Prognostic Impact of *EGFR* Driver Mutations on Postoperative Disease Recurrence in Lung Adenocarcinoma

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Abstract. *Aim: The purpose of this study was to investigate the prognostic significance of epidermal growth factor receptor (EGFR) sensitizing mutations in patients with lung adenocarcinoma who underwent complete surgical resection. Patients and Methods: We retrospectively reviewed the clinical records of 164 patients with lung adenocarcinoma who underwent surgery from 2003 to 2010. Seventy-four patients harbored EGFR mutations; two with exon 18 mutations, 27 with exon 19 mutations, and 45 with exon 21 mutations. Results: There were more female patients and more never-/light smokers among patients with EGFR mutations than among patients without EGFR mutations. Patients with EGFR mutations had a trend for better disease-free survival and overall survival compared to patients without EGFR mutations (p=0.068 and p=0.049, respectively). Patients with exon 21 mutations had significantly better disease-free survival than patients with exon 19 mutations (p=0.027). Conclusion: Adenocarcinomas harboring EGFR exon 21 mutation were less malignant than adenocarcinomas harboring exon 19 mutation.*

Since its discovery in 2004, epidermal growth factor receptor (*EGFR*) mutation in lung adenocarcinoma has been vigorously studied (1, 2). Detection of *EGFR* mutations in patients with lung adenocarcinoma is now one of the most important tests performed before treating patients, particularly for those with advanced-stage disease, since the existence of sensitizing mutations predicts the efficacy of EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment (3, 4). However, the prognostic impact of adenocarcinomas harboring *EGFR* mutations after surgery remains controversial, partially because EGFR-TKI treatment prolongs the post-recurrence survival of patients with *EGFR* mutation-positive cancer (5-7). Therefore, disease-free survival (DFS) after surgery could represent a more precise prognosis of the postoperative patient course compared to overall survival (OS) (7, 8). In the present study, we investigated the prognostic impact, primarily for DFS, of lung adenocarcinoma with *EGFR* sensitizing mutations, and separately considered the two major mutations.

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Patients and Methods

We retrospectively reviewed the clinical records of patients with lung adenocarcinoma who underwent complete resection with segmentectomy or more major procedures from 2003 to 2010 at the Department of Surgery and Science, Kyushu University Hospital. Patients treated with chemotherapy or radiotherapy before surgery were excluded. One hundred and sixty-four patients had records of their clinical features available for the present analyses, including *EGFR* mutation status. These patients consisted of 74 with tumors harboring *EGFR* mutations (*EGFR*mut), namely two patients with exon 18 mutations, 27 with exon 19 mutations, and 45 with exon 21 mutations; and 90 with tumors without *EGFR* mutation (*EGFR*wt). Surgical procedures consisted of 13 segmentectomies, 149 lobectomies, and two pneumonectomies. Histological diagnosis of tumor cell type was based on the World Health Organization histological classification of lung tumors. Pathological stages were determined using the seventh edition of the TNM classification system of the Union for International Cancer Control (9). Overall, 54 (32.9%) patients received postoperative chemotherapy: 26 received oral tegafur-uracil, 11 received an oral S-1 regimen within a clinical trial, 13 received platinum-based chemotherapy (eight cisplatin and five carboplatin), two received other chemotherapy regimens and one received postoperative radiotherapy. Routine check-ups including a physical examination, blood cell counts, serum chemistry, serum tumor markers including carcinoembryonic antigen, and chest X-rays were performed on an outpatient basis four times a year for the first 3 years, and thereafter twice annually. Computed tomography was performed twice a year for the first 3

years, and thereafter at least annually. Brain magnetic resonance imaging, and bone scintigraphy or fluorodeoxyglucose positron emission tomography were performed annually. The median follow-up time was 60.2 months (0.2-84 months). DFS was defined as the postoperative period until diagnosis of recurrence or patient death due to any cause. OS was defined as the postoperative period until patient death of any cause. Our Institutional Review Board approved this retrospective study (Kyushu University, IRB No. 204).

EGFR mutation analysis. *EGFR* mutation tests used the peptide nucleic acid-locked nucleic acid (PNA-LNA; Mitsubishi Chemical Medience, Tokyo, Japan) polymerase chain reaction (PCR) clamp method with formalin-fixed paraffin-embedded sections of surgical specimens (10).

