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ORIGINAL RESEARCH

The Prognosis of Advanced Non-Small Cell Lung Cancer Patients with Precision-Targeted Therapy Guided by NGS Testing or Routine Testing

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Purpose: We aim to observe the potential survival benefits of driver gene-guided targeted therapy in advanced non-small cell lung cancer (NSCLC) patients compared to non-targeted therapy. Additionally, the study aims to assess whether Next-generation sequencing technology (NGS)-guided targeted therapy can provide survival advantages for advanced NSCLC patients compared to conventional Epidermal growth factor receptor (*EGFR*)/anaplastic lymphoma kinase (*ALK*) gene detection.

Methods: Clinical data, genetic testing results, and treatment information of 1663 advanced lung cancer patients diagnosed by pathology from January 2013 to June 2019 in Jiangsu University Affiliated Lianyungang Hospital were collected. Propensity score matching survival analysis was used to evaluate the differences in overall survival(OS) between groups.

Results: In the unadjusted survival curve, targeted therapy patients had significantly longer median OS than non-targeted therapy patients (28.3 months vs 15.4 months, Hazard ratio (HR) = 0.5426, 95% confidence interval (CI) 0.4768–0.6176, P < 0.0001); the conclusion was the same after propensity score matching analysis, with targeted therapy group patients having significantly prolonged OS median (27.5 months vs 14.8 months, HR = 0.5572, 95% CI 0.4796–0.6474, P < 0.0001). In the unadjusted survival curve, the NGS group had a significantly prolonged median OS compared to the conventional gene detection group (23.4 months vs 21.2 months, HR = 1.243, 95% CI = 1.017–1.519, P = 0.0495). However, after propensity score matching analysis, no statistically significant difference existed in the median OS between the two patient groups (23.1 months vs 21.5 months, HR = 1.288, 95% CI = 0.9557–1.735, P = 0.0926). Further analysis demonstrated no advantage in the five-, three-, and two-year survival rates of the NGS group compared to conventional gene detection group patients. However, the one-year survival rate of the NGS group was significantly increased (83.2% vs 68.1%, HR = 0.4890, 95% CI = 0.3170–0.7544, P = 0.0015).

Conclusion: Driver gene-guided targeted precision therapy significantly prolonged the median OS of advanced NSCLC patients compared to non-targeted therapy. NGS detection did not improve the median OS of advanced NSCLC patients compared to conventional *EGFR/ALK* gene detection but increased the one-year survival rate of patients.

Keywords: non-small cell lung cancer, NGS, *EGFR*, *ALK*, prognosis

Introduction

More driver genes of NSCLC are being discovered as detection technology and basic medicine advance, and corresponding targeted drugs are being developed. *EGFR* and *ALK* are driver genes, and corresponding small molecule tyrosine kinase inhibitors (TKIs) targeted drugs that have brought NSCLC treatment into the era of precisely targeted therapy. Targeted therapy greatly improves the survival of advanced NSCLC patients compared to traditional platinum-based double-drug chemotherapy.[1–7] The *EGFR* and *ALK* driver gene tests are increasingly used for late-stage NSCLC patients. NGS is becoming widely used in clinical applications due to its unique advantages as detection technology develops. It can identify rare driver gene mutations and evaluate clinical trials of other targeted therapies.[8,9] Presley et al[10] conducted

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a retrospective analysis of 5668 patients with stage IIIB/IV or unresectable non-squamous NSCLC who visited community cancer institutions in the United States from January 1, 2011, to July 31, 2016. The unadjusted survival analysis revealed that the NGS group had a 35.9% 12-month mortality rate, while the *EGFR/ALK* routine gene testing group had a 49.2% mortality rate ($P < 0.01$). According to instrumental variable analysis, NGS sequencing and the 12-month mortality rate did not correlate (predicted 12-month death probability: NGS group had 41.1%, routine testing had 44.4%; the difference was −3.6% [95% confidence interval (CI), −18.4% to 11.1%]; $P = 0.63$). This result is consistent with the survival analysis results matched by propensity score (42.0% vs 45.1%; hazard ratio (HR) = 0.92 (95% CI, 0.73–1.11) $P = 0.40$), indicating that NGS guided the treatment of a small number of patients, but did not improve survival compared to routine *EGFR/ALK* gene testing. Targeted therapy has become a standard diagnosis and treatment for Chinese lung cancer patients, and the development of NGS is becoming more widespread. However, there is a lack of relevant research regarding whether NGS can provide greater survival benefits to Chinese patients with advanced lung cancer than routine *EGFR/ALK* testing.

An increasing number of lung cancer driver genes and corresponding targeted drugs, such as *ROS1, MET, RET, BRAF, HER2, PIK3CA, NTRK, FGFR1*, and *DDR2*, have entered clinical practice along with *EGFR* and *ALK* genes with the continuous development of targeted precision therapy for lung cancer.[11,12] Large-scale international studies data have demonstrated that individualized precision treatment guided by driver genes improves patient survival. Research on the survival benefits of driver gene-guided targeted therapy in China for advanced lung cancer patients compared to conventional chemotherapy is limited. This study aims to observe whether NGS gene sequencing-guided precision treatment for advanced NSCLC can provide greater survival benefits than conventional *EGFR/ALK* gene testing-guided treatment. Additionally, it aims to determine whether driver gene-guided targeted therapy for advanced NSCLC patients can extend patient OS compared to non-targeted therapy in China, providing real-world research data to guide better driver gene testing and corresponding precision targeted therapy for advanced NSCLC patients.

