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ORIGINAL ARTICLE

Basic fibroblast growth factor shows prognostic impact on survival in operable non-small cell lung cancer patients

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Angiogenesis; basic fibroblast growth factor; non-small-cell lung cancer; prognosis.

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Abstract

Background: The important role of angiogenesis displaying in tumor development and metastasis has been generally realized. Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and endostatin (ES) are critical members of angiogenesis modulating the balance between pro-angiogenenic and anti-angiogenenic factors. The aim of this study was to evaluate the circulating level of these factors in serum and explore their prognostic significance in 96 operable non-small cell lung cancer (NSCLC) patients.

Methods: Pre-operational serum VEGF, bFGF, and ES were determined by commercially available enzyme-link immunosorbent assay for 96 NSCLC patients and compared to a cohort of healthy controls (n = 51). Values were correlated with clinicopathological features and overall survival (OS).

Results: The pretreatment serum levels of VEGF, bFGF and ES in NSCLC were significantly higher than in the healthy control ($P < 0.001$, $P = 0.009$ and $P = 0.016$, respectively). Univariate survival analysis showed that a high bFGF level correlated with shorter OS and remained an independent factor in multivariate analysis (hazard ratio [HR] = 1.918, 95% confidence interval [CI], 1.061–3.464). In the squamous subtype, a high bFGF indicated a particularly poor prognosis (HR = 2.609, 95% CI, 1.188–5.729).

Conclusions: bFGF is an independent predictor of poor survival in patients with NSCLC. For patients with high serum bFGF, aggressive antitumor treatments should be given after surgery. Approaches targeting the bFGF signaling pathway should be considered as potentially promising therapeutic strategies in NSCLC, especially for the squamous subtype.

Introduction

In recent years, cancer has become a major public health problem in China and in many other parts of the world. Among various malignant tumors, the incidence and cancer specific mortality is highest in lung cancer. Approximately 85% of lung cancers are classified as non-small cell lung cancer (NSCLC). In NSCLC, different therapies are offered according to stage. Early stage NSCLC patients are usually offered surgery and then selectively are offered adjuvant chemotherapy, while advanced cases are often treated with chemotherapy and radiotherapy. However, there is a subset of patients who have a particularly poorer prognosis even in the same stage. There is a need for reliable parameters, apart from the tumor node metastasis (TNM) system, that could add prognostic information to generate more reasonable personalized therapy. A variety of factors have been reported as predictors for favorable or unfavorable prognosis.

Anti-angiogenic therapy, one of the most promising antitumor therapeutic strategies, whose rationale is based on tumor growth inhibition by starving cancer cells of vital nutrients[1–3] principally consists of two classes of drugs: suppression of pro-angiogenic factors (bevacizumab [Avastin, Genetech, San Francisco, CA, USA], sunitinib [Sutent, Pfizer,

New York, USA], sorafenib [Nexavar, Baye, Leverkusen, Germany]), or enhancement of anti-angiogenic factors (endostar, Endu, Simcere, Nanjing, China). Additionally, there are dozens of anti-angiogenic compounds under development in clinical trials. The balance of angiogenesis is dependent on the modulation between pro-angiogenic and anti-angiogenic factors.[4] The correlation between angiogenic cytokines, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), Angiopoietin and Notch, and recurrence or survival of patients with solid or haematopoietic cancer has been documented. One of the most crucial regulators of angiogenesis is VEGF, which was first identified by Senger *et al*. as a vascular permeability factor secreted by tumor cells.[5] VEGF activates mainly two tyrosine kinase receptors: VEGF receptor (R-)1 and VEGFR-2. VEGFR-1, expressed in vasculature, can act as a negative regulator of angiogenesis, while VEGFR-2 plays a primary role in angiogenesis.[6] The prognostic value of VEGF in NSCLC is still controversial. Kondo *et al*. first recognized the potential of VEGF as a tumor marker for malignant disease.[7] bFGF is another well known inducer of angiogenesis and wound healing, with a complex biological effect[8] acting through transmembrane tyrosine kinase receptors (mainly fibroblast growth factor receptors FGFR-1 and FGFR-2) with high affinity.[9] bFGF and VEGF work synergistically *in vitro* and *in vivo*.[10,11] Endostatin (ES) has been found to be the strongest anti-angiogenic factor.[12,13] Recombinant ES has been in clinical use in some solid cancers in China. Ribonucleic acid (RNA) interference-mediated silencing of VEGF and bFGF suppresses ES secretion in pancreatic carcinoma cells.[14] High levels of ES have occasionally been correlated with poorer survival. The balance between pro-angiogenic and anti-angiogenic factors determines whether endothelial cells stay in a state of angiogenic homeostasis, or move on to the state of neovascularization, instigating tumor proliferation, migration, and metastasis.[15]

