Caspian Journal of Internal Medicine 2025 (Winter); 16(1): 66-72
DOI: 10.22088/cjim.16.1.66

Original Article

Fibroblast growth factor receptor 1 gene (FGFR1) amplification in non-small cell lung cancer (NSCLC) by real-time PCR

Sanaz Homayounfar (MD) [1]
Hossein Ayatollahi (MD) [2]
Gordon Ferns (MD) [3]
Reza Hemmatan Attarbashi (DVM) [2]
Masoumeh Gharib (MD) [4]
Maryam Sheikhi (Msc) [2]
Zahra Khoshnegah (PhD) [5]
Payam Siyadat (PhD) [6]
Amirhossein Jafarian (MD) [2*]

1. Department of Pathology, Mashhad University of Medical Sciences, Mashhad, Iran
2. Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3. Division of Medical Education, Brighton and Sussex Medical School, Brighton, UK
4. Departments of Infectious Diseases and Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
5. Department of Laboratory Hematology and Blood Banking, Faculty of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran
6. Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran

*** Correspondence:**
Amirhossein Jafarian, Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

E-mail: jafarianah@mums.ac.ir
Tel: +98 5138012584

Received: 14 Oct 2023
Revised: 8 Nov 2023
Accepted: 30 Jan 2024
Published: 19 Oct 2024

Abstract

Background: Comprehensive molecular assessment of cancers could open up new horizons for novel therapies. Fibroblast growth factor receptor 1 (FGFR1) gene amplification has been previously demonstrated in non-small cell lung cancer (NSCLC) patients. The current study aimed to evaluate the prevalence of FGFR1 gene amplification and its association with clinical and demographic data in a group of NSCLC patients.

Methods: The present study was performed on eighty-eight NSCLC patients who underwent bronchoscopy or surgery in Qaem Hospital, Mashhad, between 2010 and 2016. FGFR1 gene amplification was detected using real-time PCR assay on DNA extracted from paraffin-embedded tissue blocks of patients. Also, patients' clinical and demographic data, such as their survival, were evaluated. Statistical analysis was carried out using SPSS software.

Results: Seventeen (19.31%) out of eighty-eight patients with NSCLC presented FGFR1 gene amplification. Besides, we found a significant association between FGFR1 amplification and cigarette smoking (p-value= 0.01; OR: 4.08). Although cases with squamous cell carcinoma (SCC) showed a higher prevalence of FGFR1 amplification compared to adenocarcinoma patients, the difference was not statistically significant (p-value> 0.05). In addition, our findings showed no relationship between FGFR1 gene amplification and other clinical and demographic factors, including age, sex, grade, tumor operability, and survival.

Conclusion: The frequency of FGFR1 amplification is estimated at 20% in the current study (26% in SCC versus 11% in adenocarcinoma; p-value= 0.07). Moreover, we found a direct association between FGFR1 amplification and cigarette smoking. However, no significant relationship with survival or other factors was observed.

Keywords: FGFR1, Fibroblast growth factor receptor 1, Real-time PCR, Non-small cell lung cancer, Gene amplification.

Citation:
Homayounfar S, Ayatollahi H, Ferns G, et al. Fibroblast growth factor receptor 1 gene (FGFR1) amplification in non-small cell lung cancer (NSCLC) by real-time PCR. Caspian J Intern Med 2025; 16(1): 66-72.

Lung cancer has one of the highest incidence and mortality rates among cancers worldwide. Despite decades of research, systemic treatments have failed in most lung cancer cases. The 5-year survival rate is estimated to be only about 10% in non-small cell lung carcinoma (NSCLC) (1-3). Cancer is the third leading cause of death in Iran, and lung cancer remains the second leading cause of cancer death after gastric cancer in Iran (4, 5). More than 70% of lung cancer patients represent an advanced disease at diagnosis, and men are five times more likely to be affected (6). Tobacco smoking has been increasing globally, especially in developing countries. Similarly, the prevalence of lung cancer has also been rising. Tobacco smoking remains by far the leading risk factor for lung cancer worldwide. Approximately 60% of new lung cancer cases occur in older smokers (≥ 100 cigarettes throughout life for more than one year) (5, 7).