Statistics. Intergroup differences in patient characteristics, including age, gender, smoking status [in pack-years (PY]), surgical procedure, T status, N status, pathological stages and adjuvant treatment were assessed using χ^2 test. Survival curves were estimated using the Kaplan–Meier method and assessed by log-rank test. A terminal event for DFS was defined as the disease recurrence and death from any cause. Univariate survival analysis was performed using the Cox proportional hazards model. In multivariate survival analysis, variables including age, gender, smoking, pStage, Histology and adjuvant chemotherapy were analyzed. Statistical differences were considered to be significant if the *p*-value was less than 0.05. All data were analyzed using StatView J5 (SAS, Tokyo, Japan).

Results

Differences in clinicopathological features and postoperative survival among patients with adenocarcinoma according to EGFR mutation status. Firstly, we compared the clinicopathological factors between patients with *EGFR* mutation and those without (Table I). Patients with *EGFR*mut were more likely to be female and to be never- or light smokers than *EGFR*wt patients. *EGFR*mut patients had a trend for better DFS than *EGFR*wt patients (5-year DFS: *EGFR*mut=72.8%, EGFRwt=59.5%; $p=0.068$) and had a significantly better OS than *EGFR*wt patients (5-year OS: *EGFR*mut=88.9%, *EGFR*wt=73.2%; $p=0.049$) (Figure 1). Multivariate analysis showed that pathological stage was an independent prognostic factor for both better DFS [stage II+III: hazard ratio (HR)=5.2, $p<0.0001$] and better OS (stage II+III: HR=5.2, $p<0.0001$) (Table II).

Since pathological stage was associated with a survival difference in multivariate analysis, DFS and OS were re-assessed in patients with stage I disease (Figure 2). Almost identical results were observed among patients with stage I disease as among all patients (5-year DFS: *EGFR*mut=86.6% *vs*. *EGFR*wt=72.3%, $p=0.058$; 5-year OS: *EGFR*mut=97.5% *vs*. *EGFR*wt 83.9%, $p=0.055$).

Differences in clinicopathological features and postoperative survival among adenocarcinoma patients with EGFR mutation according to mutation type. We next compared clinicopathological features and postoperative survival among patients with two major *EGFR* mutations: exon 19 deletion (Ex19del) and exon 21 point mutations (Ex21). There were no differences in clinicopathological features between the two groups, except for administration of adjuvant therapy (Table III). Patients with Ex21 received less adjuvant therapies than did patients with Ex19 del.

When prognoses were compared between the two groups, patients with Ex21 had significantly better DFS than patients with Ex19del (5-year DFS: Ex19=53.3%, Ex21=84.4%, $p=0.027$; Cox regression survival analysis: HR=0.36, $p=0.034$) (Figure 3a). In contrast, OS was not different between patients with Ex19del and those with Ex21 (5-year OS: 95.0%; *vs*. 84.8%, respectively; $p=0.70$) (Figure 3b). Among patients with stage I disease with Ex21, no recurrences or deaths have been observed during the follow-up period, while the 5-year DFS and OS rates of patients with stage I disease with Ex19del were 64.6% and 93.3%, respectively (Figure 3c and d). The statistical significance was not calculated because no events were observed for Ex21 patients.

Table I. *Clinicopathological characteristics of patients with adenocarcinoma according to epidermal growth factor receptor (EGFR) mutation status*.

Factor	Category	*EGFR*mut (n=74)	*EGFR*wt (n=90)	*p*-Value
Age	<65 Years	20	37	0.060
	≥65 Years	54	53	
Gender	Male	21	55	<0.0001
	Female	53	35	
Smoking*	0	47	31	<0.0001
	≤30 PY	18	11	
	>30 PY	5	41	
Surgical procedure	Segmentectomy	8	5	**
	Lobectomy	65	84	
	Pneumonectomy	1	1	
pT	T1	48	45	0.056***
	T2	24	35	
	T3	2	9	
	T4	0	1	
pN	N0	59	69	0.60
	N1	8	9	
	N2	7	12	
pStage	I	55	61	0.57
	II	12	16	
	III	7	13	
Adjuvant therapy	No	51	59	0.65
	Yes	23	31	

*EGFR*mut: With *EGFR* mutation; *EGFR*wt, with wild-type *EGFR*; PY, pack-year. *A total of 153 patients were available for analysis. **No statistical analysis was performed since the number of patients with some factors was less than 5. ***The statistical analysis was performed comparing between T1 and T2+T3+T3.

