Clinical Significance of Plasma CEA Levels in the Patients with Cervical Carcinoma during Follow-Up

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Carcinoembryonic antigen (CEA) has been studied in the field of gynecologic malignancy to determine whether it can be used as a tumor marker for early detection of recurrence or evaluation of therapeutic results. From January 1985 through December 1989, a total of 239 cervical cancer patients were entered for an analysis of plasma CEA level in the group with cervical cancer compared to the control group consisting of 65 normal healthy women and 18 women with benign gynecologic disease.

Plasma CEA levels appear to be directly related with the tumor extension and as stages advance, the incidence of patients with abnormal plasma CEA levels is increased.

Also, there seems to be a little higher incidence of abnormal CEA levels in patients with adenocarcinomas or adenosquamous carcinoma but not statistically significant because of small number of patients.

When the patients developed recurrence, plasma CEA levels are markedly elevated in the majority, particularly in patients with hepatic metastases. In conclusion, serial plasma CEA checks could be used to detect recurrence during follow-up after treatment of cervical cancer.

Key Words: CEA, cervix cancer

INTRODUCTION

Since Gold and Freedman[1,2] first reported CEA, a tumor associated antigen in 1965 within the tissue extracts from adenocarcinoma of the colon and in fetal colonic mucosa, many investigators have reported elevated levels of this antigen in patients with malignancies both of endodermal[3~5] and nonendodermal[6~8] origin and benign conditions such as bronchitis, liver cirrhosis, inflammatory bowel diseases, emphysematous lung diseases, obstructive biliary tract diseases and chronic renal failure.

Thereafter, CEA has been studied extensively in gynecologic malignancies and has been reported to be elevated in the serum of 30% to 65% of ovarian cancer[9~11] 43% to 69% of cervical cancer[9,12~20], 32% to 63% of endometrial cancer[9,11,18] and 33% to 57% of vulvar cancer[9,11,21].

Although the lack of cancer specificity[22] of CEA has limited its use as an effective diagnostic method, much interest has been expressed concerning its possible role as a biochemical marker for detection of subclinical recurrences following therapy.

This study was undertaken to determine the followings;

1) The incidence of elevated plasma CEA levels in patients with invasive cervical cancer.

2) The usefulness of serial CEA determinations in the follow-up after treatment with surgery and/or radiotherapy of patients with carcinomas of the cervix to detect recurrent disease.

MATERIALS AND METHODS

Subjects for this analysis were 239 patients with invasive cervical cancer who were evaluated and treated at the department of Radiation Oncology, Korea University Hospital from Jan. 1985 to Dec. 1989.

All the patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) after work up which FIGO recommended.

With the aid of computerized axial tomography, we can evaluate tumor size, extension, pelvic and para-aortic lymph node status more effectively. Each tumor was classified histologically as large cell nonkeratinizing, keratinizing squamous cell carcinoma, adenocarcinoma, small cell carcinoma and adenosquamous cell carcinoma according to the criteria of Reagan et al[24].

Fifty four patients with stage I and an additional seven patients with stage IIA and B were treated by radical hysterectomy with or without intracavitary irradiation or a combination of two treatments due to high risk of local recurrence after pathological examination.

The remaining patients were all treated with radiation therapy alone. The techinques of radiation therapy have been previously reported[24] and will be described briefly.

External irradiation was given from a Cobalt-60 teletherapy unit, Patients with I and IIA with small primary lesion were treated initially with external pelvic irradiation with tumor dose of 20~30 Gy in 2.5~3.5 weeks and then intracavitary insertion was performed using Fletcher-Suti Delclos applicator with Cesium-137 sources and followed by external irradiation of 10~20 Gy/1.5~2.5 weeks with midline shielding.

Patients with more advanced disease received 54 Gy/6 weeks of external therapy, followed by intracavitary Cesium applications.

Thus total tumor and paracervical doses varied from 80 to 100 Gy and 50 to 70 Gy respectively.

Plasma CEA quantitative determinations were done by Pharmacia CEA radioimmunoassay kit which is a two-site immunoradiometric assay using two different antibodies in excess. 3 ml of blood were drawn into tube and centrifused for the plasma.

During first incubation, CEA in the sample reacts with anti-CEA-^{125}I antibodies (raised in rabbit). The formed CEA-anti-CEA-^{125} I-comples is separated from excess tracer by addition of anti CEA-antibodies (raised in sheep) and double antibody immunoadsorbent followed by centrifugation and decanting.

