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Dynamic Monitoring of Genetic Change Patterns and Their Prognostic Significance in Lung Cancer Patients (Postprint)

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Abstract

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 in lung cancer patients and its prognostic significance.

Methods Tissue samples or peripheral blood ctDNA before and after lung cancer progression were obtained for genetic testing, clinical characteristics within different gene mutation type groups were compared, patient treatment and survival prognosis data were followed up, and survival regression analysis was performed on enrolled patients.

Results A total of 217 lung cancer patients were screened and enrolled, successfully followed up to clinical endpoints, and all underwent genetic sequencing analysis. The overall distribution of gene mutations in tissue samples before and after progression showed: wild-type changed from 70 cases (32.3%) to 95 cases (43.78%); mutant type from 147 cases (67.7%) to 122 cases (56.22%); 19DEL mutation from 64 cases (29.49%) to 67 cases (19.82%); 21 L858R mutation from 74 cases (34.10%) to 64 cases (23.96%); T790M mutation from 2 cases (0.92%) to 45 cases (20.74%); and TP53 and other rare mutations or combined rare mutations from 20 cases (9.2%) to 84 cases (38.71%). All the above gene changes were statistically significant ($P < 0.05$). The proportion of gene-clearance NSCLC patients, defined as those whose gene status changed from wild-type to mutant type or from mutant type to wild-type before and after progression, accounted for 30.9% (67/217), while non-gene-clearance type accounted for 69.1% (150/217). Monitoring gene clearance demonstrated poor predictive efficacy for progression-free survival (PFS); no statistically significant differences in PFS were observed in either the total cohort of 217 NSCLC patients or the subgroup of 134 advanced NSCLC patients. However, for overall

survival (OS) data, NSCLC patients with gene-clearance type exhibited significantly longer OS in both groups.

Conclusion The gene mutation status of NSCLC patients is dynamically changing before and after disease progression. After lung cancer progression, the proportion of wild-type patients increased significantly compared to mutant type, and the proportion of classical mutations decreased while the proportion of concomitant mutations increased. 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 gene status changes helps to guide treatment in a timely manner to achieve optimal clinical benefit.

Full Text

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

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Abstract

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

Methods: Tissue samples or peripheral blood ctDNA were obtained before and after cancer progression for genetic testing. Clinical characteristics were

compared across different gene mutation type groups. Patient treatment and survival prognosis data were followed up, and survival regression analysis was performed on enrolled patients.

Results: A total of 217 lung cancer patients were screened, enrolled, and successfully followed up to clinical endpoints, all undergoing genetic sequencing analysis. The overall gene mutation distribution in tissue samples before and after progression showed that wild-type cases increased from 70 (32.3%) to 95 (43.78%), while mutated cases decreased from 147 (67.7%) to 122 (56.22%). The 19DEL mutation decreased from 64 (29.49%) to 67 (19.82%), 21 L858R mutation decreased from 74 (34.10%) to 64 (23.96%), T790M mutation increased from 2 (0.92%) to 45 (20.74%), and rare mutations or combined rare mutations such as TP53 increased from 20 (9.2%) to 84 (38.71%). All these genetic changes were statistically significant ($P < 0.05$). Gene clearance-type NSCLC patients, defined as those whose gene status changed from wild-type to mutant or mutant to wild-type during dynamic monitoring, accounted for 30.9% (67/217) of the cohort, while non-gene clearance-type patients accounted for 69.1% (150/217). Monitoring gene clearance showed poor predictive value for progression-free survival (PFS), with no statistically significant differences in either the overall 217-patient NSCLC group or the 134-patient advanced NSCLC subgroup. However, for overall survival (OS), gene clearance-type NSCLC patients in both groups showed significantly longer OS.

Conclusion: The gene mutation status of NSCLC patients is dynamically variable before and after disease progression. After cancer progression, the proportion of wild-type patients increases significantly compared to mutant-type, with classical mutation proportions decreasing while concomitant mutation proportions increase. Patients with 19DEL mutations show a higher proportion of T790M emergence after progression. While monitoring gene clearance has limited predictive power for PFS, gene clearance-type may indicate longer OS benefit. Dynamic monitoring of gene status changes helps guide timely treatment adjustments for optimal clinical benefit.

