A population-based study of outcomes in patients with surgically resected non-small cell lung cancer with anaplastic lymphoma kinase-rearranged mutations: A matched-pair study

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Abstract. The present study aimed to evaluate clinical outcomes in patients with surgically resected non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK)-rearranged mutations. A matched-pair analysis in completely resected ALK-rearranged NSLC patients and those with neither ALK nor epidermal growth factor receptor (EGFR) mutations diagnosed at 11 institutes was performed between April 2008 and March 2019. A total of 51 patients with surgically resected ALK-rearranged NSCLC were included. Women constituted 68.6%, and smokers 29.4%. The median age was 65 years. In matched-pair analysis, disease-free survival and overall survival did not differ between patients with ALK-rearranged mutations and those without mutations. Post-recurrence survival in patients with ALK mutations was longer than that of patients with neither ALK nor epidermal growth factor receptor mutations. ALK genetic testing should be performed, even in elderly patients with NSCLC. Favorable prognosis might be expected after appropriate treatment for patients with recurrent ALK-mutated disease.

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Introduction

Lung cancer is an important public health problem and the leading cause of cancer death worldwide, with more than 1.38 million deaths worldwide (1,2). The prognosis of lung cancer remains dismal in which 15% of patients have a 5-year survival rate regardless of stage (3). Mutational and proteomic profiling studies have led to the identification of molecular driver mutations in lung cancer (4). EGFR mutations, as the first driver mutation gene in lung cancer, has brought about a large paradigm shift in lung cancer treatment (5). With this as a breakthrough, the research of driver genes for lung cancer was greatly accelerated. Among the driver genes that are currently being confirmed, EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangement are so far the most frequent and clinically important carcinogenic driver mutations in non-small-cell lung cancer (NSCLC) patients. The identification of anaplastic lymphoma kinase (ALK) rearrangement mutations and the introduction of ALK tyrosine kinase inhibitors (ALK-TKI) have dramatically changed the treatment of advanced or recurrent NSCLC patients with ALK rearranged mutations (6-8). The value of ALK-TKIs has been demonstrated in randomized trials (6-8), and they are currently first-choice drugs for patients with advanced or recurrent NSCLC harboring ALK-rearranged mutations. In surgically-resected lung adenocarcinoma patients with

ALK rearranged mutations, however, controversy persists as to whether the ALK-rearranged mutations is an unfavorable prognostic factor (9-23). Previous reports have variously indicated ALK-rearranged mutations was a favorable prognostic factor (9,10), an unfavorable factor (11-18), or a factor not associated with prognosis (19-23). Such different results might be related to the small number of patients with ALK rearranged mutations, and the large difference in the background between patients with and without ALK rearranged mutations. That is, the frequency of ALK rearranged mutations was higher among young patients, female patients and non-smokers (6,13-15,24-26). In addition, it is still unclear whether the presence or absence of the ALK mutations is associated with post-recurrence survival (PRS). Differences in patient background might also be related to the relationship between ALK mutations and PRS. Therefore, in order to clarify these two issues, it was necessary to match the patient backgrounds and compare the survival of patients with and without ALK mutations. There are several ways to match different patient backgrounds and compare different groups, including matched-pair analyses. In the present study, we compared disease-free survival (DFS), overall survival (OS), and PRS in patients with surgically resected NSCLC with ALK mutations and those without the mutations. The primary aims of the present study were to elucidate whether ALK-rearranged mutations in patients with surgically resected disease was associated with OS, and to clarify whether patients with ALK mutations had a longer PRS.

