Br. J. Surg. Vol. 66 (1979) 120–123

A reappraisal of the value of carcinoembryonic antigen in the management of patients with various neoplasms

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SUMMARY

Eight hundred and eight patients with histologically proved malignant disease had carcinoembryonic antigen (CEA) estimations performed at the time of tissue diagnosis. An elevated level was found in 384 of 518 patients with gastrointestinal neoplasms (74 per cent) and in 162 of 290 patients with other neoplasms (56 per cent). No correlation was found between CEA elevations and tumour differentiation. There was a good correlation between tumour staging and CEA levels for patients with colorectal cancer; the more advanced the tumour, the higher the CEA.

Several illustrative cases are presented and the role of CEA assay in the diagnosis and management of neoplasia is discussed. CEA assay is a poor screening test for neoplastic disease, but serial CEA monitoring is valuable in the detection of residual or recurrent cancer.

CARCINOEMBRYONIC antigen (CEA) was first described by Gold and Freedman in 1965 and was hailed as a specific tumour marker for colonic cancer (Thompson et al., 1969; Nugent and Hansen, 1971). Further studies with this antigen have shown that levels are elevated in a large proportion of patients with a variety of malignant and benign diseases (Zamcheck et al., 1972; Martin et al., 1976). Its value in the diagnosis and management of neoplastic disease needs to be redefined. We have correlated the results of all CEA estimations over the past 5 years in patients with histologically proved malignant disease and have studied several cases serially to demonstrate the value of CEA estimation in prognosis and management.

Patients and methods

Between March 1972 and January 1978, CEA estimations were performed on sera from 808 patients with histologically proved malignant disease at the University of Chicago. All assays were performed by the Hansen Z-gel method (Hansen et al., 1971) (Hoffman–LaRoche Inc.), a normal value being less than 2·5 μg/l; all determinations were first performed by the indirect method and those sera with a value greater than 20 μg/l were re-evaluated by the direct method. The initial CEA levels were recorded within 6 weeks of a tissue diagnosis being obtained, and all values were correlated with the surgical pathology reports. In those patients with cancers of the gastrointestinal tract note was taken of the histological differentiation; and for colonic cancers the staging was recorded by the revised Dukes' method of Astler and Coller (1954).

Results

A CEA level was obtained for 290 patients with a variety of non-gastrointestinal neoplasms; 56 per cent of this group had a CEA greater than 2·5 μg/l at the time of tissue diagnosis, and 60 per cent produced an elevated CEA at some time (*Table I*). There was a total of 526 gastrointestinal neoplasms; an elevated CEA was produced by 76 per cent of the adenocarcinomas, 60 per cent of the squamous carcinomas and 75 per cent of the APUD tumors (*Table II*). The CEA level in patients with various gastrointestinal neoplasms was compared with cellular differentiation (*Fig.* 1); no correlation could be found. In patients with colorectal cancer, the most advanced tumours as determined by the modified Dukes' classification gave rise to the highest percentage of elevated CEA levels (*Fig.* 2).

Fig. 3 illustrates results in 4 representative patients with colorectal cancer.

Case 1: D. B., a 78-year-old female, presented in April 1978 with a 3-year history of change of bowel habit. A CEA level was >1200 μg/l and barium enema revealed a caecal cancer. She underwent a right radical hemicolectomy for a well-differentiated C2 cancer, and 1 month later her CEA had fallen

Table I: RESULTS OF CEA ASSAYS ON PATIENTS WITH NON-GASTROINTESTINAL NEOPLASMS

Primary neoplasm	No. of patients	CEA>2·5 μg/l: At time of tissue diagnosis (%)	CEA>2·5 μg/l: At any time (%)
Lung	54	66·7	72·2
Breast	54	68·5	72·2
Kidney	9	66·7	66·7
Hodgkin's disease	18	22·2	27·8
Prostate	21	66·7	71·4
Testis	2	50	50
Gynaecological (misc.)	18	66·7	66·7
Thyroid	4	50	50
Bladder	10	60	60
Lymphoma (non-Hodgkin)	32	15·6	18·8
Sarcoma (misc.)	5	0	20
Skin (misc.)	10	30	40
Total	290	55·9	60·3

Table II: RESULTS OF CEA ASSAYS ON PATIENTS WITH GASTROINTESTINAL NEOPLASMS

Primary neoplasm	No. of patients	CEA>2·5 μg/l: At time of tissue diagnosis (%)	CEA>2·5 μg/l: At any time (%)
Oropharynx (squamous)	39	58·8	58·8
Oesophagus (squamous)	18	61·6	66·7
Stomach (adeno)	69	59·4	78·3
Cholangiocarcinoma	11	72·7	100
Hepatoma	12	75	75
Pancreas (adeno)	77	80·5	89·6
APUD tumours	8	75	75
Small bowel (adeno)	6	83·3	83·3
Colon (adeno)	283	78·8	86·2
Anus (squamous)	3	66·7	100
Total			
Adenocarcinoma	458	76	85·6
Squamous cancer	60	60	63·3

