

## Clinical Values of Carcinoembryonic Antigen (CEA) in Lung Cancer

Yasunori KOGA, Koichiro SHIBATA, Toshio ONITSUKA,  
Koichiro SAKODA, Takami MAEDA, Shigehito HAMASUNA,  
Toshiro KARIYA, Norio WAKE, Masato SAKIHAMA,  
Yoshikazu MINE, Yasunori MATSUZAKI,  
Makoto YOSHIOKA, Tsutomu YONEZAWA,  
Susumu CHIYOTANDA, Ryo SEKIYA, Kunihide NAKAMURA,  
Mami HAYASHI, Masao TOMITA

*Second Department of Surgery  
Miyazaki Medical College,  
Kiyotake, Miyazaki, 5200, Japan*

Received for publication, September 15, 1981

The plasma levels of the carcinoembryonic antigen (CEA) were measured in 62 consecutive lung cancer patients by Sandwich method using Dinabot Kit in order to certify the clinical values. When its level would exceed 5 ng per ml, it was regarded as being a positive. In patients with benign lung diseases, its level was lowered with a range of 2 to 1 ng per ml, even a maximum of 3 ng per ml in cases with bronchiectasis. The majority of positive cases in the CEA plasma level measured were far advanced cancer patients indicated as the Stage III and IV of the Japanese clinical stage classification. According to the histological classification, the positive rate of 50 per cent was in adenocarcinoma, 24 per cent in squamous cell carcinoma and 29 per cent in undifferentiated carcinoma respectively.

According to the TNM classification, the positive rates of the plasma CEA were increased in both T<sub>2</sub> and T<sub>3</sub> rather than T<sub>1</sub>, in N<sub>2</sub> rather than N<sub>1</sub> and N<sub>0</sub>, whereas there was no significant difference between M<sub>0</sub> and M<sub>1</sub>.

According to the finding of cell differentiation, their positive rates were enhanced in well differentiation of squamous cell carcinoma although there were no definite changes

---

古賀 保範, 柴田 紘一郎, 鬼塚 敏男, 迫田 耕一郎, 前田 隆美, 浜砂 重仁, 仮屋 敏郎,  
和氣 典雄, 崎浜 正人, 三根 義和, 松崎 泰憲, 吉岡 誠, 米沢 勤, 千代反田 亮,  
関屋 輔, 中村 都英, 林 麻美, 富田 正雄,

in the degree of differentiation in adenocarcinoma. In undifferentiated carcinoma, especially oat cell carcinoma, the CEA plasma values did not respond to be positive.

According to operative procedures of either curative or non-curative operation, the CEA plasma level was greatly high in patients undergoing non-curative operation when compared to those undergoing curative one.

Other influential factors on the CEA plasma level were found in serum protein level over 7 g per dl and the increased numbers of positive responses of skin tests to SK-SD, Candida, PPD and PHA antigens.

In the course of postoperative period, the rapid decrease immediately after excision of the tumor mass was seen in well differentiated squamous cell carcinoma. When recurrence or metastasis might develop elsewhere in the body, the slight increase in the CEA plasma level was not noted until cancer tumor apparently grew so as to be able to detect cancer recurrence with the use of clinical tools, its level gradually rose at interval of approximately a 7 month duration.

It was concluded that the CEA measurement was useful for determination of the staging of cancer and evaluation of the effectiveness in various kinds of the treatments. It, however, was not yet helpful to detect an early cancer.

## INTRODUCTION

The trial of making a diagnosis of cancer with the measurement of cancer-producing substance is now prevailing with an advances in the radioimmunoassay method. The clinical application for either  $\alpha$ -fetoprotein or the CEA measurements has been popular so far.

It is well known that the plasma CEA detected by Gold and Freedman in 1965 is thought to be specific in the colon cancer. It, however, has become evident that the CEA is not only specific in the colon cancer but also detectable in various cancers of the lung, the stomach and the breast.