Materials and Methods

Study Subjects

The study subjects were determined using the lung cancer database in a retrospective cohort study from the Affiliated Lianyungang Hospital of Jiangsu University. Participants were eligible if they had been diagnosed with stage IIIB-IV NSCLC and underwent driver gene testing, pathology, or cytology confirmation at the Affiliated Lianyungang Hospital of Jiangsu University between January 2013 and June 2019. Patients with other concurrent active cancer signs within the six months preceding the diagnosis of advanced NSCLC were excluded. All patients underwent either NGS or routine gene testing, including *EGFR* and *ALK*. NGS has any multi-gene panel testing, including the nine genes as molecular biomarkers (*EGFR, ALK, ROS1, KRAS, HER2, BRAF, MET, RET*, and *NTRK*) mentioned in the National Comprehensive Cancer Network (NCCN) guidelines. All patients received first-line antitumor therapy and had at least two documented clinical visits on or after January 1, 2013. Patient baseline clinical data, including age, gender, smoking history, pathological type, family cancer history, comorbidities, medical insurance, initial stage at diagnosis, driver gene status, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and OS were collected. The staging was performed using the seventh edition TNM staging system jointly developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). Patients who underwent NGS testing were considered the treatment group, while patients who underwent routine *EGFR/ALK* testing were considered the standard group in this study. The study was approved by the Medical Ethics Committee of the Affiliated Lianyungang Hospital of Jiangsu University. All patients signed informed consent. Our study was conducted in accordance with the Declaration of Helsinki.

Treatment, Therapeutic Evaluation and Follow-Up

All patients received first-line anti-tumor treatment, including targeted therapy, chemotherapy, and immunotherapy. The therapeutic efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, categorizing response as complete remission (CR), partial response (PR), stable disease (SD), or disease progression (PD). OS was defined as the duration between the first-line treatment and death or until the end of follow-up on June 1,

2020. Follow-up was performed for all patients. Survival analysis was performed using propensity score matching, with OS as the outcome. One- and two-year survival rates were analyzed in detail. Secondary outcomes included genetic changes and the treatments received.

Statistical Analysis

The chi-square test was used to compare the clinical characteristics and treatment distribution between the NGS and conventional testing groups. Propensity score matching was used to address the potential confounding due to significant differences in clinical characteristics. Multivariate logistic regression analysis was performed to evaluate the propensity score based on age, sex, smoking status, staging at first diagnosis, year of diagnosis, *EGFR* or *ALK* mutation status, comorbidities, treatment with only one modality, and treatment with first- or second-line or third- or fourth-line immunotherapy. Before conducting survival analysis with propensity score matching, the data quality of each variable was carefully considered. Comorbidities were evaluated using ICD-9 and ICD-10 diagnosis codes, and the categories were summarized according to Elixhauser et al. The comorbidity score was calculated by adding the number of comorbidities (0, 1–2, and ≥ 3).[13] According to Presley et al, six covariates were set as exact covariate matching items to avoid significant survival bias caused by certain patient characteristics.[10] *EGFR* or *ALK* mutation, treatment with only first-line therapy, year of diagnosis, treatment with first- or second-line immunotherapy, and treatment with third- or fourth-line immunotherapy. Virtual variables were used for missing data (smoking status and *EGFR* or *ALK* mutation) because they were not missing at random. One-to-one matching was performed using the nearest neighbor algorithm (ratio = 1, caliper = 0.01 standard deviation). Survival results were estimated and compared using the Kaplan-Meier method (time 0 = the start of the first row) and the Log rank test. The results included median OS, HR, and 95% CI. All statistical tests were two-sided, and the P-value < 0.05 was considered statistically significant. Statistical analysis was performed using R software (version 3.6.0) with the MatchIt package (version 3.0.2) from the R Project for Statistical Computing and the Institute for Mathematical Statistics.

