


ORIGINAL ARTICLE

The prognostic implications of *EGFR* mutation and *ALK* rearrangement for the long-term outcomes of patients with resected lung adenocarcinomas

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Keywords

Adenocarcinoma; anaplastic lymphoma kinase; epidermal growth factor receptor; prognosis; survival analysis.

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Abstract

Background: To investigate the prognostic impact of epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) rearrangement for the overall survival (OS) of patients with surgically treated lung adenocarcinomas.

Methods: A total of 689 patients with stage I–III lung adenocarcinomas (male: female = 334:355; median age, 64 years) underwent complete surgical resection between 2007 and 2013. The prognostic impact of *EGFR* mutation and *ALK* rearrangement on OS was analyzed using Cox regression analysis. Certain clinicopathological prognostic factors (i.e., age, sex, smoking status, nodule type, solid portion size, pathologic stage, adenocarcinoma subtype, and history of adjuvant chemotherapy) were included for adjustments of the hazard ratio (HR).

Results: *EGFR* mutation was observed in 438 patients (64%) and *ALK* rearrangement was seen in 28 patients (4%). Multivariable-adjusted Cox regression demonstrated that the prognostic effect of *EGFR* mutation on OS differed by age (HR, exp.[−5.199 + 0.064*age]). The adjusted HR for *EGFR* mutation was 0.14 (95% CI: 0.05–0.36; $P < 0.001$) at 50 years, 0.26 (95% CI: 0.15–0.46; $P < 0.001$) at 60 years, and 0.50 (95% CI: 0.31–0.81; $P = 0.005$) at 70 years. However, the effect of *ALK* rearrangement on OS was without statistical significance ($P > 0.05$).

Conclusions: *EGFR* mutation was independently prognostic of the long-term outcomes of patients with surgically treated lung adenocarcinomas. A more favorable prognostic effect was seen in younger than in older patients. *ALK* rearrangement was not associated with OS.

Introduction

Epidermal growth factor receptor (*EGFR*) mutation is a well-known predictive marker of *EGFR* tyrosine kinase inhibitors (TKIs) in patients with advanced non-small cell lung cancers (NSCLCs).¹ Accordingly, *EGFR* TKI is generally the standard first-line treatment administered to patients with activating mutations. Nevertheless, the prognostic value of *EGFR*

mutation is controversial, particularly in patients with surgically resected NSCLCs. The prognostic role of other driver mutations, including anaplastic lymphoma kinase (*ALK*) rearrangement, is subject to the same ambiguity. Thus, solid evidence is presently lacking in this regard.

Performing an evaluation to determine the prognostic potential of driver mutations in a surgical cohort is vital, given the fact that this population differs from patients

with advanced lung cancers who have not received prior treatment. Patients undergoing complete curative resection may experience postoperative recurrence, decreased pulmonary function, or poor performance due to lung surgery.² Therefore, the survival dynamics of these patients are unique, and prognostic factors should be analyzed separately for this subset. It is thought that integrative prognostication using the anatomic elements of the tumor-node-metastasis staging system, as well as the non-anatomical elements, i.e., genetic profiles (e.g., *EGFR* and *ALK* status), expedites accurate preoperative risk stratification and therapeutic planning.

Notably, there has been substantial heterogeneity in the methodologies of prognostic studies regarding driver mutations associated with resected lung cancer in terms of smoking status, cancer stage, histology, and imaging characteristics. Potential confounders require adjustment or stratification to determine the true prognostic effect of driver mutations. In addition, overall survival (OS) is considered to be an appropriate endpoint in the era of *EGFR* TKI, which prolonged survival in patients with metastatic lung cancers. Accordingly, this can lead to the decoupling between disease-free survival and OS in patients with *EGFR*-mutant lung cancers.

The aim of this study was to investigate the prognostic implications of *EGFR* mutation and *ALK* rearrangement for the OS of patients with surgically treated lung adenocarcinomas, having made adjustments to several important clinicopathologic prognostic factors.

Methods

This retrospective research was approved by the Institutional Review Board of Seoul National University Hospital. The requirement for written informed consent was waived.

Study population

Patients undergoing curative surgical resection without neoadjuvant chemo- and/or radiotherapy for lung adenocarcinoma were retrospectively identified at our tertiary referral hospital between October 2007 and December 2013 following a search of the electronic medical records (EMRs). Of 1466 patients, 1075 were subject to mutational analysis for both *EGFR* and *ALK*.

