

Original Article

Comparison of clinicopathological and molecular features between young and old patients with lung cancer

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Abstract: *Objective:* To investigate whether features of lung cancer in young patients differ from those of elderly patients. *Method:* A retrospective analysis was made to compare clinicopathological and molecular characteristics between 272 young patients under 40 years old (young Group) with lung cancer and 167 elderly patients over 60 years old (elderly group). *Results:* The young group had significantly higher proportions of females, adenocarcinoma, and were well differentiated, without lymph node metastasis, and were of lower clinical stage as compared with the elderly group ($P < 0.05$). The positive rate of ALK in the young group was significantly higher than in the elderly group (17.01% vs. 4.17%, $P < 0.05$), but there was no significant difference between the mutation rate of EGFR and ROS1 in two groups. However, the distribution of EGFR mutation sub-types in the two groups was significantly different, with the proportion of 19del in the young group being significantly higher than that in the elderly group. *Conclusions:* The young patients with lung cancer have distinct features compared with elderly patients, and may have different mechanisms of tumorigenesis.

Keywords: Lung neoplasms, adenocarcinoma, young adult

Introduction

Lung cancer is one of the most lethal cancers in the world [1, 2], and the age of onset of lung cancer is around 60 years old. Lung cancer in young adults under 40 years old is uncommon, but the number of young patients is increasing. It has been suggested that young patients with lung cancer are a higher proportion of females with adenocarcinomas, and are more aggressive and therefore have a poorer prognosis compared with elderly patients in early studies [3-5]. However, we found that more and more young lung cancer patients tend to be in early stages. Whether the features of lung cancer in young patients have new changes is unclear. In this study, the clinicopathological and part of molecular data of 272 patients under 40 years old were retrospectively analyzed by comparing with 167 cases of lung cancer patients aged over 60 years old.

Materials and methods

Patients

The clinicopathological data of 272 young patients under 40 years old (young group) and 167 patients over 60 years old (elderly group) with lung cancer was collected in the First Affiliated Hospital College of Medicine, Zhejiang University, Zhejiang University from January 2013 to October 2016. Part of the data was not available. In the young group, there were 98 males and 174 females. In the elderly group, there were 107 males and 60 females. All cases were confirmed by histopathology or cytology. The data is shown in **Table 1**.

Histological evaluation

The histological type was classified according to 2015 WHO classification of lung neoplasm [6] Carcinoma in situ and atypical hyperplasia,

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Table 1. Clinicopathological characteristics of patients with lung cancer in young and elderly group

	Young group		Elderly group		P
	No.	(%)	No.	(%)	
Total	272		167		
Specimen type					<0.01
Surgery	198	(72.8)	78	(46.7)	
Biopsy	74	(27.8)	89	(53.3)	
Gender					<0.01
Males	98	(36.0)	107	(64.1)	
Females	174	(64.0)	60	(35.9)	
Smoking					<0.01
Non-smokers	231	(86.8)	71	(42.5)	
Smokers	35	(13.2)	96	(57.5)	
Histology					<0.01
Premalignant	38	(14.0)	1	(0.6)	<0.01
Adenocarcinoma	198	(72.8)	90	(53.9)	<0.01
Squamous cell carcinoma	16	(5.9)	49	(29.3)	<0.01
Small cell carcinoma	6	(2.2)	20	(12)	<0.01
Other	14	(5.1)	7	(4.2)	0.65
Differentiation					<0.01
Well	121	(44.5)	47	(28.1)	
Moderate	55	(20.2)	26	(15.6)	
Poor	96	(35.3)	94	(56.3)	
Lymph node metastasis					<0.01
Without	172	(63.2)	55	(32.9)	
With	79	(29.0)	94	(56.3)	
Unknow	21	(7.7)	18	(10.8)	
Clinical stage					<0.01
Premalignant	38	(14.6)	1	(0.7)	
I	102	(39.2)	44	(28.9)	
II	21	(8.1)	13	(8.6)	
IIIA	19	(7.3)	21	(13.8)	
IIIB	9	(3.5)	18	(11.8)	
IV	71	(27.3)	55	(36.2)	
Clinical symptom					0.02
Cough	113	(41.5)	103	(61.7)	0.48
Dyspnea or chest pain	75	(27.6)	50	(30.0)	0.59
Fever	16	(5.9)	7	(4.2)	0.44
Hemoptysis	26	(9.6)	40	(24.0)	<0.01
None	94	(34.6)	32	(19.2)	<0.01

Part of data was not available.

which have been proven to have 100% disease-free survival and no recurrence of survival after surgical resection, were considered to be the same disease in this study. The clinical stage of the disease was determined based on the TNM classification of the Union for International Cancer Control (UICC) [7].

