

Rôle of carcinoembryonic antigen in bronchial carcinoma

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Ford, C. H. J., Newman, C. E., and Lakin, J. (1977). *Thorax*, 32, 582-588. **Rôle of carcinoembryonic antigen in bronchial carcinoma.** It has been reported that lung cancer patients often have raised carcinoembryonic antigen (CEA) levels but the significance of this in diagnosis and follow-up has yet to be established. The results of 256 preoperative investigations in patients with lung cancer are reported. Sequential values after radical surgery and chemotherapy and immunotherapy have been performed in 57 patients during treatment and outpatient follow-up. Ninety-nine per cent of preoperative values were more than 5 ng/ml and 41% were greater than 15 ng/ml. Only 6% reached diagnostic levels for malignancy (greater than 50 ng/ml) and adenocarcinomas formed 47% (7 out of 15) of these. Sequential estimations in patients during and after treatment showed fluctuations which were related to disease status in 7 (32%) of 22 who have developed secondary disease. In three patients levels of greater than 50 ng/ml preceded clinical evidence of recurrence, and two patients have developed very high levels but have not yet developed other evidence of recurrent disease. It is concluded that raised CEA levels in lung cancer are infrequent, but in those patients who have or develop raised levels sequential investigation may be of value in monitoring response to treatment and clinical course.

Carcinoembryonic antigen (CEA) was first identified in extracts of human colonic adenocarcinoma and fetal gastrointestinal tissue by Gold and Freedman (1965a, 1965b). Thompson *et al.* (1969) showed that CEA could be detected in the sera of patients with gastrointestinal malignancy but not in sera from patients with other cancers, nor in normal individuals. However, extensive investigations of CEA as a diagnostic test established that raised serum CEA levels were found in non-gastrointestinal malignancies (Lo Gerfo *et al.*, 1971; Vincent and Chu, 1973) as well as in a variety of non-malignant conditions (Koldovský, 1974). It is well established that serum CEA levels are raised in 38-80% of lung cancer patients (Lo Gerfo *et al.*, 1971; Laurence *et al.*, 1972; Puzstaszeri and Mach, 1973; Vincent and Chu, 1973; Hansen *et al.*, 1974; Pauwels and Van der Straeten, 1975; Newman *et al.*, 1976). Similarly, 33-68% of bronchitics (Hansen *et al.*, 1974; Pauwels and Van der Straeten, 1975), 12% of patients with varied pulmonary disease (Lo Gerfo *et al.*, 1971), and 47% of patients with pneumonia (Hansen *et al.*, 1974) have been shown

to have raised serum CEA levels. Thirteen to 22% of cigarette smokers also have raised CEA levels (Hansen *et al.*, 1974; Stevens *et al.*, 1973). Bronchial carcinoma patients commonly have bronchopneumonic changes and are cigarette smokers and chronic bronchitics. A further complication is the cross-reactivity that antisera to CEA demonstrate with normal tissue components which have been variously named NGP, NCA, CCEA2, NCA2, BCGP, and FSA (von Kleist *et al.*, 1972; Mach and Puzstaszeri, 1975; Terry *et al.*, 1974).

These findings leave doubt as to the value of serum CEA levels both as a cancer diagnostic test and as a serum monitor of disease status in patients with bronchial carcinoma although its role as a sensitive indicator in some lung cancer patients who undergo therapy has been demonstrated (Vincent and Chu, 1973; Newman *et al.*, 1976). The present study was undertaken as part of a screen of preoperative sera from bronchial carcinoma patients. Some of these patients have received adjuvant chemotherapy or immunotherapy, and serial serum samples have been

analysed to investigate the relationship between CEA levels and changes in disease status.

Material and methods

ASSAY

Serum samples from patients were separated within four hours of venepuncture and stored at -20°C ready for testing. The assay used was a modified double antibody radioimmunoassay (Egan *et al.*, 1972; Booth *et al.*, 1973) performed in the Department of Experimental Pathology.