Result

Patient Clinical Characteristics, Genetic Testing, and Treatment Information

Basic Clinical Characteristics and Genetic Testing Information of 1663 Patients

This study included 1663 patients with advanced NSCLC, with 969 male and 694 female patients. There were 822 patients aged 60 or younger and 841 patients over 60, with a median age of 61 (19–86) years. Among them, 845 patients had no underlying diseases, 756 had 1–2, and 62 had ≥ 3. Among 1663 patients, 862 had no smoking history, 756 had a smoking history, and 45 had unknown smoking history. There were 484 patients with a family history of tumors, 985 without, and 194 with an unknown family history of tumors. A total of 1308 patients had adenocarcinoma, 210 had squamous cell carcinoma, and 145 had other NSCLC. When first diagnosed, 60 patients had stage I, 55 had stage II, 277 had stage III, and 1271 had stage IV. This study diagnosed 165, 210, 254, 301, 310, 317, and 106 patients between 2013 and 2019, respectively. Regarding genetic testing, 197 patients were in the NGS detection group, and 1466 patients were in the routine gene detection group. The genetic testing results revealed that 759 patients (45.6%) had *EGFR* gene mutations, 78 patients (4.7%) had *ALK* mutations. The proportion of Exon 20 non-exon T790M primary resistance mutations was 1.0% (17/1663). Regarding tumor treatment, 909 patients received targeted therapy, while 754 patients did not. In this study, 1202 patients received chemotherapy, whereas 461 did not; 593 patients received radiotherapy, while 1070 did not; 70 patients received immunotherapy, whereas 1593 did not; and 625 patients received only first-line treatment, and 1038 received second-line or higher treatments (Table 1).

Comparison of Basic Clinical Characteristics Between the NGS Group and the Routine Group

The NGS group included 197 patients, while the conventional gene testing group included 1466 patients, with a proportion of 11.8% (197/1663) undergoing NGS testing. The NGS group included 99 male and 98 female patients; 22 patients aged ≤ 45 years, 52 patients aged 46–55 years, 75 patients aged 56–65 years, 46 patients aged 66–75 years, and two patients aged ≥ 76 years; 67 patients with comorbidities, including 66 patients with 1–2 comorbidities and one patient with ≥ 3 comorbidities; 130 patients without comorbidities; 110 patients had no smoking history, 86 patients had

Table 1 Basic Clinical Characteristics of 1663 NSCLC Patients

Clinical Features	No (Case)	%
Age at diagnosis (age)		
≤60	822	49.4
>60	841	50.6
Sex		
Male	969	58.3
Female	694	41.7
Comorbidities		
0	845	50.8
1–2	756	45.5
≥3	62	3.7
History of smoking		
No	862	51.8
Yes	756	45.5
Unknown	45	2.7
Family history of tumors		
No	985	59.2
Yes	484	29.1
Unknown	194	11.7
Pathology type		
Adenocarcinoma	1308	78.7
Squamous cell carcinoma	210	12.6
Not specifically mentioned NSCLC	145	8.7
Staging at diagnosis		
I	60	3.6
II	55	3.3
III	277	16.7
IV	1271	76.4
The year of diagnosis		
2013	165	9.9
2014	210	12.6
2015	254	15.3
2016	301	18.1
2017	310	18.6
2018	317	19.1
2019	106	6.4
Genetic detection method		
NGS	197	11.8
Routine genetic testing	1466	88.2
EGFR gene		
Positive	759	45.6
Negative	847	51.0
Unknown	57	3.4
ALK gene		
Positive	78	4.7
Negative	1508	90.7
Unknown	77	4.6
Targeted therapy		
Yes	909	54.7
No	754	45.3

(*Continued*)

Table 1 (Continued).

Clinical Features	No (Case)	%
Radiotherapy		
Yes	593	35.7
No	1070	64.3
Chemotherapy ± antiangiogenic therapy		
Yes	1202	72.3
No	461	27.7
Immunotherapy		
Yes	70	4.2
No	1593	95.8
Only 1-line treatment		
Yes	625	37.6
No	1038	62.4

Abbreviations: NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase.

smoking history, and one patient had unknown smoking history. The stage distribution at the time of initial diagnosis was as follows: four patients with stage I, four patients with stage II, 16 patients with stage III, and 173 patients with stage IV. The number of cases diagnosed in 2013, 2014, 2015, 2016, 2017, 2018, and 2019 were 0, 3, 4, 44, 58, 60, and 28, respectively. Regarding gene testing, 111 patients were *EGFR*-positive, 86 were *EGFR*-negative, and one patient's gene status was unknown. Nine patients were *ALK*-positive, 187 were *ALK*-negative, and one patient's gene status was unknown. Among the patients who underwent NGS testing before first-, second-, third-, fourth-, fifth-, and sixth-line treatments, there were 132, 45, 7, 5, 1, and 2 patients, respectively. The specific number of patients tested in other lines was unknown. The conventional gene testing group had 870 male and 596 female patients; 82 patients aged ≤ 45 years, 350 aged 46–55 years, 580 aged 56–65 years, 387 aged 66–75 years, and 67 aged ≥ 76 years; 751 patients with comorbidities, including 690 patients with 1–2 comorbidities and 61 patients with ≥ 3 comorbidities; 715 patients without comorbidities; 752 patients had no smoking history, 670 patients had smoking history, and 44 patients had an unknown smoking history. The stage distribution at the time of initial diagnosis was as follows: 56 patients with stage I, 51 patients with stage II, 261 patients with stage III, and 1098 patients with stage IV. The number of cases diagnosed in 2013, 2014, 2015, 2016, 2017, 2018, and 2019 were 165, 207, 250, 273, 252, 241, and 78, respectively. Regarding gene testing, 648 patients were *EGFR*-positive, 761 were *EGFR*-negative, and 57 had unknown gene status; 69 cases were *ALK*-positive, 1321 were *ALK*-negative, and 76 had unknown genetic status (Table 2).