The primary purpose of this study was to characterize NSCLC with VEGF, bFGF, and ES serum levels and to evaluate the effect of these markers on the prognosis of NSCLC patients.

Patients

From February 2007 to July 2008, 96 patients who consecutively underwent curative pulmonary surgery at the Department of Thoracic Surgery at the Beijing Chest Hospital were included in this study. All patients were confirmed as NSCLC by pre-operative biopsy and postoperative tumor tissue. Chest computed tomography examinations, ultrasound scanning, radioisotope bone scans, brain magnetic resonance imaging, and blood examinations were selectively performed when necessary to determine clinical stage. Tumors removed during surgery were examined and staged based on TNM descriptions and the stage grouping system of the International Association for the Study of Lung Cancer. Pathological stage was distributed as follows: IA in 22, IB in 22, IIA in 11, IIB in four, and IIIA in 37 patients. The histological type in this study included 36 adenocarcinoma, 51 squamous carcinoma, seven adeno-squamous carcinoma, and two large cell carcinoma. At diagnosis, 37 cases (38.5%) had developed lymph node invasion. Clinical and pathological features are summarized in Table 1, including 80 men and 16 women with

Table 1 Patients and tumor characteristics

Characteristics	Number (%)
Median age (range)	61 (36–84)
Gender	
Male	80 (83.3)
Female	16 (16.7)
Smoking status	
Current or ever	69 (71.9)
Never	27 (28.1)
TNM Stage	
I	44 (45.8)
II	15 (15.6)
III	37 (38.5)
Tumor stage	
T1	34 (35.4)
T2	50 (52.1)
T3	8 (8.3)
T4	4 (4.2)
Node invasion	
N0	59 (61.5)
N1	5 (5.2)
N2	32 (33.3)
Tumor size (cm, range)	4.1 (1.2–8.5)
Tumor location	
Left main bronchus	1 (1.0)
Left upper lobe	19 (19.8)
Left lower lobe	14 (14.6)
Right upper lobe	35 (36.5)
Right middle lobe	9 (9.4)
Right lower lobe	18 (18.8)
Histology type	
Adenocarcinoma	36 (37.4)
Squamous carcinoma	51 (53.1)
Adeno-squamous carcinoma	7 (7.3)
Large cell carcinoma	2 (2.1)
Resection margin	
Negative	87 (80.6)
Positive	9 (9.4)
Surgical treatment	
Wedge lobectomy	4 (4.2)
Lobectomy	76 (78.9)
Pneumonectomy	16 (16.8)
Adjuvant chemotherapy	
Yes	56 (58.3)
No	40 (41.7)

TNM, tumor node metastasis.

a median age of 61 (range 36–84 years). Patients who survived less than two months after surgery or with a tumor history within the last five years were not included. None of the patients received pre-operative treatment in this cohort. In addition, 51 blood samples from healthy donors verified by physical exam and matched by gender and age were chosen as the control group. This study was conducted according to the principles of the Declaration of Helsinki and approved by the ethical committees of the Beijing Chest Hospital, Capital Medical University. All participants signed written informed consent. Cause-specific overall survival (OS) was defined as the time from primary surgery until death as a result of lung cancer or the date of last follow-up. The follow-up time ranged from three to 87 months. During this period, all recruited patients had been followed. By the time of the final analysis, 56 (58.3%) patients had died, including one non-cancer related death.

