Fibroblast Growth Factor Receptor 1 Gene Amplification in Nonsmall Cell Lung Cancer

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Abstract

Objective: To review the prevalence and prognostic significance of fibroblast growth factor receptor 1 (FGFR1) amplification and to establish an association between FGFR1 amplification and the clinical characteristics of nonsmall cell lung cancer (NSCLC).

Data Sources: We searched PubMed for English-language studies published between January 2010 and May 2016.

Study Selection: We included all relevant articles, with no limitation of study design.

Results: FGFR1 amplification was reported in 8.7–20.0% of NSCLC cases and was significantly more frequent in squamous cell carcinomas (SCCs) (9.7–28.3%) than in adenocarcinomas (ADCs) (0–15.0%). The rates of FGFR1 amplification were as follows: males, 13.9–22.1%; females, 0–20.1%; Stage I NSCLC, 9.3–24.1%; Stage II NSCLC, 12.9–25.0%; Stage III NSCLC, 8.2–19.5%; Stage IV NSCLC, 0–12.5%; current smokers, 13.3–29.0%; former smokers, 2.5–23.0%; and nonsmokers, 0–22.2%. Overall survival was 43.9–70.8 months in patients with FGFR1 amplification and 42.4–115.0 months in patients with no FGFR1 amplification; disease-free survival was 22.5–58.5 months and 52.4–94.6 months, respectively.

Conclusions: FGFR1 amplification is more frequent in SCCs than in ADCs. The association between FGFR1 amplification and clinical characteristics (gender, smoking status, and disease stage) and the prognostic significance of FGFR1 amplification in NSCLC remain controversial.

Key words: Fibroblast Growth Factor Receptor 1; Gene Amplification; Lung Cancer; Prognosis

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related mortality despite improved diagnosis and therapy.¹ Non-small cell lung cancer (NSCLC) accounts for 75% of all lung cancers and includes two predominant subtypes, adenocarcinoma (ADC) and squamous cell carcinoma (SCC), which comprise 40% and 25% of NSCLCs, respectively. Due to the lack of specific symptoms, most lung cancer patients are in the mid or late stage of the disease when they were diagnosed. Although diagnostic approaches, treatment techniques, and surgical levels toward lung cancer treatment have been improved greatly in recent years, most lung cancer patients still have bad prognosis, with 5-year survival rates fluctuating around 15%.² It is of great significance in treatment selection and patient survival rate increase to look for factors relevant to lung cancer prognosis.

Fibroblast growth factor receptor 1 (FGFR1) has been identified as one of the emerging molecular targets for the treatment of SCC of the lung,³–⁵ and several early-phase clinical trials of FGFR1 inhibitors are currently being undertaken in NSCLC.⁶–⁸ Alterations of the FGFR gene have been recognized in many epithelial malignancies, including amplifications in gastric, breast, oral squamous cell, ovarian, and bladder carcinomas,⁹,¹⁰ and more recently in squamous NSCLC. Previous studies of FGFR1 amplification in lung cancer have focused on SCC.¹¹–¹³ This review summarizes the current knowledge of FGFR1 amplification in nonsmall cell lung cancer.

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amplifications in the main subtypes of NSCLC. The next sections describe the prevalence and prognostic significance of FGFR1 amplification and report the clinical characteristics associated with FGFR1 amplification in NSCLC.

**ROLE OF FIBROBLAST GROWTH FACTOR RECEPTOR 1 IN ONCOGENESIS**

FGFR1 is a member of the Type 4 family of receptor tyrosine kinases, which consists of the closely related and highly conserved FGFRs 1–4. All these proteins are transmembrane receptors composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular part that contains the functionally relevant tyrosine kinase domain. Constitutive activation of FGFR1 occurs basically by three major mechanisms: gene amplification, translocation, or activating mutations. Compared to FGFR gene mutation and translocation, gene amplification of FGFR is most well studied. FGFR1 amplification is associated with poor prognosis[14] and one of the most frequent genetic changes in breast cancer.[15,16] Amplification of FGFR1 has additionally been reported in SCC of the head and neck (17%) as well as of the esophagus (28.6%).[17,18] Translocations of FGFR1 have originally been described in a myeloproliferative hematological disorder which has now been referred to as an “8p11 myeloproliferative syndrome characterized by FGFR1 translocation” by the current WHO classification system. Very recently, FGFR1 translocations have been additionally found in a subset of glioblastoma multiforme and in rhabdomyosarcoma.

