RESEARCH ARTICLE

Clinical Features of Lung Cancer in Japanese Patients Aged Under 50

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Abstract

The proportion of lung cancer patients under 50 years old is small at approximately 5-10%, but as with patients older than 50, the number is on the rise. Although lung cancer treatment strategies have undergone extensive transformation in recent years based on the presence or absence of oncogenic driver mutations, there are few reports regarding these mutations in the young or the relationship between clinical setting and prognosis. Therefore, we conducted a study of clinical features in 36 patients under the age of 50 who were diagnosed with primary lung cancer from October 2008 to November 2015. The 22 patients in stages I through III A underwent operations, and all 17 whose lung cancer were detected through screening were candidates for surgery. Gene analysis was conducted for 26 (72.2%); 10 (38.5%) were positive for EGFR gene mutations, and ALK gene translocation was present in 4 (15.4%). In stage IV patients, the median progression free survival (PFS) in the ALK translocation positive and negative patients was 518 days and 130 days, respectively, and the median overall survival (OS) was not reached and 280 days, respectively. A trend toward extended PFS (p=0.203) and OS (p=0.056) was observed in patients positive for ALK translocation. We must strive for early detection by increasing screening rates and evaluate oncogenic driver mutations important for prognosis of lung cancer in the young.

Keywords: Lung cancer - young patients - oncogenic driver mutations - gene translocation

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Introduction

According to the Japan Lung Cancer Registry Study, the number of lung cancer patients under 50 years old has sharply increased, but make up a small percentage of all lung cancer patients at approximately 5-10% (Sawabata, 2014). However, as with patients over 50, the absolute number is on the rise (Sawabata, 2014). Additionally, although the prognosis for lung cancer in the young is considered poor because it is often diagnosed when the disease is already advanced, relatively favorable prognoses have been reported in cases where surgery was performed (Bourke et al., 1992; Capewell et al., 1992; Icard et al., 1992; Minami et al., 2001). The EGFR gene mutation is said to be present in 30-50% of Japanese lung adenocarcinoma patients, and the ALK gene translocation in 4-5% (Kohno et al., 2013). However, there are few reports on the frequency and prognosis of gene mutations in lung cancer in the young. Therefore, in this study, we investigated the clinical features of primary lung cancer in patients under the age of 50.

Materials and Methods

We conducted a retrospective study of 36 patients under the age of 50 who were diagnosed with primary lung cancer at Fukuoka University Hospital from October 2008 to November 2015. The age, sex, smoking history, method of detection, histological type, clinical stage, gene mutation (EGFR gene mutation, ALK gene translocation), treatment, and prognosis of these patients were investigated. EGFR gene testing was conducted using the polymerase chain reaction (PCR) clamp method on biopsy tissue, cells from bronchial lavage, or pleural effusion, while ALK gene testing was conducted on biopsy samples using immunostaining or the FISH method (Lindeman et al., 2013). Survival curves were generated by the Kaplan-Meier method and statistically verified using the log-rank test. All procedures were performed in accordance with the ethical principles expressed in the 1995 Declaration of Helsinki. The institutional review board of Fukuoka University Hospital approved this retrospective study.

Results

Patients Background

Patient ages ranged from 31 to 49 with a median of 43. Nine were 30-39, 13 were 40-44, and 14 were 45-49. There were 23 men (63.9%) and 13 women (36.1%) with a ratio of 1.8:1. Among 36 patients, 22 (61.1%) acknowledged a history of smoking, including 18 of 23 men (78.3%) and