Blood samples and enzyme-link immunosorbent assay examination

For blood examinations, 3 mL of peripheral venous blood was drawn prior to surgery into commercially available ethylenediaminetetraacetic acid tubes (Greiner Bio-One Gmbh, Kremsmunster, Austria) and allowed to stand for at least 30 minutes at room temperature to ensure complete clotting. Blood samples were then centrifuged at 3000 rpm for 15 minutes and the supernatant was stored at −80°C until required for analysis. Serum ES, bFGF, and VEGF concentrations from patients and healthy controls were determined in duplicate using a quantitative sandwich enzyme immunoassay technique (bFGF and ES, R&D Systems, Minneapolis, MN, USA; VEGF, Jingmei Technology, Beijing, China). The mean optical density was used to calculate concentration from the standard curve. All procedures were carried out strictly according to the manufacturers' instructions.

Statistical analysis

Statistical analysis was conducted using SPSS 16 software (SPSS, Inc., Chicago, IL, USA). Because of the asymmetric distributions of VEGF, bFGF, and ES, continuous data were expressed as median and interquartile range (IQR). Categorical data were compared by chi-square or Fisher's exact tests. Comparisons of continuous variables between the two groups were performed using the Mann–Whitney test. The Kruskal-Wallis test was used in cases of multiple groups. Linear correlations were assessed by calculating the non-parametric Spearman's rho. The patient who died from non-cancer related factors was censored in survival analysis. Serum VEGF, bFGF, and ES were first examined as continuous variables in univariate Cox regression survival analysis. Then, the first, second, and third quartiles were examined as possible thresholds because there had been no identification of a widely accepted cut-off. If a cut-off point showed prognostic significance, it was used to dichotomize the samples into low and high groups. Multivariate analysis was performed with a backward stepwise Cox proportional hazard model to screen the independent predictors. $P < 0.05$ was considered statistically significant (two-sided).

Results

Serum vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and endostatin (ES) concentrations in non-small cell lung cancer

The median serum VEGF, bFGF, and ES concentrations were 722.7 pg/mL (IQR, 457.6–1090.2 pg/mL), 18.8 pg/mL (IQR, 12.6–26.5 pg/mL), and 69.5 ng/mL (IQR, 53.8–83.2 ng/mL), respectively, in NSCLC. The levels measured in lung cancer patients were higher than those found in the controls, who had median serum levels of 367.3 pg/mL (IQR, 209.9–557.7 pg/mL), 12.5 pg/mL (IQR, 6.5–23.4 pg/mL), and 52.1 ng/mL (IQR, 45.5–83.1 ng/mL), respectively. The levels were significantly higher in the NSCLC than in the control group ($P < 0.001$, $P = 0.009$, and $P = 0.016$ Table 2).

Correlations of VEGF, bFGF, and ES concentration with clinical data

As shown in Table 3, pre-operative VEGF was significantly associated with gender ($P = 0.017$) and smoking status ($P = 0.014$). However, the difference between VEGF level and smoking status disappeared when analysis was performed separately in the male or female subgroups. High serum VEGF and ES levels tended to occur in the same patients ($P = 0.051$). bFGF concentration correlated marginally with lymph node invasion ($P = 0.068$).

