Original Article

Clinicoradiopathological features and prognosis according to genomic alterations in patients with resected lung adenocarcinoma

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Background: We investigated the clinicoradiopathological features and prognosis according to genomic alterations in patients with surgically resected lung adenocarcinoma.

Methods: Patients who underwent surgical resection for pathologic stage I, II, or IIIA lung adenocarcinoma between 2009 and 2016 and for whom results regarding *EGFR* mutation, ALK immunohistochemistry (IHC), and *KRAS* mutation were available were included. Clinicoradiopathological characteristics, genomic alterations, and disease-free survival were analyzed retrospectively.

Results: Of 164 patients, 86 (52.4%) were female and 94 (57.3%) were never-smokers. The most common imaging patterns were part-solid lesion (67.7%) followed by solid (26.2%) and non-solid (6.1%) lesions. *EGFR* mutation, ALK IHC, and *KRAS* mutation were positive in 95 (57.9%), 9 (5.5%), and 11 (6.7%) patients, respectively. *EGFR* mutation positivity was associated with female sex, never-smoker, subsolid pattern on radiological examination, and acinar or papillary predominant histologic subtype. ALK IHC positivity was associated with longer maximal diameter, advanced stage, solid pattern on radiological examination, solid predominant histologic subtype, and distant metastasis during follow-up. *KRAS* mutation positivity was associated with male sex, smoker, solid pattern on radiological examination, and invasive mucinous adenocarcinoma on histologic analysis. In multivariable analysis, ALK IHC positivity and lymph node involvement were independently associated with recurrence. However, solidity was not an independent risk factor for recurrence.

Conclusions: Genomic alterations are associated with clinicoradiopathologic features in patients with resected lung adenocarcinoma. Identifying genomic alterations could help to predict the prognosis of early-stage lung adenocarcinoma.

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Keywords: Lung adenocarcinoma; solidity; epidermal growth factor receptor (EGFR); anaplastic lymphoma kinase (ALK); Kirsten rat sarcoma viral oncogene homolog (KRAS)

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Introduction

With advances in genomic analysis, various genomic alterations that contribute to the development of cancer have been identified. Targeting these genomic alterations has become an important therapeutic option in patients with neoplasms, and this approach is changing the therapeutic paradigm (1). In lung adenocarcinoma, epidermal growth factor receptor (*EGFR*) gene mutation, anaplastic lymphoma kinase (*ALK*) gene rearrangement, and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene mutation are the most frequently detected genomic alterations (2). Recent studies demonstrated that agents targeting *EGFR* mutation or *ALK* rearrangement, including EGFR tyrosine-kinase inhibitors (TKIs) and ALK TKIs, respectively, increased the response rate and progression-free survival in patients with lung adenocarcinoma (3-5). However, there are no approved target agents for cases with *KRAS* mutation. Instead, the presence of a *KRAS* mutation can indicate a poor prognosis with regard to survival and be a predictor of a poor response to EGFR TKIs (6).

In terms of the radiological evaluation of lung adenocarcinoma, computed tomography (CT) is a cost-effective and non-invasive tool in the diagnosis, treatment, and follow-up of lung cancer. Since the introduction of low-dose spiral CT as a screening tool, the early diagnosis of lung cancer has increased (7,8). Particularly, early-stage lung adenocarcinoma may be detected on CT as solid or subsolid nodules, which can be further classified as non-solid or part-solid nodules (9). A higher proportion of ground-glass opacity (GGO) is correlated with a better prognosis, and recent guidelines recommended the management of nodules according to their solidity (10-12). Recently, it was reported that *EGFR* mutation was associated with GGO and *ALK* rearrangement was shown to present a solid pattern on chest CT (13,14). However, the associations of radiological features and prognosis in relation to genomic alterations in early-stage lung adenocarcinoma remain uncertain. Therefore, we investigated the clinicoradiopathological features and prognosis according to genomic alterations in patients with stage I-IIIA resected lung adenocarcinoma.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1716).