On the contrary, many lung cancer patients have quit for decades (fewer than 100 cigarettes in a lifetime). Interestingly, one in five women and one in twelve men diagnosed with lung cancer have never smoked (5, 7). As the efficacy of conventional cytotoxic chemotherapy has reached a plateau in NSCLC, there is an urgent need to develop new therapeutic strategies (7-9). The FGFR1 gene is on chromosome 8 at position p11.23 and consists of 24 exons. This gene is also known as H2, FLT2, BFGFR, FLG, CEK, KAL2, and CD331 (9-11), which encodes FGFR 1, a protein involved in cellular processes such as cell division and maturation, growth regulation, angiogenesis, wound healing, and fetal development. FGFR1 is a transmembrane protein that acts as a bridge between the intra- and extracellular space. The binding of FGF1 to FGFR1 receptors triggers a cascade of cellular chemical reactions, leading to tyrosine kinase activity (12, 13). The malfunction of the FGFRs-FGFs signaling axis may increase the survival of tumoral cells in early stages and the rate of invasion and metastasis, thereby leading to poor prognosis and reduced survival. It is hypothesized that cigarettes may cause DNA damage on bronchial epithelial cells by inducing FGFR1 amplification leading to an increased risk of carcinogenesis (14). Some studies proposed that the FGFRs-FGFs axis may play a role in repairing small airways in chronic obstructive diseases caused by cigarette smoking (15). Increasing data have demonstrated higher FGFR1 levels in NSCLC patients (16-20). In addition, FGFR1 gene amplification has also been shown using fluorescent in situ hybridization (FISH) (20-23). However, the association between FGFR1 gene status and lung cancer has not been fully elucidated. Herein, we determined the frequency of FGFR1 gene amplification in Iranian patients with NSCLC and its possible association with patients' survival and clinicopathological characteristics. Our findings may provide further light on the screening and prognosis of these patients and may help choose a suitable targeted therapy for these patients.

Methods

Patients: Eighty-eight (65 males and 23 females; mean age: 60 years) patients undergoing bronchoscopy or surgery in Qaem Hospital of Mashhad from 2010 to 2016 were finally diagnosed with NSCLC and were included in the present study. All cases were thoroughly reviewed, and the initial diagnosis, histological type, and tumor grading were all reassessed by two accomplished pathologists. Clinical and demographic data, including age, sex, cigarette smoking, and the tumor's surgical operability status, were retrieved from patients' medical records. The time interval between the diagnosis and death or between the diagnosis and phone call in living patients was considered the survival time. Survival analysis was conducted for 70 out of 88 patients because we could not contact eighteen of them. Patients alive during contact or those deceased because of reasons other than lung cancer were regarded as censored data in the survival analysis. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were collected from the archive of the pathology department, and those blocks with a sufficient amount of tumor and stroma were selected. The Ethics Committee of Mashhad University of Medical Sciences reviewed and approved the study protocol (IR.MUMS.fm.rec.1395.271).

DNA extraction and quality assessment: According to the manufacturer's instructions, genomic DNA was extracted from FFPE NSCLC tissues using the Tissue DNA Extraction Mini Kit (YTA, IRAN, Cat No: YT9030). DNA concentration was determined using a Nanodrop spectrophotometer (Nanodrop thermo 2000, Finland) and adjusted to a 2.5 ng/ml concentration. We used 2 µl of each DNA for PCR assay.

Real-time PCR assay*:* FGFR1 copy number alterations were analyzed by a Step-one Real-Time PCR System (Applied Biosystems, Foster City, USA) using a SYBR Green qPCR Master mix (YTA, Cat No: YT2551, IRAN). Sequences of specific primers for FGFR1 amplification were as forward primer, 5'-ACTGCAGAACTGGGATGTGG-3', and reverse primer, 5'-ACCACATCACCTGCAACCAT-3' (reverse). GAPDH (glyceraldehyde-3-phosphate dehydrogenase), a housekeeping gene, was used as the internal control. The cycling condition comprised the initial denaturation at 95˚C for 5 minutes, 40 cycles at 94˚C for 15 seconds, 60˚C for 30 seconds, and 72˚C for 34 seconds. The FGFR1 gene amplification was analyzed compared to the control gene using the delta-delta CT method and fold change calculation. Positive FGFR1 amplification was defined as an FGFR1 /GAPDH copy number ratio of >2. According to previous studies, a *ratio* of 2 can be defined as an optimal cut-off value. Samples <2 were considered negative, and samples>2 were regarded as positive (18, 19). As shown in fig 1, to evaluate the efficiency of real-time PCR for the genes FGFR1 and GAPDH, a series of diluted DNA copies of these genes were prepared and subjected to real-time PCR reactions. The resulting CT graph was plotted against the initial DNA concentration, and the slope of the line was determined. The efficiency of the reaction was then computed using the formula: Efficiency= [10 (-1/slope)]-1. The PCR efficiency for the FGFR1 gene was determined to be 97%, with a slope of -3.4 and a y-intercept of 38.8.