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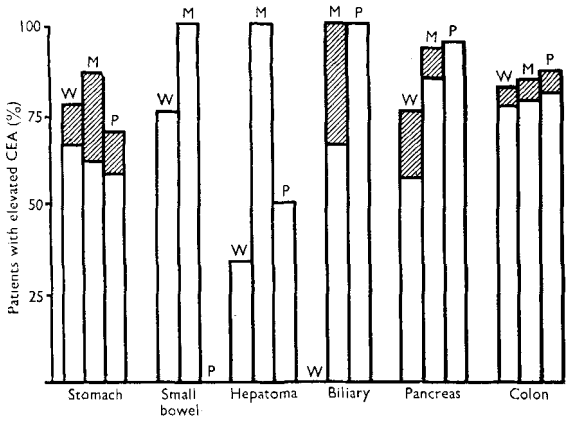

Fig. 1. Patients with gastrointestinal neoplasms divided by cellular differentiation (W, well, M, moderately and P, poorly differentiated) showing the percentage with an elevated CEA at the time of tissue diagnosis (white bars) and the total percentage that develop an elevation at any time (hatched bars).

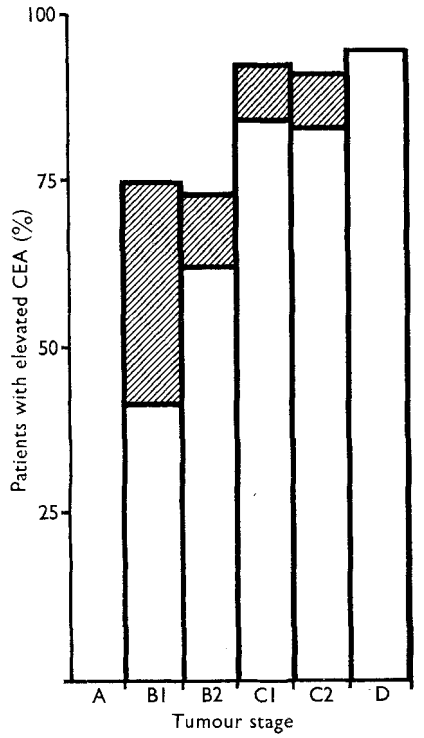

Fig. 2. Patients with colorectal cancer divided by stage showing the percentage with an elevated CEA at the time of tissue diagnosis (white bars) and the total percentage that develop an elevation at any time (hatched bars).

to 4 μg/l. The CEA then rose to 6 μg/l at 3 months, and 185 μg/l at 9 months; liver scan and chest X-ray at that time revealed multiple metastases.

Case 2: H. D., a 70-year-old female, presented in December 1975 with a change of bowel habit. Investigation revealed a colonic mass and a CEA of 9·6 μg/l. A colectomy was performed for a moderately differentiated C2 cancer of the descending colon. In June 1976 a repeat CEA was still elevated at 7·6 μg/l and further investigation revealed a small rectal

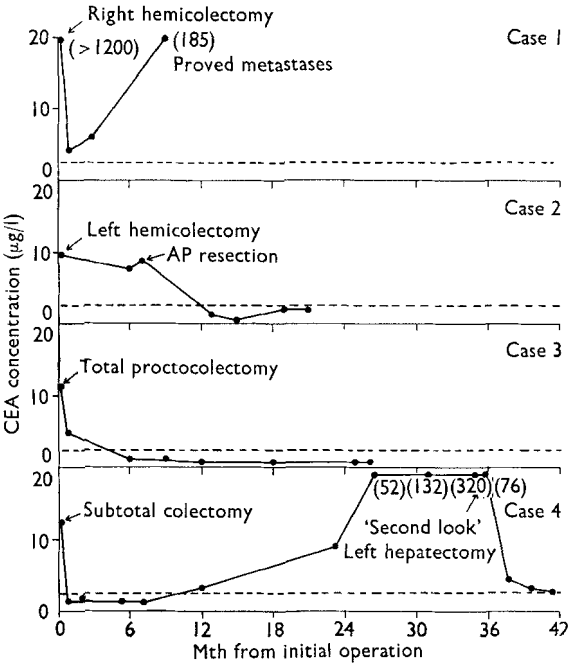

Fig. 3. Results of serial CEA estimations performed on 4 patients with colorectal cancer.

tumour (<1 cm in diameter). Following an abdominoperineal resection CEA levels fell to normal and the patient remains symptom-free with normal CEA levels 18 months later.