Keywords: epidermal growth factor receptor inhibitor; gene detection; tumor progression; tumor recurrence; mutation pattern; survival benefit

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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 improving tumor patients' survival time and quality of life [1-2]. However, due to current limitations in tumor diagnosis, 75% of patients present with locally advanced or metastatic disease at diagnosis, resulting in poor long-term survival rates and overall prognosis [3].

The gene 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 NSCLC targeted therapy, certain cell populations develop drug resistance or escape due to specific existing or newly acquired gene mutations, representing an important mechanism of disease progression that induces recurrence and metastasis [5-6].

The discovery of differential genes related to NSCLC tumor progression and the application of targeted drugs guided by precise genetic testing are of great significance for determining treatment protocols, predicting prognosis, and improving patients' quality of life and survival [7-8]. This study employed gene sequencing technology to analyze tumor-related gene mutations and fusion status in NSCLC patients' cancer tissue samples or peripheral blood ctDNA before and after disease progression, exploring the patterns of gene mutation during lung cancer progression and preliminarily revealing the predictive value of these mutation patterns for patient survival benefits.

Methods

1.1 Case Sources

This study enrolled NSCLC patients who underwent genetic testing at the Department of Integrative Oncology and Lung Cancer Center of China-Japan Friendship Hospital between December 2018 and December 2021. The hospital ethics committee approved the study (Ethics No.: 2018-99-K71), and all patients signed informed consent forms.

1.2 Diagnostic Criteria

Diagnostic criteria followed the "Guidelines for Standardized Diagnosis and Treatment of Lung Cancer (2011 Edition)" [9] for primary lung cancer diagnosis. Tumor staging was based on the 8th edition of the International Association for the Study of Lung Cancer (IASLC) staging standards [10]. Pathological classification referred to the 2015 WHO 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 comprised: pathologically confirmed primary NSCLC; complete medical history and at least two tissue or ctDNA molecular pathology test results; disease recurrence confirmed by pathology or imaging evaluation, or disease progression after treatment; age 18-80 years; Eastern Coopera-

tive Oncology Group (ECOG) performance status (PS) score of 0-4; signed informed consent. Patients meeting all criteria were included.

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

1.4 Pathological and Molecular Testing

Based on our hospital' s actual workflow, primary surgical samples underwent routine pathological re-examination with relevant information recorded. DNA extraction for molecular testing included genomic DNA from fresh biopsy tissue samples and ctDNA purified from peripheral blood. Tissue specimens comprised formalin-fixed paraffin-embedded (FFPE) samples from primary or metastatic tumors. Blood specimens were collected using professional Streck BCT tubes following standard procedures, avoiding direct blood impact on tube walls, with 10 mL of peripheral blood 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 NSCLC testing samples and suspicious re-examination samples, driver gene molecular testing for specific gene variations could be performed as needed (including at least 9-gene sequencing for EGFR, ALK, ROS1, RET, KRAS, PIK3CA, ERBB2, MET, and BRAF). EGFR mutations were detected using the Human EGFR Gene Mutation Detection Kit (fluorescent PCR method) (Amoy Diagnostics, China), strictly following kit instructions to detect 21 somatic mutations in exons 18-21 of the EGFR gene. ALK gene fusions were detected using VENTANA ALK IHC or Vysis ALK Apart FISH (Abbott). ROS1 gene fusions were detected using reverse transcription PCR (RT-PCR). NGS detection used high-throughput resequencing technology based on probe capture for relevant gene variation detection, with laboratory technical support provided by Shanghai OrigiMed Co.

1.5 Data Collection and Management

1.5.1 Initial Patient Data Collection: Clinical data for each enrolled patient were collected, including name, age, gender, hospitalization number, smoking history, relevant family disease history, previous tumor history and treatment process, TNM staging, and at least two genetic test results. All data were recorded in Case Report Forms (CRF).

