Original Article

# Carcinoembryonic antigen in pleural effusion of patients with lung adenocarcinoma: a predictive marker for EGFR mutation

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**Background:** Carcinoembryonic antigen (CEA) can reflect tumor growth, recurrence and metastasis, and also predict the clinical efficacy of the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI). In the present study, we investigated the association between CEA in serum and pleural effusion (PE) and EGFR mutations in patients with lung adenocarcinoma.

**Methods:** We retrospectively investigated 114 lung adenocarcinoma patients with malignant pleural effusion (MPE). CEA levels in serum and MPE were measured by immunoradiometric assay, we analysed the correlation between CEA and EGFR mutation status.

**Results:** Fifty-three cases had EGFR mutation (46.5%). EGFR mutations were more common in females, patients with high levels of PE (≥107.2 ng/mL) and serum CEA (≥87 ng/mL). There was no significant difference in EGFR mutation rate between in tumor tissue and PE samples (49.3% *vs.* 41.9%, P=0.440). The result of receiver operating characteristic (ROC) indicated that the cut off value of CEA in MPE was 107.2 ng/mL, which had the highest sensitivity (SEN) and specificity (SPE) for predicting EGFR mutation [SEN 66%, and SPE 62.3%, AUC =0.668, 95% confidence interval (CI): 0.569–0.767, P=0.025]. The combination of gender, smoking history, serum and MPE CEA level had a higher calculated AUC (0.718, 95% CI: 0.622–0.813, P=0.000). Moreover, multivariate analysis showed that CEA level in MPE but not in serum was confirmed as the only independent factor associated with EGFR gene mutation status (P=0.026) with an odds ratio of 2.885 (95% CI: 1.137–7.317).

**Conclusions:** MPE CEA can probably serve as a predictive marker for EGFR mutation in advanced lung adenocarcinoma. Combining gender, smoking history, and CEA has a relatively better predictive value. However, detecting EGFR mutations in lung adenocarcinomas is necessary for determining EGFR-TKI treatment in clinic.

**Keywords:** Lung adenocarcinoma; malignant pleural effusion (MPE); serum; carcinoembryonic antigen (CEA); epidermal growth factor receptor mutation (EGFR mutation)

Submitted Jan 18, 2019. Accepted for publication May 27, 2019.
doi: 10.21037/tcr.2019.06.10
**View this article at:** http://dx.doi.org/10.21037/tcr.2019.06.10

## Introduction

Lung cancer is one of the most common malignant tumors worldwide and the 5-year survival rate was as low as 16% (1), of which non small cell lung cancer (NSCLC) accounts for approximately 80% to 85%, and lung adenocarcinoma about 40%. More than 70% of the patients present with an advanced stage at initial diagnosis, and had lost radical surgery opportunity. At present, the targeted EGFR therapy has achieved great progress. Multiple clinical studies have shown that EGFR-tyrosine kinase inhibitors (EGFR-TKIs) had a better therapeutic effect on NSCLC patients with EGFR mutations (2-9). Therefore, it is particularly important to detect EGFR mutations status before anti-tumor therapy, but EGFR gene detection sometime has some limitations because of limited tumor tissue, especially in advanced stage patients. Thus, it is necessary to uncover a safer and more reliable clinical screening method to predict EGFR mutation status.

Carcinoembryonic antigen (CEA) is widely used in clinical practice to predict treatment efficacy, prognosis, metastasis, and recurrence, etc. (5,10-12), and serum and pleural effusion (PE) are easy to obtain. However, it is still not clear whether CEA in serum and PE could be used as a biomarker to predict EGFR mutation, particularly in PE. The aim of our study is to investigate the correlation between EGFR mutation and CEA from serum and PE in advanced lung adenocarcinomas patients.

## Methods

### *Patient selection*

A total of 114 patients who were cytologically or histologically confirmed as lung adenocarcinomas with malignant pleural effusion (MPE) referred to a single institution (Jiangsu Province People's Hospital, Nanjing, China) from November 2013 to May 2017. The following inclusion criteria were: (I) not receiving any anti-tumor therapy previously; (II) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (III) having normal hepatic, renal and hematologic functions, and no concomitant serious complications; (IV) having complete case; (V) obtaining written informed consents.

The study was approved by Medical Ethical Committee at Jiangsu Province People's Hospital. Each patient before study-related procedures had signed the informed consent.

