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Original Articles

A Correlation between *EGFR* Gene Mutation Status and Bronchioloalveolar Carcinoma Features in Japanese Patients with Adenocarcinoma

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Background: The presence of epidermal growth factor receptor (*EGFR*) mutations in gefitinib-naive lung cancer patients has been reported to be higher in females, in non-smokers, in Japanese, and in adenocarcinoma patients, especially in bronchioloalveolar carcinoma (BAC). To further investigate the prevalence of *EGFR* mutations in relation to pathological factors, we evaluated *EGFR* mutations in series of Japanese adenocarcinoma patients who had never been treated with gefitinib.
Methods: In the previous studies, we examined mutation status in the tyrosine kinase domain of EGFR, exon18 through exon21, in 112 primary lung adenocarcinoma samples. Using these data, adenocarcinomas were histologically classified according to the presence or absence of bronchioloalveolar components.
Results: Among 112 patients, 48 had adenocarcinoma with BAC components. Those with adenocarcinomas with BAC components had higher frequency of *EGFR* mutation (28/48, 58%) than those with non-BAC adenocarcinoma (24/64, 37%, $P = 0.036$). Male patients had the same trend; 12/23 (52%) male patients with adenocarcinoma with BAC components and 10/47 (21%) of those with non-BAC adenocarcinoma had *EGFR* mutation ($P = 0.0135$) but there was no correlation between the *EGFR* mutation status and with/without BAC components in 42 female patients ($P = 0.30$). Among 11 male non-smokers, patients with adenocarcinoma with BAC components had a tendency to have *EGFR* mutation more frequently than those with non-BAC adenocarcinoma ($P = 0.061$). In clear contrast, the frequency of *EGFR* mutation did not differ significantly between male smoker patients with adenocarcinoma with BAC components and those with non-BAC. Among patients with adenocarcinoma with BAC components, those with adenocarcinoma with *EGFR* gene mutation had a significantly better 5 year survival than those with adenocarcinoma with wild-type (85.7 versus 46.0%, $P = 0.0017$).
Conclusions: Adenocarcinomas with BAC components in male non-smokers seem to predict the presence of *EGFR* mutation. Half of female adenocarcinoma patients with *EGFR* mutation exhibit adenocarcinomas with non-BAC suggesting a different behavior from those in males. The prognosis of patients with adenocarcinoma with BAC components with *EGFR* gene mutation is predicted to be better than that of patients with adenocarcinoma with BAC components with wild-type *EGFR* gene.

Key words: lung cancer – EGFR – mutation – BAC

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INTRODUCTION

Bronchioloalveolar carcinoma (BAC) is a form of adenocarcinoma (1). In the past, BAC was a rarely diagnosed neoplasm

that accounted for ~3% of lung cancers; however, several studies documented a dramatic increase in its incidence (14.7–24% of all lung cancers) (2). Further distinguishing BAC from other types of non-small cell lung cancer (NSCLC) is a higher percentage of females, a younger age distribution and a higher incidence in non-smokers (3). Although the revised WHO definition strictly defines BAC as having absolutely no evidence of invasion, adenocarcinoma can display a range of BAC features from predominant BAC with only a small focus of invasion to a lesion that has BAC features only at the peripheral of the tumor (4). Previous work demonstrated that BAC, BAC with focal invasion and adenocarcinoma with BAC features have similar clinical course characterized by relatively long survival, a higher incidence of intrathoracic recurrence and second primary lung cancers, and less frequent distant metastasis (5).

Gefitinib, a synthetic anilinoquinazoline that specifically inhibits epidermal growth factor receptor (EGFR) tyrosine kinase, has been used to treat advanced, chemotherapy-refractory NSCLC, yielding clinical responses of 9–19% (6,7). The partial clinical responses to gefitinib have been observed most frequently in Japanese, in females, in non-smokers, and in patients with adenocarcinoma (6,8,9), especially in patients with BAC (9). Last year, the molecular mechanisms underlying clinical responsiveness to gefitinib in NSCLC have been shown to correlate with somatic mutations in the kinase domain of *EGFR* gene by two groups (10,11). Lynch et al. (10) reported that most of their *EGFR* mutations occurred in BAC (they regarded an adenocarcinoma with any element of BAC as BAC). However, *EGFR* mutations were detected in only one case of BAC not treated with gefitinib in the series of Paez et al. (11). Thus, the relationship between the *EGFR* mutation and BAC components in adenocarcinoma is not yet clear. To further investigate possible pathological factors related to the presence of *EGFR* mutations, we evaluated a series of 112 Japanese lung adenocarcinoma patients who had never been treated with gefitinib with special reference to the presence of BAC components.