Methods

Patient selection and clinical assessment

Patients who underwent surgical resection for pathologic stage I, II, or IIIA lung adenocarcinoma at Samsung Medical Center between 2009 and 2016 and for whom results regarding *EGFR* mutation, ALK immunohistochemistry (IHC), and *KRAS* mutation were available were included in this retrospective observational study. Patients who had undergone treatment for lung cancer before surgery, such as chemotherapy or radiotherapy, which could alter the pathological results were excluded. Patient characteristics, including age, sex, smoking status, surgical procedure type, recurrence, and outcomes were obtained from medical records.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC 2018-03-125) and individual consent for this retrospective analysis was waived. All data were anonymized and de-identified prior to analysis.

Radiological evaluation

All selected patients underwent chest CT within 2 months prior to surgery. While CT examinations were performed at multiple institutions with variable protocols, thin-section chest CT images that could indicate non-solid lesions based on the consensus of two experienced radiologists were reviewed. They independently measured diameters and categorized tumors according to CT features: solidity (non-solid, part-solid, and solid), presence of spiculation, lobulation, pleural tagging, air-bronchogram, and bubble lucency. Non-solid lesions were characterized by hazy increased attenuation that did not obliterate the bronchial

and vascular margins, part-solid lesions were those with both GGO and soft tissue attenuation, and solid lesions were defined as those with homogeneous soft tissue attenuation (9,15).

The extent of GGO in each lesion was evaluated quantitatively using the GGO proportion. For each entire tumor and its solid portion, regions of interest were delineated on the axial images to generate a volume of interest with a semiautomated approach. The longest diameter was estimated from three-dimensional tumor measurements of regions of interest. The maximal diameter of the lesion was multiplied by its longest perpendicular diameter to obtain the total area on lung windows. To calculate the solid area on lung windows, the maximal diameter of the solid portion was multiplied by its longest perpendicular diameter. GGO proportion was defined as follows:

GGO proportion (%) =100×[1− (solid area on lung windows)/(total area on lung windows)].

Histopathological evaluation

Pathologic tumor, node and metastasis (TNM) staging was performed following the *International Association for the Study of Lung Cancer* (IASLC) proposals for the 8th edition of TNM classification for lung cancer (16). For histological subtyping, we classified lesions following the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) histologic classification of lung adenocarcinoma categorized according to the predominant histologic subtype (17).

EGFR and KRAS mutations and ALK IHC

To evaluate *EGFR* and *KRAS* gene mutations, extracted genomic DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tissue. DNA sequencing for *EGFR* mutations in exons 18, 19, 20, and 21 was performed using real-time polymerase chain reaction (PCR) and a peptide nucleic acid (PNA) clamping EGFR Mutation Detection Kit (Panagene, Inc., Daejeon, Korea). *KRAS* mutations in exons 12 and 13 were evaluated by Sanger sequencing. ALK protein expression was evaluated by IHC (1:40, NCL-ALK, clone 5A4, Novocastra, Newcastle upon Tyne, UK) with FFPE tissue. Diffuse and strong cytoplasmic positivity of tumor cells was considered positive for ALK IHC (18). Although it was well known that there was a good correlation between the results of ALK IHC and fluorescence in situ hybridization (FISH) (19), *ALK* discordant (IHC-positive/FISH-negative) cases were also reported (20,21). In the previous studies, *ALK* discordant (IHC-positive/FISH-negative) cases showed *ALK* gene amplification (20) and responsiveness to ALK-TKI (21). In this study, ALK IHC positivity was regarded as a surrogate marker for *ALK* gene rearrangement or amplification (19).

Statistical analysis

For descriptive statistics, the means with standard deviation or medians with interquartile range (IQR) were used for continuous variables. Frequencies with percentages were presented for categorical variables. Continuous variables were analyzed by one-way analysis of variance, Kruskal-Wallis test, or Mann-Whitney U test. To evaluate categorical variables, Pearson's χ^2 test or Fisher's exact test was used. For post hoc analysis, the Mann-Whitney U test, Pearson's χ^2 test, Fisher's exact test, and Bonferroni's correction were performed.

