Carcinoembryonic Antigen (CEA) as a Prognostic and Monitoring Test in Clinically Complete Resection of Colorectal Carcinoma

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The prognostic and postoperative monitoring capabilities of the CEA assay were compared to pathological staging of the operative specimens, clinical followup including endoscopy, radiology and scanning techniques, as well as DNCB skin testing and laboratory enzyme determinations (alkaline phosphatase and transaminase). A total of 46 patients with curative resection for colorectal carcinoma were studied. This included 23 patients with recurrent tumors compared to 23 long-term survivors without signs of recurrence at the time of the study. Preoperative CEA determinations were a good prognostic tool comparable to pathological staging of the specimen. Postoperative CEA monitoring was the earliest sign of recurrence in 14 of 23 patients and was positive at the time of recurrence determined by other methods in 20; it was negative in only three cases. The incidence of false positive results among the non recurrent group became a lesser problem when repeated elevated values were required before considering the patient as having a recurrence. From these data, it seems reasonable to propose the use of a second-look operation in patients with maintained elevation of circulating CEA and no clinical signs of tumor presence, if we are to treat recurrence at an early stage. Chemotherapy would be an alternative way to deal with this problem, since the absence of clinical signs in general correlate with small bulk of tumor which at this time may be more susceptible to chemotherapeutic agents.

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CARCINOEMBRYONIC ANTIGEN is a tumor-associated antigen identified in colorectal carcinoma tissue in 1965 by Gold and Freedman.[4] This discovery was followed by a search for this antigen in patient's sera which succeeded when Thomson and co-workers[17] described a method to detect nanogram quantities of the antigen in the serum of patients who have tumors of the digestive tract. The method was further elaborated [2,5] and evaluated in patients with other cancers and non-cancerous diseases. Initially thought to be specific for colorectal cancer, it soon became obvious that elevation of this circulating antigen was present in several different malignancies as well as in some non-malignant diseases.[8,12,15] A larger clinical experience has been accumulated since and the significance of the test as a diagnostic tool in colorectal carcinoma has been defined in part at least by cooperative studies.[6,13]

The prognostic value of preoperative determinations as well as postoperative monitoring to diagnose recurrence, progression or regression for a number of tumors has also been discussed by several authors.[1,3,7,9–11,18] The present study was undertaken in order to assess for colon cancer: 1) The value of preoperative CEA as a prognostic tool, 2) Its correlation to tumor staging using a TNM and Duke's classification, 3) The usefulness of postoperative monitoring with periodic CEA determinations, 4) The correlation of CEA with other clinical and laboratory tests.

Materials and Methods

The records of 271 patients with histologically proven colorectal carcinoma were reviewed. A total of 66 patients had complete resection with preoperative and postoperative CEA determinations over a period of time longer than 6 months. All patients with a second primary occurring at any time during the period of observation were excluded from the study. These patients had one preoperative and one postoperative determination at 4 days, 2 weeks, one month and then every 3 months, except for those patients undergoing additional treatment

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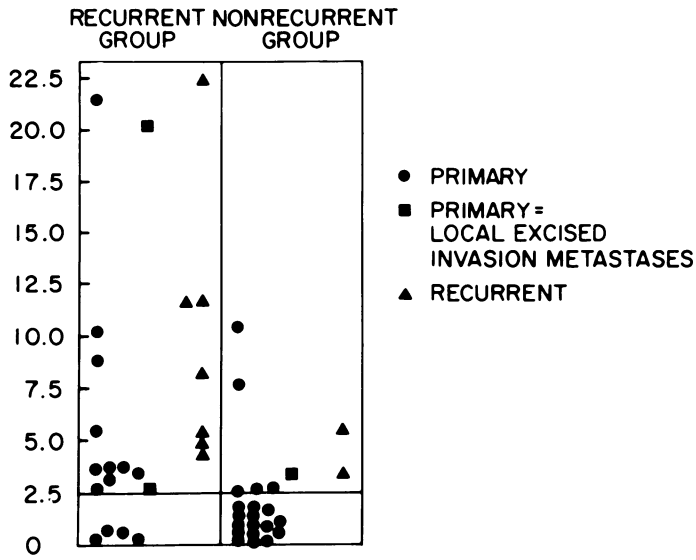

FIG. 1. Nineteen of 23 patients who developed recurrence had CEA values above 2.5 ng/ml as opposed to 8 among the 23 control patients.

such as radiation or chemotherapy in which case, they were tested on a monthly basis. The method used was that of Hansen as described by Chu and Reynoso.[2]

