

Comprehensive Molecular Characterization of Young Chinese Patients with Lung Adenocarcinoma Identified a Distinctive Genetic Profile

HELEI HOU,^a HUA ZHU,^a HAN ZHAO,^b WEIHUA YAN,^b YONGJIE WANG,^c MAN JIANG,^a BIN LIU,^d DONG LIU,^a NA ZHOU,^a CHUANTAO ZHANG,^a PANSONG LI,^e LIANPENG CHANG,^e YANFANG GUAN,^e ZHE WANG,^f XIAOPING ZHANG,^f ZHUOKUN LI,^g BINGLIANG FANG,^h XIAOCHUN ZHANG^a

Departments of ^aMedical Oncology, ^bPathology, and ^cThoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao University, Qingdao, People's Republic of China; ^dDepartment of Medical Oncology, Affiliated Hospital of Shandong Academy of Medical Sciences, Jinan, People's Republic of China; ^eGeneplus-Beijing Institute, Beijing, People's Republic of China; ^fDepartment of Clinical Laboratory, BGI-Shenzhen, Shenzhen, People's Republic of China; ^gBGI-Qingdao Institute, Qingdao, People's Republic of China; ^hDepartment of Thoracic and Cardiovascular Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Lung adenocarcinoma • Young age • Next-generation sequencing • Genetic profile

ABSTRACT

Background. Occurrence at a younger age has been demonstrated to be associated with a distinct biology in non-small cell lung cancer. However, genomics and clinical characteristics among younger patients with lung adenocarcinoma remain to be determined. Here we studied the potentially targetable genetic alterations by next-generation sequencing (NGS) assay in young Chinese patients with lung adenocarcinoma.

Materials and Methods. Seventy-one surgically resected lung adenocarcinoma tissue samples from patients aged less than 45 years were collected with informed consent from all patients. Targeted NGS assays were used to identify actionable genetic alterations in the cancer tissues. Additionally, the genomic and clinicopathologic characteristics of 106 patients with lung adenocarcinoma who received NGS testing over the same period were analyzed retrospectively.

Results. The frequencies of targetable genetic alterations in 177 patients with lung adenocarcinoma were analyzed by

defined age categories, which unveiled a distinctive molecular profile in the younger group, aged less than 45 years. Notably, higher frequency of *ALK* and *HER2* genetic alterations were associated with young age. However, a reverse trend was observed for *KRAS*, *STK11* and *EGFR* exon 20 mutations, which were more frequently identified in the older group, aged more than 46 years. Furthermore, concurrent *EGFR/TP53* mutations were much more prevalent in the younger patients (81.6% vs. 46.8%), which might have a poor response to treatment with epidermal growth factor receptor tyrosine kinase inhibitor.

Conclusion. In this study, NGS assay revealed a distinctive genetic profile in younger patients with adenocarcinoma. High frequency of concurrent *EGFR/TP53* mutations was found in the younger patients, which especially warranted personalized treatment in this population. *The Oncologist* 2018;23:1008–1015

Implications for Practice: Further investigation is needed to understand the genomics and clinical characteristics of young patients with lung adenocarcinoma. In the present study, hybrid capture-based next-generation sequencing assays were used to identify targeted genetic alterations in young lung adenocarcinoma patients. Young patients with lung adenocarcinoma, aged less than 45 years, harbored a higher frequency of *ALK* and *HER2* genetic alterations compared with patients aged more than 46 years. Dramatically, concurrent *EGFR/TP53* mutations were much more prevalent in younger patients, which had a poor response to treatment with epidermal growth factor receptor kinase inhibitor. These results reveal a distinctive genetic profile in younger patients with adenocarcinoma, which might improve the treatment of this subpopulation.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide [1]. Prior studies have clearly demonstrated that occurrence at a younger age is associated with a

distinct biology that guides treatment in a number of cancers [2, 3]. NSCLC is considered to be a disease of the elderly, and young adult patients represent only a small proportion of

Correspondence: Xiaochun Zhang, M.D., Ph.D., Department of Medical Oncology, Affiliated Hospital of Qingdao University, Qingdao University, 16 Jiangsu Road, Qingdao, 266005, People's Republic of China. Telephone: 086053282913271; e-mail: zxc9670@126.com Received November 29, 2017; accepted for publication February 9, 2018; published Online First on April 26, 2018. <http://dx.doi.org/10.1634/theoncologist.2017-0629>

patients [4, 5]. Notably, NSCLC among young adults has been found to have an increasing incidence rate [6].

