Dynamic Monitoring of Gene Mutation Patterns in Lung Cancer Patients and Their Prognostic Significance: Postprint

Authors: Xue Chongxiang, Lu Xingyu, Liu Zhening, Dong Huijing, Zheng Yumin, Cui Huijuan, CUI Huijuan

Date: 2023-05-05T00:00:00+00:00

Abstract

Background Targeted therapy represented by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has significantly prolonged survival in patients with EGFR mutations, with relatively mild adverse effects, and has become the preferred treatment modality for advanced driver gene-positive non-small cell lung cancer. Dynamic monitoring of treatment progression and post-progression gene mutation patterns in NSCLC patients through genetic testing will facilitate the provision of more practical, effective, and long-term stable individualized targeted therapy guidance.

Objective To compare the differences in gene mutation characteristics before and after disease progression in non-small cell lung cancer (NSCLC) and to analyze the patterns of dynamic gene monitoring and their prognostic significance.

Methods This study collected data from NSCLC patients who underwent genetic testing at the outpatient or inpatient departments of the Integrated Traditional Chinese and Western Medicine Oncology Department and Lung Cancer Center of China-Japan Friendship Hospital between January 2007 and December 2021, established a lung cancer genetic testing database, and recorded the number and results of genetic tests before and after disease progression. Patients were divided into a gene clearance group and a non-gene clearance group based on gene clearance status, and baseline characteristics and survival outcomes were compared between the two groups.

Results A total of 217 patients were screened, enrolled, and successfully followed up to the clinical endpoint. The distribution of overall gene mutations in tissue samples before and after progression showed that wild-type changed from 70 cases (32.3%) to 95 cases (43.8%), mutant type from 147 cases (67.7%) to 122 cases (56.2%), 19DEL mutation from 64 cases (29.5%) to 67 cases (19.8%),

21 L858R mutation from 74 cases (34.1%) to 64 cases (24.0%), T790M mutation from 2 cases (0.9%) to 45 cases (20.7%), and TP53 and other rare mutations or combined rare mutations from 20 cases (9.2%) to 84 cases (38.7%). Among the 217 NSCLC patients, 67 were classified as gene clearance type and 150 as non-gene clearance type. Comparisons of baseline characteristics between gene clearance and non-gene clearance patients showed statistically significant differences only in history of lung disease (P=0.032) and history of targeted therapy (P=0.001). The median progression-free survival (PFS) was 9.8 months and 11.8 months in the gene clearance and non-gene clearance groups, respectively, with no statistically significant difference [HR=0.89, 95%CI (0.66, 1.20), P=0.310]. In 134 advanced-stage patients, the median PFS was 8.1 months and 9.8 months in the gene clearance and non-gene clearance groups, respectively, with no statistically significant difference [HR=0.83, 95%CI (0.58, 1.19), P=0.359]. The median overall survival (OS) was 50.5 months and 28.5 months in the gene clearance and non-gene clearance groups, respectively, with a statistically significant difference [HR=0.56, 95%CI (0.41, 0.78), P<0.0001]. In 134 advanced-stage NSCLC patients, the median OS was 45.5 months and 24.9 months in the gene clearance and non-gene clearance groups, respectively, with a statistically significant difference [HR=0.55, 95%CI (0.37, 0.81), P=0.0002].

Conclusion The gene mutation status in NSCLC patients is dynamically changing before and after disease progression; after lung cancer progression, the proportion of wild-type significantly increased compared to mutant type, with a decrease in classical mutations and an increase in concomitant mutations. Patients with 19DEL mutation had a higher proportion of T790M emergence after progression. Monitoring gene clearance has insufficient predictive power for PFS, but gene clearance type may predict longer OS benefit. Dynamic monitoring of changes in gene status helps guide timely treatment to achieve optimal clinical benefit.

