Int J Clin Exp Med 2019;12(5):5812-5819
www.ijcem.com /ISSN:1940-5901/IJCEM0079664

Original Article

Prognostic value of carcinoembryonic antigen level in advanced lung adenocarcinoma

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Received May 15, 2018; Accepted January 6, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: Objective: The objective of this study was to detect expression of carcinoembryonic antigen (CEA) level in patients with advanced lung adenocarcinoma as well as its impact on overall survival. Method: A total of 270 advanced lung adenocarcinoma patients were enrolled in this study. Chest CT, MRI, whole body bone imaging, and pathologic biopsy examination assessment were performed for tumor staging. Serum CEA level was detected to investigate its correlation with clinical features and prognosis. Results: Serum CEA level was correlated with CEA positive intensity in cancer tissue (r = 0.781, P = 0.009). Serum CEA level was positively related with TNM stage, M status, and cell differentiation. Patients with late TNM stage, worse differentiation, and distant metastasis showed higher CEA content (P < 0.05). The five-year survival rate in patients with elevated CEA (> 5 ng/ml) was lower than that in patients with normal CEA level (42.5% vs 79.6%). Multivariate analysis showed that TNM stage, metastasis, differentiation and whether serum CEA normal or not were independent risk factors that may affect prognosis. Serum CEA elevation demonstrated the largest risk (β = 1.052, P = 0.012). Conclusion: Serum CEA elevation is an independent prognostic factor for patients with non-small cell lung adenocarcinoma.

Keywords: CEA, non-small cell lung cancer, lung adenocarcinoma, mortality, prognosis

Introduction

Lung cancer is one of the most common cancers in clinic with the highest related death rate. About 80% of the patients were in advanced stage at the time of being diagnosed accompanied with metastasis. Thus, clinical survival prognosis is poor [1-3]. Lung adenocarcinoma belongs to non-small cell lung cancer (NSCLC) accounting for about 40% of all types. It originates from the bronchial mucosa epithelium that more likely appears in women who are non-smokers. Different from small cell lung cancer and central squamous cell carcinomas, lung adenocarcinoma often distributes in the peripheral lung. Due to less sensitivity to radiotherapy treatment, it is advocated to receive surgery resection in early stage. The TNM staging system is the most important basis for patient prognosis assessment. Some studies also reported other related prognostic factors, such as oncogene and/or tumor suppressor gene, the dynamics of tumor cell proliferation, and neovascularization. However, for patients that require surgical treatment, the abovementioned factors are difficult to obtain in a short time because of complications, expense, and low positive rate [4, 5]. With the progress of the research, lung cancer related tumor markers have been identified, but none show high sensitivity and specificity [6]. Carcinoembryonic antigen (CEA) is one of the most commonly used serum markers that are found in colorectal cancer [7], gastric cancer [8], pancreatic cancer [9], and breast cancer [10]. Numerous studies have shown that the high CEA level is associated with poor prognosis of advanced cancer [11, 12]. Other scholars thought that it is only a marker for advanced cancer that cannot be treated as an independent prognostic factor [13-16]. Combining with the clinical significance and low cost, the relationship between CEA level and advanced lung adenocarcinoma was investigated in this study, with the aim of pro-

Table 1. TNM staging characteristics

Item		Cases
TNM stage	T2	72 (26.7%)
	T3	123 (45.6%)
	T4	75 (27.7%)
	pN0	148 (54.8%)
	pN1	68 (25.2%)
	pN2	54 (20%)
	M0	124 (45.9%)
	M1	146 (54.1%)
	IIB	27 (10%)
	III	189 (70%)
	IV	54 (20%)

viding reference for clinical treatment and improving prognosis.

Materials and methods

Objects of study

In total, 270 advanced lung adenocarcinoma patients in The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital, Nanjing, China) were treated between January 2007 and December 2009. The male/female ratio was 11:16, and the mean age was 67.26 (20-89) years old. Patients together with other tumors or received chemo-radiotherapy were excluded. All patients were over stage IIB. Considering the limited number of cases, advanced lung cancer was defined as lymph node metastasis, pleural metastasis, and part of airway obstruction. Analyses were of 220 cases (216 cases in stage IIB and III, and 4 cases in stage IV) that received complete tumor resection, including lobectomy or pneumonectomy with regional lymph node cleaning. The others received partial tumor lobectomy or conservative treatment. Chest CT, MRI, whole body bone imaging, and pathologic biopsy examination assessment were performed for tumor staging according to TNM stage standard published by International Association for the Study of Lung Cancer (IASLC) in 2009 (**Table 1**). This study obtained informed consent from objects or family members and was approved by the Ethics Committee of The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital, Nanjing, China).