Patients who developed NSCLC at a young age have unknown risk factors and are poorly studied [7, 8]. Controversy persists regarding the relative prognosis of young patients compared with older patients with NSCLC. Study from the National Cancer Data Base showed that overall survival in younger patients with NSCLC is better than in older patients, with greater benefit seen in only earlier stages [5]. A retrospective analysis found that the prognosis of younger patients with NSCLC was poor, especially when the patients were not screened for driver mutations and the platinum-based doublet was the most frequently used treatment scheme [4]. Consequently, the molecular signature and clinical behavior of NSCLC in young patients must be defined, and a unique treatment approach can then be developed to improve the outcome of this population.

Few reports have focused on the incidence of targeted genetic alterations in younger patients with NSCLC, including lung adenocarcinoma, yet it now draws increasing research. Recent data have suggested that younger patients with lung adenocarcinoma had distinctive molecular features and harbored a high prevalence of targeted genetic alterations such as *ALK* rearrangement [9–13]. However, no difference of oncogenic mutations was found between Chinese younger and older patients with lung adenocarcinoma in a prior small study [14]. In terms of the prevalence of *EGFR* mutations in young patients with lung adenocarcinoma, the findings of several recent studies were controversial [9, 10, 13]. Consequently, multiple factors, including definition of young age, race, the relative rarity of young patients with lung adenocarcinoma, and the different genetic testing assays used, complicate and challenge this study.

Despite the larger number of potentially targeted genetic alterations identified in lung adenocarcinoma, only a few driven genes were studied in the aforementioned research in young patients via low throughput assays. In this study, broad, hybrid capture-based next generation sequencing (NGS) assays were used to identify targeted genetic alterations in young patients with lung adenocarcinoma, which could provide comprehensive knowledge of the genomics of this population.

MATERIAL AND METHODS

Patients and Samples

The diagnosis of adenocarcinoma was confirmed by hematoxylin and eosin staining. All formalin-fixed, paraffin-embedded tissue samples were reviewed by qualified pathologists to confirm the diagnosis of adenocarcinoma and ensure >30% tumor content. Staging of patients was assessed according to the 8th edition of the tumor, node and metastasis classification for lung cancer [15]. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Signed informed consent was obtained from all patients included in the study. All the experiments were carried out in accordance with the guidelines of the Ethics Committee of the Affiliated Hospital of Qingdao University and the National Health and Family Planning Commission of the People's Republic of China.

NGS-Based Assay

In this study, tissue samples from 177 patients were analyzed by NGS assay using three versions of capture-based targeted

sequencing panel. The details of this NGS assay may be found in the supplemental online Material and Methods, and gene lists of three versions of capture-based targeted sequencing panel are shown in supplemental online Table 1. Targeted genetic alterations were found in 28 genes in all 177 patients. However, only 16 of the 28 genes covered by all the three versions of NGS assay were selected for further analysis (supplemental online Fig. 1). This analysis focused on targetable genetic alterations annotated by categories of evidence Level 1–3 and Level R1 in OncoKB (Memorial Sloan Kettering Cancer Center, New York, NY, <http://oncokb.org/>).

Statistical Analysis

The experimental data are presented as mean \pm standard error. Pearson's chi-squared test, Fisher's exact test and Student's *t* test were used to analyze the gene mutation status and patient characteristics between the two groups. For all the tests, *p* values were two tailed. Statistical significance was defined as *p* < .05.

RESULTS

Design of the Study and Patient Characteristics

Between January 2013 and June 2016, we consecutively screened 2,535 patients who had surgically resected lung cancer diagnosed as adenocarcinoma. Among these patients, 106 were aged less than 45 years and accounted for 3.9% of the total cases. Tissue samples were collected from 72 patients and analyzed by NGS assay. Additionally, 105 consecutive adenocarcinoma cases that had received NGS assay during the above period were retrospectively collected. The design of the study may be found in supplemental online Figure 1.

The clinical characteristics of all 177 patients with lung adenocarcinoma with NGS assay are shown in Table 1. The average age of all patients was 51.5 years (range, 27–85 years); 62.7% (111/177) patients were women, and 71.2% (126/177) were never smokers. There were 1.7% (3/177) patients with stage 0 disease, 31.1% (55/177) with stage I disease, 8.5% (15/177) with stage II disease, 15.3% (27/177) with stage III disease, and 43.5% (77/177) with stage IV disease. One hundred sixty-seven primary tumor tissue samples and 10 metastasis biopsies were collected for NGS analysis.

