Non–small cell lung cancer in the very young: Higher EGFR/ALK mutation proportion than the elder

Chien-Hui He[a,b], Jen-Fu Shih[a,c], Shinn-Liang Lai[a,c], Yuh-Min Chen[a,d,*]

[a]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, China Medical University, Taichung, Taiwan, ROC; [c]School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC; [d]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC

Abstract

Background: This study aimed to analyze pathologic characteristics, treatment, prognosis, and tumor epidermal growth factor receptor/anaplastic large-cell lymphoma kinase (EGFR/ALK) mutation proportion of non–small cell lung cancer (NSCLC) patients aged <40 years at diagnosis.

Methods: We retrospectively reviewed data of NSCLC patients diagnosed at Taipei Veterans General Hospital between June 2007 and December 2014, aged <90 years at the time of the diagnosis.

Results: We found 5051 cases of NSCLC, including 168 patients who were <40 years (younger group) and 4883 patients aged 40 to 89 years (older group). We found that the younger group had a significantly higher proportion of the EGFR mutation (22.6% vs 16.2%, $p = 0.026$) and the ALK mutation (4.2% vs 0.5%, $p < 0.001$) than the older group. Although the younger group included more stage IV patients (60.1% vs 49.6%, $p = 0.002$), it had a better overall survival (OS) rate (1 year: 73.7% vs 66.2%, $p = 0.043$; 5 years: 44.4% vs 33.7%, $p = 0.004$) (median survival time: 55 vs 26 months, $p = 0.002$). About the histologic subtype of NSCLC, the younger group presented less frequent cases of squamous cell carcinoma (4.2% vs 16.1%, $p < 0.001$), whereas the adenocarcinoma subtype was similarly frequent in the two groups (76.8% vs 76.5%, $p = 0.924$).

Conclusion: The OS rate in younger NSCLC patients was higher than that in the older NSCLC patients, despite the higher rate of stage IV NSCLC patients in the younger group. This survival benefit is most likely due to the higher proportion of the EGFR and ALK mutations and the corresponding tyrosine kinase inhibitor treatment.

Keywords: Adenocarcinoma; Carcinoma, non–small cell lung; Mutation

1. INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide.[1] Although it occurs mostly in older patients, there is a subset of patients diagnosed at a younger age (<40 years). Several studies had shown that the younger group had a higher proportion of females, nonsmokers, stage IV disease, and better survival rate.[2–6] However, most of these studies did not include tumor epidermal growth factor receptor/anaplastic large-cell lymphoma kinase (EGFR/ALK)-mutation data, especially for the younger group. We retrospectively studied the differences between the younger and the older patients diagnosed with non–small cell lung cancer (NSCLC), including pathology type, treatment characteristics, and EGFR/ALK mutation status.

*Address correspondence. Dr. Yuh-Min Chen, Department of Chest Medicine, Taipei Veterans General Hospital, 201,Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: ymchen@vghtpe.gov.tw (Y.-M. Chen).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000311.

Journal of Chinese Medical Association. (2020) 83: 461-465.

Received November 30, 2018; accepted January 13, 2020.

doi: 10.1097/JCMA.0000000000000311.

2. METHODS

We retrospectively reviewed the data of NSCLC patients diagnosed at Taipei Veterans General Hospital (TPEVGH) between June 2007 and December 2014, aged <90 years at the time of diagnosis. Patients were divided into two groups: <40 and 40 to 89 years, based on two previous large cohort studies conducted in the United States.[5,7] We excluded patients with histology-confirmed small-cell lung cancer and those who underwent non-standard treatment. All the patients were staged based on the seventh edition of The American Joint Committee on Cancer (AJCC) cancer staging manual, and they had been validated. The clinical data we collected included age, gender, smoking history, histology reports, date of death or last follow-up, initial treatments, Eastern Cooperative Oncology Group (ECOG) status, and EGFR and ALK mutations status. We basically performed the EGFR mutation test in stage IIIB and IV adenocarcinoma patients. Sixty-five patients in the young group underwent EGFR mutation testing from the total of 108 patients, and 56 of the 65 patients with stage IIIB and IV were diagnosed as adenocarcinoma. In case the EGFR test was negative, the ALK mutation testing was performed. To test for the ALK mutation, we used the immunohistochemistry kit from Roche (the VENTANA ALK D5F3 CDx assay). EGFR mutation testing was performed with the Cobas 4800 EGFR mutation assay V2 (Roche).