The Kaplan-Meier method was used to estimate disease-free survival, which was assessed from the date of surgery to the date of diagnosis of first recurrence on medical records. The log-rank test was performed to identify differences in disease-free survival according to genomic alterations and solidity. Multivariable analyses with Cox proportional-hazards regression and stepwise selection were carried out using variables with $P<0.05$ on univariable analysis and clinically relevant variables (age, sex, and smoking status) to identify risk factors for recurrence after surgery. During stepwise variable selection, variables with $P<0.10$ on univariable analysis and clinically relevant variables were entered and those with $P\geq0.05$ were removed (22). Firth's penalized maximum likelihood estimation method was implemented due to rare events in Cox regression model. With 95% confidence intervals (CIs), $P<0.05$ was taken to indicate statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org), and IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 164 patients with surgically resected lung

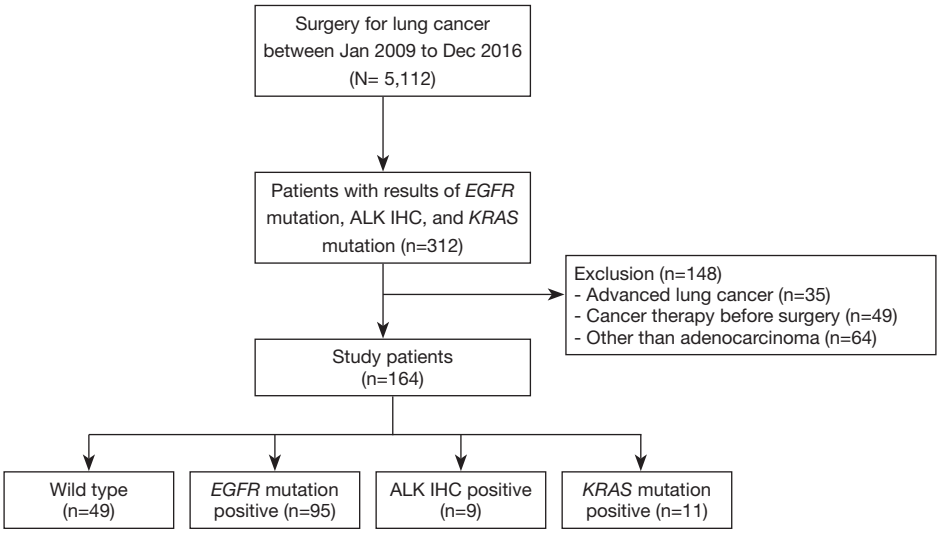

Figure 1 Flow diagram of subject enrollment.

adenocarcinoma were included in analysis (*Figure 1*) and the baseline characteristics of these patients are summarized in *Table 1*. The mean age was 60.7 years, 86 patients (52.4%) were female, and 94 patients (57.3%) were never-smokers. The most common imaging patterns were part-solid lesion (67.7%) followed by solid lesion (26.2%) and non-solid lesion (6.1%). With regard to surgical procedure, 122 patients (74.4%) underwent lobectomy, and limited resection including segmentectomy or wedge resection was performed in 42 patients (25.6%). All patients included in this study achieved R0 resection and 158 patients (96.3%) received lymph node dissection or sampling. Most patients had a diagnosis of pathologic stage I (79.9%) lung adenocarcinoma followed by stage II (11.0%) and stage IIIA (9.1%). Acinar predominant subtype (68.3%) was the most common histologic subtype followed by solid predominant subtype (7.9%) and papillary predominant subtype (6.7%). The median follow-up period after surgery was 50.0 (IQR, 29.5–53.0) months. Recurrences developed in 32 patients (19.5%) during the follow-up period. Among these patients, 2 patients (1.2%) had only locoregional relapse; 26 patients (15.9%) had distant metastasis alone; and the remainder (4 patients, 2.4%) had both locoregional relapse and distant metastasis (*Table 1*).

Genomic alterations

With regard to genomic alterations, patients had *EGFR* mutation (95/164, 57.9%), ALK IHC positivity (9/164, 5.5%), and *KRAS* mutation (11/164, 6.7%). In terms of subtypes of *EGFR* mutation, 47 patients (47/95, 49.5%) were positive for the L858R point mutation and 41 patients (41/95, 43.2%) were positive for an exon 19 deletion. Patients with ALK IHC positivity had an IHC score of 2 (6/9, 66.6%) or 3 (3/9, 33.3%), and all patients with a *KRAS* mutation had a missense mutation in codon 12 (11/11, 100%) (*Table 2*).

