Demographics, Risk Factors and Survival Analysis of Lung Cancer in Young Adults (<30 Years) in China-A Retrospective Cohort Study

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Abstract

Background

Lung cancer in very young adults in China aged <30 is on the rise and the clinicopathological characteristics of this unique population are incomplete and are yet to be elucidated. Our study aims to explore the characteristics, trends and distinctive features of lung cancer this age group to provide more information that can aid in developing optimal treatment regimens and improve prognosis for this exclusive age group.

Method

A retrospective review of 141 lung cancer patients admitted at our hospital from August 2011 to October 2021 was performed. The focused age group in our study was 18-30 years old. The data collected included demographics, tumor pathology, gene mutations, and treatment. Overall survival and prognosis were systematically analyzed.

Results

From a total of 141 of young lung cancer patients, 139 were included in final analysis. The gender distribution in our series favored female(65.5%), and only 7.2% of the study cohort had a history of smoking. Adenocarcinoma was the most common histological type in our study, presenting 93.5% of all patients. The most common stages at diagnosis was stage I(61.2%) and stage IV(30.2%). Genetic testing was performed in only 24.5% (34/139) of the patients. From the 23/34 patients in our study who tested positive for a genetic mutation, 19 (82.3%) were stage IV. The most common gene mutation was Anaplastic Lymphoma kinase(ALK) rearrangement observed in 13/23 (56.5%) gene mutation positive patients. Among stage IV NSCLC, OS was longer in patients who received targeted therapy, compared to the patients not receiving target therapy: 88 months vs 24 months (95% CI: 0.15-1.0, $p=0.0282$).

Conclusion

Lung cancer in the young adult population has particular characteristics (Common in female, non-smoker and adenocarcinoma patients). Higher stages of disease were observed in those with a gene mutation (notably ALK rearrangement). Although the sample size was small, the current data suggests a higher mutation rate in the younger population. These findings have fundamental implications for practice and we propose that all patients under 30 diagnosed with lung cancer should undergo genetic testing so they can receive personalized treatment and therefore achieve better outcomes.

Introduction

Lung cancer is the leading cause of mortality worldwide, responsible for almost 30% of all cancer-related deaths in China [1]. In the last few decades, there has been an exponential increase in incidence and mortality owing to lung cancer [2, 3]. Lung cancer is also the most common cancer type and cause of death due to cancer in China, responsible for 0.72 million deaths in 2020 [4].

It is well known that increasing age is associated with an increased risk of developing lung cancer, with an average age being about 70 years at diagnosis. Lung cancer incidence in younger Chinese populations, aged less than 45 is only about 3.5% [5]. In recent years, there has been a surge of lung cancer in the young adult population, especially within Chinese populations [6, 7].

Generally, clinical characteristics, presentation, demographics, treatment and outcomes of disease are quite different between the younger (≤ 45 years) and older population. Common risk factors in the older population include tobacco usage, exposure to air pollution, carcinogens, and radiation. Adenocarcinoma is more commonly observed in patients in early-onset disease compared to the elderly population [8]. Current data shows a predominance of female patients with adenocarcinoma in the younger populations with a more advanced stage at diagnosis [9–11]. Frequency of oncogenic driver mutations such as ALK, RET, epithelial growth factor receptor (EGFR), ROS1 and others have also been found to be higher in those with early onset disease than in the elderly population [12–14]. The studies available discussing these differences are quite limited and the data is highly variable as well. Genomic characteristics in the very young population (<30) with lung cancer in the Chinese cohort have yet to be elucidated.

Our understanding of risks in regards to lung cancer in younger patients, specifically in the under 30 years subgroup is very limited and only a handful of large-scale studies have been conducted in young Chinese lung cancer patients. Therefore, it is necessary to conduct further studies to confirm current demographics and further explore this unique population and clarify current controversies. Our study aims to explore the characteristics, trends and distinctive features of lung cancer in ages ranging from 18-30 years from The First Affiliated Hospital, College of Medicine, Zhejiang University, in order to provide more information that can aid in developing optimal treatment regimens and improve prognosis for this exclusive age group.