Patients and methods

Patients. This was a retrospective study in which all medical institutions covering one prefecture in our country participated. We included patients who were diagnosed as having ALK-rearranged NSCLC between April 2008 and March 2019. Patients, who had undergone surgery before the diagnostic method of ALK fusion mutations was approved by medical insurance in our country in May 2012 and were diagnosed as having ALK-rearranged NSCLC during the study period, were included in the study. Controls were 232 patients who were diagnosed as having neither ALK rearrangement mutations nor epidermal growth factor (EGFR) mutations and had had surgical resections during the study period at the Mito Medical Center and Mito Kyodo General Hospital. The control matched-pair patients were those among the 232 control patients whose main clinical characteristics were consistent with ALK-rearranged mutated patients, including age, sex, performance status, pathological stage, and smoking habit, which are known prognostic factors for NSCLC patients. Histopathological diagnoses were defined according to the World Health Organization classification system, and the patients were staged according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system (8th edition). The patient characteristics, efficacy, safety, DFS, OS were evaluated using patient data extracted from the database of each institution. DFS was calculated from the date of surgery to the recurrence or any cause of death and OS was the interval from the date of surgery to the date of death, or latest follow-up contact. PRS was defined as the interval between the date of recurrence and to the date of death or latest follow-up contact.

The present non-interventional and observational retrospective study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. This study was approved by the Institutional Review Board of the Mito Kyodo General Hospital-Mito Medical Center, University of Tsukuba (no. 16-66, 18-15) or independent ethics committees associated with each study institute. Written comprehensive informed consent for reporting clinical course was obtained from each patient at the time of admission.

Measurement of ALK fusion gene. Analysis of ALK fusion mutations was performed by the respective assay method used by each institution, such as fluorescence *in situ* hybridization (FISH) and immunohistochemistry (IHC), using biopsy specimens, cytology specimens and plasma specimens.

Statistical analysis. All analyses were performed using SPSS version 23 (IBM Corporation). Differences in proportions between two independent groups were compared using the χ^2 test. The Mann-Whitney U test was used to compare two groups of sample data. The survival rate was analyzed by the Kaplan-Meier method and comparisons performed using the log-rank test. The effects of clinicopathological factors on survival were analyzed using the Cox proportional hazards model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological features in patients with ALK-rearranged mutations. During the study period, 129 patients were diagnosed as having ALK-rearranged NSCLC. The analysis of ALK fusion mutation was examined using FISH in 78 patients, IHC in 30 patients, and both tests in 21 patients. Fifty-eight patients had surgical resection. Among them, 51 patients had curative complete resection. Seven patients were excluded from this study because they did not have no curative resection. Table I shows the clinicopathological features of the 51 with ALK mutations who had curative complete resection and 232 completely resected controls who had neither ALK-rearranged mutations nor EGFR mutations. Proportions of all the features in these two groups of patients except for performance status were different.

In 51 patients with ALK-rearranged mutations, the median age was 65 (range, 32-82) years. Presence of ALK fusion mutation was confirmed in FISH, IHC, and both tests in 27, 19 and 5 patients, respectively. There were 16 (31.4%) males and 35 females. Fifty (98.0%) patients had good performance status (Eastern Cooperative Oncology Group 0-1). Fifteen (29.4%) of them were non-smokers. All 51 patients had adenocarcinoma. The median maximum diameter of the primary lesion was 20 mm (range, 12-82 mm). At the time of initial diagnosis, 21 patients (41.2%) were diagnosed as having pathological stage IA-B, 14 (27.5%) patients with IIA-B, and 16 (31.4%) patients with IIIA. The average 5-year survival rate of the 51 patients who underwent complete resections was 84.0%.

Table I. Clinicopathological characteristics of enrolled patients: 51 surgically resected patients with ALK mutation and 232 surgically resected controls who had neither ALK rearranged mutation nor EGFR mutations.

Characteristics	Resected patients with ALK mutation	Resected controls with neither ALK nor EGFR	P-value
Age (year), median, range	65, 32-82	70, 39-89	<0.001
Sex			<0.001
Male	16	748	
Female	35	84	
Performance status			0.078
0	41	149	
1	9	78	
2	1	5	
Smoking status			0.516
Never	36	151	
Past or current	15	81	
P-stage			<0.001
IA-IB	21	162	
IIA-IIB	14	37	
IIIA	16	33	
5-year survival (%)	84.0	69.8	0.059

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

Table II. Clinicopathological characteristics of patients matched according to clinical characteristics: 38 patients with ALK-rearranged mutation and 38 patients with neither ALK nor EGFR mutation.