Univariate survival analysis

As continuous variables, serum VEGF and ES did not show any correlation with OS, while a significant positive

Table 2 Comparison of serum levels of VEGF, bFGF and ES between patients and controls

Variables	Groups	N	Median	IQR	*P*
VEGF (pg/mL)	Patients	96	722.7	457.6–1090.2	<0.001
	Control	51	367.3	209.9–557.7	
bFGF (pg/mL)	Patients	96	18.8	12.6–26.5	0.009
	Control	51	12.5	6.5–23.4	
ES (ng/mL)	Patients	96	69.5	53.8–83.2	0.016
	Control	51	52.1	45.5–83.1	

bFGF, basic fibroblast growth factor; ES, endostatin; IQR, interquartile range; VEGF, vascular endothelial growth factor.

Table 3 The relationship between preoperational serum VEGF, bFGF, ES and clinicopathologic parameters in NSCLC

	VEGF		bFGF		ES	
Variables	Median (IQR)	*P*	Median (IQR)	*P*	Median (IQR)	*P*
Gender						
Male	831.90 (500.48–1127.28)	0.017[a]	18.78 (12.78–26.45)	0.825[a]	67.10 (53.25–83.33)	0.387[a]
Female	504.20 (107.20–629.23)		22.41 (11.84–30.50)		70.50 (59.45–90.43)	
Smoking status						
Current or Ever	815.10 (508.48–1181.15)	0.014[a]	18.68 (12.36–26.33)	0.494[a]	69.50 (53.30–83.15)	0.961[a]
Never	508.40 (130.50–867.30)		21.54 (12.64–29.38)		67.30 (56.20–85.30)	
TNM						
I	852.90 (504.58–1090.15)	0.451[b]	17.74 (11.42–23.89)	0.090[b]	69.00 (54.68–85.25)	0.269[b]
II	701.70 (504.20–1307.30)		14.91 (13.40–26.46)		83.50 (53.20–97.50)	
III	555.80 (367.60–1112.4)		22.50 (15.29–31.28)		64.30 (53.05–78.00)	
Node invasion						
N0	831.90 (528.20–1090.15)	0.117[a]	16.79 (12.07–25.90)	0.068[a]	69.65 (53.70–92.85)	0.305[a]
N1–2	525.20 (341.80–1127.33)		22.03 (15.10–29.34)		66.35 (54.00–78.00)	
Tumor stage						
T1	722.70 (412.88–1087.05)	0.935[b]	17.93 (11.99–26.17)	0.230[b]	67.45 (55.43–81.60)	0.468[b]
T2	722.70 (501.43–1089.48)		18.78 (12.20–25.08)		70.70 (53.50–86.38)	
T3&T4	775.25 (204.13–1826.83)		28.08 (15.33–37.52)		59.40 (48.98–78.53)	
Histological type						
Adenocarcinoma	718.50 (502.48–1065.38)	0.689[a]	16.79 (11.42–23.36)	0.469[a]	69.65 (56.65–82.40)	0.907[a]
SCC	722.70 (393.90–1197.20)		18.68 (12.26–29.23)		70.10 (53.40–85.30)	
Margin						
Positive	760.50 (499.60–1074.85)	0.980[a]	21.54 (14.11–75.71)	0.715[a]	70.10 (62.45–79.35)	0.782[a]
Negative	722.70 (434.60–1123.90)		18.87 (12.45–26.51)		68.50 (53.20–85.30)	
bFGF		0.788[c]				
ES		0.051[c]		0.727[c]		

[a]*P* value is calculated by Mann–Whitney test. [b]*P* value is calculated by Kruskal-Wallis test. [c]*P* value is calculated by Spearman's correlation. bFGF, basic fibroblast growth factor; ES, endostatin; IQR, interquartile range; NSCLC, non-small cell lung cancer; SCC, squamous carcinoma; TNM, tumor node metastasis; VEGF, vascular endothelial growth factor.

