

Relationship between serum carcinoembryonic antigen level and epidermal growth factor receptor mutations with the influence on the prognosis of non-small-cell lung cancer patients

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Objective: To investigate the relationship between serum carcinoembryonic antigen (CEA) level and epidermal growth factor receptor (EGFR) gene mutations in non-small-cell lung cancer (NSCLC) patients and to analyze the influence of CEA level on postoperative survival time in lung cancer patients.

Methods: A total of 296 patients who were treated in Thoracic Surgery Department of Henan Provincial Chest Hospital from September 2011 to September 2013 were recruited. The level of tumor markers, such as CEA, was determined before the surgery, and EGFR gene mutations were detected after surgery. Thereby, the relationship between tumor makers, including CEA, and EGFR mutation and its influence on prognosis could be investigated.

Results: Among 296 patients, the positive rate of EGFR gene mutation was 37.84% (112/296); the mutation occurred more frequently in nonsmokers, adenocarcinoma patients, women, and patients aged <60 years ($P<0.05$). Both tumor markers and chemosensitivity indicators were related to the profile of EGFR mutations. Elevated squamous cell carcinoma and Cyfra21-1 as well as positively expressed ERCC1 were more common in patients with wild-type EGFR ($P<0.05$), whereas increased CEA level was observed more frequently in patients with EGFR gene mutation ($P=0.012$). The positive rate of EGFR gene mutations was higher as the serum CEA level increased, that is, the positive rate in patients with serum CEA level <5, 5–20, and >20 $\mu\text{g/L}$ was 39.81%, 45.32%, and 65.47%, respectively ($P=0.004$). Logistic regression analysis showed that CEA level was an independent factor in predicting EGFR gene mutations, and serum CEA level was also an independent factor in affecting the prognosis of NSCLC patients, as the overall 2-year survival rate was 73.86% in elevated CEA group and 86.43% in normal group ($P<0.01$).

Conclusion: The prognosis of NSCLC patients receiving resection can be predicted according to serum CEA level, which is associated with EGFR mutations in NSCLC patients and provides a preliminarily guidance for EGFR mutations.

Keywords: serum carcinoembryonic antigen, epidermal growth factor receptor, non-small cell lung cancer, resection, prognosis

Introduction

Lung cancer is one of the malignant tumors causing human deaths, of which non-small-cell lung cancer (NSCLC) accounts for 85%. Although chemoradiotherapy techniques and traditional operation methods have greatly improved, the survival rate of NSCLC patients is still <20%.^{1,2} At present, in the clinical diagnosis and treatment of NSCLC, molecular targeting therapy using epidermal growth factor receptor (EGFR) as the target

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is prominent. EGFR is closely associated with neovascularization, tumor invasion, and metastasis, can be mutated and/or overexpressed, and guides the tumor growth through signal transduction.³ EGFR gene mutation is of great significance in formulating treatment measures of lung cancer and predicting the prognosis. Serum carcinoembryonic antigen (CEA) is a vital indicator in predicting the efficacy of targeted therapy and chemotherapy as well as the postoperative recurrence and metastasis. However, it is still unclear whether CEA can predict EGFR gene mutation and its influence on NSCLC patients undergoing surgery. The current study was designed to investigate the relationship between CEA level and EGFR gene mutations in lung cancer patients and to analyze the influence of CEA levels on postoperative survival time of lung cancer patients.

Materials and methods

Data collection

The study was approved by the institutional research ethics committee of Henan Provincial Chest Hospital. A total of 296 lung cancer patients (mean age: $[59.1 \pm 5.4]$ [range: 29–90] years) who received standard radical resection in Henan Provincial Chest Hospital between September 2011 and September 2013 were recruited. Among them, the proportion of the patients aged <60 and ≥ 60 years was 53.04% (157/296) and 46.96% (139/296), respectively. Inclusion criteria were 1) having a clear preoperative diagnosis of lung cancer; 2) exclusion of metastasis in brain, liver, adrenal gland, and contralateral lung by preoperative chest computed tomography (CT), brain CT or magnetic resonance imaging, and abdomen B ultrasound, and exclusion of distant metastasis by whole-body electroconvulsive therapy (some underwent positron emission tomography–CT); 3) not receiving any preoperative anticancer therapy, such as radiotherapy and chemotherapy; 4) undergoing complete resection; 5) having complete case and follow-up data, except for patients who died within 30 days after operation; 6) obtaining written informed consent from the subjects or their families. All enrolled patients had been confirmed by pathological examination to have not undergone other adjuvant therapies before surgery and to have undergone the conventional detection test for tumor marker at Day 7 before surgery.

