Urological Research 2, 79-83 (1974)
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The Prognostic Value of Carcinoembryonic Antigen in Carcinoma of the Prostate

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Received: January 8, 1974

Summary. Seventy-six patients with carcinoma of the prostate had 392 serial plasma carcinoembryonic antigen determinations performed over a 15 month interval in an attempt to determine the prognostic value of this test. - Sixteen of the 28 patients with decreasing serial CEA levels had active disease and nineteen of the 31 patients with rising serial CEA level had inactive disease. No difference in CEA patterns was seen in patients undergoing various types of therapy. - It does not appear that plasma CEA as presently constituted is an accurate prognostic test for the follow-up of carcinoma of the prostate.

Key words: Carcinoembryonic antigen, prostatecancer-prognosis.

Introduction

In 1965 Gold (1) reported the presence of a specific protein in the serum of patients with colon carcinoma that was present in fetal serum, but absent from the serum of normal individuals. This he called carcinoembryonic antigen (CEA). CEA is a glycoprotein with a specific amino acid sequence (2). Gold felt that this protein was specific for colon carcinoma, but it has subsequently been found by LoGerfo (3), Laurence (4), and others (5, 6) to be present in numerous other tumor systems. Moore (7) also noted its presence in patients with several types of benign diseases of the gastrointestinal tract.

CEA determinations were initially reported to be accurate in diagnosing 97% of patients with carcinoma of the colon (8), but were found to be much less accurate in detecting localized lesions (19%) compared to metastatic or disseminated cancer (100%) (9). Since there were many false negatives in low stage cancers the future of CEA as a diagnostic or screening test for malignancy has become less bright. But several authors (10, 11, 12) have commented that, while CEA may not be useful as a screening test for cancer, it could serve in the prognosis and followup of patients with malignant disease. After baseline CEA dterminations, a rise following therapy would indicate either inadequate therapy initially or a relapse after adequate therapy. Moore (11) has suggested that serial CEA assays may "provide a rational basis for a second look operation".

In an attempt to evaluate CEA for its prognostic value in the management of patients with cancer we have followed 76 patients with cancer of the prostate with multiple CEA determinations over a 15 month period. The changes in the patient's serial CEA levels were then correlated with their clinical status. An effort was also made to determine the effect of therapy on the serial CEA assays. This paper is a summary of these results and a report of the potential prognostic value of CEA in this one tumor system, carcinoma of the prostate.

Materials

Seventy-six patients with histologically proven carcinoma of the prostate from the Urology Tumor Section of the Department of Urology, Cook County Hospital were studied between 1 January, 1972 and 1 April, 1973. These patients had 392 plasma CEA samples drawn. The CEA determinations were drawn at about monthly intervals and no patients had samples drawn at less than a fourteen day interval.

The patients were clinically evaluated as to the status of their disease, which was determined to be either active or inactive. The clinical evaluation was based on standard physical, radiologic, and laboratory findings which included rectal examination, intravenous pyelograms, bone survey and scans, and acid and alkaline phosphatases. Patients with carcinoma of the prostate who were considered to have active disease had any or a com-

bination of the following: 1. clinical or radiographic evidence of persistent or recurrent tumor; 2. rising acid and/or alkaline phosphatases; 3. significant weight loss; 4. the appearance of an enlargement, or pain at the site of metastasis; and 5. a decreasing hematocrit. Patients with inactive disease were those without the above criteria, following either radical surgery, radiation or hormone therapy or who were not receiving therapy.

The patients were also divided into those receiving therapy and those not receiving therapy. Therapy was either hormonal (1 mg diethystilbesterol daily), operative (radical retropubic prostatectomy), or cobalt radiation (5 000 to 7 000 R). All of the patients receiving radiation also received protocol hormone therapy. Two of the six patients who had radical prostatectomy received 1 mg diethystilbestrol daily. None of these patients had their therapy changed after the initial therapy.

Methods

Ten ml of venous blood was collected for each CEA determination. The blood was centrifuged in a refrigerated centrifuge and stored at -4° C until it was shipped in dry ice to the Roche Cancer Research Diagnostic Laboratory for assay. The CEA measurements were performed by the radioimmunoassay technique described by Hansen (13). A plasma level of 2. 5 ng/ml or over of carcinoembryonic antigen was considered positive.

