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RESEARCH ARTICLE

Investigation of age and smoking in NSCLC patients with uncommon EGFR mutations

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ABSTRACT

Investigation of age and smoking in NSCLC patients with uncommon EGFR mutations

Introduction: *In addition to the two common epidermal growth factor receptor (EGFR) mutations, there are many uncommon mutations. Due to the high number of uncommon types, as well as the rarity of patients, there is lack of information regarding patient demographics, especially age distribution and smoking status. Against this background, we conducted an analysis to clarify the background of patients with uncommon EGFR mutations, especially considering their age distribution and smoking status.*

Materials and Methods: *We retrospectively reviewed the medical records of non-small cell lung cancer (NSCLC) patients diagnosed in a multicenter clinical practice from 2002 to 2023. Patients included all cases of non-advanced and advanced NSCLC with uncommon EGFR mutations.*

Results: *Information on 158 patients with uncommon EGFR mutation was collected. Median age was 72 years, with the age distribution showing that most patients were in their 70s. There was a significant difference between the proportion of patients aged up to 59 years and the proportion aged 75 years or older. In 88 patients with a smoking habit history, a significant correlation was found between smoking index and age. Among non-smokers, there was a peak between ages 70 and 74, which was older than the peak among smokers.*

Conclusion: *Even in elderly patients and NSCLC patients with a history of smoking, although it is unclear whether EGFR mutation is common or uncommon, EGFR gene testing should be performed considering the possibility of these patients being EGFR-positive.*

Key words: *Epidermal growth factor receptor; non-small cell lung cancer; uncommon mutation; age*

ÖZ

Nadir görülen EGFR mutasyonları olan KHDAK hastalarında yaş ve sigara kullanımının araştırılması

Giriş: *İki yaygın epidermal büyüme faktörü reseptörü (EGFR) mutasyonuna ek olarak, pek çok mutasyon da vardır. Nadir görülen tiplerin çokluğu ve hastaların nadirliği nedeniyle, hasta demografik özellikleri, özellikle yaş dağılımı ve sigara içme durumu hakkında bilgi eksikliği bulunmaktadır. Bu arka plana dayanarak, nadir görülen EGFR mutasyonlarına sahip hastaların geçmişini, özellikle yaş dağılımlarını ve sigara içme durumlarını göz önünde bulundurarak açıklığa kavuşturmak için bir analiz gerçekleştirilmiştir.*

Materyal ve Metod: *2002'den 2023'e kadar çok merkezli bir klinik uygulamada teşhis edilen küçük hücreli dışı akciğer kanseri (KHDAK) hastalarının tıbbi kayıtlarını retrospektif olarak inceledik. Hastalar, yaygın olmayan EGFR mutasyonları olan tüm ileri evre olmayan ve ilerlemiş KHDAK vakalarını içeriyordu.*

Bulgular: *Yaygın olmayan EGFR mutasyonuna sahip 158 hasta hakkında bilgi toplandı. Ortalama yaş 72 idi ve yaş dağılımı çoğu hastanın 70'li yaşlarda olduğunu gösteriyordu. Elli dokuz yaşına kadar olan hastaların oranı ile 75 yaş ve üzeri hastaların oranı arasında anlamlı bir fark vardı. Sigara içme öyküsü olan 88 hastada sigara içme indeksi ile yaş arasında anlamlı ilişki saptandı. Sigara içmeyenler arasında 70 ile 74 yaşları arasında bir zirve vardı ve bu, sigara içenler arasındaki zirveden daha düşüktü.*

Sonuç: *Yaşlı hastalarda ve sigara içme öyküsü olan KHDAK hastalarında bile, EGFR mutasyonunun yaygın mı yoksa nadir mi olduğu belirsiz olsa da, bu hastaların EGFR pozitif olma olasılığı göz önünde bulundurularak EGFR gen testi yapılmalıdır.*

Anahtar kelimeler: *Epidermal büyüme faktörü reseptörü; küçük hücreli dışı akciğer kanseri; yaygın olmayan mutasyon; yaş*

INTRODUCTION

The epidermal growth factor receptor (EGFR) mutation was the first driver gene discovered for non-small cell lung cancer (NSCLC) (Attili) (John). Among EGFR mutations, *Ex19* deletion and *Exon 21 L858R* are two of the most common mutations, and there are multiple uncommon mutations (1,2). Among the uncommon mutations, *G719X*, *L861Q*, and *S768I* mutations are relatively frequent (1,2). Therefore, there have been many reports that treat these mutations collectively as major uncommon mutations (1,2). It is known that patients with these gene mutations respond to second-generation EGFR-tyrosine kinase inhibitors (TKIs), but patients with Exon 20 insertions do not respond to EGFR-TKIs (3,4). At present, the existence of patients with many compound mutations with common or uncommon EGFR mutations has been recognized (4). Not only are they rare, but they are also genetically heterogeneous populations, and their responses to therapeutic drugs are not the same. As such, there are not many studies investigating patient backgrounds, such as age and smoking, in detail (5-19). In particular, only a few studies have shown information on more than 100 patients with uncommon mutations (6-8,11,13,15,18).