Association Between Targeted Genetic Profile and Age

In prior studies, age cutoff points of 40 [10–12, 14, 16], 45 [17], 46 [5], and 50 [13, 18] years have all been identified as young age at NSCLC diagnosis. In this study, the frequency of targeted genetic alterations across three age groupings was compared to determine a reasonable age cutoff point. As shown in Figure 1, the difference of targeted genetic alterations between the first two groups was statistically insignificant (*p* = .566). However, the first two groups were statistically different from the third group (aged more than 46 years). Specifically, patients aged less than 40 years and patients between 41 to 45 years of age harbored a much higher frequency of *ALK* arrangement (25.0% vs 9.8%, *p* = .077) than patients aged more than 46 years (1.1%). We therefore identified an age at diagnosis of 45 years as a cutoff point to differentiate the younger and the older patients.

Table 1. Clinical characteristics of 177 patients with lung adenocarcinoma with next-generation sequencing assay

Parameters	Total (n = 177), n	Younger group (n = 87), n	Older group (n = 90), n	p value
Age, yr, mean ± SEM (range)	51.5 ± 13.0 (27–85)	40.2 ± 4.5 (27–45)	62.5 ± 8.3 (47–85)	<.001
Gender				.013
Male	66	24	42	
Female	111	63	48	
Smoking history				<.001
Never	126	74	52	
Former/current	51	13	38	
Stage				<.001
0	3	3	0	
I	55	37	18	
II	15	10	5	
III	27	25	2	
IV	77	12	65	
Tumor sample source				.747
Primary	167	83	84	
Metastatic	10	4	6	

Abbreviation: SEM, standard error of the mean.

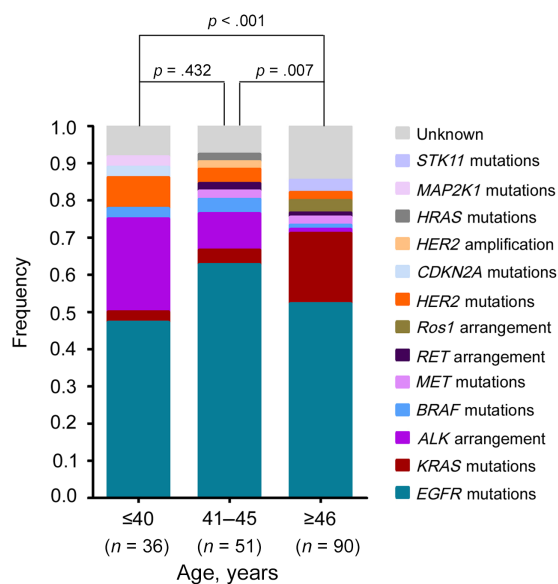


Figure 1. The genetic profiles in different age groups of patients with lung adenocarcinoma. One hundred seventy-seven patients with lung adenocarcinoma patients were enrolled, and tissue samples were analyzed by NGS assays. The frequency of targeted genetic alterations across three age groupings was compared to determine an age cutoff point that could differentiate young patients with a distinctive molecular profile. Statistical significance was defined as $p < .05$.

Prevalence of Targeted Genetic Alterations in Younger Patients with Lung Adenocarcinoma

Of the 177 lung adenocarcinoma patients, 87 less than 45 years of age were assigned to the younger group, and 90 more than 46 years of age were enrolled in the older group. There was significant difference in the distribution of age, gender, smoking history, and stage between the younger and older age groups (Table 1). More women, fewer smokers, and more early adenocarcinoma

were found in the younger group. The difference of tumor sample source between the two groups was not significant.

Potentially targetable genetic alterations were detected in 90.8% of younger patients. The specific alterations that were observed in the most common actionable targets included the following: *EGFR* ($n = 49$, 56.3%), *KRAS* ($n = 3$, 3.4%), *ALK* ($n = 14$, 16.1%), *BRAF* ($n = 3$, 3.4%), *RET* ($n = 1$, 1.1%), *HER2* mutations ($n = 5$, 5.7%), *CDKN2A* ($n = 1$, 1.1%), *HER2* amplification ($n = 1$, 1.1%), *HRAS* ($n = 1$, 1.1%), and *MAP2K1* ($n = 1$, 1.1%; Fig. 2A). Additionally, potentially targetable genetic alterations were identified in 85.6% of older patients and included the following: *EGFR* ($n = 47$, 52.2%), *KRAS* ($n = 17$, 18.9%), *ALK* ($n = 1$, 1.1%), *BRAF* ($n = 1$, 1.1%), *MET* ($n = 2$, 2.2%), *RET* ($n = 1$, 1.1%), *ROS1* ($n = 3$, 3.3%), *HER2* mutations ($n = 2$, 2.2%), and *STK11* ($n = 3$, 3.3%; Fig. 2B). A significant difference was seen between the younger and the older groups in targeted genetic profile identified by NGS ($p < .001$; Fig. 2C). Most importantly, 80.5% (70/87) of younger patients harbored genetic alterations mapping to therapies approved by the National Comprehensive Cancer Network (NCCN) Guidelines (version 1.2018 updates, Non-Small Cell Lung Cancer) approved therapies, compared with 54.4% (49/90) of older patients.

