Carcinoembryonic antigen: 3 years' experience in a cancer clinic

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Long-term studies on multiple plasma samples of 988 patients with carcinoma of entodermal origin indicate that, especially for patients with colorectal cancer, repeatedly elevated or rising carcinoembryonic antigen (CEA) values are a sign of poor prognosis when found preoperatively, postoperatively or during chemotherapy. Persistently elevated CEA values in postoperative patients apparently free of disease are a useful marker for early detection of recurrence or metastases. Normal CEA values are of little or no prognostic value.

Des études à long terme, portant sur un grand nombre d'échantillons plasmatiques prélevés chez 988 patients souffrant d'un carcinome d'origine entodermique, indiquent que, particulièrement chez les patients porteurs d'un cancer du colon ou du rectum, des mesures fréquemment élevées ou en augmentation de l'antigène carcinoembryonnaire (ACE) sont l'indice d'un mauvais pronostic lorsqu'elles sont retrouvées avant ou après l'opération, ou durant la chimiothérapie. Après l'opération l'obtention de valeurs d'ACE constamment élevées chez des patients apparemment exempts de lésion constitue un indice utile pour la détection précoce des récidives et des métastases. Des valeurs normales d'ACE n'ont que peu ou pas de valeur pronostique.

In this paper we present the results of a prospective study correlating plasma carcinoembryonic antigen (CEA) values with the clinical status and course of 988 patients with entodermally derived malignant tumours. Specifically we correlated a) the CEA value with presence or absence of malignant disease as determined clinically or by other investigations, or both; b) the CEA value in the first plasma sample in 1972, or in a preoperative sample, with recurrence of cancer; c) elevated CEA values with recurrence of surgically resected cancers; and d) CEA values at intervals during follow-up of patients undergoing chemotherapy for recurrence, with response to treatment.

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Patients and methods

Clinical, investigative and pathologic data

All 988 patients were registered at the Dr. W.W. Cross Cancer Institute, and histories, physical findings, progress notes and results of investigations were available for study. In general the examining physician was not aware of previous CEA values; hence these usually did not influence the extent of clinical investigation. In addition, the time and method of determining the diagnosis, the treatment and, following surgical resection, the site, size, pathologic diagnosis and grade of the resected tumour were recorded for most and were available for this study. Appropriate information, including clinical and investigative data, was also available at the time of each CEA determination.

Plasma samples

Blood was collected in a tube containing ethylenediamine tetra-acetic acid (EDTA); the plasma was separated within 1 hour and kept at −20°C until tested. Samples were obtained from 48 healthy volunteers, 159 patients with nonmalignant disease and 988 patients with entodermal primary malignant disease (of the gastrointestinal tract in 962 and of the respiratory tract in 26).

CEA assay

The zirconyl phosphate method (Z-gel) with CEA kit reagents (Hoffmann-La Roche) was used. CEA values of 5 ng/ml or less were considered normal for the purpose of this study.

Results

Overall correlation

CEA values for all healthy volunteers and patients with nonmalignant disease were 5 ng/ml or less. Of the 988 patients with entodermal primary malignant disease, a positive correlation — presence of malignant disease and elevated CEA values (in 213) or absence of malignant disease and normal CEA values (in 556) — was found in 78%, whereas a negative correlation — presence of malignant disease and normal CEA values (in 145) or absence of malignant disease and elevated CEA values (in 74) — was found in 22% (Table I). To date, 21 of 74 patients (28%) with no apparent malignant disease at the time of initial elevated CEA values have shown recurrence of tumour. Another 21 of 556 patients (3.8%) originally free of malignant disease and with normal CEA values have had a recurrence — 11 with increasing CEA values and 10 with persistently normal CEA values.

CEA as a prognostic marker

Among 100 consecutive patients with pre-existing or existing entodermal primary malignant disease CEA values were determined in 1972; 17 were lost to follow-up, 2 died of unrelated causes and the remaining 81 have been followed up for at least 3 years. The distribution of types of cancer among the 81 patients followed up is set forth in Table II; this table also relates CEA values to the type of cancer and the clinical course.