Full Text

Dynamic Monitoring of Gene Changes and Its Prognostic Value in Lung Cancer Patients

XUE Chongxiang[1],[2], LU Xingyu[1], LIU Zhening[1], DONG Huijing[1], ZHENG Yumin[1], CUI Huijuan[2]*

[1]Graduate School, Beijing University of Chinese Medicine, Beijing 100029, China

[2]Department of Integrative Oncology, China-Japan Friendship Hospital, Beijing 100029, China

*Corresponding author: CUI Huijuan, Professor/Doctoral supervisor; E-mail: chjzryhyy@sina.com

Abstract

Background: Targeted therapy, represented by epidermal growth factor receptor-targeting tyrosine kinase inhibitors (EGFR-TKIs), has significantly prolonged survival in patients with EGFR mutations and become the preferred treatment for advanced non-small cell lung cancer (NSCLC) patients with driver gene mutations, offering relatively mild adverse reactions. Dynamic monitoring of treatment progression and post-progression gene mutation patterns through genetic testing in NSCLC patients will help provide more effective, long-term, and stable individualized targeted therapy guidance.

Objective: To compare the characteristics of gene mutations before and after disease progression in NSCLC patients and analyze the patterns of dynamically monitored gene changes and their prognostic significance.

Methods: We collected data from NSCLC patients who underwent genetic testing at the Department of Integrated Medicine and Lung Cancer Center of China-Japan Friendship Hospital between January 2007 and December 2021, establishing a lung cancer genetic testing database to record the number and results of genetic tests performed before and after progression. Patients were divided into gene clearance and non-gene clearance groups based on gene clearance status, and baseline characteristics and survival outcomes were compared between the two groups.

Results: A total of 217 patients were enrolled and successfully followed up to their clinical endpoint. The distribution of total gene mutations in tissue samples before and after progression showed that wild-type cases increased from 70 (32.3%) to 95 (43.8%), while mutant-type cases decreased from 147 (67.7%) to 122 (56.2%). Specifically, 19DEL mutations decreased from 64 (29.5%) to 67 (19.8%), 21 L858R mutations decreased from 74 (34.1%) to 64 (24.0%), T790M mutations increased from 2 (0.9%) to 45 (20.7%), and rare mutations or concomitant rare mutations such as TP53 increased from 20 (9.2%) to 84 (38.7%). Among the 217 NSCLC patients, 67 were classified as gene clearance type and 150 as non-gene clearance type. The two groups showed statistically significant differences only in history of lung disease (P=0.032) and history of targeted therapy (P=0.001). The median progression-free survival (PFS) was 9.8 months and 11.8 months in the gene clearance and non-gene clearance groups, respectively, with no significant difference [HR=0.89, 95%CI (0.66, 1.20), P=0.310]. For the 134 advanced-stage patients, median PFS was 8.1 months and 9.8 months, respectively, also showing no significant difference [HR=0.83, 95%CI (0.58, 1.19), P=0.359]. However, median overall survival (OS) was significantly longer in the gene clearance group at 50.5 months versus 28.5 months in the non-gene clearance group [HR=0.56, 95%CI (0.41, 0.78), P<0.0001]. Similarly, among the 134 advanced NSCLC patients, median OS was 45.5 months and 24.9 months, respectively, showing a statistically significant difference [HR=0.55, 95%CI (0.37, 0.81), P=0.0002].

Conclusion: The gene mutation status in NSCLC patients changes dynami-

cally before and after disease progression. After progression, the proportion of wild-type increases significantly compared to mutant-type, with a marked decrease in classical mutations and an increase in concomitant mutations. Patients with 19DEL mutations show a higher proportion of T790M mutation after progression. While monitoring gene clearance has limited predictive value for PFS, the gene clearance type may predict longer OS benefit. Dynamic monitoring of gene status changes helps guide timely treatment to achieve optimal clinical benefit.