In terms of all the identified targeted genetic alterations, only the distribution of *KRAS* mutations and *ALK* arrangement differed significantly between the younger and older age groups (supplemental online Table 2). Compared with the older group, *KRAS* mutation was less frequent in the younger population (3.4% vs. 18.9%; $p = .002$), whereas *ALK* arrangement was significantly higher in the younger group (16.1% vs. 1.1%; $p < .001$; Fig. 3A, B). A comparable prevalence of *EGFR* mutations was identified between the younger and the older groups (56.3% vs. 52.2%; $p = .653$), whereas the distribution of *EGFR* mutation subtypes between the two groups was significantly different ($p = .024$; Fig. 3C, D). Among patients with *EGFR*-mutant lung adenocarcinoma, *EGFR* exon 19 del and L858R were most frequently detected (Fig. 3D). Of all the mutation

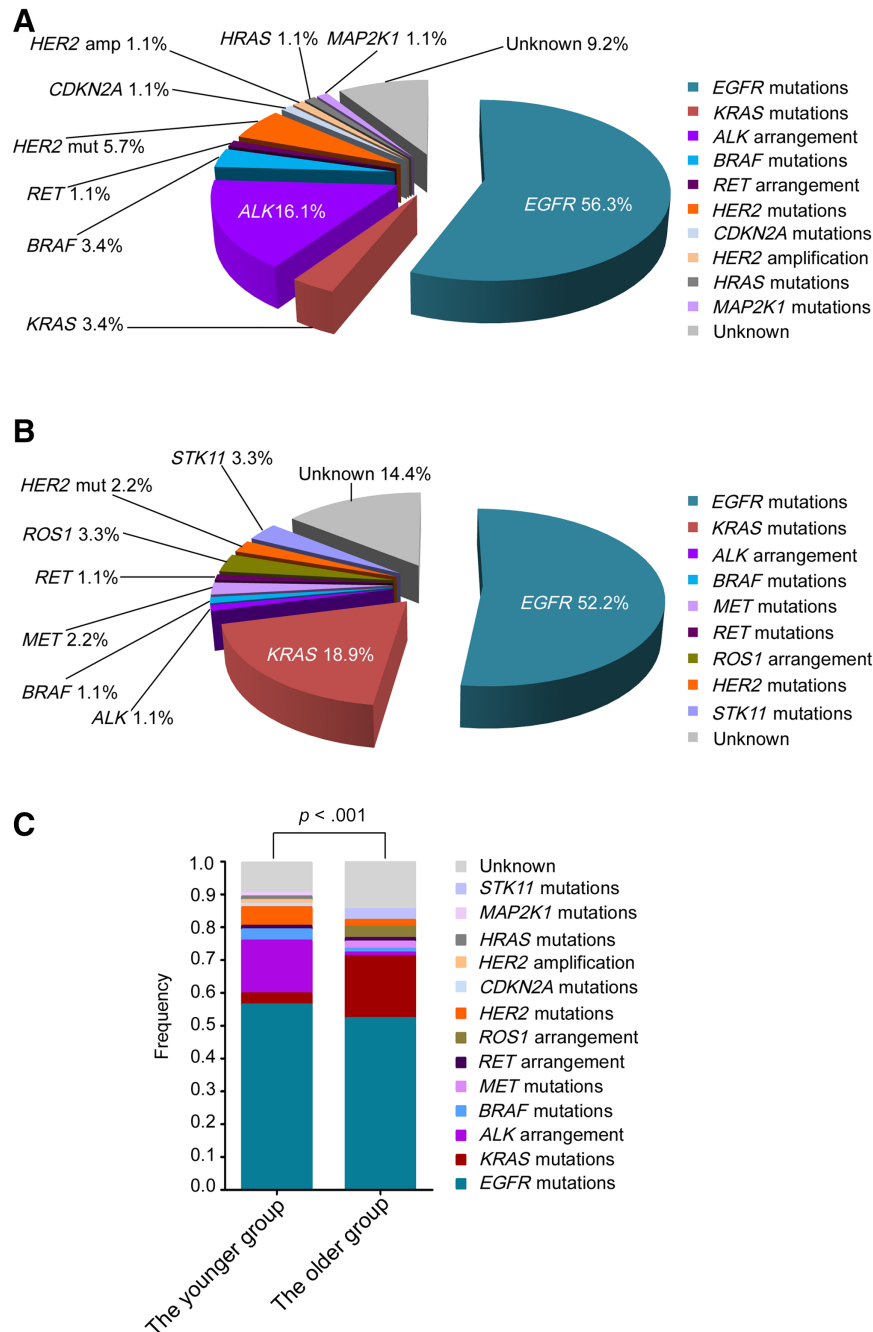


Figure 2. The targeted genetic profiles of younger and older patients with lung adenocarcinoma. **(A):** The targeted genetic profile of the younger patients, aged less than 45 years. **(B):** The targeted genetic profile of the older patients, aged more than 45 years. **(C):** The comparative analysis of the frequency of targeted genetic alterations between the younger and the older group. Statistical significance was defined as $p < .05$.

Abbreviations: amp, amplification; mut, mutation.

subtypes, exon 20 insertion was less frequent in the younger group ($p = .005$), whereas the frequencies of the remaining mutation subtypes were similar between the two groups (supplemental online Table 3).