Characteristics	Resected patients with ALK mutation	Resected controls with neither ALK nor EGFR	P-value
Age (year), median, range	65, 40-82	67, 46-82	0.763
Sex			0.807
Male	13	12	
Female	25	26	
Performance status			0.361
0	30	33	
1	8	5	
Smoking status			0.622
Never	13	11	
Past or current	25	27	
P-stage			0.841
IA-IB	20	22	
IIA-IIB	9	9	
IIIA	9	7	
Recurrence during the study period			0.803
Present	11	12	
Absent	27	26	
5-year survival	77.5	71.5	0.820

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

Clinicopathological features and survival in matched-pair patients. Table II shows the clinicopathological characteristics of 38 ALK-rearranged mutated patients and 38 matched-pair control patients whose main clinical characteristics were

Table III. Clinicopathological characteristics of pair-matched recurrent patients: Patients with ALK-rearranged mutation and patients with neither ALK-rearranged mutation nor EGFR mutation.

Characteristic	Patients with ALK	Patients with neither ALK nor EGFR	P-value
Number of patients	11	12	
ALK-TKI therapy after recurrence			
Present	9	0	
Absent	2	10	
Period until recurrence, median (range)	4 (1-62) months	17 (2-94) months	0.104
Survival status			0.059
Dead	3	8	
Alive	8	4	
Survival from recurrence	14 (1-91) months	7 (1-72) months	0.487

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

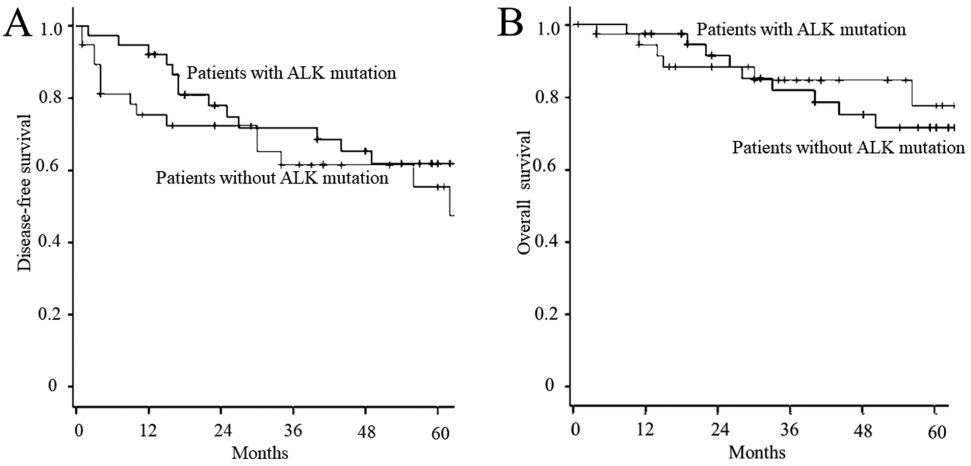

Figure 1. Comparison of disease-free survival and overall survival after surgery between the two groups of patients with or without ALK-rearranged mutation. (A) Disease-free survival and (B) overall survival after surgery of the 38 ALK-rearranged mutated patients and 38 matched-pair control patients. ALK, anaplastic lymphoma kinase.

matched to patients with ALK-rearrangements. In these two matched groups of patients, 11 and 12 patients experienced recurrence during the study period. DFS and OS from the surgery in these two groups of patients are shown in Fig. 1. There was no significant difference between these two groups in either DFS (P=0.303) or OS (P=0.820).

Post-recurrence survival. Table III shows the time to recurrence, the administration of ALK-TKI after recurrence, and PRS in the two groups of patients. As for these, there were no differences between the two groups. As shown in Fig. 2, patients with ALK-rearranged mutations had longer PRS compared with those who had neither ALK nor EGFR mutations (P=0.042).