### *Detection of EGFR gene mutation and CEA*

Specimens of peripheral blood and paired PE were obtained immediately before treatment. Serum and PE CEA levels were measured by immunoradiometric assay. The normal range of CEA was determined as <4.7 ng/mL. The status of EGFR mutations from exon 18 to 21 was identified using the Human EGFR Gene Mutation Detection Kit (AmoyDx, Xiamen, China), which is based on the Amplified Refractory Mutation System (ARMS).

### *Statistical analysis*

All statistical analyses were performed using SPSS17.0 statistics software. Continuous variables were analyzed by *t*-tests. Fisher's exact test or Pearson's chi-square test procedure was used to compare categorical variables. Receiver operating characteristic (ROC) curves were constructed to determine cut-off values and evaluate the role of CEA in predicting EGFR mutations. Logistic regression analysis was employed to estimate the relationship between EGFR mutation and various factors. All reported P values were two-tailed, and P values less than 0.05 were considered statistically significant.

## Results

### *Patient characteristics and EGFR mutation status*

A total of 114 advanced adenocarcinoma patients with MPE were enrolled, and the main characteristics of the patients are shown in *Table 1*. There were 65 men and 49 women, with a median age of 50 (range, 29–83) years. Among all patients, EGFR gene mutations were detected in 53 of 114 cases (46.5%). The major mutation types were the exon 19 deletion (n=27, 50.9%) and the L858R point mutation in exon 21 (n=17; 32.1%). Other mutations included L861Q point mutation in exon 21 (n=1; 1.9%), exon 20 mutation (n=1; 1.9%), and exon 18 mutation (n=1; 1.9%). Additionally, 6 patients had point mutations at two sites, including 3 cases with L858R mutation in exon 21 and T790M mutation in exon 20, 2 cases with exon 18 mutation and L861Q mutation in exon 21, 1 case with exon 18 mutation and S7681 mutation in exon 20.

### *EGFR mutations and clinical features*

We used Pearson's chi-square test to evaluate the relationship

 

**Table 1** Main characteristics of 114 advanced adenocarcinoma patients with malignant pleural effusion

| Characteristic | Patients | |
|---|---|---|
| | Number | Ratio (%) |
| Gender | | |
| Male | 65 | 57 |
| Female | 49 | 43 |
| Age | | |
| <60 | 46 | 40 |
| ≥60 | 68 | 60 |
| ECOG PS | | |
| 0 | 25 | 22 |
| 1 | 84 | 74 |
| 2 | 5 | 4 |
| Smoking history | | |
| Yes | 44 | 39 |
| No | 70 | 61 |
| Brain metastasis | | |
| Yes | 10 | 9 |
| No | 96 | 84 |
| Unknown | 8 | 7 |
| Bone metastasis | | |
| Yes | 37 | 32 |
| No | 67 | 59 |
| Unknown | 10 | 9 |
| Lymph nodes metastasis | | |
| Yes | 72 | 63 |
| No | 31 | 27 |
| Unknown | 11 | 10 |
| EGFR status | | |
| EGFR+ | 53 | 46.5 |
| L858R | 17 | 32.1 |
| 19 deletion | 27 | 50.9 |
| Exon21 L861Q | 1 | 1.9 |
| Exon18 | 1 | 1.9 |
| Exon20 | 1 | 1.9 |
| L858R/T790M | 3 | 5.7 |
| Exon18/L861Q | 2 | 3.8 |
| Exon18/S7681 | 1 | 1.9 |
| EGFR– | 61 | 53.5 |

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

between the incidence of EGFR gene mutations and clinical factors, the results were showed in *Table 2*. EGFR mutations were significantly more frequent in females than males (57.1% *vs.* 38.5%, P=0.048). There were no significant differences in age, smoking history, detection samples, lymph node metastasis, bone metastasis and brain metastasis between EGFR mutant and wild-type groups.

