Original Article

Prognostic Significance of Preoperative Serum Carcinoembryonic Antigen Level in Lung Adenocarcinoma but not Squamous Cell Carcinoma

Masaki Tomita, MD, Yasunori Matsuzaki, MD, Masao Edagawa, MD, Tetsuya Shimizu, MD, Masaki Hara, MD, and Toshio Onitsuka, MD

Objectives: Clinical significance of measurement of preoperative serum carcinoembryonic antigen (CEA) level in patients with non-small cell lung cancer was investigated.
Methods: Consecutive 271 adenocarcinoma and 112 squamous cell carcinoma patients of non-small cell lung cancer referred to our institute were included in this study. There were 214 men and 169 women, ages ranged from 19 to 90 years, with an average of 64.46 years. Curative resection was performed for 220 adenocarcinoma and 93 squamous cell carcinoma patients. Serum level of CEA was measured before staging or resection of cancer.
Results: There is a trend toward a correlation between serum CEA level and stage of the diseases, however, serum CEA level was not always related to tumor node metastasis (TNM) status. In patients with adenocarcinoma, survival rate of patients with an elevated serum CEA level was significantly lower than that with a normal serum CEA level. Multivariate analysis showed that prognostic significance of serum CEA level was TNM staging independent in patients with adenocarcinoma. On the other hand, serum CEA level was not related to patients' survival in patients with squamous cell carcinoma.
Conclusions: Elevated preoperative serum CEA level is a TNM staging independent prognostic factor for patients with adenocarcinoma but not for those with squamous cell carcinoma. (Ann Thorac Cardiovasc Surg 2004; 10: 76–80)

Key words: carcinoembryonic antigen (CEA), non-small cell lung cancer, adenocarcinoma, squamous cell carcinoma

Introduction

The best predictor of outcome in non-small cell lung cancer is the tumor node metastasis (TNM) classification of the patients.[1,2] The TNM stage is known to be a heterogeneous subcategory, and several authors have suggested some significant prognostic factors, such as oncogene and/or tumor-suppressor gene expression,[3-5] tumor cell proliferation kinetics[6,7] and angiogenesis.[8]

However most of these factors cannot be obtained preoperatively. Recent studies demonstrated that preoperative induction therapy might improve surgical outcome of non-small cell lung cancer patients.[9] Therefore preoperative prognostic factors might be important and different therapeutic approaches for non-small cell lung cancer patients can be performed according to preoperative prognostic factors. Preoperative therapeutic planning of non-small cell lung cancer is, however, currently performed based on TNM staging only in many centers.

The carcinoembryonic antigen (CEA) is a serum marker that has been one of the most commonly used to date. Several reports have indicated that elevated preoperative serum CEA levels are associated with more advanced disease and with very poor survival after surgical resection.[10-16] Despite these reports, the preoperative serum CEA level has not been incorporated into the evaluation of patients considered for resection of non-small

From Department of Surgery II, Miyazaki Medical College, Miyazaki, Japan

Received August 18, 2003; accepted for publication November 13, 2003.
Address reprint requests to Masaki Tomita, MD: Department of Surgery II, Miyazaki Medical College, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan.

Table 1. Patients characteristics

	Number. of patients	
	Adenocarcinoma	Squamous cell carcinoma
T1	128	21
T2	72	47
T3	23	31
T4	48	13
pN0	148	56
pN1	18	18
pN2	54	19
M0	244	107
M1	27	5
Stage I	129	42
Stage II	27	20
Stage III	89	45
Stage IV	26	5
Complete resection	220	93
Incomplete resection/none resection	51	19

cell lung cancer. Some clinicians might believe that serum CEA level is only a marker of advanced disease but not an independent prognostic factor. Because serum CEA level is an importantance preoperative factor and inexpensive to carry out we examine whether preoperative measurements of serum CEA level added useful prognostic data or not.

Materials and Methods

Patients

Consecutive 383 non-small cell lung cancer patients (271 adenocarcinoma and 112 squamous cell carcinoma) referred to our department during the period 1996 to 2001 were included in this study (Table 1). Of these, 220 adenocarcinoma and 93 squamous cell carcinoma patients received complete resection which consisted of either a lobectomy or a pneumonectomy together with the regional lymph nodes dissection. Other remaining patients received incomplete resection or did not undergo surgical options. For patients with complete resection, pathologic TNM staging was recorded, while in the others clinical staging was recorded. The clinical stage had been diagnosed using the following: chest roentgenography, chest computed tomography (CT), abdominal CT scan, brain magnetic resonance imaging, and general bone scintigraphy.