Analysis of clinicoradiological and pathological features in relation to genomic alterations

Analyses of the characteristics of each nodule according to genomic alterations indicated that *EGFR* mutation was significantly associated with female sex (P=0.001), never-smokers (P=0.001), part-solid lesions on radiological examination (P<0.001), and acinar or papillary predominant subtype on histological analysis (P<0.001). ALK IHC positivity was associated with longer maximal diameter (P=0.012), solid lesions on radiological examination (P<0.001), advanced pathologic stage (P=0.009), solid predominant subtype on histological analysis (P<0.001), and distant metastasis during follow-up (P<0.001). *KRAS* mutation positivity was associated with male sex (P=0.001), smokers (P=0.001), solid lesions on radiological examination (P<0.001), and invasive mucinous adenocarcinoma on histological analysis (P<0.001) (*Table 3*).

Radiological morphology and genomic alterations

In terms of subsolid and solid lesions according to genomic

Table 1 Baseline characteristics

Variables	Number
Age (years)	60.7±8.9
Sex, female, n (%)	86 (52.4)
Never-smoker, n (%)	94 (57.3)
Imaging pattern, n (%)	
Non-solid	10 (6.1)
Part-solid	111 (67.7)
Solid	43 (26.2)
Surgery, n (%)	
Extent of resection	
Wedge resection	18 (11.0)
Segmentectomy	24 (14.6)
Lobectomy	122 (74.4)
Mediastinal lymph node dissection or sampling[†]	158 (96.3)
R0 resection	164 (100.0)
Pathologic stage[‡], n (%)	
Stage I	131 (79.9)
Stage II	18 (11.0)
Stage III	15 (9.1)
Histologic subtype[§], n (%)	
Nonmucinous MIA	6 (3.7)
Invasive adenocarcinoma	
Lepidic predominant	8 (4.9)
Acinar predominant	112 (68.3)
Papillary predominant	11 (6.7)
Micropapillary predominant	1 (0.6)
Solid predominant	13 (7.9)
Invasive mucinous adenocarcinoma	7 (4.3)
Enteric	2 (1.2)
Unclassified	4 (2.4)
Follow-up duration after surgery (months)	50.0 (29.5–53.0)
Recurrence, n (%)	32 (19.5)
Locoregional relapse	6 (3.7)
Ipsilateral lung	1 (0.6)
Regional lymph node	5 (3.0)
Distant metastasis	30 (18.3)
Contralateral lung	13 (7.9)
Pleura	7 (4.3)
Brain	7 (4.3)
Bone	6 (3.7)
Liver	1 (0.6)
Kidney	1 (0.6)

Data are presented as the mean ± standard deviation, median (IQR), or number (%). [†], mediastinal lymph node dissection was performed in 145 patients (88.4%); [‡], IASLC 8th edition of the TNM classification for lung cancer; [§], 2011 IASLC/ATS/ERS histologic classification of lung adenocarcinoma. MIA, minimally invasive adenocarcinoma.

alterations, ALK IHC positivity was associated with solid lesions compared to patients positive for *EGFR* mutation (P<0.001) or wild type (P=0.006) (*Figure 2A*). ALK IHC positivity was related to a lower GGO proportion on chest CT compared to positive *EGFR* mutation (P=0.012) or wild type (P=0.030) (*Figure 2B*).

Risk factors for recurrence after surgery

In univariable analysis, solid lesion, ALK IHC positivity, non-lepidic or acinar predominant subtype, pathologic T2–4 stage, lymph node involvement, and administration of adjuvant chemotherapy were risk factors for recurrence. However, the administration of adjuvant chemotherapy could be related to advanced stage of the disease and was excluded from the multivariable analysis to avoid collinearity. In multivariable analysis, ALK IHC positivity (HR =2.750, 95% CI, 1.097–6.897; P=0.031) and lymph node involvement (HR =7.594, 95% CI, 3.497–16.487; P<0.001) were independent risk factors for recurrence (*Table 4*). The disease-free survival rate according to genomic alterations was significantly lower in patients with ALK IHC positivity than in those with other genomic alterations (P<0.001); the median disease-free survival was 24.0 months (95% CI, 15.2–32.8) in patients with ALK IHC positivity and not reached in those with other genomic alterations (*Figure 3*).