This study was undertaken to elucidate clinical values of CEA measurement for lung cancer in terms of evaluating the prognosis and making a diagnosis of metastasis and recurrence.

## MATERIAL AND METHOD

Sixty-two consecutive patients with lung cancer were subjected in this study. These patients were summarized in Table 1 according to the staging classification and histological types. Sixty-five per cent of the patients were categorized into Stage III or IV of clinical staging, 40 per cent were adenocarcinoma, 42 per cent were squamous cell carcinoma and 18 per cent were undifferentiated carcinoma according to the histological types.

The CEA plasma levels in 46 patients were measured in pre and postoperative periods with the use of Dinabot Kit by Sandwich method. When the level of the CEA exceeded 5 ng per ml, it was regarded as being positive.

Table 1 Cases eligible for this study

J. J. C STAGE	histology	Cases	total
IV	undiff larg	—	9 (5)
	small	3 (1)	
	sq	—	
	ad	6 (4)	
III	undiff larg	1 (1)	31(21)
	small	5 (3)	
	sq	14(10)	
	ad	11 (7)	
II	undiff larg	—	8 (8)
	small	—	
	sq	5 (5)	
	ad	3 (3)	
I	undiff larg	2 (2)	14(12)
	small	—	
	sq	7 (6)	
	ad	5 (4)	
	total		62(46)

( ) CEA measured cases

## RESULTS

A comparative study was made between CEA level and disease staging, and CEA plasma level and histological types as shown in Fig 1. Positive CEA plasma level was shown in Stage III and IV patients except for patients with undifferentiated carcinoma of Stage I.

Eighty-eight per cent of the positive CEA were an advanced cancer of Stage III and IV.

In non-cancer patients with benign lung tumor and bronchiectasis, the CEA plasma level was compared as a control. It ranged from 1 to 2 ng per ml with a maximum of 3 ng per ml. Adenocarcinoma was high positive rate of 50 per cent whereas positive of squamous cell carcinoma was 24 per cent and that of undifferentiated carcinoma was 29 per cent according to the histological types.

The relationship of the CEA plasma level to a modality of TNM classification was shown in Table 2. According to T-factor, the CEA plasma level has remained high as the number of T became increased. The same attitudes were seen in-N factor, in particular, N<sub>2</sub> yielded the high CEA values. In M factor, M<sub>1</sub> led to considerably high values of the CEA as well. There were statistically significant differences ( $p < 0.05$ ) between T<sub>1</sub> and T<sub>2</sub> T<sub>3</sub>, N<sub>0</sub> N<sub>1</sub> and N<sub>2</sub> but there were no differences between T<sub>2</sub> and T<sub>3</sub>, N<sub>0</sub> and N<sub>1</sub>, M<sub>0</sub> and M<sub>1</sub>.

The relationship of the CEA plasma level to the histological types and cell differentiation was indicated in Fig 2. There was no significant difference in adenocarcinoma