For some patients, both approved drugs and experimental agents were simultaneously available because the patients harbored several different actionable alterations (supplemental online Fig. 2). *HER2* mutations, *HER2* amplification and *STK11* mutations commonly overlapped with other targeted alterations. When only the genetic alterations with the optimal clinical option were exhibited, no significant difference was

identified in these genes between the younger and the older groups (Table 2). However, taking into account all the single and concurrent genetic alterations, a high frequency of *HER2*-targeted alterations and a low frequency of *STK11* mutations were found in the younger group (*HER2* 13.8% vs. 4.4%; $p = .037$; *STK11* 1.1% vs. 8.9%; $p = .035$; Fig. 3E, 3F).

TP53 Mutations in Younger Patients with Lung Adenocarcinoma

Among the genetic alterations without available targeted agents identified by NGS assay, the most frequently mutated

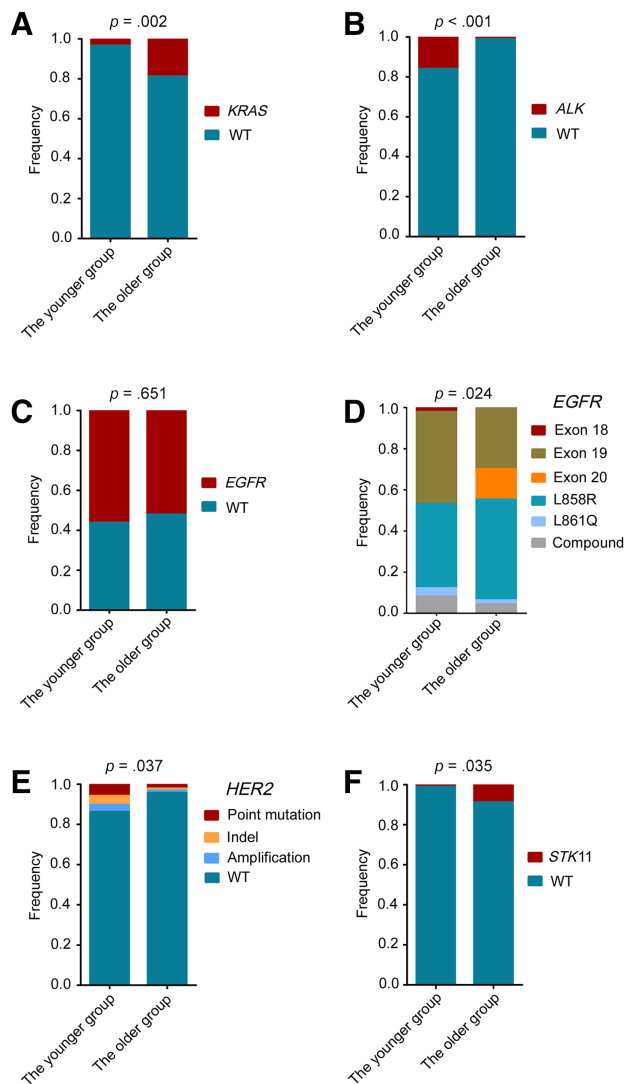


Figure 3. The distribution of representative targeted genetic alterations between the younger and older patients with lung adenocarcinoma. The comparative analysis of *KRAS* mutations (A), *ALK* arrangements (B), *EGFR* mutations (C), *EGFR* mutation subtypes (D), *HER2*-targeted genetic alterations (E), and *STK11* mutations (F) between the younger and the older groups. Statistical significance was defined as $p < .05$.