For statistical analysis, we used chi-square test and Fisher's exact test to assess the significance of the categorical variables.

Poisson regression was used to assess the trend of EGFR/ALK mutations in different age groups. Median overall survival (OS) was estimated using the Kaplan-Meier method. The log-rank test was used to detect the significance. Statistical significance was determined at $p \leq 0.05$. IBM SPSS software version 22 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. RESULTS

A total of 5051 NSCLC cases were diagnosed at TPEVGH from June 2007 to December 2014, of which 2979 were men and 2072 were women. At the time of the diagnosis, 168 patients (3.32%) were <40 years and 4883 patients (96.68%) were aged 40 to 89 years (Table 1). There was no statistically significant difference in gender ($p = 0.515$), ECOG level ($p = 0.070$), and in surgical treatment status ($p = 0.122$). About histologic subtypes, a lower percentage of squamous cell carcinoma was found in the younger group than in the older group (4.2% vs 16.1%, $p < 0.001$). There was no statistical difference in the proportion of adenocarcinoma between the two age groups (76.8% vs 76.5%, $p = 1.000$). Compared with older patients, a higher percentage of younger patients was diagnosed with stage IV (60.1% vs 49.6%, $p = 0.002$, Table 1 and Supplementary Table 1), EGFR mutations (22.6% vs 16.2%, $p = 0.026$), ALK mutations (4.2% vs 0.5%, $p < 0.001$), and as nonsmoking (56.5% vs 54.3%, $p < 0.001$). The stage IV EGFR mutation positive lung adenocarcinoma rate was 60.7% in the younger group vs 54.59% in the older group. We performed a multivariate analysis. The results show that age did not have a major impact on OS ($p = 0.836$). ECOG ≥2 ($p < 0.001$), EGFR mutation status ($p < 0.001$), and smoking status ($p < 0.001$) have significantly affected OS.

The proportion of the EGFR (p for trend = 0.02) and ALK (p for trend < 0.001) mutations decreased gradually as the age increased (Fig. 1A, B, Table 2). Patients with

Table 1

Characteristics of patients with NSCLC aged <40 years and those aged 40 to 89 years

Characteristic	Age <40 y N = 168	%	Age 40-89 y N = 4883	%	*p*
Sex					
Male	95	56.5	2884	59.1	0.515
Female	73	43.5	1999	40.9	
ECOG					
0-2	160	95.2	4447	91.1	0.070
3-5	8	4.8	436	8.9	
Histologic diagnosis					
Adenocarcinoma	129	76.8	3734	76.5	1.000
SqC	7	4.2	784	16.1	<0.001*
Large cell	0	0	9	0.2	
NSCLC-NOS	16	9.5	25	0.5	
Others[a]	16	9.5	331	6.8	
Smoking					
Y	65	38.7	2190	44.8	<0.001*
N	95	56.5	2653	54.3	
Not known	8	4.8	40	0.8	
Surgery					
No surgery	114	67.9	2929	60.0	0.122
Segmentectomy or lobectomy	41	24.4	1479	30.3	
Port-A implantation	13	7.7	475	9.7	
EGFR/ALK mutation					
EGFR mutation	38	22.6	789	16.2	0.026*
EGFR wild-type	27	16.1	657	13.5	
EGFR not done	103	61.3	3437	70.4	
ALK mutation	7	4.2	23	0.5	<0.001*
ALK wild-type	7	4.2	134	2.7	
ALK not done	154	91.7	4726	96.8	
Primary treatment					
S(S, S + C, S + CR)	44	26.2	1552	31.8	0.125
RT	0	0	226	4.6	0.004*
CCRT	19	11.3	488	10.0	0.577
C	41	24.4	1153	23.6	0.812
TKI (TKI, TKI + S, TKI + R, TKI + C)	43	25.6	1119	22.9	0.417
No treatment/lost to follow-up after first visit	21	12.5	345	7.1	0.008*
Median survival (95% CI), mo	55.0	31.55-78.45	26.0	24.32-27.67	0.002*
Clinical stage					
I–IIIb	52	31.0	2171	44.5	0.002*
IV	101	60.1	2423	49.6	
Not completed	15	8.9	288	5.9	

C = chemotherapy; CCRT = concurrent chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; EGFR/ALK = epidermal growth factor receptor/anaplastic large-cell lymphoma kinase; NSCLC-NOS= non–small cell lung cancer, not otherwise specified; R = radiation; S = surgery; Sqc = squamous cell carcinoma; TKI = tyrosine kinase inhibitor.