association between higher bFGF and a poorer prognosis was found (hazard ratio [HR] = 1.009, $P = 0.001$). Different cut-off points were examined to stratify the samples in order to ensure that the conclusion had realistic significance. Finally, the third quartile was used to dichotomize the sample into high and low groups as a cut-off point. High serum bFGF (>26.54 pg/mL) was a significant predictor of shorter OS (HR = 1.863, 95% confidence interval [CI], 1.049–3.309, Table 4). The median survival time in the high group was 17 months, compared to 58 months in the low group. Stratification by other values did not display statistical significance. The OS of the whole group was 83.3% at one year, 60.4% at three, and 44.8% at five years. The comparison between high and low groups divided by the third quartile was 70.8% *versus* 87.5% at one year, 37.5% *versus* 68.1% at three, and 29.2% *versus* 50.0% at five years (Table 5). The influence of gender, smoking status, age, T stage, N stage, histological type, TNM stage, resection margin, and adjuvant chemotherapy details on OS were analyzed in a univariate Cox proportional hazard model (Table 6). As expected, T, N, and TNM stages also showed statistical significance in univariate analysis.

Table 4 Univariate survival analysis of serum VEGF, bFGF and ES level as continuous and categorical variables

	VEGF		bFGF		ES	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Continuous	1.000 (1.000–1.001)	0.304	1.009 (1.003–1.014)	0.001	0.992 (0.981–1.002)	0.125
Categorical						
First quartile	1.361 (0.702–2.637)	0.361	1.604 (0.845–3.044)	0.148	0.720 (0.397–1.306)	0.280
Second quartile	1.317 (0.774–2.240)	0.310	1.458 (0.858–2.477)	0.163	1.037 (0.611–1.760)	0.892
Third quartile	1.342 (0.741–2.431)	0.332	1.863 (1.049–3.309)	0.034	0.733 (0.386–1.391)	0.342

bFGF, basic fibroblast growth factor; CI, confidence interval; ES, endostatin; HR, hazard ratio; VEGF, vascular endothelial growth factor.

Table 5 Survival rate at one, three and five years in terms of different bFGF serum levels

Variables	One-year survival rate (%)	Three-year survival rate (%)	Five-year survival rate (%)
Whole	83.3	60.4	44.8
bFGF			
High	70.8	37.5	29.2
Low	87.5	68.1	50.0

Serum levels above the third quartile were identified as basic fibroblast growth factor "(bFGF)-high," while serum levels below the third quartile were identified as "bFGF-low."

To fully explore the prognostic value of the serum bFGF level, subgroup analysis was conducted. Patients with squamous carcinoma, smoking history or in stage III, with a serum bFGF level above the cut-off point indicated worse five-year OS survival (Table 7). It is noteworthy that a high bFGF level in the squamous subtype showed a particularly poor prognosis (HR = 2.609, 95% CI, 1.188–5.729).

Multivariate survival analysis

To explore prognostic factors affecting OS, three factors that were significant prognostic factors in univariate analysis (T stage, N stage, and serum bFGF level) were entered into the multivariate Cox proportional hazard model by backward stepwise method. T and N stages correlated significantly with TNM stage, so the pooled TNM stage, so pooled TNM stage was not chosen in this analysis. T stage, N stage, and bFGF level all remained significant in multivariate analysis (Table 6). A high bFGF level was an independent predictor of poor survival (HR = 1.918, 95% CI, 1.061–3.464).

Table 6 Univariate and multivariate analysis for survival predictors in NSCLC

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
≥61				
<61	0.916 (0.539–1.556)	0.745		
Gender				
Female				
Male	1.206 (0.590–2.465)	0.608		
Smoking status				
Non-smoking				
Smoking	1.346 (0.733–2.471)	0.338		
T stage				
T1				
T2	1.645 (0.882–3.071)		2.800 (1.255–6.427)	
T3&T4	5.715 (2.553–12.790)	<0.001	4.985 (2.638–9.420)	0.002
N stage				
N0				
N1–2	2.649 (1.553–4.518)	<0.001	2.409 (1.384–4.191)	0.002
Histological type				
Non-SCC				
SCC	0.712 (0.419–1.211)	0.210		
bFGF				
Low				
High	1.863 (1.049–3.309)	0.034	1.918 (1.061–3.464)	0.031
TNM stage				
I				
II	2.893 (1.297–6.450)			
III	4.858 (2.586–9.126)	<0.001		
Resection margin				
Negative				
Positive	1.294 (0.554–3.024)	0.551		
Adjuvant chemotherapy				
No				
Yes	0.834 (0.490–1.419)	0.503		