In view of this, we conducted this study to clarify clinical characteristics, with particular focus on age and smoking history, of NSCLC patients with uncommon EGFR mutations.

MATERIALS and METHODS

The medical records of all NSCLC patients diagnosed at 14 medical institutions in our prefecture from July 2002 to December 2023 were examined. Based on the World Health Organization classification, the pathological diagnosis of each NSCLC patient was made (20). Before starting treatment, all patients underwent TNM classification using head computed tomography or magnetic resonance imaging, bone or positron emission scan, and abdominal ultrasound and/or computed tomography (21). At the time of NSCLC diagnosis, the following patient background characteristics were investigated: Sex, age, Eastern Cooperative Oncology Group performance status (PS), clinical stage, presence of EGFR mutation and EGFR mutation subtype. The 'number of cigarettes smoked per day' and 'years of smoking' were also investigated. The product of these indices was used as the smoking index (22,23).

For statistical analyses, the Chi-squared test was used to test for differences in proportions. The Mann-Whitney U test was used to compare values between two unmatched groups, such as patient age and smoking index. Correlations were examined using the Spearman correlation coefficient. A P-value less than 0.01 was considered to indicate a significant difference.

This study was approved by the Institutional Review Board of University of Tsukuba Mito Medical Center/ Mito Kyodo General Hospital (NO-23-53) and by each institute that participated in this study.

RESULTS

Characteristics of Patients

During the study period, clinical information on 158 patients with uncommon EGFR mutations was collected from 14 institutions. Median age of these patients was 72 years (range, 35-92 years), and there were 86 male and 72 female patients. There were 153 patients with adenocarcinoma and five patients with other histological types. The clinical stage was IA-IIIC in 83 patients, and IVA-B in 75 patients. With regard to PS, 137 patients had PS 0-1, and 21 patients had PS 2-4. There were 98 patients with major uncommon mutations, *G719X*, *L861Q*, and *S768I*, 41 with compound mutations, and 19 with Exon 20 insertions. Shows the age distribution of all patients Figure 1. The highest number of patients were in their 70s. There were 25 patients aged up to 59 years, and 47 patients aged 75 years or older. There was a significant difference between the proportion of patients aged up to 59 years and that aged 75 years and older (p= 0.0046).

Comparison Among Uncommon EGFR Mutations

A comparison of patient background factors was performed with patients with three major mutations, *G719X*, *L861Q*, and *S768I*, as Group 1, patients with compound mutations as Group 2, and patients with Exon 20 insertions as Group 3. Patient background factors among the three groups are shown in Table 1. There were no significant differences in age, sex histology, clinical stage, or PS among the three groups. In addition, we focused on smoking and compared the percentage of non-smokers, the percentage of light smokers (smoking index of 100 or less), and the smoking index, but there were no significant differences among the three groups.

Correlation and Comparison between Age and Smoking Index in the Three Groups Due to Uncommon EGFR mutations

Figure 2-A shows the correlation between smoking index and age in all 158 patients. There was no significant correlation between smoking index and age in these patients (Spearman's rank correlation co-efficient p= 0.9059, p= 0.009). Next, we investigated the correlation between smoking index and age among the 88 smokers. The results are shown in Figure 2-B. For smokers only, there was a significant correlation between smoking index and age (Spearman's rank correlation co-efficient p= 0.0002, p= 0.397).

Patients were divided into non-smokers and smokers, and their age distributions are shown in Figures 3-A and B. In both groups, 70 non-smokers and 88 smokers, the most modal value for age was in the 70s. For non-smokers, the peak was at ages 70-74,