Materials And Methods

Study Design

Data was retrospectively collected from 141 patients aged 30 and younger at admission and were pathologically diagnosed with lung cancer from August 2011 until October 2021 The First Affiliated Hospital, College of Medicine, Zhejiang University. The data collected included (A) personal data: name, age, sex, (B) smoking status and history, (C) tumor pathology and stage, (D) gene mutations, if any, (E) treatment. Disease was staged according to the seventh edition of the TNM (tumor, node, and metastasis) classification system. Smoking status was divided into two categories: non-smokers and smokers (including current and previous smokers). The Ethics Committee of The First Affiliated Hospital,

College of Medicine, Zhejiang University approved this study. All patients provided informed consent for the use of their clinical data and tumor tissues for research

Gene Mutation Assessment

Molecular alterations were retrospectively assessed from the archived tumor sample when possible. Gene mutations were assessed using a PCR-based pyrosequencing assay, which includes EGFR, KRAS, BRAF, HER2, and MET, ALK and ROS1 translocations, and ALK positive results were confirmed by fluorescent in situ hybridization (FISH).

Statistical analysis

Survival analysis was performed for each group using the Kaplan-Meier method with log-rank statistics. All statistical analyses were performed using the GraphPad Prism 8 software. Statistical significance was defined as $p \leq 0.05$.

Results

Patient Characteristics

The initial patient population consisted of 143 patients (92 female, 64.3%; 51 male, 35.6%). Due to lack of follow-up data, 4 patients (3 male, 1 female) were excluded from the final patient population. The final patient population studied consisted of 139 patients (91 female, 65.5%; 48 male, 34.5%), ranging from ages 18 to 30 years. From final patient population, 10 patients (7.2%) had a history of smoking, of which all were male.

Non-small cell lung cancer (NSCLC) was the most common type of lung cancer found in our cohort, consisting of 134 (96.4%). Of these 134 patients, 130 were diagnosed with lung adenocarcinoma (87 female, 66.9%; 43 male, 33.1%) and 4 with squamous cell carcinoma (3 male, 75%; 1 female 25%). The 10 patients with a smoking history were all diagnosed with NSCLC (9 male adenocarcinoma, 90%; 1 male squamous cell carcinoma, 10%). Small cell lung cancer (SCLC) was diagnosed in only 2 male patients. Finally, 3 females were diagnosed with other miscellaneous cancers including mucoepidermoid, neuroendocrine and lymphoepithelial, respectively.

A majority of the patients were diagnosed early in the disease course with a total of 85 (61.5%) stage I patients (62 female, 72.9%; 23 male, 27.1%). Distribution of patients in the other stages are as follows: 3 stage II patients (3 female, 100%); 5 stage III patients (3 female, 60%; 2 male, 40%); 42 stage IV patients (22 female, 52.4%; 20 male, 47.6%); 4 stage 0 (Carcinoma In Situ; CIN) (3 male, 75%; 1 female, 25%). Patient demographics are illustrated in Table 1.

Table 1
Demographics of study population

Demographic characteristics	Studied population (<i>n</i> = 139, %)
Median age (year, range)	26.9 (18-30)
Sex	
Male	48 (34.5)
Female	91 (65.5)
Smoking status	
Non-smoker	129 (92.8)
Formal or current smoker	10 (7.2)
Pathological type	
Adenocarcinoma	130 (93.5)
Small cell carcinoma	2 (1.4)
Squamous cell carcinoma	4 (2.9)
Mucoepidermoid carcinoma	1 (0.72)
Neuroendocrine carcinoma	1 (0.72)
Lymphoepithelial carcinoma	1 (0.72)
Disease Stage	
CIN	4 (2.9)
I	85 (61.2)
II	3 (2.2)
III	5 (3.6)
IV	42 (30.2)
CIN: carcinoma in situ	

Out of the final 139 patients, gene testing was performed in 34 patients (21/34 female; 13/34 male). Gene testing was positive in 23 patients (15 female; 8 male) and negative in 11 patients (6 female, 5 male). The most common gene mutation was ALK fusion observed in 13/23 patients, 9/15 female and 4/8 male. Other mutations noted were EGFR-19 deletion in 6/23 patients (3/15 female, 3/8 male), and ROS1 fusion in 4/23 patients (3/15 female, 1/8 male). In addition, out of the 23 positive patients, 19 patients (12 female, 4 male) were noted to be stage 4 in the disease course. 3/23 of the patients (2

female, 1 male) were observed to be stage 3 and 1/23 of the patients (1 female) was observed to be stage 2. Data regarding gene mutations is presented in Table 2 and illustrated in Figures 1 and 2.

