PAPERS AND ORIGINALS

Carcinoembryonic Antigen in Management of Colorectal Carcinoma

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Summary

Carcinoembryonic antigen (C.E.A.) estimation has been used in the preoperative assessment of colorectal carcinoma patients and has been shown to give a useful guide to the presence of metastatic disease and ultimately to a poor prognosis if the serum concentration is 100 ng/ml or more. C.E.A. has been shown to be a more reliable index of tumour spread than either clinical examination or serum alkaline phosphatase estimation. Raised C.E.A. levels of less than 100 ng/ml do not, however, necessarily imply a poor prognosis. Routine C.E.A. estimation may have a valuable role in the assessment of the colorectal cancer patient by identifying those likely to benefit from postoperative chemotherapy.

The test has also been assessed in a group of patients attending cancer follow-up clinics after radical resection of a colorectal tumour. Raised C.E.A. occurred in most of those developing recurrent disease, and in several patients a rising C.E.A. level preceded clinical or biochemical evidence of recurrence. C.E.A. estimation is a superior guide and of clinical importance when applied to the follow-up of the colorectal cancer patient.

Introduction

The applications of serum carcinoembryonic antigen (C.E.A.) immunoassay to diagnostic clinical practice have been disappointing after the initial promising report (Thomson *et al.*, 1969). In most studies in patients with carcinoma of the colon and rectum between 30% and 60% of patients with localized

disease have raised levels, while the positivity approaches 100% when dissemination has occurred (Laurence *et al.*, 1972; Dhar *et al.*, 1972; Booth *et al.*, 1973). The diagnosis of metastases is not always easy to make, even at operation, but is important since it may affect clinical management. Objective remissions are occasionally obtained with chemotherapeutic agents (Moertel, 1973), and successful hepatic lobectomy for secondary malignancy is not unknown (Flanagan and Foster, 1967; Allan *et al.*, 1972). Thus C.E.A. estimation might give additional useful information about tumour status in patients with colorectal carcinomata.

Experimental observations suggest that the liberation of tumour cell surface glycoprotein results in a decrease in immunogenicity and an increase in metastasizing ability of tumours, perhaps the result of inhibition of cell-mediated immunity (Kim and Carruthers, 1972). C.E.A., itself a glycoprotein, is located on the surface of the carcinoma cell, and on the basis of these observations Laurence *et al.* (1972) have suggested that patients with undetectable or normal C.E.A. levels should expect a favourable course whereas the prognosis should be poor in patients with raised preoperative levels.

We have previously reported that C.E.A. levels return to normal after successful resection of a colonic tumour and that many patients with recurrent disease have raised levels (Booth *et al.*, 1973). The prognosis for recurrent colonic carcinoma is not always hopeless and some authorities have advocated the use of routine second-look operations (Gilbertsen and Wangenstein, 1962). Thus it is conceivable that routine C.E.A. estimation will be of value in detecting tumour recurrence at a time when further radical surgery is possible.

We report here the value of C.E.A. estimation in the detection of metastatic disease from carcinoma of the colon and rectum and as a guide to prognosis after radical surgery. Preliminary observations have also been made in a group of patients attending surgical follow-up clinics after radical resection of the tumour.

Patients and Methods

One hundred and four patients with carcinomata of the colon and rectum attending the General Hospital, Birming-

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ham, for surgical resection were assessed by full clinical examination, chest radiology, estimation of serum concentrations of albumin, globulin, bilirubin, alkaline phosphatase, and aspartate aminotransferase (SGOT), and estimation of C.E.A. levels. After laparotomy the diagnosis was confirmed by histological examination. On the basis of the operative findings the patients were allocated to one of three groups. Group 1 consisted of 67 patients in whom the tumour was apparently localized (Duke's grade A, B, or C) when radical surgery was performed. Group 2 consisted of 11 patients in whom the tumour was apparently localized but advanced. These patients either were inoperable or only palliative surgery was performed. Group 3 consisted of 22 patients with metastatic disease in the liver and sometimes other sites and four patients with metastatic disease in other sites with no liver metastases evident.

Twenty patients in group 1 had their tumour status reviewed two years after the initial operation and were further divided into a group who developed recurrent disease and a group who remained tumour free.