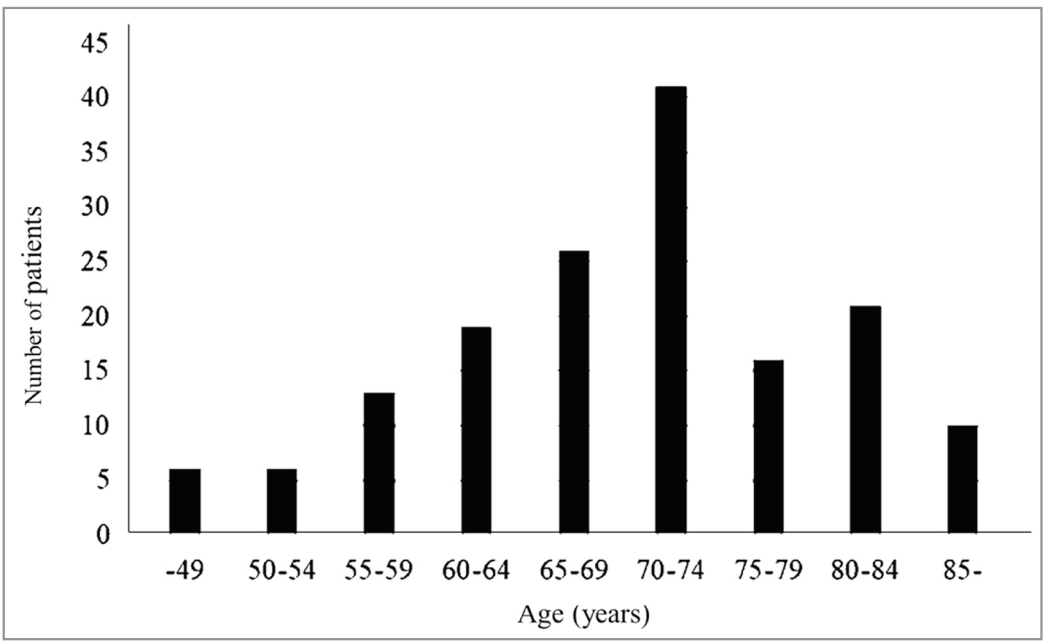

Figure 1. Age distribution of all 158 NSCLC patients with uncommon EGFR mutation (86 male patients and 72 female patients).

Table 1. Comparison of patient background factors among the three groups of patients: Group 1 (major mutations, *G719X*, *L861Q*, and *S768I*), Group 2 (compound mutations), and Group 3 (Exon 20 insertions)

	Group 1	Group 2	Group 3	p
Number of patients	98	41	19	
Age, median (range) years	72 (47-92)	68 (38-92)	73 (35-89)	0.2664
Sex				
Male	50 (51.0%)	23 (56.1%)	13 (68.4%)	0.3670
Female	48 (49.0%)	18 (43.9%)	6 (31.6%)	
Pathology				
AD	95 (96.9%)	39 (95.1%)	19 (100%)	0.6014
Others	3 (3.1%)	2 (4.9%)	0 (0%)	
Stage				
IA-IIIC	53 (54.1%)	20 (48.8%)	10 (52.6%)	0.8497
IVA-B	45 (45.9%)	21 (51.2%)	9 (47.4%)	
PS				
0-1	85 (86.7%)	36 (87.8%)	16 (84.2%)	0.9237
2-4	13 (13.3%)	5 (12.2%)	3 (15.8%)	
Non-smoker	45 (45.9%)	18 (43.9%)	7 (36.8%)	0.7653
Smoker	53 (54.1%)	23 (56.1%)	12 (63.2%)	
Non-light-smoker (SI< 100)	48 (49.0%)	19 (46.3%)	9 (47.4%)	0.8583
Smoker	50 (51.0%)	22 (53.7%)	10 (52.6%)	
SI, median (range)	130 (0-2400)	180 (0-1600)	150 (0-1500)	0.6227

AD: Adenocarcinoma, PS: Performance status, SI: Smoking index.

