

Original Article

Comprehensive analysis of lung adenocarcinoma patients with gefitinib as first-line, second-line and third-line treatment

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Abstract: Objective: To evaluate the prognostic factors of overall survival (OS) and progression-free survival (PFS) of lung adenocarcinoma patients received gefitinib as first-line, second-line and third-line treatment. Methods: Total of 43 lung adenocarcinoma patients hospitalized in Taian City Central Hospital of Shandong province from May 2006 to August 2012 were incorporated into our retrospective study according to the inclusion and exclusion criteria. The mean follow-up was 20.4±9.1 months. The information of patients was recorded as gender, age, smoking, complications, organ metastasis (liver, bone, brain and adrenal gland), tumor stage, EGFR (epidermal growth factor receptor) mutation, adverse effect, gefitinib-response, gefitinib therapeutic regimen. Chi-square test and t-test were performed to analyze collection data, Log-rank was performed to univariate analysis of OS and PFS among groups. Results: The median overall survival of 43 patients was 19 months (95% confidence interval: 16-22 months). Univariate analysis displayed that tumor stage, EGFR mutation and organ metastasis were prognostic factors of OS and PFS ($P<0.05$); gender, age, smoking, complications, organ metastasis, tumor stage, EGFR mutation, adverse effect, gefitinib therapeutic regimen were not prognostic factors of OS and PFS among groups. Conclusion: Tumor stage, EGFR mutation and organ metastasis were prognostic factors of OS and PFS of lung adenocarcinoma patients.

Keywords: Lung adenocarcinoma, prognosis factor, gefitinib, tumor stage, EGFR mutation, metastasis

Introduction

Lung cancer is leading cause of cancer death according to the global cancer statistics. An estimated 1.8 million new lung cancer cases occurs in 2012, accounting for about 13% of total cancer diagnosis [1]. In china, lung cancer is the leading cause of death with estimated deaths of 529 thousand, and estimated new cases is 341 thousand each year. Majority of patients are diagnosed advanced lung cancer at the time of diagnosis [2], and lose the favorable chance of resection surgery.

Lung cancer is classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) according to histopathology appearance. NSCLC including adenocarcinoma, squamous cell and large cell lung cancer, accounts

for 80-85% lung cancer. Lung adenocarcinoma is a common pathology subtype and accounts for 40% of NSCLC [3].

Gefitinib is an oral EGFR receptor tyrosine kinase inhibitor and is the first targeted drug approved for NSCLC. Iressa (gefitinib) is firstly approved in Japan for the treatment of advanced NSCLC in 2002 [4]. In china, Iressa is approved for locally advanced or metastatic NSCLC patients with failure of platinum-based and docetaxel chemotherapy in 2005 year [5]. Gefitinib is recommended to apply for the second-line and third-line regimen for advanced NSCLC based on IRESSA Survival Evaluation in Lung Cancer (ISEL) [6] and Chinese clinical trial [7]; following that Iressa is approved as first-line regimen for advanced NSCLC or metastatic NSCLC patients in 2010 year [8].

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Table 1. Patients' demographics and clinical characteristic

Characteristic	Number	Percentage (%)
Age (years)		
Mean \pm SD	60.8 \pm 12.2	
Median	62	
Range	30-81	
Sex		
Male	22	51.2
Female	21	48.8
History of smoker		
Never smoker	28	65.1
Ever smoker	15	34.9
Complication		
With	19	44.2
Without	24	55.8
Hypertension	14	32.6
Diabetes	4	9.3
Coronary artery disease	4	9.3
EGFR mutation		
Mutation	26	60.5
Non-mutation	17	39.5
Metastasis		
Yes	10	23.3
No	33	76.7
Tumor stage		
IIIA	15	34.9
IIIB	15	34.9
IV	10	23.2
Unknown	3	7
Treatment line of gefitinib		
First line	14	32.6
Second line	24	55.8
Third line	3	7
Unknown	2	4.6

Currently, platinum-based chemotherapies are standard first-line regimen for advanced NSCLC treatments according to the NCCN guidelines [9], but the efficacy of chemotherapy is limited, and serious adverse effect such as inhibition of bone marrow hematopoietic system is observed, brings about pain suffering of patients.