Treatment methods

All the patients adopted the surgery-based comprehensive treatment, with 14 receiving total pneumonectomy, 267 pulmonary lobectomy, and 15 lung segment/wedge resection. The patients with Stage IB or higher lung cancer were given postoperative adjuvant therapy mainly using cisplatin/carboplatin combined

with paclitaxel/vinorelbine/gemcitabine. For the patients exhibiting postoperative recurrence, multisite metastasis, and distant metastasis of mediastinal lymph nodes, postoperative radiotherapy was performed (a total of 127 cases), whereas for those with positive EGFR mutation, postoperative EGFR-tyrosine kinase inhibitor (TKI) therapy was given auxilially, and the remaining received the adjuvant therapy after recurrence and metastasis.

Postoperative follow-up

Follow-up was started from the day of surgery and ended on the last follow-up day or when the patient died. The follow-up methods were performed mainly by outpatient service, reexamination, letters, and telephone. The overall survival (OS) rate was calculated from the day of surgery to the last follow-up day or to patients' death (calculated in months). The disease-free survival (DFS) was the period from the day of surgery to the day when recurrence and metastasis were detected for the first time (calculated in months). The last follow-up visit occurred in January 2016.

Statistical methods

SPSS 19.0 statistical analysis software package was adopted for data analysis. Paired *t*-test was applied for comparison of continuous variables among groups; χ^2 -test was used for comparison of classified variables; Kaplan–Meier method was adopted to calculate the survival rate; log-rank test was employed for single-factor analysis; Cox proportional hazard model was used for multiple-factor analysis; logistic regression analysis was employed to analyze the relationship between EGFR gene mutation and various factors. Values of $P < 0.05$ was considered statistically significant.

Results

Influences of EGFR mutations on EGFR-TKI treatment

Among 296 patients, 27 received EGFR-TKI treatment, including 25 with EGFR mutations showing squamous carcinoma or adenocarcinoma and two with wild-type EGFR exhibiting adenocarcinoma on postoperative pathology. By comparing EGFR-TKI reactions at 19 vs 21 exons, no statistical significance was seen in DFS and OS ($P > 0.05$).

Relationships between clinicopathological factors and EGFR mutations

Based on the results of the postoperative detection of EGFR gene mutation, a positive result was found in 112 patients (37.84%), including five cases of exon 18 and 20 mutations, 58 cases of exon 19 deletion mutation, and 49 cases of exon 21

point mutations. Additionally, three cases had point mutations at two sites, accounting for 2.68% (3/112) of all mutation cases. A total of 36 males and 76 females were found to have mutations; 95 cases (84.82%) had adenocarcinoma, five cases (6.25%) had large-cell lung carcinoma, and eight cases (7.14%) had squamous carcinoma; 68 cases (60.71%) had never smoked and 44 cases (39.29%) were smokers or had smoked; 166 cases (56.08%) had Stage I disease, 39 cases (13.18%) had Stage II disease, and 91 cases (30.74%) had Stage III disease. According to the results of the comparisons between wild-type and EGFR mutation groups, patients with adenocarcinoma, females, and nonsmokers were prone to EGFR mutations (Table 1).

Relationship between tumor markers with chemosensitivity indicators and EGFR mutations

Within 1 week before surgery, all these patients underwent conventional detection of tumor markers, including CEA,

cytokeratin (Cyfra21-1), neuron-specific enolase, squamous cell carcinoma (SCC) antigen, and tissue polypeptide-specific antigen. The results indicated that CEA levels in patients with positive EGFR mutations increased more frequently, whereas changes of SCC and Cyfra21-1 levels were more common in patients with negative EGFR mutations ($P < 0.05$). The stratification analysis indicated no statistical difference in the potential relationship between tumor markers and different point mutations (exons 19 and 20) ($P > 0.05$). From the immunohistochemical results, the negative expression of ERCC1 was more common in patients with EGFR mutations (Table 2). Logistic regression analysis was performed for the clinical factors, probably affecting the EGFR mutation prediction, so as to explore deeply the relationship between EGFR mutation and CEA level, and the results demonstrated that CEA level was an independent factor in predicting EGFR gene mutation (Table 3). The positive rate of EGFR mutation in patients with serum CEA level < 5 , $5-20$, and > 20 $\mu\text{g/L}$ was 39.81%, 45.32%, and