Table 2 Basic Clinical Data of Patients in NGS Group and Routine Group

Clinical Features	Groups		P value
	NGS Group (n=197)	Routine Group (n=1466)	
Age			
≤45	22	82	0.003
46–55	52	350	
56–65	75	580	
66–75	46	387	
≥76	2	67	
Sex			
Male	99	870	0.015
Female	98	596	

(*Continued*)

Table 2 (Continued).

Clinical Features	Groups		P value
	NGS Group (n=197)	Routine Group (n=1466)	
Comorbidities			
0	130	715	<0.0001
1–2	66	690	
≥3	1	61	
History of smoking			
No	110	752	0.037
Yes	86	670	
Unknown	1	44	
Staging at diagnosis			
I	4	56	<0.0001
II	4	51	
III	16	261	
IV	173	1098	
Time of diagnosis (years)			
2013	0	165	<0.0001
2014	3	207	
2015	4	250	
2016	44	273	
2017	58	252	
2018	60	241	
2019	28	78	
EGFR gene			
Positive	111	648	<0.0001
Negative	86	761	
Unknown	0	57	
ALK gene			
Positive	9	69	0.001
Negative	187	1321	
Unknown	1	76	
NGS sequencing time			
Before first-line treatment	132		
Before second-line treatment	45		
Before third-line treatment	7		
Before four-line treatment	5		
Before five-line treatment	1		
Before the six-line treatment	2		
Else	5		

Abbreviations: NGS, Next-generation sequencing; *EGFR*, Epidermal growth factor receptor; *ALK*, Anaplastic lymphoma kinase.

Survival

OS of All Patients

The median OS of 1663 advanced NSCLC patients who underwent genetic testing was 21.9 months, with one-, three-, and five-year survival rates of 71.7%, 33.5%, and 22.0%, respectively (Figure 1).

Comparison of OS Between Patients Receiving Targeted and Non-Targeted Therapy

Among all patients with driver gene testing, those who received targeted therapy (n = 909) had significantly higher median OS than those who did not (n = 754, 28.3 months vs 15.4 months, HR = 0.5426, 95% CI 0.4768–0.6176, P < 0.0001). After

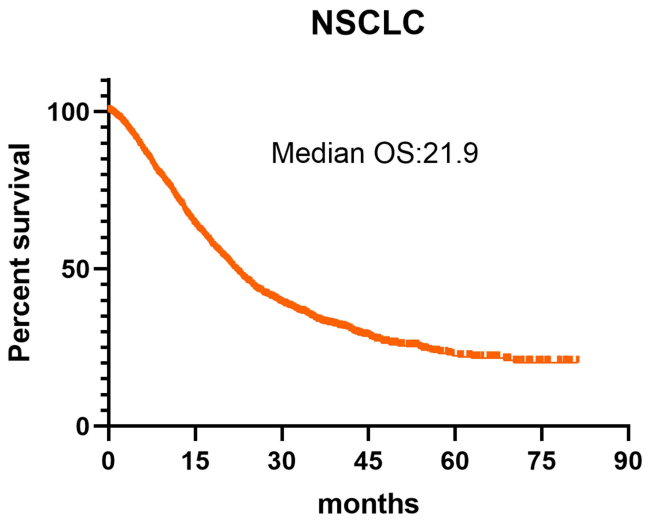

Figure 1 Overall survival of 1663 NSCLC patients.

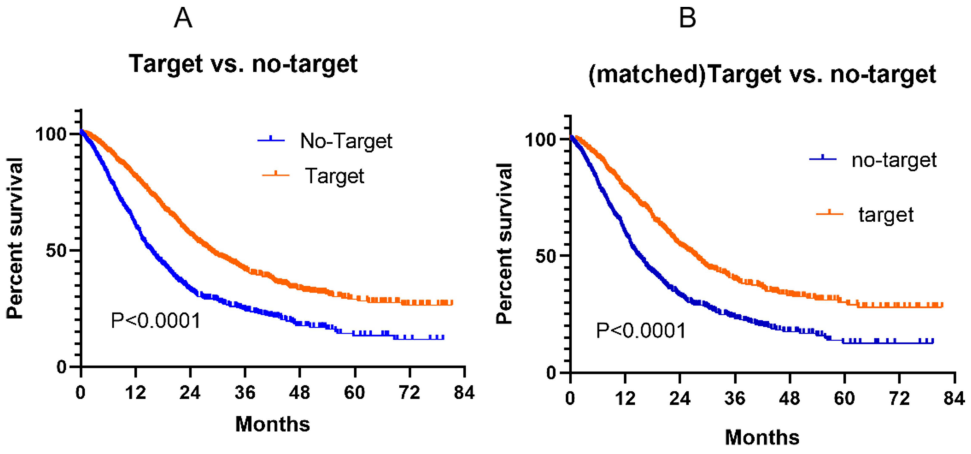

Figure 2 Comparison of OS between targeted therapy group and non-targeted therapy group.
Notes: (**A**) Unadjusted survival comparison between targeted therapy group and non-targeted therapy group. (**B**) Matched survival comparison between targeted therapy group and non-targeted therapy group.

matching 567 pairs of patients based on their propensity scores, the same conclusion was reached: the targeted therapy group had significantly higher median OS (27.5 months vs 14.8 months, HR = 0.5572, 95% CI 0.4796–0.6474, P < 0.0001, Figure 2).