The radioactivity in the pellet is then measured. The radioactivity is directly proportional to the concentration of CEA in the sample. If the sample contains more than 100 ng/ml of CEA, it should be diluted for accurate determination. The lowest detection limit was 0.05 ng/ml and the upper limit of normal plasma CEA value was taken for 2.5 ng/ml.

Sixty-five healthy women and 18 patients with benigh gynecologic disease served as the normal control group.

The follow-up visits were scheduled every 1-3 months during the first two years and every 4-6 months thereafter. Patients suspected of persistent or recurrent cancer were seen more frequently. In addition to pelvic and physical examination, a smear from the cervix or vaginal vault was taken and biochemical screening (liver function and CBC) and plasma CEA check were done at each visit. When serial CEA values or symptoms suggested recurrence, ultrasound examination, bone scan and abdominopelvic CT scan were performed to detect recurrent disease.

Six patterns of serial CEA values were derived by comparing post-treatment levels with pretreatment values and comparing follow-up levels with post-treatment or previous follow-up values.

RESULTS

1. Pretreatment CEA Levels

Of the 239 patients studied in this analysis, only 188 patients were eligible for pretreatment CEA analysis because the remaining 51 stage I patients who were treated with operation plus radiation

Table 1. The Ranges of Carcinoembryonic Antigen Values in the Patients and Controls

	Total Patients	CEA values (ng/ml)				
		< 2.5	2.5–4.9	5.0–9.9	10–20	> 20
Healthy Women	65	63 (97%)	2 (3%)	0	0	0
Benign Gynecologic Diseases	18					
PID	2	2 (100%)	0	0	0	0
Myoma Uteri	13	12 (92%)	1 (8%)	0	0	0
Ovarian Cyst	3	3 (100%)	0	0	0	0
Invasive Cervix Cancer	188	74 (40%)	41 (22%)	44 (23%)	20 (11%)	9 (5%)

therapy did not have preoperative CEA values.

Plasma CEA levels prior to treatment were elevated (>2.5 ng/ml) in 60% of the patients with cervical cancer, whereas 3% of healthy women and 5.5% of patients with benign gynecologic diseases had CEA values greater than 2.5 ng/ml. (Table 1). The difference in the incidence of elevated CEA levels between patients with cervical cancer and healthy women or patients with benigh gynecologic diseases was statistically significant in mean values of CEA levels by student t-test (P value=0.008). The sensitivity of plasma CEA in patients with cervical cancer was 60.6% and specificity was 96.4%. Carcinoembryonic antigen values greater than 5.0 ng/ml were obtained in 39% of patients with cervical cancer and no one had CEA values greater than 5 ng/ml in the control group. There was no significant age difference of patients who had elevated plasma CEA levels and those who had normal plasma levels of antigen.

As seen in Fig. 1, abnormal plasma CEA levels in cervical cancer patients ranged from 2.5 ng/ml to 533 ng/ml (Mean=6 ng/ml), and in the control group, plasma CEA levels were 0.84~3.5 ng/ml (Mean=1.59 ng/ml). The incidence of elevated plasma CEA level was directly related to the stage or extent of disease. (Table 2) 41.2% of patient with stage I had increased plasma CEA values, whereas more than 60% of patient with advanced disease had elevated CEA levels.

The correlation between elevated plasma CEA titers and cell types is presented in Table 3. Among the 188 patients eligible, 19 patients were excluded in the analysis of pathologic classification because they were transferred from other clinics without information about histologic classification. Plasma CEA levels were more consistently elevated in patients with endocervical adenocarcinoma or adenosquamous cell carcinoma subtypes than in patients with squamous cell carcinoma varieties (Table 3). Within 3 subtypes of squamous cell carcinoma, CEA levels were more often elevated in large cell nonkeratinizing type than keratinizing or small cell type (64.6% vs 56.2%, 25%). This difference was not statistically significant.