LIMITS OF TEST

The reproducibility of the test was assessed by repeatedly testing serum samples of known 'low', 'medium', and 'high' CEA values over a period of several months.

	Low (ng/ml)	Medium (ng/ml)	High (ng/ml)
Mean	9.3	19.9	135.5
SD	1.7	2.7	18.2
SE	0.3	0.5	3.9
Coefficient of variation	18.3	13.6	13.4

From the coefficient of variation it can be seen that the test to test variability is similar in all three groups, being slightly greater in the low category than in the other two categories. The upper limit of the normal range with this test is 15 ng/ml.

PATIENTS

Preoperative serum samples were collected from 302 patients admitted to one of three hospitals for investigation of suspected bronchial carcinoma. CEA estimations were performed routinely on these. Forty-six have been excluded from this report because no resection was performed and histology of biopsy specimens obtained at bronchoscopy or thoracotomy was inadequate or inappropriate, or because complete data were not available. The remaining 256 patients consisted of 36 patients assessed to be inoperable and 220 patients who had a radical or palliative surgical resection. Fifty-seven of these patients have entered the Birmingham clinical trial of adjuvant therapy after radical resection of bronchial carcinoma and have been followed for one to 25 months (Newman *et al.*, 1977). All have received high-dose combination chemotherapy at approximately one and two months after operation. At the second treatment 24 also received passive immunotherapy. Patients are reviewed and serum samples collected at 4, 8, and 14 weeks from operation. Radionuclide scans of bone, brain, and liver and full skeletal survey with conventional radiographs are performed at 8 weeks.

Thereafter clinical review, collection of sera, and radionuclide scanning occur every three months, and radiographic skeletal surveys every six months. In some instances samples were also taken during treatment and weekly after treatment.

Results

The distribution of raised CEA levels in 256 patients is shown in Figure 1. One per cent have values of less than 5 ng/ml, 58% were between 5 and 14 ng/ml, and 41% greater than 15 ng/ml. Only 6% were greater than 50 ng/ml. Of 27 adenocarcinomas, 7 (26%) had levels greater than 50 ng/ml, a much higher incidence than in the other histological groupings (Table). Of 220 patients who had their tumour resected, an adequate examination of lymph nodes on the specimen was performed in 207. In 106 (51.21%) with tumour spread to lymph nodes, the mean CEA was 28.08 (4.5-500) compared with 19.03 (4.5-230) in the nodes negative cases, a difference which is not statistically significant. The influence of type of operation and lymph node involvement was also investigated and comparison between each of these groups does not reach statistical significance. The Whitley Mann U Test was used to assess significance.

Table Mean and >50 ng/ml incidence of serum CEA in bronchial carcinoma patients

Classification	Total No.	Mean CEA (ng/ml)	Range	No > 50 ng/ml	%
Adenocarcinoma	27	51.65	9.5-240	7	25.93
Oat cell	13	13.21	5.5-42.5	0	0
Anaplastic	29	31.68*	5.5-500	2	6.9
WDSCC†	50	14.44	5.8-49.8	0	0
PDSCC‡	101	18.34	4.5-245	4	3.96
Inoperable	36	26.07	5.3-380	2	5.56
Total	256			15	5.86

*If one reading of 500 ng/ml is excluded the mean becomes 14.95 (range 5.5-107.5).

†Moderately/well differentiated squamous cell carcinoma.

‡Poorly differentiated squamous cell carcinoma.