Based upon their serial plasma CEA assays the patients were considered to have either a normal, a rising, or a falling CEA level.

If all of the serial CEA determinations were less than 2. 5 ng/ml, the serial CEA level was considered normal. If overall, the serial CEA assays were increasing and any determination was above 2. 5 ng/ml, the serial CEA was considered a rising CEA. If overall, the serial CEA determinations were decreasing from a level above 2. 5 ng/ml the serial CEA was considered a falling CEA.

A "misleading" serial CEA assay was a sequence of serial CEA determinations which did not reflect the patient's clinical status. That is, falling serial CEA determinations in a patient with active disease, or rising serial CEA determinations in a patient with inactive disease.

Results

Of the 76 patients studied, 31 had clinically active disease and 45 had clinically inactive disease (Table 1). Seventeen patients had persistently normal plasma CEA determinations. Thirty-one of the 76 patients had a rising serial CEA and 28 patients had a falling serial CEA. In no patient did the CEA determination remain consistenly elevated at the same level.

Table 1. Status of disease

Status of Disease	No. of Patients
Active	31
Inactive	45
Total	76

The status of the disease in these 76 patients was correlated with the serial CEA levels (Table 2). Fourteen of the 17 patients with normal CEA determinations had inactive disease. Nineteen of 31 patients with a rising serial CEA had inactive disease, and 16 of 28 patients with a falling serial CEA had active disease.

Table 2. Serial CEA and Status of Disease

Serial CEA		Status of Disease	
Normal CEA	17	Active	- 3
		Inactive	- 14
Rising CEA	31	Active	- 12
		Inactive	- 19
Falling CEA	28	Active	- 16
		Inactive	- 12
		Total	76

Thirty five of the 59 patients (60 %) with a changing serial CEA assay had "misleading" serial CEA determinations relative to their clinical status (Table 3). Inactive disease in 19 of 31 patients with a rising serial CEA represented an error of 61 % and active disease in 16 of 28 patients with a falling serial CEA represented an error of 59 %. The percentage error for changing (either rising or falling) serial CEA assays was 60 % (35 of 59 patients).

Table 3. Accuracy of Serial CEA Determinations

"Misleading" Serial CEA Assays		% Error
Rising CEA with inactive disease:	19 of 31	61 %
Falling CEA with active disease:	16 of 28	59 %
Total	35 of 59	60 %

Table 4. Therapy and Serial CEA Determinations

Therapy	Normal Active Disease	Serial CEA Inactive Disease	Rising Active Disease	Serial CEA Inactive Disease	Falling Active Disease	Serial CEA Inactive Disease	
Hormones alone	3	8	7	11	10	8	47
Radiation & Hormones	0	2	2	0	1	2	7
Surgery & Hormones	0	0	0	2	0	0	2
Total Hormones	3	10	9	13	11	10	56
Surgery alone	0	2	0	1	0	1	4
No Therapy	0	2	3	5	5	1	16
Total no Hormones	0	4	3	6	5	2	20
Over all	3	14	12	19	16	12	76

All of the patients had their therapy recorded (Table 4). Fifty-six of the 76 patients received hormones. Forty-seven of these 56 patients received hormones alone, seven received hormones plus radiation, and two patients were treated with hormones and radical surgery. Twenty patients received no hormones. Four patients had radical surgery alone and sixteen patients received no active therapy (Table 4). Only one patient died of cancer of the prostate. He had a rising level with active disease.

Of the 35 patients with "misleading" serial CEA assay (Table 5), 24 patients (69%) were receiving hormones (13 rising serial CEA's with inactive disease and 11 falling CEA's with active disease) and 11 were not receiving hormones. Of the 24 patients with correct serial CEA determinations, 19 (83%) were receiving hormones (9 rising serial CEA with active disease and 10 falling serial CEA's with inactive disease) and 5 were not (Table 5). Serial CEA's in the 16 patients that received no therapy did not seem to predict prognosis any more accurately than in the treatment groups (Table 6).

Discussion

The initial appeal of CEA as a cancer screening test was based on the report of Thomson (8) who noted a 97% accuracy rate in diagnosing digestive tract cancer. This enthusiasm was re-inforced when CEA was reported in the blood of patients with non-entodermal cancer.