The important advances achieved over the past decade through identifying oncogenic mutations in lung ADC have led to several efforts to screen for targetable oncogenes in SCC of the lung. FGFR1 amplification has been detected in SCC of the lung, with lower frequency in lung ADC.[19,20] Lung cancer cells harboring FGFR1 amplification exhibit a highly tumorigenic phenotype, and FGFR1 regulates the stem cell-like phenotype of SCC of the lung.[21]

**DETECTION OF FIBROBLAST GROWTH FACTOR RECEPTOR 1 AMPLIFICATION BY FLUORESCENCE IN SITU HYBRIDIZATION**

There are currently no validated antibody assays on the market, which could reliably detect FGFR1 expression levels quantitatively or semiquantitatively using paraffin-embedded tumor samples. Reliable FGFR1 fluorescence in situ hybridization (FISH) probes are now commercially available. In this review, we focused on the detection of FGFR1 amplification by FISH. In FISH, the FGFR1 gene locus is labeled with a green fluorochrome and the centromeric reference probe (CEN8) is labeled with an orange fluorochrome. Before hybridization, samples are cut into 5-μm sections, deparaffinized, and pretreated with the commercial pretreatment kit Vysis. Hybridization is performed overnight in a humidified chamber at 37°C.

Next, slides are washed with Vysis washing solution and counterstained with 4’,6-diamidino-2-phenylindole.

We searched PubMed for English-language studies published between January 2010 and May 2016 using the terms “FGFR1” OR “fibroblast growth factor receptor 1” and “lung cancer” OR “lung carcinoma” or combinations thereof, and the references cited in the identified studies or reviews were also used to complete the search. The variability of FGFR1 amplification rates as determined by FISH is related to differences in the definition of a positive result and in interpretation of results. Table 1 shows the results of the literature search about FGFR1 amplification cutoff values and methods.

**FIBROBLAST GROWTH FACTOR RECEPTOR 1 AMPLIFICATION IN NONSMALL CELL LUNG CANCER EPIDEMIOLOGY**

FGFR1 is one of the most frequently amplified genes in human cancer. Many researchers studied the prevalence of FGFR1 amplification in patients with NSCLC. Table 2 shows results of our literature search. From January 2010 to May 2016, 11 studies were identified and included in the final analysis. Statistics were not included for three of those studies due to alternative diagnoses focusing on SCC. In those three studies, FGFR1 amplification rates were 13.0% (34/262), 18.2% (22/121), and 16.0% (37/226).[19,21,24] FGFR1 amplification was reported in 8.7–20.0% of NSCLC cases. FGFR1 amplification was significantly more frequent in SCCs (9.7–28.3%) than in ADCs (0–15.0%).

The prevalence of FGFR1 amplification was 30.0% (3/10) in pleomorphic carcinomas[4] and 13.0% (3/23) in large cell carcinoma (LCC).[25] Russell et al.[27] confirmed that...
**FGFR1** amplification was 16.7% (1/6) and 21.7% (5/23) in pleomorphic carcinomas and LCC, respectively.

**Association between Fibroblast Growth Factor Receptor 1 Amplification and Clinical Characteristics**

The following clinical characteristics were extracted from each study: gender, smoking status, and disease stage. When referring to smoking status, we defined never smokers as adults who never smoked or smoked fewer than 100 cigarettes in their lifetime; former smokers were those who smoked at least 100 cigarettes but currently do not smoke; current smokers were people who smoked 100 cigarettes in their lifetime and currently smoke. Nonsmokers were defined as both former smokers and never smokers. 

Seven studies were identified and included in the final analysis [Table 3]. **FGFR1** amplification was reported in 13.9–22.1% of male NSCLC patients and in 0–20.1% of female NSCLC patients. Cihoric et al.[25] and Russell et al.[27] found that **FGFR1** amplification was significantly more frequent in male patients (14.8% and 17.1%, respectively) compared with female patients (5.9% and 8.5%, respectively).

**FGFR1** amplification occurred in 13.3–29.0% of current smokers, 2.5–23.0% of former smokers, and 0–22.2% of never smokers. Kim et al.[19] Craddock et al.[23] and Russell et al.[27] reported that the frequency of **FGFR1** amplification was significantly higher in current smokers than in former smokers and never smokers. As the smoking dosage increased, so did the rate of **FGFR1** amplification. However, the remaining studies considered that there was no significant correlation between **FGFR1**-positive status and other clinicopathological features including smoking history. **FGFR1** amplification occurred in 9.3–24.1% of Stage I (IA and IB), 12.9–25.0% of Stage II (IIA and IIB), 8.2–19.5% of Stage III (IIIA and IIB), and 0–12.5% of Stage IV NSCLC cases. Cihoric et al.[25] found a significant correlation between higher tumor stage and **FGFR1** amplification rate. However, the remaining studies found contradictory results.

**Discussion**

The ability to identify target oncogenic alterations in NSCLC has been a major advance in the management of patients. An important aspect of translating these molecular alterations into clinical practice is to develop assays that can quickly and reliably identify specific aberrations in clinical specimens. **FGFR1** has recently emerged as a promising target in NSCLC. Our review reports that the prevalence of **FGFR1** amplification was 8.7–20.0% in NSCLC and was significantly higher in SCC (9.7–28.3%) than in ADC (0–15.0%). The prevalence of **FGFR1** amplification was 13.0–21.7% in LCCs and 16.7–30.0% in pleomorphic carcinomas.