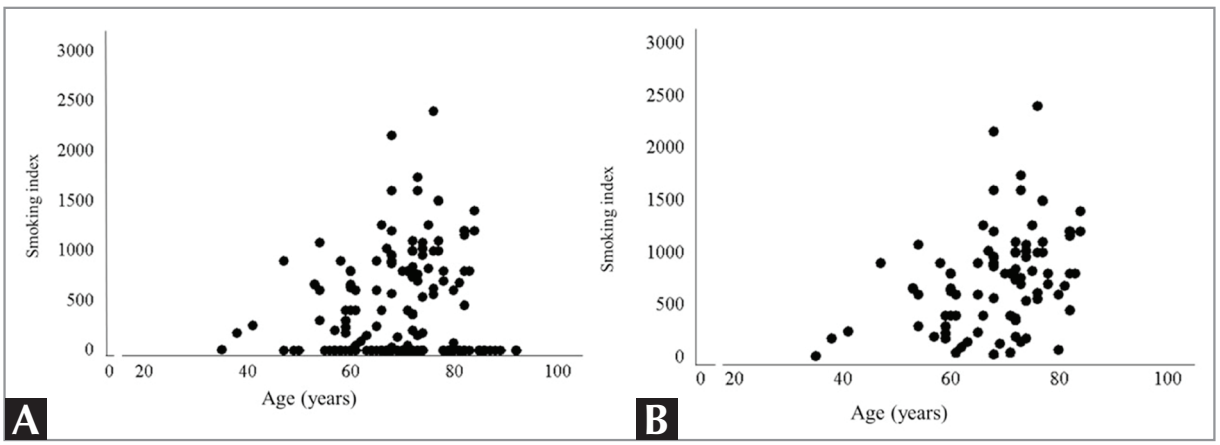

Figure 2. Correlation between smoking index and age in all 158 NSCLC patients **(A)**. There was no significant correlation between smoking index and age in these patients (Spearman's rank correlation co-efficient p= 0.9059, p= 0.009). Correlation between smoking index and age in 88 NSCLC patients with smoking habit **(B)**. There was a significant correlation between smoking index and age (Spearman's rank correlation co-efficient p= 0.0002, p= 0.397).

and for smokers, it was at ages 65-69. There was a significant difference in the age distribution of the non-smoker and smoker groups (p= 0.0192, Chi-squared test).

DISCUSSION

This study confirmed the following results: The median age of the 158 patients with EGFR uncommon mutations was 72 years. Regarding the age distribution of all patients, the most modal value for age was in the 70s. There was a significant difference between the proportion of the patients aged up to 59 years and the proportion of those aged 75 years or older. In 88 patients with a smoking habit, a significant correlation was found between the smoking index and age. Among non-smokers, there was a peak between ages 70 and 74, which was older than the peak among smokers.

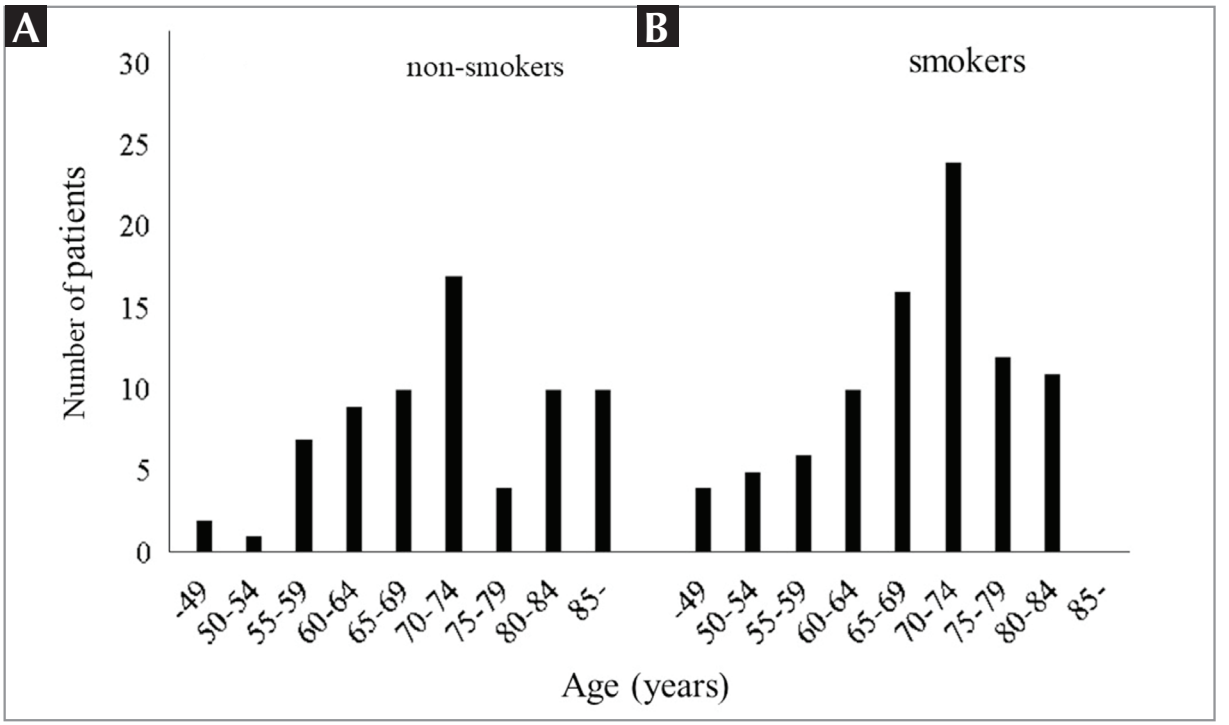

Figure 3. Age distribution of 70 NSCLC patients without smoking habit **(A)** and 88 NSCLC with smoking habit **(B)**. Significant difference in the age distribution between these two groups of patients (p= 0.0192, Chi-squared test).