Preoperative CEA values

CEA concentrations were determined in 64 patients shortly before operation for "cure", and all have been followed up for at least 6 months (Table III). Among these 64, CEA values exceeded 5 ng/ml in 29 patients, and in 16 (55%) of these recurrence or metastases occurred. On the other hand,

Table I—Carcinoembryonic antigen (CEA) values and clinical status of patients with primary cancer of entodermal origin

	Nos. of patients with clinical evidence of neoplasm	
CEA value	Positive	Negative
Normal*	145†	556‡
Elevated*	213‡	74†

*Normal value ⩽ 5 ng/ml; elevated value > 5 ng/ml for all tables.
†Negative correlation between clinical status and CEA value (219 patients [22%]).
‡Positive correlation between clinical status and CEA value (769 patients [78%]).

Table II—Correlation for 81 patients with cancer between clinical status and CEA values in 1972, and clinical status in 1975

Site of primary tumour	Date and nos. of patients: November 1972 — Evidence of malignant disease	CEA values		November 1975 — Free of malignant disease	Clinical progression
Colon (n = 60)	Negative: 49	Normal	46	41*	5*
		Elevated	3	1	2*
	Positive: 11	Normal	4	0	4
		Elevated	7	0	7*
Elsewhere (n = 21)	Negative: 15	Normal	13	7*	6
		Elevated	2	1	1*
	Positive: 6	Normal	4	1*	3
		Elevated	2	0	2*

*Good correlation between CEA values and prognosis.

Table III—Preoperative CEA value as prognostic marker in 64 patients with colorectal cancer

Preoperative CEA value	Recurrence within 9 months
Normal (n = 35)	11 (31%)*
Elevated (n = 29)	16 (55%)*

*Difference not significant.

among 35 patients with CEA values of less than 5 ng/ml, the disease progressed within 6 months in 11 (31%).

"False-negative" CEA values

Of 74 patients in whom CEA values exceeding 5 ng/ml were detected when the patients presented but in whom there were no signs of malignant disease, follow-up data for 3 months or longer were available for 44 (Table IV). Of these, 40 had a primary colorectal cancer and in 21 progression of the disease has been proven. The proportion with progression was highest (90%) in those with higher CEA values (> 25 ng/ml) and lowest (37%) in those with moderately increased CEA values (5 to 10 ng/ml). The other four had a primary tumour in the stomach (three) or biliary tract (one); in two of these patients recurrence has since developed.

CEA values in patients receiving chemotherapy

In 40 patients with metastatic cancer of the colon, pancreas or stomach who were treated with chemotherapeutic agents, CEA values were determined before and regularly during and after treatment. Increasing CEA values were recorded in 11 of these patients and the disease in all of them progressed during treatment. In 29 patients with stable or decreasing CEA values, the disease progressed clinically in 17, it arrested in 8 and improvement was noted in 4 (Table V).

Discussion

The introduction of chemotherapy has not yet substantially improved survival of patients with carcinoma of the colon.[1] It seems obvious that early diagnosis of primary, recurrent or metastatic disease might be an important determinant in the effective treatment of colonic cancer.

The concentration of circulating CEA alone is not useful as a diagnostic clue to primary carcinoma of the colon in so far as it is only elevated in an appreciable number of patients when the tumour has infiltrated regional lymph nodes.[2-4] Other diagnostic methods, such as sigmoidoscopy and contrast-medium radiography, are far more useful as single diagnostic tests. However, when all three methods are combined, diagnosis becomes more accurate.[5]

CEA values are most useful in the follow-up of patients after resection for "cure" of a carcinoma of the colon.[3,6,7] These values are correlated with Duke's grading[2-4] but seem to be highest for the most differentiated tumours.[4,6] As a long-range prognostic marker, elevated CEA values have been claimed by some[3,4] to be a sign of poor prognosis, while Booth and colleagues,[8] after a 2-year follow-up of 23 patients, found no correlation between CEA values and progression of the disease.

In our series, the follow-up time has been short and the differences between these two groups not statistically significant, but a trend seems to exist towards an association between normal CEA values and a better prognosis.

CEA values in all patients with entodermally derived cancer

Results indicate that an elevated CEA value in a patient after resection for "cure" is indicative of poor prognosis. In our series, 287 patients had elevated CEA concentrations (Table I); 213 had known malignant disease and in 24 more a tumour was clinically detectable within 1 year.