2. Serial CEA Determination

Of the 188 Patients eligible for analysis of pretreatment CEA values, 88 patients had serial CEA determinations during follow-up which ranged from 3 to 55 months (mean: 26 months, median: 24 months) after completion of therapy or until patients experienced recurrences. The average number of CEA determinations was 6 times and

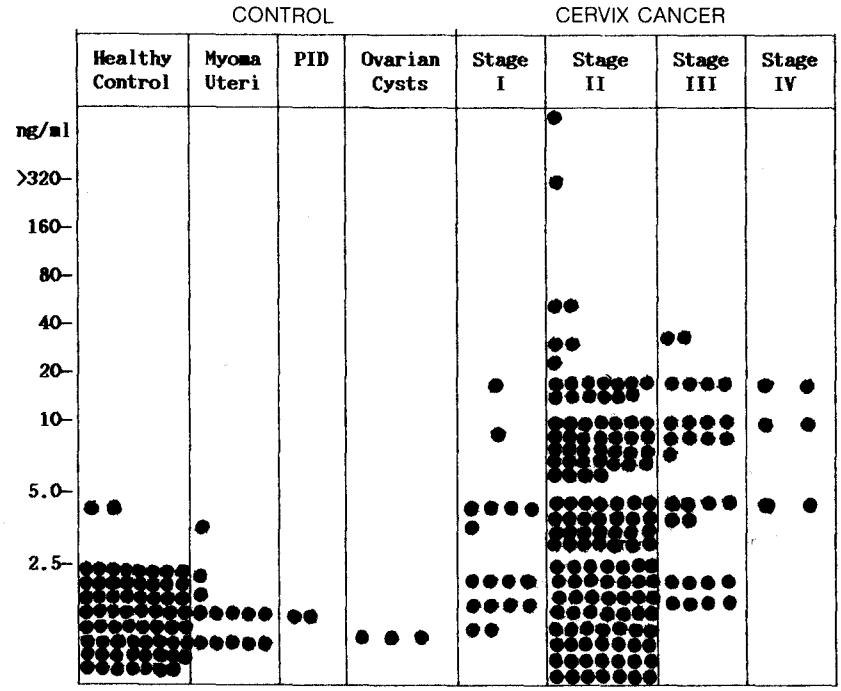

Fig. 1. Distribution of CEA Values for 188 Patients with Cervical Cancer prior to Radiatherapy and 83 Normal Controls.

Table 2. Distribution of Carcinoembryonic Antigen Values by the Stages

Stage	No. of Patients	CEA values (ng/ml)				
		< 2.5	2.5–4.9	5.0–9.9	10–20	> 20
IA & B	17	10 (59%)	5 (29%)	1 (6%)	1 (6%)	0 (0%)
IIA	37	14 (38%)	9 (24%)	9 (24%)	3 (8%)	2 (5%)
IIB	99	42 (42%)	19 (19%)	23 (23%)	10 (10%)	5 (5%)
IIIA	13	3 (23%)	2 (15%)	4 (31%)	2 (15%)	2 (15%)
IIIB	16	5 (31%)	4 (25%)	5 (31%)	2 (13%)	0 (0%)
IVA	3	0 (0%)	1 (33%)	1 (33%)	1 (33%)	0 (0%)
IVB	3	0 (0%)	1 (33%)	1 (33%)	1 (33%)	0 (0%)
Total	188	74 (40%)	41 (22%)	44 (23%)	20 (11%)	9 (5%)

Table 3. Distribution of Carcinoembryonic Antigen Values by Cell Types

Cell Type	No. of Patients	CEA values (ng/ml)				
		< 2.5	2.5–4.9	5.0–9.9	10–20	> 20
LCNK	82	29 (35%)	19 (23%)	19 (23%)	11 (13%)	4 (5%)
LCK	73	32 (44%)	16 (22%)	14 (19%)	7 (10%)	4 (5%)
Small Cell	4	3 (75%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)
Adeno	4	1 (25%)	1 (25%)	2 (50%)	0 (0%)	0 (0%)
Adenosqu	6	0 (0%)	2 (33%)	2 (33%)	1 (17%)	1 (17%)
Total	169					

LCNK : Large cell non-keratinizing, LCK : Large cell keratinizing, Adeno : Adenocarcinoma, Adenosqu : Adenosquamous cell carcinoma

Table 4. The Change Patterns of Serial CEA Values in the 88 Patients and Rate of Recurreuce

Pattern#	No. of Recurrence 28.5% (25/88)	No. of No-recurrence 71.5% (63/88)
L– L– L	2 (8%)	27 (43%)
H– L– L	1 (4%)	29 (46%)
L– H– L	0 (0%)	1 (1.5%)
H– L– H	9 (36%)	6 (9.5%) *
H– H– H	9 (36%)	0 (0%)
L– L– H	4 (16%)	0 (0%)

: Refer to explanation in text

* : 4 patients with follow-up period of 14–32 months and 1 patient with heavy-smoking (36 months), 1 patient with GB stone (18 months)

ranged from 2 to 12. In 88 patients (25 recurrences and 63 non-recurrences) longitudinal CEA patterns were analyzed. The following 6 patterns emerged: (1) continuously low CEA levels (designated as LLL); (2) high pretreatment, low post-treatment and low follow-up values (HLL); (3) low pretreatment, high post-treatment and low follow-up values (LHL); (4) high pretreatment, low post-treatment and rising follow-up values (HLH); (5) continously high CEA levels above normal value (HHH) (6) low pretreatment, low post-treatment and rising follow-up values (LLH).

