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Correlation between computed tomography findings and epidermal growth factor receptor and *KRAS* gene mutations in patients with pulmonary adenocarcinoma

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Abstract. We examined the correlation between computed tomography (CT) findings and the incidence of epidermal growth factor receptor (*EGFR*) and *KRAS* mutations in lung adenocarcinoma. We analyzed the tumors of 136 patients with surgically resected primary lung adenocarcinoma. CT scans were evaluated for the presence of ground grass opacity (GGO), spiculation and the maximum diameter of the tumor was measured. SMart Amplification Process (ver. 2) was used to detect the presence of *EGFR* and *KRAS* mutations. *EGFR* and *KRAS* mutations were found in 56 (41.1%) and 25 (18.4%) of the 136 cases, respectively. Although no significant association was found between GGO and *EGFR* mutations (p=0.07), the *EGFR* mutation occurred more frequently in male patients with GGO than in those without GGO (p=0.04). The *KRAS* mutation occurred more frequently in patients whose tumor diameter was ≥31 mm than in those whose tumor diameter was <30 mm (p=0.003). Evaluation of CT findings may be helpful for determining the presence of *EGFR* and *KRAS* mutations, particularly when it is not possible to obtain a tumor specimen.

Introduction

Recently, several investigations have shown that mutations in the epidermal growth factor receptor (*EGFR*) and the *KRAS* gene are significant prognostic factors for non-small cell lung cancer (NSCLC) (1-3). *EGFR* and *KRAS* mutations occur in 8-10% and 20-50% of NSCLC patients, respectively, whereas the *EGFR* mutation has been reported to occur in 27-56% of East Asian patients with NSCLC and the *KRAS* mutation occurs in 5-15% of those patients (1-5). Activating mutations in the tyrosine kinase domain of the *EGFR* gene are associated with sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib (6). Gefitinib and erlotinib are synthetic small molecules that have been used to treat patients with unresectable or recurrent NSCLC, and the presence of *EGFR* mutations has been reported to be a good predictor of gefitinib and erlotinib effectiveness (3,6). Moreover, NSCLC patients who are refractory to TKIs often harbor *KRAS* mutations, suggesting that *KRAS* activation might confer TKI resistance by activating signaling pathways downstream of *EGFR* (2). Furthermore, these two mutations have been reported to be mutually exclusive (1). It is essential that physicians are able to readily identify these mutations to develop better therapeutic strategies.

EGFR and *KRAS* mutations have been detected in resected lung cancers using direct sequencing of DNA samples (2,3). Recently, more sensitive methods have been used to detect *EGFR* mutations, such as the peptide nucleic acid-locked nucleic acid PCR clamp (PNA-LNA PCR clamp) and high-resolution melting analysis (HRMA) (7-10). However, these methods are often not suitable for small biopsy specimens (11). We hypothesized that if the presence of the *EGFR* and *KRAS* mutations were correlated with morphological features of the tumor that could be shown using diagnostic imaging modalities, such as computed tomography (CT) scans, mutation status could be predicted in patients who had unresectable lung cancer or relapse after surgery whose tissue could not be obtained for *EGFR* and *KRAS* mutation status analysis.

In the last decade, many investigators have reported that preoperative CT scan findings were related to pathological features and postoperative prognosis (12,13). In the present study, we evaluated the internal tumor structure and ground glass opacity (GGO) using thin-section CT images.

Yano *et al* (14) reported a possible association between a high ratio of GGO components in small peripheral adeno-

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carcinoma and the presence of *EGFR* mutations, particularly among female patients. However, the correlation between CT findings and *EGFR* or *KRAS* mutation status has not been fully established. In particular, it is unclear whether a correlation exists between the CT findings in pulmonary adenocarcinoma and *KRAS* mutations. The aim of the present study was to evaluate the correlation between CT findings and *EGFR* and *KRAS* mutation status in peripheral lung adenocarcinoma in a larger group of patients than previous studies.