Serial C.E.A. measurements were made on 124 patients attending regular follow-up clinics after radical resection of a colorectal carcinoma between January 1967 and June 1973. Five patients were studied from the time of the initial laparotomy, the remainder being included between six months and five years after operation. The determinations were made at varying intervals but at every outpatient clinic attendance over a period of up to two years. Patients were also assessed by full clinical examination, estimation of haemoglobin and sedimentation rate, and the liver function tests outlined above. Sigmoidoscopy was carried out at least every 12 months and barium enema examination every two years. Tumour recurrence was established by histological examination after operation or at necropsy or by definite clinical evidence of metastatic disease progressing to death (in two cases). In no instances were clinical decisions, such as to perform second-look laparotomy, make an earlier follow-up appointment, or make further investigations, made on the basis of the C.E.A. level.

Serum samples for C.E.A. estimation were stored at -20°C until used and assays were carried out without knowledge of the clinical details. C.E.A. levels were estimated using the double antibody radioimmunoassay as described by Egan *et al.* (1972) and as subsequently modified by Laurence *et al.* (1972). A synopsis of this method has been published previously (Booth *et al.*, 1973). The upper limit of normal has been established at 15 ng/ml as the result of a study of a normal population (Booth *et al.*, 1972).

Results

C.E.A. MEASUREMENT AS INDEX OF METASTATIC DISEASE

Raised levels of C.E.A. were recorded in 37 patients with resectable tumours of the colon and rectum (55%) and in 22 with metastatic disease (85%; fig. 1). Nineteen patients had levels of 100 ng/ml or more and a radical operation was undertaken in only two, of whom one developed signs of metastatic disease and died soon afterwards and the other (concentration 105 ng/ml) was clinically tumour free three months after surgery. Hepatic secondary deposits were present at laparotomy in 22 patients (table I), and in only four of these was there preoperative clinical and serum biochemical abnormality suggestive of metastases. In nine others there was biochemical abnormality alone (hepatic alkaline phosphatase > 13 K.A. units/100 ml, SGOT > 40 units/ml). In three of these patients the biochemical abnormality was a minimally raised alkaline phosphatase level (13-20 K.A. units/100 ml), and indeed similar increases were equally frequent in those without metastases (fig. 2). Of nine such patients four have already lived two years without developing evidence

FIG. 1—C.E.A. levels in three groups of patients with colonic carcinoma before operation. In group 3 ● = patients with hepatic metastases, ○ = patient with metastatic disease in other sites with no evidence of liver metastases. Dotted line represents upper limit of normal.

TABLE I—Comparison of C.E.A. Results with Clinical and Biochemical Indices of Metastatic Spread in Patients with Hepatic Metastases from Colonic Carcinoma

	No. of Patients	No. with raised C.E.A. (> 15 ng/ml)	No. with C.E.A. > 100 ng/ml
No preoperative evidence for hepatic metastases ..	9	7	3
Abnormal liver function test results only ..	9	9	6
Clinical and biochemical evidence of hepatic metastases ..	4	4	2
Total ..	22	20	11

FIG. 2—Comparison between concentrations of C.E.A. and serum alkaline phosphatase. ● = patients with apparently localized disease. ★ = patients with hepatic metastases present at operation. ★ = patients with distant metastases in other organs but not in liver. Dotted lines represent upper limits of normal.

of recurrence or spread. Of nine patients with liver metastases and no preoperative abnormality either clinically or in serum biochemistry (table I) seven showed increased C.E.A. concentrations. C.E.A. was also raised in all 13 patients with preoperative suspicion of tumour spread, and in eight of these serum levels were at least 100 ng/ml. Though less frequent, levels of greater than 100 ng/ml were also seen in three of the nine patients with hepatic metastases proved at laparotomy for which there was no preoperative clinical or biochemical evidence.

In four patients with metastases to organs other than the liver, including omentum, peritoneum, bone, and distant lymph nodes, C.E.A. levels were normal in two and over 100 ng/ml in two others.

PREOPERATIVE C.E.A. LEVELS AS GUIDE TO LONG-TERM PROGNOSIS

Twenty patients in whom C.E.A. estimations were made before operation were reviewed two years after radical surgery (fig. 3). Eleven either died of recurrent disease or developed histologically proven recurrent tumour, while nine remained tumour free at the time of writing. Raised C.E.A. levels were recorded in seven with a recurrent tumour and four who remained free of tumour, but the difference in incidence of raised C.E.A. and the difference between the mean C.E.A.