The 6 patterns and the number of patients with recurrences and non-recurrences are shown in Table 4. The majority of non-recurrence patients (59/63) was distributed among the first 3 patterns (LLL, HLL, LHL), whereas patients with recurrence were present in the remaining 3 patterns (HLH, HHH, LLH) (20/25). Six patients without recurrence were present in HLH. One patient in this pattern is a heavy-smoker without evidence of disease after 36 months follow-up. Another patient was clinically free but recently noticed a gall bladder stone which

might explain a rising CEA level.

The remaining 4 patients have not yet had sufficient follow-up time (less than 24 months except one patient with 32 months).

Interestingly, there were no patients without recurrence in pattern HHH and LLH.

The time elapsed when the abnormal pretreatment plasma CEA levels returned to normal following therapy was dependent on the therapeutic method used. For the patients in the HLL and HLH patterns, pretreatment plasma CEA levels returned to normal within 4 weeks after completion of radiotherapy for 51% of patients (23/45) and plasma CEA levels of remaining patients returned to normal between 8 weeks and 80 weeks. Overall, the average time for abnormal pretreatment CEA levels to normalize was 11.2 weeks. (range: 4~80 weeks) The relationship between pretreatment CEA level and the incidence of recurrence or persistent disease was analyzed. Of a total of 25 patients with recurrence, pretreatment plasma CEA levels were elevated in 76% (19/25) of patients, whereas, 56% (35/63) of the patients without recurrence had elevated plasma CEA values.

There was no significant difference by chi-square test (P value=0.13) but analyses showed abnormal pretreatment plasma CEA values were related with increased incidence of recurrences. Most of recurrent disease were documented by levels showed continuous rising values or patients complained of symptoms or signs suggestive of recurrence except supraclavicular neck node recurrences which were confirmed pathologically.

Analysis between plasma CEA levels before or at the time of recurrence and sites of recurrence is illutrated in. Plasma CEA levels were elevated in 91% (20/22 recurrence sites) with extrapelvic sites and in 85% (11/13 sites) with pelvic recurrent sites. And, CEA values (>5.0 ng/ml) were higher in extrapelvic than pelvic recurrent site (73% vs 46%).

Specifically, plasma CEA seemed to be most consistently elevated when cervical cancer had metastasized to the liver, bone or lung.

The highest absolute plasma concentrations occured in the presence of hepatic metastasis.

Plasma CEA levels in 2 patients with hepatic metastasis were 28.3 and 305 ng/ml respectively.

Fifty-four stage I patients were treated primarily with radical hysterectomy with or without pelvic lymphadenectomy and received pelvic irradiation.

Of those, only 3 patients had pretreatment CEA values and were included in the analyses. Postoperative CEA values, which were usually checked within 4-6 weeks after operation, were within upper normal limit in 92% (50/54) of these patients. 26 patients have been followed with serial CEA determinations and 4 patients had recurrent disease with marked increased plasma CEA levels except one

Table 5. Carcinoembryonic Antigen Values by the Site of Recurrence

Sites of Recurrence	No. of pts	CEA values (ng/ml)				
		< 2.5	2.5–4.9	5.0–9.9	10–20	> 20
Pelvic	13					
Parametrium	5		3		1	1
Pelvic wall	4	1	1	1	1	
Vagina	1	1				
Uterus	1				1	
Rectum	2		1		1	
Extrapelvic	22					
Liver	2					2@
Lung	5	1	2	1		1#
Bone	1					1
Nodes	14	1	2	1	6	4
Total*	35					

* Included 4 patients who were treated with operation plus postoperative radiotherapy. 5 patients showed 2 sites of recurrence concurrently at CEA measurement.

@ CEA values of 28.3 and 305, # CEA value of 257 ng/ml.

patient who had recurrent disease on the vaginal stump.