Table 2 Summary of genomic alterations in patients with lung adenocarcinoma

Variables	Number, n (%)
EGFR mutation	
Wild type	69/164 (42.1)
Mutation positive	95/164 (57.9)
Exon 18 G719X point mutation	2/95 (2.1)
Exon 19 deletion	41/95 (43.2)
Exon 20 insertion	1/95 (1.1)
Exon 21 L858R point mutation	47/95 (49.5)
Exon 21 L858R or L861Q point mutation	3/95 (3.2)
Exon 21 L858R and K860I point mutation	1/95 (1.1)
ALK IHC	
Negative	155/164 (94.5)
Positive	9/164 (5.5)
IHC 2+	6/9 (66.7)
IHC 3+	3/9 (33.3)
KRAS mutation	
Wild type	153/164 (93.3)
Mutation positive	11/164 (6.7)
Missense in codon 12	11/11 (100.0)

EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene homolog gene.

Discussion

Our data suggest that *EGFR* mutation is associated with part-solid or subsolid lesions on radiological examination and acinar or papillary predominant subtype on histological analysis. ALK IHC positivity was detected more frequently in patients with large or advanced stage tumors, solid lesions on radiological examination, solid predominant subtype on histological analysis, and distant metastasis during follow-up. *KRAS* mutation was related to solid lesions on radiological examination and invasive mucinous adenocarcinoma on histological analysis. With regard to disease-free survival, ALK IHC positivity and lymph node involvement were risk factors for recurrence.

Previous studies yielded inconsistent results regarding the association between *EGFR* mutation and the presence of GGO patterns. Most studies reported that *EGFR* mutation was linked to lesions with a higher proportion of GGO (23,24). However, Glynn *et al.* (25) reported no significant correlation between *EGFR* mutation and a GGO component. Two other studies indicated that *EGFR* mutation was more common in lesions with a >50% solid component in comparison to cases with a lower solid proportion (26,27). In the present study, *EGFR* mutation was associated with a higher GGO percentage compared to ALK IHC positivity or *KRAS* mutation. Additionally, *EGFR* mutation was detected more frequently in part-solid or subsolid lesions, which were partly composed of GGO components. These discrepancies between studies may have been mediated by the prevalence of *EGFR* mutation in the study population or use of different methods for quantification and classification of the GGO component. In terms of histological features of *EGFR* mutation, no significant findings have been reported with papillary predominant subtype, but Wang *et al.* (28) reported that patients with lepidic or acinar predominant adenocarcinoma tended to have an *EGFR* mutation. These findings were partially inconsistent with our results, which may have been due to the inclusion of advanced lung adenocarcinoma patients with various manifestations (29).

Findings from previous studies regarding the correlation between ALK-positive lung cancer and its GGO component suggested that ALK-positive lesions were more likely to present with solid components on CT, consistent with our results (13,30). However, a study of lung cancer from early to advanced stages reported that lesions <20 mm in size were more likely to be *ALK* fusion-positive tumors (31). With regard to histological features, Wang *et al.* (28) reported that *ALK* rearrangement was associated with solid predominant subtype, as shown in our study. For ALK IHC, in this study, 7 of 9 IHC-positive cases (2+ or 3+) were further evaluated by *ALK* FISH at the time of recurrence. Of 7 cases examined, 6 cases were positive for *ALK* FISH (>15% rearranged signals). However, one case positive for ALK IHC (3+) was negative for *ALK* FISH and received cytotoxic chemotherapy instead of ALK-TKI due to a financial issue. Unfortunately, the patient expired due to the progression of the disease. In the previous studies, *ALK* discordant (IHC-positive/FISH-negative) cases were related to *ALK* gene amplification (20) and 13 (100%) of 13 discordant (IHC-positive/FISH-negative) cases responded to ALK-TKI (21). Therefore, the discrepancies between IHC and FISH data seem to be associated with biological events rather technical issues. Recent NCCN guidelines also acknowledged FDA-approved ALK IHC (D5F3 CDx Assay) as a stand-alone test, not requiring confirmation by