Table 1. Correlation between *EGFR* mutation and clinicopathological factors

	Wild-type	Mutated	Total
Gender			
Male	48 (69)	22 (31)	70†
Female	12 (29)	30 (71)	42†
Smoking status			
All			
Non-smoker	16 (33)	33 (67)	49#
Smoker	44 (70)	19 (30)	63#
Male			
Non-smoker	5 (45)	6 (55)	11
Smoker	43 (73)	16 (27)	59
Female			
Non-smoker	11 (29)	27 (71)	38
Smoker	1 (25)	3 (75)	4
Pathological findings			
All			
Non-BAC	40 (63)	24 (37)	64*
BAC components	20 (42)	28 (58)	48*
Male			
Non-BAC	37 (79)	10 (21)	47*
BAC components	11 (48)	12 (52)	23*
Female			
Non-BAC	3 (18)	14 (82)	17
BAC components	9 (36)	16 (64)	25
Total	60 (54)	52 (46)	112

Data are presented as *n* (%).
BAC, bronchioloveolar carcinoma.
†$P < 0.0001$,
#$P = 0.0001$,
*$P < 0.05$.

MATERIALS AND METHODS

Patients

We studied 112 surgically resected adenocarcinomas. These surgical resections were undertaken at the Department of Surgery II, Nagoya City University Hospital between 1997 and 2002. The research was approved by the Institutional Review Board of Nagoya City University Hospital. Patients' age ranged from 38 to 82 years old (mean 64.3 years). There were 70 male and 42 female patients. 'Non-smoker' was defined as those who had never smoked until the operation, and 'smoker' was defined as those who had smoked by the time of the operation (including the ex-smokers). Forty-nine (44%) patients were non-smokers. Eleven (15%) of 70 males were non-smokers, whereas 38 (90%) of 42 females were non-smokers. Using genomic DNA prepared from these 112 samples, DNA sequencing was already performed (11,12,13).

Pathologic Evaluation

BAC feature was defined pathologically as exclusively papillolepidic and/or replacement type growth. Pathology specimens of all the patients were examined independently by an in-house pathologist and one out-house pathologist (N.L.) who were unaware of the patient's outcome. The final decision for adenocarcinoma classification was made by N.L. Adenocarcinomas were classified into one of the following: 'non-BAC' (adenocarcinoma without BAC), 'adenocarcinoma with BAC features' (adenocarcinoma with both solid and BAC features) or 'BAC'(tumor was basically composed of BAC). In all analysis, adenocarcinoma with BAC features and BAC were combined and shown as 'adenocarcinoma with BAC components' as opposed to 'non-BAC'. Zero percent of