The following exclusion criteria were applied: (i) patients with synchronous or metachronous lung cancers ($n = 145$); (ii) a pathologic diagnosis of atypical adenomatous hyperplasia or adenocarcinoma *in situ* ($n = 110$); (iii) a pathologic diagnosis of invasive mucinous adenocarcinoma ($n = 48$); (iv) patients with pleural metastasis identified intraoperatively ($n = 19$); (v) adenocarcinoma subtypes not available ($n = 57$); (vi) the absence of a preoperative chest

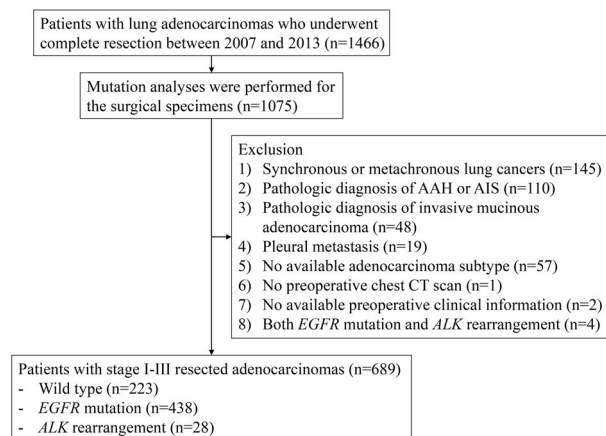


Figure 1 Flow diagram of patient inclusion and exclusion. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor.

computed tomography (CT) scan ($n = 1$); and (vii) the absence of available preoperative clinical information (i.e., smoking history) ($n = 2$). Patients with both *EGFR* mutation and *ALK* rearrangement were also excluded ($n = 4$). A total of 689 patients participated in the study (Fig 1).

Data collection

The patient characteristics (age and sex), date of surgery, surgical mode (lobectomy or sublobar resection), history of adjuvant therapy, smoking status (never smoker, ex- or current smoker), nodule location (upper lobe or other lobes), pathologic diagnosis, driver mutations (*EGFR* and *ALK*), pathologic stage based on the seventh edition of the American Joint Committee on Cancer staging system,³ and predominant adenocarcinoma subtype according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification were obtained from the EMRs.⁴ Pathologic diagnosis and adenocarcinoma subtype were confirmed by board-certified pathologists at our hospital as part of routine clinical practice. The adenocarcinoma subtypes were categorized into three groups for the statistical analysis: (i) minimally invasive adenocarcinoma and lepidic predominant adenocarcinoma; (ii) acinar or papillary predominant adenocarcinoma; and (iii) micropapillary or solid predominant adenocarcinoma.^{5,6}

The nodule characteristics were evaluated using preoperative chest CT scans. Nodule type was determined according to one of the following patterns for each nodule: (i) pure ground-glass (100% ground-glass opacity [GGO]); (ii) GGO-dominant ($50\% \leq \text{GGO} < 100\%$); (iii) solid-dominant ($0\% < \text{GGO} < 50\%$); or (iv) solid (0% GGO).⁷

The solid portion size (effective diameter) was obtained after manual volumetric segmentation of the entire nodule.⁷ Solid portion segmentation was achieved within the manually drawn regions-of-interest for the nodule using fuzzy C-means clustering. The effective diameter (that of the sphere where the volume equals the solid portion volume) was then calculated.⁷ The solid portion was considered to be a substitute for the pathologic invasive component^{8,9} not directly measured with regard to the surgical specimens in this study. The solid portion size was categorized as ≤ 3 , >3 to ≤ 5 cm, >5 to ≤ 7 cm, or > 7 cm.⁸ Reviews of the images were performed by a single board-certified thoracic radiologist (H.J.L. with 20 years of chest CT experience).

The primary endpoint was OS, measured from the date of surgery to the date of death from any cause. The last known surviving patients were censored at the date of the last outpatient visit.