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4 of 13 women (30.8%); 15 (68.2%) were heavy smokers at 400 or more on the Brinkman Index. Screening led to detection in 17 patients (47.2%) and symptoms in 19 (52.8%). Symptoms included 9 with coughing, 5 with fever, 5 with pain, 4 with cranial nerve symptoms, 2 with bloody sputum, 1 with difficulty breathing, 1 with sputum, 1 with weight loss, and 1 with lymph node enlargement. The histological type was adenocarcinoma in 27 patients (75.0%), small cell carcinoma in 3 (8.3%), polymorphous cancer in 2 (5.6%), squamous cell carcinoma in 1 (2.8%), adenosquamous carcinoma in 1 (2.8%), and not otherwise specified (NOS) in 2 (5.6%). The clinical stage was I A in 9 patients (25.0%), I B in 3 (8.3%), II A in 3 (8.3%), II B in 1 (2.8%), III A in 6 (16.7%), III B in 2 (5.6%), and IV in 12 (33.3%). The clinical stages of the 17 patients whose cancers were detected by screening were I A in 9 (52.9%), I B in 3 (17.6%), and III A in 5 (29.4%); no III B/IV patients were observed. All 22 patients whose stages were I through III A underwent surgery; 1 underwent combined modality therapy and 13 underwent chemotherapy.

Table 1. Patient Characteristics

No. of patients	36
Sex	
Male	23
Female	13
Mean age years (range)	43 (31-49)
30~39 (years)	9
40~44 (years)	13
45~49 (years)	14
Smorking status (%)	
Never smoker	14 (38.9)
Smoker	22 (61.1)
Heavy Smoker	15 (41.7)
Mass screening (%)	17 (47.2)
Symptomatic (%)	19 (52.8)
Cough	9 (25.0)
Fever	5 (13.9)
Pain	5 (13.9)
Neurological symptom	4 (11.1)
Hemoptysis	2 (5.6)
Dyspnea	1 (2.8)
Sputum	1 (2.8)
Weight loss	1 (2.8)
Swelling of lymph node	1 (2.8)
Histology (%)	
Adenocarcinoma	27 (75.0)
Small cell carcinoma	3 (8.3)
Pleomorphiccarcinoma	2 (5.6)
Adenosquamous cell carcinoma	1 (2.8)
Squamous cell carcinoma	1 (2.8)
Others	2 (5.6)
Clinical stage (%)	
IA	9 (25.0)
IB	3 (8.3)
IIA	3 (8.3)
IIB	1 (2.8)
IIIA	6 (16.7)
IIIB	2 (5.6)
IV	12 (33.3)
Type of EGFR mutation	
Exon 19 deletion	7
L858R	3
ALK translocation	4

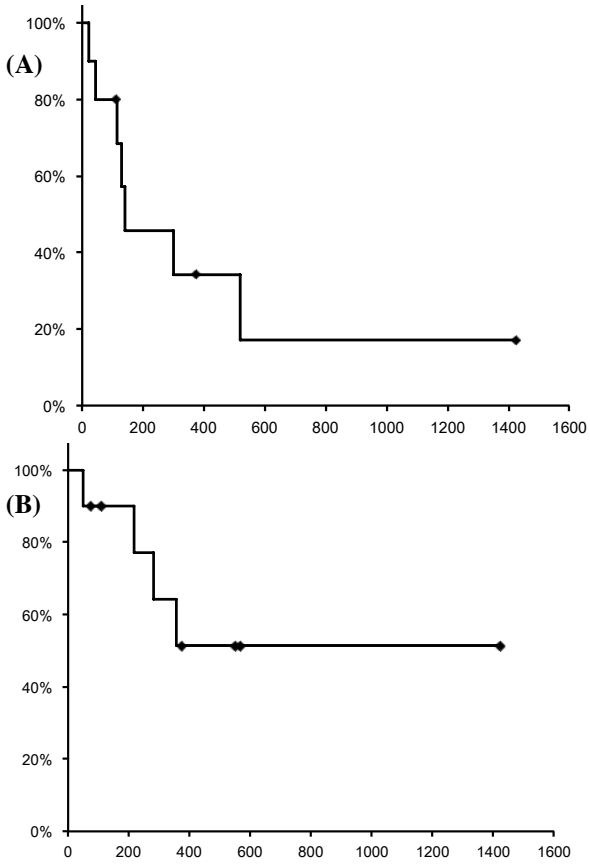

Figure 1. Progression-free Survival (A) and Overall Survival (B) in All Stage IV Patients