Similarly, the PCR efficiency for the GAPDH gene was found to be 93%, with a slope of -3.5 and a y-intercept of 39.6. Furthermore, as depicted in fig 2, the specificity of PCR reaction for FGR1 and GAPDH was analyzed using melting curve analysis post PCR reactions. The melting curve is a reliable method for identifying the presence of non-specific products such as primer-dimers, which may appear as additional peaks in the melting curve.

Statistical analysis: The sample size was calculated using the prevalence formula of n= z2(p)(1-p)/d2 with a relative accuracy of 10 % and 80 % power. The prevalence rate of 32%, presented by a previous study by Sasaki et al., was employed for estimating the sample size (20). Statistical data were collected from clinical and laboratory observations and analyzed by SPSS Version 16 software. The relationships between grouped variables were analyzed by the Fisher and chi-square tests. Survival was assessed using the Kaplan-Meier test, log-rank, and cox regression. P-values of less than 0.05 were considered statistically significant (figure 3).

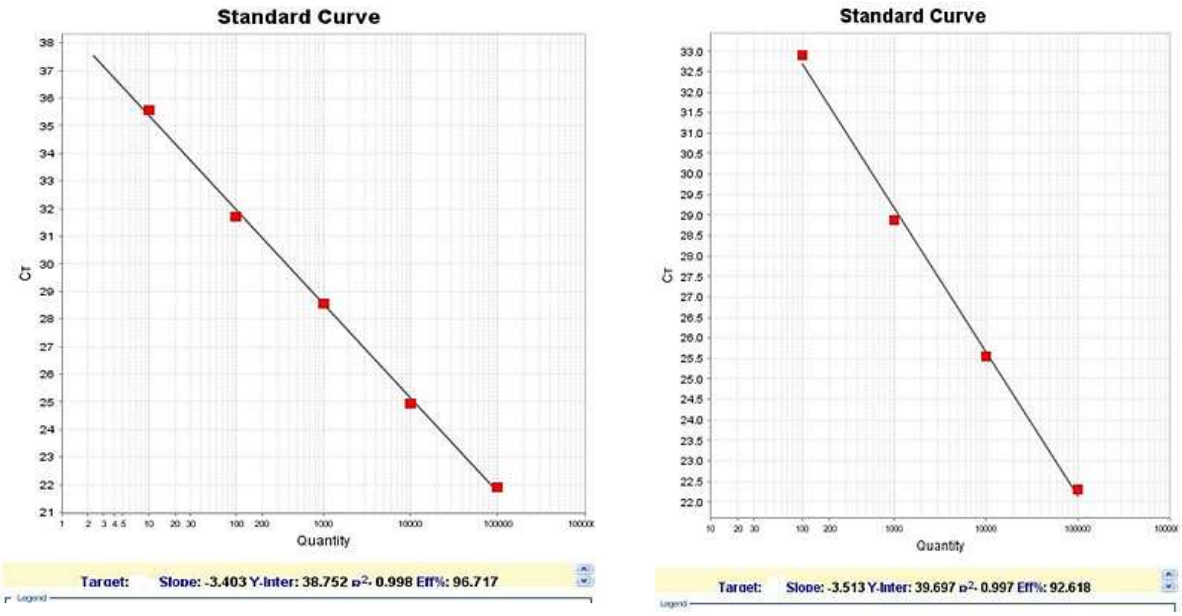

Figure 1. Real time PCR efficiency for standard curves of FGFR1 and GAPDH genes using serial dilution of DNA from FGFR1 and GAPDH genes

