Variations of the carcinoembryonic antigen level in the plasma of patients with gynecologic cancers during therapy

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In 63 patients with histologically proved gynecologic carcinoma, circulating carcinoembryonic antigen (CEA) was determined by radioimmunoassay before and at two intervals after treatment. Thirty-one patients of 63 had CEA values over 2.5 ng. per milliliter before treatment. In general, the CEA levels were low compared to those found in endodermal carcinoma. The percentage of elevated CEA values was slightly higher in cases of carcinoma of the cervix and corpus uteri than in those of carcinoma of the ovary. All patients with CEA levels greater than 2.5 ng. per milliliter treated by complete surgical resection of tumor showed a drop of CEA levels to below 2.5 ng. per milliliter seven weeks after operation. In contrast, patients with palliative therapy showed no change in CEA values. About half of the patients treated with a complete course of internal and external radiotherapy showed a drop of CEA levels to below 2.5 ng. per milliliter, whereas the other patients showed fluctuating CEA values. No correlation between clinical status and evolution of CEA levels in these patients could be drawn at the present time. The CEA test seems to be of little value for the early diagnosis of gynecologic carcinoma but appears to be interesting for the evaluation of therapy and the follow-up of patients with diagnosed cases.

AN IMPORTANT DEVELOPMENT in tumor immunology has been the description of tumor-associated antigens, which are present in certain cancers and absent or present in very low quantity in normal tissues. Such types of antigens have been identified in various human tumors, including liver,[1] colon,[2] ovary,[3] and cervix[4] carcinoma.

The carcinoembryonic antigen (CEA) was originally described by Gold and Freedman[2] as a glycoprotein present exclusively in carcinoma of the digestive tract and in the digestive organs of the human fetuses of the first and second trimesters of gestation. By means of a sensitive radioimmunoassay, it was found that nanogram levels of CEA could be detected in the serum of patients suffering from colon carcinoma.[5] This observation raised a considerable interest with the hope that the CEA test could be used as a screening method for early diagnosis of digestive cancers. Unfortunately, when larger series of patients were tested, it was found that nonmalignant diseases like ulcerative colitis, cirrhosis of the liver, and bronchial emphysema could also give rise to slightly elevated CEA values.[6-11] More interesting was the fact that patients with carcinoma derived from organs other than colon, including stomach, pancreas, liver, lung, and prostate,[6-11] and even gynecologic carcinoma[7-9, 12] had positive CEA values.

The purpose of the present work is to determine the usefulness and limitations of the CEA test in the diagnosis and follow-up of gynecologic cancer

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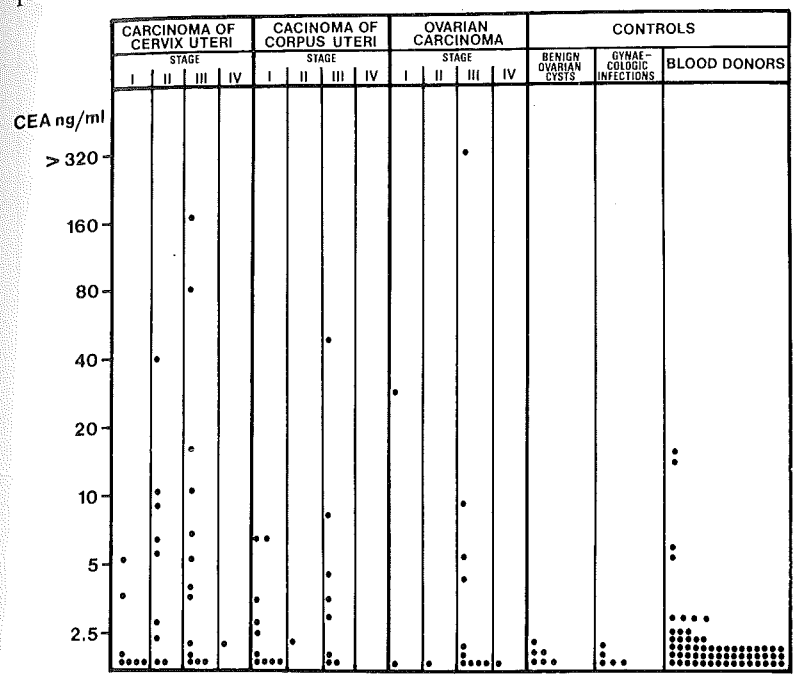
Table I. Individual values of plasma CEA (nanograms per milliliter) obtained before treatment in all patients with gynecologic cancer and in the control subjects