Among the 66 patients with clinically complete resection, a total of 23 developed metastatic or regional recurrence. This group of 23 patients was compared with a group of 23 patients clinically free of disease which included all the patients without recurrence and a followup longer than 14 months at the time of this report. The patients who did have recurrence did so between three and 21 months post resection, with only one developing recurrence after 18 months. The non-recurrent patients had preoperative and postoperative CEA determinations and their postoperative followup period ranged between 14 and 46 months with a mean value of 25 months with only 4 patients having less than 18 months followup. The

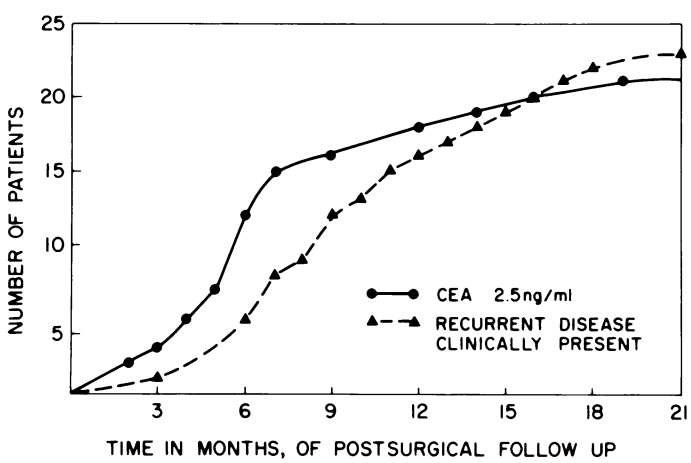

Fig. 2. Following curative resection, CEA usually is elevated in patients developing recurrence 3½ months before disease is clinically evident.

23 patients from the recurrent group consisted of 10 men and 13 women with ages ranging from 41 to 81 and a mean of 63 years. The mean age for the non recurrent group was also 63 years with a range from 28 to 86. There were 8 men and 15 women in this group.

Results

Preoperative CEA Values

In 19 of 23 patients (83%) who underwent curative resection, but later developed recurrence, the preoperative CEA values were above the levels considered as normal, or 2.5 nanograms per cc (Fig. 1).

Only 8 patients had preoperative elevations among the 23 patients in the non recurrent group and only three of these were above the 4 nanogram mark as compared to 14 from the recurrent group. It should be mentioned that two of these patients from the non recurrent group already had recurrent disease when entered into the study prior to resection so that it is likely that their tumor may still recur again. The mean CEA value for the recurrent group is 9.7 ng/ml while for the non recurrent group it is 2.5 ng/ml with a t value of 2.242, for the difference between the means of indicating a statistically significant difference at the 1% level.

Postoperative CEA Values

Twelve patients from the recurrent group and 20 from the non recurrent group demonstrated CEA levels within the 12th postoperative week which were above the preoperative values, while for 8 among the recurrent and 2 among the non recurrent patients CEA fell to levels below the preoperative ones. In the majority of patients, the values of CEA were stabilized by the 12th postoperative week.

An elevation above normal which persisted was present in 20 patients who developed recurrence, at the time of recurrence (87%) and became later elevated in one. In another patient, the CEA was low at the time of a small perineal implant which was resected with all later values still negative and the continued absence of clinical evidence of disease. The last patient from the recurrent group, although he had high preoperative values, never did show a rise in his serum antigen levels after abdominoperineal resection despite evidence of pulmonary metastases three months postoperatively.

Fig. 2 shows the mean time of detectable rise in CEA for all those patients in whom disease recurred. The mean lead time is a little more than 3 months. We also note that two patients never did show an elevation as discussed above.

Among the 20 patients with elevated values at the time of recurrence, 14 had their values abnormally elevated more than 3 months before clinical detection of metastases. For those 14 patients, there is a significant 5½

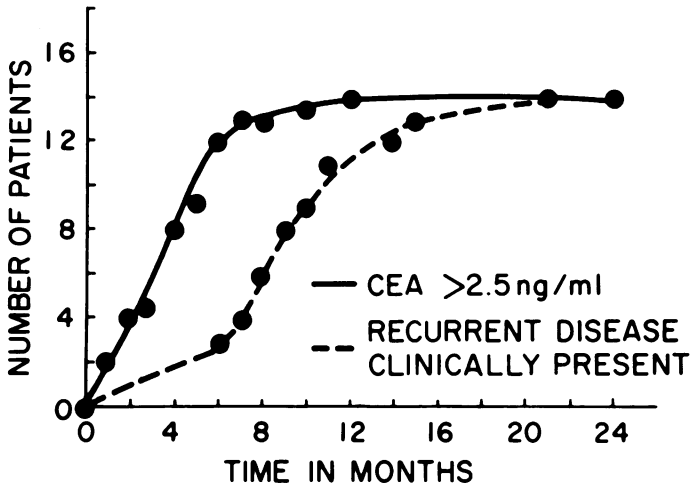

FIG. 3. Following curative resection 14 of 23 patients demonstrated a rise in CEA more than 3 months before recurrence was otherwise detected.

months lead time in detection of recurrent tumor as against other clinical means of detection (see Fig. 3).