Further stratification revealed that 726 patients with driver gene mutations who received targeted therapy had the longest median OS at 31.5 months, while 644 patients without driver gene mutations who received conventional treatment had the shortest median OS at 15.2 months. Moreover, 183 patients without driver gene mutations receiving targeted therapy had a median OS of 21.1 months, while the 110 patients with driver gene mutations receiving conventional treatment had a median OS of 16.0 months (P < 0.0001, Figure 3).

Comparison of OS Between NGS and *EGFR*/*ALK* Conventional Gene Testing Groups

The unadjusted survival curve revealed an absolute difference in median OS between the two groups (23.4 months vs 21.2 months, HR = 1.243, 95% CI = 1.017–1.519, P = 0.0495). After propensity score matching, median OS did not differ significantly between 187 matched patients (23.1 months vs 21.5 months, HR = 1.288, 95% CI = 0.9557–1.735, P = 0.0926, Figure 4).

Further analysis of patient survival at 60, 36, 24, and 12 months revealed that the NGS group had higher unadjusted survival rates than the conventional gene testing group (with P-values less than 0.05). However, after propensity score

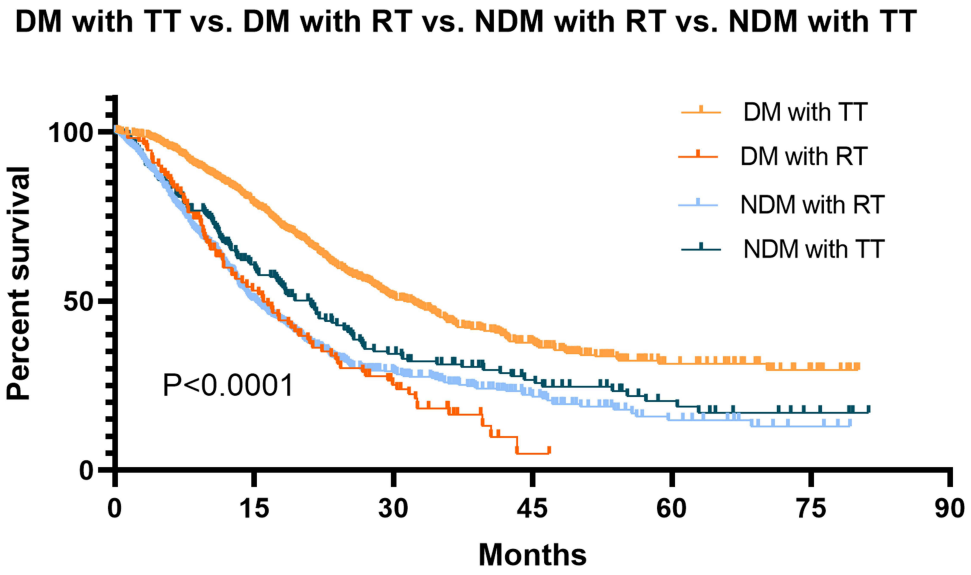

Figure 3 OS comparison of patients with different driving genes and treatment methods.

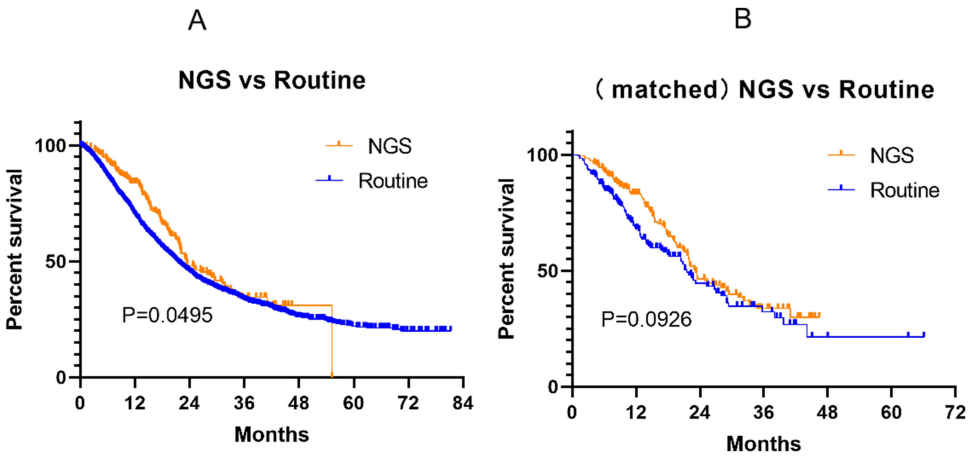

Figure 4 Comparison of OS between the NGS group and routine group.
Notes: (**A**) Unadjusted survival comparison between the NGS group and routine group. (**B**) Matched survival comparison between the NGS group and routine group.

matching, no significant differences were observed in the five- and three-year survival rates between the NGS and the conventional gene testing groups (with P-values greater than 0.05), whereas the one-year survival rate was higher in the NGS group (83.2% vs 68.1%, HR = 0.4890, 95% CI = 0.3170–0.7544, P = 0.0015, Figure 5).