The studies display that Asian, never smoker, lung adenocarcinoma patients could get better prognosis after acquired gefitinib treatment [10]; overall survival and objective response rate of Asian patients is obviously significant

longer than White patients [11]. The Chinese Clinical Trial shows the most common adverse effect of gefitinib including rash (44%), skin itch (15.7%) and diarrhea (10.1%) [7], which is generally well tolerated in these studies.

Total of 43 patients with metastatic, failure of previous chemotherapy/radiotherapy NSCLC, were enrolled in the retrospective study. The aim was to evaluate prognosis factors of gefitinib treatment for providing the basis of clinical treatment, prolonging patients' survival time, and improving life quality of patients.

Patients and methods

Patients

Total of 43 lung adenocarcinoma patients were incorporated into our retrospective study according to the inclusion and exclusion criteria. The variants including age, gender, smoking, complication, tumor stage, EGFR mutation, metastasis, adverse effect and gefitinib therapeutic regimen were recorded. All patients were followed up until their last visit in hospital or death.

Inclusion and exclusion criteria

Inclusion criteria: 1. explicit diagnosis of middle-stage and advanced lung adenocarcinoma; 2. previously treated with radiotherapy/platinum-based chemotherapy or not; 3. acquired gefitinib treatment including first-line, second-line and third-line regimen. Exclusion criteria: 1. diagnosis of early-stage lung adenocarcinoma; 2. unknown EGFR mutation.

Assessment criteria

Response to gefitinib is categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the response evaluation criteria in solid tumors criteria [12]. CR is defined as the disappearance of all target lesions; PR is defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; PD is defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; SD is defined as neither sufficient

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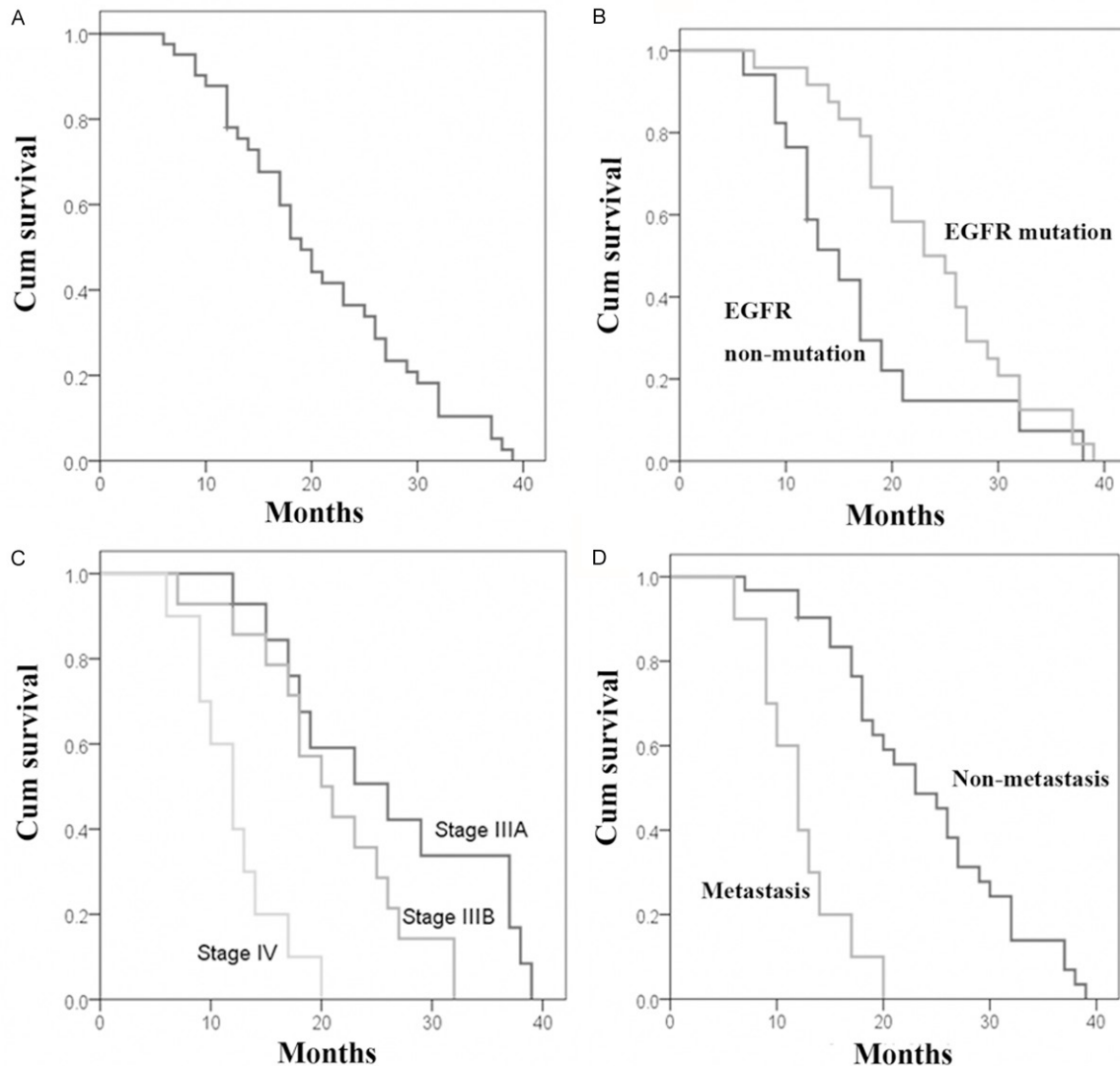