CEA detection

Tumor specimens were fixed in 4% paraformaldehyde and embedded for section. CEA expression in tumor tissue was observed by immunohistochemistry. Rabbit antihuman CEA monoclonal antibody was purchased from Abcam. After dewaxing, slices were blocked by 0.03% H_2O_2 and FBS. Then the slice was incubated in primary antibody at 4°C overnight and secondary antibody at room temperature for 60 minutes. The slices were detected after developed by DAB-H_2O_2 for 20 minutes. CEA positive intensity judgement: -, no coloration; +, positive cell < 15%; ++, positive cell at 15%~50%; +++, positive cell > 50%. A total of 2 ml peripheral blood was extracted and the serum was separated and stored at -80°C. Serum CEA level was detected by two-site immune-enzymatic assay (Tosoh Co. Yamaguchi, Japan). The normal upper threshold of the analysis was 10 ng/ml. CEA level ≤ 5 ng/ml was considered as low or normal expression, while it > 5 ng/ml was treated as high expression. The time interval between CEA detection and staging or resection was less than one week. Follow-up data including cause of death and death time was obtained from family member consult. Follow-up time was 1 to 91 months. Correlation analysis was performed according to serum CEA level and CEA positive expression intensity in cancer tissue.

Statistical analysis

Patients' basic information was compared using student t-test or Mann-Whitney U test. The relationship between serum CEA level and cancer tissue CEA positive expression intensity was analyzed by Spearman rank correlation. Serum CEA elevation was performed by Chi-square test. Survival curve was established through Kaplan-Meier method and analyzed by log rank test. Multivariate analysis was determined by Cox regression model to assess the prognostic value of CEA on overall survival. All statistical analysis was performed on SPSS 19.0 software. $P < 0.05$ was considered as statistically significant.

Results

Cancer tissue CEA expression positively correlates with serum CEA content

The patients were divided into a low group and a high group according to serum CEA content (**Figure 1**). Spearman rank correlation analysis revealed that serum CEA content was positively correlated with CEA expression intensity in tissue ($r = 0.781$, $P = 0.009$) (**Table 2**).

