Int J Clin Exp Med 2016;9(11):21663-21671
www.ijcem.com /ISSN:1940-5901/IJCEM0027095

Original Article

Fibroblast growth factor receptor 4 is not an independent prognostic biomarker in patients with lung adenocarcinoma

Shengli Yang[1,2*], Dakai Xiao[3*], Yuejian Wang[1], Jie Yang[1], Zhongyang Chen[2,4], Jinglong Li[2,5], Guilin Peng[2,3], Liyan Huang[3], Huiming He[3], Hui Pan[3], Jianxing He[3]

[1]The First People's Hospital of Foshan, Foshan 528000, Guangdong, China; [2]Graduate School of Southern Medical University, Guangzhou 510515, Guangdong, China; [3]Department of Thoracic Surgery, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, Guangdong, China; [4]Guangzhou Women and Children Hospital, Guangzhou 510010, Guangdong, China; [5]The University of Hong Kong-Shenzhen Hospital, Shenzhen 518019, Guangdong, China. [*]Equal contributors.

Received March 2, 2016; Accepted August 15, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: The aim of this study was to evaluate the clinical significance of fibroblast growth factor receptor 4 (FGFR4) in lung adenocarcinoma. The expression of FGFR4 in 128 samples of lung adenocarcinoma was assessed with quantitative PCR and immunohistochemistry. The correlations between FGFR4 and clinicopathologic features were analyzed with Chi-square test. Kaplan-Meier survival curve and Cox regression model were also used to evaluate the prognostic value of FGFR4. The results showed that FGFR4 expression was lower in non-small cell lung cancer (23.4%, 30/128), which was significantly associated with T stage (P=0.02), N stage (P=0.02), TNM stage (P=0.03), pleural invasion (P=0.03) and differentiation (P=0.02). Univariate analysis showed that FGFR expression was significantly associated with 5-year survival in lung adenocarcinoma. However, multivariate analysis (P=0.877) did not support FGFR4 as an independent prognostic factor in lung adenocarcinoma. In conclusion, FGFR4 expression was not an independent prognostic biomarker in patients with lung adenocarcinoma and further larger randomized controlled studies were needed to elucidate the significance of FGFR4 in lung adenocarcinoma.

Keywords: Fibroblast growth factor receptor 4, lung adenocarcinoma, prognosis, biomarker

Introduction

As the most common cancer, Lung cancer is the leading cause of cancer-related mortality all over the world [1-3]. Of lung cancer, non-small cell lung cancer (NSCLC) accounting for up to 85% of cases is the predominant histological type [4]. The overall 5-year survival rate of NSCLC is estimated extremely low at roughly 15% and surgical resection is no longer available due to late stage in more than 2/3 of NSCLC patients [5]. Lung adenocarcinoma and squamous cell carcinoma (SCC), each accounting for about 40% of NSCLC cases, are two major histology subtypes of NSCLC. Previous studies have shown that fundamental different mechanisms were found in these two subtypes of lung cancer. Although several biomarkers have been proved to be related with NSCLC angiogenesis, progression, or prognosis [6, 7], there is still no effective predictive or prognostic biomarker clinically used, partly because of different histological types. With the rising mortality and morbidity of lung cancer in the world [8], it is necessary to seek effective biomarkers for prognosis.

Fibroblast growth factor receptors 4 (FGFR4) belongs to FGFR family which has been demonstrated to be involved in the progression and prognosis of multiple types of cancers [9]. By interacting with its ligands, FGF related signaling could be activated. Previous studies have shown that FGFR4 overexpression or mutation was significantly associated with poor prognosis in multiple types of cancers, including hepatocellular carcinoma, prostate, breast, pancreatic, gynecologic gastric cancers, cholangiocar-

Table 1. Patient demographic data

Characteristics	No. (%)
Gender	
Male	78 (60.9)
Female	50 (39.1)
Age	
≤60 yrs	77 (60.2)
>60 yrs	51 (39.8)
Smoking	
No	63 (49.2)
Yes	65 (50.8)
Level of CEA (ng/ml)	
<5.0	67 (52.3)
≥5.0	61 (47.7)
Lung lobe	
Right	65 (50.8)
Left	63 (49.2)
T stage	
T1	48 (37.5)
T2	69 (53.9)
T3/T4	33 (25.8)
N Stage	
N0	68 (53.1)
N1	27 (21.1)
N2	33 (25.8)
TNM stage	
I	32 (25.0)
II	63 (49.2)
III/IV	33 (25.8)
Pleural invasion	
Yes	50 (39.1)
No	78 (60.9)
Differentiated	
Well	71 (55.5)
Poor	57 (44.5)

TNM stage was classified according to the 7th edition of the tumor node metastasis classification of the International Union Against Cancer (UICC).

cinoma, and rhabdomyosarcoma [10-13]. Moreover, Huang et al recently showed that FGFR4 is an independent prognostic biomarker in NSCLC [14]. However, the clinical significance of FGFR4 in the lung adenocarcinoma has not been elucidated yet.