[a]Typical carcinoid, sarcomatoid carcinoma, mucoepidermoid carcinoma, adenoSqC, and poorly different carcinoma.

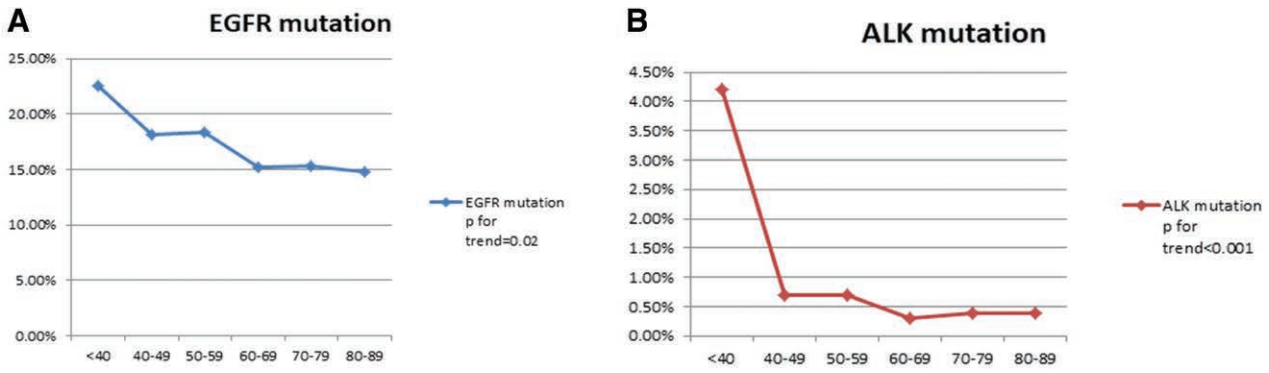

Fig. 1 A, EGFR mutation rate decreased as age increased. B, ALK mutation rate decreased as age increased. ALK = anaplastic large-cell lymphoma kinase; EGFR = epidermal growth factor receptor.

Table 2

EGFR/ALK mutation rate in different age groups

	Age, y						
TKI mutation	**<40**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	
EGFR mutation	38	77	204	203	197	108	*p* for trend = 0.02
	22.6%	18.1%	18.4%	15.2%	15.3%	14.8%	
ALK mutation	7	3	8	4	5	3	*p* for trend <0.001
	4.2%	0.7%	0.7%	0.3%	0.4%	0.4%	

ALK = anaplastic large-cell lymphoma kinase; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

ALK mutation were younger than those who were negative (p = 0.023; Supplementary Table 4)

A higher percentage of younger patients received first-line treatment with tyrosine kinase inhibitor (TKI) than older patients, although with no statistical significance (25.6% vs 22.9%, p = 0.417, Table 1). In contrast, a higher percentage of older patients received radiotherapy alone (p = 0.016) as a first-line treatment option.

The younger group had a higher OS rate than the older group, in all stages (1-year OS: 73.7% vs 66.2%, p = 0.043; 5-year OS: 44.4% vs 33.7%, p = 0.004; Fig. 2 and Supplementary Table 2) and in stage IV patients (1-year OS: 68.3% vs 52.7%, p = 0.021; 5-year OS: 22.1% vs 11.9%, p = 0.002; Fig. 3 and Supplementary Table 3). They had less radiotherapy alone (0% vs 4.6%, p = 0.004) as primary treatment. A higher percentage of patients in the younger group were lost to follow-up (12.5% vs 7.1%, p = 0.008).