In the non recurrent group of patients, there is one patient whose postoperative values were all positive and who had a repeatedly negative work-up for signs of recurrence. This patient is a chronic and heavy smoker. One patient has had very irregular values over a followup period of 31 months with no evidence of recurrence to date. Her liver disease was established by examination with an elevated alkaline phosphatase and SGOT. There are 4 other patients with transitory elevations of 2 and 3 (2 of these had 3 consecutive elevated values) consecutive CEA values who have later become negative for a prolonged period of time and who remain without evidence of disease at present. There are 4 additional patients who demonstrated a single isolated value which was elevated, but in whom a repeat value was normal. (A total of 278 determinations have been done in the 23 patients in whom disease has not recurred.) The remaining 13 patients in the non recurrence group never showed an elevation of CEA subsequent to the 12th postoperative week.

Disregarding the isolated elevations, we still have 6 patients (out of the 23 non recurrent individuals) with false positive results. Two of these have clear cut associated benign cause for these elevations and of the other 4, 2 were elevated over a span of 3 values.

Considering those patients in the two groups together who could be staged, there were 12 patients with recurrent or metastatic disease (Duke's D) at the time of clinically complete resection; 11 of them had elevated preoperative CEA values and nine of them have developed recurrence to date (Tables 1 and 2).

Seventeen patients who had nodal metastasis (Duke's C) had elevated CEA values in 8 of 11 who recurred and

TABLE 1A. *Extent of Disease and Antigen Level in Recurrent Patients*

Disease Stage and Preoperative CEA							
Localized (Duke's A&B)		Nodal Involvement (Duke's C)		Local Recurrence (Duke's D)		Metastases (Duke's D)	
TNM	vs CEA	TNM	vs CEA	TNM	vs CEA	TNM	vs CEA
T3	1.4	T2N1	0.5	T4 (R)*	7.1	T3N2M1	2.5
T4	3.3	T3N1	4.6	T4(R) *	8.5	T4N2M1	21.8
T4	4.3	T3N1	4.6	T4 (R)*	11.3	M1 (R)*	4.0
		T3N1	13.1	T4 (R)*	128.3	M1 (R)*	5.1
		T3N2	2.8			M1 (R)*	10.8
		T3N3	0.0				
		T3N3	9.4				
		T4N1	3.9				
		T4N1	5.0				
		T4N1	27.0				
		T4N2	0.0				
Mean: $\bar{x}$=3.0		$\bar{x}$=6.0		$\bar{x}$=38.8		$\bar{x}$=9.0	

*(R) Recurrent disease from previously resected Colorectal carcinoma.

TABLE 1B. *Extent of Disease and Antigen Level in Non Recurrent Patients*

Disease Stage and Preoperative CEA							
Localized (Duke's A&B)		Nodal Involvement (Duke's C)		Local Recurrence (Duke's D)		Metastases (Duke's D)	
TNM	vs CEA	TNM	vs CEA	TNM	vs CEA	TNM	vs CEA
T1	0.0	T2N1	0.3	T3 (R)*	0.3	T4N1M1	4.0
T2	0.5	T2N1	0.4	T3 (R)*	6.4		
T2	0.5	T2N1	2.0				
T2	0.6	T3N1	0.6				
T2	1.2	T3N1	0.8				
T3	1.7	T4N1	2.5				
T3	0.0						
T3	0.9						
T3	1.7						
T3	1.8						
T3	2.7						
T3	4.0						
T3	8.0						
T3	12.8						
Mean: $\bar{x}$=2.7		$\bar{x}$=1.1		$\bar{x}$=3.4		$\bar{x}$=4.0	

*(R) Recurrent disease from previously resected colorectal carcinoma.

TABLE 2. *Recurrence of Disease in Patients After Complete Resection of Colorectal Carcinoma as Compared to Their Extent of Disease and Preoperative CEA Levels*

	Total No. Patients	Preoperative CEA > 2.5
Localized Tumor (Duke's A & B)	17	6
Recurrence	3	2
Nonrecurrence	14	4
Nodal Metastasis (Duke's C)	17	9
Recurrence	11	8
Nonrecurrence	6	1
Recurrent and Metastatic (Duke's D)	12	11
Recurrence	9	9
Nonrecurrence	3	2

TABLE 3. *Alkaline Phosphatase and SGOT Monitoring*

RECURRENT GROUP	#Patients
Always normal (failed to elevate)	16*
Elevated at the time of metastases	4
Elevated before evidence of metastases	3
Elevations within 6 weeks of major surgery as well as isolated elevations followed by normal values were eliminated.	
NON RECURRENT GROUP	
Always low (normal)	5
Isolated elevation	8
Temporary elevation	5†
Permanent elevation	5
Elevations within 6 weeks of major surgery excluded	

*In three patients of this group there was an elevation several months after obvious recurrence.