Table 3 Clinicoradiopathological features according to genomic alterations

Variables	Wild type (n=49), n (%)	EGFR Mutation positive (n=95), n (%)	ALK IHC positive (n=9), n (%)	KRAS Mutation positive (n=11), n (%)	P value
Age (years)	61.1±8.5	59.8±8.0	64.7±14.1	63.3±13.0	0.298
Sex, female	18 (36.7)	62 (65.3)	4 (44.4)	2 (18.2)	0.001
Never-smoker	22 (44.9)	66 (69.5)	4 (44.4)	2 (18.2)	0.001
Diameter (mm)	24.4 (17.4–29.3)	24.5 (18.1–30.6)	35.7 (31.2–39.8)	29.2 (20.3–41.2)	0.012
Image pattern					<0.001
Non-solid	4 (8.2)	4 (4.2)	0 (0.0)	2 (18.2)	
Part-solid	32 (65.3)	74 (77.9)	1 (11.1)	4 (36.4)	
Solid	13 (26.5)	17 (17.9)	8 (88.9)	5 (45.5)	
Spiculation	23 (46.9)	45 (47.4)	6 (66.7)	8 (72.7)	0.303
Lobulation	28 (57.1)	67 (70.5)	7 (77.8)	7 (63.6)	0.387
Pleural tags	25 (51.0)	66 (69.5)	6 (66.7)	7 (63.6)	0.182
Air-bronchogram*	21 (42.9)	57 (60.0)	1 (11.1)	6 (54.5)	0.016
Bubble lucency	7 (14.3)	18 (18.9)	0 (0.0)	2 (18.2)	0.593
Pathologic stage†					0.009
Stage I	43 (87.8)	77 (81.1)	4 (44.4)	7 (63.6)	
Stage II	2 (4.1)	9 (9.5)	3 (33.3)	4 (36.4)	
Stage III	4 (8.2)	9 (9.5)	2 (22.2)	0 (0.0)	
Histologic subtype‡					<0.001
Nonmucinous MIA	2 (4.1)	3 (3.2)	0 (0.0)	1 (9.1)	
Invasive adenocarcinoma					
Lepidic predominant	3 (6.1)	4 (4.2)	0 (0.0)	1 (9.1)	
Acinar predominant	34 (69.4)	73 (76.8)	2 (22.2)	3 (27.3)	
Papillary predominant	1 (2.0)	10 (10.5)	0 (0.0)	0 (0.0)	
Micropapillary predominant	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	
Solid predominant	3 (6.1)	5 (5.3)	4 (44.4)	1 (9.1)	
Invasive mucinous	3 (6.1)	0 (0.0)	0 (0.0)	4 (36.4)	
Enteric predominant	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Unclassified	1 (2.0)	0 (0.0)	3 (33.3)	0 (0.0)	
Recurrence					<0.001
Locoregional relapse	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	
Distant metastasis	3 (6.1)	16 (16.8)	5 (55.6)	2 (18.2)	
Locoregional relapse and distant metastasis	0 (0.0)	4 (4.2)	0 (0.0)	0 (0.0)	

Data are presented as the mean ± standard deviation, median (IQR), or number (%). *, *post hoc* between-group comparison did not show a significant difference; †, IASLC 8th edition of the TNM classification for lung cancer; ‡, 2011 IASLC/ATS/ERS histologic classification of lung adenocarcinoma. *EGFR*, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinas; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene homolog gene; MIA, minimally invasive adenocarcinoma; Invasive mucinous, invasive mucinous adenocarcinoma.

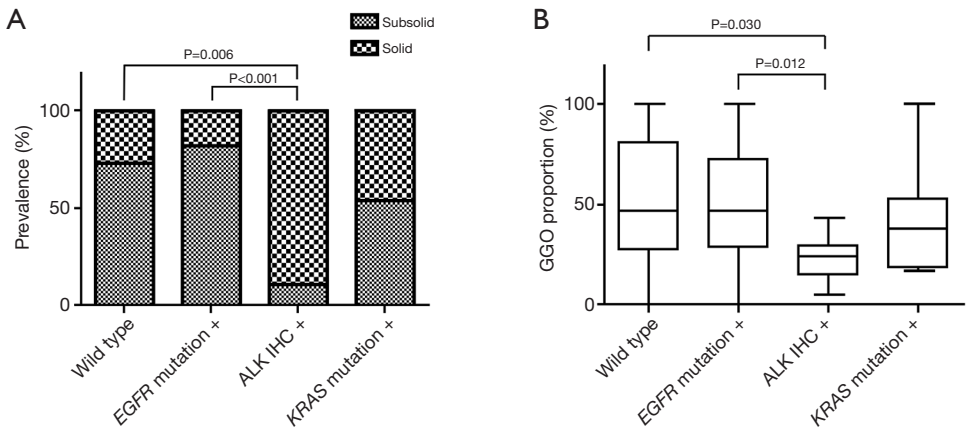

Figure 2 Solidity according to genomic alterations. (A) Prevalence of subsolid and solid lesions according to genomic alteration. (B) Ground-glass opacity (GGO) proportion and genomic alterations. *EGFR*, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene homolog gene.