Case 3: M. H., a 41-year-old female with known ulcerative colitis, was seen in January 1975 when a routine check-up disclosed two colonic strictures. Her CEA at this time was 11·2 μg/l. A total proctocolectomy was performed for a moderately differentiated B2 cancer of the splenic flexure, and her CEA levels fell to normal. She is clinically free of tumour with normal CEA levels 2 years later.

Case 4: H. B., a 69-year-old male, presented in November 1973 with a change in bowel habit. Investigation revealed two colonic cancers and a CEA of 12·4 μg/l. Subtotal colectomy was performed for two moderately differentiated C2 cancers and the CEA fell to 1·2 μg/l. Serial CEA levels began to rise 12 months postoperatively and reached 52 μg/l at 28 months; investigations at this time showed no evidence for recurrent or metastatic disease. The CEA remained elevated and, on this evidence alone, a 'second look' laparotomy was performed at 36 months. A solitary metastasis in the left lobe of the liver was removed; CEA concentration was 2·8 μg/l 6 months later.

Discussion

Several antigens have now been described that are present in significant amounts only in neoplastic and fetal tissues (Gold and Freedman, 1965; Abelev, 1974; Gelder et al., 1978). The development of radioimmunoassays allows reliable measurement of the plasma concentrations of these antigens, and several have now been evaluated as tumour markers. The description by Gold (Gold and Freedman, 1965) of CEA and initial reports of its specificity for entodermal cancers (Thompson et al., 1969; Nugent and Hansen, 1971) provoked widespread interest, and it is now the most thoroughly evaluated of the oncofetal antigens. Several assay techniques have been described for CEA: we have employed the Hansen Z-gel method (Hansen et al., 1971), which has been manufactured

Table III: NUMBER OF PATIENTS WITH AN ELEVATED CEA

	No. of patients in group	No. of patients with a CEA greater than 2·5 μg/l	10·0 μg/l
Pancreatic cancer patients	52	43 (83%)	20 (39%)
Other cancer patients	51	33 (65%)	16 (31%)
Benign disease patients	67	31 (46%)	4 (6%)

Table IV: THE DIAGNOSTIC ABILITY OF AN ELEVATED CEA FOR MALIGNANT DISEASE TAKING TWO UPPER LIMITS OF NORMALITY

	CEA > 2·5 μg/l (%)	CEA > 10·0 μg/l (%)
Prevalence	60·6	60·6
Sensitivity	73·8	35·0
Specificity	53·7	94·0
Accuracy	65·9	58·0
Predictive value of a positive test	71·0 (3·1%)*	90·0 (10·6%)*
Predictive value of a negative test	57·1 (99·0%)*	48·5 (98·6%)*

The predictive value of a positive test is (true positive tests/all positive tests), and the predictive value of a negative test is (true negative tests/all negative tests).
* These predictive values may be recalculated and projected to a theoretical population with a 2 per cent prevalence of malignant disease, as shown in parentheses (Vecchio, 1966).

into kits by Hoffman–LaRoche. This assay is relatively simple, although it involves several steps and is time-consuming.

Experience with this assay in over 10 000 patients from Europe and America has shown that 97 per cent of normal people have a value less than 2·5 μg/l; the remaining 3 per cent tending to be heavy smokers (Roche Diagnostics, 1976). Initial evaluation of CEA in colonic cancer patients revealed an elevated level in 96 per cent (Thompson et al., 1969), but this was a selected group with advanced disease and a more realistic figure is around 80 per cent (Zamcheck, 1975; Martin et al., 1976). Further evaluation of CEA found values greater than 2·5 μg/l in patients with a variety of gastrointestinal tumours, particularly of the pancreas (Khoo and Mackay, 1973; Dilwari et al., 1975), where 90 per cent positive results have been frequently reported, and also in other malignant disorders, though the percentage of positive results is not as high (Stewart et al., 1974; DiSaia et al., 1977). Our figures (*Tables I, II*) are in agreement with published series.

CEA assay cannot provide a reliable screening test for malignant neoplasms as levels are frequently elevated in patients with benign disease. Elevated levels have been found in association with pancreatitis (Dilwari et al., 1975), cholecystitis (Martin et al., 1976), inflammatory bowel disease (Martin et al., 1976), liver disease (Bullen et al., 1977) and rectal polyps (Doos et al., 1975; Martin et al., 1977). While this reduces the value of CEA assay as a screening test for malignant disease, an elevation can be used to monitor these diseases. Bullen et al. (1977) found an elevated CEA in up to 70 per cent of patients with liver disease and found the CEA level to be useful in distinguishing acute from chronic liver damage. Martin et al. (1977) reported an elevated CEA in 40 per cent of patients with rectal polyps and noted that he level fell to normal after polypectomy. It has been suggested that the value of CEA as a screening test for malignant disease could be improved by taking a level of 10 μg/l as the upper limit of normal (Concannon et al., 1973, 1974). CEA levels were assayed as part of a prospective diagnostic protocol for pancreatic cancer at this institution and the results have been reported elsewhere (Wood and Moossa, 1977). To illustrate the effect of increasing the upper limit of normal from 2·5 to 10 μg/l we have evaluated the test in a group of 170 patients (*Tables III, IV*).