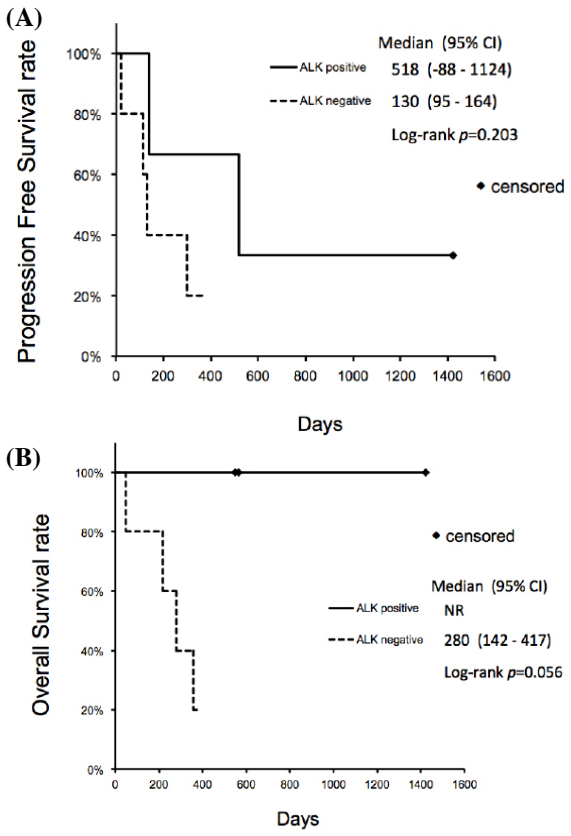

Figure 2. Progression-free Survival (A) and Overall Survival (B) in Patients Positive or Negative for the ALK Translocation

EGFR gene mutation and ALK gene translocation

Gene analysis was conducted in 26 patients (18 men, 8 women); the EGFR gene mutation was present in 10 (38.5%) and the ALK gene translocation in 4 (15.4%). Among the 10 patients positive for the EGFR gene mutation, 3 of 5 men and 2 of 5 women had a history of smoking; 7 of the 10 (70.0%) had the exon19 deletion mutation and 3 (30.0%) had exon21 L858R. Among the 4 patients positive for the ALK gene translocation, 3 (75.0%) were men and 1 (25.0%) was a smoker. Of the 21 patients with adenocarcinoma who had gene mutation analysis, the EGFR mutation was present in 47.6% and the ALK gene translocation in 19.0%.

Prognosis

The overall 1-year survival rate was 85.2% and the 2-year survival rate was 77.3%. The patients who underwent surgery had a 1-year survival rate of 94.1% and a 2-year survival rate of 93.3%, while the patients who did not undergo surgery had a 1-year survival rate of 70.0% and a 2-year survival rate of 42.9%. For 12 patients (33.3%) with stage IV non-small cell lung cancer, the median for progression-free survival (PFS) was 139 days, and the median for overall survival (OS) was not reached (Figure 1). The median PFS in the ALK translocation positive patients and the ALK translocation negative patients was 518 days and 130 days, respectively (Figure 2A), and the median OS was NR and 280 days, respectively (Figure 2B). A trend toward extended PFS (p=0.203) and OS (p=0.056) was observed in patients positive for the ALK translocation compared to the negative patients (Figure 2).

Discussion

There is no clear age cutoff for lung cancer in the young, but based on the sharp increase in the number of patients under 50 in the Japan Lung Cancer Registry Study (Sawabata, 2014), we investigated the clinical features in patients under 50, in whom lung cancer is considered relatively rare. Women account for a large proportion of these patients; with a male-to-female ratio of 1.8:1; this study reflects the trend toward a higher proportion of women among lung cancer patients relative to the proportion among patients with other cancers (Inoue et al., 2014). Of the patients studied, 61.1% acknowledged a history of smoking, including 78.3% of the men and 30.8% of the women. Among these, 68.2% were heavy smokers at 400 or more on the Brinkman Index. In 2014, the smoking rate was 30.3% for men and 9.8 for women. Broken down by age, the rate was 29.4% for men in their 20s, 36.6% for men in their 30s, and 38.5% for men in their 40s; the rate was 10.0% for women in their 20s, 13.0% for women in their 30s, and 14.8% for women in their 40s (Ministry of Health, 2015). Although the smoking rate has been gradually declining, in this study, the rate of patients who acknowledged a history of smoking was high (61.1%), with a high proportion of heavy smokers, suggesting a causal relationship with early-onset lung cancer.