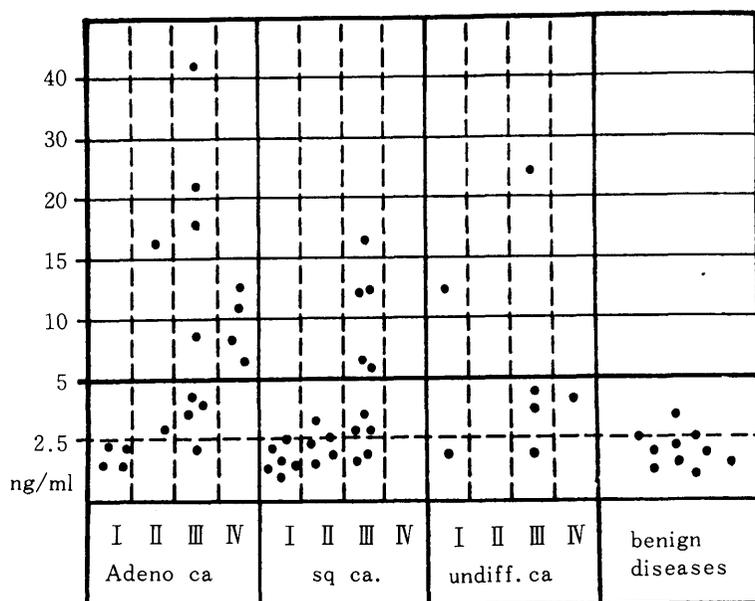


Fig 1 Relationship between CEA value and staging, histological type

between CEA plasma level and the degree of cell differentiation, that is, 38 per cent of the CEA positive rate in well differentiation, 67 per cent in moderate and 50 per cent in poor. Meanwhile, the positive rate was high in squamous cell carcinoma, that is, 50 per cent in well differentiation, 13 per cent in moderate and 14 per cent in poor. The patients with undifferentiated carcinoma were a few in number but the positive CEA values were not encountered, especially in oat cell carcinoma.

In patients with the positive CEA values, only two patients were capable of undergo surgical treatment, one was adenocarcinoma, the other large cell carcinoma. Meanwhile, the CEA positive rates were shown as 50 per cent (6/12) in those who underwent relative curative operation and as 71 per cent (5/7) in those who underwent non-curative operation as shown in Fig 3.

In non-operated group which included the patients with either preoperatively wide spread metastasis or undifferentiated carcinoma integrity, the CEA positive rate was only 50 per cent. In view of plasmic protein and CEA level, 48 per cent of the CEA positive rate showed more than 7g per dl in plasma protein, whereas 18 per cent was

Table 2 Relationship between CEA value and TNM classification

T	C.E.A	No
T <sub>1</sub>	1.9	(8)
T <sub>2</sub>	5.7	(24)
T <sub>3</sub>	9.5	(14)
N		
N <sub>0</sub>	2.8	(13)
N <sub>1</sub>	4.8	(10)
N <sub>2</sub>	8.7	(23)
M		
M <sub>0</sub>	4.7	(41)
M <sub>1</sub>	8.1	(5)

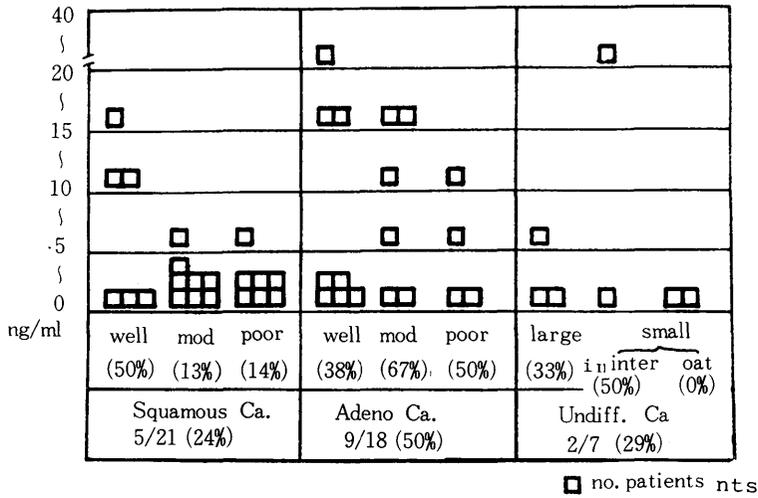


Fig 2 Relationship between CEA value and histological type including the degree of cell differentiation