†Two or more consecutive elevated values with later return to normal.

in only one out of 6 who did not recur. There were 17 patients with localized tumors (Duke's A and B) 3 of whom developed recurrence (two with elevated CEA), while 4 of 14 who did not recur had abnormal values. There is a clear increased incidence of elevated values as disease stage progresses with 11 of 12 patients seen initially with recurrent or metastatic disease having elevated plasma values.

DNCB Skin Testing

A total of 14 patients of the recurrent group who had not been previously sensitized and 13 of the non recurrent patients were skin tested with 500 micrograms of an acetone solution of DinitroChloroBenzene (DNCB). There was no significant difference in delayed hypersensitivity response between the two groups either preoperatively or postoperatively. In these patients with technically curatively resected colorectal carcinoma, the DNCB skin test results as performed by us at the time of the study do not correlate with the stage of tumor (TNM) or with serum CEA levels.

Alkaline Phosphatase and SGOT in the Postoperative Followup

Elevations of alkaline phosphatase and SGOT occurring within 6 weeks of major surgery were disregarded. Single isolated elevations follow by normal values when repeated were also excluded. Among the 23 patients with recurrence, 16 had normal values at the time of obvious evidence of metastases, but three of the 16 turned positive at 3, 4 and 5 months post-recurrence respectively (Table 3). In four patients, the alkaline phosphatase was elevated at the time of recurrence and in only three others, it preceded the clinical evidence of metastases (two occurring in the liver and one in the abdominal wall). Interestingly, in these three patients in whom the alkaline phosphatase or the SGOT were elevated before recurrence, this elevation occurred earlier than the CEA elevation in each instance. In the non recurrent group of patients, alkaline phosphatase and SGOT were always low in only 5 of 23 patients. In 8 patients, there were single occasional elevations of either one or both enzymes with later return to normal values. In 5 patients, one or both enzymes has been elevated in all determinations without any manifestation of recurrence, while in the remaining 5 individuals, there were temporary consecutive elevations with later return to normal enzyme values. The enzyme values did not correlate with our CEA results, and correlated poorly with the disease state (Table 3).

Discussion

Our findings demonstrate the usefulness of the CEA assay when used preoperatively for estimating prognosis in colon cancer and for the prompt recognition of recurrence during postoperative monitoring of those patients who have undergone clinically complete resection for this malignancy. In general, patients with more advanced disease have a poorer prognosis and higher CEA levels. This agrees with previous reports by Holyoke,[7] Lo Gerfo[9] and their co-authors. CEA correlates well with TNM and Duke's staging of tumor, but CEA is usually superior to staging as a prognostic reference. In addition it is easier to perform, faster and more economical.[14] When monitoring resected patients for prompt recognition of recurrence, the CEA assay is usually superior to other available techniques when used in conjunction with endoscopy, biopsy and radiology, as was found by McCartney.[11]

We found no correlation between transient CEA elevations and clinical recurrence, but persistent or increasingly elevated levels meant the presence of metastases, except for two patients in the non recurrent group who although without clinical evidence of metastases at present, are suspected of bearing sub-clinical amounts of neoplasia. These findings correspond with those of Sorokin et al.[16]

Our data suggest that between 3 and 18 months, 3 successive elevations of CEA showing a rise gives a better than 90% certainty of the presence of recurrent disease and in appropriate patients would perhaps justify second look or other therapy. Single values are not reliable and even two successive elevated values may be misleading in 20% of patients. We recommend that if an elevated CEA value is encountered, the test should be repeated at 10 day to 2 week intervals, if necessary times two.

If our current data continue to be valid, an initial CEA value greater than 4.5 ng/ml will predict a greater than 80% chance of recurrence within 18 months of resection so that this parameter may turn out to be useful in the future as a means of deciding on adjuvant therapy.

Alkaline phosphatase and SGOT correlate poorly with presence or absence of recurrence when used to monitor resected patients. When these enzymes are used to

monitor colon cancer patients for recurrence, the frequency of both false positive and false negative results is much higher than is the case for CEA. Postoperatively CEA proved to be an excellent monitor, detecting 20 of 23 recurrences at the time of clinical diagnosis of recurrence and in 14 patients preceding clinical diagnosis of recurrence by any other test by more than 3 months.

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