Keywords: Lung neoplasms; Epidermal growth factor; Epidermal growth factor receptor inhibitor; Genetic testing; Tumor progression; Mutation patterns; Survival benefit; Prognosis

Introduction

With the popularization of genetic testing technology and the development of targeted drugs, targeted therapy has achieved remarkable progress in the comprehensive treatment of non-small cell lung cancer (NSCLC), significantly extending patient survival and improving quality of life [1-2]. However, current diagnostic capabilities remain relatively limited, with 75% of patients presenting at locally advanced or metastatic stages, resulting in poor long-term survival rates and overall prognosis [3].

The genetic status of lung cancer patients is not static, and changes in genes before and after tumor progression may provide valuable references for diagnosis and treatment. During tumor evolution, different cells acquire distinct genetic variation information and develop into different clonal populations [4]. In targeted therapy for lung cancer, certain cell populations develop drug resistance due to specific gene mutations they already possess or new mutations that occur, becoming an important mechanism of disease progression and inducing recurrence and metastasis [5-6]. The discovery of differential genes related to NSCLC progression and the application of targeted drugs guided by precise genetic testing are crucial for determining treatment plans, predicting prognosis, improving quality of life, and extending survival [7-8]. This study analyzed tumor-related gene mutations and fusion status in cancer tissue samples or peripheral blood ctDNA of NSCLC patients before and after tumor progression using gene sequencing technology to explore gene mutation patterns and preliminarily reveal the predictive value of these patterns for patient survival benefit.

Methods

1.1 Patient Population

This study collected data from NSCLC patients who underwent genetic testing as outpatients or inpatients at the Department of Integrated Medicine and Lung Cancer Center of China-Japan Friendship Hospital between January 2007 and December 2021. We established a lung cancer genetic testing database to record the number and results of genetic tests and screened patient information according to inclusion and exclusion criteria. This study was approved by the hospital's Ethics Committee (approval number: 2018-99-K71), and all patients signed informed consent forms.

1.2 Diagnostic Criteria

Diagnostic criteria followed the "Chinese Medical Association Oncology Branch Lung Cancer Clinical Diagnosis and Treatment Guidelines (2021 Edition)" [9] for NSCLC diagnosis. Tumor staging was based on the International Association for the Study of Lung Cancer (IASLC) 8th edition staging criteria [10]. Pathological classification referred to the 2021 World Health Organization histological classification of lung tumors [11]. Treatment response evaluation followed the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [12]. All patients were diagnosed with progressive disease (PD) after treatment.

1.3 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Pathologically confirmed primary NSCLC; (2) Complete medical history data with at least two molecular pathology test results from tissue or ctDNA; (3) Post-treatment recurrence or disease progression confirmed by clinical pathology or imaging; (4) Age between 18-80 years; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-4. Patients meeting all criteria were included.

Exclusion criteria: (1) Patients who received blood transfusion within 2 weeks; (2) Patients who refused to participate in the clinical trial. Patients meeting any exclusion criterion were excluded.

1.4 Pathological and Molecular Testing

For patients with primary surgical samples, routine pathological review and genetic testing information were conducted, and genetic testing was repeated after disease progression. DNA extraction for molecular testing included genomic DNA extracted from fresh biopsy tissue samples and purified ctDNA from peripheral blood. Tissue sample collection included formalin-fixed paraffin-embedded (FFPE) samples from primary or metastatic tumor tissues. Blood samples were collected using professional Streck BCT tubes following standard blood collection procedures, avoiding direct blood impact on tube walls. A sufficient volume of 10 ml peripheral blood was collected and stored at 15-30°C. For

patients undergoing treatment cycles (radiotherapy, chemotherapy, etc.), blood was collected before treatment or 2 weeks after a single treatment session. For routine lung cancer testing samples and re-examination of suspicious samples, molecular testing for specific gene variations could be performed as needed, including sequencing of at least EGFR, ALK, ROS1, RET, KRAS, PIK3CA, ERBB2, MET, and BRAF genes.