There were very few cases with T4 or M1 disease in patients with complete resection. To investigate the relationship between serum CEA level and T4 or M1 disease, we included patients without complete resection in the present study. Patient ages ranged from 19 to 90 years old (mean, 64.46 years). Serum CEA level was measured by means of the two-site immunoenzymometric assay (Tosoh Co.; Yamaguchi, Japan); the normal upper limit for this assay was 5 ng/ml. The time interval between serum CEA examination and staging or surgical resection was less than a month in all the patients. The follow-up information, including cause of death, was acquired through clinic follow-up notes and direct or family contact.

Patients were subdivided into two groups; adenocarcinoma and squamous cell carcinoma. The serum CEA level was compared according to stage, T status, M status and clinical stage in all patients. The relationship between serum CEA level and N status and patients' survival were evaluated in patients with complete resection.

Statistical analysis

Characteristics of the patients were compared using the t test or the Mann-Whitney U test. Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log rank test. Factors related to prognosis were analyzed by multivariate analyses according to the Cox proportional hazards model. Statistical calculations were conducted with StatView (SAS Institute Inc., Cary, NC) and values of p less than 0.05 were accepted as significant.

Results

TMN stage

In patients with adenocarcinoma, as shown in Table 2, a

Table 2. Relationship between serum CEA level and TNM staging

	Adenocarcinoma		Squamous cell carcinoma	
	Serum CEA level (mean ± SD)	p value	Serum CEA level (mean ± SD)	p value
Stages I-II	4.3±3.5	p<0.005	5.1±3.6	p<0.01
Stages III-IV	35.3±96.9		7.5±5.0	
T1-2	11.3±45.6	NS	5.2±3.6	p<0.005
T3-4	34.7±99.5		7.7±5.1	
N0-1	8.4±23.9	NS	5.2±3.4	NS
N2	11.4±13.2		6.5±4.5	
M0	8.9±17.1	p<0.05	5.9±4.1	p<0.05
M1	102.6±191.0		10.5±7.7	

CEA, carcinoembryonic antigen; NS, not significant.

significant difference in serum CEA level was observed between stages I-II and stages III-IV (p<0.005). There were also significant differences in serum CEA level between M0 and M1 (p<0.05). However we could not find significant differences in serum CEA level between T1-2 and T3-4 (p=0.058), and N0-1 and N2 (p=0.25).

In patients with squamous cell carcinoma, significant differences in serum CEA level were noted between stages I-II and stages III-IV (p<0.01), T1-2 and T3-4 (p<0.005), and M0 and M1 (p<0.05). On the other hand, there were no differences in serum CEA level between N0-1 and N2 (p=0.16).

Survival

Patients' survival was investigated using patients with complete resection. As shown in Fig. 1A, the 5-year survival rate of adenocarcinoma patients with normal and elevated serum CEA level was 77.6% and 42.5%, respectively (p<0.001). In contrast, in patients with squamous cell carcinoma (Fig. 1B), the 5-year survival rate was 63.3% and 57.8%, respectively (p=0.734).

Multivariate analysis was also performed using patients with complete resection. Pathologic stage, pT status, pN status and serum CEA level were entered into the Cox proportional hazards model by a forward stepwise procedure. As shown in Table 3, serum CEA level was a TNM staging independent prognostic factor in patients with adenocarcinoma (p=0.019), while it was not independent in those with squamous cell carcinoma (p=0.467).

Discussion

In our results, elevated serum CEA level was not always related to TNM stage. The reported results of correlation between serum CEA level and TNM staging in non-small cell lung cancer are controversial despite extensive studies.[10-16] These controversial results are difficult to interpret. A possible variables in these studies was use of different population of the studied patients. With regard to N status, Takamochi et al.[17] reported that the elevated serum CEA level is a clinical predictor of N2 disease. However we could not find a significant difference in serum CEA level between N0-1 and N2.

Our results showed that serum CEA level is a TMN staging independent prognostic factor for patients with adenocarcinoma. Several studies also have found that the prognosis was poor for patients with high preoperative serum CEA levels.[10-16] Thus it is suggested that even if a