The patients with carcinoma of the cervix, the corpus uteri, and the ovary have been separated according to the degree of spreading with the use of the classification of the International Federation of Gynecology and Obstetrics. The four blood donors who had plasma CEA values higher than 5 ng. were heavy cigarette smokers.

patients after surgical, radiotherapeutic, and chemotherapeutic treatments.

Material and methods

One hundred and eighty-nine CEA determinations were performed in the plasma of 63 patients with histologically proved gynecologic tumors (10 ml. of blood was collected in tubes containing 33 mg. of dry ethylenediaminetetracetic acid–K_3 [EDTA-K_3]). All tests were performed in duplicate before treatment as well as two and seven weeks after the beginning of therapy. Control subjects consisted of 60 apparently healthy blood bank donors and 11 patients with benign gynecologic diseases (5 infections and 6 ovarian cysts). The radioimmunoassay was performed by the method of Thomson and associates,[5] modified by Mach and co-workers.[10, 11] The major modification is that duplicates of 2 ml. of plasma instead of 5 ml. of serum are extracted with perchloric acid. The sensitivity of the test is between 1 and 2 ng. per milliliter. The reliability of this method was demonstrated in a recent study organized by the National Institute of Health, in which the CEA levels of 94 blood specimens obtained from different patients were tested simultaneously by 11 different laboratories. Our results showed 82 to 90 per cent correlation with those obtained by seven laboratories participating in the study, including those of S. Das, V. L. Go, P. Gold, H. Hansen, F. Martin, C. Todd, and N. Zamcheck.

Results

Individual CEA values observed before treatment in 63 patients with carcinoma of the cervix, corpus uteri, and ovary are presented in Table I. The cases are separated according to the degree of spreading, with the use of the classification of the International Federation of Gynecology and Obstetrics. Among the 63 patients studied, 20 (32 per cent) had elevated CEA levels over 5 ng. per milliliter, 11 (17 per cent) had borderline CEA values (2.6 to 5 ng. per milliliter) and 32 (51 per cent) had levels below the arbitrary limit of 2.5 ng. per milliliter. The percentage of values over 2.5 ng. per milliliter in the three different types of carcinoma was 53 per cent for patients with cervical carcinoma, 53 per cent for those with carcinoma of the corpus, and 36 per cent for those with ovarian carcinoma. If the degree of spreading of the carcinoma of the three different localizations is considered, one sees that only 42 per