1.5 Data Collection and Management

1.5.1 Clinical baseline data collection: At enrollment, we collected patient age, sex, tumor location, tumor stage, surgical status, pleural metastasis, smoking history, family history, tumor history, lung disease history, and at least two genetic test results. All data were recorded in Case Report Forms (CRF). Smoking history was defined as smoking at least one cigarette per day for one consecutive year or having quit smoking for less than one year. Smoking history was assessed using the smoking index classification: smoking index = number of cigarettes per day × years of smoking; $ $200 pack-years was considered light smoking, >200 to <400 pack-years moderate smoking, and $ $400 pack-years heavy smoking. Drinking history was defined as consuming >1 standard drink per day on average (equivalent to 45 ml liquor/360 ml beer/120 ml wine) for one consecutive year or having quit drinking for less than one year.

1.5.2 Data entry and management: Database administrators compiled the database using Microsoft Excel 2019 software for data entry and management. Two data administrators independently performed double entry and verification. After database establishment, the principal investigator, statistical analysis personnel, and data administrators locked the database before analyzing genetic testing results starting in December 2018.

1.5.3 Patient follow-up: Follow-up began after patients signed informed consent forms, with a frequency of once every 3 months. Follow-up content included patient treatment information, survival information, and adverse events. The follow-up endpoint was clinical death or study completion, with the last follow-up date being July 20, 2022.

1.5.4 Grouping: Gene clearance was defined [13] as a change from positive gene mutation results to wild-type negative results, or from wild-type negative results to positive gene mutation results during dynamic gene monitoring. Patients were divided into gene clearance and non-gene clearance groups based on gene clearance status.

1.6 Statistical Analysis

Statistical analysis and visualization were performed using SPSS 25.0 (IBM, USA) and GraphPad Prism 8 software. Categorical data were expressed as relative numbers and compared between groups using the ^{2} test. Continuous data were expressed as ($\bar{x}\pm s$) and compared between two groups using independent t-tests. Kaplan-Meier method was used to plot survival curves, and Log-rank

test was used for survival curve comparison. P<0.05 was considered statistically significant.

Results

2.1 Clinical Baseline Characteristics

A total of 304 NSCLC patients were screened, with 217 successfully followed up to their clinical endpoint. The mean age was (65.1$±$11.6) years, with 48 early-stage (Stage I-II) patients and 169 mid-to-late-stage (Stage III-IV) patients. Baseline information for the 217 NSCLC patients who received two genetic tests before and after progression is shown in .

2.2 Genetic Profile of 217 NSCLC Patients

EGFR mutations accounted for 67.7% (147/217), ALK mutations for 0.5% (1/217), and no mutations for 29.0% (63/217). Classical mutations (21 L858R and 19DEL) accounted for 61.8% (134/217), including 21 L858R mutations at 32.3% (70/217) and 19DEL mutations at 29.5% (64/217). Non-classical mutations accounted for 9.2% (20/217), including primary T790M (0.9%, 2/217), G719X (1.4%, 3/217), 20ins (0.9%, 2/217), KRAS (0.9%, 2/217), TP53 (0.9%, 2/217), and others, as shown in [Figure 1: see original paper].

A total of 485 genetic test results were included. As shown in [Figure 2: see original paper]A, 82.0% (178/217) of patients underwent genetic testing twice, 12.4% (27/217) three times, and 5.5% (12/217) four times or more. [Figure 2: see original paper]B shows the comparison of genetic testing sample sources: first tests included peripheral blood 15.2% (33/217), primary tissue 78.3% (170/217), pleural effusion 5.5% (12/217), and metastatic lesions 0.9% (2/217); second tests included peripheral blood 60.4% (131/217), primary tissue 35.0% (76/217), pleural effusion 3.2% (7/217), and metastatic lesions 1.4% (3/217); third tests included peripheral blood 76.9% (30/39), primary tissue 20.5% (8/39), and pleural effusion 2.6% (1/39); fourth tests included peripheral blood 75.0% (9/12), primary tissue 16.7% (2/12), and pleural effusion 8.3% (1/12).