Of 57 patients followed sequentially, 46 had determinations preoperatively and at four to seven weeks postoperatively; a mean fall of 30.83 (0.5-209.2) ng/ml occurred in 28 and a mean rise of 8.5 (1-34.7) ng/ml in 18. Five patients had preoperative levels greater than 50 ng/ml, and in each case resection of tumour was followed by a dramatic fall in CEA four to seven weeks postoperatively (240 to 155, 190 to 125, 245 to 50.5, 230 to 20.8, 127 to 50). A further patient, PC, is shown in

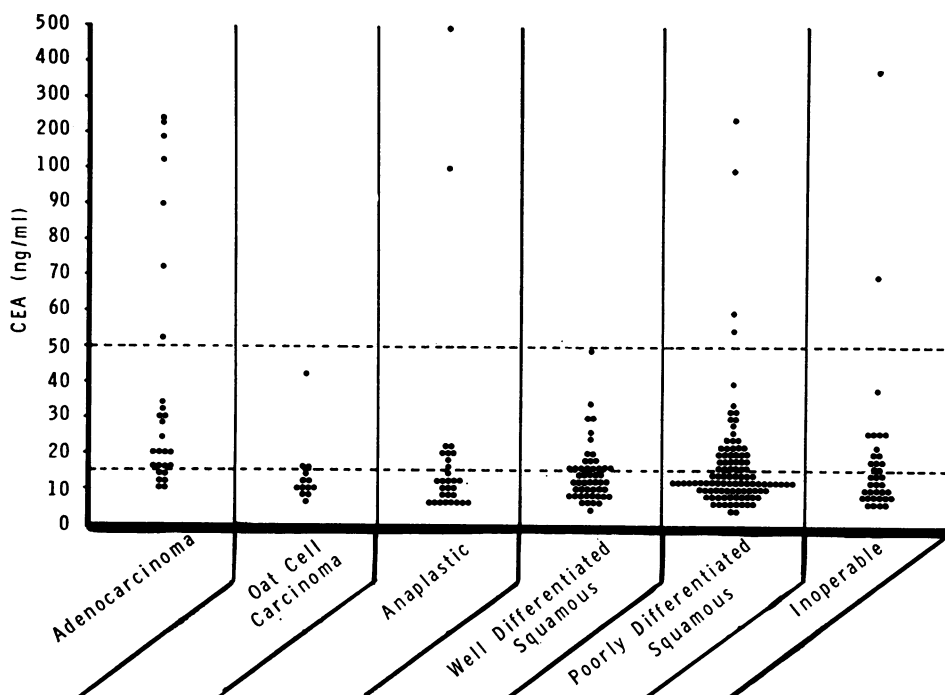


Fig. 1 Distribution of serum CEA levels in patients with bronchial carcinoma. Upper dotted line: lower limit for cancer diagnostic range. Lower dotted line: upper limit for normal range.

Figure 2. His preoperative value of 42.5 ng/ml fell to 12.3 ng/ml within five weeks of operation.

In 44 patients, preoperative levels of less than 50 ng/ml have remained at non-diagnostic levels throughout follow-up and were uninfluenced by overt recurrent disease when this occurred in 15 of them. Four further patients showed delayed transient rises to 40.5, 41.5, 50.0, and 60.5 ng/ml which were not maintained and remain of uncertain clinical significance. One patient had a preoperative level of less than 30 ng/ml which later rose to cancer diagnostic levels with recurrent disease.

Five patients with preoperative levels greater than 40 ng/ml have CEA levels which have shown cancer diagnostic levels during treatment and follow-up. If Figs 3, 4, and 5 are considered, some implications of the prognostic value of CEA in patients with raised preoperative levels can be seen. For patient NB (Fig. 3) there was a fall in CEA level after resection but within 10 weeks of operation this patient had developed clinical evidence of secondaries which has persisted. The CEA level has not reflected this until recently when a significant rise from 15 to 37 ng/ml has been observed. However, patients RG (Fig. 4) and GL (Fig. 5) both showed a massive decrease in

CEA level postoperatively, but for RG the level nine weeks after operation was 33 ng/ml whereas for GL it was 22 ng/ml at 11 weeks. At that time it was considered that this might suggest a more favourable prognosis for patient GL. From the follow-up of these patients it can be seen that for RG clinical evidence of secondaries was present from 4 months but the CEA level did not rise above 50 ng/ml until definite secondaries were confirmed at 7.75 months and this patient subsequently died 11 months after operation. However, patient GL has no clinical, radiographic or scan evidence of secondaries although recently the CEA level has risen and strongly suggests the presence of occult metastases. Although the CEA level for patient RG at second treatment was not cancer diagnostic, we suggest that this type of pattern in some patients is indicative of residual disease. In future, in patients such as RG and GL the CEA pattern might be used to provide information on the timing and monitoring of any further therapy.