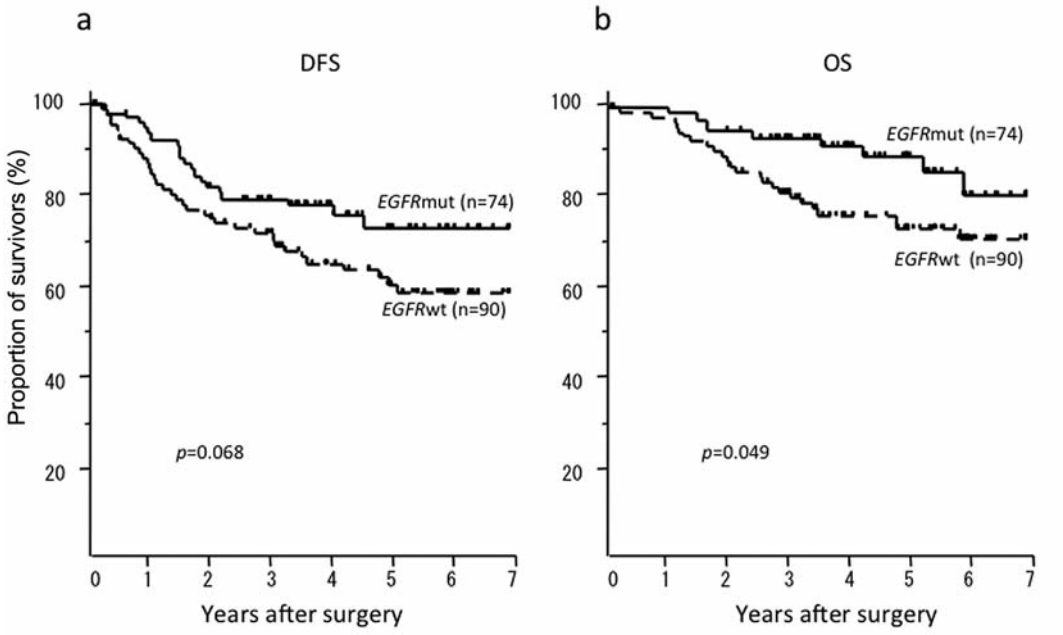

Figure 1. *Curves of postoperative disease-free survival (DFS) (a) and overall survival (OS) (b) for patients with adenocarcinoma according to epidermal growth factor receptor (EGFR) mutation status. EGFRmut: EGFR mutation; EGFRwt: EGFR wild-type.*

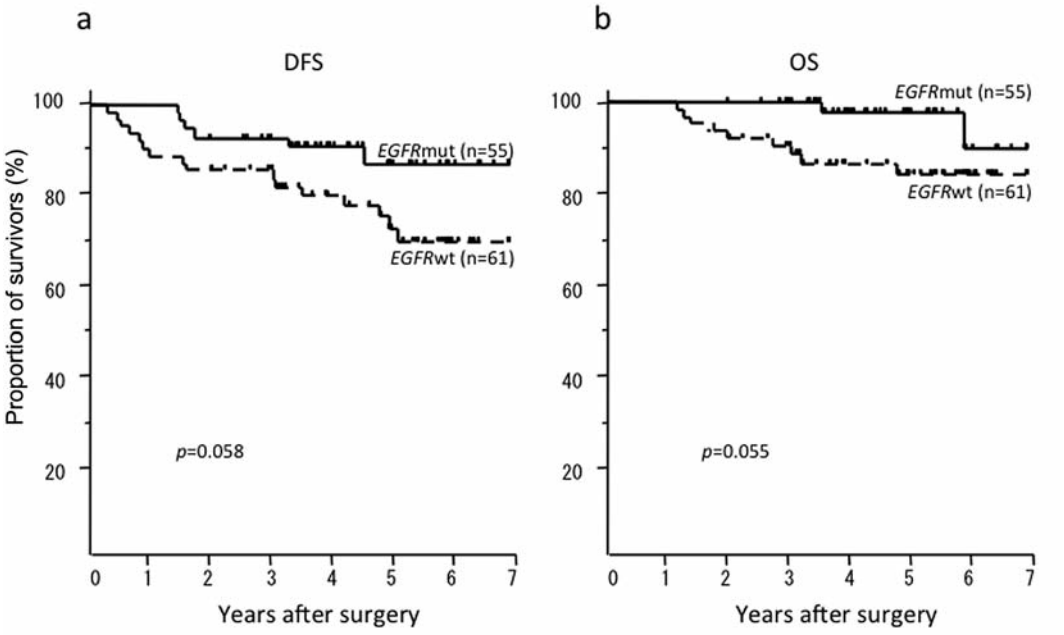

Figure 2. *Curves of postoperative disease-free survival (DFS) (a) and overall survival (OS) (b) for patients with stage I adenocarcinoma according to epidermal growth factor receptor (EGFR) mutation status. EGFRmut: EGFR mutation; EGFRwt: EGFR wild-type.*