Discussion

It is well known that the proportion of patients with ALK-rearranged mutations is higher among young patients, female patients, and non-smokers (6,13-15,24-26). The characteristics of younger patients were comparable to previous studies (13-15,24,25). The percentage of non-smokers was higher among patients with ALK-rearranged mutations than among patients without ALK mutations (8,12-14,16,20,21,23). The high percentage of non-smokers was also comparable among patients with ALK mutations who underwent resections (13,14,16,21). Only a study by Blackhall *et al* reported a high percentage of smokers (9). In the present study, the proportion of female patients and non-smokers was 68.6 and 29.4%, respectively, consistent with previous studies (10,12-14,16,20,21,23). However, the median age in our patients was 65 years, which was older than that of patients in previous studies (13-15,24,25). Our data suggested that there might be more patients with surgically resectable ALK-rearranged NSCLC over the age of 60 years and those with a smoking habit. Therefore, evaluation of ALK fusion events might need to be proactively pursued in elderly NSCLC patients. It has been controversial whether the prognosis of patients with ALK-rearranged NSCLC is better than that of patients without ALK-rearranged mutations (9-23).

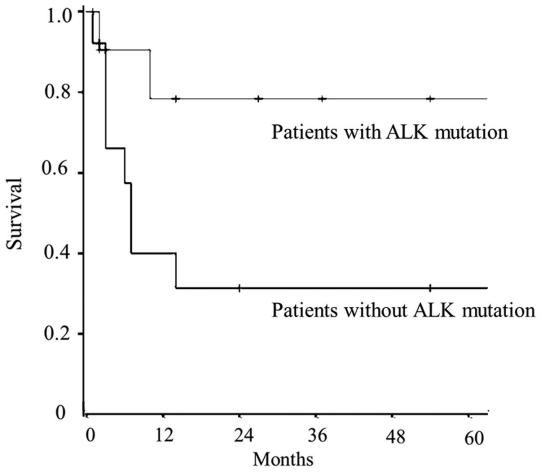

Figure 2. Comparison of post-recurrence survival between the two groups of patients with or without ALK-rearranged mutation. Survival time after recurrence in the 38 ALK-rearranged mutated patients and 38 matched-pair control patients. ALK, anaplastic lymphoma kinase.

Previous studies on the survival of ALK-mutated patients focused on one of three groups: All ALK-mutated patients; patients with advanced or recurrent disease; and patients who underwent resections (9-23). Survival results in these studies were inconsistent among the three patient groups (9-23). Particularly among studies of patients who underwent resections (9,13-17,19,21,22), some reports indicated a good prognosis in patients with ALK-rearranged mutations (9) while other reports indicated poor prognosis (13-17). Yet other reports indicated that the ALK-rearranged mutations was not associated with prognosis (19,21,22). Except for a study Blackhall *et al*, all were small with up to 50 patients, and control patients in these studies were those without ALK-rearranged mutations resected at the same study period (9,13-17,19,21,22). As described above, the proportion of young, female, and non-smoking patients was higher in patients with ALK-rearranged mutations than in those without (6,13-17,24-26). As a result, it might be that patients with ALK-rearranged mutations and those without ALK mutations had significantly different backgrounds that might account for the different prognosis. Therefore, we consider a simple comparison of patient groups with different background factors an inappropriate methodology. Matched-pair analysis, which matches factors known to be important prognostic factors, was considered one of the suitable statistical analyses to be applied. However, there have been only two studies analyzed using this statistical method (9,23). One was a study of only 28 patients with clinical stages III and IV (23). Although this report showed that there was no difference in the survival of patients with and without ALK mutations, this result only applied to patients with advanced disease (23). Another report was by Blackhall *et al* in 80 patients who underwent resections with pathological stages I through III (9). They reported that patients with ALK-rearranged mutations were associated with better OS (9). Our matched-pair analysis, which matched some clinical characteristics, however, showed that DFS and OS in patients with ALK mutations were not significantly different from those with neither ALK nor EGFR mutations. EGFR mutations are the most frequent driver gene recognized at present (6,8). However, Blackhall *et al* did not mention the exclusion of patients with EGFR mutations (9). In addition, their cohort had a very high percentage of patients with a smoking history, with 81.7% of ALK-mutated patients being current or past smokers (9). In our study, 70.6% of ALK-mutated patients had a smoking history. The inconsistency between the study by Blackhall *et al* and ours might be related to a difference in the background of the ALK-rearranged patients studied.