Table 2. Clinicopathological factors in patients with *EGFR* gene mutation

Patient #	Exon	Mutaton type	Age	Gender	Pathological type	Smoking status
1	18	G719S	46	Female	BAC	−
2	19	Del1a	51	Male	Non-BAC	+
3	19	Del1a	51	Male	Non-BAC	+
4	19	Del1a	58	Male	BAC	−
5	19	Del1a	61	Male	BAC	+
6	19	Del1a	70	Male	Non-BAC	+
7	19	Del1a	70	Male	Non-BAC	+
8	19	Del1a	71	Male	Non-BAC	+
9	19	Del1a	43	Female	Non-BAC	+
10	19	Del1a	53	Female	Non-BAC	−
11	19	Del1a	53	Female	BAC	−
12	19	Del1a	63	Female	BAC	−
13	19	Del1a	64	Female	BAC	−
14	19	Del1a	68	Female	BAC	−
15	19	Del1a	68	Female	BAC	−
16	19	Del1a	78	Female	BAC	−
17	19	Del1a	79	Female	Non-BAC	−
18	19	Del1b	40	Male	BAC	+
19	19	Del1b	45	Male	BAC	−
20	19	Del1b	51	Male	Non-BAC	+
21	19	Del1b	67	Male	Non-BAC	+
22	19	Del1b	79	Female	Non-BAC	−
23	19	Del2	67	Male	Non-BAC	+
24	19	Del4	58	Male	BAC	−
25	19	Del4	67	Male	BAC	+
26	19	Del4	47	Female	Non-BAC	−
27	19	Del4	60	Female	BAC	−
28	19	Del4	69	Female	Non-BAC	−
29	19	Del6	73	Female	BAC	−
30	19	Novel Ins	63	Male	Non-BAC	+
31	19	15Del	48	Female	Non-BAC	−
32	20	InsV	72	Male	BAC	−
33	20	2319-20Ins	53	Female	Non-BAC	+
34	21	L858R	38	Male	BAC	+
35	21	L858R	64	Male	BAC	−
36	21	L858R	67	Male	Non-BAC	+
37	21	L858R	72	Male	BAC	−
38	21	L858R	74	Male	BAC	+
39	21	L858R	58	Female	Non-BAC	−
40	21	L858R	60	Female	BAC	−
41	21	L858R	60	Female	BAC	−
42	21	L858R	60	Female	BAC	−
43	21	L858R	60	Female	BAC	−
44	21	L858R	62	Female	Non-BAC	+
45	21	L858R	66	Female	BAC	−
46	21	L858R	68	Female	Non-BAC	−
47	21	L858R	70	Female	BAC	−
48	21	L858R	71	Female	Non-BAC	−
49	21	L858R	72	Female	BAC	−
50	21	L858R	76	Female	Non-BAC	−
51	21	L858R	82	Female	Non-BAC	−
52	21	L861Q	61	Male	BAC	+

BAC, bronchioloveolar carcinoma.

area of BAC features was the threshold to discriminate adenocarcinoma with BAC components from non-BAC.

Statistical Analysis

Fisher's exact test and multivariate analysis using the logistic regression model were used to compare frequencies of clinicopathologic variables or to analyze the contribution of each variables with *EGFR* mutation using Stat View (version 5; SAS Institute, Inc., Cary, NC, USA) software, and the difference was considered significant when the P-value was <0.05. The post-operative 5 year overall survival rate was analyzed using the Kaplan–Meier method, and differences in survival rates were assessed using the log-rank test. When the P-value was <0.05, it was concluded that there was significant difference.

RESULTS

EGFR Mutation and Pathologic Classification

Mutations in the kinase domain of the *EGFR* gene were detected in 52 of 112 (46.0%) adenocarcinomas (Table 1). Fifty-two *EGFR* gene mutations consisted of 1 G719S mutation in exon18, 29 deletion and 1 insertion type mutations in exon19, 2 insertion type mutations in exon20, 1 L861Q and 18 L858R mutations in exon20 (Table 2). There were no correlations between the exon carrying mutation and clinicopathological factors (gender, smoking status and pathological findings) (Table 3). Also there were no correlations between the pattern of mutation and clinicopathological factors (Table 3). We have previously reported the *EGFR* mutation percentage as 15/58 (25.9%) among Japanese NSCLC. The *EGFR* mutation status from adenocarcinoma was significantly higher than our previous data from all NSCLC ($P = 0.0130$). The mutation was higher in females (30/42, 71.4%) than in males (22/70, 31.0%) ($P < 0.0001$) (Table 1).

Among 112 patients, 48 patients had adenocarcinomas with BAC components (adenocarcinoma with BAC features and BAC); 25 (60%) of 42 females and 23 (33%) of 70 males had adenocarcinomas with BAC components ($P = 0.001$)

Table 3. Correlation between pattern of *EGFR* mutation, the exon carrying *EGFR* mutation and clinicopathological factors