2.3 Gene Mutation Results in NSCLC Patients Before and After Progression

Before progression, among 217 NSCLC patients, wild-type accounted for 70 cases (32.3%) and mutant-type (including 19DEL, 21 L858R, 20 T790M, and rare mutations) for 147 cases (67.7%), including 19DEL mutations in 64 cases (29.5%), 21 L858R mutations in 74 cases (34.1%), and 20 T790M mutations in 2 cases (0.9%). After progression, wild-type accounted for 95 cases (43.8%) and mutant-type for 122 cases (56.2%), including 19DEL mutations in 67 cases (19.8%), 21 L858R mutations in 64 cases (24.0%), 20 T790M mutations in 45

cases (20.7%), and at least 84 cases (38.7%) with rare mutations or concomitant rare mutations, as shown in .

2.4 Multiple Gene Mutation Results in 217 NSCLC Patients

Among patients with wild-type results in the first genetic test ([Figure 3: see original paper]A), 74.6% (47/63) remained wild-type after progression, 4.8% (3/63) developed 21 L858R mutations, and 6.3% (4/63) developed 19DEL mutations, which could subsequently combine with 20 T790M mutations (4.8%, 3/63). The proportion of rare mutations after progression included TP53 at 3.2% (2/63) and ERBB2 at 3.2% (2/63).

Among patients with 19DEL mutations in the first genetic test ([Figure 3: see original paper]B), 48.4% (31/64) converted to wild-type after progression, 3.1% (2/64) converted to 21 L858R mutations, and 46.9% (30/64) retained 19DEL mutations. After progression, 20 T790M mutations accounted for 39.1% (25/64), with 18.8% (12/64) showing 20 T790M mutation combined with 19DEL mutation and 17.2% (11/64) showing simple 20 T790M mutation. The proportion of rare mutations after progression included TP53 at 9.4% (6/64), MET amplification at 3.1% (2/64), and PIK3CA at 3.1% (2/64).

Among patients with 21 L858R mutations in the first genetic test ([Figure 3: see original paper]C), 32.9% (23/70) converted to wild-type after progression; among those undergoing third or more tests, 90.0% (63/70) converted to wild-type. 1.4% (1/70) converted to 19DEL mutations, and 58.6% (41/70) retained 21 L858R mutations. After progression, 20 T790M mutations accounted for 18.6% (13/70), with 14.3% (10/70) showing 21 L858R mutation combined with 20 T790M mutation and 4.3% (3/70) showing simple 20 T790M mutation. The proportion of rare mutations after progression included TP53 at 8.6% (6/70), MET amplification at 2.9% (2/70), EGFR amplification at 2.9% (2/70), and PIK3CA at 2.9% (2/70).

Among patients with non-classical mutations in the first genetic test ([Figure 3: see original paper]D), primary 20 T790M mutations accounted for 5.0% (1/20), and secondary 20 T790M mutations for 15.0% (3/20). 20.0% (4/20) included 21 L858R mutations in multiple tests before and after progression. EGFR gene 18 G719X mutations accounted for 30.0% (6/20), 20 S768I mutations for 10.0% (2/20), and 20ins mutations for 10.0% (2/20). Other rare mutations included TP53 at 40.0% (8/20), KRAS at 15.0% (3/20), EGFR amplification at 10.0% (2/20), and PIK3CA at 15.0% (3/20).

2.5 Clinical Characteristics of Different NSCLC Patient Groups

Among 217 NSCLC patients, 67 were gene clearance type and 150 were non-gene clearance type. Except for history of lung disease (P=0.032) and history of targeted therapy (P=0.001), no statistically significant differences were found in other clinical characteristics between the gene clearance and non-gene clearance groups (P>0.05), as shown in .