Discussion

We demonstrated in the present study that patients with adenocarcinoma harboring *EGFR* sensitizing mutations had a trend for better DFS and had a statistically better OS than did patients with other types of adenocarcinoma in the univariate survival analysis. When the two major sensitizing mutations were compared with each other, DFS was significantly better in patients with Ex21 than in patients with Ex19del. Multivariate survival analysis for DFS

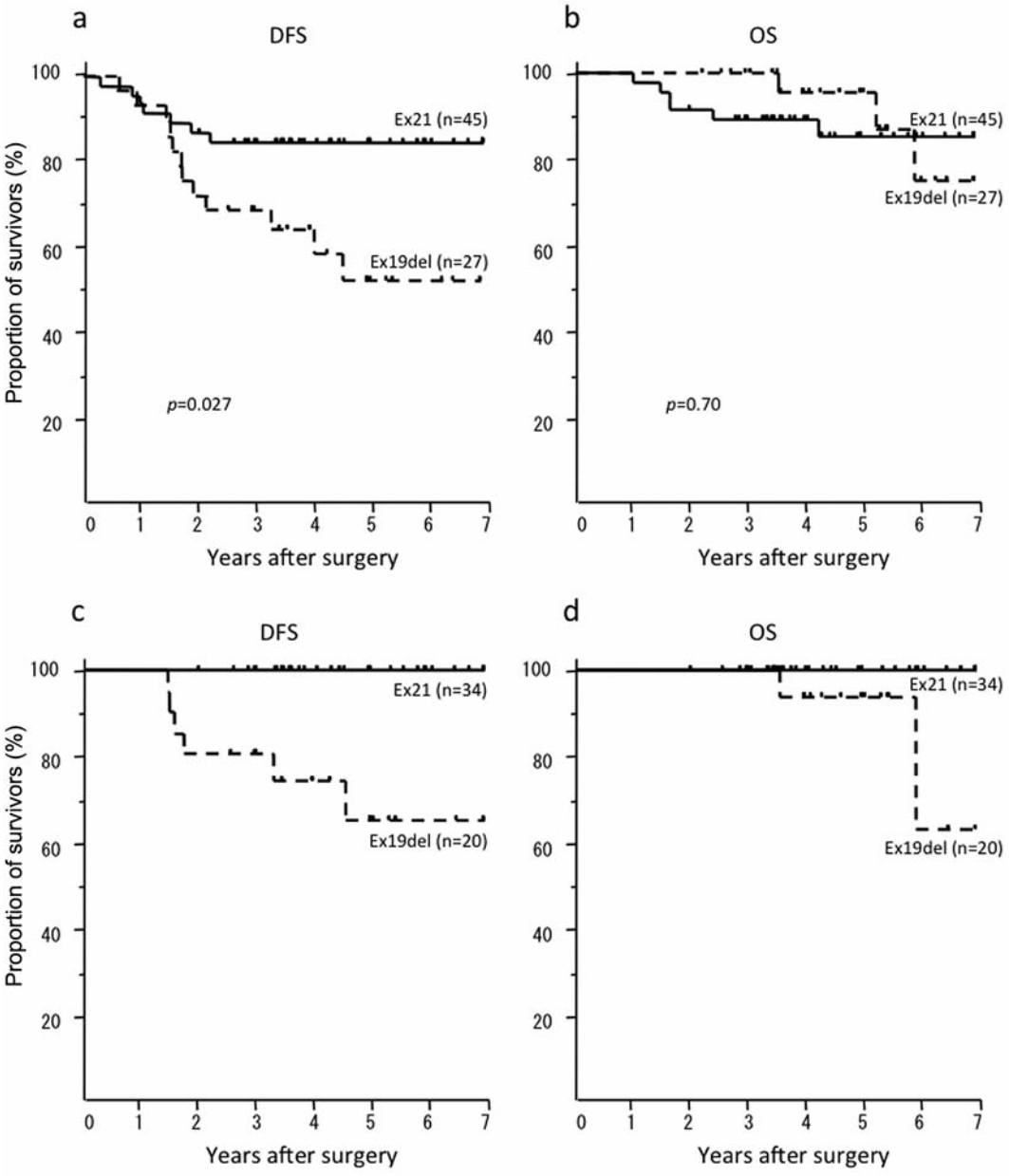

Figure 3. *Curves of postoperative disease-free survival (DFS) (a) and overall survival (OS) (b) for patients with adenocarcinoma according to epidermal growth factor receptor (EGFR) mutation site. Curves of postoperative DFS (c) and OS (d) for patients with stage I adenocarcinoma according to EGFR mutation site. Ex19del, Exon 19 deletion mutation; Ex20, exon 20 mutation.*

confirmed that Ex21 led to a trend for a better survival among *EGFR*mut patients. To our knowledge, this is the first study to show a favorable prognosis of Ex21 compared with Ex19del with respect to DFS.

EGFR sensitizing mutations have been demonstrated to be an excellent predictive marker for EGFR-TKI treatment in advanced, non-surgical patients with stage IIIB or IV NSCLC (3, 4). A prognostic role for these mutations in patients with advanced disease has also been observed in some clinical studies, such as TRIBUTE and IPASS (11, 12). In these trials, patients with *EGFR* mutations tended to have a better prognosis regardless of treatment, even among those who received conventional chemotherapy without EGFR-TKIs. However, regarding postoperative survival after complete resection, an attempt to evaluate the prognostic impact of *EGFR* mutations appears to be more complicated.

Table II. *Multivariate analyses for disease-free survival (DFS) and overall survival (OS) in patients with lung adenocarcinoma who underwent complete resection.*

Factor	Category	DFS			Overall survival		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Gender	Male	1			1		
	Female	0.80	0.44-1.5	0.47	0.67	0.31-1.4	0.29
pStage	I	1			1		
	II, III	5.2	2.6-11	<0.0001	5.2	2.5-11	<0.0001
EGFR status	Wild-type	1			1		
	Mutant	0.70	0.38-1.30	0.25	0.60	0.27-1.3	0.21
Adjuvant therapy	No	1					
	Yes	1.4	0.45-1.7	0.70			

HR, Hazard ratio; CI, confidence interval; PY, pack-year.