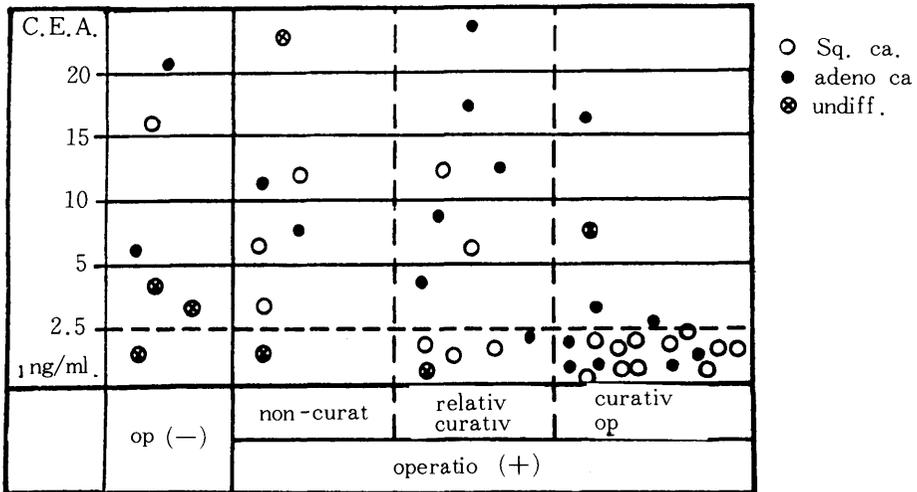


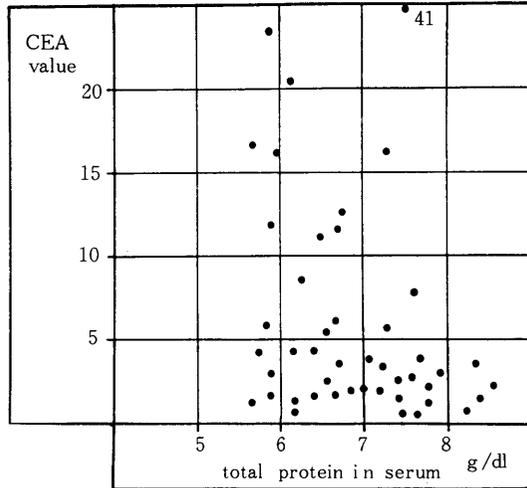
Fig 3 Relationship between CEA value and operative procedure including the degree of operative radicality

below 7g per dl (Fig 4).

Based on the results of evaluating the immune responses to SK-SD, Candida, PPD and PHA antigens by skin tests the positive numbers of skin tests were compared with the positive CEA rates. While positive skin tests would be only one in number, the CEA positive rate was 44 per cent, if two 38 per cent, if three 25 per cent and if four 25 per cent respectively, These, however, were not statistically significant (Fig 5).

In comparison of its prognosis with the CEA plasma level, (Fig 6). the prognosis for the positive CEA patients was very poor due to far advancing cancer. Nevertheless,

early deaths within 12 months after surgery were encountered even in the negative CEA patients since these included either poorly differentiated squamous cell carcinoma or undifferentiated carcinoma. Meanwhile, its prognosis has been compared with the classifications of the staging, histological type and the degree of cell differentiation. It closely correlated with staging, that is, Stage I patient had a better prognosis regardless of the histological types in either adenocarcinoma or squamous cell carcinoma.