Serum levels above the third quartile were identified as basic fibroblast growth factor "(bFGF)-high," while serum levels below the third quartile were identified as "bFGF-low." CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; SCC, squamous carcinoma; TNM, tumor node metastasis.

Table 7 Five-year survival rate in terms of bFGF levels in different subgroups

Clinical features	Five-year overall survival rate		
	bFGF- low	bFGF- high	*P*
Smoking status			
Current or Ever	48.1	17.6	0.027[a]
Never	55.0	57.1	1.000[b]
Histological type			
SCC	61.1	26.7	0.025[a]
Non-SCC	38.9	33.3	1.000[b]
N stage			
N0	63.6	43.8	0.711[a]
N1–2	33.3	0	0.076[b]
TNM stage			
I & II	60.4	63.6	0.843[a]
III	29.2	0	0.038[b]

Serum levels above the third quartile were identified as basic fibroblast growth factor "(bFGF)-high," while serum levels below the third quartile were identified as "bFGF-low." [a]*P* value is calculated by Chi-square test. [b]*P* value is calculated by Fisher's exact test. SCC, squamous carcinoma; TNM, tumor node metastasis.

Discussion

With the molecular biology analysis conducted in recent years, angiogenesis has attracted attention and further understanding has been gained in this field, although not all reports have been consistent. VEGF is the most frequently studied member. In a meta-analysis that included 5386 patients with NSCLC from 51 studies, combined HRs suggested that VEGF overexpression had an unfavorable impact on survival of NSCLC and small cell lung cancer patients.[16] Published studies on circulating VEGF and its impact on survival in NSCLC are less frequent than those assessing tumor bFGF expression. Some studies revealed an inverse association between circulating levels and survival. Other studies did not find any correlation between circulating VEGF and survival.[17] Our present study showed that VEGF was not a good index in risk stratification in NSCLC. ES, as the most potent anti-angiogenic factor, did not reveal a clinical value in adding prognostic information to the TNM system in this study.

Basic fibroblast growth factor is a potent mitogen and a survival factor in many experimental models that are of potential relevance in cancer biology.[18,19] The FGFRs binding to FGF lead auto phosphorylation of intracellular tyrosine residues, subsequently activating various signaling pathways downstream of FGFR, which is involved in cell migration, cell differentiation, and instigating tumor cell proliferation, invasion, and survival in various tumor types.[20] bFGF upregulates the expression of matrix metalloproteinase-1 (MMP-1),[21] hepatocyte growth factor,[21] B-cell lymphoma 2,[22] Survivinv,[23] MMP9, and –13[24] and resulted in a gain of invasive and anti-apoptosis properties. In the present study, serum bFGF was higher in patients with relatively advanced TNM stage; therefore, bFGF could reflect a more aggressive phenotype. In addition, the FGF pathway may serve as an angiogenic growth factor pathway that allows the tumor to escape VEGF inhibition.[25]