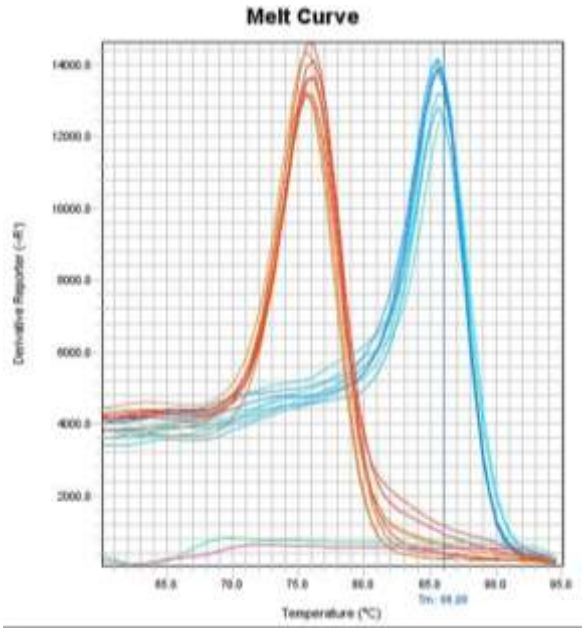

Figure 2. Specificity of the real time PCR based on melt-curving analysis for FGFR1 and GAPDH genes

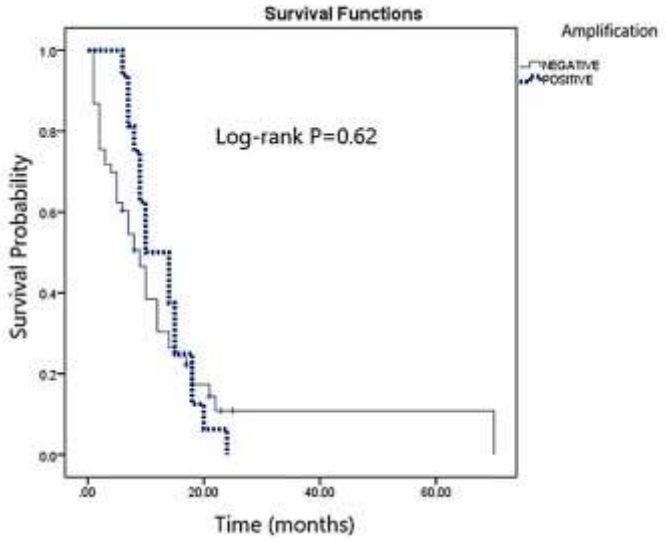

Figure 3. Kaplan-Meier survival curve based on the amplification of FGFR1 gene

Results

Our study consisted of 88 NSCLC patients. The patients' median age was 60 years, and the majority of patients were males (n=65, 73.9%). Concerning the disease subtype, 46 (52.3%) patients were diagnosed with SCC. Moreover, 42 (47.7%) cases were classified as adenocarcinoma. Furthermore, patients' demographic and clinicopathological data are presented in table 1. FGFR1 amplification was observed in seventeen out of eighty-eight (19.31%) patients, according to the criteria defined for amplification (fold change>2, 95% CI: 0.612-10.17).

Despite the higher prevalence of amplification in SCC compared to adenocarcinoma patients, the difference was not statistically significant (SCC 26.1% VS adenocarcinoma 11.9%; P= 0.09). Among the patients in this study, 33 (37.5%) mentioned a smoking history, and 55 (62.5%) cases stated that they had never smoked. In the group without FGFR1 gene amplification, 22 (31%) subjects had a smoking history, and 49 (69%) patients were non-smokers. In the group with FGFR1 amplification, 11 (64.7%) patients had a smoking history, and six (35.3%) were non-smokers. Based on these findings, FGFR1 gene amplification was significantly correlated with smoking status (smoker 33.3% VS non-smoker 10.9%; P =0.01, OR= 4.08).

However, we found no significant association with other demographic or clinicopathological data, including age (≥65 vs< 65 years; P = 0.33), sex (male vs. female; P = 0.34), tumor grade (1, 2, 3. P= 0.48), and tumor operability (operable vs. inoperable; P= 0.08). Also, we found no significant relationship between FGFR1 amplification and survival. As illustrated in fig 3, the survival status of patients with FGFR1 gene amplification (n = 17, 10 ± 4.9 months, CI= 5.1-14.9) and patients with normal FGFR1 copy number (n = 71, 9 ± 2.5 months, CI= 6.52-11.48) was not significantly different (Log-Rank; P= 0.62).