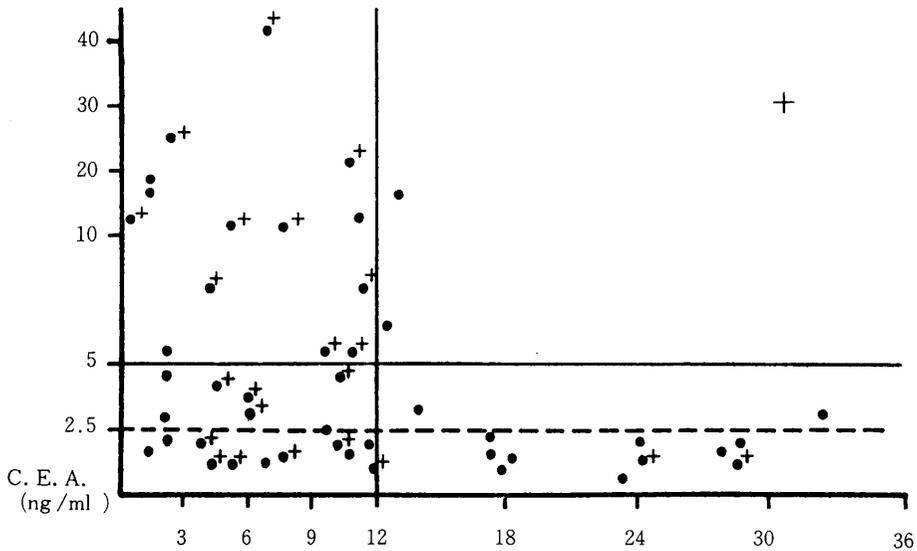


Fig 6 Relationship between preoperative CEA value and its prognosis

On the other hand, undifferentiated carcinoma demonstrated a poor prognosis. According to the degree of cell differentiation, poorly cell differentiation yielded worse prognosis, irrespective of the histological types between adenocarcinoma or squamous cell carcinoma.

In the follow-up period of 3 months following surgery, (Fig 7), preoperatively positive CEA patients with well differentiated squamous cell carcinoma were changed to a negative after the tumor bulk was excised. In the adenocarcinoma patients, early increases in the CEA plasma levels were noted in the postoperative course whereas they reduced temporarily, reflecting an operative effectiveness of resection of the tumor mass.

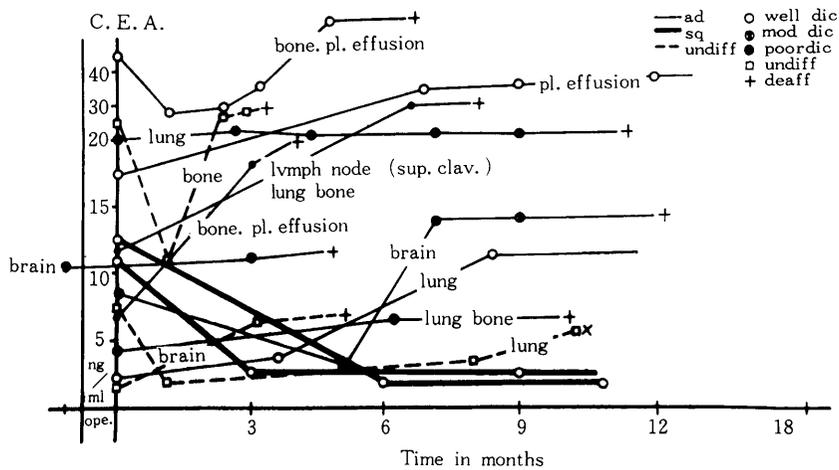


Fig 7 Pre- and postoperative course in patients with positive CEA and metastatic foci

Its prognosis was highly poor and mean survival was a 7 month duration after the CEA values remained positive.

## DISCUSSION

The various markers are now available for detecting cancer and estimating its prognosis in the course of cancer treatment<sup>1)</sup>, in particular, the CEA is more popular and helpful for either the establishment of diagnosis and screening, or the detection of a recurrence or metastasis. In lung cancer, the positive CEA rate is high and its clinical significance has been evaluated<sup>2)</sup>.

There are various methods of the CEA level measurement such as Kit, RIA, Z-gel, two Kit assay and so on. The normal ranges obtained from these methods individually varied on an average but these values closely correlate each other<sup>3)</sup>. CEA plasma level is not specific in malignant diseases<sup>4)</sup>. As a rule, the CEA plasma level is not so high in benign diseases as compared with malignant diseases. In this series, one patient with bronchiectasis of benign diseases showed a maximum of 3 ng per ml in CEA plasma level.

It is clear that the CEA plasma level correlates well with advancing stage of this disease and it reflects that the high CEA plasma level is consistent with a result of poor prognosis. When the CEA plasma levels would exceed 6 ng per ml as cited by Concannon<sup>5)</sup>, there was no long-term survivor. According to TNM classification of lung cancer, it is highly influenced in T<sub>3</sub> rather than T<sub>1</sub> T<sub>2</sub>, N<sub>2</sub> rather than N<sub>0</sub> N<sub>1</sub> and M<sub>1</sub> rather than M<sub>0</sub>.