Discussion

Our study included 1663 patients with advanced NSCLC. Patients who underwent NGS testing were divided into six periods for survival analysis: before the first-, second-, third-, fourth-, fifth-, and sixth-line treatments. Moreover, most patients underwent NGS testing before receiving first- (67.0%), second- (22.8%), third- (3.5%), and fourth-line (2.5%) treatments, thus avoiding the bias caused by testing before the fifth or more treatments. The NGS group had 197 cases, whereas the conventional gene sequencing group had 1466 cases. The proportion of patients who underwent NGS testing was 11.8% (197/1663), slightly lower than the reported testing rate of 15.4% in Presley CJ's study of US community hospital.[10] The proportion of NGS testing in coastal cities in China has reached the testing standard of US community hospitals. However, the proportion of NGS testing in lung cancer patients in China remains low due to the relatively late start of technology and high costs.

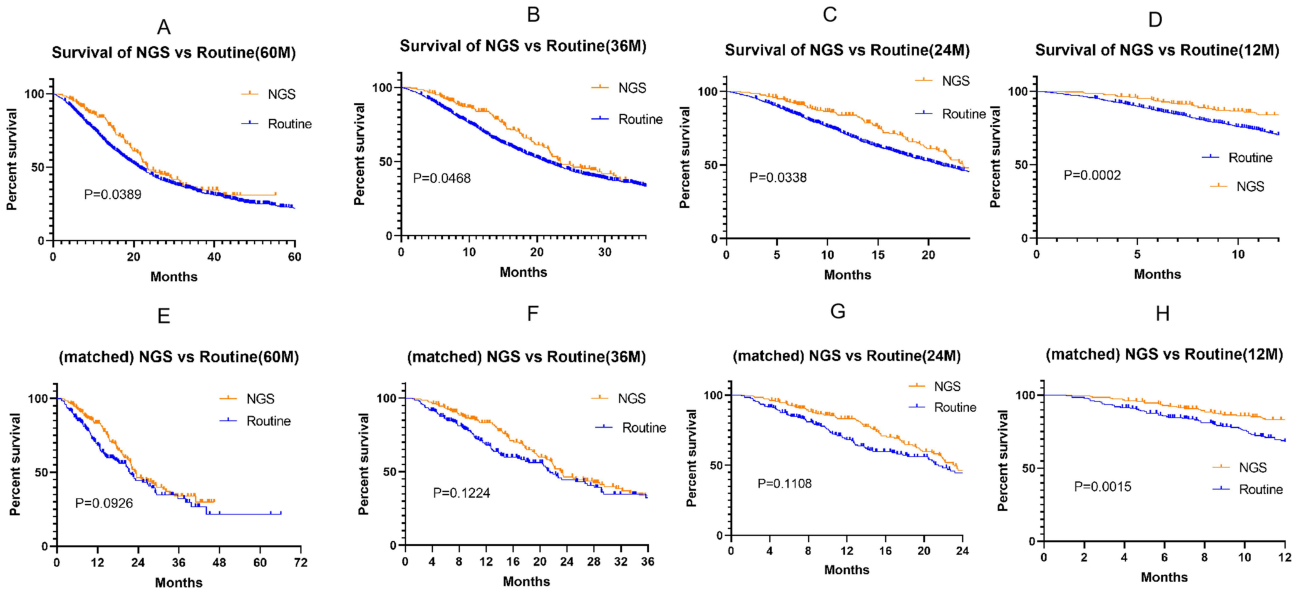

Figure 5 Comparison of 5-year, 3-year, 2-year, and 1-year survival rates between the NGS group and routine group.
Notes: (**A**) Unadjusted 5-year survival rate comparison between the NGS group and routine group. (**B**) Unadjusted 3-year survival rate comparison between the NGS group and routine group. (**C**) Unadjusted 2-year survival rate comparison between the NGS group and routine group. (**D**) Unadjusted 1-year survival rate comparison between the NGS group and routine group. (**E**) Matched 5-year survival rate comparison between the NGS group and routine group.(**F**) Matched 3-year survival rate comparison between the NGS group and routine group.(**G**) Matched 2-year survival rate comparison between the NGS group and routine group.(**H**) Matched 1-year survival rate comparison between the NGS group and routine group.