2.6 Impact of Gene Mutation Results on Survival in 217 NSCLC Patients

2.6.1 Comparison of progression-free survival between gene clearance and non-gene clearance groups: The median progression-free survival (PFS) was 9.8 months and 11.8 months in the gene clearance and non-gene clearance groups, respectively, with no statistically significant difference [HR=0.89, 95%CI (0.66, 1.20), P=0.310, [Figure 4: see original paper]A]. For the 134 advanced-stage patients, median PFS was 8.1 months and 9.8 months, respectively, also showing no significant difference [HR=0.83, 95%CI (0.58, 1.19), P=0.359, [Figure 4: see original paper]B].

2.6.2 Comparison of overall survival between gene clearance and non-gene clearance groups: The median overall survival (OS) was 50.5 months and 28.5 months in the gene clearance and non-gene clearance groups, respectively, showing a statistically significant difference [HR=0.56, 95%CI (0.41, 0.78), P<0.0001, [Figure 5: see original paper]A]. For the 134 advanced NSCLC patients, median OS was 45.5 months and 24.9 months, respectively, also showing a statistically significant difference [HR=0.55, 95%CI (0.37, 0.81), P=0.0002, [Figure 5: see original paper]B].

Discussion

The introduction of gefitinib in China in 2005 marked the beginning of the targeted therapy era for lung cancer. Targeted therapy has significantly prolonged survival in patients with EGFR mutations and become the preferred treatment for advanced NSCLC patients with driver gene mutations, offering relatively mild adverse reactions [14]. However, the median resistance time for most EGFR-TKIs is less than one year, making monitoring of resistance points and treatment of subsequent resistance targets urgent clinical problems and current research hotspots [15-16]. Precise genetic diagnosis is the prerequisite for individualized treatment of lung cancer patients, and systematic research on gene mutations related to lung cancer progression is crucial for improving basic pathology, prognosis prediction, and diagnosis and treatment levels [17]. This study included 217 NSCLC patients who underwent genetic testing before and after treatment and were successfully followed up to their clinical endpoint to observe and explore the dynamic changes in EGFR and concomitant gene mutations before and after treatment.

Our results showed that comparing pre- and post-treatment genetic test results, the proportion of wild-type increased significantly compared to mutant-type after disease progression, with a marked decrease in classical mutations such as 19DEL and 21 L858R, and an increase in concomitant mutations. The 20 T790M resistance mutation appeared at a higher rate in patients with 19DEL mutations compared to wild-type or 21 L858R mutation patients after progression. Comparative analysis of clinical characteristics between patients with and

without gene clearance showed higher gene clearance rates in those with a history of lung disease and those receiving targeted therapy. Previous studies have shown that mutation genes decrease after chemotherapy [18], possibly because the proportion of circulating tumor cells released into the blood decreases after treatment, leading to negative ctDNA monitoring results in blood. Meanwhile, decreased mutation genes indirectly prove treatment effectiveness.

This study followed up 217 NSCLC patients for PFS and OS. Monitoring gene clearance had poor predictive value for PFS, with no statistically significant differences in either the total patient group or the 134 advanced-stage patients. However, for OS, NSCLC patients in the gene clearance group had significantly longer OS. The dynamic changes in EGFR gene mutations before and after treatment predict better treatment efficacy and survival benefit. Dynamic gene monitoring can assist in predicting clinical treatment efficacy. The later the tumor stage and the larger the tumor burden, the higher the pre-treatment ctDNA level may be. If tumor patients are sensitive to radiotherapy and chemotherapy, their ctDNA levels will decrease after treatment, suggesting very effective treatment, and these patients may also obtain survival benefits. On the other hand, if patients are in locally advanced stages but ctDNA is negative before treatment, the situation is more complex: the tumor remains in a localized position, ctDNA has not been released into the blood, or ctDNA in the blood cannot reflect the tumor status [19-20].

This study preliminarily reveals the survival prediction role of dynamic gene monitoring in the process of lung cancer progression and identifies gene change characteristics closely related to NSCLC survival benefit. The innovation of this study lies in using real-world tumor progression mutation analysis combining tissue samples, ctDNA samples, and optimized NGS testing to ensure high-quality research results. With the development and popularization of NGS technology, the proportion of patients undergoing NGS platform lung cancer genetic testing has relatively increased. Our data show that comparing NGS test results before and after tumor progression, in addition to known common resistance mutations such as T790M and TP53, there may be potential resistance mutations such as L792H, although the identification and treatment strategies for these resistance genes require further research.