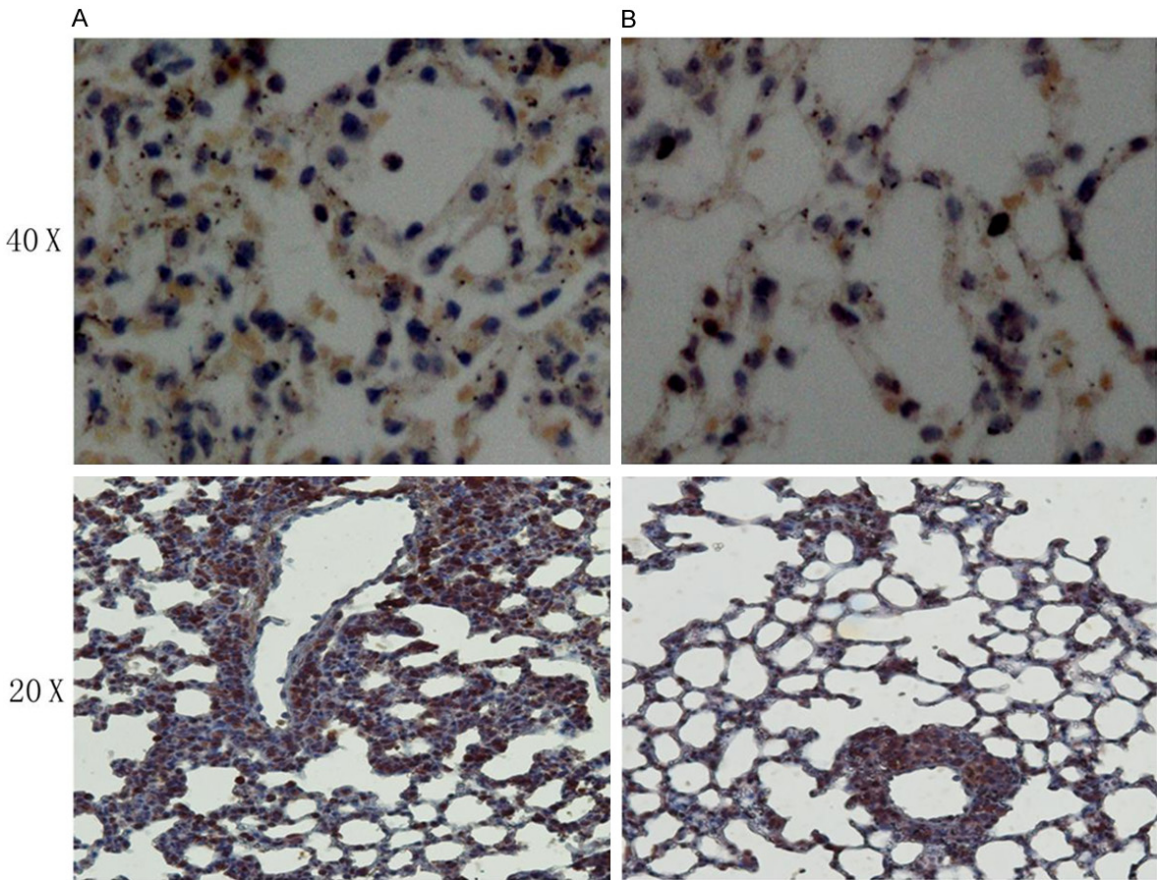

Figure 1. Immunohistochemistry analysis of tissue CEA expression in patients with positive serum CEA (A) and negative serum CEA (B).

Table 2. Relationship between cancer tissue CEA expression and serum CEA content

Group	Cases	Mean rank	Mann-Whitney U value	*P* value
Low group (≤ 5 ng/mL)	100	105.15	3340.5	0.003
High group (> 5 ng/mL)	170	187.10		

Serum CEA is associated with TNM stage, differentiation and metastasis

Since tissue CEA expression was found to be positively correlated with serum CEA content, and serum CEA detection had the advantage of convenient, rapid, and cheap, it has more important clinical significance. Thus, the relationship between serum CEA and basic clinical features was analyzed. As shown in **Table 3**, serum CEA level showed statistical differences among stage II, III, and IV, differentiation degree, and metastasis ($P < 0.05$). Age, gender, cancer tissue size, T stage, and N stage were lack of significant relationship with serum CEA level. CEA detection positive rate also presented similar relationship as CEA content with TNM stage, metastasis, and differentiation.

CEA level is associated with overall survival

Complete follow-up data was obtained from 221 of 270 cases. As shown in **Figure 2**, five-year survival rate in patients with low (< 5 ng/ml) and high CEA level (> 5 ng/ml) was 79.6% and 42.5%, respectively ($P < 0.001$). Multivariate analysis including age, gender, tumor size, differentiation, T stage, N stage, TNM stage, and serum CEA level in the Cox regression analysis model showed that TNM stage, metastasis, differentiation, and whether serum CEA normal or not were independent risk factors that may affect prognosis (**Table 4**). Serum CEA elevation demonstrated the largest risk ($\beta = 1.052$ $P = 0.012$). The death risk of patients with distant metastasis was 1.977 times of

Table 3. Relationship between serum CEA and basic clinical features

		Cases	Serum CEA	*P* value	Cases (positive rate)	χ^2	*P* value
Age (year)	≤ 60	115	23.6 ± 15.1	0.294	74 (64.3%)	0.165	0.685
	> 60	155	25.6 ± 15.7		96 (61.9%)		
Gender	Male	110	25.3 ± 14.5	0.106	76 (69.1%)	2.989	0.084
	Female	160	22.5 ± 13.1		94 (58.8%)		
Tumor size (cm)	≤ 2	66	21.5 ± 13.7	0.262	35 (53.0%)	3.696	0.055
	> 2	204	24.0 ± 16.3		135 (66.2%)		
Differentiation	Well	82	18.7 ± 10.2	< 0.001	48 (52.5%)	9.299	0.010
	Middle	104	22.8 ± 13.7[a]		58 (55.7%)		
	Poor	84	33.5 ± 16.8[a,b]		64 (76.2%)		
TNM stage	T2	72	25.1 ± 17.6	0.090	42 (58.3%)	3.702	0.157
	T3	123	29.8 ± 18.7		74 (60.2%)		
	T4	75	31.6 ± 19.4		54 (72.0%)		
	N0	148	28.1 ± 19.6	0.198	91 (61.5%)	0.895	0.639
	N1	68	31.2 ± 18.9		42 (61.8%)		
	N2	54	33.3 ± 19.1		37 (68.5%)		
	M0	195	20.1 ± 12.4	< 0.001	112 (57.4%)	9.196	0.002
	M1	75	35.2 ± 16.9		58 (77.3%)		
	Stage II	110	15.4 ± 8.9	< 0.001	57 (51.8%)	13.802	0.001
	Stage III	85	26.1 ± 14.2[c]		54 (63.5%)		
	Stage IV	75	36.1 ± 17.5[c,d]		59 (78.7%)		