Although many prior reports stated that lung cancer in the young advances quickly and has a poor prognosis (Bourke et al., 1992; Whooley et al., 1999), there have also been many reports of relatively favorable prognosis in cases where excision was performed (Andou et al., 1992; Icard et al., 1992; Minami et al., 2001). In this study, all 22 patients in stages I through III A underwent surgery, and all 17 whose illnesses were detected through screening were candidates for surgery. An integrated research analysis conducted by the Ministry of Health, Labour and Welfare reported that the lung cancer mortality rate resulting from screening was reduced by 44%, and a significant reduction in mortality was observed regardless of age (Sagawa et al., 2003). The fact that all patients in this study whose illnesses were detected through screening were candidates for surgery suggests that early detection is important for the young as well. However, the Japan Cancer Society targets those 40 or over for lung cancer screening, and the screening rate for the young is low; these are issues to address in the future.

The Japan Lung Cancer Registry Study reported that adenocarcinoma accounted for 78.7% of the histological types of lung cancer in the young in Japan (Inoue et al., 2014), and a high proportion of adenocarcinoma was observed in this study as well, with 75.0% adenocarcinoma, 8.3% small cell carcinoma, and 2.8% squamous cell carcinoma. A high proportion of women is cited as one reason that adenocarcinoma is common in lung cancer in the young; the proportion of women in this study was also high, and 12 of 13 female patients (92.3%) had adenocarcinoma. Additionally, 15 of 23 male patients (65.2%) had adenocarcinoma, while 2 (8.7%) had small cell carcinoma and 1 (4.3%) had squamous cell carcinoma. Recently, there have been reports that squamous cell carcinoma has been decreasing along with the decrease in smoking rates, and that adenocarcinoma is also increasing in men (Saika and Sobue, 2014). However, the results of this study show a high proportion of adenocarcinoma despite the large number of heavy smokers in the sample; we can surmise that many confounding factors such as smoking and gene mutation are involved.

The EGFR gene mutation is observed frequently in women, nonsmokers, cases of adenocarcinoma, and Asians, while it has been reported that the ALK gene translocation is common in women, the young, and cases of adenocarcinoma (Nakanishi, 2015; Takeuchi et al., 2016). It is thought that the mean age of onset for lung cancer with the ALK gene translocation is about 10 years earlier than that without the ALK gene translocation; in Japan, 17% of non-small cell lung cancer patients under 60 and 36% of lung adenocarcinoma patients under 50 are reportedly positive for the ALK gene translocation (Sakairi et al., 2010; Enomoto et al., 2013). It has also been reported that the positive rate for the EGFR gene mutation increases with increasing age of onset for nonsmoking female adenocarcinoma patients (Zhang et al., 2012). In this study, gene analysis was conducted for 26 patients; 10 (38.5%) were positive for the EGFR gene mutation, and the ALK gene translocation was present in 4 (15.4%). The frequency of the EGFR gene mutation was generally the same as the frequency of lung adenocarcinoma in Japanese people overall, while the ALK gene translocation was frequently observed in the young, as in prior reports.

Additionally, although the number of cases is small, a trend toward extended PFS and OS has been observed in patients in an advanced stage who are positive for the ALK gene translocation compared to patients who are negative (Figure 1, 2). Although the number of patients in this study was small, the results suggest that the presence or absence of the ALK gene translocation can determine prognosis in the young as well; thus, more patients must be studied in the future.

A relative increase in adenocarcinoma is predicted in the future based on factors such as the decreasing smoking rate, but because adenocarcinoma frequently develops peripherally and tends not to be accompanied by symptoms, we must strive for early detection by increasing screening rates. Additionally, because there is a strong possibility that the presence or absence of genetic abnormalities is consequential in the prognosis of lung cancer in the young as well, the search for genetic abnormalities should be actively promoted.

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