Patients and methods

Patients. Surgically resected specimens of peripheral primary adenocarcinoma of the lung were obtained from 136 consecutive patients who underwent surgery at the Gunma University Hospital or Maebashi Red Cross Hospital between October 2002 and March 2008. After surgical removal, a portion of each sample was immediately frozen and stored at -80˚C until DNA extraction. Institutional approval was obtained, as was written informed from all patients.

CT findings. CT was performed using helical or multi-detector scanners. Conventional CT images were obtained serially with 7-10 mm section thickness and 7-10 mm section spacing. High-resolution CT (HRCT) images at the level of the tumor lesion were obtained serially with 1-2 mm section spacing. Images were reconstructed using a high-frequency algorithm and photographed with a window level of -600 H and a window width of 2000 H as a 'lung window'. The following thin-section CT factors were evaluated by two independent clinicians: the maximum diameter of the tumor, the presence of spiculation and GGO. GGO was defined as a hazy increase in lung attenuation, without obscuring the underlying bronchial or vascular structures (15). Two observers who were unaware of the pathological staging, prognosis and gene mutation status reviewed each HRCT scan of the 136 patients and evaluated the GGO ratio of the tumor (GGO/tumor ratio; G/T ratio), which was calculated using the maximum length of the GGO on the slices where the tumor was the largest. The G/T ratio was calculated as $(D_{GGO}-D_{SOL})/D_{GGO}$, where D_{GGO} was the largest area of the tumor, including the GGO, and D_{SOL} was the largest solid area of the tumor excluding the GGO (Fig. 1). Additionally, the maximum diameter of the tumor and the presence of spiculation were evaluated. Discrepancies between the observers were resolved by discussion and recording of the measurements they agreed on.

EGFR and KRAS mutation analysis. Genomic DNA was extracted from an approximately 3-5 mm cube of tumor tissue using a DNA Mini Kit (Qiagen, Hilden, Germany), and serially diluted to 20 ng/μl.

EGFR mutations in exons 19 and 21 were detected using a non-radioactive single-strand conformation polymorphism (Non-RI-SSCP) (7) and the SMart Amplification Process (ver. 2) (SmartAmp2) (16,17). The SMartAmp2 method is a unique genotyping technology that can detect a mutation in a single step in 30 min under isothermal conditions. It is based on strand-displacing DNA polymerase activity and can amplify and detect mutations directly from simple lung cancer sample preparations (16,17).

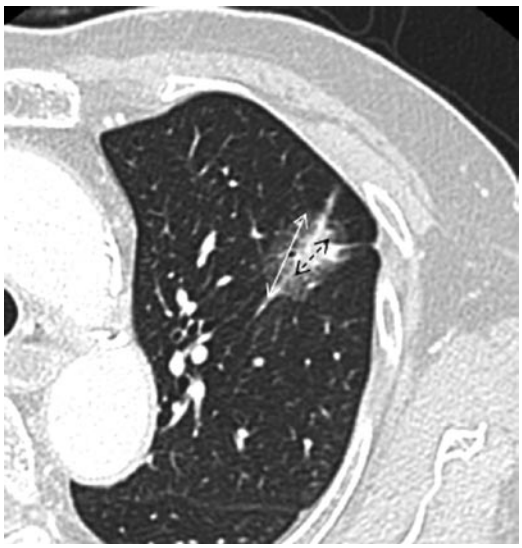

Figure 1. Computed tomography (CT) scan shows localized ground glass opacity (GGO) with increased attenuation at the center of the tumor in the left upper lobe of the lung. The maximum diameter of the GGO (continuous line) and the diameter of the solid part (dotted line) were determined using thin-section CT. The G/T ratio was calculated at 55%.

The *KRAS* mutation was also detected using the SmartAmp2 assay using DNA extracted from tumor tissue (18). The *EGFR* and *KRAS* Mutation Detection Kit for SmartAmp2 assay was obtained from K.K. DNAFORM (Yokohama, Japan).