Table 1. Demographic and clinicopathologic data of NSCLC patients

Variable	Amplified group	Non-amplified group	P-value
Gender			
Male	11 (64.7%)	54 (76%)	0.34
Female	6 (35.3%)	17 (24%)	
Age (years)			
<65	12 (70.6%)	41 (57.7%)	0.33
>=65	5 (29.4%)	30 (42.3%)	
Smoking status			
Never smoker	6 (35.3%)	49 (69%)	0.01
Smoker	11 (64.7%)	22 (31%)	

Variable	Amplified group	Non-amplified group	P-value
Histologic type			
SCC	12 (70.6%)	34 (47.9%)	0.09
Adenocarcinoma	5 (29.4%)	37 (52.1%)	
Differentiation			
Well	4 (23.5%)	25 (35.2%)	
Moderate	7 (41.2%)	30 (42.3%)	0.48
Poor	6 (35.3%)	16 (22.5%)	
Operability			
Operable	6 (35.3%)	42 (59.2%)	0.07
Inoperable	11 (64.7%)	29 (40.8%)	

Discussion

Comprehensive knowledge regarding tumorigenesis changes in NSCLC patients could pave the way for better treatment and management of patients. Also, developing rapid and reliable methods for identifying these molecular aberrations is crucial, especially in clinical settings (24-26). The current study evaluated the frequency of FGFR1 gene amplification in a group of NSCLC patients from northeast Iran and investigated its association with patients' survival and clinical data. Our results may be helpful for screening and prognosis assessment of lung cancer patients. According to real-time PCR assay, our study revealed that the FGFR1 gene copy number was elevated in 19.3% of NSCLC patients. In addition, FGFR1 amplification was more frequently found in SCC than in adenocarcinoma patients. However, we found no statistically significant difference (P-value= 0.09).

Furthermore, this amplification occurred more frequently in smokers than non-smokers (P-value= 0.01). On the contrary, our findings suggested no association between FGFR1 amplification and patients' survival or other demographic and clinical factors (P> 0.05). A previous investigation by Weiss et al. showed the amplification of 8p11-12 (containing the FGFR1 gene) in a significant percentage of SCC cases of lung cancer (22% of patients) (20). A study by Sasaki et al., utilizing real-time PCR, found FGFR1 amplification in 32% of patients. However, Kim et al., using the FISH technique, showed a lower frequency of only 13% in their patients. One possible explanation for the difference observed between these studies may be the different methods used to detect FGFR1 amplification (22, 25). In addition, several other studies assessing the FGFR1 amplification in NSCLC patients using the FISH technique showed relatively significant variations in their results. Despite using a similar method, their differences may be attributable to multiple factors, such as the difference in defining the cut-off value and other variables in the testing process. Noteworthy that one of the main disadvantages of the FISH method is its challenging and manual procedure, which may limit its routine clinical utility (26). Therefore, we evaluated FGFR1 amplification with real-time PCR assay because of its simplicity and automated and quantitative process.

After comparing the findings of Weiss et al. and Tran et al. with those of the current study, it seems that, unlike EGFR mutation that is more frequent in Asian countries than in western countries, the frequency of FGFR1 amplification is not significantly different between diverse ethnic groups (20, 21). In this study, the prevalence of FGFR1 gene amplification was 26% and 11% in SCC and adenocarcinoma patients, respectively, which is in concordance with the results of Tran et al., using the SISH (Silver in Situ Hybridization) technique (24% frequency in SCC VS 11.3% in adenocarcinoma) (21). Moreover, our study's prevalence of FGFR1 amplification was consistent with previous studies, which used FISH assays (22%, 20 %, and 21%) (20, 27-29). While different studies have shown that the prevalence of FGFR1 gene amplification is greater in SCC than in adenocarcinoma patients, the frequencies recorded for adenocarcinoma are diverse. Although a higher prevalence of amplification in SCC was observed in this study, similar to Kohler and Gadgeel's studies, it was not statistically significant ($p > 0.05$). One justification may be patient selection bias (26, 30). In concordance with other studies, we also found a significant correlation between FGFR1 gene amplification and cigarette smoking (20, 26). This association suggests that FGFR1 amplification is an oncogenic aberration in SCC patients, possibly triggered by cigarette smoking. Some studies have shown heavier smokers have higher FGFR1 amplification frequency (20 % in smokers with 45 or more packets per year). Based on these findings, heavy smokers with SCC can be a high-risk

population for FGFR1 gene amplification (22). Similar to previous studies, we found no significant association between other demographic and clinical factors, including age, gender, differentiation, staging, operability, and survival with FGFR1 gene amplification (21, 31-33). On the contrary, few studies showed a higher prevalence in male patients (25). Besides, some studies suggested FGFR1 amplification as a prognostic factor (34, 35). However, its prognostic effect has yet to be fully delineated. While some previous studies consider it a poor prognostic factor (22), others regarded it as a favorable prognostic marker (21). Some reports found no difference in the survival of lung cancer patients with or without FGFR1 amplification (32, 33). Therefore, more research is needed to highlight this controversial issue (31).