In patient EB (Fig. 6) radiographic and scan evidence of skeletal metastases persisted from the time of treatment at 2.75 months although the patient remained free from definite clinical evidence of disease until 8.75 months. In this patient

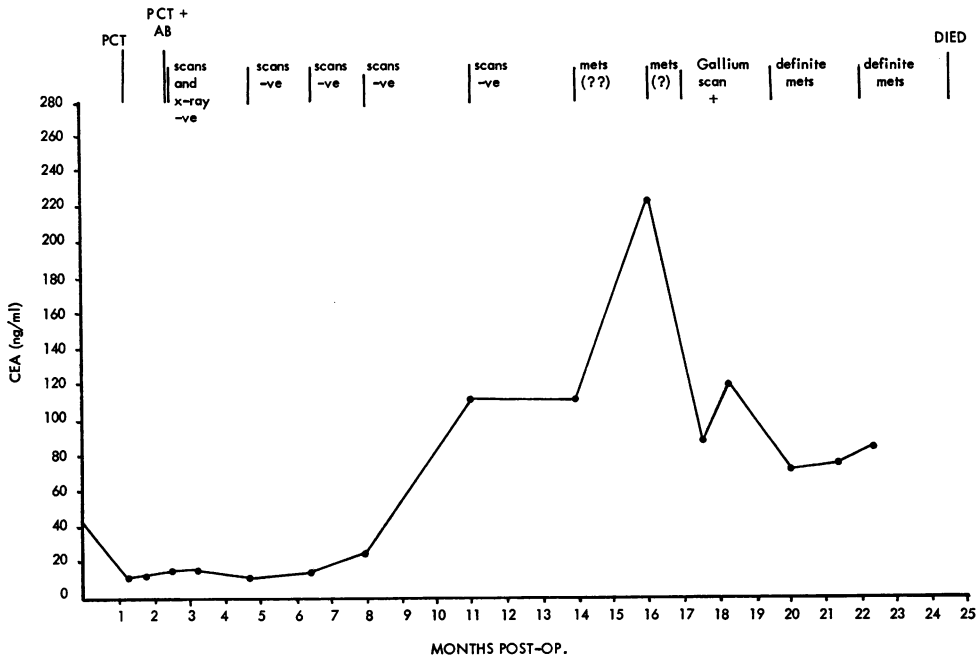


Fig. 2 PC, 32 years, oat cell carcinoma. Pneumonectomy, nodes +ve. PCT—polychemotherapy; PCT+AB—polychemotherapy and antibody; scans+(?)—suspicious scans; mets (??) or mets (?)—suspicious clinical, but not definite, evidence of metastases.

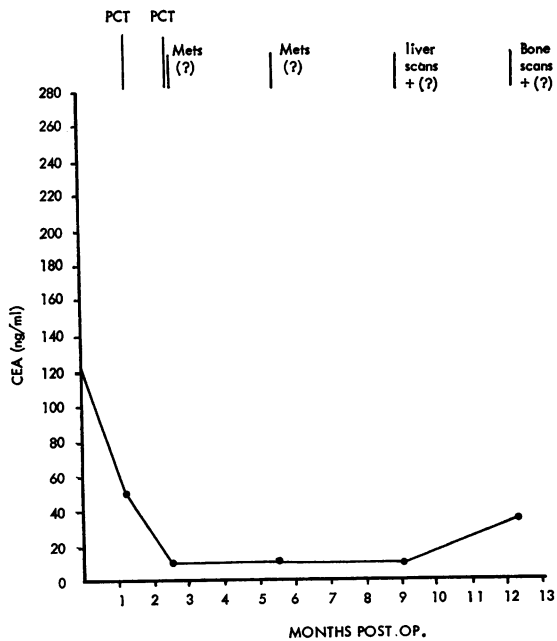


Fig. 3 NB, 67 years, adenocarcinoma. Lobectomy, nodes +ve. See legend to Fig. 2.