DISCUSSION

The search for circulating tumor-specific antigen in human malignancies has been the object of investigation for many years and recently focused on the glycoprotein and glycolipid components present in the normal cell membrane. It was however, detectable at increased levels in the serum of patients with malignancies for early diagnosis and evaluation of therapeutic effects of cancers. Since Gold and Freedman[1,2] first reported cancer-associated antigen, CEA in 1965 within the tissue extracts from adenocarcinoma of the colon and fetal colonic mucosa, elevated levels of CEA were reported in endodermal[3~5] and nonendodermal[6~8] origin malignancies as well as in benign[25~28] conditions. In 1971, elevated CEA levels were first reported by Logefo et al[4]. Thereafter, various immunologic techniques[29] have shown the presence of at least one antigen associated with the invasive state. Of these antigens CEA has been localized on the squamous cervical cancer cell membrane[30] and investigated thoroughly about this tumor marker.

The incidence of elevated pretreatment plasma CEA level in invasive cervical cancers was reported to be from 43% to 70% which corresponds with our results (61.4%). However, when we adopt the upper normal limit of CEA value as more than 5 ng/ml, the percentage of elevated plasma CEA level in cervical cancer patients decreases to 39.1%. This cut-off level of plasma CEA between patients with cervical cancer and the normal population is very important to interpret results correctly. For this purpose we used control groups which included 65 healthy women and 18 patients with benign gynecologic diseases. Plasma CEA levels in control groups ranged from 0.84 to 3.5 ng/ml and the mean value was 1.59 ng/ml.

The percentage of elevated plasma CEA levels in the control groups of our analysis was 3.6% (3/83), and other investigators[12,16,18] reported 5.6 ~13% positivity.

As expected, there was significant difference in CEA level positivity between patients with cervical cancer and control groups (P value=0.008). To determine a reasonable cut-off value for plasma CEA level, we used histograms in both groups and revealed 95 percentile of control group was 2.4 ng/ml, but no such value showed in study group because diffuse distribution of CEA values.

Immunocytochemical study[31] of carcinoembryonic antigen in cervical cancer tissues showed that nearly all noninvasive and invasive squamous lesions were positive but there was some variation in severity of staining.

Degree of positive staining for CEA depended to some extent on the cellular subtypes of invasive carcinomas. For instance, small cell carcinomas frequently lacked stainable CEA, while large cell nonkeratinizing carcinomas showed a stronger reaction than their keratinizing counterparts. Especially, adenocarcinomas of the endocervix showed moderate to strong reaction for CEA[32]. The relationship between cell types and plasma CEA level was analyzed by van Nagell et al[12,15]. Their results showed 48% of keratinizing and nonkeratinizing squamous cell carcinomas had elevated CEA values. Plasma CEA levels were more consistently elevated in patients with endocervical adenocarcinomas than in patients with squamous cell carcinoma. Our results illustrated in Table-3 were similar to those of van Nagell et al even though small numbers of patients with adenocarcinoma, small cell carcinoma and adenosquamous cell carcinoma in each category precluded meaningful statistical analysis.

However, the general lack of correlation between tissue CEA positivity and plasma CEA levels emphasized that many factors including the number of CEA producing tumor cells, host metabolism of CEA and antigen excretion, are related to plasma concentration[33].

For example, plasma CEA levels were related more to total tumor burden than to tumor CEA concentration alone. As seen in Table-2, there is a progressive increases in the percentage of patients with abnormal values as stage increases from 41.2% in stage I to 83.3% in stage IV. Many authors reported the same trend[9,12,14~17,19,34,35].

As seen in Table 4, when recurrent diseases developed, plasma CEA levels were elevated in the majority of patients (22/25, 88%). On the contrary, 90% (57/63) of nonrecurrent patients had normal CEA values during follow-up whether the pretreatment CEA values were abnormal or not. Even though gradual rising of post-treatment CEA values was an important clue to perform various clinical and radiologic studies to detect recurrence site except supraclavicular nodes which we could evaluate easily, such finding may be of potenital clinical importance in detection of recurrences by serial CEA determinations. However, pretherapy plasma

CEA levels were of no value in predicting which patient would develop recurrence.