Figure 1. Overall survival curves analysis using Kaplan-Meier analysis and the Log-Rank test: A. Overall survival curve of all patients; B. Comparison among EGFR mutation and EGFR non-mutation group; C. Comparison among different tumor stages including IIIA, IIIB and IV stages; D. Comparison among metastasis and non-metastasis group.

shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started.

PFS is defined as time interval from patients acquired treatment for first time to objective disease progression or death for any reason. OS is defined as time interval from patients acquired treatment for first time to any cause of death, for those patients were still alive for last follow-up, the last contact was the end date.

Ethic

The retrospective study was approved by the Ethic Committee of Taian City Central Hospital

and in accordance the tenets of the Helsinki Declaration. The ethics committee approved the relating screening, inspection, and data collection of the patients. All of research objects fully understood the whole treatment process and signed informed consent.

Statistics analysis

Continuous data were described as median value and range, and discrete data were described as mean \pm standard deviation (SD). The Kaplan-Meier method was used for univariate analyses of overall survival and progression-free survival; the log-rank test was used to determine whether differences in survival were

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Table 2. Univariate analysis of prognostic predictors for overall survival rate of lung adenocarcinoma

Parameters		χ^2	df	p-value
Age (years)	≤60, >60	0.007	1	0.934
Gender	Male, Female	0.748	1	0.387
History of smoker	Never, ever	0.103	1	0.748
Complication	With, without	0.007	1	0.932
Hypertension	With, without	0.483	1	0.487
Diabetes	With, without	0.619	1	0.431
CAD	With, without	0.496	1	0.481
Tumor stage	IIIA, IIIB, IV	23.54	2	<0.001
EGFR mutation	Yes, No	4.34	1	0.037
Metastasis	With, without	24.72	1	<0.001
Liver metastasis	With, without	4.026	1	0.045
Bone metastasis	With, without	6.147	1	0.013
Brain metastasis	With, without	35.138	1	<0.001
Treatment line of gefitinib	First, second, third	4.33	2	0.115
Adverse effect				
Diarrhea	Severe, moderate	0.095	1	0.758
Rash	Severe, moderate	0.005	1	0.946

CAD: Coronary artery disease, P<0.05 was considered significant.

Table 3. The survival rate of significant prognosis factors of overall survival

Parameters	Median OS (months), range	Overall survival (%)		
		1 year	2 year	3 year
Tumor stage				
IIIA	26, [14.4, 37.6]	92.9±6.9	50.6±14.4	33.8±13.7
IIIB	20, [14.5, 25.5]	85.7±9.4	35.7±12.8	0
IV	12, [15.1, 20.9]	60±15.5	0	0
EGFR mutation				
No	15, [9.9, 20.1]	58.8±11.9	14.7±9.5	7.4±7
Yes	23, [17.2, 28.8]	91.7±5.6	50±10.2	12.5±6.8
Metastasis				
With	12, [9, 15]	40±15.5	0	0
Without	23, [17.8, 28.2]	90.3±5.3	48.6%±9.3	13.9%±6.4

OS: overall survival.

statistically significant. P<0.05 was considered as significance; statistical analysis was performed using SPSS version 19.0.