Table 1 Mutant epidermal growth factor receptor (EGFR) or wild-type EGFR with clinicopathologic features in patients with nonsmall cell lung cancer

Variable	Wild-type EGFR	Mutant EGFR	χ^2	P-value
Age (years)			5.101	0.014
<60	82	75		
≥ 60	102	37		
Sex			53.778	< 0.001
Male	140	36		
Female	44	76		
Location			0.002	0.899
Left	88	53		
Right	96	59		
Histology			109.066	< 0.001
Adenocarcinoma	45	95		
Squamous carcinoma	123	8		
Large cell carcinoma	10	5		
Other	6	4		
Smoking status			47.671	< 0.001
Never	59	68		
Current/former	125	44		
Surgery			2.097	0.312
Segment/wedge resection	7	8		
Lobectomy	158	109		
Pneumonectomy	9	5		
Pathologic stage			4.562	0.113
I	102	64		
II	19	20		
IIIA	48	43		
LN metastasis			4.018	0.245
N ₀	102	64		
N ₁	19	20		
N ₁ + N ₂	30	26		
N ₂	18	17		

Abbreviation: LN, lymph node.

Table 2 Epidermal growth factor receptor (EGFR) mutations and tumor markers and immunohistochemical indicators

Tumor markers	Wild-type	Mutation	χ^2	P-value
CEA ($\mu\text{g/L}$)			5.102	0.014
<5	123	67		
≥ 5	26	35		
SCC ($\mu\text{g/L}$)			14.579	<0.001
<1.5	121	98		
≥ 1.5	18	4		
Cyfra21-I ($\mu\text{g/L}$)			6.972	0.012
<3.3	91	70		
≥ 3.3	57	32		
NSE ($\mu\text{g/L}$)			0.813	0.364
<15.2	94	71		
≥ 15.2	58	31		
TPSA ($\mu\text{g/L}$)			0.223	0.635
<80	42	59		
≥ 80	4	8		
ERCCI			11.678	0.001
Positive	71	27		
Negative	90	94		
VEGF			0.006	0.913
Positive	123	82		
Negative	19	11		
Syn			1.937	0.159
Positive	44	35		
Negative	102	51		
TS			0.476	0.482
Positive	54	27		
Negative	57	36		
Tubulin			0.034	0.828
Positive	69	46		
Negative	40	19		
CD56			0.619	0.443
Positive	10	6		
Negative	36	32		

Abbreviations: CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma; Cyfra21-I, cytokeratin; NSE, neuron-specific enolase; TPSA, tissue polypeptide-specific antigen; VEGF, vascular endothelial growth factor.

65.47%, respectively ($P=0.004$). Thus, we found that the rate of EGFR gene mutations increased as the serum CEA level increased.

Influence of CEA level on the survival time of NSCLC patients

A total of 90 patients showed an increase in CEA level. Both OS and DFS in the normal CEA level group were higher than those in the increased CEA level group, with 2-year OS and DFS of 86.43% and 79.5% vs 73.86% and 50.46%, respectively ($P<0.01$), as shown in Figure 1. As shown by Cox proportional hazard model analysis, CEA level was an independent factor affecting the postoperative survival time for NSCLC patients (odds ratio =1.747; $P=0.031$).

Table 3 Logistic analysis of predictive factors for incidence of epidermal growth factor receptor (EGFR) mutation

Variable	SE	OR	95% CI for OR	B	P-value
Sex	0.347	0.299	0.152–0.589	–1.211	<0.001
Male					
Female					
Histology	0.370	0.090	0.042–0.189	–2.383	<0.001
Adenocarcinoma					
Nonadenocarcinoma					
Smoking status	0.346	1.153	0.585–2.276	0.143	0.688
Never					
Current/former					
CEA ($\mu\text{g/L}$)	0.321	0.518	0.276–0.973	–0.654	0.040
<5					
≥ 5					
SCC ($\mu\text{g/L}$)	0.520	1.872	0.677–5.181	0.628	0.229
<1.5					
≥ 1.5					
Cyfra21-I ($\mu\text{g/L}$)	0.399	0.738	0.377–1.441	–0.299	0.375
<3.3					
3.3					
ERCCI	0.327	0.981	0.518–1.859	–0.021	0.951
Positive					
Negative					

Abbreviations: CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma; Cyfra21-I, cytokeratin; SE, standard error; OR, odds ratio; CI, confidence interval.