	One base substitution	Deletion/ insertion	Exon 19	Exon 21	Total
Gender					
Male	6 (27)	16 (73)	15 (68)	6 (27)	22
Female	14 (47)	16 (53)	15 (50)	13 (43)	30
Smoking status					
All					
Non-smoker	15 (45)	18 (55)	17 (50)	15 (44)	33
Smoker	5 (26)	14 (74)	13 (72)	4 (22)	19
Male					
Non-smoker	2 (33)	4 (67)	3 (50)	2 (33)	6
Smoker	4 (25)	12 (25)	12 (75)	4 (25)	16
Female					
Non-smoker	13 (48)	14 (52)	14 (54)	12 (46)	27
Smoker	1 (33)	2 (67)	1 (25)	1 (25)	3
Pathological findings					
All					
Non-BAC	7 (29)	17 (71)	16 (67)	7 (29)	24
BAC components	13 (46)	15 (54)	14 (50)	12 (50)	28
Male					
Non-BAC	1 (10)	9 (90)	9 (90)	1 (10)	10
BAC components	5 (42)	7 (58)	6 (50)	5 (42)	12
Female					
Non-BAC	6 (43)	8 (57)	7 (50)	6 (43)	14
BAC components	8 (50)	8 (50)	8 (50)	7 (44)	16
Total	20 (38)	32 (62)	30 (58)	19 (36)	52

Data are presented as *n* (%).

(Table 4). Among patients with adenocarcinoma with BAC components, 10 (43%) of 23 males had BAC, and 12 (48%) of 25 females had BAC ($P = 0.7799$) (Table 4). *EGFR* mutations were found in 24 of 64 patients with non-BAC adenocarcinoma (Table 1), including 16 at exon19, 1 at exon20 and 7 at exon21 (Table 2), and in 28 of 48 patients with adenocarcinoma with BAC components (Table 1), including 1 at exon18, 14 at exon19, 1 at exon20 and 12 at exon21 (Table 2).

In all adenocarcinoma patients, there was a correlation between *EGFR* mutation and adenocarcinoma with BAC components ($P = 0.0358$). In female patients, both patients with adenocarcinoma with BAC components (16/25) and with non-BAC (14/17, $P = 0.3$) had similar *EGFR* mutation status. But in male patients, there was a higher percentage of *EGFR* mutation in patients with adenocarcinoma with BAC components (12/23) than with non-BAC (10/47, $P = 0.0135$) (Table 1). There was a tendency towards a higher *EGFR* mutations ratio at exon21 in patients with adenocarcinoma with BAC components (12/48) when compared to patients with non-BAC (7/64, $P = 0.0737$) (Table 3).

Table 4. Correlation between BAC components and smoking status and the ratio of *EGFR* mutation

	Non-BAC	BAC components	Total
Gender			
Male	47 (21%)	23 (52%)	70 (31%)
Female	17 (82%)	25 (64%)	42 (71%)
Smoking status			
All			
Non-smoker	17 (65%)	32 (69%)	49 (67%)
Smoker	47 (28%)	1 (38%)	63 (30%)
Male			
Non-smoker	3 (0%)	8 (75%)	11 (55%)
Smoker	44 (23%)	15 (40%)	59 (27%)
Female			
Non-smoker	14 (79%)	24 (67%)	38 (71%)
Smoker	3 (100%)	1 (0%)	4 (75%)
Total	64 (38%)	48 (58%)	112 (46%)

Data are presented as *n* (ratio of *EGFR* mutation : %).

Pathologic Classification and Clinical Factors

There was a higher ratio of patients with adenocarcinoma with BAC components in non-smokers than smokers (65.3 versus 25.4%, $P < 0.0001$). Similarly in male patients, non-smokers had a significantly higher ratio of adenocarcinoma with BAC components compared with smokers (72.7 versus 25.4%, $P = 0.0041$). But in female patients, there was no correlation between smoking habit and BAC components ($P = 0.286$) (Table 4).

EGFR Mutation and Clinical Factors

In all patients, there was a higher percentage of *EGFR* mutation in non-smokers than smokers (67.3 versus 30.2%, $P = 0.0001$). In male patients, there were a tendency towards a higher ratio of *EGFR* mutation in non-smokers than smokers (54.5 versus 27.1%, $P = 0.0877$), but in female patients, there was no correlation between *EGFR* mutation and smoking status ($P > 0.9999$) (Table 1). It is of note that among male non-smokers, those with *EGFR* mutation were exclusively with adenocarcinoma with BAC components. In clear contrast, both in female non-smokers, patients with BAC components and with non-BAC had similar frequencies of *EGFR* mutation (Table 4).

