

# Immunohistochemical Localization And Monoclonal Antibodies Quantitative Measurement Of Carcinoembryonic Antigen (CEA) In Cervical 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 cervical malignancies.

**Methods:** The study included 68 patients divided into three groups :Group A:20 patients with malignant cervical tumors; Group B: 12 patients with benign cervical lesions, Group C: 36 women without any gynaecologic disorder. Serum level of CEA was measured prior to treatment and following therapy. Formalin - fixed and paraffin - embedded tissue blocks taken from 2 different sites were prepared. Immunohistochemical staining for CEA was performed.

**Results:** The mean pre-treatment serum CEA values and the mean difference in serum levels were significantly higher in malignant cervical lesion. The mean pre-treatment serum CEA levels were significantly higher in positively stained lesions. The mean pre-treatment serum CEA levels was significantly higher in positively stained cases of squamous cell carcinomas The mean serum CEA Values before treatment were significantly higher in positively stained carcinomas in stage IIa (P 0.049).The mean difference between pre- and post-treatment serum CEA was significantly higher in positively stained carcinomas in stage IIa (P 0.01). the mean difference in serum CEA levels was significantly higher in stage IIb in comparison with stage I.

**In conclusion:** immunohistochemical identification of CEA in tumor tissue and monoclonal antibodies quantitative measurement of CEA in human serum may be a useful adjunct in the management protocol of patients with cervical malignancies.

## INTRODUCTION

An estimated 12,800 cases of invasive cervical cancer are expected to occur in the United States, with about 4,800 women dying from this disease. Worldwide, cervical cancer is the second or third most common cancer.<sup>(1)</sup>

The measurement of tumor-associated antigens as tumor markers in the serum is useful for early diagnosis, differential diagnosis, and the determination of remission after therapy in cases of malignancy. <sup>(2)</sup>.

Carcinoembryonic antigen (CEA) is one of the first known tumor 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>(3)</sup>

CEA expression may be a useful diagnostic tool and a useful marker for identifying those at risk for progressive cervical neoplasia.<sup>(4)(5)</sup>

In this work we try through the study of CEA in the serum and tissues to evaluate the significance of including this tumor marker in the management protocol of patients with cervical 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]: 20 patients with malignant cervical tumors, the majority of them were squamous cell carcinoma (18 cases)

;while cervical adenocarcinoma were only 2 cases.

**Group : 12 patients with benign cervical lesions,5 of them had endocervical polyps,2 with adenomatous hyperplasia, and 5 cases with normal cervical specimens without apparent histologic abnormalities obtained from removed uteri of leiomyoma bearing women.**

Group [C]: 36 women without any apparent gynaecologic disorder. They were age matched with the tumor 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:

Careful history, clinical examination and investigations

Clinical staging for malignant lesions in group A according to the International Federation of Gynaecology and Obstetrics (FIGO) staging systems (6).

Serum samples were collected from the patients in groups A and B 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 physical and cytological examinations of the cervix or vagina. A radiological examination was only performed if there was a clinical indication for it.

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.

Surgical specimens from tumors (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,Carpenteria,CA) for 60 minutes and with polyclonal enzyme (Dako Carpenteria,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 for 30-60 seconds.

According to Charpin et al (1982) (7)- 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 cervical tumors 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.

## RESULTS

The mean pre-treatment serum CEA values and the mean difference in serum levels were significantly higher in malignant cervical lesions in comparison with the benign ones .The mean difference between pre- and post – treatment

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serum CEA significant in malignant cervical lesions (P 0.001) (Table 1).

**Figure 1**

Table (1) : Mean values of serum CEA before and after treatment and the difference between them in the different types of cervical lesions.

Type of lesion	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	12	1.27 ± 1.04	b	0.82 ± 0.42	a	0.45 ± 0.77	b	0.22	2.01	0.070
Malignant	20	7.20 ± 3.72	a	1.26 ± 0.69	a	5.94 ± 3.36	a	0.75	7.91	0.001
Control group	25	1.02 ± 0.87	b							

S.D : Standard deviation P : Probability level  
S.E : Standard error T : Paired t : test  
dt : Duncan's multiple range t-test  
Means with the same letters are not significantly different at P=0.05

The mean pre-treatment serum CEA levels were significantly higher in positively stained lesions in comparison with the negative ones in both benign (P 0.01) and malignant (0.005) cervical lesions. After treatment these relations were statistically insignificant (Table 2)

**Figure 2**

Table (2) : Serum CEA before and after treatment in different types of cervical lesions according to their reaction to tissue stain.

