

Preoperative carcinoembryonic antigen levels correlated with postoperative pathological staging in bronchial carcinoma

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ABSTRACT Serum carcinoembryonic antigen (CEA) levels were obtained before operation in 214 patients undergoing diagnostic tests for suspected bronchial carcinoma, and the results correlated with the postoperative, pathological stage of disease. Positive CEA levels (> 10 ng/ml) were observed in 40% (8/20) of stage 1, 58.5% (31/53) of stage 2, 85.2% (69/81) of stage 3, and 92.3% (24/26) of stage 4 patients with bronchial carcinoma. Furthermore, the mean CEA levels increased with stage of disease, and the differences between mean levels were found to be significant in stages 1 and 2 versus 3 and 4 ($p < 0.001$). This suggests a positive correlation between the preoperative CEA level and tumour burden defined by pathological staging. When the results were compared with the histological type of lung carcinoma, CEA elevations occurred most frequently with adenocarcinoma, followed by undifferentiated and squamous cell carcinoma, reflecting perhaps the origin of this oncofetal antigen from the endodermally derived bronchial mucosa. These data indicate that preoperative serum CEA levels quantitatively reflect the extent of tumour assessed pathologically at operation and confirm the potential usefulness of this antigen as a biological tumour marker in the management of bronchial neoplasms.

Carcinoembryonic antigen (CEA) is a highly antigenic glycoprotein which is gaining clinical acceptance as a biological tumour marker for an increasing number of neoplastic disorders. In the case of bronchial carcinoma, a number of clinical studies in the past 10 years have demonstrated elevations of serum levels of CEA in patients with this neoplasm.¹⁻⁵

Recent investigations have begun to define the precise role that the measurement of CEA may assume in the management of patients with bronchial neoplasms. Carcinoembryonic antigen determinations obtained before operation and sequentially after pulmonary resection have been shown to be potentially useful in the determination of prognosis and operability,⁶ in the

definition of the extent of disease for adjuvant therapy,⁷ and as a monitor for recurrent bronchial carcinoma after pulmonary resection.^{8,9}

As a prerequisite to the use of CEA levels in the management of patients with bronchial carcinoma, it is imperative to determine how well serum CEA determinations quantitatively reflect the extent of tumour determined pathologically at operation. The present study was begun to define more precisely the correlation between preoperative CEA levels and the histological type and extent of bronchial carcinoma determined by postsurgical pathological staging methods.

PATIENT POPULATION

Serum samples for CEA analysis were obtained before invasive diagnostic procedures from all patients admitted to the Thoracic Surgery Service, Frenchay Hospital, Bristol with suspected bronchial carcinoma. Patients found to have significant medical illness other than bronchial

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carcinoma were excluded. Of 214 patients included in this study, 180 were found to have bronchial carcinoma and 34 active benign pulmonary disease, principally pneumonia, empyema, or tuberculosis.

CEA ASSAY

Blood samples for analysis were drawn by venepuncture, allowed to clot, centrifuged, and stored at -20°C until analysed for CEA at the Charing Cross Hospital, London. The assay employed is an automated indirect radioimmunoassay using Enzacryl linked anti-CEA antiserum and ^{125}I -labelled purified CEA.¹⁰ The anti-CEA antiserum was raised to immunopurified CEA-2B.¹¹ The mean serum CEA level for this assay has been determined to be 5 ng/ml in normal, healthy volunteers and the upper limit of normal set at 10 ng/ml (mean level +2 SD).

STAGING METHODS

All patients with carcinoma underwent post-surgical pathological staging using a variety of preoperative anatomical techniques and the results of operation. Chest radiographs with selective tomography and liver function tests were obtained and bronchoscopy and biopsy performed in each case. Radioisotopic scans were obtained if the serum alkaline phosphatase was found to be elevated or if clinical evidence of metastases was present. The surgical procedures employed were as follows: 122 patients (57%) underwent pulmonary resection; 42 patients (19.6%) were explored and found to have unresectable tumours; 25 (11.6%) underwent bronchoscopy with or without mediastinoscopy and were found to have benign disease, or carcinoma with involvement of the carinal or superior mediastinal nodes; and 25 (11.6%) were staged by peripheral node biopsy or scans and found to have distant metastases.

During operation, radical lymph node dissection was uniformly performed in resectable cases. Nodes were identified and submitted separately at all levels. In cases found to be unresectable, biopsies were obtained from the primary tumour and involved adjacent structures or mediastinal nodes. The final staging system (table 1) was a modification of the TNM system currently proposed by the American Joint Committee for Cancer Staging.¹²

Results

The preoperative CEA levels observed in the 214 patients studied are shown in the figure.