Statistical analysis. We were interested in any association between *EGFR* or *KRAS* mutations and various patient characteristics, including age, gender, smoking history, pathological stage of disease and CT findings. Unpaired t-tests were used to compare means and χ^2 test and Fisher's exact test were used to compare proportions. A p-value of 0.05 was deemed to indicate statistical significance. Statistical analyses were carried out using the StatView software (ver. 5.0; SAS Institute, Cary, NC, USA).

Results

Patient characteristics associated with the EGFR and KRAS mutations. Table I shows the patient characteristics and *EGFR* mutation status. *EGFR* mutations were found in 56 (41.1%) of the 136 cases. The mean age of the patients did not differ between the *EGFR* mutation and wild-type groups. *EGFR* mutations were significantly more frequent in women than in men (p=0.005), and the wild-type gene was found significantly more often than the *EGFR* mutation in patients who had a history of smoking (p=0.0001). We observed no significant association between pathological cancer staging and the presence of the *EGFR* mutation.

Table II shows the patient characteristics and *KRAS* mutation status. We found that 25 (18.4%) of the 136 cases had a *KRAS* mutation. No significant association was observed between the presence of the *KRAS* mutation and mean age (p=0.7), gender (p=0.25), smoking status (p=0.19) or pathological cancer staging (p=0.21). The *KRAS* mutation was detected only in patients who had the wild-type *EGFR*; thus,

Table I. Patient characteristics and *EGFR* gene status.

	Mut (n=56) no. (%)	WT (n=80) no. (%)	p-value
Mean age (range)	65 (40-79)	67 (36-84)	0.08
Gender			
Male	17 (28)	43 (72)	0.005
Female	39 (53)	37 (47)	
Smoking history			
Yes	15 (24)	48 (76)	0.0001
No	41 (56)	32 (44)	
Pathological stage			
I	40 (40)	59 (60)	0.84
II	5 (50)	5 (50)	
III	11 (41)	16 (59)	

EGFR, epidermal growth factor receptor; Mut, mutation; WT, wild-type.

Table II. Patient characteristics and *KRAS* gene status.

	Mut (n=25) no. (%)	WT (n=111) no. (%)	p-value
Mean age (range)	67 (36-83)	66 (42-84)	0.7
Gender			
Male	13 (22)	47 (78)	0.25
Female	12 (16)	64 (84)	
Smoking history			
Yes	11 (18)	49 (82)	0.19
No	14 (18)	62 (82)	
Pathological stage			
I	16 (16)	83 (84)	0.21
II	1 (10)	9 (90)	
III	8 (30)	19 (70)	

Mut, mutation; WT, wild-type.

our findings support previous reports indicating that the *EGFR* and *KRAS* mutations may be mutually exclusive.

Distribution of patients with EGFR and KRAS mutations according to CT findings. The presence of spiculation, GGO and the maximum tumor diameter was assessed and the correlation with the mutations was determined (Table III). The *EGFR* mutation was detected in 35 (36%) of the 96 tumors with spiculation and in 21 (52%) of the 40 tumors with no spiculation. Although the frequency of *EGFR* mutations was higher in tumors with no speculation, it was not statistically significant (p=0.06). The maximum tumor diameter was ≤30 mm in 103 (76%) of the 136 patients. Of those, 46 (45%) harbored the *EGFR* mutation, whereas the mutation was found in 10 (30%) of the 33 patients who had a maximum tumor diameter ≥31 mm; this difference was not statistically significant (p=0.1). GGO was found in 59 (43%) of 136 tumors and the *EGFR* mutation was present in 29 (49%) of those. The *EGFR* mutation was found in 27 (35%) of the 77 tumors with no GGO. Although the *EGFR* mutation was observed more frequently in tumors with GGO than in those with no GGO, the difference was not statistically significant (p=0.07). Table IV shows the correlation between GGO and *EGFR* mutation status and gender. GGO was observed in 36 (47%) of 76 female patients and in 23 (38%) of 60 male patients. GGO occurred more frequently in female patients than in male patients, but the difference was not statistically significant (p=0.11). In the female patients, 19 (52%) of the tumors with GGO and 20 (50%) of tumors with no GGO had *EGFR* mutations; this difference was not statistically significant (p=0.49). In male patients, *EGFR* mutations were detected in 10 (43%) of 23 tumors that had GGO, whereas the mutation was detected in 7 (19%) of 37 tumors with no GGO. This difference was statistically significant (p=0.04). Thus, male patients with GGO had significantly more *EGFR* mutations than did those with no GGO.