In NSCLC, plasma ctDNA usually matches tumor tissue highly and can well reflect patient tumor burden. It has been proven to be a substitute for tissue testing with equivalent clinical guidance value [16,18]. Although current guidelines recommend prioritizing tumor tissue paraffin specimens for genetic testing, a considerable number of people cannot obtain tissue or cytological specimens, and blood ctDNA biopsy is recommended to compensate for the insufficient and inaccessible tumor tissue samples [19]. However, this study still has certain limitations, such as differences in genetic testing methods and sample heterogeneity, so we could not evaluate the potential clinical significance of specific gene mutations in lung cancer progression diagnosis, treatment, and prognosis analysis. Therefore, large cohort studies are necessary to accurately determine the value

of tissue and ctDNA genetic testing in prognosis evaluation and prediction.

In summary, the gene mutation status in NSCLC patients changes dynamically before and after treatment. After lung cancer progression, the proportion of wild-type increases significantly compared to mutant-type, with a marked decrease in classical mutations such as 19DEL and 21 L858R, and an increase in concomitant mutations such as T790M and TP53. Patients with 19DEL mutations show a higher proportion of T790M mutation after progression compared to wild-type or 21 L858R mutation patients. While monitoring gene clearance has limited predictive value for PFS, the gene clearance type may predict longer OS benefit. Dynamically monitoring gene status changes during treatment and adjusting patient treatment plans according to gene status changes can reduce treatment blindness and achieve optimal clinical benefit.

References

[1] SIEGEL R L, MILLER K D, FUCHS H E, et al. Cancer Statistics, 2021[J]. CA: a cancer journal for clinicians, 2021, 71(1): 7-33. DOI: 10.3322/caac.21654.

[2] BRAY F, FERLAY J, SOERJOMATARAM I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424. DOI: 10.3322/caac.21492.

[3] ZHANG S, SUN K, ZHENG R, et al. Cancer incidence and mortality in China, 2015[J]. Journal of the National Cancer Center, 2021, 1(1): 2-11.

[4] Wu ZM, Liu P, Yu LL, et al. Detection of quantitative KRAS gene mutations in circulating tumor DNA from colorectal cancer patients[J]. Basic Medicine and Clinical Practice, 2018, 38(2): 180-184. DOI: 10.16352/j.issn.1001-6325.2018.02.007.

[5] WILLIAMS D S, MOURADOV D, BROWNE C, et al. Overexpression of TP53 protein is associated with the lack of adjuvant chemotherapy benefit in patients with stage III colorectal cancer[J]. Mod Pathol, 2020, 33(3): 483-495. DOI: 10.1038/s41379-.

[6] Fu GM, Liu P, Wu F, et al. Characteristics of T790M mutation in peripheral blood of advanced NSCLC patients progressed after first-generation EGFR-TKIs treatment[J]. Chinese Journal of Lung Diseases: Electronic Edition, 2021, 14(2): 169-173. DOI: 10.3877/cma.j.issn.1674-6902.2021.02.007.

[7] Jin P, Feng H, Liu QQ, et al. Bioinformatics analysis of genes associated with high recurrence risk in early-stage non-small cell lung cancer[J]. Chinese Journal of Biologicals, 2018, 31(1): 35-40. DOI: 10.13200/j.cnki.cjb.002050.

[8] Liu P, Wu YH, Zhou LJ, et al. Prognostic analysis of advanced non-small cell lung cancer patients with different genetic subtypes[J]. Chinese Journal of

Lung Cancer, 2017, 20(11): 741-750. DOI: 10.3779/j.issn.1009-3419.2017.11.04.