Results

Patients baseline information

43 patients were enrolled in our retrospective study, including 22 males (51.2%) and 21 females (48.8%). The median age was 62 years [range: 30-81 years]. As **Table 1** shown, 15 cases (34.9%) were smoker and 28 cases

(65.1%) were never smoker; 19 patients were with complication: 14 cases with hypertension, 4 cases with diabetes and 4 cases with coronary heart disease, 4 cases with cerebral infarction, 2 cases with chronic obstructive pulmonary disease, and 1 case with obsolete pulmonary tuberculosis; tumor stage: 15 cases (34.9%) were IIIA stage, 15 cases (34.9%) were IIIB stage and 10 cases (23.3%) were IV stage; 26 cases (60.5%) were with EGFR mutation, 17 cases (39.5%) were without EGFR mutation; 10 cases were with lesion's metastasis including 6 cases with brain metastasis, 4 cases with liver metastasis, 4 cases with bone metastasis and 1 case with adrenal gland metastasis, as **Figure 1** shown; the cases of gefitinib using as first-line regimen, second-line regimen, third-line regimen was 14, 24, 3, respectively; drug related to adverse effects were diarrhea and rash, 11 cases (25.6%) suffered severe diarrhea and 32 cases (74.4%) suffered moderate diarrhea; 6 cases (14%) suffered severe rash and 37 cases (86%) suffered moderate rash.

Response to treatment with gefitinib

Non-case obtained CR of gefitinib treatment. 14 cases received first-line gefitinib treatment, 4 cases (28.6%) obtained PR, 4 cases (28.6%) obtained SD and 6 cases (42.8%) obtained PD, the overall response rate was 57.2%. 24 cases received gefitinib as second-line treatment, 15 cases (62.5%) obtained PR, 6 cases (25%) obtained SD and 3 cases (12.5%) obtained PD. 3 cases received third-line gefitinib treatment, 1 case obtained PR and 2 cases obtained SD.

Univariate analysis of overall survival

43 cases were included in overall survival (OS) analysis. The median OS was 19 [range: 16-22]

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Table 4. Univariate analysis of prognostic predictors for progression-free survival rate of lung adenocarcinoma

Parameters		χ^2	df	p-value
Age (years)	≤60, >60	0.399	1	0.527
Gender	Male, Female	1.842	1	0.175
History of smoker	Never, ever	0.525	1	0.469
Complication	With, without	0.3	1	0.584
Hypertension	With, without	2.371	1	0.124
Diabetes	With, without	3.027	1	0.082
CAD	With, without	2.004	1	0.157
Tumor stage	IIIA, IIIB, IV	10.921	2	0.004
EGFR mutation	Yes, No	4.245	1	0.039
Metastasis	With, without	11.047	1	0.001
Liver metastasis	With, without	3.915	1	0.048
Bone metastasis	With, without	2.093	1	0.148
Brain metastasis	With, without	24.318	1	<0.001
Treatment line of gefitinib	First, second, third	1.472	2	0.479
Adverse effect				
Diarrhea	Severe, moderate	0.312	1	0.577
Rash	Severe, moderate	0.032	1	0.858

CAD: Coronary artery disease, P<0.05 was considered significant.

Table 5. The survival rate of significant prognosis factors of progression-free survival

Parameters	Median PFS (months), range	PFS survival (%)		
		1 year	2 year	3 year
Tumor stage				
IIIA	17, [10.8, 23.2]	70±14.5	20±12.6	0
IIIB	12, [8.3, 15.7]	50±13.4	7.1±6.9	0
IV	8, [0.8, 15.2]	16.7±15.2	0	0
EGFR mutation				
No	10, [6.9, 13.1]	30±14.5	0	0
Yes	17, [11.5, 22.5]	63.6±10.3	13.6±7.3	0
Metastasis				
With	8, [0.8, 15.2]	16.7±15.2	0	0
Without	17, [11, 23]	61.5±9.5	11.5±6.3	0

PFS: progression-free survival.

months. the 1 year, 3 year, 5 year survival rate was 78±6.5%, 36.4±7.7%, 10.4±4.9%, respectively. Univariate analyses were performed to obtain risk factors, as **Table 2** shown, tumor stage, EGFR mutation, lesions' metastasis were risk factor of patients' overall survival. The three univariate analyses were analyzed by Kaplan-meire and overall survival curve were obtained, as **Table 3** and **Figure 1** shown, the median OS of IIIA was 26 [range: 14.4-37.6] months, 3 year survival rate was 33.8±13.7%, obviously better

prognosis than IIIB and IV tumor stage; the median OS of EGFR mutation patients was 23 [range: 17.2-28.8] months, 3 year survival rate was 12.5±6.8%, obviously better prognosis than patients with EGFR non-mutation; the median OS of metastasis patients was 12 [range: 9-15] months, 3 year survival rate was 13.9±6.4%, obviously better prognosis than patients with non-metastasis.