Table III. *Clinicopathological characteristics of adenocarcinoma patients with epidermal growth factor receptor (EGFR) mutation.*

Factor	Category	Ex19del (n=27)	Ex21 (n=45)	*p*-Value
Age	<65 Years	7	12	0.95
	≥65 Years	20	33	
Gender	Male	7	13	0.79
	Female	20	32	
Smoking*	0	20	27	**
	≤30 PY	6	11	
	>30 PY	0	4	
Surgical procedure	Segmentectomy	3	5	**
	Lobectomy	23	40	
	Pneumonectomy	1	0	
pStage	I	20	34	0.89***
	II	5	6	
	III	2	5	
Adjuvant therapy	No	15	35	0.03
	Yes	12	10	

Ex19del, Exon 19 deletion mutation; Ex20, exon 20 mutation; PY, pack-year. *A total of 68 patients were available for analysis. **No statistical analysis was performed since the number of patients with some factors was less than 5. ***The statistical analysis was performed comparing between stage I and II+III.

Table IV. *Multivariate analyses for disease-free survival (DFS) in patients with epidermal growth factor receptor (EGFR) mutation-positive adenocarcinoma.*

Factor	Category	DFS		
		HR	95% CI	*p*-Value
pStage	I	1		
	II, III	12	3.3-41	0.0001
EGFR status	Ex19del	1		
	Ex21	0.41	0.16-1.06	0.067
Adjuvant therapy	No	1		
	Yes	0.60	0.18-2.0	0.40

HR, Hazard ratio; CI, confidence interval; PY, pack-year; Ex19del, exon 19 deletion mutation; Ex20, exon 20 mutation.

Many studies have assessed the postoperative prognostic value of *EGFR* mutations; the majority of results from these studies can be divided into two general types. I) Although patients with *EGFR* mutations had better OS than patients with other types of NSCLC in univariate analysis, the statistical significance of this difference disappeared in multivariate analyses that included other clinicopathological variables (6, 8), as shown in the present study. II) No prognostic differences were observed in either univariate or multivariate analyses (13-15). Despite this negative series of studies, a small number of studies demonstrated significantly better survival in patients with EGFR mutations (7, 16). Izar *et al*. investigated 307 patients with stage I NSCLC who underwent surgical resection with curative intent and whose tumor *EGFR* mutation status was evaluated. The study investigators excluded patients who received any type of chemotherapy or radiotherapy, as well as patients with stage II to IV disease to reduce any influence of patient or treatment heterogeneity. They recorded significantly better OS in patients with *EGFR* mutations compared to patients without the mutations.

