.E : Standard error; Means with the same letters are not

significantly different at  $P = 0.05$

## **DICUSSION**

The purpose of this study was to explore the relationship between serum CEA levels in patients with ovarian tumours and the histological expression of CEA in the tumour cells.

All the benign and borderline ovarian tumours in the present study had negative serum CEA levels ( $< 5$  ng/ml) before and after treatment (Table 1). The incidence of abnormal CEA values (cut-off level 2.5 ng/ml) in benign pelvic masses was reported by Inoue et al. (1992)<sup>(9)</sup>, to be 2.5%. Tholander et al. (1990)<sup>(10)</sup>, showed an elevated serum CEA ( $> 5$  ng/ml) in 13% of the cases of benign adnexal tumours and in 27% of the cases of borderline tumours. CEA was elevated in 7% of women with benign adnexal masses and in 12% with tumours of low malignant potential and in 33% of women with a frankly invasive epithelial ovarian cancer<sup>(11)</sup>. The difference in the technique of serum assay and the small number of borderline lesions in the current investigation may account for the difference in our results and others.

On the other hand, 47.6% of the malignant ovarian tumours had negative serum values of CEA while 52.4% showed positive serum levels ( $> 5$  ng/ml). After treatment all the malignant group were seronegative for CEA (Table 1). Stall and Martin (1981)<sup>(12)</sup>, found that the mean incidence of elevated serum levels of CEA in ovarian carcinomas was around 40%. Pre-treatment serum CEA was elevated ( $> 2.5$  ng/ml) in 29% of those reported by Tholander et al. (1990)<sup>(10)</sup>, who used a polyclonal anti-serum for CEA assay and in 21.5% of ovarian carcinomas investigated by Inoue et al. (1992)<sup>(9)</sup>, and in 33% of cases with frankly invasive epithelial ovarian carcinoma investigated by Roman et al. 1998<sup>(11)</sup>.

The mean pre-treatment serum CEA was significantly higher in malignant ovarian tumours in comparison with the other group (Table 1). This is in agreement with the finding of Inoue et al (1992)<sup>(9)</sup>.

After treatment serum CEA was found to have decreased in all tumour patients. The findings in this respect are comparable to those of previously reported studies<sup>(13)(14)</sup>.

## **REACTION OF OVIARTUMOURS TO CEA IMMUNOSTAIN**

In this current work, 12.5% of the benign ovarian tumours were positive for CEA tissue stained (Table II). Tohya et al

(1986)<sup>(15)</sup>, showed positive staining in 25% of the cases of benign ovarian tumours but all their studied cases were of mucinous type. Neunteufel and Britenecker (1989)<sup>(16)</sup>, reported a lower incidence (16.7%) of positive staining.

The technique of immunohistochemical staining used by these groups of investigators was the same as ours. Using different methods of tissue stain, Motoyama et al (1990)<sup>(17)</sup> found positive staining of benign ovarian tumours in 30.9% of the cases.

On the other hand, all the borderline ovarian tumours showed a negative reaction for CEA tissue staining (Table II). This result appears to be contradictory to the 55% positive staining of Tohya et al. (1986)<sup>(15)</sup>, 11% of Dietel et al. (1986)<sup>(14)</sup>, 31.25% of Neunteufel and Britenecker (1989)<sup>(16)</sup>, and 70% of Motoyama et al. (1990)<sup>(17)</sup>. The borderline lesions in the present study did not show definite CEA immunostaining. Again the small number of borderline lesions in the current investigation may account for the difference in our results and others.

As a whole, 90% of all the positively stained ovarian tumours were malignant (Table II). These results are consistent with the incidence of positive staining of ovarian carcinomas (45.45%) detected by Neunteufel and Britenecker (1989)<sup>(16)</sup>, using the same tissue staining technique.

Tohya et al. (1986)<sup>(15)</sup>, found positive staining in 100% of the cases of ovarian carcinomas but all the studied cases were of the mucinous type. Motoyama et al. (1990)<sup>(17)</sup>, reported positive staining of ovarian carcinomas in 37.79% of the cases but they employed methods of immunostaining different from that used in the present investigation.

The mean pre-treatment serum CEA in positively stained malignant ovarian tumours (13.2 ng/ml) was highly significant in comparison with the negatively stained ones (2.9 ng/ml) as observed in table (II). These findings are in agreement with those of Motoyama et al. (1990)<sup>(17)</sup>.

## **DEGREE OF POSITIVITY OF STAINING REACTION OF OVIARTUMOURS**

As shown in table (II), 12.5% of the benign ovarian tumours showed positive staining for CEA, all of them were in the (+1) degree of positivity. Charpin et al. (1982)<sup>(8)</sup>, showed a (+2) degree of positivity (same grading system of tissue staining reaction) but they used a different method of immunostaining and their cases were of the mucinos type

only.

Positive staining in malignant ovarian tumours was found in 42.9% of the studied cases, 33.3% of them had a (+1) degree of reaction, while the remaining 9.52% showed a higher level of positivity (+3) as shown in table (II). Charpin et al. (1982) (8), found that positively stained ovarian carcinomas were distributed between 3 levels of positivity as follows : 13.0% in (+1), 13.0% in (+2) and 6.5% in (+3). Although they had the same system of grading of tissue staining but they used a different technique of immunohistochemical staining. Motoyama et al.(1990) (17), found different percentage distributions of positively stained ovarian carcinomas among the various grades of positive staining reaction. However, direct comparison with their results is not possible because they used different grading system and staining techniques.

Among the negatively stained ovarian carcinomas 83.3% of the cases had negative pre-treatment serum CEA levels (< 5 ng/ml), and 16.7% had positive levels (> 5 ng/ml). Whereas, all the positively stained malignant ovarian tumours (+1 and +3 degrees) showed a positive pre-treatment serum CEA, after treatment all the studied ovarian carcinomas were seronegative for CEA. The association between the positivity of tissue stain for CEA and the positive serum levels was also proved by Motoyama et al. (1990) (17).

Although the mean pre- and post-treatment serum CEA were below the cut-off level of the present study in negatively stained ovarian carcinomas (degree "0"), yet the mean difference in serum levels were significant. An important finding which should be considered here is that 16.7% of negatively stained carcinomas had positive pre-treatment serum CEA levels (> 5 ng/ml). In the (+1) degree the result is comparable to those of Motoyama et al. (1990) (17), and is a logical outcome of the high mean pre-treatment and low mean post-treatment serum levels. As regards the (+3) level of positivity the mean difference in serum CEA levels were insignificant because of the small number of cases in this group.

In conclusion this study indicates that immunohistochemical identification of CEA in tumour tissue and of monoclonal antibodies quantitative measurement of CEA in human serum is a useful adjunct in the management protocol of patients with ovarian malignancies. However further studies are required to fully ascertain the utility of this technique.

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