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The clinical significance of the pattern of elevated serum carcinoembryonic antigen (CEA) levels in recurrent colorectal cancer

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SUMMARY

Serial serum carcinoembryonic antigen (CEA) assays were performed in 148 patients after potentially curative surgery for colorectal cancer. Thirty-seven patients developed proved recurrent tumour in a follow-up period of 2–5 years. Elevated CEA levels were recorded in 36 of these patients and in 27 rising levels preceded clinical symptoms of recurrent tumour. Two distinct patterns of CEA rise were observed: a 'fast' rise in which serum concentrations reached 100 μg/l within 6 months of the first elevation and a 'slow' rise in which concentrations remained less than 75 μg/l for at least 12 months. The majority of patients with the 'fast' rise had metastatic spread, whereas most patients with a 'slow' rise had local recurrence alone. This differential pattern may help to predict the site of recurrent tumour.

SERUM carcinoembryonic antigen (CEA) assay is a valuable adjunct to clinical examination in postoperative monitoring of patients after surgery for colorectal cancer (1, 2). Rising CEA levels usually predict metastatic tumour recurrence several months before clinical detection (3, 4). The value of the CEA test in predicting local recurrence is less well established however, since the grossly elevated levels found characteristically in patients with distant, and especially liver, metastases occur less frequently. Furthermore, local recurrence may be difficult to confirm, particularly in asymptomatic patients.

This present study assessed sequential changes in CEA levels in patients after apparently curative surgery for colorectal cancer to determine whether the pattern of CEA changes could help to predict the site of recurrent disease and prognosis.

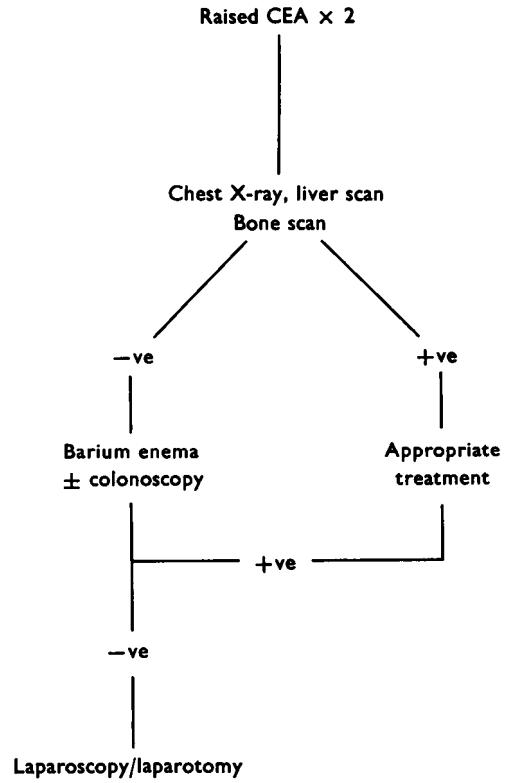

Fig. 1. Investigation protocol for patients with two consecutively elevated serum CEA levels.

Patients

One hundred and forty-eight patients who had undergone apparently curative surgery for adenocarcinoma of the colon and rectum between January 1974 and December 1976 were studied. All patients had localized, easily resectable primary tumours, without evidence of distant metastases at the time of initial surgery. Patients were seen at 3–6-monthly intervals after operation and were followed for between 20 and 56 months, or until death. Accurate data on survival were obtained. CEA measurements were performed at each follow-up visit. Patients with two consecutively elevated CEA levels were submitted to a planned programme of investigations designed to locate recurrent tumour (*Fig.* 1). CEA levels were assayed by a double antibody radioimmunoassay on unextracted serum (5). The upper limit of normal was 25 μg/l, based on our study of a normal population. Test sensitivity was defined as the percentage of patients with recurrent disease correctly identified and test specificity as the percentage of patients without recurrent disease correctly identified (6).

Statistical analysis of actuarial survival curves was made using the log rank test (7).