Table 1 *Preoperative CEA elevations in patients with bronchial carcinoma correlated with pathological stage of disease*

Stage grouping	Number of patients	Incidence of positive CEA levels (> 10 ng/ml)
1. Stage 1 T ₁ N ₀ M ₀	20	8/20 (40%)
2. Stage 2 T ₁ N ₁ M ₀ T ₂ N ₀ M ₀ T ₂ N ₁ M ₀	53	31/53 (58.5%)
3. Stage 3 T ₃ N ₀ M ₀ T ₃ N ₁ M ₀ N ₂ with any T M ₀	81	69/81 (85.2%)
4. Stage 4 M ₁ with any T or N	26	24/26 (92.3%)
Total series with carcinoma	180	132/180 (73.3%)

The mean serum CEA levels measured in each pathological stage of bronchial carcinoma are summarised in table 2. Differences between the mean CEA levels of each stage were statistically significant ($p < 0.001$), with the exception of stage 1 versus stage 2.

Using 10 ng/ml as the level above which significant CEA elevations occur when compared to normal control subjects, it was found that positive CEA levels were present in 40% (8/20) of stage 1, 58.5% (31/53) of stage 2, 85.2% (69/81) of stage 3, and 92.3% (24/26) of stage 4 patients (table 1). The mean CEA level in the group studied with active benign pulmonary disease was 6.45 ± 4.79 ng/ml (SD). The upper limit at which significant elevations occur when compared to this disease control group was, therefore, set at 16 ng/ml (mean level + 2 SD). When compared to the disease control group, significant CEA elevations (>16 ng/ml) were found in 25% (5/20) of stage 1, 35.9% (19/53) of stage 2, 54.3% (44/81) of stage 3, and 73.1% (19/26) of stage 4 patients. When the results were correlated with the histological type of tumour found at oper-

Table 2 *Mean preoperative CEA levels (\pm SEM) grouped according to the pathological stage of bronchial carcinoma*

Group	Mean CEA level (ng/ml \pm SEM)
1 Benign active pulmonary	$6.45 \pm 0.83^*$
2 Stage 1	$10.55 \pm 1.79^\dagger$
3 Stage 2	$14.77 \pm 1.55^\ddagger$
4 Stage 3	$25.68 \pm 2.20^\S$
5 Stage 4	$61.84 \pm 10.57^\S$

Significance using the unpaired Student *t* test

* $p < 0.25$ versus 1; $p < 0.001$ versus 2, 3, 4

† NS

‡ $p < 0.001$ versus 1, 2

§ $p < 0.001$ versus 1, 2, 3

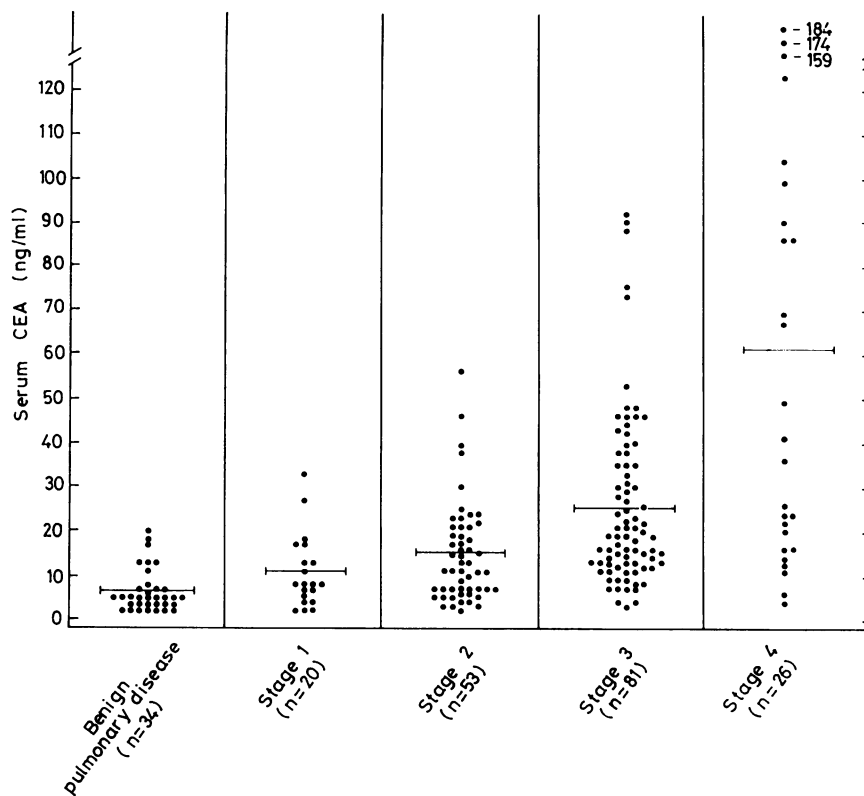


Figure Scattergram showing individual preoperative CEA values observed in each pathological stage of disease. Horizontal solid lines represent mean CEA levels.

ation, CEA levels were found to be most frequently elevated in the presence of adenocarcinoma, followed by undifferentiated large and small cell carcinoma, and squamous cell carcinoma (table 3). Of the patients with benign, active, inflammatory pulmonary diseases, 20.6% (7/34) had significant elevations compared to normal control subjects. The overall incidence of preoperative CEA elevations (>10 ng/ml) observed in patients with bronchial carcinoma in this study was 73.2% (132/180).