But this early hope for CEA as a cancer diagnostic test was dampened when its accuracy was subsequently (9) reported to be less than 50% in early or localized colon carcinoma and when it was discovered (7) in benign gastrointestinal disorders and even in normal individuals, albeit in reduced amounts (14).

Attention was shifted from the diagnostic role of CEA to its potential value as a prognostic test in

Table 5. Hormone Therapy and Accuracy of Serial CEA Determination

Patients Receiving Hormones	% Receiving Hormones
Incorrect Serial CEA Determinations: 24 of 35	69 %
Correct Serial CEA Determinations: 19 of 24	83 %

Table 6. Patients Receiving no Therapy and Accuracy of Serial CEA Determinations

Disease Status	Correct Determinations	% Correct Determinations
8 Actives	3	38 %
8 Inactives	3	38 %

patients with cancer. Moore (15) reported on 19 patients with colon carcinoma who had pre- and postoperative CEA determinations. Eleven patients who had no known metastases had normal CEA levels following surgery; seven patients with persistent disease had elevated CEA levels after surgery. But one patient with persistent disease had normal CEA's before and after therapy. This represents a prognostic accuracy of 94%.

Laurence (4) followed 87 patients with gastrointestinal and mammary carcinoma postoperatively, and found that in 84 patients the plasma CEA levels accurately reflected the patient's clinical status. He also noted that most elevated preoperative levels returned to normal limits in two to six days following surgery. Reynoso (12) reported on three patients with successfully treated neuroblastomas whose CEA levels returned to normal following therapy. A note of caution among these generally optimistic reports on the prognostic value of plasma CEA was voiced by Dhar (9) who indicated that four of 16 patients with negative postoperative CEA assays had recurrent cancer of the colon.

Elevated plasma CEA levels have also been found to be present in patients with genitourinary malignancies. The percentage of patients with cancer of the prostate with positive CEA assays ranges from a low 25% (16) to a high of 59% (17). In a further evaluation of the stage of these tumours both authors reported a reduced diagnostic accuracy in lower staged (A and B) lesions compared with higher staged (C and D) lesions.

Since serial CEA assays appear to have some prognostic value in the follow-up of patients with gastrointestinal cancer we reviewed our data to see if this was also the case for prostatic carcinoma. In this study we noted that 19 of the 31 patients with rising serial CEA levels had inactive disease compared to 12 who had active malignancy. Therefore 61% of these 31 patient's serial CEA's were "misleading". The same was true for the 28 falling serial CEA levels in which 16 patients had active malignancy while 12 patients had inactive disease: 59% of these 27 patients were incorrectly accessed by the use of this test. Thirty-five of these 59 patients with either rising or falling serial CEA assays had "misleading" serial CEA determinations for a false serial CEA assay rate of 60%. If those 17 patients with normal serial CEA determinations (3 or whom had active disease, leaving 14 who were correctly accessed) are added to the overall "misleading" serial CEA assay rate is 38 of 76 patients or 50%.

A 40% to 50% accuracy rate in diagnosing the course of a patient's prostatic cancer is inadequate. Moore (15) and LoGerfo (18) reported 94% and 100% accuracy rates for serial CEA assays in predicting the presence of residual carcinoma of the colon. The serial CEA determination for the prognosis of the clinical courses of patients with prostatic cancer therefore seems far less accurate than serial CEA assay is in predicting the course of patients with colon cancer.

In an attempt to determine the cause of the 50% "misleading" serial CEA assay rate in prostatic carcinoma the therapy given these 76 patients was reviewed. Twenty-four of the 35 patients (69%) with incorrect serial CEA results were being treated with hormones while 19 of the 24 (83%) patients with correct serial CEA results were being treated with hormones. More patients on hormones had correct serial CEA assays than those not on hormones. Thus, hormone therapy alone cannot acount for the inaccuracy of the serial CEA test.

A more probable explanation for this prognostic inaccuracy lies in the source of the test antisera. The presently available CEA test is dependent upon radiolabeled antisera that has been raised against human colon carcinoma specific antigen. One would not necessarily expect this antibody to be accurate in identifying prostate tumor specific antigen. Antigens (neoantigens?) unique to carcinomatous prostatic tissue are presently being employed for the production of antisera which hopefully will facilitate initiation of more diagnostic and prognostic tests for carcinoma of the prostate. At the present time the currently available CEA tests do not appear to be specific enough to be of great prognostic value in the management of patients with carcinoma of the prostate.

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