We constructed a multivariate logistic regression model to determine factors that are significantly associated with *EGFR* mutation. This result revealed that in all patients gender had a tendency to be an independent factor that affected *EGFR* mutation ($P = 0.0512$). In male patients BAC components was an independent factor ($P = 0.032$), but in female patients neither BAC components nor smoking status were independent factors ($P = 0.188$ and $P = 0.886$, respectively).

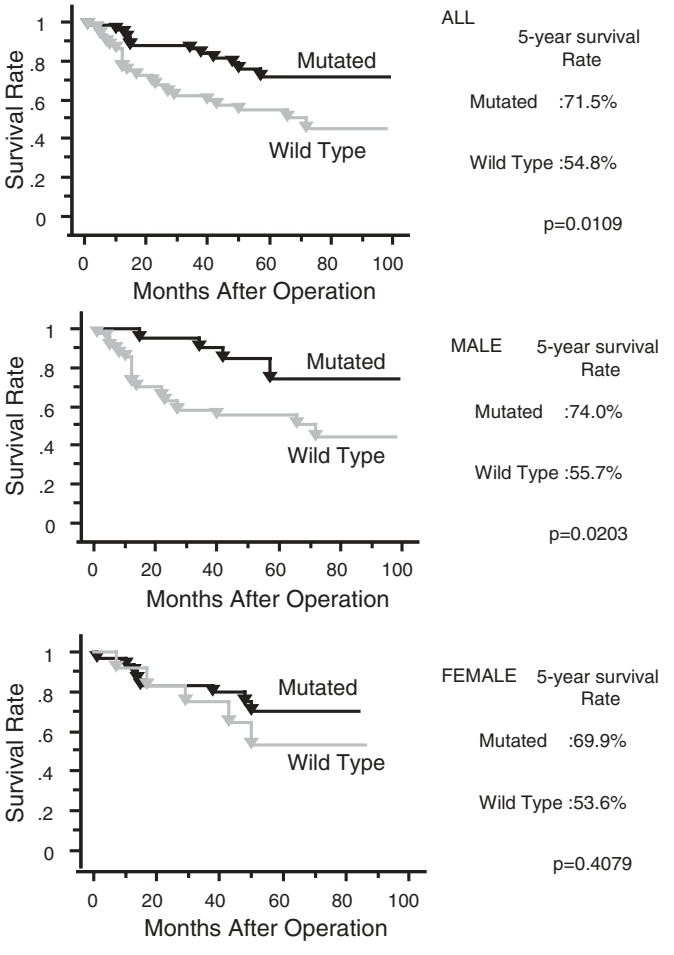

Figure 1. Overall survival rate according to *EGFR* mutation.

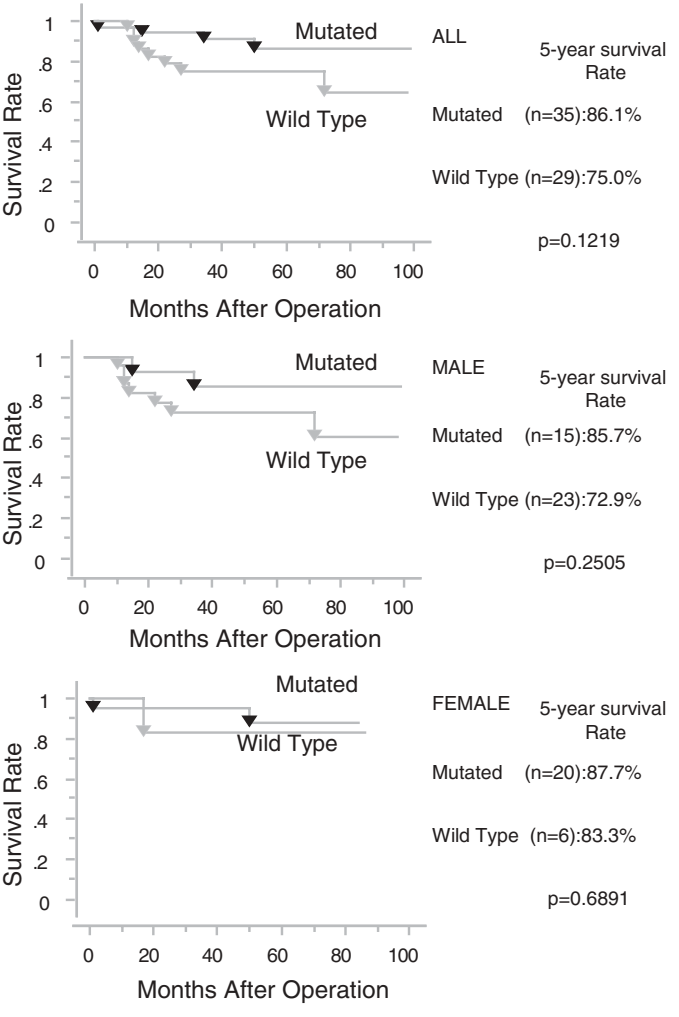

Figure 2. Overall survival rate according to *EGFR* mutation in pStageI.