Table 2
Genetic Status Assay

Genetic status assay (n = 139)	n	%
Driver gene mutation-positive	23	16.5
<i>ALK Fusion</i>	13	9.4
<i>EGFR-19 Deletion</i>	6	4.3
<i>ROS1 Fusion</i>	4	2.9
Driver gene mutation-negative	11	7.9
No genetic testing during hospitalization	105	75.5

Treatment

Surgery was conducted for 62.6% (87/139) of patients. Of 87 patients with surgery records, 20 had undergone thoracic radiotherapy treatment, 6 patients received additional of adjuvant therapy and 3 patients received neoadjuvant chemotherapy. For the 21 patients (15.1%) who were unable to undergo surgery (stages IIIb, IIIc and IV patients), received chemotherapy (14 patients) or chemotherapy plus immuno-checkpoint inhibitors (ICIs) (7 patients) at first-line. The 19 (13.7%) stage IV patients with gene mutations received molecular targeted treatment at first line which included crizotinib, gefitinib and alectinib. 12 patients (8.6%) refused any therapy. The treatment data is presented in Table 3.

Table 3
Treatment regimen of the study population

Treatment	n=139
Surgery(Stage I+II+IIIa)	87 (62.6%)
<i>No adjuvant therapies</i>	<i>79</i>
<i>Addition of adjuvant therapies</i>	<i>6</i>
<i>Neoadjuvant chemotherapy</i>	<i>3</i>
<i>Thoracic radiotherapy</i>	<i>20</i>
Chemotherapy at first-line (Stage IIIb+IIIc+IV)	21 (15.1%)
<i>Only chemotherapy</i>	<i>14</i>
<i>Chemotherapy +ICIs</i>	<i>7</i>
Targeted Therapy at first-line (Stage IV)	19 (13.7%)
<i>Crizotinib</i>	<i>17</i>
<i>Gefitinib</i>	<i>5</i>
<i>Alectinib</i>	<i>1</i>
Refused Therapy	12 (8.6%)
ICIs: Immuno-checkpoint inhibitors	

Survival

Amongst the 139 patients in the final cohort, 9 patients were lost for follow-up for the survival analysis(2 patients at stage I and 7 patients at stage IV). The median overall survival (OS) of the CIN was not reached, and ranged from 29 to 76 months. For the stage I patients the median OS was not-reached, and ranged from 13 to 126 months. The median OS for the stage II, stage III, stage IV patients were 44 months (range 26-58months), 22 months (range 12.3-25months) and 24 months (range 2.0-100 months), respectively(Figure 3A). Among stage IV NSCLC, OS was longer in patients who received targeted therapy when a druggable molecular alteration (*ALK* or *ROS1* rearrangement or *EGFR*) was found, compared to the patients without received target therapy: 88 months vs 24 months (95% CI: 0.15-1.0, p=0.0282) (Figure 3B).

Discussion

Lung cancer is a leading cause of morbidity and mortality globally [15, 16]. The increase in number of young lung cancer patients in China is garnering much attention in the recent years, but the data available currently is very limited. In our study, we focus on a very young population aged under 30 years

and aim to investigate the demographics and traits that may be associated with young lung cancer patients.

Our study collected 139 young adults (under age 30). There were several major findings in this study. Firstly, lung cancer frequently occurred in young women than young men, and most patients did not have a history of smoking or family history of lung cancer. Secondly, adenocarcinoma was the most common histological type in young lung cancer patients. Thirdly, the presence of a gene mutation was associated with a higher stage on diagnosis.

The gender distribution in our series favored female (65.5% of cases), in agreement with previous studies [9, 17], but another study in Chinese young adults found a predominance of males in their cohort. This may be due to a larger range of age studied by Li et al. (20-45 years), but our cohort only ranged from patients aged 18-30 years [18].

It has been well established that smoking is a major risk factor and also an independent prognostic factor for lung cancer [19, 20]. Wang et al. have reported that cancer-related death in 75% of males and 18% of females are attributable to tobacco use in China [21]. Regarding smoking status influencing development of cancer in younger patients, there has been some disagreement. The study population of Li et al. found that 72% of their study population were smokers and therefore concluded that smoking is also a major risk factor in their study [18]. On the contrary, only 7.2% of our patients were found to have a history of smoking. Although occupational, environmental or family history was not collected in our study, we believe that another element, environmental or genetic might play a more prominent role in the development of lung cancer in the very young Chinese population [22]. Particularly in females, passive exposure to pollutants and household exposure could be a more attributable link to the development of lung cancer [23, 24]. Most patients in our study had no smoking history, therefore leading us to believe another environmental or genetic element may be associated with the increase in young lung cancer patients in China and further exploration in this subgroup is worth further investigation.