Although pre-operational levels of serum VEGF, bFGF, and ES were remarkably higher than in healthy controls, only an increased bFGF level was correlated with poor survival. Of five studies on the prognostic value of circulating bFGF, three studies reported a negative prognostic impact (which was supported by our study), one indicated bFGF as a good prognostic factor, and one was inconclusive.[15] According to earlier *in vivo* and *in vitro* studies, these results were explainable. VEGF and bFGF are both essential for tumor growth, progression, and metastasis and they demonstrate a synergistic effect;[26] however, their expression has possibly altered over time. VEGF as the primary crucial pro-angiogenic factor initiates the angiogenesis switch, but is not of first importance to the whole process. When the tumors have reached a certain size, other angiogenic factors, such as bFGF and transforming growth factor alpha, can substitute adequately for VEGF.[27,28] In our study, VEGF failed to be a useful marker of long-term survival. Patients with lower FGF levels showed a significantly longer median survival time (17 vs. 58 months). When tested in the Cox proportional hazard model, the bFGF level remained statistically significant, as well as the TNM stage. When subgroup analysis was performed in squamous lung cancer patients, a higher bFGF concentration was clearly observed in cases with shorter survival. A similar conclusion was found in stage III patients. To date, the proliferative dependency of FGF-FGFR signaling has predominantly been observed in squamous and large cell lung cancer cell lines that are frequently intrinsically resistant to EGFR inhibitors and prohibited in use of bevacizumab (Avastin) because of the risk of hemorrhage.[29–31] Anaplastic lymphoma kinase inhibitor crizotinib was largely confined to an adenocarcinoma subtype.[32] Upregulation of the FGF2 and FGFR3 genes in an established xenograft model possessing acquired resistance to bevacizumab was reported, while inhibition of the FGFR in resistant tumors led to the restoration of sensitivity to bevacizumab.[33] There is a paucity of personalized targeting treatment of squamous lung cancer, which constitutes the major histology type of NSCLC. Research performed on the bFGF pathway will hopefully create a breakthrough in the search for targeted therapy in squamous NSCLC.[34] In this study, the cut-off value of 26.54 pg/mL produced a more distinct survival difference in the squamous holotype. FGF signaling inhibitors should be further explored because of the survival difference, especially in squamous lung cancer. In general, more aggressive anti-tumor treatment (radio or chemotherapy) is needed to improve the survival of NSCLC patients carrying higher bFGF levels, particularly those with a squamous subtype or advanced TNM stage.

The identification of such factors is of pivotal importance for the further improvement of NSCLC prognosis and might facilitate an individual risk-benefit assessment for treatment strategies. More intensive therapy should be scheduled for patients with squamous lung cancer or advanced stage with higher bFGF levels. A reliable identification with an angiogenic-related factor would not only be desirable for risk assessment, but also for the implementation of angiogenesis targeted treatment. Currently, several FGF pathway inhibitors are being investigated in clinical trials. How do we determine the population responsive to FGF signaling targeted agents? The answer remains unclear.

The significant difference between the two groups indicates that angiogenic factors are involved in either the cause or systemic response to the malignancy.[15] Poor survival of lung cancer is largely a result of the lower efficiency of early diagnosis. Considering nonspecific complaints of lung cancer in early stage and especially the poor prognosis, novel screening tools are urgently needed to assist doctors screening lung cancers, in order to improve patients' outcome. Tumor markers in daily clinical use, such as carcinoembryonic antigen, neuron-specific enolase, squamous cell carcinoma antigen, and cytokeratin 19 fragments 21-1, were not sensitive or specific enough to screen for early stage lung cancer. These angiogenic serum cytokines could be studied deeply for diagnostic ability as screening markers.

In contrast to circulating serum evaluation, immunohistochemical examination of these factors in tumor tissue is reduced by the availability of adequate surgical specimens. A determination of circulating angiogenic markers, as a non-invasive and observer-independent method, could theoretically reflect the overall angiogenic activity of the tumor burden and assist doctors with therapy schedules according to individual angiogenic factor expression levels.

Our study is limited by the relatively small sample size; studies with larger samples should be conducted to verify our conclusion.

Conclusion

We conclude that a high serum bFGF level was associated with poor survival in NSCLC patients. A circulating bFGF level had a more significant prognostic influence to squamous lung cancer and stage III cases. Because there have been limited studies conducted in circulating bFGF in NSCLC, confirmatory studies need to be carried out before its use in clinical decision-making.

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Conflict of interest

No authors report any conflict of interest.

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