Abbreviation: WT, wild type.

gene was *TP53*. *TP53* mutations were comparably identified in the younger and the older group (56.3% vs. 48.9%; $p = .367$; Fig. 4A). However, concurrent *TP53* mutations were more frequent in *EGFR*-mutated patients than *ALK* arrangement patients (64.6% vs. 13.3%, $p < .001$; Fig. 4B). Notably, among the *EGFR*-mutant patients, concurrent *TP53* mutations were identified more frequently in the younger group compared with the older patients (81.6% vs. 46.8%; $p < .001$; Fig. 4C). Progression-free survival (PFS) data were available for 10 patients harboring concurrent *EGFR* and *TP53* mutations who had a median PFS of 5.2 months after treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs; Table 2). One patient (case #4) harboring *EGFR* exon 19del and *TP53* D259V experienced disease progression after 3.8 months of erlotinib maintenance treatment (Table 2, supplemental online Fig. 3).

DISCUSSION

NSCLC in young patients attracts increasing attention and accounts for less than 5.0% of all patients [5, 16, 17, 19]. Many studies have suggested that NSCLC in the young has unique characteristics, with greater percentages of female patients, adenocarcinoma, and never smokers [5, 7, 14, 17]. Younger patients with lung adenocarcinoma, especially those at an advanced stage, had no significantly better overall survival than older patients despite undergoing more aggressive treatment [14]. Although care of lung adenocarcinoma is rapidly changing with advances in genomic testing and the development of next-generation targeted agents, the molecular pathologic features of young patients have not been well investigated. A recent report demonstrated that younger age was associated with an increased likelihood of harboring a targetable genotype in NSCLC, including lung adenocarcinoma [13]. Most of the previous data on molecular features in young patients with lung adenocarcinoma have been discordant, and only a few driven genes have been studied using non-NGS assays [9, 10, 12–14]. Comprehensive genomic profiling using NGS could detect potentially targetable alterations missed by non-NGS assays and accelerate the development of targeted agents for rare mutational events [20, 21]. In this study, the genetic profile in young patients with lung adenocarcinoma was comprehensively identified by broadly targeted NGS testing. Patients under the age of 45 years harbored a distinctive genetic profile, and age 45 might be a useful age cutoff by which lung adenocarcinoma in the young could be defined. Notably, younger patients harbored a much higher rate of genetic alterations with NCCN-approved targeted agents than older patients. This is the first study demonstrating an association between young age and comprehensive genetic profile in lung adenocarcinoma.

Specifically, a higher frequency of *ALK* and a lower frequency of *KRAS* were identified in younger patients with lung adenocarcinoma, which were consistent with previous studies [9, 10, 13]. However, there have also been studies finding a similar prevalence of these genetic mutations, which might attributed to the small number of young cases [14, 22]. Additionally, our NGS study suggested an association between age and uncommon genetic alterations usually missed by standard genotyping. A higher frequency of *HER2*-targeted alterations and a low frequency of *STK11* mutations were identified in the younger patients in this study. A previous report by Kosuke Tanaka et al. also found that the frequency of *HER2* mutations was significantly higher in younger patients with adenocarcinomas compared with the older group [10]. However, a nonsignificant trend toward younger age at diagnosis was seen for *HER2* in a recent study, in which only *HER2* in-frame insertion in exon 20 was studied [13]. The above findings highlighted that all types of *HER2*-targeted alterations, including amplification, could be a valuable target in young patients with lung adenocarcinoma.