In this study, we detected the expression of FGFR4 in 128 cases of lung adenocarcinoma with quantitative real-time PCR and immunohistochemistry (IHC), and analyzed the correlation between FGFR4 and the clinicopathologic features in lung adenocarcinoma.

Material and methods

Patients and follow-up

Samples of lung adenocarcinoma and adjacent tissues were obtained from the department of thoracic surgery of our hospital with approval of the patients and the Ethical Committees. One hundred twenty eight patients with lung adenocarcinoma who underwent pulmonary lobectomy during January 2006 and December 2010 were included in this study. Patients were included according to the criteria as follows: 1) available follow-up data; 2) available and enough samples; 3) radical resection without chemotherapy, radiotherapy and targeted therapy. The pathological diagnosis and proper IHC selection were performed by two experienced pathologists. Pathologic tumor-node-metastasis (pTNM) classification was based on the 7th International Union Against Cancer.

IHC and evaluation

All lung tissue specimens were fixed by 10% formalin and embedded in paraffin, followed by sequential section cutting (3 μm) and xylene deparaffinization. Slides with section were immersed in citrate buffer (pH=6.0) and heated in a microwave oven for 30 minutes to achieve antigen retrieval. After that, specimens were treated with 3% H_2O_2 in methanol for 20 minutes to block endogenous peroxidase enzyme. Tissues were incubated with diluted primary antibody (1:100) at 4°C overnight and then with corresponding biotinylated secondary antibody and streptavidin-peroxidase complex was applied at 37°C for 30 minutes. Finally, slides were reacted with 3,3'-diaminobenzidine solution and counterstained before microscopy processing. Phosphate-buffered saline instead of primary antibody was used as the negative control, with the same other procedures, whereas hepatocarcinoma sections with high FGFR4 expression were used as positive control.

The evaluation of IHC section was performed by 2 experienced pathologists. Combination of staining intensity and positive cell percentage was used as the criterion. The percentage scores of immunoreactive cells were defined as follows: 0 for <10% positive cells; 1 for 10%-30% positive cells; 2 for 30%-50% cells; and 3 for >50% cells. The staining intensity can be described as follows: 0 for negative staining; 1 for weak staining (yellow); 2 for moderate stain-

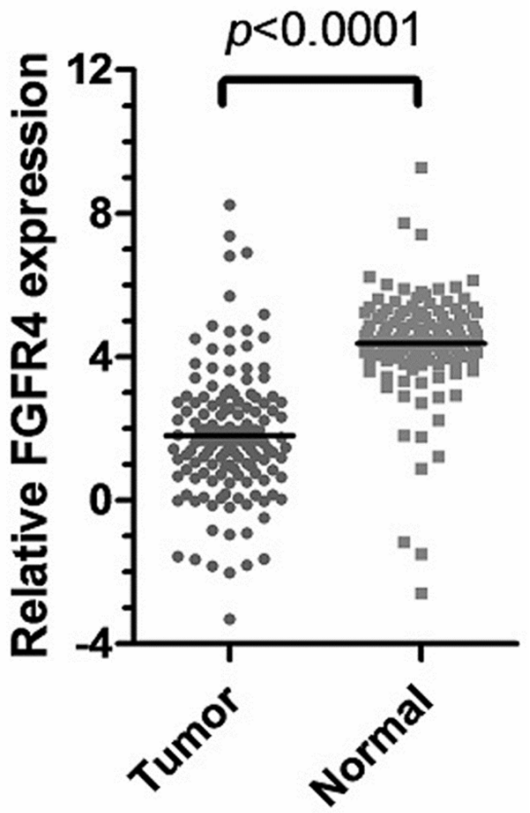


Figure 1. Expression of fibroblast growth factor receptor 4 (FGFR4) mRNA in lung adenocarcinoma and adjacent tissues.

ing (brown); and 3 for strong staining (deep brown). The final IHC score was defined as the addition of the staining intensity score and the positive cell score. The criteria for high FGFR4 expression and low FGFR4 expression were arbitrarily defined as follows: 0-1 for negative staining (-); 2-3 for weak positive (+); 4-5 for moderate positive (++); and 6 for strong positive (+++).

