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# Carcinoembryonic Antigen in Patients with Urologic Cancers*

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Summary. 101 patients with urologic malignancies were studied for the presence of plasma carcinoembryonic antigen (CEA) employing the radioimmunoassay technique of Hansen. 59% of prostate cancer patients, 76% of bladder cancer patients and 33% of renal cancer patients were CEA positive. There were more positive CEA determinations in patients with higher stage and grade tumors. There were more false positives and false negatives among those patients receiving hormones or radiation. - In summary CEA appears to be present in patients with urologic malignancies. Care should be taken in interpreting CEA results in patients receiving hormones or radiation.

Key words: Urologic malignancies, carcinoembryonic, antigens, radioimmunoassay, radiation, hormones.

Tumors are antigenic. Although long suspected, tumor antigenicity was first scientifically demonstrated by Foley in 1953 (3). Numerous tumor associated antigens have been described and included: alpha-fetoglobulin (1). T Globulin (15), gastric juice fetal sulfoglycoprotein (6), regan isoenzyme (12), and CEA. Carcinoembryonic antigen or CEA was first described by Gold in 1965. (4) It has been characterized as a protein-polysaccharide complex with a sedimentation constant of 6.9 to 8.5, a molecular weight of 200 000 and containing 14 amino acid residues and six carbohydrate constituents (5).

Gold initially isolated CEA from colon carcinoma, but it has since been found in many other solid tumors. Reports on the accuracy of plasma CEA determinations in histologically proven carcinoma have varied between 72% and 97% (13, 16, 17).

Concern has been expressed over the high rate of false positive CEA determinations in benign disease. LeBel (8) reported positive CEA results of between 66% in diverticulitis and 77% in benign colitis. More disturbing are the false negative results in localized tumors. If the test is to become a potential cancer screening device, patients with early resectable lesions must be detected.

This investigation was undertaken to determine the accuracy of the plasma CEA test in urologic patients with malignancies and to ascertain its value as a test for detection of cancer of the genitourinary tract. Plasma CEA determinations in patients with urologic neoplasms were correlated with their clinical states, the stages and grades of their tumors, and the types of therapy accorded them.

## Materials

One hundred eighty-nine blood samples were obtained from 101 patients. The patient population was composed of 88 males and 13 females and included both in-patients and out-patients on the Urology Service of Cook County Hospital. There were 68 cases of prostatic malignancies (Table 1), which accounts for the preponderance of males in the study. Twenty-one patients with bladder tumors were included, as well as nine with renal

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Table 1. Carcinoembryonic antigen determinations in patients with urologic tumors

| Organ | No. | Pos. | % | Neg. | % |
|---|---|---|---|---|---|
| Prostate | 68 | 40 | 59 | 28 | 41 |
| Bladder | 21 | 16 | 76 | 5 | 24 |
| Kidney | 9 | 3 | 33 | 6 | 67 |
| Other G. U. | 3 | 1 | 33 | 2 | 67 |
| | 101 | 60 | 59 | 41 | 41 |

tumors. There were also three other tumors: a seminoma, a pheochromocytoma, and a penile carcinoma.

All patients had histologically proven malignancies. They were further evaluated as to the status of their diseases: inactive or active. To have been classified as inactive, a patient had to have been free of evident disease for at least one year. Active disease was present in those patients with proven malignancies prior to therapy or those whose diseases had progressed subsequent to therapy. The prostatic, bladder, and renal malignancies were further evaluated as to stages and grades, as well as to types of therapy accorded the patient.

## Method

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. (7) A plasma level of 2.5 ng/ml or over of carcinoembryonic antigen was considered positive.

## Results

1. All Urologic Tumors. There were 99 CEA-positive assays (52%) among the 189 determinations done on the 101 patients with urologic tumors (active or inactive). Most of these patients had more than one previous CEA determination. The high consistency of either positive or negative determinations for individual patients allowed us to consider the patients as either CEA positive or negative.

Sixty (59%) of the 101 urologic patients were CEA positive. Fifty-four of the 101 patients had inactive disease; 47 had active tumors (Tables 1 and 2).

2. Prostate. The 68 cases of prostatic carcinoma were all histologically verified adenocarcinomas (Table 3). Twenty-two patients had an early stage lesion (A and B) and all of these tumors were low grade (I and II); 46 lesions were high stage (C and D), and 21 of these were high grade (III and IV).

Forty-three of the prostate patients had inacve disease and 25 had active disease (Table 4). Twenty of the 43 (47%) patients with inactive disease had positive determinations. Twenty of the 25 patients with active disease had a positive plasma CEA (80%) yielding a 20% false negative rate.