The main limitation of the current study includes the low sample size, which might have limited statistical power. In addition, due to the small sample size, the effect of cigarette smoking on FGFR1 gene amplification was not adjusted by the bias effect of gender. More comprehensive studies using larger sample sizes and employing multiple techniques such as hybridization, PCR, and SNP microarray and their combination with immunohistochemical evaluations are warranted to compare gene amplification with gene expression. Our findings revealed that the frequency of FGFR1 gene amplification in NSCLC is significant. However, no relationship was found between FGFR1 amplification and the survival of patients with NSCLC. The presence of FGFR1 gene amplification in a significant portion of patients with NSCLC may highlight its importance as a potential marker for targeted therapy for these patients.

Acknowledgments

The authors wish to thank all the people who participated in this study.

Funding: grant number 950474.

Conflict of interests: The authors state that there is no conflict of interest in the publication of this article.

Authors' contribution: Conceptualization and study design (Amirhossein Jafarian), Sample collection and processing (Sanaz Homayounfar), Data analysis (Masoumeh Gharib), Statistical analysis and interpretation (Hossein Ayatollahi), Writing - review and editing (Zahra Khoshnegah, Gordon Ferns, Payam Siyadat).

References

1. Gomez-Casal R, Bhattacharya C, Ganesh N, et al. Non-small cell lung cancer cells survived ionizing radiation treatment display cancer stem cell and epithelial-mesenchymal transition phenotypes. Mol Cancer 2013; 12: 94.
2. Elakad O, Lois AM , Schmitz K , et al. Fibroblast growth factor receptor 1 gene amplification and protein expression in human lung cancer. Cancer Med 2020; 9: 3574-83.
3. Šutić M, Vukić A, Baranašić J, et al. Diagnostic, predictive, and prognostic biomarkers in non-small cell lung cancer (NSCLC) management. J Pers Med 2021; 11: 1102.
4. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012, cancer incidence and mortality worldwide: IARC CancerBase No. 11 France: International agency for research on cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 18/12/2013.
5. Miao JL, Zhou JH, Cai JJ, Liu RJ. The association between fibroblast growth factor receptor 1 gene amplification and lung cancer: a meta-analysis. Arch Med Sci 2020; 16: 16–26.
6. Etemad K, Gouia MM, Ramazani R, Modirian M, Partovi A, Arjomandpour M. National cancer registeration report. Iran: Iran ministry of health; 2009. Available from: https://ghdx.healthdata.org/series/iran-national-cancer-registry. Accessed Oct, 19, 2024.
7. Qin J, Xie F, Wang F, Lu H. mRNA Expression of FGFR1 as potential marker for predicting prognosis of surgical resection of small cell lung cancer may be better than protein expression and gene amplification. J Cancer 2020; 11: 4691-9.
8. Moes-Sosnowska J, Chorostowska-Wynimko J. Fibroblast growth factor receptor 1-4 genetic aberrations as clinically relevant biomarkers in squamous cell lung cancer. Front Oncol 2022; 12: 780650.
9. Naghan PA, Hosseini M, Seyed Alinaghi SA, et al. A clinicopathologic study of lung cancer cases in Iran. Tanaffos 2009; 8: 28-36.
10. Horn L, Lovly CM, Johnson DH. Neoplasms of the lung. In: Harrison, T. R‹Harrison's principles of internal medicine. 18thed. New York: The McGraw-Hill Companies, Inc 2015; pp: 2800.
11. Gene. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information 2004. Available from: https://www.ncbi.nlm.nih.gov/gene/2260. Accessed Mar, 08, 2018.