### *EGFR mutations and CEA levels*

Patients harboring EGFR mutations were more likely to have higher serum and MPE CEA levels than wild-type (71.4±215 *vs.* 100.1±200.5 ng/mL, P=0.465; 229.3±344.8 *vs.* 422.2±410.9 ng/mL, P=0.008), however, there was no significant difference in serum CEA levels between two groups. An ROC curve analysis was carried out to evaluate whether the serum and PE CEA levels could predict EGFR mutation status, and find out that cut-off value of serum CEA point was 87 ng/mL, and the AUC was 0.59 (95% CI: 0.485–0.696, P=0.097) (*Figure 1A*). According to the selected cut-off value, the best efficacy was observed with a sensitivity (26.4%) and specificity (91.8%). ROC analysis resulted in 107.2 ng/mL as the predicting cut-off point for PE CEA, the AUC was 0.668 (95% CI: 0.569–0.767, P=0.025) (*Figure 1B*), and the SEN and SPE were 66% and 62.3%, respectively, with the best efficiency. The combination of gender, smoking history, serum and PE CEA level had a higher calculated AUC (0.718, 95% CI: 0.622–0.813, P=0.000) (*Figure 2*), and the SEN and SPE were 64.2% and 77%, respectively.

We divided the patients with advanced lung adenocarcinomas into two groups according to the cut-off value, and found that in patients with high PE and serum CEA levels (CEA ≥107.2, and ≥87 ng/mL), the EGFR mutation rate was significantly higher compared with those obtained in cases with low CEA levels (60.3% *vs.* 32.1%, P=0.003, and 73.7% *vs.* 41.1%, P=0.009).

We kept all variables with P<0.6 in a multivariate logistic analysis (*Table 3*), which showed an elevated odds ratio of 2.111 (95% CI: 0.738–6.035) in gender, 1.252 (95% CI: 0.416–3.769) smoking history, 2.325 (95% CI: 0.661–8.182) and 2.885 (95% CI: 1.137–7.317) serum and PE CEA level. However, the PE CEA level was confirmed as an independent factor of predicting EGFR mutations.

## Discussion

EGFR mutation detection has become standard practice

 

**Table 2** Pathological characteristics with relation to EGFR mutations

| Characteristic | Patients | EGFR mutation status | | P |
|---|---|---|---|---|
| | | Positive | Negative | |
| Gender | | | | 0.048 |
| Male | 65 | 25 | 40 | |
| Female | 49 | 28 | 21 | |
| Age | | | | 0.537 |
| <60 | 46 | 23 | 23 | |
| ≥60 | 68 | 30 | 38 | |
| Smoking history | | | | 0.086 |
| Yes | 44 | 16 | 28 | |
| No | 70 | 37 | 33 | |
| Brain metastasis | | | | 0.333 |
| Yes | 10 | 6 | 4 | |
| No | 96 | 41 | 55 | |
| Bone metastasis | | | | 0.177 |
| Yes | 37 | 20 | 17 | |
| No | 67 | 27 | 40 | |
| Lymph nodes metastasis | | | | 0.504 |
| Yes | 72 | 33 | 39 | |
| No | 31 | 12 | 19 | |
| Test samples | | | | 0.440 |
| PE | 71 | 35 | 36 | |
| Tumor tissue | 43 | 18 | 25 | |
| Serum CEA level (ng/mL) | | | | 0.009 |
| <87 | 95 | 39 | 56 | |
| ≥87 | 19 | 14 | 5 | |
| PE CEA level (ng/mL) | | | | 0.003 |
| <107.2 | 56 | 18 | 38 | |
| ≥107.2 | 58 | 35 | 23 | |

CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor.

in determining treatment strategy of NSCLC patients; however, it is often impaired by inoperability and inadequate tumor tissue sample. Therefore, predicting EGFR gene mutation is likely to be helpful in clinical practice for patients undergoing TKI treatment. Our study retrospectively reviewed the clinical data from 114 patients with untreated advanced lung adenocarcinoma patients with MPE in Chinese population. We evaluated the association between the EGFR mutation and a comprehensive set of clinical factors, especially CEA which is widely used in clinical practice. We found that serum and PE CEA levels associated with EGFR mutations, and MPE CEA was an independent clinical factor of predicting EGFR mutation status. However, ROC analysis revealed that the AUC of

 