In the present study, we obtained another important finding. PRS of patients with ALK-rearranged mutations was significantly longer than that of patients without the mutations. Clinical trials in ALK-TKIs included patients with advanced, as well as those with recurrent disease (6-8), and retrospective clinical studies also included these patients (6-8). However, there have been no reports comparing PRS of patients with ALK mutations and that of patients without the mutations. This was the first study to compare PRS of patients with or without ALK rearranged mutations using matched-pair analysis. We matched clinical factors considered as major prognostic factors. ALK-TKI treatment seemed to be the reason why the survival of patients with ALK-rearranged mutations was longer than that of patients without the mutations. Whether the presence of the ALK fusion gene itself is associated with prognosis, or whether administration of TKI is associated with prognosis, is not a major problem in actual practice. If the patient with the ALK fusion gene mutations relapses, administering TKI is a standard treatment. Clarification of these reasons should be left to future biological studies. Our findings were derived from a small number of patients treated with ALK-TKIs, and need to be confirmed by future studies.

In this research, we chose the matched-pair analysis because we wanted to make the clinical and pathological variables as even as possible in comparison the survival with ALK rearranged mutations. We matched background characteristics that were previously associated with prognosis, such as age, gender, performance status, pathological stage, and smoking habit. Regarding OS, no difference could be confirmed between the two patients with or without ALK rearrangement mutations. This might relate to the short observation period and the small number of patients. Alternatively, it might suggest that 'curative resections' had overwhelmingly larger impact on contributing to overall survival than 'ALK rearrangement mutations and presence of ALK-TKI treatment' did.

The present study had several limitations. Firstly, it was a retrospective study with patients from miscellaneous backgrounds. Secondly, the methods for examining ALK-fusion gene mutations were not unified. For ALK examination, FISH and immunostaining were performed. Patients who confirmed the presence of the ALK fusion gene by both examinations were also included. The effects of the difference in detection sensitivity of these measurements on our results could not be fully investigated. Comprehensive screening with next generation sequencer was not used in this study population. Thirdly, the limited number of patients and the short period of investigation were also limitations. Fourthly, it was a matched-pair study with a one-to-one patient ratio, but it would be favorable to include more control patients with matched clinical characteristics. Fifthly, as for the survival, our study could not analyze the presence of the ALK mutations and the use of ALK-TKI separately. At present, administration of

ALK-TKI is the standard treatment in recurrent patients with ALK mutations, so it is not realistic to consider these separately in clinical practice. Despite these limitations, we suppose that our data from ALK-rearranged patients collected by multiple institutions will provide clinically meaningful information.

In summary, DFS and OS of patients with ALK-rearranged mutations were not significantly different from those with neither ALK nor EGFR mutations. PRS of patients with ALK-rearranged mutations was significantly longer than that of patients without the mutations. ALK-TKI treatment after recurrence might play an important role. It is important to treat patients with resected ALK-rearranged NSCLC with consideration of driver gene mutations. Successful treatment with ALK-TKI might be required, even for patients who experience recurrence after surgery. In order to fully elucidate these relationships, it is necessary to accumulate information obtained, not only by clinical trials, but also from clinical practice.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MI, NH, KF, HSa and YS designed the study. MI, HIc, SU, KI, OI, RN, YI, HS, MaK, KK, MoK, SY, MS, NK, KF collected the data. MI, KM and HSa analyzed the data and prepared the article. All authors approved the final version of the article.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Mito Kyodo General Hospital-Mito Medical Center, University of Tsukuba (approval no. 16-66, 18-15).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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