Univariate analysis of progression-free survival

32 cases were included in PFS analysis due to 11 patients were lack of PFS information. The median progression-free survival was 15 [range: 12.6-17.4] months. the 1 year, 3 year, 5 year survival rate was 53.1±8.8%, 9.4±5.2%, 0%, respectively. As **Table 4** shown, tumor stage, EGFR mutation, lesions' metastasis were risk factor of patients' PFS. The three univariate analyses were analyzed by Kaplan-meire and overall survival curve were obtained, as **Table 5** and **Figure 2** shown, 3 year PFS was IIIA, IIIB and IV tumor stage was 0% of all. the median PFS of IIIA was 17 [range: 10.8-23.2] months, 2 year survival rate was 20±12.6%, obviously better prognosis than IIIB and IV tumor stage; the median OS of EGFR mutation patients was 17 [range: 11.5-22.5] months, 2 year PFS rate was 13.6±7.3%, obviously better prognosis than patients with EGFR non-mutation; the median PFS of metastasis patients was 17 [range: 11-23] months, 2 year survival rate was 11.5±6.3%, obviously better prognosis than patients with non-metastasis.

Discussion

In this retrospective study, tumor stage, EGFR mutation and metastasis were prognostic significance factors; gender, age, smoking, complications, organ metastasis, tumor stage, EGFR mutation, adverse effect, gefitinib therapeutic

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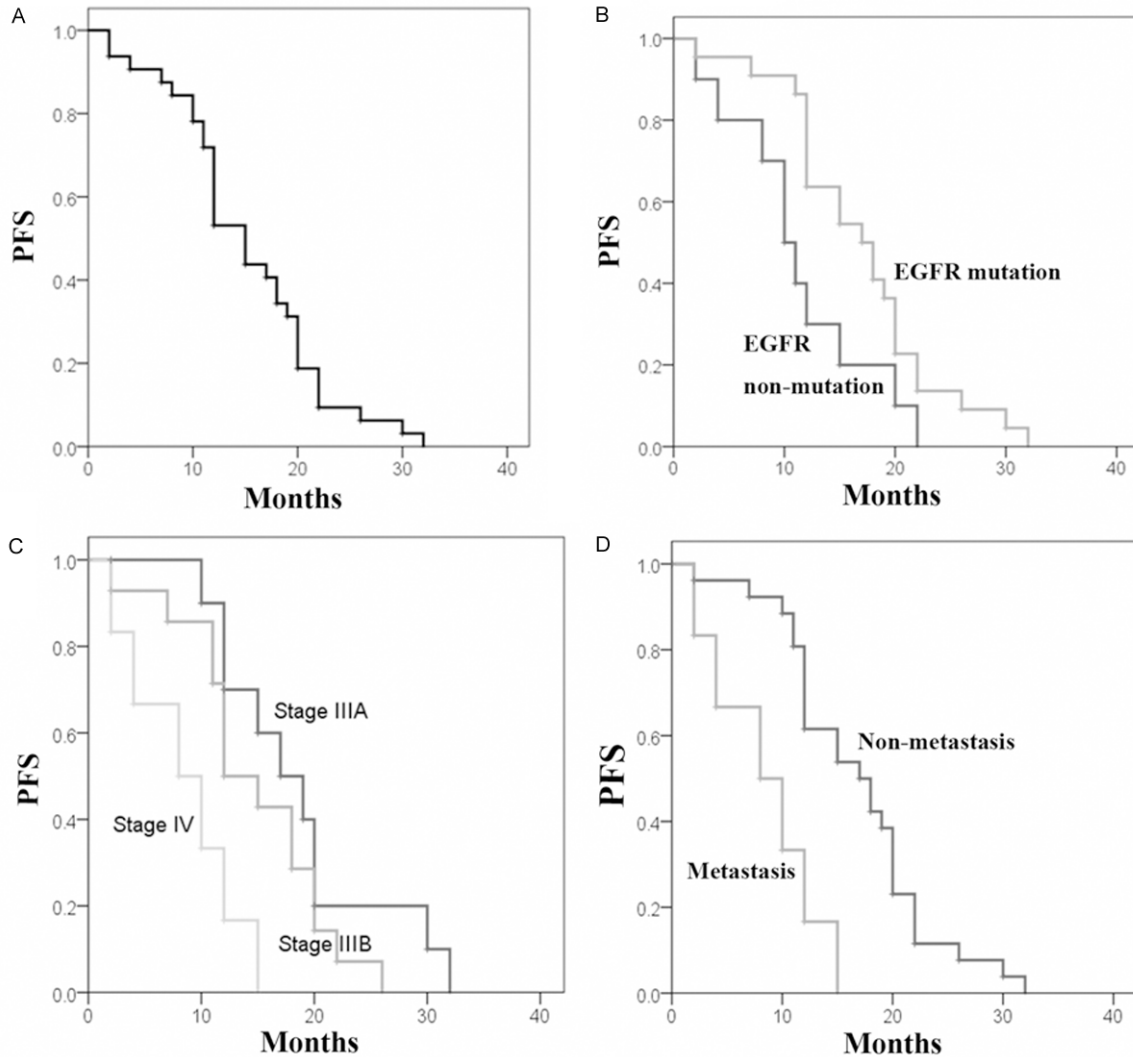