The Survival Analysis According To *EGFR* Mutation

In all patients, the 5 year survival rate for the patients with adenocarcinomas with wild-type *EGFR* gene was 54.8%, while that for those with mutation was 71.5% ($P = 0.0109$). In male patients, 5 year survival of those with wild-type *EGFR* gene and those with mutation was 55.7 and 74.0%, respectively ($P = 0.0203$). In female patients, 5 year survival of those with wild-type *EGFR* gene and those with mutation was 53.6 and 69.9%, respectively ($P = 0.4079$) (Fig. 1).

For Stage I patients, the 5 year survival rate for those with wild-type *EGFR* gene was 75.0%, while that for those with mutation was 86.1% ($P = 0.1219$). In male Stage I patients, 5 year survival for those with wild-type *EGFR* gene and those with mutation was 72.9 and 85.7%, respectively ($P = 0.2505$). In female Stage I patients, 5 year survival for those with wild-type and those with mutation was 83.3 and 87.7%, respectively ($P = 0.6891$) (Fig. 2).

In the patient group with non-BAC tumor, there were no significant differences in survival between those with *EGFR* wild-type and those with mutation (5 year survival rate 60.7 and 56.8%, respectively, $P = 0.5832$). In marked contrast, in patient group with adenocarcinoma with BAC components, there was a significant difference in survival rate between those with wild-type *EGFR* gene and those with mutation (5 year survival rate 46.0 and 85.7%, respectively, $P = 0.0017$) (Fig. 3).

Analysis of *EGFR* DNA Copy Number

The *EGFR* gene amplification of 61 samples was analyzed by quantitative real-time PCR. Four of 61 cases were found to have *EGFR* DNA amplification (*EGFR* copy number >3). All four patients were male, two were non-smokers and had *EGFR* mutation (L858R), and three had BAC components. The *EGFR* amplification did not correlate with *EGFR* mutation or with any of the clinicopathological factors.

DISCUSSION

In this paper, pathological features having BAC components correlated with *EGFR* mutation status in all patients and male patients; 28/48 (58%) patients with adenocarcinoma with BAC components and 24/64 (38%) patients with non-BAC adenocarcinoma had *EGFR* mutation ($P = 0.0358$). This result was

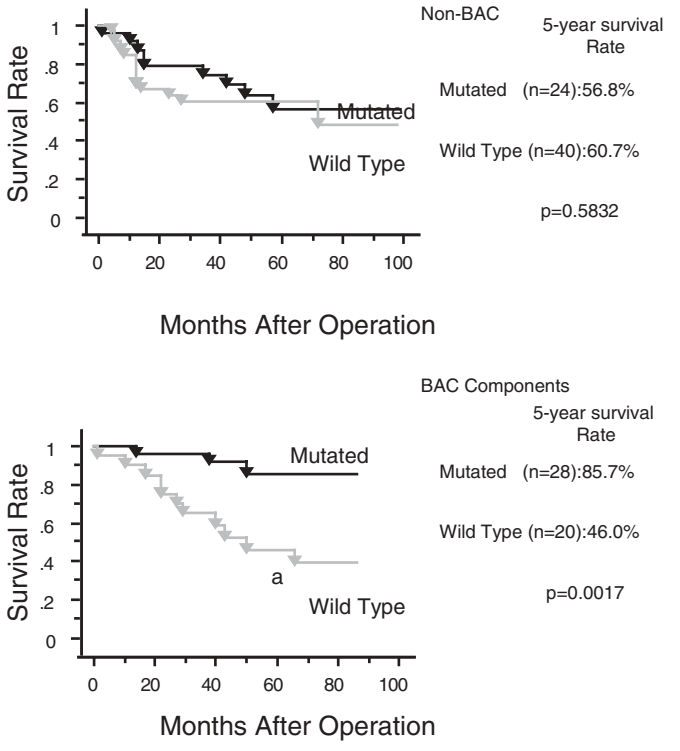

Figure 3. Overall survival rate according to *EGFR* mutation and non-BAC/adenocarcinoma with BAC components.