Molecular detection

Formalin fixed and paraffin embedded tissue blocks were cut in 3 or 5 μ m thickness. 10 slices of 5 μ m were collected for DNA and RNA isolation. All extraction were carried out using DNA/RNA extraction kit (AmoyDx, Xiamen). EGFR mutation and ROS1 fusion were tested using ARMS Detection kit (AmoyDx, Xiamen). 1 slice of 3 μ m was tested for EML4-ALK fusion by immunohistochemistry (Roth, Germany, 1:500).

Statistical analysis

Statistical analysis was performed using the SPSS statistics software (Version 17.0, Chicago). The correlation of young and elderly groups with clinicopathological characteristics were studied via Chi-square test. *P* value <0.05 was considered as to be statistically significant.

Results

General character

In the young group, there were 98 males and 174 females, 35 smokers and 231 non-smokers. In the elderly group, there were 107 males and 60 females, 96 smokers, and 71 non-smokers. The male to female ratio and the proportion of smokers in the young group was significantly lower than the elderly group (1.78:1 vs. 0.56:1; 13.2% vs. 57.5%).

Clinicopathological characteristics

The young group comprised 11 atypical hyperplasia, 27 adenocarcinomas in situ, 198 adenocarcinomas, 16 squamous cell carcinomas, 4 adenocarcinoma of squamous cell carcinoma, 6 small cell carcinomas, 5 undifferentiated carcinomas, 4 adenoid cystadenocarcinomas, and 1 mucoepidermoid carcinoma. There were 121 cases of well differentiated, 55 cases of moderately differentiated and 96 cases of poorly differentiated tumors. In comparison to the elderly group, adenocarcinoma was more frequently found, whereas

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Table 2. Molecular characteristics of patients with lung cancer in young and elderly group

	Young group		Elderly group		P
	No.	(%)	No.	(%)	
EGFR					0.76
Mutation	38	(41.3)	25	(43.9)	
Wild type	54	(58.7)	32	(56.1)	
ALK					<0.01
Positive	25	(17.0)	4	(4.1)	
Negative	122	(83.0)	94	(95.9)	
ROS1					0.45
Positive	0	(0.0)	1	(2.1)	
Negative	75	(100)	46	(97.9)	
EGFR mutation types					0.01
19DEL	28	(30.4)	8	(14.0)	
L858R	8	(8.7)	12	(21.1)	
Other types	2	(2.2)	5	(8.8)	
Wild type	54	(58.7)	32	(56.1)	

squamous cell carcinoma was less frequently observed in the young group. The differentiation of tumors in the young group was also better than the elderly group.

There were 79 cases with lymph node metastasis and 172 cases without lymph node metastasis in the young group. According to the clinical TNM classification, there were 38 patients with preinvasive lesions, 102 with stage I disease, 21 with stage II, 19 with stage IIIA, 9 with stage IIIB, and 71 with stage IV. The proportion of advanced-stage patients (stage III and IV) in the young group was significantly higher than that in the elderly group (Table 1).

Clinical symptom

Most patients were symptomatic at the time of diagnosis. There were 13.2% patients had no symptoms at initial presentation in the elderly group, whereas there were 34.6% patients that had no symptoms in the young group which was significantly more than in the elderly group. Cough was the most common presenting symptom in both the young and elderly groups, followed by dyspnea, or chest pain. Hemoptysis was more frequently in the elderly group than the young group ($P < 0.01$).