Figure 2. Progression-free survival curves analysis using Kaplan-Meier analysis and the Log-Rank test: A. Progression-free survival of all patients; B. Comparison among EGFR mutation and EGFR non-mutation group; C. Comparison among different tumor stages including IIIA, IIIB and IV stages; D. Comparison among metastasis and non-metastasis group.

regimen were not prognostic significance factors of overall survival and PFS according to the survival analysis study.

The TNM staging system for all solid tumors was devised by Pierre Denoix between 1943 and 1952, tumor size, extension of the primary tumor, lymphatic involvement, and the presence of metastasis are used to classify the progression of cancer [13]. The patients enrolled in our study were classified as IIIA, IIIB and IV according to TNM staging system. As **Tables 1** and **3** shown, univariant analysis shown tumor stage was one of prognostic significance factors of OS and PFS. Kaplan-Meire analysis of

tumor stage displayed that clinical outcome of IIIA was favorable prognostic significance factor, better than IIIB and IV; IV shown the worst prognostic outcome. 2-year overall survival of IIIA, IIIB was $50.6 \pm 14.4\%$, $35.7 \pm 12.8\%$ compared to IV was 0%.

It is reported that the EGFR mutations rate in the Asian population was estimated to 51% (range: 22-64%) [14], in our study, EGFR accounted for 60.5%. Gefitinib as first line regimen treated elderly patients of Japan with EGFR mutations is shown efficacy [15]. EGFR mutations mainly occur in exon 18-21 of intracellular tyrosine kinase (TK) sequence, includ-

ing more than 30 mutations. Gefitinib-resistance mutations including T790M, L858Q, D761Y and T854A are not sensitive to gefitinib [16, 17]. EGFR mutations except of gefitinib-resistance mutations are defined as activating mutations due to mediate ligand-dependent EGFR-TK activating. The most common mutation is deletion E746-A750 of exon 19 and L858R of exon 21 [18-20], accounts for 90% mutations. Our data displayed that both of OS and PFS of EGFR mutations patients were significant longer than non-EGFR mutation patients ($P < 0.05$).

Advanced lung adenocarcinoma often is accompanied by distant metastasis commonly consists of liver, brain and bone metastasis. A number of studies report that distant metastasis is poor prognostic factor of OS. In our study, patients with liver metastasis and bone metastasis had shorter PFS and OS than those without liver and bone metastasis did ($P < 0.05$). Liver metastasis predicts poorer prognosis in advanced lung adenocarcinoma patients received first-line gefitinib [21].

There are limitations in the retrospective study. Firstly, on account of the limited sample size of the study, independent prognosis factors were not analyzed. Secondly, multi-center, large sample size, prospective study should be analyzed to elucidate tumor stage IIIA, EGFR mutation and non-metastasis are favorable prognosis factors of advanced lung adenocarcinoma.

Disclosure of conflict of interest

None.

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