Table 2. CEA determinations and states of diseases

| Organ | No. | Inactive | CEA Pos. | False+ CEA% | Active | CEA Neg. | False- CEA% |
|---|---|---|---|---|---|---|---|
| Prostate | 68 | 43 | 20 | 47% | 25 | 5 | 20% |
| Bladder | 21 | 6 | 4 | 67% | 15 | 3 | 20% |
| Kidney | 9 | 4 | 1 | 25% | 5 | 3 | 60% |
| Other G. U. | 3 | 1 | 0 | 0% | 2 | 1 | 50% |
| Totals | 101 | 54 | 25 | 46% | 47 | 12 | 26% |

Table 3. CEA determinations correlated with stages and grades of prostate malignancies

| | Stage | | | | | |
|---|---|---|---|---|---|---|
| | A, B | | C, D | | | |
| Grade | Patients | CEA Positive | Patients | CEA Positive | Total Patients | CEA Positive |
| I, II | 22 | 10 | 25 | 15 | 47 | 25 |
| III, IV | 0 | 0 | 21 | 15 | 21 | 15 |
| Totals | 22 | 10 | 46 | 30 | 68 | 40 |

Table 4. CEA determinations correlated with clinical states and types of therapy

| | Clinic Status | | | | | |
|---|---|---|---|---|---|---|
| Type of Therapy | Inactive | | Active | | | |
| | Pt's | CEA Positive | Pt's | CEA Positive | Tot Pt's | CEA Positive |
| Non-Hormonal | 10 | 5 | 11 | 11 | 21 | 16 |
| Hormonal | 33 | 15 | 14 | 9 | 47 | 24 |
| Totals | 43 | 20 | 25 | 20 | 68 | 40 |

Of the 47 patients who were treated with hormones, 24 had positive CEA determinations. Of the remaining 21 patients who did not have hormone therapy, 16 had positive CEA determinations (Table 4). Of these patients (not treated hormonally), the 11 with active disease were all CEA positive.

3. Bladder. The 21 patients with bladder tumors included 16 with transitional cell lesions, three with squamous cell lesions, and two with adenocarcinoma. Three of the five patients with low stage lesions (0, A, $B_1$) had a low grade tumor (I, II) (Table 5). Sixteen patients had high stage lesions ($B_2$, C, D); of these, ten were high grade (III and IV). Twelve patients had received radiotherapy (2 000 - 6 000 R): nine of these patients had active disease and three had inactive disease. Nine of the irradiated patients were CEA positive (3 received 2 000 R, 4 received 3 - 5 000 R and 2 received 6 000 R). The three CEA negative patients with active disease had received in excess of 6 000 R of radiotherapy (Table 6).

4. Kidney. Of the nine patients with renal tumors, eight had renal cell carcinomas and one had a Wilm's tumor. Four patients had low stage lesions (A and B) and five had high stage lesions (C and D): 33% were CEA positive.

Four of the patients with renal cancer had inactive disease; one of these patients had a positive CEA. The other five patients had active disease; three of them were CEA negative. This is a 25% false positive rate and a 60% false ne-

Table 5. CEA determinations correlated with stages and grades of bladder malignancies

| | Stage | | | | | |
|---|---|---|---|---|---|---|
| | O A $B_1$ | | $B_2$ C D | | | |
| Grade | Pt's | CEA Positive | Pt's | CEA Positive | Tot Pt's | CEA Positive |
| I, II | 3 | 1 | 6 | 5 | 9 | 6 |
| III, IV | 2 | 2 | 10 | 8 | 12 | 10 |
| Totals | 5 | 3 | 16 | 13 | 21 | 16 |

Table 6. CEA determinations in patients with bladder tumors correlated with clinical states and types of therapy clinic status

| Type of Therapy | Clinic Status | | | | | |
|---|---|---|---|---|---|---|
| | Inactive | | Active | | | |
| | Pt's | CEA Positive | Pt's | CEA Positive | Pt's | CEA Postitive |
| Non Radiated | 3 | 1 | 6 | 6 | 9 | 7 |
| Radiated | 3 | 3 | 9 | 6 | 12 | 9 |
| Totals | 6 | 4 | 15 | 12 | 21 | 16 |

gative rate. All of these patients had been treated by nephrectomy, except one who was hospitalized too late in the course of his disease and who subsequently expired; he was CEA positive. The Wilm's tumor patient had active disease at the time of CEA was determined; she was CEA positive.