Most studies to date on patients with uncommon EGFR mutations have focused on stage III-IV patients (5-7,10,12-17), and very few reports have included data on patients at all stages (9,19). Furthermore, the number of patients evaluated in these previous studies has been very small; 26 and 40 patients, respectively (9,19). In past surveys of patients with stage III-IV disease and uncommon EGFR mutations, the proportion of female patients was 37%-75% (5-7,9-19), and the proportion of patients with PS 0-1 was 60%-100% (6,9,10,12-17). The proportion of patients with adenocarcinoma was 16.7% in a study of 291 patients by Evans et al. (11), but other studies have generally reported proportions over 90% (5,7,10-17). In previous studies involving more than 100 patients, uncommon mutations have been classified into three groups: Major uncommon mutations, *G719X*, *L861Q*, and *S768I*; compound mutations; and Exon 20 insertions (6,7,11,13,15,18). Our study involved a relatively large number of patients, including patients at all stages of NSCLC from stage IA to stage IVB. In this survey, 42.4% were women, 86.7% were patients with PS 0-1, and 96.8% were adenocarcinoma patients. Focusing on uncommon mutation subtypes, 98 patients (62%) had major, 41 (25.9%) had compound, and 19 (12%) had Exon 20 insertions. It is known that the positive rate of EGFR mutations in NSCLC differs between Asians and Caucasians (24), and it was necessary to confirm these background factors. However, these results were not significantly different from previous studies (5-19).

In previously conducted EGFR-TKI clinical trials, median age of the patients with uncommon EGFR mutations was 58-64 years (6,12,14). In a recent TKI clinical trial of over 40 patients with uncommon EGFR mutations, median age has been found as 72 years (19). On the other hand, in most studies in clinical practice except one (11), median age has been found as 59-68 years (5,7-11,13,15-18). The exception is a study of 291 patients in the United Kingdom by Evans et al., in which the average age is 70.1 years (11). The results from clinical practice from Evans et al. and our study suggest that even patients older than 70 years might harbor uncommon EGFR mutations (11). Not conducting a search for driver genes in NSCLC due to advanced age should be avoided, as this might limit treatment options.

In studies conducted so far, the proportion of smokers among patients with uncommon EGFR mutations has been found as 44%-59% in clinical trials (12,14) and as 48%-69% in clinical practice, except for one study

from India involving 40 patients, which has shown a non-smoking rate of 83% (7,9,10,13,15-18). In the present study, the proportion of non-smokers was 44.3%. Although it has been reported that the proportion of smokers is higher in patients with uncommon EGFR mutations than in patients with common mutations, to the best of our knowledge, there have been no reports that have considered both smoking history and age (13). The results of this study show that in both groups, 70 smokers and 88 non-smokers, the most modal value for age was in the 70s. On the other hand, there was a significant difference in age distribution between the non-smoker and smoker groups. In other words, the number of patients increased up to the age of 74 in both non-smoking and smoking groups, and after that, the distribution showed a difference between the two groups. A significant correlation was found between age and smoking index in patients with smoking history. It has been speculated that this is not simply due to an increase in the number of years of smoking, but that there may be some other cause that remains unknown.

Although the above novel findings were obtained, this study has some limitations. We used several testing methods for EGFR mutations, but comparisons could not be made because the testing methods were not integrated due to the multicenter nature of the study, and there was no information on EGFR gene-negative patients who were treated around the same time. In addition, the study period was long because it was intended to collect a large number of patients. However, there are few reports that have investigated more than 150 patients, and we do believe that the information obtained might be useful for the future medical treatment of patients with uncommon EGFR mutations.

CONCLUSION

The implementation of driver gene testing for NSCLC is expected to provide important information for selecting treatment options tailored to the patient. Therefore, even in NSCLC patients who are elderly or who have a history of smoking, although it is unclear whether EGFR mutations are common or uncommon, EGFR gene testing should be performed in case an EGFR mutation is present.

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Ethical Committee Approval: This study was obtained from General Hospital Mito Kyodo Hospital Director of Hospital Ethics Committee (Decision no: 23-53, Date: 13.12.2023).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: YM, SO, KM, HS

Analysis/Interpretation: YM, SO, KM, HS

Data acqusition: YM, MT, TK, TL, TN, TS, KM, RN, KI, TS

Writing: YM, KM, HS

Clinical Revision: HS

Final Approval: HS, NH

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