FIG. 3—Preoperative C.E.A. levels in patients with apparently resectable tumours reviewed two years after radical surgery. Group A = patients developing recurrent or metastatic disease. Group B = patients remaining clinically tumour free. Dotted line represents upper limit of normal. Solid lines represent means.

levels of the two groups was not significant ($P > 0.5$). The only patient in whom the preoperative C.E.A. concentration was greater than 100 ng/ml rapidly developed clinical evidence of tumour spread and died six months later.

C.E.A. ESTIMATION AND DETECTION OF TUMOUR RECURRENCE

Unequivocal tumour recurrence occurred in 18 patients between seven and 50 months after radical surgery for carcinoma of the colon and rectum and raised C.E.A. levels were seen in 16 (table II). In most patients the C.E.A. estimation was first made at a time when there was clinical suspicion of recurrent disease though in two of these patients previous estimations had been made (cases 6 and 18). Further, apparently useful, radical surgery was carried out in four patients (cases 1, 2, 3, and 4), including one who developed a second primary tumour, and of these the C.E.A. levels were 7 ng, 18 ng, 11 ng, and 65 ng/ml respectively. All follow-up patients with levels over 100 ng/ml proved to have inoperable recurrence.

Of the remaining 106 patients without definite evidence of recurrent disease raised C.E.A. levels were seen in 29 on at least one occasion. A rising or persistently raised C.E.A. level was seen in 10 patients (fig. 4) and in three clinical or radiological signs of metastatic disease have since developed (cases 19, 22, and 25). In case 19 the C.E.A. level was 225 ng/ml at the time of the patient's routine attendance at follow up, where she was observed to be well and apparently tumour

FIG. 4—Persistent or rising C.E.A. increases in patients without definite proof of recurrent disease. ★ = attendances at clinic when tumour recurrence was suspected on clinical grounds only. Dotted line represents upper limit of normal.

TABLE II—C.E.A. Results and Clinical Status of Patients with proven Recurrent Carcinoma of Colon or Rectum

Case No.	Time after Surgery (Months)	Site of Recurrence	C.E.A. Results (ng/ml)		Clinical Course
			Previous Levels	Level at Time Recurrence Diagnosed	
Patients in whom further Radical Surgery was undertaken					
1	50	Small bowel mesentery		7	Recurrence excised, well 16 months after second operation
2	16	Retroperitoneal		18	Recurrence excised, well 18 months after second operation
3	19	Anastomotic site		11	Recurrence excised
4	27	Abdominal wall		20	Recurrence inoperable 8 months after original recurrence, died 12 months later
	48	Second primary tumour of sigmoid colon		65	Tumour localized (grade B), completely excised, well, with no evidence of recurrence, 6 months later
Patients with Localized Recurrence too Extensive for further Radical Surgery					
5	25	Vagina and pelvis		17	Tumour too extensive for excision, treated by radiotherapy
6	11	Pelvis	11	23	Tumour recurrence inoperable, previous C.E.A. estimation made 6 months before recurrence diagnosed
7	14	Perineal wound		7	Recurrence inoperable, treated with radiotherapy and 5-fluoro-uracil, 3 months later C.E.A. 45 ng/ml.
8	21	Perineal wound		245	Recurrence inoperable
9	7	Anastomotic site		115	Recurrence inoperable
10	9	Anastomotic site		55	Recurrence inoperable
Patients with Recurrence at Metastatic Sites					
11	40	Lung		500	Right upper lobectomy confirmed presence of metastatic adenocarcinoma. After operation C.E.A. remained >500 ng/ml, symptom free for 12 months, since developed marked hepatomegaly
12	19	Lung		23	Signet-ring malignant cells present in pleural fluid
13	26	Lung		42	No histological proof of recurrence, chest x-ray appearances consistent with multiple metastases
14	24	Lung and peritoneum		80	Recurrence inoperable, died of metastatic disease 3 months later
15	24	Liver		150	No histological proof of recurrence, died 3 months later
16	26	Liver		500	No histological proof of recurrence, died 5 months later
17	19	Liver		200	Recurrence inoperable, alive 14 months later after 5-fluoro-uracil chemotherapy
18	16	Undetected	90	—	No clinical evidence of recurrent disease at time of C.E.A. estimation, died of carcinomatosis 4 months later but no C.E.A. estimation at this time

free. Several weeks later she was admitted to hospital with acute intestinal obstruction which failed to settle with conservative therapy, and at subsequent laparotomy a band adhesion was found without any evidence of recurrent tumour. Six months later, however, she had developed clinical and radiological features of bony metastases. One patient (case 22) since developed hepatomegaly and ascites and the patient in case 25 developed radiographical evidence of pulmonary metastases. In a fourth patient (case 27) we clinically suspected recurrence at the anastomotic site; this patient received prophylactic 5-fluorouracil therapy for the first nine months of observation, during which period the C.E.A. level rose and subsequently fell. Five other patients with rising C.E.A. levels (cases 21, 23, 24, 26, and 28) remained well clinically at the time of writing with no physical signs of recurrent disease and with normal serum liver function test results. One patient (case 20) with chronic respiratory disease, in whom a colonic polyp with carcinoma in situ had been removed, showed a persistently raised C.E.A. level after polypectomy. Clinical and barium enema examinations failed to detect any evidence of malignant disease.