Compared with *ALK* arrangements, the prevalence of *EGFR* mutations in young patients with lung adenocarcinoma were highly controversial, as shown in supplemental online Table 4. Both a higher and a lower frequency of *EGFR* mutations have been identified in younger patients with lung adenocarcinoma, compared with their older counterparts [10, 13, 18]. In this study, no difference of all types of *EGFR* mutations or *EGFR*-sensitive mutations was found between the younger and the older

Table 2. Clinical data for partial patients with concurrent *EGFR* and *TP53* mutations

Cases	Age, yr	Sex	Smoking status	Stage	<i>EGFR</i> mutation status	Other actionable genetic alteration	<i>TP53</i> mutation	<i>EGFR</i> TKIs	Response	PFS, mo
#1	38	F	Never	IIIA	L747_A750del+p.L747_T751delinsS	<i>EGFR</i> amplification	I251F	Gefitinib (second line)	PR	4.7
#2	41	F	Never	IIA	E746_A750delELREA	—	H179R	Gefitinib	PR	11.4
#3	42	F	Never	IV	L858R	<i>EGFR</i> amplification	R110L	Gefitinib	PR	3.0
#4	43	F	Never	IV	E746_A750delELREA	—	D259V	Erlotinib (second line)	PD	3.8
#5	54	F	Never	IV	E745_T751delinsL	<i>EGFR</i> amplification	V272L	Icotinib	PR	6.7
#6	55	F	Never	IV	L858R	<i>HER2</i> amplification	M246V	Icotinib (second line)	PD	1.1
#7	62	M	Former	IV	E746_A750delELREA	<i>RICTOR</i> amplification; NF1 G311*	F113Y	Erlotinib (second line)	PD	2.0
#8	52	F	Never	IV	A763_Y764insFQEA	—	C238G	Gefitinib	PR	8.8
#9	57	F	Never	IV	L858R	<i>EGFR</i> amplification	c.919 + 1G>T	Gefitinib	PR	5.0
#10	58	M	Former	IV	L858R	<i>MDM2</i> amplification	D208G	Gefitinib	PR	5.6

Abbreviations: —, None; *EGFR*, epidermal growth factor receptor; F, female; M, male; PD, progressive disease; PFS, progression-free survival; PR, partial response.

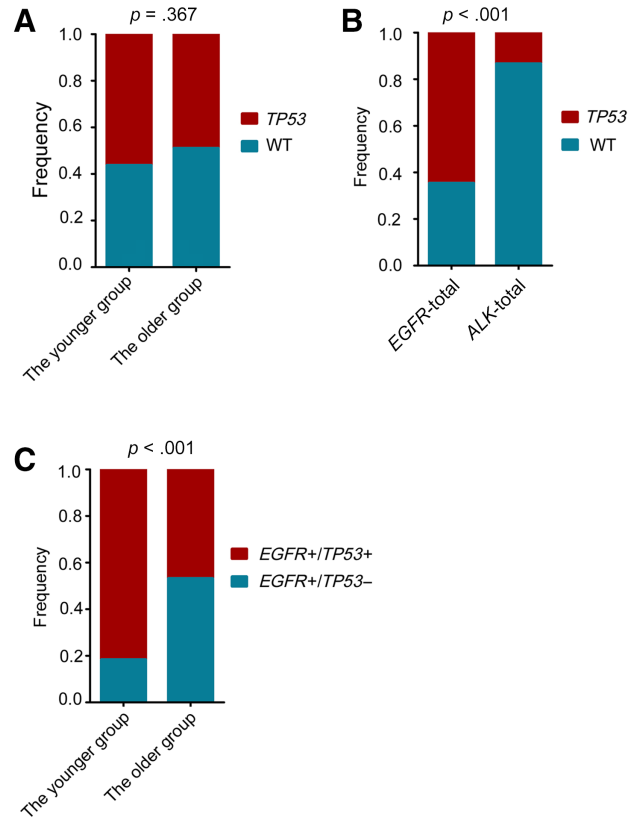


Figure 4. Mutation analysis of the *TP53* gene. **(A):** The comparative analysis of *TP53* mutations between the younger and the older groups. **(B):** Analysis of *TP53* mutations between patients with *EGFR* mutant and *ALK*-arranged lung adenocarcinoma. **(C):** Analysis of concurrent *EGFR/TP53* mutations between the younger and the older groups. Statistical significance was defined as $p < .05$. Abbreviation: WT, wild type.

patients. Our findings were consistent with another three studies in young patients with lung adenocarcinoma [9, 14, 22]. Interestingly, the *EGFR* exon 20 insertions, which predict resistance to clinically available *EGFR* TKIs, were less frequent in younger patients in our study. The conflicting data in the aforementioned research on *EGFR* prevalence in young patients with lung cancer might be attributed to race, age cutoffs, and pathology, which calls for further study.