The associations between the *KRAS* genotype and CT findings are summarized in Table III. *KRAS* mutations were found in 9 (15%) of 59 tumors with GGO and in 16 (21%) of 77 tumors without GGO. *KRAS* mutations were found in 19 (20%) of 96 tumors with spiculation and in 6 (15%) of 40 tumors without spiculation. The *KRAS* genotype did not correlate with the presence of spiculation or GGO (p=0.34 and 0.27, respectively). In contrast, *KRAS* mutations were found in 12 (36%) of 33 tumors >31 mm in diameter and in 13 (13%) of 103 tumors <30 mm in diameter (p=0.003). Thus, patients with a tumor ≥31 mm in diameter had a *KRAS* mutation significantly more frequently than did patients with a tumor ≤30 mm. The results of the analysis of GGO and *KRAS* mutation status in males and females are shown in Table IV. *KRAS* mutations were detected in three (13%) of 23 male and 6 (17%) of 36 female patients with GGO positive tumors, whereas *KRAS* mutations were detected in 10 (27%) male and 6 (15%) female patients with GGO negative tumors. No significant correlation was found between the presence of *KRAS* mutations and the existence of GGO in males (p=0.17) or females (p=0.69).

EGFR and KRAS mutations according to G/T ratio. Table V shows the *EGFR* and *KRAS* mutation status stratified by the G/T ratio. Patients were divided into two groups according to G/T ratio: 24 (18%) patients with a G/T ratio ≥50% and 112 (82%) patients with a G/T ratio <50%. In the 24 patients with a G/T ratio ≥50%, *EGFR* mutations were found in 12 (50%) of the tumors, whereas *EGFR* mutations were found in 44 (39%) of the 112 tumors with a G/T ratio <50%. *EGFR* mutations tended to occur more frequently in patients with a G/T ratio ≥50% than in those with a G/T ratio <50%; however, the difference was not statistically significant (p=0.22). *KRAS* mutations were observed in two (8%) of the 24 patients with a G/T ratio ≥50% and in 23 (21%) of 112 patients with a G/T ratio of <50%. Although the difference was not statistically significant, *KRAS* mutations were more frequently observed in patients with a G/T ratio of <50% than in those with a G/T ratio of ≥50% (p=0.13). When we further divided the

Table III. Distribution of patients with *EGFR* and *KRAS* mutation according to CT findings.

	EGFR genotype			*KRAS* genotype		
CT findings	Mut no. (%)	WT no. (%)	p-value	Mut no. (%)	WT no. (%)	p-value
Spiculation (+)	35 (36)	61 (64)	0.06	19 (20)	77 (80)	0.34
Spiculation (-)	21 (52)	19 (48)		6 (15)	34 (85)	
Max diameter ≤30 mm	46 (45)	57 (55)	0.1	13 (13)	90 (87)	0.003
Max diameter ≥31 mm	10 (30)	23 (70)		12 (36)	21 (64)	
GGO (+)	29 (49)	30 (51)	0.07	9 (15)	50 (85)	0.27
GGO (-)	27 (35)	50 (65)		16 (21)	61 (79)	

GGO, ground glass opacity; Mut, mutation; WT, wild-type.

Table IV. Correlation between GGO status and the *EGFR* and *KRAS* mutation in each gender.