4. DISCUSSION

Lung cancer is usually diagnosed after 50 years of age and is relatively rare in younger patients.[8,9] Previous studies showed

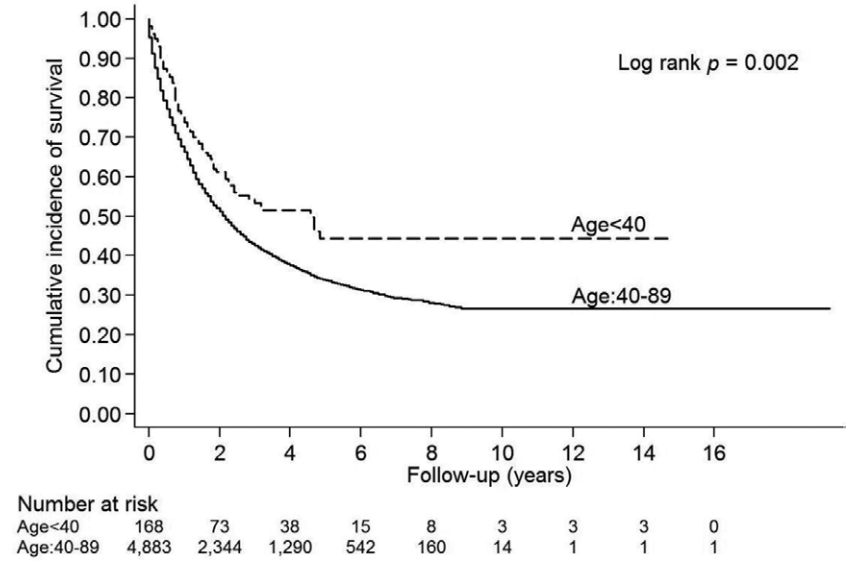

Fig. 2 Overall survival curve in all stage patients (log-rank), p =0.002.

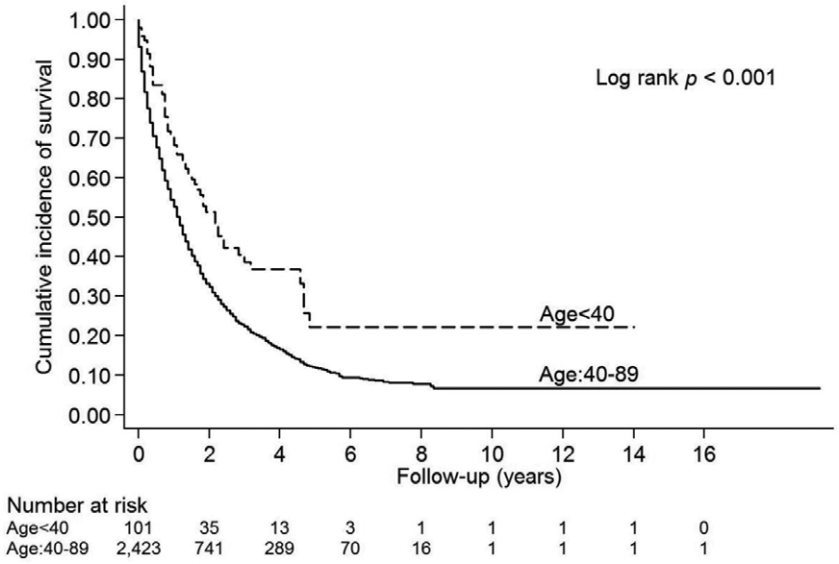

Fig. 3 Overall survival curve in stage IV patients (log-rank), $p < 0.001$.

controversial results on patients' clinical presentation and prognosis, even in multicenter cohort studies.[5–8] Due to the new targeted therapies that became available in recent years, patients' survival rate has significantly improved.[10] To determine whether young NSCLC patients have different clinical presentation and prognosis, especially the response TKI treatment, than older patients, we conducted the present study. A previous study by Nugent et al[3] found that the median survival rate of the younger group was better in stages I to IIIA, with no difference in inoperable patients. Our findings of better OS rate in the younger group in all stages (Fig. 2) were compatible with the results from previous studies,[3,6] and we even found a better OS in stage IV younger patients (5-year OS: 22.1% vs 11.9%, $p < 0.001$; Fig. 3). However, the current results are not consistent with the findings from 30 years ago from our hospital.[11] The prognosis of NSCLC patients improved over the past decades, with patients having a better survival rate, especially after the introduction of EGFR-TKI and ALK-TKI treatments, used for the past 15 years.