Kris et al[14] reported a retrospective study of 733 advanced lung cancer patients who received at least one genetic test, including *EGFR, ALK, KRAS, BRAF, ERBB2, MET, PIK3CA, MEK1, NRAS*, and *AKT1*, at 14 research centers in the US from 2009 to 2012. They indicated that 28% of patients (275/1007) chose targeted therapy or clinical research. Patients with driver genes who received corresponding targeted drugs had the longest median OS of 3.5 years, while patients with driver genes who did not receive corresponding targeted drugs had a median survival of only 2.4 years, and patients without driver genes had the shortest median OS of 2.1 years ($P < 0.001$). A meta-analysis of 570 studies and a total of 32,149 patients conducted by Schwaederle et al[15] exhibited that personalized precision therapy had a higher median RR (31% vs 10.5%, $P < 0.001$) and prolonged median PFS (5.9 months vs 2.7 months, $P < 0.001$) and OS (13.7 months vs 8.9 months, $P < 0.001$) than non-personalized treatment. Personalized precision therapy using genomic biomarkers had longer median PFS and OS than the protein biomarkers (all $P < 0.05$). Personalized precise treatment with driver gene guidance is associated with lower treatment-related mortality than non-personalized therapy (median 1.5% vs 2.3%, $P < 0.001$) and improves patient survival. Tsimberidou[16] compared advanced NSCLC patients (n = 143) with driver genes undergoing matched targeted therapy to untreated patients (n = 236) in the phase-I clinical trial. The results indicated that patients receiving matched therapy had a higher ORR (12% vs 5%, $P < 0.0001$), longer median PFS (3.9 months vs 2.2 months, $P = 0.001$), and longer median OS (11.4 months vs 8.6 months, $P = 0.04$). Matched therapy was an independent predictor of response ($P < 0.015$) and PFS ($P < 0.004$) in multivariate analysis. Presley[10] reported that median OS in advanced NSCLC patients with driver genes was significantly improved with targeted therapy than in patients who did not receive targeted therapy (18.6 months vs 11.4 months, $P < 0.001$). Personalized strategies are independent predictors of better prognosis and fewer toxic deaths in malignant tumors.[15] Most research present that driver gene-guided precise, personalized therapy significantly improves patient prognosis. However, a Phase II multicenter study conducted in France by Le Tourneau[17] revealed that the study included adult patients with any type of metastatic solid tumor with treatment-resistant standard therapy. Patients were tested and identified molecular changes matched with one of 10 regimens, including 11 available molecular targeted drugs (erlotinib), and were randomly assigned to matched molecular targeted drugs (experimental group) or physician-selected treatment (control group). The median Progression-free survival (PFS) was 2.3 months in the experimental group and 2.0 months in the control group (HR = 0.88, 95% CI = 0.65–1.19, $P = 0.41$). Beyond their indications, molecularly targeted drugs do not improve progression-free survival compared to physicians' treatment methods. Our research exposed that the median OS of 1663 advanced NSCLC patients who underwent genetic testing was 21.9 months, and the five-

year survival rates were 22.0%. The median OS of patients receiving (n= 909) targeted therapy was significantly higher for patients with driver gene testing than for patients who did not receive (n = 754) targeted therapy (28.3 months vs 15.4 months, HR = 0.5426, 95% CI 0.4768–0.6176, P < 0.0001). After matching analysis, the conclusion was the same, and the median OS of patients receiving targeted therapy was significantly extended (27.5 months vs 14.8 months, HR = 0.5572, 95% CI 0.4796–0.6474, P < 0.0001). Consistent with previous reports[10,14,15] our research indicates that targeted therapy guided by driver genes can significantly improve the prognosis of Chinese lung cancer patients and further consolidate the position of targeted therapy in treating NSCLC. However, phase II clinical trial results by Le Tourneau[17] were negative, possibly related to the enrollment criteria. The study's enrollment criteria were advanced metastatic solid tumors that were difficult to treat. Further subgroup analysis may be required to demonstrate the value of targeted precision treatment guided by driver genes. We further stratified the patients and discovered that patients with driver gene mutations who received targeted therapy had the longest median OS of 31.5 months, while 644 patients without driver gene mutations who received conventional treatment had the shortest median OS of 15.2 months. The median OS of the 183 patients without driver gene mutations who received targeted therapy was 21.1 months, while the median OS of the 110 patients with driver gene mutations who received conventional treatment was 16.0 months (P < 0.0001). Our results exhibit that patients treated with targeted therapy without driver genes have a longer median OS than those treated with conventional therapy with driver genes, inconsistent with the meta-analysis results reported by Schwaederle et al,[15] whose conclusion revealed that the prognosis of patients receiving targeted therapy without driver genes was worse than conventional chemotherapy. Possible reasons for this analysis are as follows: our study is based on an Asian population, where different races have different driver genes, resulting in significant differences in the types of targeted drugs and survival outcomes. Additionally, with the rapid progress of research, the clinical application of targeted therapy has become more diverse, and the proportion of Chinese patients receiving multi-line treatments is greater than that of foreign patients.