RNA extraction and real-time polymerase chain reaction analysis

Total RNA was purified from homogenized cancer tissue with TRIzol reagent according to the manufacturer's instructions. Reverse transcription and cDNA synthesis were performed using PrimeScript RT reagent Kit (Takara) and quantitative polymerase chain reaction (qPCR) was realized by using QuantiTect SYBR Green PCR system (Qiagen) according to the manufacturer's instructions. β-actin was applied as an internal control. The sequences of primers used for real-time PCR experiments were designed following previous study and shown as follows: FGFR4 forward: 5'-AGGAGCCAGGAAGGCAGTT-3'; FGFR4 reverse: 5'-CCTCCAGGGACAAGACTGGA-3'; β-actin forward: 5'-TCCTTCCTGGGCATGGAGTCCT-3'; β-actin reverse: 5'-TGCCAGGGCAGTGATCTCCT-3'.

Statistical analysis

All statistical analyses were performed with SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Quantitative and categorical data were expressed as Mean ± Standard Deviation (SD) and percentage, respectively. The difference of the mean value between different groups was analyzed with Student's *t*-test. The correlation between FGFR4 expression and the clinicopathologic features were analyzed with chi-square test. The univariate analysis was performed with the Kaplan-Meier survival curve method, and statistical differences were compared with a log-rank test. The multivariate analysis was carried out with Cox regression model. $P<0.05$ was considered to be statistically significant.

Results

Patient characteristics and FGFR4 expression

This study includes 128 lung adenocarcinoma patients (**Table 1**). The mean age of patients was 56±11 years old. Most patients (60.9%) were male in the cohort. The clinicopathologic parameters, including location, CEA level, lymph node metastasis, pleural invasion, differentiation and smoking, were recorded based on the patient data. To compare the FGFR4 expression in tumor tissue or adjacent normal tissue, we detected the FGFR4 mRNA level from all the lung adenocarcinoma tissue with quantitative PCR. It turned out that FGFR4 mRNA level in tumor tissues was significantly lower than that in normal tissues (**Figure 1**). We also divided the cohort into FGFR4 high-expression and low-expression groups according to the IHC criteria described in "Materials and methods". In our study, FGFR4 expression was mainly observed in both cytoplasm and membrane (**Figure 2A-H**). Statistically, the lower rate of FGFR4 expression was found in lung adenocarcinoma tissue 23.4% (30/128) (**Table 2**).

Correlation between FGFR4 and clinicopathologic factor in lung adenocarcinoma

To confirm the risk factors correlated to FGFR4 expression, we performed the association analyses between FGFR4 expression and clin-