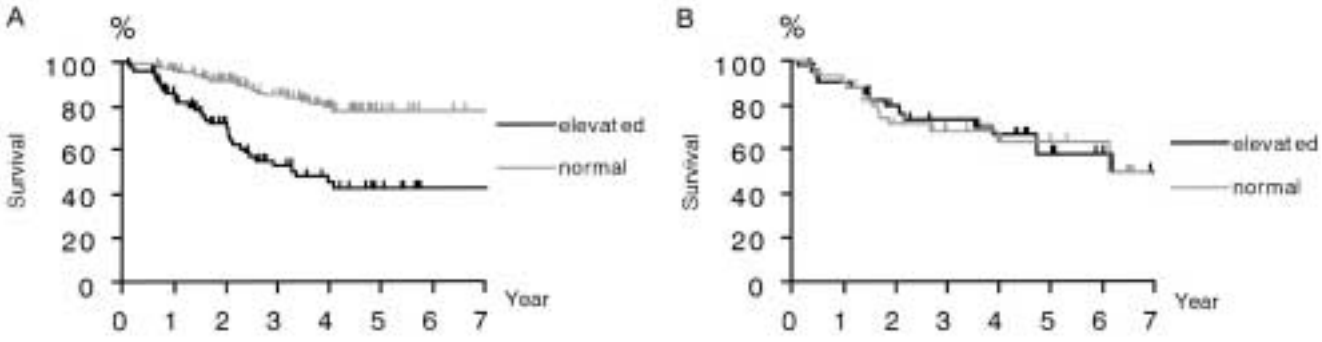

Fig. 1. Survival of patients according to serum CEA level in patients with adenocarcinoma (A) and squamous cell carcinoma (B).

Table 3. Multivariate analysis

Adenocarcinoma			
	Hazard ratio	95% confidence interval	p value
pStage	2.923	1.219-2.735	0.004
pT	2.038	1.010-1.662	0.042
pN	2.762	1.147-2.246	0.006
Serum CEA level	2.342	1.118-3.498	0.019
Squamous cell carcinoma			
	Hazard ratio	95% confidence interval	p value
pStage	1.953	0.145-1.004	0.050
pT	2.688	1.327-6.246	0.007
pN	2.721	1.325-5.658	0.006
Serum CEA level	0.728	0.366-1.585	0.467

CEA, carcinoembryonic antigen.

patient has an early clinical stage, the prognosis might be poor when the preoperative serum CEA level is high. Taken together with our results and previous studies,[10-16] serum CEA level is important and an adjunct to conventional TNM staging for patients with adenocarcinoma although the exact mechanism of elevated serum CEA level in non-small cell lung cancer remains unclear. Furthermore, serum CEA has been also reported to be a useful predictor of recurrence.[18,19]

In the present study, we did not investigate the critical level of serum CEA of prognostic significance. Dent et al.[11] reported that patients with a serum CEA level greater than 20 ng/ml had a poor prognosis. Stokes et al.[12] reported that patients with a serum CEA level above 40.9 ng/ml (their normal upper limit was 20.9 ng/ml) had recurrence and metastasis. Vincent et al.[13] reported that 42 of 49 patients with serum CEA level greater than 15 ng/ml had locally advanced inoperable disease. Concannon et al.[14] indicated that 16 of 21 patients with serum CEA level greater than 20 ng/ml had stage IV disease at the time of thoracotomy. Icard et al.[15] found that a critical serum CEA level of prognostic significance at 30 ng/ml. Many kits to measure serum CEA levels are available and the results vary with each assay. Thus there might be some cross-reactive normal antigens that are calculated by some kits, and the maximum normal serum level of CEA ranges from 2.5 to 6.9 ng/ml.[20] Care is needed when evaluating such archival data stored in medical records.

In contrast to patients with adenocarcinoma, we failed to find clinical significances of serum CEA level for patients with squamous cell carcinoma. The reason for no prognostic significance of serum CEA level for patients with squamous cell carcinoma is difficult to interpret. It was reported that serum CEA level in adenocarcinoma is significantly higher than that in squamous cell carcinoma,[13,16] in agreement with our results. Therefore adenocarcinomas might characteristically produce higher values than squamous cell carcinomas.[13] It is generally accepted that morphological tumor heterogeneity in lung cancer is occasionally found.[21,22] For example, some lung squamous cell carcinomas demonstrate features of adenocarcinoma. Therefore it might be hypothesized that elevated serum CEA level in squamous cell carcinoma patients might originate from the component of adenocarcinoma but not squamous cell carcinoma. This might be one of possible reasons for no prognostic significance of serum CEA level for patients with squamous cell carcinoma. Since the exact mechanism of elevated serum CEA level in non-small cell lung cancer remains unclear, further studies are required.

Previously reported biological prognostic factors[3-8] require surgical specimen and cannot be obtained preoperatively, and some of these factors are available only as research tools. Currently, serum CEA level is the inexpensive and routinely available preoperative factor. Despite current advanced diagnostic procedures for preoperative staging, our results showed a role for preoperative serum CEA level as an adjunct to conventional staging for adenocarcinoma patients. Further studies are required to determine whether the adjuvant therapy might improve the outcome for adenocarcinoma patients with elevated serum CEA level.

In conclusion, elevated preoperative serum CEA level is a TNM staging independent prognostic factor for patients with adenocarcinoma but not for those with squamous cell carcinoma.