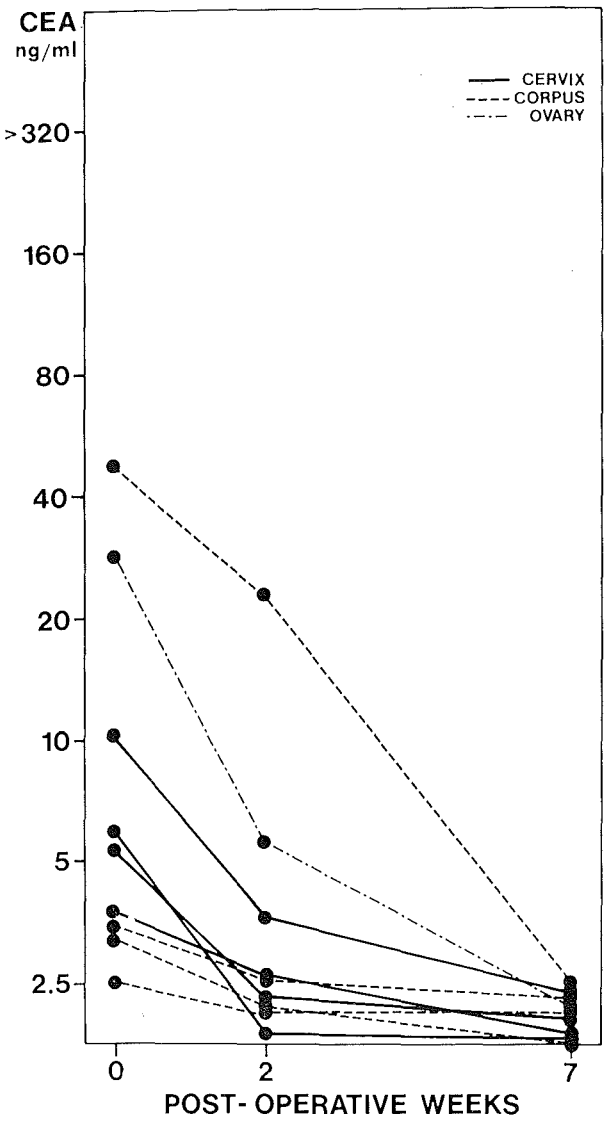


Fig. 1. Variation of plasma CEA levels (nanograms per milliliter) in patient with complete tumor resection.

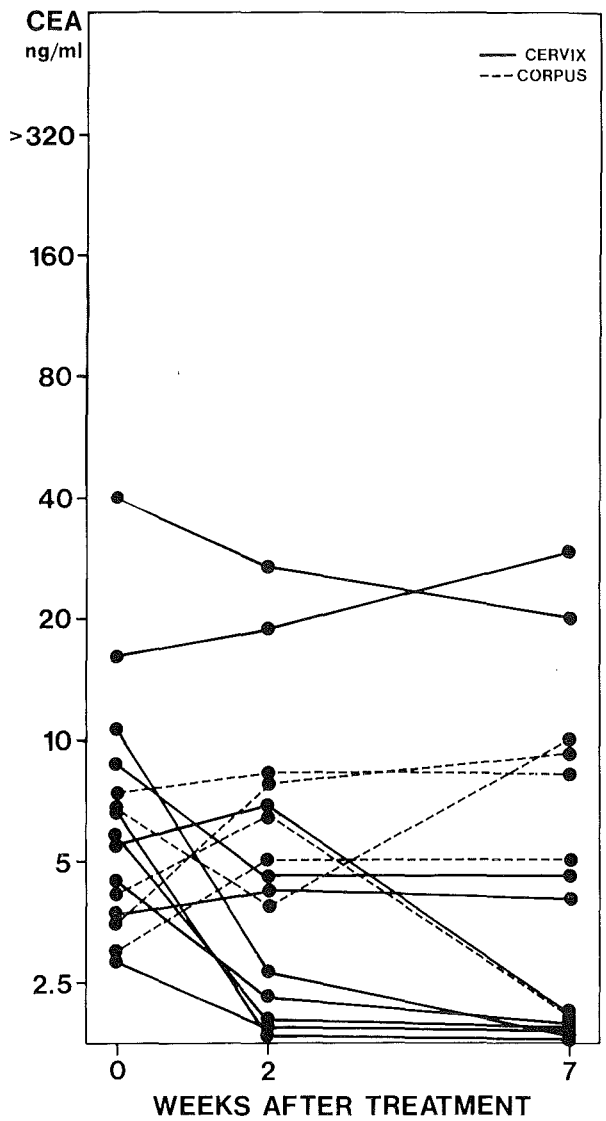


Fig. 2. Variation of plasma CEA levels (nanograms per milliliter) in patients treated by a complete course of internal and external radiotherapy.

cent of all patients with Stage I carcinoma had CEA values above 2.5 ng. per milliliter, whereas 54 per cent of all those with Stage II carcinoma and 52 per cent of all those with Stages III and IV carcinoma had values above this limit. Only seven patients had CEA values above 15 ng. per milliliter, and among them three who had values over 80 ng. per milliliter died within six months and were found at autopsy to have liver metastasis.