EGFR and *ALK* gene testing has gradually become routine for NSCLC, especially for lung adenocarcinoma patients. Compared to *EGFR/ALK* single-marker gene testing, NGS technology can evaluate multi-gene panels of tens to hundreds of genes, including sequencing the entire genome for coding and non-coding region insertion mutations, point mutations, copy number variations, and structural variations,[18–21] thus providing a high level of genomic sequencing and comprehensive genomic characterization information that can guide the development of personalized treatment strategies.[22] NGS, with its high throughput, rapid sequencing speed, low sample usage, and high sensitivity, can easily identify more mutation-driving genes, screen for patients benefiting from targeted therapy, maximize its benefits and reduce treatment-related adverse events. Therefore, NCCN guidelines recommend extensive genomic sequencing for testing and clinical guidance.[23] However, the clinical community has always been concerned that NGS, as a genetic testing method, may increase overall medical costs, and evidence regarding the clinical utility and cost-effectiveness of NGS testing is scarce.[24] Recently, two international retrospective studies on the clinical and economic value of NSCLC-based NGS testing (examining 30 genes) compared to *ALK/EGFR* single-gene testing have begun to address this issue. Presley et al[10] reported on 5668 patients with stage IIIB/IV or unresectable non-squamous NSCLC in community oncology practices in the United States. The unadjusted survival analysis results disclosed that the 12-month mortality rate was 35.9% for the NGS group and 49.2% for the conventional testing group, with a statistically significant difference (P < 0.001). The instrumental variable analysis revealed no correlation between NGS sequencing and 12-month mortality rate (predicted 12-month mortality rates were 41.1% with NGS and 44.4% with conventional testing; the difference was −3.6%, 95% CI = −18.4% to 11.1%, P = 0.63). This result was consistent with the propensity score matching survival analysis results (42.0% vs 45.1%, HR = 0.92, 95% CI = 0.73–1.11, P = 0.40). NGS testing only guided treatment for a few patients and did not improve survival compared to *EGFR/ALK* conventional gene testing. Regarding treatment costs and benefits, Steuten[25] demonstrated that NGS testing had moderate cost-effectiveness compared to patients undergoing *EGFR/ALK* conventional gene testing. The lifetime total cost of NGS testing per patient was $8814 higher, and the cost-effectiveness ratio of NGS testing increased by $148,478 per year of survival gained compared to conventional gene testing. Large-scale data from community hospitals in the United States revealed that the clinical benefits and cost-effectiveness of NGS testing were low compared to *EGFR/ALK* conventional gene testing.

Our results reveal that the unadjusted survival curve has an absolute difference in median OS between the NGS testing and the *EGFR/ALK* conventional gene testing groups (23.4 months vs 21.2 months, HR = 1.243, 95% CI = 1.017–1.519, P = 0.0495). After propensity score matching, the difference in median OS between the two groups of 187 matched patients was not statistically significant (23.1 months vs 21.5 months, HR = 1.288, 95% CI = 0.9557–1.735, P = 0.0926). Our results show

that NGS testing does not improve the median OS of patients compared to *EGFR/ALK* conventional gene testing. This result is consistent with a study in community hospitals in the United States reported by Presley,[10] exhibiting a significant difference between the two groups in the unadjusted survival curve (HR = 0.69, 95% CI = 0.62–0.77, P < 0.001). However, after propensity score matching, no significant difference existed in survival between the NGS and the conventional testing groups (HR = 0.92, 95% CI = 0.73–1.11, P = 0.40).

We further analyzed the survival of patients at 60, 36, 24, and 12 months. In unadjusted survival analysis, NGS patients had higher survival rates at five-, three-, two-, and one year compared to patients with *EGFR/ALK* conventional gene testing group (P-values were all less than 0.05). However, after propensity score matching, no significant difference was observed between NGS patients and *EGFR/ALK* conventional gene testing group regarding five-, three-, and two-year survival rates (P-values were all greater than 0.05). The one-year survival rate of NGS patients was improved (83.2% vs 68.1%, HR = 0.4890, 95% CI = 0.3170–0.7544, P = 0.0015). Although NGS testing did not improve the median OS of patients compared to *EGFR/ALK* conventional gene testing, it significantly improved the one-year survival rate, indicating a positive clinical significance of NGS testing. Compared to *EGFR/ALK* conventional testing, NGS testing can identify rare mutation sites or genes beyond *EGFR/ALK*, providing precise guidance for patients in selecting targeted drugs or choosing off-label drugs in clinical trials, thus achieving personalized treatment for lung cancer.

Although our research results exhibit that NGS testing currently has limited survival and clinical benefits compared to *EGFR/ALK* routine gene testing for improving NSCLC patients, we should still recognize the positive significance of NGS testing for patients who have significantly improved survival rates in the short term, especially those with rare mutations. In the future, NGS can realize its full value by improving the gap between genomic testing and the most appropriate treatment. The healthcare system is gradually developing, and it must recognize the potential value of NGS-based testing in cancer and cancer treatment, as well as widely incorporate personalized medical strategies into medical practice. The diagnosis and treatment mode of lung cancer will continue to undergo significant changes, and single-gene testing is no longer adequate for testing requirements with the discovery of additional driver genes and the development of corresponding targeted drugs. NGS, with its unique advantages, will demonstrate its value in future clinical applications.

Conclusion

Driver gene-guided targeted precision therapy improved the OS of advanced NSCLC patients significantly compared to non-targeted therapy. NGS testing did not improve the OS of advanced NSCLC patients compared to routine *EGFR/ALK* gene testing, but it improved the one-year survival rate of patients.

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Disclosure

The authors report no conflicts of interest in this work.

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