1.5.2 Data Entry and Management: Data entry and management were performed by data administrators who compiled the database using Microsoft Excel 2019 software. Two data administrators independently performed double entry and verification. After database establishment, the principal investigator, statistical analyst, and data manager locked the database to finalize the analysis database.

1.5.3 Patient Follow-up: Enrolled patients were followed up for treatment information, survival status, and adverse events. The last follow-up date was July 20, 2022.

1.6 Grouping Labels and Statistical Methods

1.6.1 Grouping Definitions: Gene clearance type was defined as conversion from positive gene mutation results to wild-type negative results, or from wild-type negative results to positive gene mutation results during dynamic monitoring [13]. Based on TNM staging, patients were divided into early-stage (I-II) and mid-to-advanced-stage (III-IV) groups.

1.6.2 Statistical Methods: SPSS 25.0 (IBM, USA) and GraphPad Prism 8 software were used for statistical analysis and visualization. Chi-square test (^{2} test) or continuity correction test was used for comparing rates of count data. The ^{2} test evaluated relationships between gene mutation status and clinicopathological parameters. T-test or Pearson' s test analyzed continuous or non-continuous variables. Correlation analysis was used for paired data. Since measurement data were not normally distributed, median (interquartile range) was used for statistical description, and non-parametric tests were used for inter-group differences. Kaplan-Meier test compared survival curves, with $p < 0.05$ considered statistically significant.

Results

2.1 Baseline Clinical Characteristics of Enrolled Patients

A total of 304 NSCLC patients were screened, with 217 successfully followed up to clinical endpoints. The cohort included 95 males and 122 females, with a mean age of 65.1 ± 11.6 years. Clinical staging revealed 48 early-stage (I-II) cases and 169 mid-to-advanced-stage (III-IV) cases.

Table 1 Baseline clinical information of 217 NSCLC patients who underwent two genetic tests before and after progression

The baseline gene mutation profile of the 217 NSCLC patients at first detection is shown in [Figure 1: see original paper]. 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) comprised 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), and TP53 (0.9%, 2/217).

Figure 1 [Figure 1: see original paper] Baseline gene mutation results of 217 NSCLC patients

2.2 Analysis of Multiple Gene Testing in 217 NSCLC Patients

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 testing twice, 12.4% (27/217) three times, and 5.5% (12/217) four times or more. Analysis of testing methods ([Figure 2: see original paper]B) showed NGS proportions of 6.9% (15/217), 19.8% (43/217), 30.8% (12/39), and 75.0% (9/12) for the 1st, 2nd, 3rd, and $ $4th tests, respectively, while non-NGS methods accounted for 93.1% (202/217), 80.2% (174/217), 69.2% (27/39), and 25.0% (3/12), respectively. Sample source comparison ([Figure 2: see original paper]C) revealed that first tests used peripheral blood in 15.2% (33/217), primary tissue in 78.3% (170/217), pleural effusion in 5.5% (12/217), and metastatic lesions in 0.9% (2/217). Second tests used peripheral blood in 60.4% (131/217), primary tissue in 35.0% (76/217), pleural effusion in 3.2% (7/217), and metastatic lesions in 1.4% (3/217). Third tests used peripheral blood in 76.9% (30/39), primary tissue in 20.5% (8/39), and pleural effusion in 2.6% (1/39). Fourth tests used peripheral blood in 75.0% (9/12), primary tissue in 16.7% (2/12), and pleural effusion in 8.3% (1/12).

Figure 2 [Figure 2: see original paper] Genetic testing patterns in 217 NSCLC patients (A. Comparison of testing frequency; B. Comparison of NGS vs. non-NGS methods; C. Comparison of sample sources)

2.3 Comparison of Gene Mutation Results Before and After Progression

As shown in , the total EGFR mutation rate was 67.7% (147/217) before progression, with 32.3% (70/217) EGFR-negative; after progression, the total EGFR mutation rate was 56.2% (122/217), with 43.8% (95/217) EGFR-negative.