In the control group, all patients with benign gynecologic disease had CEA values below 2.5 ng. per milliliter. Among the 60 blood donors, four had levels over 5 ng. per milliliter and four had values between 2.6 and 5 ng. per milliliter. The four individuals with values over 5 ng. per milliliter were found retrospectively to be heavy cigarette smokers (more than 20 cigarettes a day for the last ten years). This is in agreement with the recent observation of Stevens and Mackay[13] and Hansen and colleagues[14] who showed that elevated CEA levels can be found in apparently healthy individuals with heavy smoking habits.

In order to follow the effect of therapy on CEA level, the 31 patients with values over 2.5 ng. per milliliter were divided into three groups according to the type of treatment:

Group 1 consisted of nine patients in whom complete surgical resection of tumor was possible. The

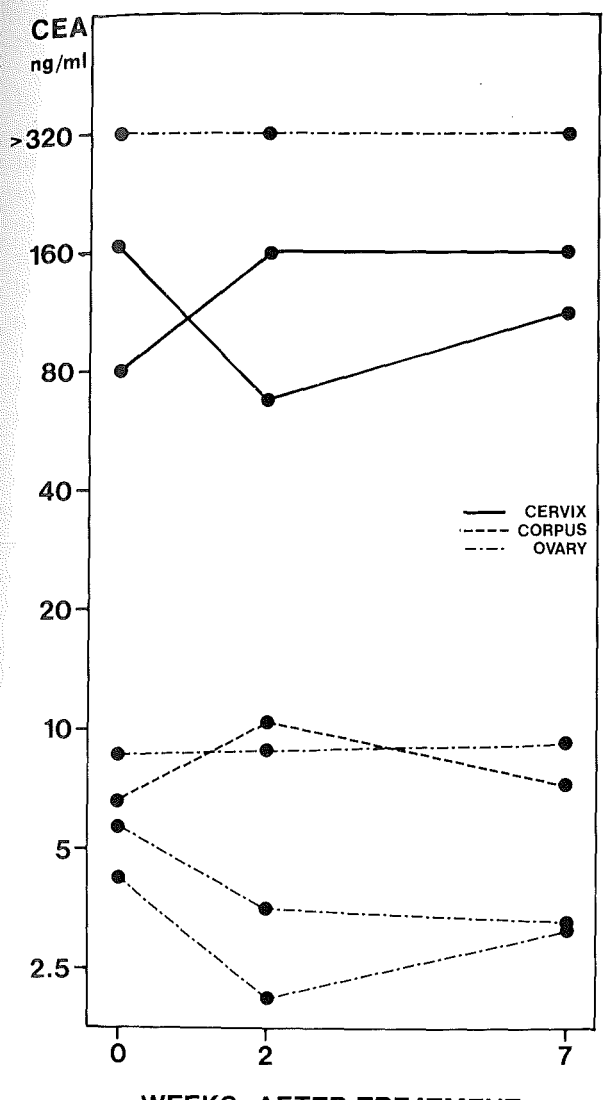


Fig. 3. Variation of plasma CEA levels (nanograms per milliliter) in patients with disseminated cancer undergoing palliative therapy.

tumors were four carcinomas of the cervix (three Stage I and one Stage II), four of the corpus uteri (three Stage I and one Stage III), and one of the ovary (Stage I). Fig. 1 shows that seven weeks after surgery, the CEA levels of all the patients of this group had dropped below 2.5 ng. per milliliter. Four patients had already reached this value two weeks after surgery. The patient with the highest value in this group (50 ng. per milliliter) had carcinoma of the corpus uteri (Stage III). The CEA level dropped only to 25 ng. per milliliter two weeks after surgery, but five weeks later it was down to 2.5 ng. per milliliter. At the present time, twelve months after surgery, this patient has a CEA value of 2.1 ng. per milliliter without clinical evidence of tumor recurrence.

Group 2 consisted of 15 patients treated by a complete course of internal and external radiotherapy. Ten patients had carcinoma of the cervix (four Stage II and six Stage III) and five had carcinoma of the corpus uteri (one Stage II and three Stage III). Among these patients (Fig. 2), seven who had relatively low CEA levels initially had levels under 2.5 ng. per milliliter at the end of treatment, whereas the levels of eight others had fluctuating values. At the present time, no correlation between evolution of CEA levels and clinical status can be drawn.