Compared with Well, [a]p<0.05; Compared with Middle, [b]p<0.05; Compared with Stage II, [c]p<0.05; Compared with Stage III, [d]p<0.05.

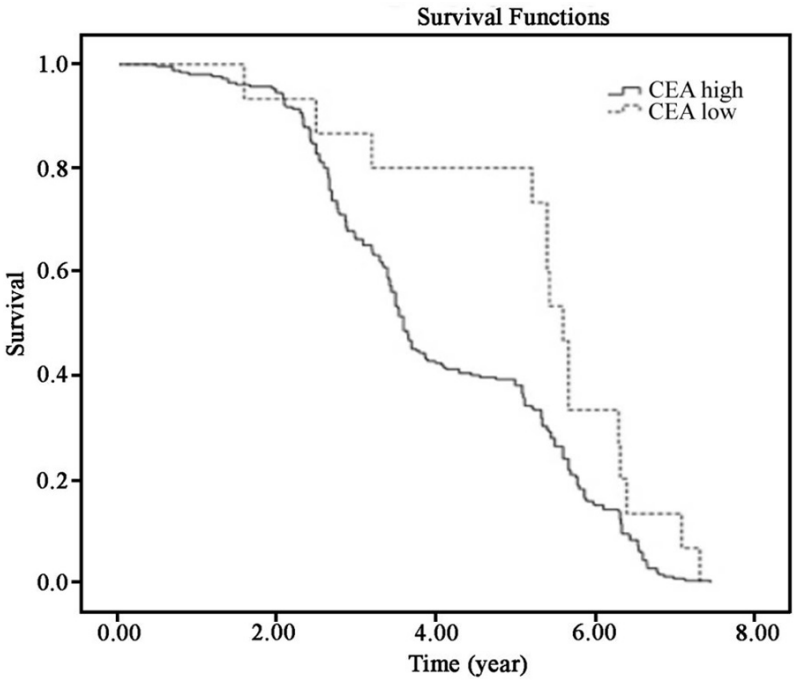

Figure 2. Survival curve related to serum CEA.

which without distant metastasis (P = 0.026). Later TNM stage represented poor prognosis (OR = 1.855, P = 0.040).

Discussion

NSCLC accounts for the majority of lung cancer. The development of surgical resection technique, chemo-radiotherapy, and targeted therapy technology has significantly improved patients' prognosis [17, 18]. However, the prognosis of advanced NSCLC patients is still poor even after clinical intervention. According to the report, the five-year survival rate for patients in stage III was only about 15% [19]. An American survey showed that there are more than 200,000 newly diagnosed lung cancer patients every year, and 150,000 deaths are associated with lung cancer. Therefore, early diagnosis becomes the most important measure for effective treatment and improving patient's prognosis and survival [20-23]. As an acid glycoprotein, CEA is a human embryo anti-

Table 4. Multivariate analysis of related influencing factors for overall survival prognosis

Parameter	Regression coefficient (B)	Standard error (S.E)	Wald	*P*	OR	95% *CI*
Age	1.035	0.589	1.94	0.181	0.915	0.678-5.221
Gender	1.521	1.664	2.956	0.323	0.882	0.231-3.201
Tumor size	1.112	0.222	12.271	0.065	3.154	0.656-8.412
Differentiation	1.468	1.011	1.113	0.022	1.613	1.437-5.632
T	1.104	1.217	3.344	0.096	1.232	0.564-3.127
N	1.211	1.565	0.434	0.314	1.544	0.478-3.462
M	1.864	0.665	1.221	0.026	1.977	1.263-6.231
TNM stage	1.256	0.927	1.165	0.040	1.855	1.156-5.268
Serum CEA elevation	2.562	0.145	2.021	0.012	2.863	1.931-8.219