Among patients followed up for 3

Table V—Correlation of CEA values in 40 patients managed with chemotherapy in whom disease progressed

Change in CEA value	Course of disease: Progression	No progression or improvement
Increasing	11*	0*
Static or decreasing	17*	12*

*Differences between these values are statistically significant (chi-square analysis).

Table IV—Recurrence of neoplasm in 44 patients with cancer of entodermal origin managed by resection for "cure" who, at time of CEA determination, were clinically free of disease but had elevated CEA values

First elevated CEA value (ng/ml)	Colon: No.	Colon: No. with progression	Stomach: No.	Stomach: No. with progression	Biliary ducts: No.	Biliary ducts: No. with progression
5.1 — 10.0	19	7*	2	1	1	1
10.1 — 25.0	11	5*	1	0	0	0
> 25.0	10	9*	0	0	0	0

*Differences between groups significant (chi-square analysis).

years (Table II) 13 of the 14 patients with initially high CEA values were seen postoperatively (1 had an inoperable carcinoma of the pancreas) and, 3 years later, 11 of these had evidence of progression of the disease and only 2 were free of disease.

CEA values in patients receiving chemotherapy

Monitoring of CEA values has been recommended for patients undergoing chemotherapy.[7,9,10] It is difficult to assess "clinical improvement" in these patients, but in our series (Table V), as in that of Ravry and associates,[7] increasing CEA values strongly suggested disease progression. Stable and decreasing CEA values have no prognostic significance, especially since a "terminal" decrease in CEA values has been described in many patients.[9] Repeatedly elevated CEA values following resection for "cure" are a strong indication of disease progression. In patients without clinical or investigational evidence of disease, a surgical "second look" may be justified. Zamcheck[9] stated that Martin and Minton had done this in 20 patients on the basis of elevated or increasing CEA values and found malignant growth in 17. In our series, 44 of 71 patients with unexplained high values of CEA were followed up for 3 months or longer, 40 of the 44 having originally had a colorectal cancer that was resected for "cure", and the CEA value was clearly associated with the rate of recurrence in these patients.

Conclusion

We have found that repeatedly elevated CEA values preoperatively, postoperatively and during chemotherapeutic treatment are an indication of disease progression and a useful marker for early detection of recurrence and metastasis, especially in patients with colorectal cancer. Normal values of CEA are of little prognostic value.

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References

1. SCHEIN PS, KISNER D, MACDONALD JS: Chemotherapy of large intestinal carcinoma — current results and future projects. *Cancer* 36: 2418, 1975
2. MACH J-P, JAEGER PH, BERTHOLET M-M: Detection of recurrence of large-bowel carcinoma by radioimmunoassay of circulating carcinoembryonic antigen (CEA). *Lancet* 2: 535, 1974
3. LOGERFO P, HERTER FP: Carcinoembryonic antigen and prognosis in patients with colon cancer. *Ann Surg* 181: 81, 1975
4. ZAMCHEK N, DOOS WG, PRUDENTE R, et al: Prognostic factors in colon carcinoma: correlation of serum carcinoembryonic antigen level and tumor histopathology. *Hum Pathol* 6: 31, 1975
5. MCCARTNEY WH, HOPPER PB: The value of carcinoembryonic antigen (CEA) as an adjunct to the radiological colon examination in the diagnosis of malignancy. *Radiology* 110: 325, 1974
6. MARTIN EW JR, KIBBEY WE, DIVECCHIA L, et al: Carcinoembryonic antigen: clinical and historical aspects. *Cancer* 37: 62, 1976
7. RAVRY M, MOERTEL CG, SCHUTT AJ, et al: Usefulness of serial serum carcinoembryonic antigen (CEA) determinations during anticancer therapy or long-term follow-up of gastrointestinal carcinoma. *Cancer* 34: 1230, 1974
8. BOOTH SN, JAMIESON GC, KING JP, et al: Carcinoembryonic antigen in management of colorectal carcinoma. *Br Med J* 4: 183, 1974
9. ZAMCHECK N: The present status of CEA in diagnosis, prognosis and evaluation of therapy. *Cancer* 36: 2460, 1975
10. SKARIN AT, DELWICHE R, ZAMCHECK N, et al: Clinical correlation with chemotherapy for metastatic gastrointestinal cancer. *Cancer* 33: 1239, 1974