12. Huret, JL. FGFR1 (fibroblast growth factor receptor 1). Atlas Genet Cytogenet Oncol Haematol 2009; 13: 821-40.
13. MedlinePlus. FGFR1 gene: Fibroblast growth factor receptor 1: National Library of Medicine (US), Genetics Home Reference. Available from: https://ghr.nlm.nih.gov/gene/FGFR1. Accessed Mar, 2018.
14. Katoh M. FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). Int J Mol Med 2016; 38: 3-15.
15. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004; 364: 709-21.
16. Kuhn H, Kopff C, Konrad J, et al. Influence of basic fibroblast growth factor on the proliferation of non-small cell lung cancer cell lines. Lung Cancer 2004; 44: 167-74.
17. Berger W, Setinek U, Mohr T, et al. Evidence for a role of FGF-2 and FGF receptors in the proliferation of non-small cell lung cancer cells. Int J Cancer 1999; 83: 415-23.
18. Volm M, Koomagi R, Mattern J and Stammier G. Prognostic value of basic fibroblast growth factor and its receptor (FGFR-1) in patients with non-small cell lung carcinomas. Eur J Cancer 1997; 33: 691-3.
19. Behrens C, Lin HY, Lee J, et al. Immunohistochemical expression of basic fibroblast growth factor and fibroblast growth factor receptors 1 and 2 in the pathogenesis of lung cancer. Clin Cancer Res 2008; 14: 6014-22.
20. Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010; 2: 62ra93
21. Tran TN, Selinger CI, Kohonen-Corish MR, et al. Fibroblast growth factor receptor 1 (FGFR1) copy number is an independent prognostic factor in non-small cell lung cancer. Lung Cancer 2013; 81: 462-7.
22. Kim HR, Kim DJ, Kang DR, et al. Fibroblast growth factor receptor 1 gene amplification is associated with poor survival and cigarette smoking dosage in patients with resected squamous cell lung cancer. J Clin Oncol 2013; 31: 731-7.
23. Rao X, Huang X, Zhou Z, Lin X. An improvement of the 2ˆ(-delta delta CT) method for quantitative real-time polymerase chain reaction data analysis. Biostat Bioinforma Biomath 2013; 3: 71-85.
24. Homaei F, Fani A, Shakeri S, et all. Fluorescent in situ hybridization and real-time quantitative polymerase chain reaction to evaluate HER-2/neu status in breast xancer. Iran J Pathol. 2017; 12: 67-73.
25. Sasaki H, Shitara M, Yokota K, et al. Increased FGFR1 copy number in lung squamous cell carcinomas. Mol Med Rep 2012; 5: 725-8.
26. Gadgeel SM, Chen W, Cote ML, et al. Fibroblast growth factor receptor 1 amplification in non-small cell lung cancer by quantitative real-time PCR. PLoS One 2013; 8: e79820.
27. Wang Y, Gao W, Xu J, et al. The role of FGFR1 gene amplification as a poor prognostic factor in squamous cell lung cancer: A meta-analysis of published data. Biomed Res Int 2015; 2015: 763080
28. Schildhaus HU, Heukamp LC, Merkelbach-Bruse S, et al. Definition of a fluorescence in-situ hybridization score identifies highand low-level FGFR1 amplification types in squamous cell lung cancer. Mod Pathol 2012; 25: 1473–80.
29. Dutt A, Ramos AH, Hammerman PS, et al. Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer. PLoS One 2011; 6: e20351
30. Kohler LH, Mireskandari M, Knösel T, et al. FGFR1 expression and gene copy numbers in human lung cancer. Virchows Arch 2012; 461: 49-57.
31. Jiang T, Gao G, Fan G, Li M, Zhou C. FGFR1 amplification in lung squamous cell carcinoma: a systematic review with meta-analysis. Lung Cancer 2015; 87: 1-7.
32. Schildhaus HU, Nogova L, Wolf J, Buettner R. FGFR1 amplifications in squamous cell carcinomas of the lung: diagnostic and therapeutic implications. Transl Lung Cancer Res 2013; 2: 92–100.
33. Craddock KJ, Ludkovski O, Sykes J, Shepherd FA, Tsao MS. Prognostic value of fibroblast growth factor receptor 1 gene locus amplification in resected lung squamous cell carcinoma. J Thorac Oncol 2013; 8: 1371-7.
34. Cihoric N, Savic S, Schneider S, et al. Prognostic role of FGFR1 amplification in early-stage non-small cell lung cancer. Br J Cancer 2014; 110: 2914-22.
35. Von Mässenhausen A, Franzen A, Heasley L, Perner S. FGFR1 as a novel prognostic and predictive biomarker in squamous cell cancers of the lung and the head and neck area. Ann Transl Med 2013; 1: 23.