Mutational analysis

The *EGFR* mutational status of the surgical specimen was analyzed using direct DNA sequencing, as previously described.^{10,11} Following the extraction of genomic tumor DNA from the paraffin sections of the tumor block, *EGFR* exons 18–21 were amplified using polymerase chain reaction (PCR). Sequencing was performed on the PCR fragments in both the sense and anti-sense directions. *EGFR* mutation was considered to be positive in the presence of activating mutations. *ALK* rearrangement was tested using fluorescence *in situ* hybridization (FISH). *ALK* FISH was deemed to be positive when $\geq 15\%$ of the tumor cells counted showed a split signal of the fluorescent probes flanking the *ALK* locus.¹² Wild-type patients were neither *EGFR*-mutant nor *ALK*-positive.

Statistical analysis

The demographic and clinical characteristics of the patients were described as frequencies and percentages for the categorical variables, and as medians and interquartile ranges (IQR) for the continuous variables. Clinicopathological variables, including age, sex, smoking status, nodule type, location, surgical mode, solid portion size, pathologic stage, adenocarcinoma subtype, history of adjuvant chemotherapy, and driver mutation status, were assessed for their prognostic value.

An evaluation of the prognostic factors was performed using the Cox proportional hazard model. After univariable analysis, variables with a *P*-value of ≤ 0.10 were considered for inclusion in the multivariable analysis. Interaction terms between driver mutation status and the other variables were also included in the multivariable

analysis. The final multivariable model was determined using stepwise selection with an entry criterion of *P*-value < 0.10 and a removal criterion of *P*-value ≥ 0.05 . The proportional hazard assumption was confirmed using the Schoenfeld residuals. The *P*-values were based on two-sided tests. A *P*-value of < 0.05 was considered to represent statistical significance. Statistical analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

The study population comprised 689 patients (334 males and 355 females; median age of 64 years; IQR of 56–70 years). *EGFR* mutation was seen in 438 patients (64%). *ALK* rearrangement was observed in 28 patients (4%). A total of 520 patients (76%) were categorized as pathologic stage I, 75 patients (11%) as stage II, and 92 patients (13%) as stage III. Solid portion size of ≤ 3 cm was attributed to 452 patients (66%), a size of >3 to ≤ 5 cm to 127 patients (18%), a size of >5 to ≤ 7 cm to 59 patients (9%), and a size of >7 cm to 51 patients (7%). Lung cancer manifested as pure ground-glass nodules in 49 patients (7%), as GGO-dominant nodules in 151 patients (22%), as solid-dominant nodules in 247 patients (36%), and as solid nodules in 242 patients (35%). Of the adenocarcinoma histologic subtypes, 56 patients (8%) had minimally invasive adenocarcinomas, 82 (12%) had lepidic predominant adenocarcinomas, 351 (51%) had acinar predominant adenocarcinomas, 99 (14%) had papillary predominant adenocarcinomas, 16 (2%) had micropapillary predominant adenocarcinomas, and 85 (12%) had solid predominant adenocarcinomas. A total of 75 patients (11%) underwent sublobar resection and 115 (17%) were treated with adjuvant chemotherapy after surgery. Deaths occurred in 96 patients (14%). The median follow-up interval was 2142 days (IQR of 1839–2505 days). The patient and lung nodule characteristics were described according to driver mutation status (Table 1).

Univariable Cox regression analysis for overall survival

The results of univariable Cox regression analysis for OS in lung adenocarcinomas are detailed in Table 2. *EGFR* mutation was significantly associated with OS (hazard ratio [HR] of 0.32; 95% confidence interval [CI]: 0.21–0.49; *P* < 0.001). By contrast, the effect of *ALK* rearrangement on OS was without statistical significance (HR of 0.54; 95% CI: 0.20–1.49; *P* = 0.232).

A *P*-value of < 0.10 was reported for age, sex, smoking status, nodule type, solid portion size, pathologic stage, adenocarcinoma subtype, and history of adjuvant chemotherapy. Consequently, these were included in multivariable Cox regression analysis, along with the respective