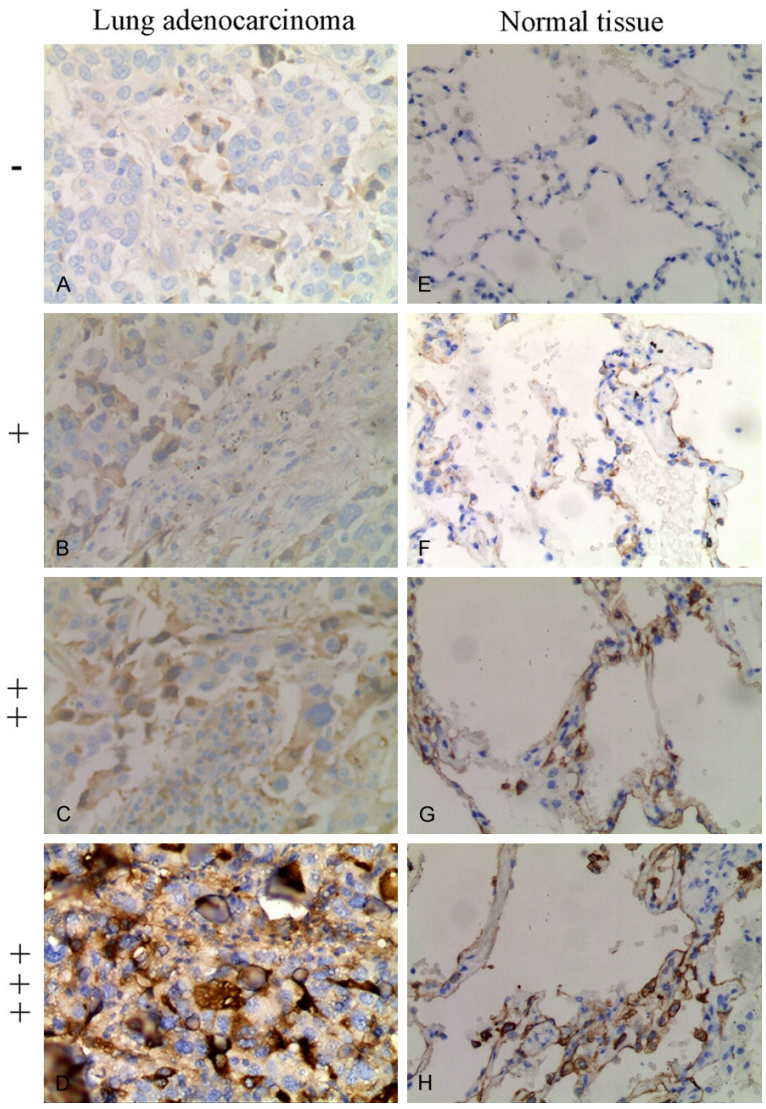


Figure 2. Immunohistochemistry analysis of expression of fibroblast growth factor receptor 4 (FGFR4) protein in lung adenocarcinoma (A-D) and normal tissue (E-H). (A) Negative; (B) Weak; (C) Moderate; (D) Strong; (E) Negative; (F) Weak; (G) Moderate; (H) Strong.

icopathologic factors in lung adenocarcinoma with the chi-square method (**Table 3**). Consequently, we found the FGFR4 low-expression group had more cases of T stage (P=0.02), N stage (P=0.02), TNM stage (P=0.03), pleural invasion (P=0.03) and differentiation (P=0.02), but not sex, age, smoking, CEA level and lung lobe location, indicating that FGFR4 may play an important role in lung adenocarcinoma differentiation and migration.

Prognostic value of FGFR4 in lung adenocarcinoma

To evaluate the prognostic value of FGFR4 in lung adenocarcinoma, we first analyzed the correlation between FGFR4 expression and the 5-year overall survival rate with univariate analysis (**Table 4** and **Figure 3J**). With the Kaplan-Meier method, we demonstrated that FGFR4 low expression was correlated to poorer prognosis in NSCLC (*P*=0.004). In the FGFR4 low-expression group, the 5-year overall survival rate was 35.9%, while in the high-expression group, the 5-year overall survival rate was 80.8% (**Table 4**). In addition, age (P=0.002), smoking (P=0.003), T stage (P=0.003), N stage (P<0.001), TNM stage (P=0.003), pleural invasion (P=0.005) and differentiation (P=0.001) were also defined as prognostic factors in lung adenocarcinoma. The 5-year overall survival rates between different classification were shown in **Table 4** and **Figure 3**.

Moreover, we further performed multivariate analysis with Cox regression model to detect whether FGFR4 was an independent prognostic factor in lung adenocarcinoma (**Table 5**). Almost all clinicopathologic features were collected into the model, including sex, age, tumor size, differentiation, lymph node metastasis, smoking, and FGFR4 expression. With multivariate analysis, we confirmed that FGFR4 was not an independent prognostic factor (*P*=0.877), with 95% confidence interval 0.395-2.970 and hazard ratio 1.083. Additionally, age (P<0.001), smoking (P<0.001), T stage (P=0.024), pleural invasion (P=0.010) and differentiation (P=0.008) were defined as independent prognostic factors, with corresponding 95% confidence interval and hazard ratio shown in **Table 5**.

Discussion

In present study, we systemically investigated the expression of FGFR4 in 128 cases of lung adenocarcinoma for the first time and found that FGFR4 expression was significantly associ-

Table 2. Expression of FGFR4 in lung adenocarcinoma and paratumor normal tissue

Origin	-/+	++/+++	χ^2	*p* value
Lung Adenocarcinoma	76.6% (98/128)	23.4% (30/128)	5.37	0.02
Normal tissue	63.3% (81/128)	36.7% (47/128)		

Table 3. Correlation between FGFR4 expression and clinicopathologic parameters

Characteristics	No. (%)	FGFR4 expression		*p* value
		Negative/ weak	Positive	
Gender				0.58
Male	78	61	17	
Female	50	37	13	
Age				0.38
≤60 yrs	77	61	16	
>60 yrs	51	37	14	
Smoking				0.46
No	63	50	13	
Yes	65	48	17	
Level of CEA (ng/ml)				0.12
<5.0	67	55	12	
≥5.0	61	43	18	
Lung lobe				0.25
Right	65	47	18	
Left	63	51	12	
T stage				0.02
T1/T2	95	68	27	
T3/T4	33	30	3	
N Stage				0.02
N0	70	48	22	
N1/N2	58	50	8	
TNM stage				0.03
I/II	90	64	26	
III/IV	38	34	4	
Pleural invasion				0.03
Yes	50	44	6	
No	78	54	24	
Differentiated				0.02
Well	71	49	22	
Poor	57	49	8	