Velde et al[34] showed that 50% of patients with recurrences had normal pretherapy plasma CEA values. In our analysis 19 out of 25 patients with recurrence had abnormal pretherapy values, and the difference between the incidence of recurrence and abnormal plasma pretreatment CEA values was not significant statistically. We also found some interesting observation. First, 4 patients with LLH pattern developed recurrences. By van Nagell's[15] analysis, one-third of the patients experiencing rapid increase in plasma CEA concentration did not have levels above 2.5 ng/ml prior to therapy and this might represent small tumor burden (early stage).

As the recurrent diseases developed with increased tumor burden they showed abnormally increased CEA values. However, the stage of the 4 patients in this pattern was II(3) and III(1) and did not correspond with the above suggestion. The second observation, also observed by Khoo and Mackay[36,37], of a persistence of an elevated CEA level even after a good clinical response to radiotherapy as in HLH pattern of our analysis, is difficult to explain. But it might be due to a residual nonproliferating tumor or to the release of CEA by cancer cells undergoing postactinic necrosis.

These patients should be followed for a longer period of time to determine whether the CEA level will drop progressively with the slow regression of the tumor, or if CEA levels were elevated persistently which means the presence of residual tumoral tissue and might subsequently cause a relapse of the disease, although the follow-up time in these 4 patients were 14, 16, 24 and 32 months respectively. Therefore, a prolonged follow-up period is necessary for the correct assessment of a potential tumor marker in invasive cervical cancer. With insufficient follow-up time, slow occult tumor growth may incorrectly be identified as a nonrecurrence case.

Several[9,15,18,19,37~39] authors analyzed serial CEA levels with follow-up ranging from 7 weeks to 5 years. Only 1 analysis[15] has been followed for more than 24 months.

The third observation was that absolute CEA level when recurrent disease developed was dependent on the site of recurrence as illustrated on Table 5. Higher values were obtained when cervical cancer metastasized to extrapelvic site compared to the pelvis. The highest absolute CEA value with hepatic metastasis in this analysis, which was observed by van Nagell[15], may be explained by Shuster's[40] experiment with radiolabeled CEA in rabbits and dogs in which he suggested that serum CEA is rapidly removed from the circulation by the liver.

The pattern of decline of pretreatment plasma CEA levels was dependent on the type of treatment utilized. As Khoo et al[36] observed, abnormal plasma CEA levels returned to normal within 4-6 weeks after complete surgical removal of tumors. This was in marked contrast to that of decline following radiation therapy. Unfortunately, most of the patients who were treated primarily with operation did not have preoperative CEA levels but postoperative CEA usually checked within 6 weeks after operation which showed that only 6 patients had abnormal values. Whereas, only 51% of the radiation therapy group, CEA values were normalized within 4 weeks after completion of radiotherapy. This difference has been attributed to the protracted release of membrane-associated antigen after radiation-induced cell damage, where, the surgery induced the abrupt removal of the antigen source.

Because CEA has low tumor specificity, it had not been used as a diagnostic tool. However, it can be suggested that by serial CEA determinations, we can detect recurrent disease as early as possible and salvage patients with recurrence by applying additional radiotherapy and/or systemic chemotherapy. Furthermore, in patients with abnormal pretreatment CEA values, high incidence of recurrence can be predicted, so close monitoring of posttreatment CEA is mandatory. It is our policy to regularly obtain serial CEA values in addition to radiologic studies including abdomino-pelvic CT and sonogram.

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= 국문초록 =

자궁 경부암 환자의 추적검사시 혈장내 CEA치 측정의 임상적 의의

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CEA 측정으로 부인과 영역악성종양의 치료결과나 재발 여부의 조기진단을 할 수 있나를 연구한 결과이다.

1985년 1월부터 1989년 12월까지 239명의 자궁경부암 환자를 대상으로 치료전과 치료후 CEA치를 체계적으로 측정했고 이를 비교하기 위하여 정상군으로 아무런 증상이 없는 건강한 부인 65명과 양성종양을 가진 18명의 부인을 상대로 CEA치를 측정하였다.

혈장내 CEA치는 종양의 진행정도와 기의 직접관계가 있는 것을 알 수 있고 종양의 기가 진행되면 될수록 CEA치가 비정상인 경우가 높아지고 있다.

또한 CEA치가 비정상인 경우 편평상피종 환자보다는 선세포나 선세포와 편평세포가 혼합된 경우 더욱 증가되는 것을 볼 수 있었다.

결론으로 혈장내 CEA을 체계적으로 측정함으로써 치료 끝난 후 추적검사시 재발의 조기발견 및 치료결과를 확인할 수 있는 좋은 방법이라는 결론을 얻었다.