Adenocarcinoma was the predominant cell type in our study as well as in previous studies.[3,6–8,9,11] We found that the younger patients had a higher rate of EGFR ($p = 0.026$) and ALK ($p < 0.001$) mutations than the older patients. Thus, a higher proportion of patients in the younger group received the first-line TKI treatment, compared with the older group, although it was not a statistically significant result. A recent study revealed that EGFR/ALK mutations are more frequent in young people in a Latin American population.[9] Patients with ALK mutation were younger, on average, than those without the mutation (Supplementary Table 4). The higher proportion of patients who had EGFR/ALK mutations in the younger group and the higher proportion of patients who received first-line TKI treatment could partly explain why the younger group had better survival rates in stage IV patients than the older group ($p < 0.001$; Fig. 3). There were less percentage in squamous cell carcinoma, and smoker in the young group, but more stage IV patients were compatible with previous studies, including our study.[3,6–8,12–14]

The limitations of our study are related to the retrospective design, to some data missing in some patients, and to the fact that not all stage IV adenocarcinoma patients were tested for EGFR/ALK mutations. We believe that further studies in this area are needed.

The present study is the first study in Asia showing that younger patients had higher proportion of EGFR and ALK mutations, and that they were more likely to receive first-line TKI treatment. They also had a better survival rate than older patients, even though the younger group had more stage IV patients than the older group.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**:74–108.
2. Lara MS, Brunson A, Wun T, Tomlinson B, Qi L, Cress R, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a California Cancer Registry analysis. *Lung Cancer* 2014;**85**:264–9.
3. Nugent WC, Edney MT, Hammerness PG, Dain BJ, Maurer LH, Rigas JR. Non-small cell lung cancer at the extremes of age: impact on diagnosis and treatment. *Ann Thorac Surg* 1997;**63**:193–7.
4. Subramanian J, Morgensztern D, Goodgame B, Baggstrom MQ, Gao F, Piccirillo J, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. *J Thorac Oncol* 2010;**5**:23–8.
5. Thomas A, Chen Y, Yu T, Jakopovic M, Giaccone G. Trends and characteristics of young non-small cell lung cancer patients in the United States. *Front Oncol* 2015;**5**:113.
6. Kuo CW, Chen YM, Chao JY, Tsai CM, Perng RP. Non-small cell lung cancer in very young and very old patients. *Chest* 2000;**117**:354–7.
7. Arnold BN, Thomas DC, Rosen JE, Salazar MC, Blasberg JD, Boffa DJ, et al. Lung cancer in the very young: treatment and survival in the National Cancer Data Base. *J Thorac Oncol* 2016;**11**:1121–31.
8. Ramalingam S, Pawlish K, Gadgeel S, Demers R, Kalemkerian GP. Lung cancer in young patients: analysis of a surveillance, epidemiology, and end results database. *J Clin Oncol* 1998;**16**:651–767.
9. Luis CR, Oscar A, Luis M, Báez-Saldaña R, Castillo-Fernández O, Blais N, et al. An international epidemiological analysis of young patients with non-small cell lung cancer (AduJov-CLICaP). *Lung Cancer* 2017;**113**: 30–6.

10. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA* 2019;**322**:764–74.
11. Tsai CM, Perng RP, Huang WL. Lung cancer in young Chinese. *Cancer Detect Prev* 1988;**11**:235–8.
12. Capewell S, Wathen CG, Sankaran R, Sudlow MF. Lung cancer in young patients. *Respir Med* 1992;**86**:499–502.
13. Bourke W, Milstein D, Giura R, Donghi M, Luisetti M, Rubin AH, et al. Lung cancer in young adults. *Chest* 1992;**102**:1723–9.
14. Green LS, Fortoul TI, Ponciano G, Robles C, Rivero O. Bronchogenic cancer in patients under 40 years old. The experience of a Latin American country. *Chest* 1993;**104**:1477–81.