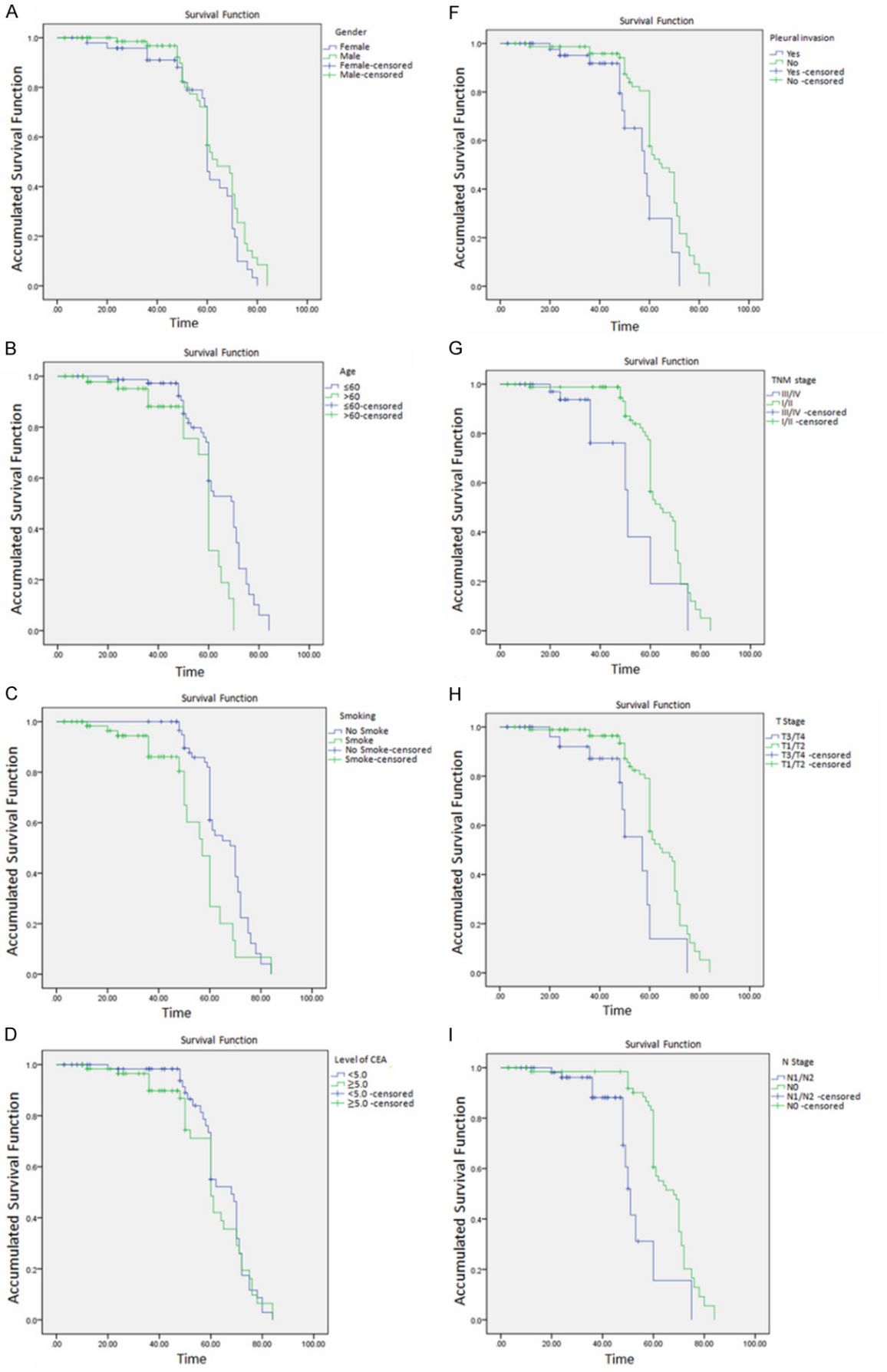
ated with T stage (P=0.02), N stage (P=0.02), TNM stage (P=0.03), pleural invasion (P=0.03) and differentiation (P=0.02). Univariate analysis showed that FGFR expression was significantly associated with 5-year survival in lung adenocarcinoma. However, multivariate (P=0.877) analysis did not support FGFR4 as an independent prognostic factor in lung adenocarcinoma.