gen specific decision factor belonging to non-specific tumor associated antigen. Its content is very few in normal circulation, and its elevation prompts tumor cell proliferation. At present, it has been used in a variety of tumors detection [24, 25]. It was reported that the CEA level in lung adenocarcinoma was significantly higher than that in squamous cell cancer and small-cell lung cancer, suggesting that CEA might be one of the most valuable markers for lung adenocarcinoma [26]. In previous studies, elevated serum CEA level was not always associated with TNM staging [27-31]. These results revealed that serum CEA was significantly correlated with TNM stage. It was in accordance with Molina study [32]. For N stage, Takamochi reported that elevated serum CEA level was a promotive factor for N2 disease [33]. However, these results failed to find significant difference in serum CEA level between N0-1 and N2 stages. CEA is a cell adhesion molecule belonging to the immunoglobulin superfamily with homogeneous and heterogeneous adhesion function. Homogeneous adhesion can promote tumor cell aggregation and tumor embolus formation, while heterogeneous adhesion promotes distant metastasis [34]. In this study, patients with distant metastasis had significantly higher serum CEA levels than those without metastasis, suggesting that elevated serum CEA may be treated as an important factor to evaluate lung cancer metastasis. In addition, the relationship between serum CEA content and TNM stage observed by this research is likely to be affected by M state, as we failed to discover correlation between serum CEA with T and N state. It was found that CEA on tumor cell surface can inhibit tumor cell differentiation and make cells maintaining in poor-differentiation status, thus promoting tumor development and deterioration [35]. This study observed that serum CEA level was higher in patients with poor differentiation, which was in accordance with Okada [36]. Salgia et al. [37] found that serum CEA content had a certain relationship with tumor size, but analysis failed to observe a similar phenomenon.

The results show that TNM stage is an important factor that may affect NSCLC patients' survival and prognosis, whereas it's OR value was lower than that of M stage, indicating distant metastasis had more significant impact on patients' prognosis than TNM stage. Muley et al. [38] confirmed that patients with high CEA level showed poor prognosis. These results demonstrate that serum CEA elevation was an independent prognostic factor for lung adenocarcinoma patient, which was in accordance with Tomita results [39]. It suggested that patients with high serum CEA level may have poor prognosis. Therefore, although the mechanism of serum CEA elevation in NSCLC patients is still unclear, current results considered that CEA is an important index for cancer patient evaluation. Some researchers have also reported that serum CEA is an effective predictor to evaluate tumor recurrence [30].

Except lung adenocarcinoma, lung squamous cell carcinoma is mostly found in male patients. A study showed that serum CEA level was significantly higher in patients with lung adenocarcinoma than that in lung squamous cell carcinoma, which was reported to relate to tumor morphological heterogeneity. Part of lung squamous cell carcinoma can present the basic features of lung adenocarcinoma. Hence, it was assumed that CEA elevation in squamous carcinoma tissue was different from the lung adenocarcinoma part. Therefore, serum CEA level

was not reported to be associated with patient's prognosis [40]. In view of the mechanism of CEA elevation in NSCLC not having been elucidated, it is necessary to do further investigation to uncover the mechanism.

Previously reported biological prognostic evaluation was often based on the specimen in the operation, which is not able to obtain preoperatively. Some of these factors were only treated as research tools. This study confirmed that serum CEA can be used as a routine assessment factor. It can effectively assess the prognosis of patients with non-small cell lung adenocarcinoma in combination with traditional pathological staging. At the same time, there are some limitations in this research. First, for the basic level of subjects was different, including distant metastasis, lung cancer progress degree, and differentiation degree, the conclusion was limited in analyzing the direct correlation relationship between CEA expression and prognosis. Hierarchical analysis is needed to increase the conclusion accuracy. Second, the number of subjects enrolled was small and the loss of follow up rate was high. Therefore, a larger scale study is required in the future to confirm these findings.

In conclusion, serum CEA elevation is an independent prognostic factor for patients with non-small cell lung adenocarcinoma. Patients with high CEA level presented shorter long-term survival and high mortality. It has a certain reference and application value because of it is a convenient and cheap detection method.

Disclosure of conflict of interest

None.

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