Type of lesions	Reaction of tissue to CEA stain	No	Serum CEA before treatment						
			Mean ± S.D	S.E	T	df	P		
Benign	-ve	9	0.86 ± 0.70	0.23	3.2	10	0.01		
	+ve	3	2.50 ± 0.99	0.57					
Malignant	-ve	4	2.95 ± 0.79	0.40	3.08	18	0.005		
	+ve	16	8.27 ± 3.37	0.84					

S.D : Standard deviation df : Student's t : test  
S.E : Standard error P : Probability level  
T : Paired t : test  
dt : duncan's multiple range t : test  
Means with same letters are not significantly different at p = 0.05

**Figure 3**

Type of lesions	No	Serum CEA after treatment					Difference in serum CEA				
		Mean ± S.D	S.E	T	df	P	Mean ± S.D	S.E	T	df	P
Benign	9	0.69 ± 0.37	0.13	2.068	10	0.066	0.16 ± 0.56	0.19	2.79	10	0.019
	3	1.20 ± 0.36	0.21				1.30 ± 0.77	0.44			2.92
Malignant	4	0.97 ± 0.17	0.09	0.929	18	0.365	1.98 ± 0.96	0.48	3.23	18	0.005
	16	1.33 ± 0.75	0.19				6.94 ± 2.98	0.75			9.32

S.D : Standard deviation  
S.E : Standard error  
T : Paired t : test

There is a progressive increase in the mean pre-treatment serum CEA and the mean difference in serum levels with the increase in the degree of tissue stain of cervical carcinomas. The serum levels of negatively stained carcinomas were significantly lower than those with (+2) and (+3) degrees of tissue stain. Among the positively stained carcinomas the (+3) tumors had significantly higher serum levels than the (+1) tumors (Table 3).

**Figure 4**

Table (3) : Comparison of the mean values of serum CEA before and after treatment and the difference between them in the different of tissue stain of cervical 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	P
-ve	4	2.95 ± 0.76	c	0.97 ± 0.62	a	1.98 ± 0.100	c	0.48	4.137	0.026
+1	4	5.21 ± 1.54	bc	0.84 ± 0.62	a	4.38 ± 1.66	bc	0.83	5.272	0.013
+ve	5	8.03 ± 4.23	ab	1.21 ± 0.79	a	6.82 ± 3.96	ab	1.77	3.858	0.018
*+3	7	10.17 ± 2.17	a	1.69 ± 0.68	a	8.48 ± 1.79	a	0.68	12.516	0.001

\* : Malignant cervical lesions with (+ 3) and (+4) levels of positivity are included in this group as the serum values of the single case present in (+4) level can not be analysed statistically.  
S.D : Standard deviation T : Paired t : test  
dt : duncan's multiple range t : test  
Means with same letters are not significantly different at p = 0.05

The mean pre-treatment serum CEA levels were significantly higher in positively stained cases of squamous cell carcinomas in comparison with their negatively stained counterparts (P 0.046). (Table 4)

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**Figure 5**

Table (4): Serum CEA before and after treatment in the negative and positive tissue stain groups of each histological type of cervical lesions.

Histological type of cervical lesions	Reaction to CEA stain	No.	Serum CEA before treatment					Serum CEA after treatment				
			Mean ± S.D	S.E	T	df	P	Mean ± S.D	S.E	T	df	P
His -1	-ve	5	1.21 ± 0.80	0.36				0.66 ± 0.50	0.23			
	+ve	-	-	-	-	-	-	-	-	-	-	-
His -2	-ve	2	0.32 ± 0.04	0.03				0.87 ± 0.1	0.07			
	+ve	3	2.49 ± 0.99	0.57	2.966	3	0.059	1.20 ± 0.36	0.21	1.23	3	0.306
His -3	-ve	2	0.53 ± 0.02	0.02				0.60 ± 0.00	0.00			
	+ve	-	-	-	-	-	-	-	-	-	-	-
His -4	-ve	2	2.97 ± 0.33	0.23				0.91 ± 0.12	0.09			
	+ve	16	8.27 ± 3.37	0.84	2.166	16	0.046	1.33 ± 0.75	0.19	0.766	16	0.465
His -5	-ve	2	2.42 ± 1.33	0.44				1.03 ± 0.25	0.18			
	+ve	-	-	-	-	-	-	-	-	-	-	-

T : Student's t : test  
 dt : duncan's multiple range t : test

His-1 : Normal cervical tissue  
 His-2 : Endocervical polyp  
 His-3 : Cervical adenomatous hyperplasia  
 His-4 : Squamous cell Carcinoma  
 His-5 : Adenocarcinoma