Results

One hundred and eight of the 148 patients had persistently normal CEA values and showed no clinical signs or symptoms of recurrent tumour (*Table I*). One patient developed signs of local recurrence 4 months before elevated CEA values were recorded. Thirty-nine patients had two consecutively elevated CEA levels and were investigated in detail. No tumour recurrence was detected in 3 patients, but the remaining 36 patients had proved tumour recurrence. Thus, test sensitivity was 36/37 (97 per cent) and test specificity was 108/111 (97 per cent).

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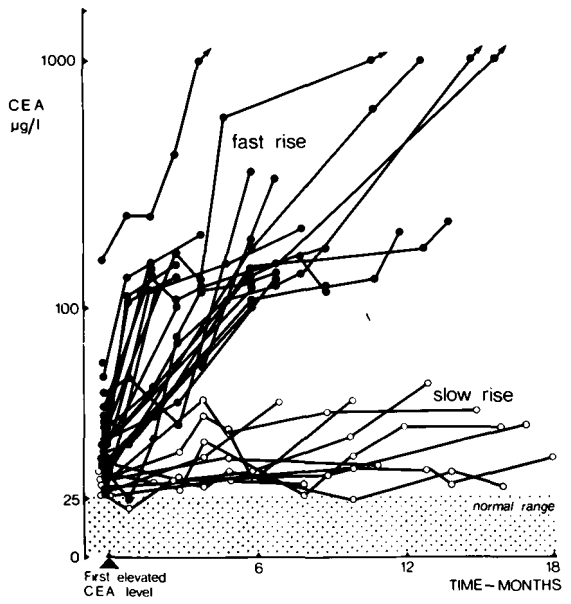

Fig. 2. Patterns of rise of CEA in patients with elevated levels after potentially curative resection for colorectal cancer.

Fig. 2 shows the serial serum CEA concentrations for the patients with tumour recurrence, plotted from the time of the first recorded elevation. Two distinct patterns in CEA rise were noted. Twenty-three patients had a fast rise in CEA levels defined as an increase in CEA concentrations to greater than 100 µg/l within 6 months of the first CEA elevation. Fourteen patients had a slow rise in which levels remained below 75 µg/l for 12 months from the first recorded CEA elevation. Many patients with a slow pattern had stable elevations of the CEA levels for several months. The fast rise represents a rate of increase in serum CEA concentrations in excess of 150 µg/l per year. By contrast, a slow rise represents a rate of rise of less than 50 µg/l per year.

The two groups were similar in the median time intervals from operation to the first elevated CEA level (fast rise 8 months; slow rise 7 months) and from either first or second elevated CEA levels to diagnosis of recurrence (fast rise 6 and 2 months; slow rise 5 and 3 months respectively).

The major difference between fast and slow patterns was in patient survival (*Fig.* 3). Patients with a fast rise in CEA level had a much poorer prognosis, the differences being highly significant ($P < 0{\cdot}005$). The relationship of the pattern of change in CEA level and site of tumour recurrence is shown in *Table II*. Nine (64 per cent) of the 14 patients with a slow pattern had local recurrence alone compared with only 8 (35 per cent) of 23 patients with a fast pattern. Fifteen (65 per cent) of 23 patients with a fast rise had distant and particularly liver metastases with or without local recurrence. However, for patients with local recurrence alone no significant difference in survival was found between patients with either fast or slow rises.

Discussion

The present study confirms and extends the application of the CEA assay as a monitor of tumour recurrence in colorectal cancer. Analysis of the patterns of change of CEA levels clearly shows that a rapid rise was associated with a high risk of metastatic disease and a poor prognosis, whereas a slow rise was associated particularly with local recurrence and a better prognosis. The survival rate for patients with local recurrence alone was the same regardless of the CEA patterns. The poorer prognosis in patients with rapidly rising CEA levels was, therefore, due to a higher proportion of patients with distant metastases. Similar patterns have