Table 4. Univariate analysis of non-small-cell lung cancer

Characteristics	No. (%)	5 year Survival rate	*p* value
Gender			0.146
Male	78	56.7	
Female	50	46.1	
Age			0.002
≤60 yrs	77	58.9	
>60 yrs	51	31.5	
Smoking			0.003
No	63	61.0	
Yes	65	26.8	
Level of CEA (ng/ml)			0.649
<5.0	67	55.1	
≥5.0	61	48.5	
Lung lobe			0.554
Right	65	56.4	
Left	63	47.3	
T stage			0.003
T1/T2	95	57.7	
T3/T4	33	13.8	
N Stage			<0.001
N0	70	60.6	
N1/N2	58	15.6	
TNM stage			0.003
I/II	90	56.6	
III/IV	38	19.0	
Pleural invasion			0.005
Yes	50	13.9	
No	78	57.7	
Differentiated			0.001
Well	71	60.4	
Poor	57	13.0	
FGFR4 expression			0.004
Low	98	35.9	
High	30	80.8	

Survival time under each category was used as the dependent variable.

The clinical significance of FGFR family, which is considered to be significantly associated with NSCLC progression, has been proved in several previous studies. FGFR1 amplication can result


A
Survival Function
Gender
Female
Male
Female-censored
Male-censored
Accumulated Survival Function
Time
B
Survival Function
Age
≤60
>60
≤60-censored
>60-censored
Accumulated Survival Function
Time
C
Survival Function
Smoking
No Smoke
Smoke
No Smoke-censored
Smoke-censored
Accumulated Survival Function
Time
D
Survival Function
Level of CEA
<5.0
≥5.0
<5.0 -censored
≥5.0 -censored
Accumulated Survival Function
Time
F
Survival Function
Pleural invasion
Yes
No
Yes -censored
No -censored
Accumulated Survival Function
Time
G
Survival Function
TNM stage
III/IV
I/II
III/IV -censored
I/II -censored
Accumulated Survival Function
Time
H
Survival Function
T Stage
T3/T4
T1/T2
T3/T4 -censored
T1/T2 -censored
Accumulated Survival Function
Time
I
Survival Function
N Stage
N1/N2
N0
N1/N2 -censored
N0 -censored
Accumulated Survival Function
Time

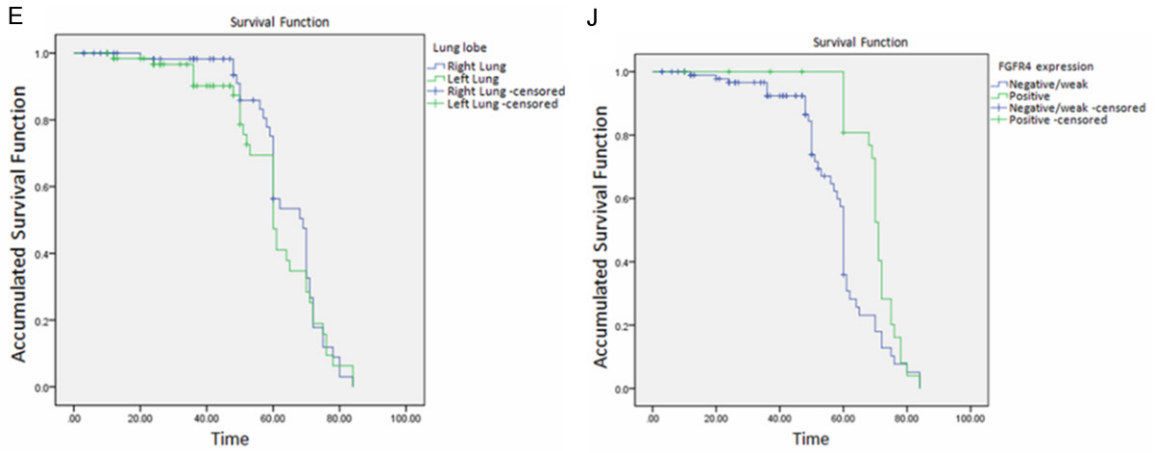


Figure 3. Kaplan-Meier curves of overall survival in lung adenocarcinoma patients classified by different risk factors. A: Gender (P=0.146); B: Age (P=0.002); C: Smoking moderate (P=0.003); D: CEA level (P=0.649); E: Lung lobe (P=0.554); F: Pleural invasion (P=0.005); G: TNM stage (P=0.003); H: T stage (P=0.003); I: N stage (P=0.003); J: FGFR4 expression (P=0.004).