Discussion

There is increasing interest in the study of

Table 3 Preoperative CEA elevations grouped according to histological type of bronchial carcinoma found at operation

Histological type of tumour	Incidence of CEA elevation (> 10 ng/ml)
1 Adenocarcinoma	19/22 (86.4%)
2 Undifferentiated large cell	20/27 (74.1%)
3 Undifferentiated small cell ("oat cell")	24/35 (68.6%)
4 Squamous carcinoma	64/96 (66.7%)
5 Benign active pulmonary disease	7/34 (20.6%)

tumour biomarkers in the assessment and management of patients with bronchial carcinoma. Elevations of serum levels of carcinoembryonic antigen (CEA) have been observed in 50–80% of patients with bronchial neoplasms, and recent studies have suggested specific uses for this marker in the management of lung cancer patients.^{6-9 13}

Tormey *et al*¹⁴ have emphasised that a biological tumour marker should be capable of quantitatively measuring the "actual clinical or subclinical tumour burden of the host." The ability of CEA to do this in patients with bronchial carcinoma has been the object of several investigations. Dent *et al*⁷ reported a positive correlation between CEA levels and the extent of intrathoracic compared with extrathoracic disease in lung cancer patients referred for palliative therapy. Gropp *et al*¹³ observed significantly higher CEA levels in patients with metastatic lung carcinoma than in those with local disease. Vincent *et al*¹⁵ could not initially demonstrate a relationship between CEA levels and the "tumour volume" present at necropsy in patients with advanced lung cancer, but later observed⁸ that serial CEA levels do parallel tumour recurrence

and progression after pulmonary resection. Similarly, a large, recent series reported by Ford *et al*⁹ demonstrated that serial postoperative CEA determinations may effectively monitor the clinical course of bronchial carcinoma and the effects of treatment for metastatic disease.

Recently, Concannon *et al*,⁶ in a study on the prognostic significance of preoperative CEA elevation in patients with bronchial carcinoma, noted a positive correlation between the incidence of CEA elevations (greater than 6 ng/ml) and the postsurgical pathological stage of disease. Postsurgical pathological staging represents the best method currently available to assess the anatomical extent of disease in patients with bronchial carcinoma.^{12 16 17} In Concannon's study of 149 patients significantly more were observed to have CEA elevations in stage 4 than in stages 1, 2, and 3 ($p < 0.01$).

The object of the present study was to determine the precise correlation between preoperative CEA levels and the anatomical extent of bronchial carcinoma determined by pathological staging. Carcinoembryonic antigen elevations (defined as greater than 10 ng/ml) were observed in 73.3% (132/180) of patients with all stages of bronchial carcinoma. The frequency with which CEA elevations were observed compared to both normal and disease control patients was found to increase with the increasing pathological stage of disease. Although overlap of individual CEA levels occurred between stages (fig), the mean preoperative CEA levels correlated positively with the pathological stages of disease. Furthermore, the differences between mean levels (table 2) were statistically significant for stages 1 and 2 versus 3 and 4 ($p < 0.001$). This suggests a strong positive correlation between the quantitative amount of CEA detected in serum and the anatomical extent of bronchial tumour determined by pathological staging.

When results were correlated with the histological type of bronchial carcinoma, CEA elevations were observed to occur most frequently with adenocarcinoma, followed by undifferentiated and squamous cell carcinoma. These data are in agreement with the findings of Ford *et al*⁹ and Pascal *et al*¹⁸ who observed a higher incidence of increased CEA in adenocarcinoma of the lung than in other histological types. Pascal has suggested that this results in part from the fact that undifferentiated and squamous tumours of the lung lose the ability to secrete oncofetal antigen through malignant cellular differentiation, while in contrast adeno-

carcinoma retains its morphological endodermal characteristics and CEA secretion. This hypothesis is appealing and merits further immunochemical investigation.

This study demonstrates that bronchial tumours secrete carcinoembryonic antigen preoperatively in amounts that correlate well with the clinical tumour burden as defined by post-surgical staging methods. Of the histological types of bronchial carcinoma studied, adenocarcinoma produced this glycoprotein most frequently, reflecting, perhaps, its origin from the endodermally derived bronchial mucosa cells. Although not specific enough for screening purposes, CEA has clinical potential as a biological tumour marker in the management of bronchial neoplasms. In our current studies, preoperative CEA determinations are obtained along with sequential postoperative levels after pulmonary resection in patients with bronchial carcinoma. The pattern of CEA elevations observed in this setting may be of great benefit in the determination of prognosis, the definition of extent of disease for adjuvant therapy, and as a means of surveillance for recurrent carcinoma after operation.

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