Table 2 Comparison of EGFR gene mutations before and after treatment in 217 NSCLC patients

The overall gene mutation distribution in 217 NSCLC patients before and after progression showed that pre-progression wild-type cases numbered 70 (32.3%), mutated cases 147 (67.7%), 19DEL mutations 64 (29.49%), 21 L858R mutations 74 (34.10%), T790M mutations 2 (0.92%), and rare or combined rare mutations 20 (9.2%). Post-progression, wild-type cases increased to 95 (43.78%), mutated cases decreased to 122 (56.22%), 19DEL mutations to 67 (19.82%), 21 L858R mutations to 64 (23.96%), T790M mutations to 45 (20.74%), and rare or combined rare mutations to 84 (38.71%). All changes were statistically significant ($P < 0.001$) ().

Table 3 Distribution of EGFR gene mutations in 217 NSCLC patients before and after treatment

2.4 Multiple Gene Mutation Results in 217 NSCLC Patients

The multiple gene mutation results are illustrated in [Figure 3: see original paper]A-D. Among patients with wild-type results at first detection ([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 (with 4.8% (3/63) subsequently acquiring T790M co-mutations). Post-progression rare mutations included TP53 (3.2%, 2/63) and ERBB2 (3.2%, 2/63).

Among patients with 19DEL mutations at first detection ([Figure 3: see original paper]B), 48.4% (31/64) converted to wild-type, 3.1% (2/64) converted to 21 L858R, and 46.9% (30/64) retained 19DEL. Post-progression T790M mutations occurred in 39.1% (25/64), including 18.8% (12/64) with T790M co-occurring with 19DEL and 17.2% (11/64) with T790M alone. Post-progression rare mutations included TP53 (9.4%, 6/64), MET amplification (3.1%, 2/64), and PIK3CA (3.1%, 2/64).

Among patients with 21 L858R mutations at first detection ([Figure 3: see original paper]C), 32.9% (23/70) converted to wild-type (with 90.0% (63/70) converting among those undergoing $ $3 tests), 1.4% (1/70) converted to 19DEL, and 58.6% (41/70) retained 21 L858R. Post-progression T790M mutations occurred in 18.6% (13/70), including 14.3% (10/70) with L858R co-mutation and 4.3% (3/70) with T790M alone. Post-progression rare mutations included TP53 (8.6%, 6/70), MET amplification (2.9%, 2/70), EGFR amplification (2.9%, 2/70), and PIK3CA (2.9%, 2/70).

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

Figure 3 [Figure 3: see original paper] Gene dynamic monitoring results in 217 NSCLC patients (A. Initially wild-type population; B. Initially 19DEL mutation population; C. Initially 21 L858R mutation population; D. Initially non-classical mutation population. The sunburst chart radiates from center outward, with each ring representing one genetic test, maximum 4 test results)

Among the 217 NSCLC patients, gene clearance-type accounted for 30.9% (67/217) and non-gene clearance-type for 69.1% (150/217). As shown in , no statistically significant differences in clinical characteristics were observed between gene clearance-type and non-gene clearance-type NSCLC patients.

Table 4 Clinical characteristic analysis of 217 NSCLC patients grouped by gene clearance status [n (%)]

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

Comparison of progression-free survival (PFS) between gene clearance-type and non-gene clearance-type groups showed median PFS of 9.8 months versus 11.8 months, respectively (HR = 0.89, 95%CI 0.66-1.20, P = 0.310) ([Figure 4: see original paper]A). In the 134 advanced NSCLC patients, median PFS was 8.1 months versus 9.8 months (HR = 0.83, 95%CI 0.58-1.19, P = 0.359) ([Figure 4: see original paper]B).

Figure 4 [Figure 4: see original paper] Comparison of progression-free survival between gene clearance-type and non-gene clearance-type groups in 217 NSCLC patients (A) and 134 advanced NSCLC patients (B)

Comparison of overall survival (OS) between gene clearance-type and non-gene clearance-type groups showed median OS of 50.5 months versus 28.5 months (HR = 0.56, 95%CI 0.41-0.78, $P < 0.0001$) ([Figure 5: see original paper]A). In the 134 advanced NSCLC patients, median OS was 45.5 months versus 24.9 months (HR = 0.55, 95%CI 0.37-0.81, P = 0.0002) ([Figure 5: see original paper]B).