Transient increases of concentration of C.E.A. to levels between 15 and 30 ng/ml were seen in six patients (fig. 5), in three within three months of the original tumour resection. In 12 patients a raised level was recorded on just one occasion, there being as yet no follow-up evidence to suggest whether the level is rising.

FIG. 5—Transient C.E.A. increases in patients without evidence of recurrent disease. In cases 29, 30, and 32 initial estimation was made within three months of radical surgery. Dotted line represents upper limit of normal.

A significant positive correlation ($P < 0.05$) between the sedimentation rate and the C.E.A. concentration was observed for the total group under surveillance. The sedimentation rate, however, proved less satisfactory in discriminating between patients with and without recurrence. A normal E.S.R. and a raised C.E.A. concentration were often recorded on the same occasion.

Discussion

Though a broad correlation has been shown between preoperative serum C.E.A. concentration and the spread of cancer this remains of little help to the clinician in most patients. It does seem, however, that where this concentration rises to 100 ng/ml it is unusual for resection to be possible, and recurrence is probably inevitable. Nonetheless, this evidence is still superior to that derived from clinical or biochemical sources and would be preferred in deciding which patients might profitably receive additional therapy. Clinical findings such as hepatomegaly are reliable but were present in only four of the 22 patients with hepatic metastases as against 11 in whom C.E.A. concentration reached 100 ng/ml. Raised serum alkaline phosphatase and SGOT are

both unreliable and misleading as not only were they inconstant in our group but they also seemed to be almost as common in those without tumour spread. Routine hepatic scintiscanning has also been advocated in the preoperative assessment of these patients, but even with this technique multiple small deposits may be missed, and false positive results are a frequent problem (Davies *et al.*, 1974).

It must be stressed that marked increases in C.E.A. are not specific for metastases to the liver but seem simply to represent spread beyond the regional lymph nodes. The test must, therefore, be used in conjunction with clinical and other findings.

Persistent raised C.E.A. more than three months after surgical resection should be assumed to indicate residual malignancy. It seems that C.E.A. concentration may take longer to fall to normal than was previously reported (Holyoke *et al.*, 1972) and the significance of a persistent postoperative increase cannot be properly assessed for three months.

Raised concentrations during the follow-up period were seen in 85% of those with tumour spread, but in few of these was the tumour then resectable. Indeed, further surgery was deemed valueless when the concentration was greater than 100 ng/ml whereas in four patients where further surgery was practicable C.E.A. levels were 7 ng, 18 ng, 11 ng, and 65 ng/ml. The three relatively low values are discouraging as to the usefulness of C.E.A. measurements in cancer follow up though the numbers are few and the single measurement of 65 ng/ml associated with a second tumour does suggest a more positive role for these measurements. This possibility seems even more likely when seen in parallel with the persistently rising concentrations in six other patients, three of whom now have clinical evidence of recurrence. Occasional minor increases occur probably for reasons of methodology and coincident illness, but at the moment it seems desirable that after resection for colorectal cancer patients should have regular C.E.A. measurements during the follow-up period. These results together with those recently reported by Sorokin *et al.* (1974) indicate that rising C.E.A. levels must be regarded as indicating progressive disease and that suitable investigations should be carried out to determine the site of the lesion. This pattern requires confirmation from a larger series, which should be provided by a prospective Medical Research Council trial now in progress.

It has been shown that circulating tumour-related antigen inhibits cell-mediated immunity directed against the growing tumour (Sjogren *et al.*, 1971; Currie and Basham, 1972). If C.E.A. were such a substance then preoperative serum concentrations should relate to prognosis as persistently high values would inhibit the immune response and encourage dissemination. Though only 20 patients were followed for two years after resection the absence of such a demonstrable relationship does not support a role for C.E.A. in this context. Furthermore, it has been shown that C.E.A. is unlikely to be implicated as the antigen inhibiting lymphocyte cytotoxicity against colonic tumour cells (Embleton, 1973), and a role for C.E.A. in the host reaction against its tumour thus seems unlikely.