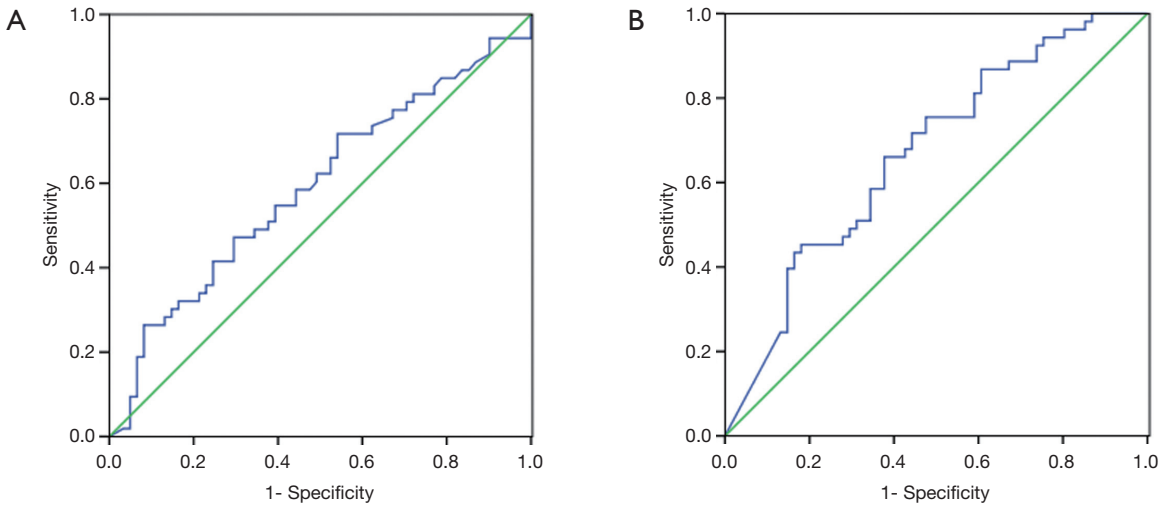


**Figure 1** Receiver operating characteristic (ROC) curves of serum and PE CEA level for predicting EGFR mutation. (A) ROC based on serum CEA level; (B) ROC based on PE CEA level. PE, pleural effusion; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor.

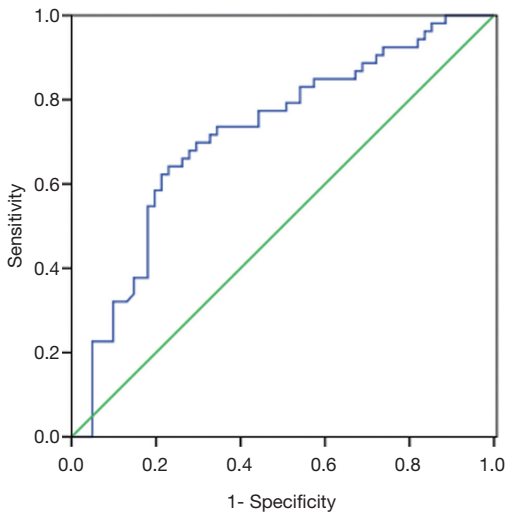


**Figure 2** Receiver operating characteristic curves of combining four factors (gender, smoking history, serum and PE CEA level) for predicting EGFR mutation. PE, pleural effusion; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor.

MPE CEA for predicting EGFR mutation status was 0.668, and the SEN and SPE were 66% and 62.3%, respectively. Therefore, we do not depend on CEA level completely to confirm the absence or presence of EGFR mutation.

In the present study, we found the positive rate of EGFR mutations accounted for about 46.5% (53/114) in lung adenocarcinoma patients with MPE, which was consistent with several other reports reporting EGFR gene mutation rate ranging from 43% to 50% in China (13-15). However, the results of a few other studies much lower (16). The different results may be due to the selected patients. Some studies included many non-adenocarcinoma patients, which may contribute to a reduction in EGFR mutation rate. EGFR mutations were shown here predominantly occur in exon 19 (19-del) and exon 21 (L858R point mutation), while the least common mutations were exon 18 G719X, exon 20 insertion, exon 20 S768I, and exon 21 L861Q mutations. Moreover, we found that EGFR gene mutations were more often observed in female from the Pearson's chi-square test results, which is also in accordance with previous studies (17-19).