Adenocarcinoma was the most common histological type in our study, presenting 67.6% of all patients. Previous studies have also concluded a higher incidence of adenocarcinoma in the younger patient population [25, 26]. In some cohorts, it has been found that a large number of young lung cancer patients present with advanced disease at diagnosis [9, 27, 28], but our study found that 61% of patients were diagnosed at stage I and 30% at stage IV. This high rate of advanced stage at diagnosis in other studies has been attributed to misdiagnosis of the younger age groups because lung cancer is generally considered to a disease of the elderly [29]. Although most of our patients were diagnosed early, one-third still presented in advanced stages. Misdiagnosis could partially explain this phenomenon, but we believe there might be another factor to advanced disease at diagnosis. From the 23 patients in our study who tested positive for a genetic mutation, 19 (82.3%) were stage IV. In comparison to the entire stage IV group, 19/42 (45.2%) of the patients had a genetic mutation. This leads us to believe that patients with a genetic mutation may present with advanced stages at diagnosis, and therefore have a poorer clinical prognosis. But, among stage IV NSCLC, the OS was longer in patients who received targeted therapy

compared to the patients without received target therapy: 88 months vs 24 months (95% CI: 0.15-1.0, $p=0.0282$). This is a significant difference in survival and therefore, we recommend all young lung cancer patients to undergo genetic testing. The limitation to our analysis that only about 24% of the patients underwent genetic testing. In order to confirm, a large number of young lung cancer patients would need to undergo genetic testing.

Our study has several limitations. Firstly, the results were limited by the lack of control group and the small sample size and the study population was restricted to only our hospital. Secondly, even though genetic testing is highly recommended, only 24% of the study population actually underwent genetic testing and hence a definite conclusion regarding the genetic demographics of our study population was not reached. Most of the patients tested for a genetic mutation were positive and a high frequency of ALK translocations were noted in agreement with other retrospective studies [10, 14, 30]. Therefore, we believe further large-scale studies are warranted for targetable driver mutations in young lung cancer patients in order to make more valid conclusions. Finally, we were not able to collect information of all the possible risk factors associated with lung cancer in our study population.

Conclusion

There is an increasing trend of lung cancer in the young Chinese population. There were a higher number of females with lung cancer and the most common type was adenocarcinoma. A high frequency of gene mutations was identified in patients who underwent gene testing with ALK translocations being the most common mutation observed. Higher stages of disease were observed in those with a gene mutation. Although the sample size was small, the current data suggests a higher mutation rate in the younger population. These findings have fundamental implications for practice and we propose that all patients under 30 diagnosed with lung cancer should undergo genetic testing so they can receive personalized treatment and therefore achieve better outcomes. Our results appear to agree with some studies, but conflict with others suggesting some level of heterogeneity amongst young lung cancer patients. To overcome the limitations discussed, further large-scale multicenter studies must be undertaken in order to further identify the characteristics and risk factors associated with lung cancer in the young adult population (<30 years). Establishment of a national databases could also prove to be helpful in identifying key features in this unique subpopulation.

Declarations

Ethics approval and consent to participate

The Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University approved this study. All methods were performed in accordance with the relevant guidelines and regulations. All patients provided informed consent for the use of their clinical data and tumor tissues for research.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no conflicts of interest.

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Author Contributions

Q.S. and J.J.Q. performed the experiment. J.Y.Z., Q.S. and J.J.Q. provided patient information, W.Z.X. and J.M.Q. collected the data, F.S.K. revised the manuscript, J.J.Q. and J.Y.Z. were responsible for study conception and design and acquiring financial support. All the authors contributed to manuscript writing, editing, and gave final approval of the manuscript.

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Figures

Figure 1

Representation of gene mutation findings in patients who underwent genetic mutation assay. A: The distribution of gene mutation in different stage. B: The distribution of gene mutation. C: The distribution of ALK fusion, EGFR-19 deletion and ROS1 fusion in the male and female population.

Figure 2

Distribution and types of mutations observed in patient population.

Figure 3

Over survival among 139 patients. A: Over survival among CIN, stage I, stage II, stage III and stage IV NSCLC patients. B: Over survival among stage IV NSCLC patients according to who received target therapy with molecular alteration compared who not received target therapy.