From *Table III* it can be seen that while 83 per cent of pancreatic cancer patients had a CEA of over 2·5 μg/l, so did 46 per cent of patients with benign disease. The effect of increasing the upper limit of normal to 10 μg/l is to reduce the positive results in benign disease to 6 per cent, at the expense of a large drop in the positive results for pancreatic cancer (39 per cent). The predictive value of a positive test must remain significantly greater than the prevalence of the disease sought (Vecchio, 1966); an effective screening test requires a high predictive value for a positive test to minimize the number of patients without malignant disease being subjected to further, and sometimes extensive, investigation. These values are shown in *Table IV* for a highly selected group of patients. When they are projected to a theoretical population with a 2 per cent prevalence of malignant disease (figures in parentheses in *Table IV*), a better estimation of the value of CEA as a screening test can be obtained. It is evident that the preferred normal level is 10 μg/l as a minimal loss in the predictive value of a negative test results in a threefold increase in the predictive value of a positive test. Even at this level, however, only 1 in 10 of the patients with a positive CEA will have malignant disease. CEA assay is thus a poor screening test for malignant disease.

A good correlation has been found between positive CEA tests and tumour staging (Zamcheck et al., 1972; Martin et al., 1976). Furthermore, the larger the tumour mass, the more CEA is produced, the highest levels being found in patients with metastatic disease, as shown in *Fig.* 2. Some authors (Martin et al., 1976) have shown that more CEA is produced by the better differentiated tumours, but we are unable to confirm this finding (*Fig.* 1); our results show no correlation between cellular differentiation and CEA levels. The effect of differentiation is difficult to estimate on its own, as the well-differentiated tumours are sometimes small and therefore less likely to produce large amounts of CEA. *Tables I* and *II* show that a small percentage of patients with an initially normal CEA develop elevations during the course of their disease. The clinical significance of this observation has not been fully evaluated and requires further investigation.

Attention has turned to the ability of serial CEA assay to detect recurrent or residual tumour at an early stage (Dhar et al., 1972; Sugarbaker et al., 1976; Martin et al., 1977). The success of Ellis and others with 'second look' procedures has prompted a more aggressive approach to the management of recurrent cancer; the success of these operations relies on early detection of recurrent tumour. An elevated CEA should fall to normal within 1 month of curative resection of a cancer (Zamcheck, 1975; Martin et al., 1976): this is well shown in *Case* 3, where the level fell below 2·5 μg/l after surgery and has remained low as the patient has remained clinically free of tumour. Failure of an elevated CEA to fall after resection is

indicative of incomplete excision or recurrence; this is seen in *Case* 2, where a persistently elevated CEA was found in the presence of a second or recurrent colonic cancer. Removal of the residual cancer resulted in the CEA level returning to normal. In *Case* 1 we see the effect of removing a bulky tumour, with CEA falling to near normal levels, only to rise as the disease progresses. Several authors (Dhar et al., 1972; Zamcheck, 1975; Martin et al., 1976) have reported CEA elevation in patients with recurrent cancer before any other clinical investigation revealed tumour, and the development of a rising CEA after apparent curative surgery now provides good grounds for a 'second look' operation, even when all other investigations are normal. This is illustrated well by *Case* 4, where the CEA level increased and remained elevated as the result of a solitary hepatic metastasis which was undetected by other investigations for over 1 year. The correlation of CEA and the response to chemotherapy has also been investigated (Skarin et al., 1974); changes in CEA levels correspond well to progression or regression of the disease. The serial assay of CEA also appears to be useful in the management of some non-gastrointestinal tract tumours, including breast and gynaecological tumours (Stewart et al., 1974; DiSaia et al., 1977).

CEA has been thoroughly evaluated over the past 10 years and its place in clinical practice can now be defined. Measurement of this antigen has little to offer in the detection of malignant disease, but a pre-treatment estimation with serial follow-up provides good estimation of the completeness of excision or effectiveness of therapy. A persistently high or rising level indicates progression of the cancer. A rising post-operative CEA level is a good indication for a 'second look' procedure.

Acknowledgement

M. J. Cooper was supported in part by a grant from the Wellcome Trust.

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Paper accepted 19 July 1978.