Table 1 Patient and tumor characteristics

Variable	Wild-type (n = 223)	<i>EGFR</i> mutation (n = 438)	<i>ALK</i> rearrangement (n = 28)	Total (n = 689)
Age (years)†	65 (58, 71)	63 (56, 70)	59 (50, 69)	64 (56, 70)
Sex				
Male	143 (64.1)	180 (41.1)	11 (39.3)	334 (48.5)
Female	80 (35.9)	258 (58.9)	17 (60.7)	355 (51.5)
Smoking history				
Never smoker	95 (42.6)	296 (67.6)	21 (75.0)	412 (59.8)
Ex- or current smoker	128 (57.4)	142 (32.4)	7 (25.0)	277 (40.2)
Nodule type				
Pure ground-glass	10 (4.5)	39 (8.9)	0 (0.0)	49 (7.1)
GGO-dominant	36 (16.1)	112 (25.6)	3 (10.7)	151 (21.9)
Solid-dominant	75 (33.6)	168 (38.4)	4 (14.3)	247 (35.8)
Solid	102 (45.7)	119 (27.2)	21 (75.0)	242 (35.1)
Location				
Upper lobe	123 (55.2)	252 (57.5)	11 (39.3)	386 (56.0)
Other lobes	100 (44.8)	186 (42.5)	17 (60.7)	303 (44.0)
Surgical mode				
Sublobar resection	35 (15.7)	40 (9.1)	0 (0.0)	614 (89.1)
Lobectomy	188 (84.3)	398 (90.9)	28 (100.0)	75 (10.9)
Solid portion size				
≤3 cm	134 (60.1)	297 (67.8)	21 (75.0)	452 (65.6)
>3 and ≤5 cm	43 (19.3)	81 (18.5)	3 (10.7)	127 (18.4)
>5 and ≤7 cm	18 (8.1)	38 (8.7)	3 (10.7)	59 (8.6)
>7 cm	28 (12.6)	22 (5.0)	1 (3.6)	51 (7.4)
Pathologic stage‡				
I	157 (70.4)	350 (79.9)	15 (53.6)	522 (75.8)
II	33 (14.8)	39 (8.9)	3 (10.7)	75 (10.9)
III	33 (14.8)	49 (11.2)	10 (35.7)	92 (13.4)
Adenocarcinoma subtype				
MIA	15 (6.7)	41 (9.4)	0 (0.0)	56 (8.1)
Lepidic predominant	24 (10.8)	57 (13.0)	1 (3.6)	82 (11.8)
Acinar predominant	107 (48.0)	236 (53.9)	8 (28.6)	351 (50.6)
Papillary predominant	31 (13.9)	63 (14.4)	5 (17.9)	99 (14.3)
Micropapillary predominant	4 (1.8)	7 (1.6)	5 (17.9)	16 (2.3)
Solid predominant	42 (18.8)	34 (7.8)	9 (32.1)	85 (12.3)
Adjuvant chemotherapy				
Yes	38 (17.0)	64 (14.6)	13 (46.4)	115 (16.7)
No	185 (83.0)	374 (85.4)	15 (53.6)	574 (83.3)
Deaths	54 (24.2)	38 (8.7)	4 (14.3)	96 (13.9)
Follow-up period (days)†	1999 (1715, 2370)	2239 (1897, 2549)	2221 (1777, 2443)	2142 (1839, 2505)

Unless otherwise specified, the numbers in parentheses are percentages. †The data are expressed as medians with interquartile ranges in parentheses. ‡Pathologic stage according to the seventh edition staging system for lung cancer. *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; GGO, ground-glass opacity; MIA, minimally invasive adenocarcinoma.

interaction terms. The Kaplan-Meier survival curves stratified according to driver mutation status are shown in Fig 2.

Multivariable-adjusted Cox regression analysis for overall survival

Multivariable-adjusted Cox regression demonstrated that the prognostic effect of *EGFR* mutation on OS differed by age (Fig 3). Patients with *EGFR* mutation experienced significantly longer survival than those with wild-type, and this relationship was dependent on the age of the patients (HR, exp.[-5.199 + 0.064*age]). Younger patients with *EGFR*

mutation experienced significantly longer OS than those with wild-type. However, with advancing age, the beneficial effect of *EGFR* mutation decreased, and the HR value became close to that of patients with wild-type. For example, the adjusted HR for *EGFR* mutation was 0.14 (95% CI: 0.05–0.36; $P < 0.001$) at 50 years of age, 0.26 (95% CI: 0.15–0.46; $P < 0.001$) at 60 years, and 0.50 (95% CI: 0.31–0.81; $P = 0.005$) at 70 years. The effect of *ALK* rearrangement on OS was seen to have an inverse relationship with age. The HR value for patients who experienced *ALK* rearrangement decreased with advancing age (HR, exp. [2.194–0.049 age]), but this finding was without statistical

Table 2 Univariable Cox regression analysis for overall survival in lung adenocarcinomas