Table 5. Multivariate analysis of non-small-cell lung cancer

Characteristics	HR	95% CI	Beta-value	*p* value
Age				
≤60 yrs	1			
>60 yrs	0.297	0.151-0.582	-1.214	<0.001
Smoking				
No	1			
Yes	0.235	0.107-0.515	-1.449	<0.001
T stage				
T1/T2	1			
T3/T4	2.281	1.099-4.734	0.825	0.027
N Stage				
N0	1			
N1/N2	1.952	0.764-4.988	0.669	0.162
TNM stage				
I/II	1			
III/IV	1.273	0.633-2.561	0.242	0.498
Pleural invasion				
Yes	1			
No	2.622	1.266-5.449	0.964	0.010
Differentiated				
Well	1			
Poor	2.521	1.266-5.019	0.925	0.008
FGFR4 expression				
Low	1			
High	1.083	0.395-2.970	0.079	0.877

Clinical features including sex, age, tumor size, differentiation, lymph node metastasis, smoking, and FGFR4 expression were used as dependent variables.

in poorer prognosis in early NSCLC [15], and the use of FGFR1 inhibitors (such as AZD4547, ponatinib [AP24534], and nintedanib [BIBF 1120]) could exert growth inhibition effect in FGFR1 overexpressed NSCLC cells in vitro and xenograft models in vivo [16, 17]. Moreover, FGFR1/3 gene fusions were reported to define a molecular subset of NSCLC with distinct clinical characteristics [18]. The diversity and redundancy of FGFR could lead to increased complexity and possibility of FGFR signaling pathway and the different outcome.

Among different FGFRs, more and more attention has been paid to FGFR4 due to its potential role as an oncogene. FGFR4 gene amplification or protein overexpression is observed in different types of cancers including hepatocellular carcinoma, prostate, breast, pancreatic, gynecologic gastric cancers, cholangiocarcinoma, and rhabdomyosarcoma [10-13]. Fang et al previously showed that the rs351855G/A polymorphisms of FGFR4 gene can be used to predict the occurrence, chemotherapy response and prognosis of NSCLC [19], which was also proved in Japanese lung cancer patients [20]. Moreover, Huang et al [14] recently examined the expression of FGFR4 in 237 samples of NSCLC with immunohistochemistry, and further evaluated the prognostic value of FGFR4 by Kaplan-Meier survival curve and Cox regression model. Their results showed that FGFR4 is an independent prognostic bio-

marker in NSCLC. Furthermore, they also demonstrated that FGFR4 can accelerate the proliferation of NSCLC cell lines, indicating FGFR4 could be a potential drug target for NSCLC. Our results were inconsistent with Huang et al's study. The difference might be caused by the different expression of FGFR4 in different subtype of NSCLC.

The limitation of this study is that a small number of patients were included. Further larger sample studies should be performed to verify the influencing factors and histopathological type in lung adenocarcinoma. Moreover, the retrospective properties of this study could result in selection bias.

In conclusion, we found that FGFR4 expression is significantly associated with T stage, N stage, TNM stage, pleural invasion and differentiation, but we failed to identify FGFR4 as an independent prognostic factor in lung adenocarcinoma.

Acknowledgements

This work was supported by National Science Foundation of China (No. 81101681).

Disclosure of conflict of interest

None.

Address correspondence to: Jianxing He, Department of Thoracic Surgery, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, Guangdong, China. Tel: +86-20-83062818; Fax: +86-20-83062818; E-mail: hejx@vip.163.com; Drjianxing.he@gmail.com

References

[1] Shiau MC, Bonavita J and Naidich DP. Adenocarcinoma of the lung: current concepts in radiologic diagnosis and management. Curr Opin Pulm Med 2007; 13: 261-6.

[2] Jett JR, Cortese DA and Fontana RS. Lung cancer: current concepts and prospects. CA Cancer J Clin 1983; 33: 74-86.

[3] Herbst RS, Heymach JV and Lippman SM. Lung cancer. N Engl J Med 2008; 359: 1367-80.

[4] Yang P, Allen MS, Aubry MC, Wampfler JA, Marks RS, Edell ES, Thibodeau S, Adjei AA, Jett J and Deschamps C. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest 2005; 128: 452-62.

[5] Siegel R, Ward E, Brawley O and Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61: 212-36.

[6] Carlini MJ, Roitman P, Nunez M, Pallotta MG, Boggio G, Smith D, Salatino M, Joffe ED, Rabinovich GA and Puricelli LI. Clinical relevance of galectin-1 expression in non-small cell lung cancer patients. Lung Cancer 2014; 84: 73-8.