not in agreement with another report from a Japanese group, which showed 10.8% (4/37) patients with adenocarcinoma with BAC components and 41.9% (13/31) patients with invasive adenocarcinoma had *EGFR* mutations (14). In agreement with our result, Marchetti et al. (15) and Sonobe et al. (16) have demonstrated that BAC histology was associated with *EGFR* mutations. Yatabe et al. (17) also reported that the characteristics of terminal-respiratory-unit type adenocarcinoma were likely to correspond to the BAC reported as a predictor of gefitinib response. The reason for these differences is not clear at present; however, the small number of patients and different patient selection may have caused the difference.

BACs are lung tumors believed to arise from bronchiolar and alveolar epithelium, with a characteristic growth pattern along the alveolar walls. Compared with other subtypes of lung cancers, BAC is characterized by distinct clinical presentation, radiographic appearance and natural history. Patients with BAC tend to be younger at diagnosis and are more likely to be female and non-smokers when compared with other lung cancers. Actually, this population was correlated with gefitinib sensitivity. These differences raise the question of whether BAC represents a separate biologic entity. It has shown that there are differences in the distribution and quality of p53, K-ras and FHIT mutations between BAC and conventional adenocarcinoma.

Previous limited data suggested that chemotherapy for BAC provides modest benefit; however, anecdotal reports of swift and durable responses after treatment with EGFR tyrosine kinase (TK) inhibitor in patients with BAC have prompted further investigation in this subset of patients (18). Two Japanese groups using the EGFR TK inhibitor gefitinib have demonstrated encouraging results (19,20). Thus, we investigated the correlation between *EGFR* mutation, gender, smoking status and BAC components. Gender and smoking status were correlated with *EGFR* mutation status, and there was a correlation between pathological BAC components and *EGFR* mutation status in all the patients and male patients, but not in female patients. Particularly of note is that among 11 male non-smokers, patients with adenocarcinoma with BAC components had a tendency to have *EGFR* mutation more frequently than those with non-BAC ($P = 0.061$). In clear contrast, the frequency of *EGFR* mutation did not differ significantly between male smoker patients with adenocarcinoma with BAC components and those with non-BAC. These results seem to suggest that in male non-smokers *EGFR* mutation tended to give rise to adenocarcinomas with BAC components, which rarely proceed to exhibit non-BAC adenocarcinoma. In females, the presence of non-BAC adenocarcinomas in half of adenocarcinomas with *EGFR* mutation suggests that the underlying oncogenic mechanisms may differ according to gender.

In male patients, the prognosis of patients with adenocarcinoma with *EGFR* mutation was better than that of patients with adenocarcinomas with wild-type, but in female patients, the prognosis of patients with adenocarcinoma with *EGFR* mutation was similar to that of patients with adenocarcinoma with wild-type. Similarly, among patients with adenocarcinoma with BAC components, the prognosis of patients with adenocarcinoma with *EGFR* mutation was better than that of patients with adenocarcinoma with wild-type, but this difference was not seen in patients with non-BAC adenocarcinoma.

These data suggest that *EGFR* mutation plays a different role in oncogenesis in male and female patients, in patients with non-BAC adenocarcinoma compared to those with adenocarcinoma with BAC components.

Our result may be useful to identify patients with possible benefit from therapy using gefitinib. For example, six of eight male non-smokers with adenocarcinoma had an *EGFR* mutation and thus may be good candidates for gefitinib therapy. However, different mechanisms other than *EGFR* mutations may exist to explain the good response of gefitinib therapy for patients with adenocarcinoma with BAC components. Actually, a case that responded using gefitinib in BAC in the absence of *EGFR* mutation has been reported (21).

In summary, BAC components in male non-smokers may predict the presence of *EGFR* mutations in adenocarcinomas. BAC components with *EGFR* gene mutation in patients with adenocarcinoma predict a better survival.

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