**Figure 6**

Histological type of cervical lesions	Reaction to CEA stain	No.	Difference in serum CEA									
			Mean ± S.D	S.E	T	df	P	t	P	Mean	S.D	dt
His -1	-ve	5	0.55 ± 0.40	0.18				3.09	0.037	0.95	0.40	b
	+ve	-	-	-	-	-	-	-	-	-	-	-
His -2	-ve	2	0.55 ± 0.14	0.10				5.59	0.113	0.56	1.15	b
	+ve	3	1.30 ± 0.77	0.44	3.205	3	0.049	2.92	0.100			
His -3	-ve	2	0.07 ± 0.02	0.01				5.07	0.124	0.07	0.02	b
	+ve	-	-	-	-	-	-	-	-	-	-	-
His -4	-ve	2	2.06 ± 0.45	0.32				6.49	0.097	6.49	3.21	a
	+ve	16	6.94 ± 2.98	0.75	2.252	16	0.039	9.31	0.0001			
His -5	-ve	2	1.89 ± 1.58	1.12				1.69	0.341	1.89	1.58	b
	+ve	-	-	-	-	-	-	-	-	-	-	-

The mean serum CEA Values before treatment were significantly higher in positively stained carcinomas in stage Iia (P 0.049) in comparison with the negatively stained ones. No significant difference between positively and negatively stained carcinomas in stage Iia. The mean difference between pre- and post-treatment serum CEA was significantly higher in positively stained carcinomas in stage Iia (P 0.01) in comparison with the negative ones. The mean difference between pre- and post-treatment serum CEA was

significant in positively stained carcinomas in the different clinical stages (Table 5). The mean pre- and post-treatment serum CEA showed no significant difference between the different clinical stages, while the mean difference in serum CEA levels was significantly higher in stage IiB in comparison with stage I (Table 5).

**Figure 7**

Table (5) : Serum CEA before and after treatment in the negative and positive tissue stain groups of each clinical stage of cervical carcinomas.

Clinical Stage	Reaction to CEA stain	No.	Serum CEA before treatment					Serum CEA after treatment				
			Mean ± S.D	S.E	T	df	P	Mean ± S.D	S.E	T	df	P
I	-ve	1	1.976	-				1.21	-			
	+ve	3	6.65 ± 2.25	1.3				1.38 ± 0.65	0.37			
Iia	-ve	2	2.97 ± 0.33	0.23				0.91 ± 0.12	0.08			
	+ve	3	7.90 ± 2.05	1.28	3.207	3	0.049	1.87 ± 0.59	0.34	2.163	3	0.119
IiB	-ve	1	3.86	-				0.85	-			
	+ve	10	8.86 ± 3.94	1.24				1.15 ± 0.80	0.25			

T : Student's t : test  
 dt : duncan's multiple range t : test

Means with the same letters are not significantly different at p = 0.05

**Figure 8**

Clinical Stage	Reaction to CEA stain	No.	Difference in serum CEA								
			Mean ± S.D	S.E	T	df	P	t	P		
I	-ve	1	0.77	-				-	-		
	+ve	3	5.27 ± 1.79	1.03				5.096	0.0364		
Iia	-ve	2	2.06 ± 0.45	0.32				6.487	0.0974		
	+ve	3	6.02 ± 1.46	0.84	3.557	3	0.038	7.145	0.019		
IiB	-ve	1	3.006	-				-	-		
	+ve	10	7.71 ± 3.43	1.08				7.115	0.0001		

## DISCUSSION

All the benign cervical lesions had negative pre-and post – treatment serum CEA (<5 ng/ml) whereas 65% of malignant cervical lesions showed positive pre-treatment serum levels (>=5 ng/ml). While a range of 24-69% was found in the literature.(8)(9)(10)(11)(12)

The mean pre-treatment serum CEA was significantly higher in malignant cervical tumors in comparison with the other 2 groups. Similar results had been also observed by previous investigators.(8)(9)(13)(14)

After treatment an obvious drop in the mean serum CEA was observed in the benign and malignant cervical lesions. The

significant drop of post – treatment serum CEA within normal limits was also observed by others.(11)(15)

### **REACTION OF CERVICAL LESIONS TO CEA IMMUNOSTAIN:**

In the present work 75% of the benign cervical lesions were negative for CEA tissue stain and only 25% were positive. Speers et al (1983)(16), found positive staining in 5% of the cases of benign cervical lesions, but all their studied group were cervical microglandular hyperplasia. On the other hand, Hurlimann and Gloor (1984)(17), working on the same type of cervical lesion (microglandular hyperplasia) did not find any positive cases.

On the other hand, the malignant cervical tumors showed 80% positivity for CEA tissue stain. Lindgren et al (1979)(18) and Van Nagell et al (1982)(19), studied positive staining in cervical squamous cell carcinomas only and they found positive results in 66.35% and 57% of the cases respectively. but the antisera they used for tissue staining was different from that of the present work.