[7] Rosell R, Bivona TG and Karachaliou N. Genetics and biomarkers in personalisation of lung cancer treatment. Lancet 2013; 382: 720-31.

[8] Lu M, Tian H, Yue W, Li L, Li S, Qi L, Hu W, Gao C and Si L. TFIIB-related factor 2 over expression is a prognosis marker for early-stage non-small cell lung cancer correlated with tumor angiogenesis. PLoS One 2014; 9: e88032.

[9] Kelleher FC, O'Sullivan H, Smyth E, McDermott R and Viterbo A. Fibroblast growth factor receptors, developmental corruption and malignant disease. Carcinogenesis 2013; 34: 2198-205.

[10] Ye YW, Zhou Y, Yuan L, Wang CM, Du CY, Zhou XY, Zheng BQ, Cao X, Sun MH, Fu H and Shi YQ. Fibroblast growth factor receptor 4 regulates proliferation and antiapoptosis during gastric cancer progression. Cancer 2011; 117: 5304-13.

[11] Sugiyama N, Varjosalo M, Meller P, Lohi J, Hyytiainen M, Kilpinen S, Kallioniemi O, Ingvarsen S, Engelholm LH, Taipale J, Alitalo K, Keski-Oja J and Lehti K. Fibroblast growth factor receptor 4 regulates tumor invasion by coupling fibroblast growth factor signaling to extracellular matrix degradation. Cancer Res 2010; 70: 7851-61.

[12] Taylor JG 6th, Cheuk AT, Tsang PS, Chung JY, Song YK, Desai K, Yu Y, Chen QR, Shah K, Youngblood V, Fang J, Kim SY, Yeung C, Helman LJ, Mendoza A, Ngo V, Staudt LM, Wei JS, Khanna C, Catchpoole D, Qualman SJ, Hewitt SM, Merlino G, Chanock SJ, Khan J. Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models. J Clin Invest 2009; 119: 3395-407.

[13] Xu YF, Yang XQ, Lu XF, Guo S, Liu Y, Iqbal M, Ning SL, Yang H, Suo N and Chen YX. Fibroblast growth factor receptor 4 promotes progression and correlates to poor prognosis in cholangiocarcinoma. Biochem Biophys Res Commun 2014; 446: 54-60.

[14] Huang HP, Feng H, Qiao HB, Ren ZX and Zhu GD. The prognostic significance of fibroblast growth factor receptor 4 in non-small-cell lung cancer. Onco Targets Ther 2015; 8: 1157-64.

[15] Cihoric N, Savic S, Schneider S, Ackermann I, Bichsel-Naef M, Schmid RA, Lardinois D,

Gugger M, Bubendorf L, Zlobec I and Tapia C. Prognostic role of FGFR1 amplification in early-stage non-small cell lung cancer. Br J Cancer 2014; 110: 2914-22.

[16] Zhang J, Zhang L, Su X, Li M, Xie L, Malchers F, Fan S, Yin X, Xu Y, Liu K, Dong Z, Zhu G, Qian Z, Tang L, Schottle J, Zhan P, Ji Q, Kilgour E, Smith PD, Brooks AN, Thomas RK and Gavine PR. Translating the therapeutic potential of AZD4547 in FGFR1-amplified non-small cell lung cancer through the use of patient-derived tumor xenograft models. Clin Cancer Res 2012; 18: 6658-67.

[17] Ren M, Hong M, Liu G, Wang H, Patel V, Biddinger P, Silva J, Cowell J and Hao Z. Novel FGFR inhibitor ponatinib suppresses the growth of non-small cell lung cancer cells over-expressing FGFR1. Oncol Rep 2013; 29: 2181-90.

[18] Wang R, Wang L, Li Y, Hu H, Shen L, Shen X, Pan Y, Ye T, Zhang Y, Luo X, Pan B, Li B, Li H, Zhang J, Pao W, Ji H, Sun Y and Chen H. FGFR1/3 tyrosine kinase fusions define a unique molecular subtype of non-small cell lung cancer. Clin Cancer Res 2014; 20: 4107-14.

[19] Fang HM, Tian G, Zhou LJ, Zhou HY and Fang YZ. FGFR4 genetic polymorphisms determine the chemotherapy response of Chinese patients with non-small cell lung cancer. Acta Pharmacol Sin 2013; 34: 549-54.

[20] Sasaki H, Okuda K, Kawano O, Yukiue H, Yano M and Fujii Y. Fibroblast growth factor receptor 4 mutation and polymorphism in Japanese lung cancer. Oncol Rep 2008; 20: 1125-30.