References

1. Mountain CF, Greenberg SD, Fraire AE. Tumor stage in non-small cell carcinoma of the lung. *Chest* 1991; **99**: 1258–60.
2. Mountain CF. Lung cancer staging classification. *Clin Chest Med* 1993; **14**: 43–53.
3. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med* 1990; **323**: 561–5.
4. Quinlan DC, Davidson AG, Summers CL, Warden HE, Doshi HM. Accumulation of p53 protein correlates with a poor prognosis in human lung cancer. *Cancer Res* 1992; **52**: 4828–31.
5. Harpole DH Jr, Herndon JE 2nd, Wolfe WG, Iglehart JD, Marks JR. A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression. *Cancer Res* 1995; **55**: 51–6.
6. Fontanini G, Macchiarini P, Pepe S, et al. The expression of proliferating cell nuclear antigen in paraffin sections of peripheral, node-negative non-small cell lung cancer. *Cancer* 1992; **70**: 1520–7.
7. Scagliotti GV, Micela M, Gubetta L, et al. Prognostic significance of Ki67 labelling in resected non small cell lung cancer. *Eur J Cancer* 1993; **29A**: 363–5.
8. Macchiarini P, Fontanini G, Hardin MJ, Squartini F, Angeletti CA. Relation of neovascularisation to metastasis of non-small-cell lung cancer. *Lancet* 1992; **340**: 145–6.
9. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994; **330**: 153–8.
10. Ford CHJ, Stokes HJ, Newman CE. Carcinoembryonic antigen and prognosis after radical surgery for lung cancer: immunocytochemical localization and serum levels. *Br J Cancer* 1981; **44**: 145–53.
11. Dent PB, McCulloch PB, Wesley-James O, MacLaren R, Muirhead W, Dunnett CW. Measurement of carcinoembryonic antigen in patients with bronchogenic carcinoma. *Cancer* 1978; **42**: 1484–91.
12. Stokes TC, Stevens JFS, Long P, Lockey E, Miller AL. Preoperative carcinoembryonic antigen and survival after resection of lung cancer. *Br J Dis Chest* 1980; **74**: 390–4.
13. Vincent RG, Chu TM, Fergen TB, Ostrander M. Carcinoembryonic antigen in 228 patients with carcinoma of the lung. *Cancer* 1975; **36**: 2069–76.
14. Concannon JP, Dalbow MH, Hodgson SE, et al. Prognostic value of preoperative carcinoembryonic antigen (CEA) plasma levels in patients with bronchogenic carcinoma. *Cancer* 1978; **42**: 1477–83.
15. Icard P, Regnard JF, Essomba A, Panebianco V, Magdeleinat P, Levasseur P. Preoperative carcinoembryonic antigen level as a prognostic indicator in resected primary lung cancer. *Ann Thorac Surg* 1994; **58**: 811–4.
16. Rubins JB, Dunitz J, Rubins HB, Maddaus MA, Niewoehner DE. Serum carcinoembryonic antigen as an adjunct to preoperative staging of lung cancer. *J Thorac Cardiovasc Surg* 1998; **116**: 412–6.
17. Takamochi K, Nagai K, Suzuki K, Yoshida J, Ohde Y, Nishiwaki Y. Clinical predictors of N2 disease in non-small cell lung cancer. *Chest* 2000; **117**: 1577–82.
18. Buccheri G, Ferrigno D. Identifying patients at risk of early postoperative recurrence of lung cancer: a new use of the old CEA test. *Ann Thorac Surg* 2003; **75**: 973–80.
19. Kao CH, Hsieh JF, Ho YJ, Ding HJ. Cytokeratin fragment 19 (CYFRA 21-1) and carcinoembryonic antigen for early prediction of recurrence of lung adenocarcinoma. *Lung* 1999; **177**: 333–7.
20. Kuroki M, Haruno M, Arakawa F, Wakisaka M, Matsuoka Y. Reaction profiles of seven enzyme immunoassay kits for carcinoembryonic antigen (CEA) analyzed with purified preparations of CEA and related normal antigens. *Clin Biochem* 1992; **25**: 29–35.
21. Hirsch FR, Ottesen G, Podenphant J, Olsen J. Tumor heterogeneity in lung cancer based on light microscopic features. A retrospective study of a consecutive series of 200 patients, treated surgically. *Virchows Arch A Pathol Anat Histopathol* 1983; **402**: 147–53.
22. Roggli VL, Vollmer RT, Greenberg SD, McGavran MH, Spjut HJ, Yesner R. Lung cancer heterogeneity: a blinded and randomized study of 100 consecutive cases. *Hum Pathol* 1985; **16**: 569–79.