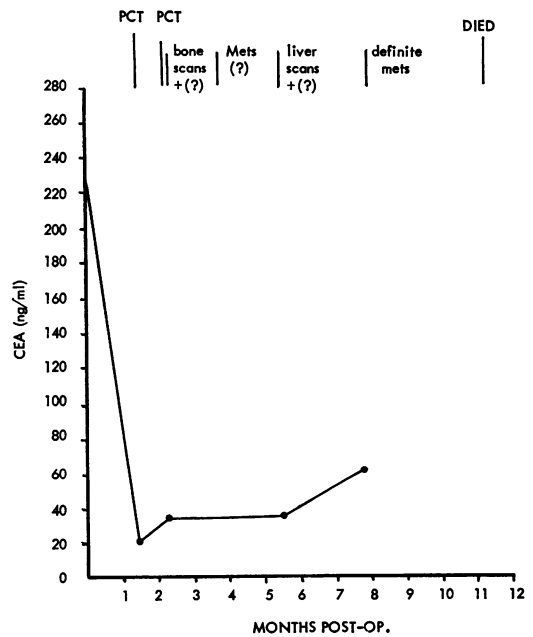


Fig. 4 RG, 47 years, adenocarcinoma. Pneumonectomy, nodes -ve. See legend to Fig. 2.

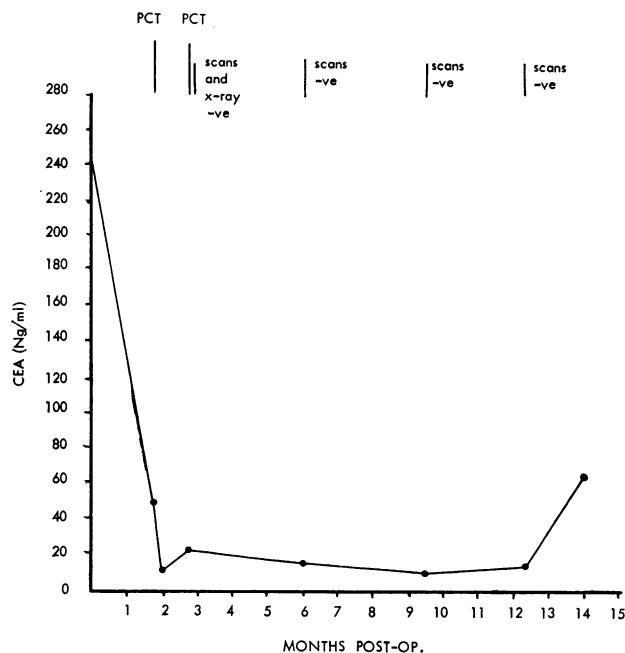


Fig. 5 GL, 57 years, poorly differentiated squamous cell carcinoma. Pneumonectomy, nodes +ve. See legend to Fig. 2.