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**Table 2: Prevalence of FGFR1 amplification in nonsmall cell lung cancer (%)**

| Author            | NSCLC (%) | SCC (%) | ADC (%) |
|-------------------|-----------|---------|---------|
| Sousa et al.[24]  | 15/76 (20.0) | 5/24 (21.0) | 5/34 (15.0) |
| Cihoric et al.[25] | 41/329 (12.5) | 35/169 (20.7) | 3/137 (2.2) |
| Toschi et al.[26]  | 74/445 (16.6) | 39/138 (28.3) | 28/243 (11.5) |
| Seo et al.[27]     | 32/369 (8.7) | 25/139 (18.0) | 7/230 (3.0) |
| Russell et al.[28] | 50/352 (14.2) | 40/178 (22.5) | 0/97 (0) |
| Tran et al.[29]    | 49/264 (18.0) | 25/101 (24.8) | 13/115 (11.3) |
| Weiss et al.[30]   | – | 15/155 (9.7) | 1/77 (0.1) |
| Schildhaus et al.[31] | 60/400 (15.0) | 58/290 (20.0) | 0/97 (0) |

**FGFR1**: Fibroblast growth factor receptor 1; NSCLC: Nonsmall cell lung cancer; SCC: Squamous cell lung cancer; ADC: Adenocarcinoma; –: Not applicable.

**Table 3: Rate of FGFR1 amplification according to clinical characteristics of patients with nonsmall cell lung cancer**

| Author              | Sex (%) | C | F | N | I | II | III | IV |
|---------------------|---------|---|---|---|---|----|-----|----|
| Cihoric et al.[25]  | Male    | 14.8 | 13.8* | – | 5.6 | 9.3 | 22.0 | – |
| Toschi et al.[26]   | Female  | 5.9  | –    | 5.6 | 9.3 | 22.0 | –   | – |
| Russell et al.[27]  | Male    | 17.3 | 17.8* | – | 7.5 | 16.2 | –    | 17.0 | – |
| Tran et al.[29]     | Female  | 13.0 | –    | 7.5 | 16.2 | –    | 17.0 | – |
| Kim et al.[30]      | Male    | 17.1 | 17.4 | 17.5 | 2.9 | 14.8 | 17.2 | 8.2 | 12.5 |
| Craddock et al.[31] | Female  | 20.1 | 21.8* | – | 0 | 18.1 | 18.6 | 19.5 | – |
| Heist et al.[32]    | Male    | 13.9 | 29.0 | 25.0 | 0 | 10.3 | 16.7 | 14.1 | – |
|                    | Female  | 22.1 | 16.3 | 23.0 | 0 | 24.1 | 12.9 | 13.8 | 0 |

*Former or current smoker; †Stage I or II; ‡Stage III or IV. **FGFR1**: Fibroblast growth factor receptor 1; C: Current smoker; F: Former smoker; N: Never smoker; –: Not applicable.
There was no consistent relationship between FGFR1-positive status and clinical characteristics across studies. Most researchers reported that FGFR1 amplification was significantly more frequent in male patients compared with female patients and that the prevalence of smoking history was higher among patients with FGFR1 amplification than among those without. However, other researches reported no significant correlation between FGFR1-positive status and clinical features including gender, smoking history, and disease stage.

The prognostic significance of FGFR1 amplification in NSCLC was also inconsistent. Cihoric et al. reported that FGFR1 amplification is common in early-stage SCC of the lung and is an independent and adverse prognostic marker. Kim et al. also reported that patients with FGFR1 amplification had significantly shorter overall survival and DFS than those without FGFR1 amplification. On the contrary, Russell et al. compared overall survival and DFS between surgically radically treated patients with pure SCC and found no significant difference in overall survival in surgically radically treated patients stratified by stage and FGFR1 amplification status. However, Tran et al. reported that FGFR1 amplification-positive patients show a tendency toward longer overall survival in univariate analysis. These inconsistent results may be caused by a variety of reasons: (1) The sample size in various series was too small to draw definitive conclusions. (2) The studies included patients with different disease stages. (3) The cutoff values were different across studies. Larger, multicenter studies will help clarify the prognostic significance of FGFR1 amplification in NSCLC.

FGFR1 has been discussed as a possible new therapeutic target. Therefore, FGFR1 amplification status should be evaluated prospectively in patients with lung SCC, LCC, and ADC. As patients with lung SCC have only limited options regarding systemic therapies, they might profit from a targeted therapy. Now, treatment with dovitinib demonstrated modest efficacy in patients with advanced SCC with FGFR1 amplification. In contrast to targeted therapy development in lung ADC, trials targeting FGFR1 in lung SCC have been generally disappointing. Gene amplification or overexpression of this target may not be a sufficiently robust predictor of efficacy for FGFR1 inhibitors. Therefore, the value of FGFR1 amplification in NSCLC has to be determined in further studies.

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**Conflicts of interest**

There are no conflicts of interest.

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