Variable	Subcategory	HR	95% CI of HR	P-value
Age (year)		1.05	1.02, 1.07	<0.001
Female sex		0.51	0.33, 0.77	0.001
Ex- or current smoker		2.04	1.36, 3.05	0.001
	(reference: never smoker)			
Nodule type	GGO-dominant	2.65	0.33, 21.18	0.358
	(reference: pure ground-glass)			
	Solid-dominant	6.47	0.88, 47.34	0.066
	Solid	12.72	1.76, 91.80	0.012
Location at upper lobes		0.80	0.54, 1.19	0.271
	(reference: other lung lobes)			
Sublobar resection		1.00	0.52, 1.92	0.994
	(reference: lobectomy)			
Solid portion size	>3 cm and ≤5 cm	2.69	1.63, 4.46	<0.001
	(reference: ≤ 3 cm)			
	>5 cm and ≤7 cm	3.68	2.04, 6.63	<0.001
	>7 cm	5.61	3.19, 9.88	<0.001
Pathologic stage [†]	II	2.95	1.69, 5.18	<0.001
	(reference: stage I)			
	III	5.89	3.78, 9.18	<0.001
Adenocarcinoma subtype	Acinar or papillary predominant	22.42	3.12, 161.18	0.002
	(reference: MIA or lepidic predominant)			
	Micropapillary or solid predominant	42.58	5.80, 312.86	<0.001
Adjuvant chemotherapy		2.60	1.69, 3.99	<0.001
Driver mutation	<i>EGFR</i> mutation	0.32	0.21, 0.49	<0.001
	(reference: wild-type)			
	<i>ALK</i> rearrangement	0.54	0.20, 1.49	0.232

[†]Pathologic stage followed the seventh edition staging system for lung cancer. *ALK*, anaplastic lymphoma kinase; CI, confidence interval; *EGFR*, epidermal growth factor receptor; GGO, ground-glass opacity; HR, hazard ratio; MIA, minimally invasive adenocarcinoma

significance ($P > 0.05$). Other independent predictors included in the Cox model were age, smoking status, solid portion size, pathologic stage, and adenocarcinoma subtype. The detailed results are outlined in Table 3.

Discussion

EGFR mutation was demonstrated to be a significant independent prognostic factor of the long-term outcomes

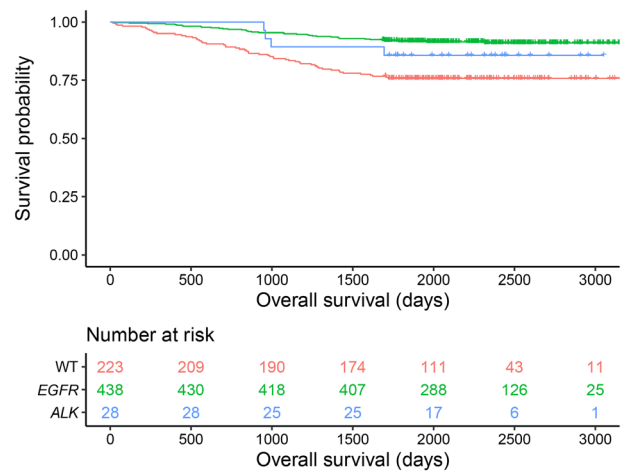


Figure 2 Kaplan–Meier curves of overall survival categorized according to driver mutation status (—, WT, —, *EGFR* mutation, and —, *ALK* rearrangement) in patients with resected lung adenocarcinomas. *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; WT, wild-type.

(OS) of patients with surgically treated lung adenocarcinomas in the current study. A more favorable prognostic effect was seen in younger than in elderly patients. However, *ALK* rearrangement was not associated with OS.