Bychkov et al (1983)(20), using our technique of tissue staining found positive staining in 88% of the cases of cervical squamous cell carcinomas. On the other hand, previous investigator studied cervical adenocarcinomas only and reported positive staining in 96%(4), 80%(21), 73%(22), and 55%(23) of the cases. The variation in results may be due to the difference in the staining procedures., or due to the irregular distribution of CEA in tissue leading to variable results of tissue staining specially if the analyzed sample was small.(17)

The mean pre-treatment serum CEA was significantly higher in tumors having positive staining reaction. These findings are in agreement with those of previous investigators.(22)(24)

According to these findings, it is expected that positively stained lesions will have higher serum CEA levels in comparison with the negative ones. However, this does not exclude that negatively stained lesions may produce CEA but their level of production is below the threshold detectable by the method of staining.

### **DEGREE OF POSITIVITY OF STAINING REACTION OF CERVICAL LESIONS:**

25% of benign cervical lesions had positive tissue staining for CEA, Comparable results were reported by previously.(16)

Others could not find a definite pattern for the distribution of positively stained cervical squamous cell carcinomas among different levels of positivity of tissue staining reaction.(17)(19)(20)(24)(25)

In the positively stained carcinomas there was a progressive increase in the percentage of cases with positive serum levels with the increase in the level of positivity of tissue reaction. After treatment the serum levels of all the studied cases were negative. These results are comparable to those of previous investigator.(24)(26)

### **HISTOLOGICAL TYPE OF CERVICAL LESIONS:**

The different histological types of benign cervical lesions had negative pre- and post – treatment serum CEA. Braun et al (1981)(27), found positive pre-treatment serum (>10 mg/ml) in 3.28% of the benign conditions they studied; but their benign group included ovariian, endometrial, breast and colonic conditions beside the cervical ones.

All the studied cervical adenocarcinomas and 27.78% of squamous cell carcinomas had negative pre-treatment serum values. Van Nagell et al (1978)(28), found an incidence of 68%. The frequency of positive cases in the study of Fritsche et al (1982)(9) was 34.28% but their cut-off level was 10 mg/ml. Meier et al (1990)(11) showed positive pre-treatment serum CEA (>3 mg/ml) in 53.85% of the cases of squamous cell carcinoma.

While Leminen (1990)(10) detected abnormal pre-treatment serum level (>3 mg/ml) in 33% of cervical adenosquamous carcinomas. The method of serum assay used by Leminen (1990)(10) and Meier et al (1990)(11) was different from that of the present work. As regards cervical adenocarcinomas variable incidences of positive pre-treatment serum CEA were reported by different authors, they showed positive value in 36% (10), 100%(11), 40%(28), and 67%(29) of the cases. After treatment the mean serum levels of CEA were negative for all the studied cases of cervical carcinomas in the current study. Comparable results were also reported.(14)(15)

The present study showed an increase in the percentage of cases with the increase in the level of positivity of tissue stain except in (+4) level which included only one case. Previous investigators did not find this relation but they used a grading system different from that of the current study.(17)(19)(20)(24). However, Nanbu et al (1988)(25), showed an increase in the percentage of cases of cervical

adenocarcinomas with the increase in the level of positivity of tissue staining.

The benign cervical lesions examined in the present work were negative for CEA tissue stain except for 60% of the cases of endocervical polyps which were positive at (+1) level of positivity. Previous investigators did not find a reaction of normal cervical tissue to CEA immuostain.(17)(25)(26)(29) Ogawa et al (1992)<sub>(30)</sub> noted, faint expression of CEA in normal squamous epithelium of the cervix and they did not consider it a positive reaction. Some of the positively stained cervical squamous cell carcinomas had negative serum levels. This results can be explained on the basis of the observation of Kjorstad and Orjasaester (1984)<sub>(31)</sub>, that some of the primary tumors although containing the antigen they did not release it. They considered these tumors as non-releasers than non-procedures.

### **CLINICAL STAGING OF CERVICAL CARCINOMAS:**

In the present study there is an observable progressive increase in the percentage of cases of cervical carcinomas with a positive pre-treatment serum CEA with the advance of clinical stages. Similar results were also reported.(10)(13)(31)<sub>(32)</sub>

The percentage of positively stained cervical carcinomas in the clinical stages did not show a specific pattern of relation. Comparable results were reported.(18)(25)

Also no definite relation could be detected on studying the distribution of positively stained carcinomas in the different clinical stages on different levels of positivity. The same findings were reported previously.(17)(25)

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