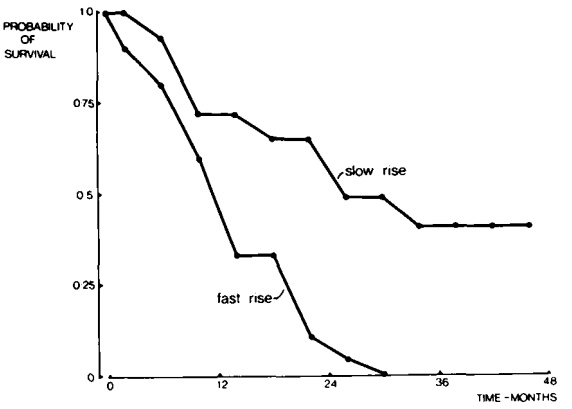

Fig. 3. Actuarial survival curves for patients with 'fast' or 'slow' increases in serum CEA levels.

Table I: CHANGES IN SERUM CEA LEVELS IN RELATION TO CLINICAL STATUS

Serum CEA levels	Range <25 µg/l	Range <40 µg/l
Remained within normal range		
No evidence of recurrence	108 (73%)	109 (74%)
Symptomatic recurrence	1 (1%)	8 (5%)
	109	117
Elevated		
No evidence of recurrence	3 (2%)	2 (1%)
Proved recurrence	36 (24%)	29 (20%)
	39	31

Table II: SITES OF TUMOUR RECURRENCE RELATED TO THE PATTERNS OF CEA ELEVATION

Site of recurrence	Total no.	Pattern of CEA increase Fast	Slow
Local	17	8	9
Local + liver	2	2	0
Local + bone	2	2	0
Local + metachronous primary	1	1	0
Liver	8	6	2
Bone	5	2	3
Lung	2	2	0
Total	37	23	14

been reported recently by Staab and colleagues (8) using the Z-gel CEA assay and a computer technique to determine the rate of change of CEA levels (slope analysis). They showed that patients with a slow pattern of CEA rise ('flat slope') had local recurrence and were more likely to benefit from 'second look' surgery.

Moertel and colleagues (9) suggested that the CEA test has limited value in patients with local recurrence, since 56 per cent of their patients with locally recurrent or residual malignant disease had CEA levels in the normal range. This may be true to some extent as the one patient in our study who developed clinical evidence of residual tumour before an elevation in CEA levels had local tumour recurrence. However, our study has shown that patients with local recurrence tend to show a different pattern of CEA elevation which should be taken into consideration when investigating tumour recurrence.

The present study highlights the importance of defining the CEA level above which tumour is suspected in determining test sensitivity and specificity. The sensitivity of the test (using two consecutive levels greater than 25 μg/l as the criterion of abnormality) in indicating recurrence disease was 97 per cent. This figure may slightly overestimate the true sensitivity since our patients were submitted to detailed investigation only if CEA levels were elevated or clinical signs and symptoms of recurrence were present. Thus, some asymptomatic patients may have been harbouring latent recurrence without elevation of CEA values. If a high cut-off level is used (greater than 40 μg/l), which is above the range found in patients with non-malignant bowel disease, it is likely that many patients, particularly those with local recurrence, will not be detected early by CEA monitoring. A lower cut-off level, based on the upper limit in normal subjects (25 μg/l), will improve the sensitivity of the test at the expense of some loss in specificity. However, we suggest that the false positive rate observed (3 per cent) is sufficiently low to be acceptable. Application of the lower cut-off level minimizes the time lag between suspected tumour recurrence and therapeutic decision, thus allowing fuller exploitation of the lead time provided by the CEA test. The effect of employing a higher cut-off level can be seen by recalculating the data using a CEA value of 40 μg/l as the criterion of abnormality (*Table I*). The test sensitivity is then reduced from 97 per cent (36/37) to 78 per cent (29/37), while specificity improves marginally (97 per cent to 99 per cent). These figures are similar to the test sensitivity of 66 per cent and specificity of 91 per cent calculated from the larger series of Neville and Cooper (10) who used a similar assay and a cut-off level of 40 μg/l.

The detection of recurrent tumour may be especially difficult in asymptomatic patients. Determination of the pattern of CEA change may be helpful both in diagnosis and in distinguishing between local recurrent and distant metastases.

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