	EGFR genotype			*KRAS* genotype		
G/T ratio	Mut no. (%)	WT no. (%)	p-value	Mut no. (%)	WT no. (%)	p-value
Male						
GGO (+)	10 (43)	13 (57)	0.04	3 (13)	20 (87)	0.17
GGO (-)	7 (19)	30 (81)		10 (27)	27 (73)	
Female						
GGO (+)	19 (52)	17 (48)	0.49	6 (17)	30 (83)	0.69
GGO (-)	20 (50)	20 (50)		6 (15)	34 (85)	

GGO, ground glass opacity; Mut, mutation, WT, wild-type.

Table V. Distribution of patients with *EGFR* and *KRAS* mutation stratified by G/T ratio.

	EGFR genotype			*KRAS* genotype		
G/T ratio (%)	Mut no. (%)	WT no. (%)	p-value	Mut no. (%)	WT no. (%)	p-value
≥50	12 (50)	12 (50)	0.22	2 (8)	22 (92)	0.13
<50	44 (39)	68 (61)		23 (21)	89 (79)	

GGO, ground glass opacity; G/T ratio, GGO/tumor ratio; Mut, mutation; WT, wild-type.

patients into five groups according to the G/T ratios of: 0%, 1-25%, 26-50%, 51-75% and 76-100%, we found no significant correlation between *EGFR* or *KRAS* mutation status and G/T ratio (data not shown).

Discussion

Recent studies have reported that *EGFR* mutations are often observed in adenocarcinomas, particularly among female patients and in Asian populations (6). More importantly, the presence of the *EGFR* mutation appears to be related to the patient's response to molecularly targeted drugs against *EGFR* tyrosine kinase, such as gefitinib and erlotinib (19). Thus, detection of the *EGFR* mutation in lung adenocarcinomas is important for determining treatment strategy. In the present study, the SmartAmp2 assay or Non-RI-SSCP was used to detect *EGFR* mutations in 53 (42.4%) of 136 patients who had adenocarcinomas. We found a significant correlation between *EGFR* mutation status and gender (p=0.005). Moreover, non-smoking was significantly associated with the presence of *EGFR* mutations (p=0.0001). Our findings confirmed those of previous reports showing an association between *EGFR* mutations in lung adenocarcinomas and gender and smoking status (1,6).

KRAS is an oncogene that plays an important role in lung cancer carcinogenesis (20). *KRAS* mutations are found in

20-50% of lung adenocarcinomas (1,4,5); however, the mutation is less common in Asian populations where it has been estimated to be 5-15% in adenocarcinomas (5,21,22). We found *KRAS* gene mutations at codon 12 in 25 of the 136 adenocarcinoma patients (18.5%). This percentage is higher than that previously reported (5,21,22) and the difference may be the result of using the SmartAmp2 method to detect *KRAS* mutations; it is more sensitive than PCR-based direct sequencing, enzyme-enriched sequencing or PNA-enriched sequencing, used in previous reports (23). Thus, our method of detecting *KRAS* mutations had a higher sensitivity than did studies using alternative methods (16). *KRAS* mutations have previously been identified in adenocarcinomas and shown to have a significant association with gender and smoking (1). The *KRAS* mutation has been detected more frequently in smokers and in male patients; however, recent studies suggest that *KRAS* mutations are not rare in never smokers or in women (24,25), a finding confirmed by our results. The high sensitivity of the SmartAmp2 assay in detecting *KRAS* mutation may explain why we did not find a significant association between *KRAS* mutations and gender (p=0.25) or smoking status (p=0.19).

Several recent investigations have reported a correlation between the presence of *EGFR* and *KRAS* mutations and pathological findings, such as bronchioloalveolar cell carcinoma (BAC) or BAC features (3,7). Moreover, BAC or BAC features are known to have a particular appearance on CT scans including GGO (26,27); thus, we expected that the appearance of GGO on CT scans would predict the presence of *EGFR* or *KRAS* mutations. It is often difficult to obtain tissue samples from patients with unresectable advanced lung cancer or who have had a relapse after surgery; thus, it would be clinically useful to be able to predict *EGFR* and *KRAS* mutation status using CT findings alone.