CEA is widely used as a good tumor marker for the diagnosis, prognosis evaluation and monition, recurrence and treatment efficiency evaluation in NSCLC. Recently, several studies focused on the relationship between EGFR gene mutation status and serum tumor markers, especially CEA. Some present studies showed that serum CEA level was able to predict the EGFR mutations (20,21). However, Pan *et al.*'s study revealed that serum CEA may not be an ideal predictor (12). Therefore, the relationship between them was still controversial. In this study, we found that patients harboring EGFR mutations were more likely to have higher serum CEA levels than wild-type, however, there was no significant difference. In addition, ROC curve analysis revealed serum CEA is not an ideal predictor, which

 

**Table 3** Multivariate analysis

| Factors | HR | 95%CI | | P value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Gender | 2.111 | 0.738 | 6.035 | 0.163 |
| Age | 1.170 | 0.500 | 2.737 | 0.718 |
| Smoking history | 1.252 | 0.416 | 3.769 | 0.689 |
| Lymph nodes metastasis | 1.284 | 0.703 | 2.346 | 0.416 |
| Test samples | 1.170 | 0.463 | 2.952 | 0.740 |
| Serum CEA levels | 2.325 | 0.661 | 8.182 | 0.189 |
| PE CEA levels | 2.885 | 1.137 | 7.317 | 0.026 |

CI, confidence interval; HR, hazard ratio; CEA, carcinoembryonic antigen; PE, pleural effusion.

was consistent with Pan *et al.*'s study (12).

Our study is different from previous publications in evaluating the association between serum biomarkers and lung adenocarcinomas. Firstly, we focused mainly on PE CEA level and its correlation with EGFR gene status, so we selected the lung adenocarcinoma patients with MPE, and we found that a positive correlation between MPE CEA level and EGFR mutation status; in other words, EGFR gene mutation was more frequently in patients with higher PE CEA levels. The multivariate logistic analysis revealed that MPE CEA was confirmed as an independent predicting factor. Secondly, the combination of gender, smoking history, serum and MPE CEA level had a higher calculated AUC. Thirdly, we found no significant difference in the EGFR mutation rate between in tumor tissue and PE samples. The result was consistent with previous studies (22-24), suggesting that PE specimens could be used for EGFR mutation detection in advanced lung adenocarcinoma patients.

Detecting EGFR mutation in lung adenocarcinoma is necessary for determining EGFR-TKI treatment in clinic. For lung cancer patients who can tolerate surgery or tumor biopsy, it is recommended to use surgical or biopsy tissue for EGFR test, and pleural fluid for advanced lung cancer patients with PE. However, EGFR mutation detection of advanced NSCLC patients has some limitations. Firstly, the best specimen is tumor tissue from surgery, whereas 70–80% NSCLC patients have difficulties to receive radical surgery at the time of diagnosis and are unable to obtain tissue samples. Secondly, another way to obtain tissue samples is tumor biopsy which has high risk of bleeding. Moreover, there are 6.4% patients for whom obtaining enough specimen for body fluid cytology is difficult (25). Therefore, not all of the patients can undergo analysis for EGFR mutation status. Based on our data, for patients who failed to perform EGFR gene detection due to various reasons, we can predict the mutation status of EGFR gene by detecting CEA levels in serum and PE combined with clinical factors, which may ultimate benefit patients with unknown mutation status of EGFR gene from the treatment of EGFR-TKI in survival with guiding significance for clinical practice.

There are some limitations in our study. Firstly, we included patients with advanced NSCLC, and only determined the lymph nodes metastasis according to CT or integrated PET/CT findings, which might have induced a results bias. Secondly, we recorded smoking history not smoking index, which may lead to deviation of the results. Moreover, although the number of patients in our study is larger than many other similar studies, it was still small, which limits the power of multivariate analyses.

In conclusion, despite some limitations, our study indicates that MPE not serum CEA can probably serve as a marker of predicting EGFR mutation status in lung adenocarcinoma patients, and a combination of gender, smoking history, serum and MPE CEA level can play a better predictive role. However, we do not depend on CEA level completely to confirm the absence or presence of EGFR mutation. Moreover, the use of PE samples for the detection of EGFR gene mutations is highly feasible.

## Acknowledgments

*Funding:* None.

 

## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.10). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethical Committee at Jiangsu Province People's Hospital and written informed consent was obtained from all patients.



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**Cite this article as:** Lv YL, Liu HB, Yuan DM, Zhou L, Jin SX, Song Y. Carcinoembryonic antigen in pleural effusion of patients with lung adenocarcinoma: a predictive marker for EGFR mutation. Transl Cancer Res 2019;8(4):1027-1034. doi: 10.21037/tcr.2019.06.10

 