Group 3 consisted of seven patients with advanced dissemination of cancer. Two patients with cervical carcinoma Stage III underwent palliative radiotherapy, another with a corpus carcinoma infiltrating the pelvis had an incomplete tumor resection, the four remaining were treated by chemotherapy with poor clinical response for ovarian carcinoma (Stage III) diagnosed at explorative laparotomy. Fig. 3 shows that in these patients no significant changes in CEA levels were observed. All these patients died within six months after treatment and were found at autopsy to have liver metastasis.

Comment

The incidence of over-all gynecologic carcinoma with elevated CEA values reported here is comparable with that observed in the limited studies already published on this subject.[7-9, 12] About half of the 63 patients in the present study had CEA values over the arbitrary limit of 2.5 ng. per milliliter and one third had levels over 5 ng. per milliliter. Among the patients with different types of gynecologic carcinoma, those with carcinoma of the corpus uteri and the cervix showed more elevated values than did those with carcinoma of the ovary. One interesting finding was that the elevated values were not present only in large metastatic cancers but also in several cases of localized tumor (Stages I and II).

However, in general, the percentage of elevated CEA levels as well as the individual CEA values were low in patients with gynecologic carcinoma compared with those observed in patients with gastrointestinal cancers.[5-11] For comparison, in a recent study with the use of the same radioimmunoassay, we found 65 per cent of CEA values greater than 5 ng. per milliliter and 33 per cent greater than 20 ng. per milliliter in 35 patients with localized colonic and rectal carcinoma (Duke's Stages A and B).[17]

If one takes into account on one hand that most

patients with gynecologic carcinoma had relatively low CEA values when already clinically symptomatic and on the other hand that several nonmalignant conditions[6-11, 14, 16] and even heavy smoking[13, 14] can give rise to slightly elevated CEA values, one should conclude that the CEA test is of little use for the early diagnosis of gynecologic carcinoma. It certainly should not be considered as a screening test for these types of cancer.

The most interesting observation of this study is the decrease of CEA level to normal values after complete surgical resection of the tumor (Fig. 1). As suggested for other types of cancer, the postsurgical CEA test should help to evaluate therapy.[5-11, 14-17] The persistence of an elevated CEA level in absence of an associated pathology strongly suggests the presence of a residual tumor.

The changes in CEA levels during the course of radiotherapy are not as clear as those observed after surgery. Only about half of the patients show a drop to below 2.5 ng. per milliliter. The persistence of an elevated CEA even after a good clinical response to radiotherapy, already observed by Khoo and Mackay,[12] is difficult to explain. It might be due to a residual nonproliferating tumor or to the release of CEA by cancer cells undergoing postactinic necrosis. These patients will be followed for a longer period of time to determine whether the CEA level will drop progressively with the slow destruction of tumor or if persistant elevated CEA indicated the presence of residual tumoral tissue which might subsequently cause a relapse of the disease.

At the present time, the most logical application of the CEA test for gynecologic carcinoma as well as for other types of carcinoma is the surveillance of patients who have shown a drop of CEA level after therapy. After surgical resection of carcinoma of the colon and rectum it has been shown that a tumor recurrence can provoke a rise in CEA level several weeks or months before the first clinical symptoms or modification of blood chemistry.[11, 14-17] This possible relatively early detection of relapse by CEA radioimmunoassay is due in part to the selection of patients with CEA-producing tumors and in part to the regularity of CEA control subjects, justified in this population with high risk of relapse. The fact of knowing the lowest postsurgical values as a CEA base line also helps to detect minor elevation of the CEA level. These arguments speak in favor of use of the CEA test (every two to three months depending on the rapidity of growth of the tumor) for the surveillance of patients with gynecologic carcinoma after therapy. However, it remains to be proved that an early warning of relapse will modify the therapeutic approach, the prognosis, and the patients' survival.

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