A relationship between *EGFR* or *KRAS* mutation status and CT findings has been previously reported. Yano *et al* (14) reported that a high ratio of GGO components may predict the presence of *EGFR* mutations. They analyzed 80 peripheral adenocarcinomas, including 38 cases with *EGFR* mutations, and found that GGO was more frequently observed in the mutation group than in the wild-type group, although the difference was not statistically significant. An analysis of the correlation between the *EGFR* mutation, nodule diameter and GGO ratio revealed that the *EGFR* mutation frequency was significantly higher in patients who had a GGO ratio ≥50% and a tumor diameter ≤3 cm than it was in patients who had a GGO ratio of <50% and a tumor diameter of ≤3 cm. Female patients who had a GGO ratio ≥50% and a tumor diameter <3 cm (10 of 12 patients; 83%) were most likely to have a high frequency of *EGFR* mutations (14). Although Yano *et al* did not find a significant association between GGO and *EGFR* mutation in all cases, they were able to identify the population with the highest frequency of *EGFR* mutations. Thus, we conducted our study using a larger sample size, a new system for analyzing *EGFR* mutations and different algorithms for CT findings.

Glynn *et al* (28) found no correlation between morphological features on a CT scan and the presence of *EGFR* or *KRAS* mutations. They studied 77 lesions from 64 patients with lung adenocarcinoma with bronchioloalveolar features. They found that 10 of 26 nodules with a GGO lesion had *EGFR* mutations and nine nodules had *KRAS* mutations. They concluded that the presence of GGO on the CT scan was not significantly associated with the presence of an *EGFR* (p=0.44) or *KRAS* mutation (p=0.77). However, Glynn *et al* only analyzed the presence of GGO and did not take into account the proportion of GGO components in the tumors. Furthermore, their sample size (26 nodules with GGO) was relatively small. Their method of analyzing GGO and a small sample size may help explain why they did not find a statistically significant correlation between CT findings and mutation status.

Our study was conducted using a simpler evaluation of CT findings and a larger group of patients than those used by Yano *et al* (14) or Glynn *et al* (28). We initially evaluated the presence of GGO in each tumor. We observed that the tumors with GGO tended to have *EGFR* mutations more frequently than did those with no GGO, though the difference did not reach statistical significance (p=0.07). This result suggested a possible correlation between the presence of GGO in a tumor and *EGFR* mutation status. *EGFR* mutations were detected in more than half of the female patients. The frequency of *EGFR* mutations was significantly higher in female patients than males; thus, we further examined the gender difference in the correlation between CT findings and *EGFR* mutation. In female patients, we found no difference in *EGFR* mutations status regardless of GGO (p=0.49). However, male patients with GGO had significantly more *EGFR* mutations than did those without GGO (p=0.04). The gender difference in the association between *EGFR* mutation status and CT findings suggests that it may be possible to predict the presence of *EGFR* mutations from CT findings in male patients. A similar tendency has been observed in the correlation between EGFR mutation status and pathological findings (26,27). Haneda *et al* (29) reported a correlation between *EGFR* mutation status and BAC in male Japanese patients who had adenocarcinomas, but found no such correlation in female patients. The frequency of *EGFR* mutations was higher in male adenocarcinoma patients with BAC than in those with no BAC (52 vs. 21%; p=0.013). Our results also revealed a gender difference in the correlation between *EGFR* status and the morphological structure of the tumors. *EGFR* mutations play a different role in the carcinogenesis of lung adenocarcinoma in male and female patients and the gender-related mechanism may influence the correlation between pathological findings and *EGFR* status (30,31). Several investigators have reported gender-related differences in the behavior of lung cancer as a result of hormonal effects on the tumor (30,31). They suggested that the effect was mediated by cross-talk between *EGFR* and estrogen receptors in the lung adenocarcinoma (32). This may partially explain the gender-related difference in the role of *EGFR* in the oncogenesis of lung adenocarcinoma.