Figure 5 [Figure 5: see original paper] Comparison of overall survival between gene clearance-type and non-gene clearance-type groups in 217 NSCLC patients (A) and 134 advanced NSCLC patients (B)

Discussion

Precise genetic diagnosis is the prerequisite for personalized lung cancer treatment. Systematic research on gene mutations related to lung cancer progression is crucial for understanding fundamental pathology, predicting prognosis, and improving diagnosis and treatment [14]. This study enrolled 217 NSCLC patients who underwent genetic testing before and after treatment, all successfully followed up to clinical endpoints, to observe and explore the dynamic changes in EGFR and concomitant gene mutations.

Comparison of pre- and post-progression test results revealed that wild-type cases increased significantly after disease progression, while classical mutations such as 19DEL and 21 L858R decreased markedly. The proportions of concomitant mutations including T790M and TP53 increased. T790M, as a resistance mutation, appeared at higher rates in 19DEL patients compared to wild-type or 21 L858R patients after progression. Clinical characteristic analysis showed that patients with lung disease history and those receiving targeted therapy had higher gene clearance rates. Previous studies have shown that mutated genes decrease after chemotherapy [13], possibly because treatment reduces the proportion of circulating tumor cells released into blood, leading to negative ctDNA results. This decrease in mutated genes indirectly proves treatment efficacy.

This study followed up PFS and OS in 217 NSCLC patients. Monitoring gene clearance showed poor predictive value for PFS, with no statistically significant differences in either the overall cohort or the 134 advanced NSCLC patients. However, for OS, gene clearance-type NSCLC patients in both groups showed significantly longer survival, indicating that dynamic changes in EGFR gene mutations before and after treatment predict better therapeutic outcomes and survival benefits.

This study preliminarily reveals the survival predictive role of dynamic gene monitoring during lung cancer progression and identifies gene change characteristics closely related to NSCLC survival benefits. The innovation of this study lies in combining tissue samples, ctDNA samples, and optimized NGS detection for real-world tumor progression mutation analysis, ensuring high-quality results. With NGS technology development and popularization, the proportion of patients undergoing NGS-based lung cancer gene testing has increased. Our data indicate that NGS testing before and after tumor progression identified not only known common resistance mutations like T790M and TP53 but also potential resistance mutations such as L792H, though the identification and treatment strategies for these resistance genes require further research. This study has limitations, including non-uniform sample sources (tissue vs. peripheral blood) and methodological differences in genetic testing, which prevented evaluation of the potential clinical significance of specific gene mutations in lung cancer progression diagnosis, treatment, and prognostic analysis.

Conclusion

In summary, the gene mutation status of NSCLC patients is dynamically variable before and after treatment. After lung cancer progression, the proportion of wild-type patients increases significantly compared to mutant-type, with marked decreases in classical mutations such as 19DEL and 21 L858R; concomitant mutations like T790M and TP53 increase proportionally. Patients with 19DEL mutations show higher rates of T790M mutation emergence after progression compared to wild-type or 21 L858R patients. While monitoring gene clearance has limited predictive power for PFS, gene clearance-type may indicate longer OS benefit. Dynamic monitoring of gene status changes during treatment, with timely adjustment of treatment protocols based on these changes, reduces therapeutic blindness and achieves optimal clinical benefit.

Author Contributions

Conceptualization and project management: XUE Chongxiang. Clinical data collection and statistical analysis: XUE Chongxiang, LU Xingyu, LIU Zhening. Figure and table preparation: LU Xingyu, XUE Chongxiang. Data verification:

DONG Huijing, ZHENG Yumin. Original draft writing, review, and editing: XUE Chongxiang, CUI Huijuan.

Conflict of Interest

All authors declare no conflict of interest.

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