Younger age was associated with an increased likelihood of harboring a targetable genotype, yet the survival of young patients with NSCLC was found to be unexpectedly poor compared with other age groups, suggesting more aggressive disease biology [13]. Prior research also implied that patients with lung adenocarcinoma of young age had poorer efficacy of *EGFR* TKIs [18]. The reason why young patients with *EGFR*-mutant adenocarcinoma had poor prognosis under *EGFR* TKI therapy is not clear, partially because of more brain metastases in this subpopulation [23]. Many mechanisms have been found to be involved in primary resistance to *EGFR* TKIs in advanced NSCLC with activating *EGFR* mutations [24]. Apart from these mechanisms, the commonly concurrent *TP53* mutations have been proved to reduce responsiveness to *EGFR* TKIs and worsen prognosis in patients with *EGFR*-mutated NSCLC [25, 26]. In this study, no higher prevalence of *TP53* mutations was found in the younger patients compared with older patients, which was not consistent to one prior finding [14]. However, we identified

much higher concurrent *EGFR/TP53* mutations in the younger patients than in their older counterparts. More importantly, follow-up data from partial patients harboring concurrent *EGFR/TP53* mutations patients have shown poor response to EGFR TKI treatment. Considering that concurrent *EGFR/TP53* mutations account for over 80% of the *EGFR*-mutant young patients, our report might disclose an important mechanism for poor prognosis and low efficiency of EGFR TKIs in this specific population. It has been reported young patients with lung adenocarcinoma tended to have a poorer prognosis and that angiogenesis of lung adenocarcinoma in young patients was more closely correlated with p53 expression than in elderly patients [27]. Consequently, the combination of erlotinib plus bevacizumab might be an optimal regimen in young patients with concurrent *EGFR/TP53*-mutant lung adenocarcinoma, warranting further well-conducted investigation to validate this deduction [28].

Although this is the first large NGS study on the molecular features of young patients with lung adenocarcinoma, several disadvantages must be considered. The patients included in this study were from a single institution and were all Chinese. Follow-up data are only available for a small number of the patients. Three versions of NGS testing were performed in this study, which resulted in complexity of sequence data analysis. In addition, the number of patients between 46 and 50 years of age enrolled in this research (only four patients) was too small to be analyzed as an age group. Therefore, further study is needed to define the age cutoff point for young patients with NSCLC who have a unique genetic profile.

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CONCLUSION

Young patients with lung adenocarcinoma are an understudied population who harbor high prevalence of *ALK* arrangement, *HER2*-targeted alterations, and concurrent *EGFR/TP53* mutations. The distinctive molecular profile identified in young patients with lung adenocarcinoma calls for more attention to personalized treatment of this population.

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AUTHOR CONTRIBUTIONS

Conception/design: Helei Hou, Xiaochun Zhang
Provision of study material or patients: Hua Zhu, Han Zhao, Weihua Yan, Yongjie Wang, Man Jiang, Dong Liu, Na Zhou, Chuantao Zhang
Collection and/or assembly of data: Helei Hou, Bin Liu, Pansong Li, Lianpeng Chang, Yanfang Guan, Zhe Wang, Xiaoping Zhang, Zhuokun Li
Data analysis and interpretation: Helei Hou, Bin Liu, Pansong Li, Lianpeng Chang, Yanfang Guan, Zhe Wang, Xiaoping Zhang, Zhuokun Li
Manuscript writing: Helei Hou, Bingliang Fang, Xiaochun Zhang
Final approval of manuscript: Helei Hou, Hua Zhu, Han Zhao, Weihua Yan, Yongjie Wang, Man Jiang, Bin Liu, Dong Liu, Na Zhou, Chuantao Zhang, Pansong Li, Lianpeng Chang, Yanfang Guan, Zhe Wang, Xiaoping Zhang, Zhuokun Li, Bingliang Fang, Xiaochun Zhang

DISCLOSURES

The authors indicated no financial relationships.

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For Further Reading:

Zong-Han Yao, Wei-Yu Liao, Chao-Chi Ho et al. Real-World Data on Prognostic Factors for Overall Survival in EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer Patients Treated with First-Line Gefitinib. *The Oncologist* 2017;22:1075-1083.

Implications for Practice:

The finding that chronic hepatitis C virus (HCV) infection might predict poor overall survival (OS) in epidermal growth factor receptor mutation-positive advanced non-small cell lung cancer (NSCLC) patients treated with first-line gefitinib may raise awareness of benefit from anti-HCV treatment in this patient population. Brain metastasis in the initial diagnosis or intracranial progression during gefitinib treatment is not a prognostic factor for OS. This study, which enrolled a real-world population of NSCLC patients, including sicker patients who were not eligible for a clinical trial, may have impact on guiding usual clinical practice.