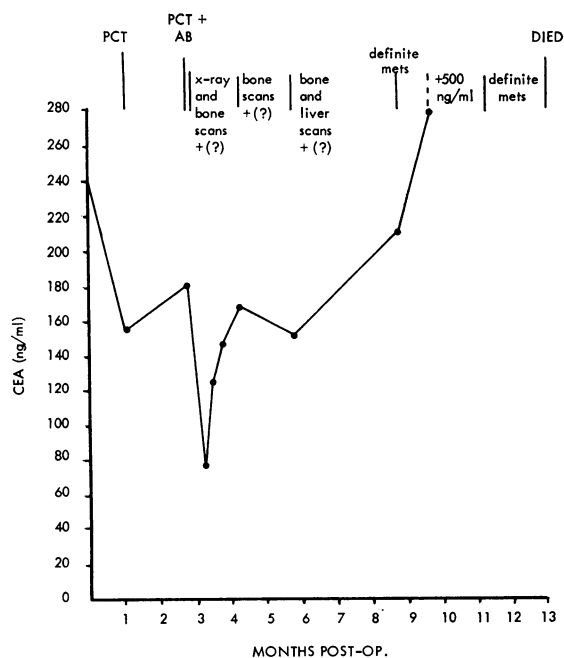


Fig. 6 EB, 54 years, adenocarcinoma. Lobectomy, nodes +ve. See legend to Fig. 2.

the CEA level appears to reflect treatment which, although apparently affecting the tumour as suggested by the decrease in CEA level after resection and therapy, is not totally effective. Clearly, prolonged treatment might be indicated in patients showing such a response to therapy without CEA levels falling to more normal levels.

In three other patients the CEA level has indicated disease status in advance of clinical evidence of secondaries. Two of these are illustrated in Figures 2 and 7 (PC, EA).

Thus in 57 patients who have been followed with sequential serum CEA estimations from one to 25 months after operation, variation in CEA levels reflecting disease status after resection of primary disease, adjuvant therapy or reappearance of secondary disease have been observed in 9 (16%). To put this in perspective, in 7 of the 22 patients on the trial who have had probable or definite clinical secondaries the CEA level has reflected the disease status (greater than 50 ng/ml) either at the same time or before evidence of secondaries. In three of these seven it was in advance of clinical evidence with a lead in time of from 3 to 8 months. Two further patients, EA and GL, have rapidly rising CEA levels with as yet no overt disease and we think it probable that this is pre-clinical evidence of metastases.

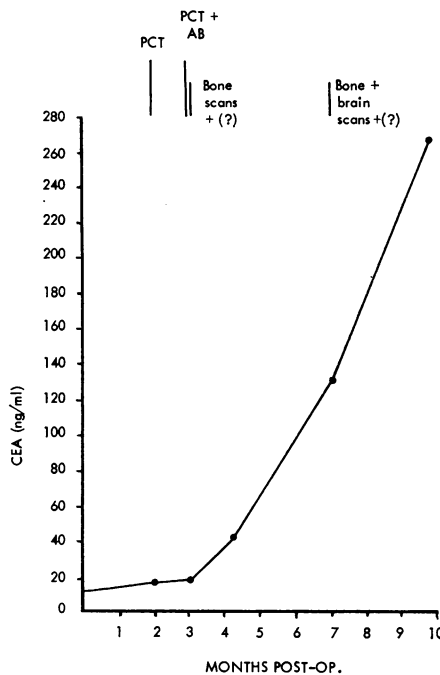


Fig. 7 EA, 52 years, poorly differentiated squamous cell carcinoma. Lobectomy, nodes -ve. See legend to Fig. 2.

Conclusion

CEA as a preoperative screening procedure for bronchogenic carcinoma is of value in only a small number of patients and reached cancer diagnostic levels in 6% in this study. Although others have found no association between raised CEA levels and histological type in lung cancer (Laurence *et al.*, 1972), in this series 26% of bronchial adenocarcinomas had levels greater than 50 ng/ml. In those lung cancer patients who develop a significantly raised CEA level, a serum cancer marker exists. Thus in 16% of 57 patients in whom serial investigations have been performed, CEA has been shown to be of value as a monitor of effect of treatment and clinical course of disease, and if only those who have definite clinical metastases are considered 32% (7 out of 22) have had raised CEA levels, three considerably in advance of clinical evidence, and two further patients have levels greater than 50 ng/ml but no other evidence of recurrent disease.

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