Some reports confirm that the CEA plasma level does not necessarily correlate with T and N factors since tissue necrosis in tumor bulk may occur as the tumor mass is increasing in size and that lymph node metastasis in the hilar portion, not extending to the mediastinum, is not in association with a high CEA plasma level. Our data supports that the CEA plasma level is higher in adenocarcinoma rather than in undifferentiated carcinoma and squamous cell carcinoma. This is substantiated by an experience with the use of immunoassay method to detect the CEA in the tumor mass and the plasma. The dense distribution of the CEA is seen in the tumor cell of adenocarcinoma with a great mobilization into the blood and it is a minimum in undifferentiated carcinoma.

Furthermore, it is noted that it has a close relationship of the CEA plasma level to leucocyte index and albumin in the serum. We also indicate on the basis of the results of this study that the CEA plasma level well correlate with a total of plasma protein, reflecting that hypoproteinemia may be caused by advanced cancer. the CEA plasma level is also influenced by the status of immune response to various kinds of the antigens. The numbers of positive skin tests to antigens are associated with the CEA plasma levels. Various influencing factors on the CEA plasma levels make their significances difficult to interpret. Determinations of the CEA offer promise of being one of the major parameters in expecting whether curative operation will be feasible or not prior to surgery. Vincent and coworkers<sup>7)</sup> proposed that a 6.65ng of the high CEA plasma level implied

no feasibility of curative operation. It is our conviction that the high CEA plasma level is more likely to mean the advancing cancer status in which surgical treatment is not advocated. In the postoperative course, it is certain that preoperative CEA plasma level quickly return to be normal in well differentiated squamous cell carcinoma although it is not evident in adenocarcinoma. And the increasing CEA plasma level is indicative of an existence of postoperative metastasis and recurrence. Vincent et al<sup>7)</sup> reported that the CEA values in the postoperative period are essential in estimating their prognoses. Minton and Martin<sup>8)</sup> reported that reoperation for local recurrence, referred to as a so-called second look operation, was mandatory when the CEA plasma level had become high for a period of postoperative follow-up study. We, however, experienced that clinical manifestation of a recurrence and metastasis had not become apparant until the CEA plasma level was increased.

#### REFERENCE

- 1) COOMES, R. C., ELLISON, M. L. and NEVILLE. A. M.: Biochemical markers in bronchogenic carcinoma. *Brit. J. Dis. Chest.*, 72: 267-287, 1978.
- 2) PETER. B. DENT, PETER. B. McCULLOGH, OLIVER. NESLEY. JAMES, et al.: Measurement of carcinoma antigen in patients with bronchogenic carcinoma. *Cancer*, 42: 1484-1491, 1978.
- 3) DICKRAN, F. NEIL. D. G.: Two kit assay of carcinoembryonic antigen compared. *Clin. Chem.*, 25: 1189, 1979.
- 4) ALSABT, E. A. K. and KAMEL, A.: Carcinoembryonic antigen in patient with malignant and non-malignant diseases. *Neoplasma*, 26: 603-209, 1979.
- 5) JOSEOH. P. C. MILTON. H. D. SHEILA E. H. et al.: Prognostic value of preoperative C. E. A. Plasma levels in patients with bronchogenic carcinoma. *Cancer*, 42: 1477-1483, 1978.
- 6) VINGENT, R. G. and CHU, T. N.: Carcinoembryonic antigen in patients with carcinoma of the lung. *J. Thorac. Cardiovasc. Surg.*, 66: 320-325, 1973.
- 7) VINCENT, R. G., CHU, T. M. and LANE, W. W.: The value of carcinoembryonic antigen in patient with carcinoma of the lung. *Cancer*, 44: 685-691, 1979.
- 8) MINTON, P. J. and MARTIN, W. E.: The use of serial C. E. A. determinations to predict recurrence of colon cancer. *Cancer*, 42: 1422-1427, 1978.