The prognostic implications of *EGFR* mutation in patients with resected lung cancers has previously been evaluated in a number of studies, and conflicting results have been reported.^{6,13–22} *EGFR* mutation was demonstrated to constitute

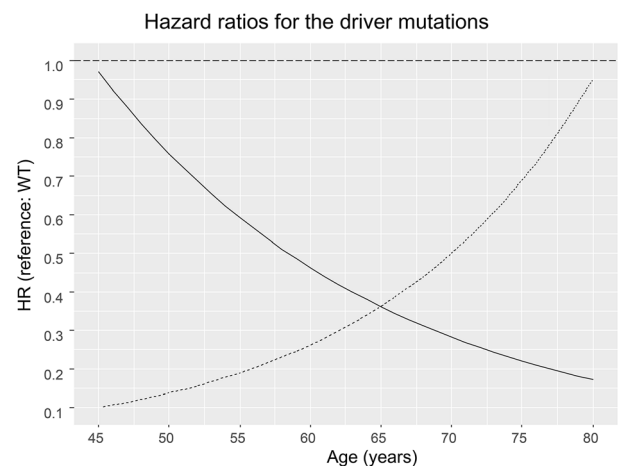


Figure 3 A plot of log-hazard ratio (HR) for driver mutation status. The favorable prognostic effect of *EGFR* mutation was seen to decrease gradually with advancing patient age ($P < 0.050$). An inverse relationship was found for *ALK* rearrangement, but the finding was not statistically significant ($P > 0.05$). *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; WT, wild-type. Group (—) *ALK* rearrangement, (---) *EGFR* mutation

Table 3 Multivariable Cox regression analysis for overall survival in lung adenocarcinomas

Variable	Subcategory	HR	95% CI of HR	P-value
Age (year)	Wild-type	1.02	0.99, 1.05	0.332
	<i>EGFR</i> mutation	1.08	1.04, 1.13	<0.001
	<i>ALK</i> rearrangement	0.97	0.89, 1.05	0.432
Ex- or current smoker (reference: never smoker)		1.61	1.02, 2.53	0.040
Solid portion size (reference: ≤ 3 cm)	>3 cm and ≤ 5 cm	1.62	0.96, 2.73	0.073
	>5 cm and ≤ 7 cm	2.08	1.11, 3.88	0.022
	>7 cm	2.95	1.62, 5.37	<0.001
Pathologic stage [†] (reference: stage I)	II	1.48	0.80, 2.73	0.208
	III	4.68	2.89, 7.58	<0.001
Adenocarcinoma subtype (reference: MIA or lepidic predominant)	Acinar or papillary predominant	8.13	1.54, 42.76	0.013
	Micropapillary or solid predominant	7.93	1.43, 42.94	0.018
Driver mutation (reference: wild-type)	<i>EGFR</i> mutation (age, 50 years)	0.14	0.05, 0.36	<0.001
	<i>ALK</i> rearrangement (age, 50 years)	0.76	0.22, 2.57	0.657
	<i>EGFR</i> mutation (age, 60 years)	0.26	0.15, 0.46	<0.001
	<i>ALK</i> rearrangement (age, 60 years)	0.46	0.17, 1.25	0.129
	<i>EGFR</i> mutation (age, 70 years)	0.50	0.31, 0.81	0.005
	<i>ALK</i> rearrangement (age, 70 years)	0.28	0.07, 1.22	0.090

[†]Pathologic stage followed the seventh edition staging system for lung cancer. *ALK*, anaplastic lymphoma kinase; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; MIA, minimally invasive adenocarcinoma.

a favorable prognostic factor in several studies,^{13,19,21} while others failed to show a significant association between *EGFR* mutation and patient survival.^{6,14,16–18,20,22} Controversially, even the results of two meta-analyses were discordant.^{23,24} *EGFR* mutations were not observed to be a prognostic factor in stage I–III resected NSCLCs (HR for OS of 0.85; 95% CI: 0.67–1.15; $P = 0.210$) in the meta-analysis performed by Zhang *et al.*²³ By contrast, these mutations were significantly associated with disease-free survival and OS in patients with resected NSCLCs (HR for OS of 0.72; 95% CI: 0.66–0.80; $P < 0.001$) in a more recent meta-analysis of 9635 patients from 32 studies.²⁴

In the current study, *EGFR* mutation was an independent prognostic factor for OS after adjusting for multiple

covariates, including age, sex, smoking status, pathologic stage, adenocarcinoma subtype, and solid portion size. The inclusion of multiple clinicopathological covariates in the Cox model was important because *EGFR* mutations have a close correlation with several well-known beneficial prognostic factors, including female sex, having never smoked, and low or intermediate tumor grades.^{22,25} Thus, it is important to determine the prognostic effect of *EGFR* mutation after adjusting for these variables in order to prevent false positive or false negative results. In this context, one of the strengths of the present study was that pathological stage, adenocarcinoma subtype, and solid portion size, all of which are powerful prognostic factors with a potential association with *EGFR* mutation, were included in the analysis.^{26–28} The substantial discrepancy between the current study findings and the reported results in the literature might be attributable to differences in the included variables. In addition, heterogeneity of the mutational status in the reference group (patients with wild-type) and the proportion of *EGFR*-mutant patients treated with *EGFR* TKIs after recurrence may have caused inconsistencies.