Molecular characteristics

EGFR, ALK, and ROS1 were detected in 92, 147, and 75 patients respectively in young

group, corresponding to 57, 96, and 47 patients in elderly group. Results by Chi square test showed that the positive rate of ALK in young group was significantly higher than the elderly group (17.01% vs. 4.17%, $P < 0.01$), but there was no significant difference between the mutation rate of EGFR and ROS1 in two groups. However, the distribution of EGFR mutation stypes in two groups was significantly different, and the proportion of 19del in young group was significantly higher than that in elderly group (Table 2).

Discussion

Lung cancer is commonly considered to occur in people over the age of 40, and most scholars define young lung cancer as lung cancer patients under the age of 40 [3, 4, 8]. The proportion of young lung cancer is very low, mostly below 10%. Similar to previous findings [3, 5, 8], our study showed that the proportion of females in the young group was significantly higher than the elderly group. However, the number of female patients was more than male patients in young group. It was different from other studies. We considered that the difference may be caused by smoking, because females were more sensitive to tobacco, and the risk of smoking induced lung cancer was higher than that of males [9, 10]. In western countries, smoking rates among young patients were as high as 73.6%-91% [5, 8], and 29.4%-63.3% was also reported in china [11-13]. In this study, only 13.2% of young patients smoked, one was female, significantly less than the elderly group. So the evidence for this hypothesis is not very strong. Of course, this may be related to second-hand smoke and the more severe air pollution in recent years, but there is no definite evidence.

Adenocarcinoma was the most frequent tissue type in the both groups, but there were more precancerous lesions and adenocarcinomas in the young group than the elderly group, otherwise, there were more squamous cell carcinoma and small cell carcinoma in the elderly group, similar to previous reports [4, 5, 8]. Early studies showed that most of young patients with lung cancer have poor differentiation, faster progress, and higher clinical stage. However, in this study, there were 35.3% cases with poor differentiation in young group which was significantly less than the elderly group. The lymph

node metastasis and advanced stage in the young group were also significantly less than what in the elderly group. There were 18% of the young patients that were diagnosed and treated at the time of atypical hyperplasia or carcinoma in situ, which is the result of the young people's attention to physical examination in recent years, the prevalence of CT screening for lung cancer detection, and improved computed tomography (CT) images with higher resolution were also contributed to found the early tumors.

As the elderly patients, young patients with lung cancer also had cough, chest pain, and other respiratory symptoms. However, 34.6% of the young patients asymptomatic, and the ratio was significantly higher than in the elderly group. Nearly half of the young patients (41.8%) were found by examination of the tumor mass. Hemoptysis was more frequently in the elderly group than the young group. Most tumors were located in the upper lobe of lung in both groups (data was not shown).

Epidermal growth factor receptor (EGFR), ALK, and ROS1 are important therapeutic targets of lung cancer. The features of EGFR mutation, which is frequently found in women, non-smokers, and those with adenocarcinoma, are well described [14-16]. We compared the EGFR mutation rates between young and elderly patients and found no significant difference between the two groups. As the most common mutation types of EGFR, patients with 19Del and L858R have different survival outcomes in response to both EGFR-TKIs and chemotherapy [17-19]. The mutation rates of 19Del and L858R were basically the same in an unselected population. However, the distribution of the two mutation types in young patients had an obvious difference compared with elderly patients. The mutation rate of 19Del was significantly higher than that of L858R in young group, while the 19Del mutation rate was lower than L858R in elderly group, and the results are consistent with the Zhang' report [20].

ALK and ROS1 rearrangement were frequently found in young female patients [21, 22]. In this study, we found that the positive rate of ALK in young patients was significantly higher than that in elderly patients, which was consistent with previous studies. But we did not find any young patients with ROS1 rearrangement, and

no statistically significant difference with elderly group was observed which may be due to small sample size.

Similar to earlier studies, young patients with lung cancer in this study also showed different features from the elderly patients, but the proportion of adenocarcinoma, well-differentiated tumors, and females were more prevalent. Lung cancer symptoms in young patients tend to be hidden, so we should improve awareness and vigilance in order to reduce misdiagnosis, while calling on young people to realize the importance of physical examination. In addition, young patients have different molecular characteristics compared to elderly patients, suggesting that both may have different mechanisms of tumorigenesis.

Disclosure of conflict of interest

None.

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