The most problematic issue in comparing postoperative OS is that patients with *EGFR* mutations most often receive EGFR-TKI treatment after recurrence; thus, OS should be prolonged by EGFR-TKIs. Furthermore, *EGFR* mutations are always accompanied by other favorable factors, such as female gender, non-smoker status, and the pathological feature of a lepidic growth pattern. Therefore, the influences of these factors always disqualify pure comparisons of OS. DFS more directly represents the malignant behavior of

surgically resected tumors than OS, since no influence of post-recurrence treatments is included. The latest meta-analysis including recently published papers demonstrated a lack of a prognostic impact of *EGFR* mutation status on DFS (17). Despite that, some other recent relatively large-scale studies did demonstrate an impact of EGFR mutation. Izar *et al*. showed significantly better DFS in patients with *EGFR* mutations than in patients without in their analysis of 256 patients with stage I NSCLC, which excluded the heterogeneity of patient characteristics (7). Lee *et al*. also demonstrated better DFS of *EGFR* mutation-positive patients in their study of resected adenocarcinoma (16). In the present study, the prognostic significance in DFS was demonstrated in the Kaplan–Meier curves, although the difference did not reach a statistically significant level in the multivariate analysis. We consider this statistical discordance in the present study was due to the small number of patients included in the analyses.

Only four studies have compared postoperative prognoses between patients with exon 19 mutations and those with exon 21 mutations. Na *et al*. reported that patients with exon 18-19 mutations had better OS than those with exon 20-21 mutations (p=0.021), while the difference in DFS between the two patient groups was not significant (18). Their study was rather small (n=32), and included various types of mutations: 16 out of 22 patients with exon 20-21 mutations actually had exon 20 mutations, which are not considered to be sensitizing mutations. Shigematsu *et al*. sequenced *EGFR* exons 18-21 of 617 samples from surgically resected NSCLCs. Their Kaplan–Meier analysis showed that patients with the exon 21 L858R mutation (n=31) had significantly better OS than patients with exon 19 deletion (n=31) (p=0.05) (13). These researchers did not provide any DFS data; however, none of the patients in their analysis underwent EGFR-targeted therapy. Liu *et al*. assessed DFS separately for patients with the two major mutations, and demonstrated that patients with exon 19 mutations had better DFS than those with exon 21 mutations (19). The results of this study directly conflict with the results of the present study. The reason for this discrepancy is not clear; however, the proportion of patients with early-stage disease differed between the two studies. In the present study, 73% of the patients with *EGFR* mutations had stage I disease, compared to only 56% of patients in the study by Liu *et al*.

An *in vitro* assessment of the kinase activity of the EGFR kinase domain harboring either major mutation revealed that the kinase activity of EFGR with Ex19del was much more intense than that of EGFR with Ex21. Furthermore, xenograft experiments with cancer cells stably transfected with EGFR mutations showed that cells with *EFGR*del746-752 increased growth activity compared to cells harboring wild-type or *EGFR*-L858R (20). These *in vitro* data support our present data that tumors harboring Ex19del have a worse prognosis than tumors harboring Ex21 or wild-type *EGFR*. However, the opposite results have also been reported, in which *Egfr*-L858R mice rapidly develop diffuse bronchioloalveolar carcinoma compared to *EGFR*-delL747-S752 animals, which display a longer tumor latency (21).

The present study has several limitations. The patients were accrued in a retrospective fashion, which may cause a variety of biases. The numbers of patients with each type of *EGFR* mutation were rather small. Therefore, further studies consisting of larger numbers of patients are warranted to confirm the results of the present study.

In conclusion, the present study demonstrated that patients with adenocarcinoma harboring *EGFR* sensitizing mutations had a trend for better DFS than patients with other types of adenocarcinoma. This prognostic difference was caused by significantly better DFS in patients with exon 21 deletion. These data suggest that adenocarcinoma harboring *EGFR* exon 21 deletion are less malignant than other types of NSCLC in the postoperative course.

Conflicts of Interest

None declared.

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