An intriguing finding of the present study was that the favorable prognostic effect of *EGFR* mutation was dependent on patient age. The difference in survival between *EGFR*-mutant and wild-type decreased with the advancing age of the patients. The rationale for this phenomenon was unclear. However, a possible hypothesis is that this occurred owing to the increased tumor mutational burden (TMB) in elderly patients.²⁹ TMB is a measure of the number of somatic mutations within a tumor, and is defined as the total number of somatic mutations per coding area of a tumor genome.³⁰ High TMB was associated with worse OS of patients with resected NSCLCs,³¹ and was also negatively associated with survival in patients with metastatic *EGFR*-mutant lung cancers treated with *EGFR* TKIs.³² Thus, it is possible that TMB was a hidden confounder in the current study with respect to the relationship between the prognostic effect of *EGFR* mutation and patient age. This issue should be assessed further in future prospective studies.

ALK rearrangement was not seen to be an independent prognostic factor for OS in the current research, although the point estimation of HR for *ALK* rearrangement was smaller than 1. Previous study results on the prognostic effect of *ALK* rearrangement on resected NSCLCs have been controversial.^{33–37} The Lungscape project, a European multi-institutional effort, reported that *ALK* FISH positivity was a predictor of enhanced OS in resected adenocarcinomas.³³ However, Paik *et al.*³⁶ indicated that *ALK* FISH positivity was not associated with disease recurrence nor OS, and Shin *et al.*³⁷ reported that *ALK* rearrangement was associated with shorter disease-free survival in resected stage IA adenocarcinomas. Kim *et al.*³⁵ reported similar

negative results for populations who had never smoked, and Chaft *et al.*³⁴ revealed that *ALK*-positive NSCLCs were associated with poorer outcomes than those of *EGFR*-mutant NSCLCs, but not *KRAS*-mutant NSCLCs. Interestingly, a recent meta-analysis conducted by Wang *et al.*³⁸ showed that *ALK* rearrangement was predictive of better survival in the general population with NSCLCs, but poorer survival in the non-smoking population. However, an association between *ALK* rearrangement and smoking status was not established in the current study.

Our study had several limitations. Firstly, the prevalence of *ALK* rearrangement was low (4%) with only 28 *ALK*-positive patients. Consequently, this limited the statistical power of the research. Analysis with a larger population and a more sensitive *ALK* testing schema (e.g., the combined use of immunohistochemistry and FISH) is warranted in future studies. Secondly, the results of treatments administered after locoregional recurrence or distant metastasis were not analyzed. Nevertheless, the current study objective was to investigate the role of driver mutation as a prognostic marker, not as a predictive marker. Thirdly, the eighth edition of the lung cancer staging system was not investigated. The study population comprised patients who had undergone surgery by the end of December 2013, prior to its implementation. Therefore, it was not feasible to obtain staging information based on this classification. Nevertheless, the solid portion size of adenocarcinomas was measured at CT as a substitute for the invasive component,⁹ a T factor in the eighth staging system. Fourthly, driver mutations other than *EGFR* and *ALK* were not included in this study. Patients with wild-type constitute a heterogeneous group, and this includes true wild-type and several other uninvestigated driver mutations (e.g., *KRAS*, *MET*, and *ROS1*). Fifthly, patient performance status (e.g., Zubrod or Eastern Cooperative Oncology Group scale) was not investigated, which is a well-known prognostic indicator.³⁹ Unfortunately, patient performance status was not recorded for a number of patients in the EMRs, and as a result could not be utilized in this study. However, we assume that the participants' performance may have been acceptable to a certain level for general anesthesia and lung resection in this surgical cohort.

In conclusion, *EGFR* mutation was demonstrated to be an independent favorable prognostic factor for the long-term outcomes (OS) of patients with resected adenocarcinomas in the present study. The favorable prognostic effect was observed to reduce gradually in elderly patients. By contrast, *ALK* rearrangement was not associated with survival.

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