Thus, pending a definitive prospective study several tentative conclusions seem possible. Firstly, preoperative C.E.A. measurements in colonic cancer give a useful guide to the probable presence of secondary tumour and ultimately to a poor prognosis if the concentration is 100 ng/ml or higher. Intermediate values are of uncertain value in this respect though this should be established by analysis of the much larger series now being assembled in the current M.R.C. trial. Secondly, C.E.A. is a more reliable indicator of tumour spread than any other single index currently available. Finally, after successful surgical resection and return of C.E.A. concentration to normal serum samples should be measured regularly and persistent and rising increases taken to indicate tumour recurrence. Used in these ways C.E.A. estimation

could contribute significantly to our understanding and management of carcinoma of the gastrointestinal tract.

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Action of Different Bran Preparations on Colonic Function

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Summary

Two different types of commercially available bran were studied. One of these was composed of flake-like particles (coarse bran) whereas the other had smaller, finer particles with a floury component (fine bran). The effectiveness of the two preparations in lowering intraluminal pressure and decreasing transit time in patients with constipation and diverticular disease was assessed. Only coarse bran promoted changes at the dose used. The physical properties of the brans were examined in an effort to explain their differing effects. It is concluded that water-holding capacity, upon which the beneficial effect of bran may depend, is a function of particle size. The greater water-holding capacity of coarse bran makes it preferable for the treatment of colonic disorders.

Introduction

The value of bran in the symptomatic treatment of diverticular disease (Painter *et al.*, 1972) and constipation (Harvey *et al.*, 1973) has been established. It has been shown that intraluminal colonic pressure is abnormally high in diverticular disease and constipation (Arfwidsson and Kock, 1964; Painter and Truelove, 1964). Gastrointestinal transit time is prolonged in diverticular disease (Findlay *et al.*, 1974) and in constipation (Kirwan and Smith, 1974), and it has been established that bran lowers intraluminal pressure and shortens the transit time in such patients (Findlay *et al.*, 1974).

This study was prompted by the observation that two types of bran differed in their appearance, in their clinical efficacy, and in their ability to lower intraluminal pressure and reduce transit time. Physical characteristics of the two brans were examined in an effort to explain their differing effect.

Methods

Two groups of patients were studied before and after taking bran 10 g twice daily for four weeks. One group took a coarse preparation of bran (Prewitt's) of which none of the particles or flakes passed through a sieve of 1-mm diameter and the other group took a fine preparation (Allinson's) which entirely passed through a sieve of 1-mm diameter pore size. Fine bran also contained appreciable amounts of endosperm (flour).

Coarse-bran Group.—This group consisted of nine patients with radiologically proved diverticular disease. Colonic motility before taking bran was measured using open-ended tubes (Smith *et al.*, 1971) and gastrointestinal transit time was measured using radio-opaque pellets (Hinton *et al.*, 1969). These investigations were repeated after four weeks of treatment with coarse bran 10 g twice daily.

Fine-bran Group.—This group consisted of five patients. Three had radiologically proved diverticular disease. Two patients complained of difficult and infrequent bowel movements and occasional abdominal pain. After investigations which failed to show any organic abnormality a diagnosis of constipation was made. Colonic motility before bran was measured using the same method as in the former group. Gastrointestinal transit time was measured using a radioisotope capsule (Kirwan and Smith, 1974). These investigations were repeated after four weeks of treatment with fine bran 10 g twice daily, and in four patients who consented to a third study the tests were again repeated after switching to the coarse bran for a further four weeks.

PHYSICAL CHARACTERISTICS OF BRANS

To determine the physical characteristics of the brans both were shaken for 90 minutes in test sieves and the flour from each bran which passed through the mesh was weighed. The acid detergent fibre, which measures the cellulose and lignin content of the brans, was determined by the method of van Soest (1963).

The water-holding capacity of a fibre is a function of the ability of the fibre to retain water and is signified by the amount of water held by 1 g of the dried material (McConnell *et al.*, 1974). It was measured for each bran by adding a known quantity of bran to a weighed tube, excess water then being added and the mixture being left to equilibrate for 24 hours. The tube was then centrifuged at 14,000 g for one hour and the supernatant was then removed leaving the bran with its associated water. The result was expressed as grammes of water per gramme of bran.

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