5. Other GU Disorders. One patient had metatastatic disease from a pheochromocytoma and was CEA-positive. One patient with a seminoma of the testis and another patient with a squamous cell carcinoma of the penis both had localized disease; both had negative CEA determinations after removal of the diseased tissue.

## Discussion

Several investigators have evaluated plasma CEA levels in patients with urologic malignancies. With different assay methods, Moore reported one patient with penile cancer who was CEA negative; he also reported seven of 17 patients with nonmalignant renal disease who were positive (11); and LeBel reported a patient with transitional cell carcinoma of the bladder to have been CEA positive (8). LoGerfo had CEA positive determinations in 25 of 52 prostatic patients with cancers, in six of 12 patients with bladder cancer, and in two of eight patients with renal cancers; the rate of CEA positives in these 72 patients was 46% (9). Reynoso observed that about 30% of 127 patients with urinary tract malignancies had CEA levels over 2.5 ng/ml (13).

None of these studies correlated stages, grades, clinical courses and treatments of the malignancies with the CEA results. Reynoso, et al, in a more recent paper, more completely described 116 urologic tumor patients with an overall CEA positive rate of 30% (14). The rate varied from a high of 46% in patients with testicular tumors (11 of 24 patients) to a low of 14% for patients with penile cancers (one of six patients). They reported rates of 44% positive for patients with renal tumors (four of nine), 27% for patients with bladder cancer (12 of 44), and 25% for patients with prostatic carcinomas (7 of 28). They also evaluated these tumors according to the stages and grades of the lesions and found relatively little correlation between these factors and CEA titers.

The results of the present study have revealed a higher rate of positive CEA determinations than previous studies. This was true not only for patients with urologic tumors as a group (59%), but for tumors of individual organs as well (bladder 76%, and prostate 59%). Reynoso described a higher positive rate for patients with kidney tumors (44%).

There is obviously a need to examine plasma CEA levels in patients with benign urologic diseases to confirm that they are normal before this test is employed clinically. We have investigated a small number of plasma samples from patients with BPH and cystitis (they were all $< 2.5$ ng/ml.) but there are too few determinations to be of any statistical value.

The number of false negatives for patients with localized tumors and the number of false positives for patients with apparently benign disease requires caution in the interpretation of CEA titers. It is an aid in the diagnosis, but should not be relied on alone to make the diagnosis.

In an effort to define more accurately the usefulness of the CEA plasma test in the diagnosis of urologic cancer, we have reviewed our false negative and false positive results. For prostatic and bladder tumors, these data have been correlated with the types of therapy. There were 12 negative CEA determinations in 47 patients with active disease, Table 2. This is a possible false negative rate of 26% in patients with active disease. There were 25 fals e positive determinations in 54 patients with inactive disease, a possible false positive rate of 46%. A partial explanation for this may be that hormonal therapy had been given to the majority of patients with prostatic carcinomas (47 of 68 patients). Twenty

of the patients receiving hormones had possible false CEA results (15 patients with inactive disease were positive and five patients with active disease were negative). Stilbestrol and bilateral orcheictomy exert a disrupting effect on the immune system (2), and this effect may have resulted in specious CEA values. Care should be taken in interpreting CEA results in patients with prostatic carcinoma being treated with hormones, since 11 of 11 patients with active disease not treated with hormonal therapy were CEA positive. Caution should also be exercised because, while hormones control prostate carcinoma, they do not necessarily cure it and can leave behind residdual viable tumor cells.

Twelve patients with bladder carcinoma were treated with radiotherapy; irradiation is also known to damage the immune system (10). Six of the 12 patients who received radiotherapy had false CEA results (three patients with inactive disease were CEA positive and three patients with active disease had negative results). Again, caution should be exercised in evaluating CEA results in patients who have had radiotherapy and have not had prior CEA determinations.

If the patients who received hormonal therapy and radiotherapy are excluded, the overall false negative rate becomes 33% and the false positive rate becomes 14%. The results of this study justify several conclusions. First, CEA is present in the plasma of patients with urologic malignancies, and perhaps in a higher percentage of patients than previously reported. Second, tumors of higher stages and grades are more accurately diagnosed. Third, there are false negative and false positive results. Fourth, types of therapy accorded to patients seem to influence results and may increase the false negative and false positive values.

In summary, this report seems to justify the conclusion that the CEA test is potentially very useful in the diagnosis of patients with urologic malignancies. The diagnostic accuracy will be enhanced when more is learned about the effect of therapy (hormones and radiotherapy) and CEA production.

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