[9] Chinese Society of Oncology, Chinese Medical Association; Chinese Medical Journals Publishing House Co., Ltd. Clinical practice guidelines for lung cancer (2021 edition) by the Chinese Society of Oncology, Chinese Medical Association[J]. Chinese Journal of Oncology, 2021, 43(6): 591-621. DOI: 10.3760/cma.j.cn112152-.

[10] GOLDSTRAW P, CHANSKY K, CROWLEY J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer[J]. J Thorac Oncol, 2016, 11(1): 39-51. DOI: 10.1016/j.jtho.2015.09.009.

[11] TRAVIS W D, BRAMBILLA E, NICHOLSON A G, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification[J]. J Thorac Oncol, 2015, 10(9): 1243-1260. DOI: 10.1097/JTO.0000000000000630.

[12] EISENHAUER E A, THERASSE P, BOGAERTS J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)[J]. Eur J Cancer, 2009, 45(2): 228-247. DOI: 10.1016/j.ejca.2008.10.026.

[13] SONG Y, HU C P, XIE Z H, et al. Circulating tumor DNA clearance predicts prognosis across treatment regimen in a large real-world longitudinally monitored advanced non-small cell lung cancer cohort[J]. Transl Lung Cancer Res, 2020, 9(2): 269-279. DOI: 10.21037/tlcr.2020.03.17.

[14] RODAK O, PERIS-DÍAZ M D, OLBROMSKI M, et al. Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and immunotherapy[J]. Cancers (Basel), 2021, 13(18): 4705. DOI: 10.3390/cancers13184705.

[15] HIRSCH F R, SCAGLIOTTI G V, MULSHINE J L, et al. Lung cancer: current therapies and new targeted treatments[J]. Lancet, 2017, 389(10066): 299-311. DOI: 10.1016/S0140-6736(16)30958-8.

[16] Chinese Society of Pathology, Chinese Medical Association; National Pathology Quality Control Center; Lung Cancer Group of Chinese Society of Oncology, Chinese Medical Association, et al. Clinical practice guidelines for molecular pathology testing of non-small cell lung cancer (2021 edition)[J]. Chinese Journal of Pathology, 2021, 50(4): 323-332. DOI: 10.3760/cma.j.cn112151-20201220-00945.

[17] Fan YP, Du M, Yu FY, et al. Research progress on driver genes, detection methods, and targeted therapy for lung cancer[J]. Modern Oncology Medicine, 2020, 28(2): 330-334. DOI: 10.3969/j.issn.1672-4992.2020.02.035.

[18] MAO X W, ZHANG Z, ZHENG X X, et al. Capture-based targeted ultradeep sequencing in paired tissue and plasma samples demonstrates differential subclonal ctDNA-releasing capability in advanced lung cancer[J]. J Thorac Oncol, 2017, 12(4): 663-672. DOI: 10.1016/j.jtho.2016.11.2235.

[19] ANAGNOSTOU V, FORDE P M, WHITE J R, et al. Dynamics of tumor and immune responses during immune checkpoint blockade in non-small cell lung cancer[J]. Cancer Res, 2019, 79(6): 1214-1225. DOI: 10.1158/0008-5472.CAN-18-1127.

[20] PHALLEN J, LEAL A, WOODWARD B D, et al. Early noninvasive detection of response to targeted therapy in non-small cell lung cancer[J]. Cancer Res, 2019, 79(6): 1204-1213. DOI: 10.1158/0008-5472.CAN-18-1082.

Author Contributions: CUI Huijuan conceptualized and managed the project; XUE Chongxiang, LU Xingyu, and LIU Zhening collected clinical data and performed statistical analysis; LU Xingyu and XUE Chongxiang created figures and tables; DONG Huijing and ZHENG Yumin verified data; XUE Chongxiang and CUI Huijuan wrote and edited the original manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Received Date: 2022-10-15
Revised Date: 2023-02-25
Editor: CUI Sha

Note: Figure translations are in progress. See original paper for figures.