Discussion

EGFR is one of the critical targets in the treatment of NSCLC, whereas EGFR gene mutations occur only in the tumor tissues, especially in NSCLC, and these mutations do not exist in normal tissue cells.⁴ Based on the present study, in nonsmoking, adenocarcinoma, and female patients, EGFR mutation rate was relatively higher and had a higher sensitivity to EGFR-TKI therapy. The population who benefit from the EGFR-TKI treatment include adenocarcinoma, nonsmoking, and female patients, which might be associated with higher EGFR gene mutation rate. In individualized treatment of NSCLC, detection of EGFR mutation is of

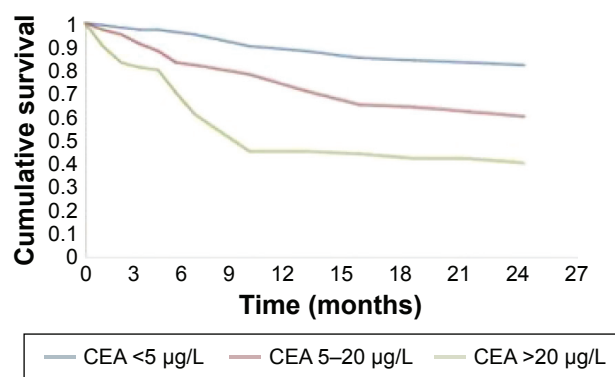


Figure 1 Influence of carcinoembryonic antigen (CEA) level on the postoperative survival of nonsmall cell lung cancer patients.

great significance. The somatic mutation of EGFR is mainly focused on exons 19 and 21. At present, only these two mutations are considered to be able to predict the efficacy of EGFR inhibitor.⁵⁻⁷ The efficacy prediction is difficult in the clinical treatment with EGFR-TKI. However, in clinical practice, predicting EGFR gene mutation state could benefit the patients undergoing EGFR-TKI treatment.

In this study, positive expression of ERCC1 reflected more wild-type EGFR gene, which was more common in squamous carcinoma, male, and smoking patients. These are the “non-dominant crowd” who were treated with EGFR-TKI. This may be the reason why positive expression of ERCC1 protein was more common in patients with negative EGFR mutations. As shown in the present study, according to preoperative detection of tumor markers in wild-type group, increased SCC and Cyfra21-1 levels were more common, which may be closely associated with squamous carcinoma. The increase of serum CEA predicted an elevation of EGFR mutation ratio, and the reason might be that activation of downstream molecules of EGFR mutant promotes antiapoptosis, and the expression level of CEA is enhanced by EGFR. Elevated CEA level can also predict the survival time and response rate of NSCLC patients undergoing EGFR-TKI treatment. In patients with increased CEA level, there is a higher EGFR-TKI response rate and maybe a longer survival time. In particular, the patients with squamous carcinoma and unknown EGFR mutation status are more likely to benefit from it.⁸

CEA is a better marker for predicting the effect of lung cancer treatment, monitoring the patients' condition of disease, and evaluating the prognosis. The results of the present study revealed that CEA level was an independent factor and was able to predict the EGFR gene mutation. The incidence of EGFR gene mutations gradually increased as the serum CEA level increased. The positive rate of mutation in patients with serum CEA level <5, 5–20, and >20 µg/L was 39.81%, 45.32%, and 65.47%, respectively. Hence, the EGFR mutation profile can be preliminarily forecast using preoperative CEA level. Studies^{9,10} have reported that staging of lung cancer was closely associated with CEA level, which was an independent factor in the prognosis of lung cancer patients. An increase of CEA level in Stage I lung cancer patients (especially for female patients) resulted in a shorter survival time. Therefore, to enhance the survival rate of such patients, adjuvant therapies could be provided in a timely manner. The results of this study indicated that the survival time was shorter in the increased CEA level group, with 2-year OS of only 73.22%, whereas it was 86.43% in the normal group, showing a statistically significant difference ($P<0.01$). By further adopting Cox risk model, we found that

CEA level was an independent prognostic influence factor for patients with resection of lung cancer.

Conclusion

The present study preliminarily reveals the relationship between EGFR mutation and CEA level, which is similar to that reported previously.^{11,12} For NSCLC patients, the preoperative detection of CEA level can be utilized to guide the adjuvant therapy of EGFR-TKI so that the total efficacy rate of EGFR-TKI might be enhanced. The preoperative CEA level could also predict the survival time of NSCLC patients. If the preoperative detection suggests an increase in the level of CEA, postoperative adjuvant therapy should be adopted selectively to maximize the total survival rate of NSCLC patients.

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Disclosure

The author reports no conflicts of interest in this work.

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