We used the G/T ratio, which was calculated as the tumor-length ratio, in our analyses rather than the GGO ratio, calculated as the tumor area ratio, used by Yano *et al* (14). We calculated the tumor-length ratio from the maximum length of the solid portion and the GGO in the tumor (Fig. 1), which can be determined readily in the clinical setting. The tumor-length ratio has been reported to be approximately the same value as the tumor area ratio and tumor volume ratio (33). We observed a tendency for the *EGFR* mutation to occur in tumors with GGO that suggests a close association between G/T ratio and the frequency of *EGFR* mutation. We divided patients into two

groups according to G/T ratio: G/T ratio ≥50% and G/T ratio <50%, similar to Yano *et al*. We found that *EGFR* mutations tended to occur more frequently the patients with a G/T ratio ≥50% than in those with a G/T ratio <50%, although the difference was not statistically significant (p=0.22). When we further divided the patients into five groups according to G/T ratio we did not find a significant correlation between *EGFR* mutation status and G/T ratio. These results suggest that the *EGFR* mutation status is more strongly correlated with the presence of GGO than with the proportion of GGO components.

A correlation between CT findings and the *KRAS* mutation was not established by Glynn *et al* (28). We found that *KRAS* mutations occurred significantly more frequently in patients who had a tumor >31 mm in diameter than in patients who had a tumor ≤30 mm. The *KRAS* mutation is thought to be an early event that plays a role in tumor initiation (34,35). Woo *et al* (36) reported that the *KRAS* mutation and a tumor size >30 mm were independent prognostic factors in stage I lung adenocarcinoma (*KRAS* mutation; HR 4.51, 95% CI 1.68-12.06, p=0.003, tumor size >30 mm; HR 4.55, 95% CI 1.61-12.82, p=0.004, respectively). At the same time, they did not find a distinct correlation between the *KRAS* mutation and tumor size. Marks *et al* (25) analyzed nearly 300 cases of patients who had genotyped lung adenocarcinomas and had not received TKI therapy. They reported that patients with the *KRAS* mutation presented with significantly later stage disease than did patients with the *EGFR*-mutation and when compared with both *EGFR* mutant and wild-type combined. Furthermore, Marks *et al* reported that patients with *KRAS* mutant tumors had a shorter overall survival than did patients with *EGFR* mutant tumors and vs. *EGFR* mutant tumors and *EGFR*/*KRAS* wild-type tumors together. These findings indicate that the *KRAS* mutation has a strong influence on the acceleration of tumor progression as well as on the carcinogenesis of lung adenocarcinoma. Our finding that the *KRAS* mutation occurred more frequently in larger tumors may reflect the effect(s) of the *KRAS* mutation.

Patients with BAC had been shown to be particularly responsive to EGFR TKIs (37). In a retrospective review of 139 patients treated with gefitinib, higher response rate were noted in adenocarcinoma with BAC features or pure BAC compared with other adenocarcinomas (38 vs. 14%, p<0.001) (38). Zakowski *et al* reported that tumors from TKI responders tended to be better-differentiated adenocarcinomas with BAC components (39). They revealed that 78% of all responders had BAC or BAC components. Considering that BAC or BAC features are known to have a particular appearance on CT scans including GGO (26,27), the recognition of the presence of GGO might result in more successful treatment with TKIs.

In conclusion, we found few correlations between CT findings and the presence of *EGFR* or *KRAS* gene mutations. We found that the *EGFR* mutation occurred more frequently in male patients with GGO than in patients with no GGO (p=0.04). Although the frequency of *EGFR* mutations was lower in male patients than in female patients, it may be possible to predict the presence of *EGFR* mutation using CT findings. Although the genetic analysis of the resected specimen provides the most accurate evaluation of *EGFR* and *KRAS* mutation status, the use of morphological features on a CT scan may be used to predict *EGFR* and *KRAS* mutation status in patients whose tumor specimens cannot be obtained.

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