Table 4 Risk factors for recurrence in patients with resected lung adenocarcinoma

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (≥61 *vs.* <61 years)	1.375	0.686–2.754	0.369			
Sex (female *vs.* male)	0.752	0.375–1.505	0.421			
Smoking status (current/former *vs.* never)	1.315	0.656–2.633	0.440			
Solidity (solid *vs.* non-solid)	4.348	2.158–8.761	<0.001			
Surgery (lobectomy *vs.* limited resection)[†‡]	3.717	0.704–19.616	0.122			
ALK IHC (positive *vs.* negative)	6.926	3.004–15.965	<0.001	2.750	1.097–6.897	0.031
Histologic subtype (others *vs.* lepidic or acinar)	2.772	1.384–5.553	0.004			
Pathologic T stage (T2–4 *vs.* T1)	3.797	1.856–7.766	<0.001			
Pathologic N stage (N1–2 *vs.* N0)	9.856	4.836–20.085	<0.001	7.594	3.497–16.487	<0.001
Adjuvant chemotherapy (yes *vs.* no)	4.774	2.326–9.797	<0.001			

[†], lobectomy *vs.* limited resection (wedge resection or segmentectomy). [‡], hazard ratios could not be calculated in the multivariable analysis as only one case of limited resection showed evidence of recurrence. HR, hazard ratio; CI, confidence interval; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry.

FISH (32).

Several studies have reported radiological features of *KRAS*-mutant lung adenocarcinoma (26,33). Although there were only two patients in their study, Chung *et al.* (26) detected a *KRAS* mutation in GGO lesions with >50% solid component. On the other hand, Rizzo *et al.* (33) found no significant difference in rate of *KRAS* mutation positivity between solid and subsolid lesions. In this study, we applied a different classification method for pulmonary lesions (i.e., non-solid, part-solid, or solid lesions) and showed that *KRAS* mutation was associated with solid lesions compared to *EGFR* mutation.

The characteristics of wild type in this study were similar to those of cases with *EGFR* mutation, especially with regard to solidity and histologic subtype. PNA clamping is a more sensitive method for the detection of *EGFR* mutations compared to direct sequencing (34). However, the similarities between *EGFR* mutation and wild type may

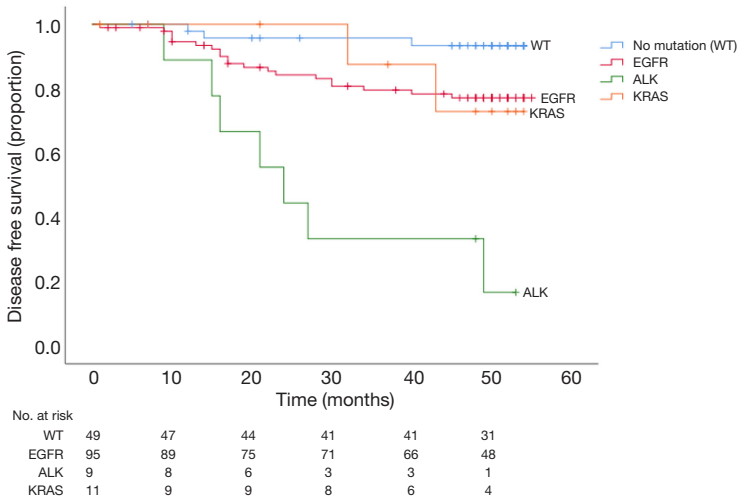

Figure 3 Disease-free survival according to genomic alterations (P<0.001; wild type, *EGFR* mutation, ALK IHC, and *KRAS* mutation). WT, wild type; *EGFR*, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog gene.

result from false-negative results for *EGFR* mutation. For example, 64.5% (78/121) of subsolid lesions were classified as having an *EGFR* mutation in the present study. On the other hand, in our previous study, about 90% of lung adenocarcinoma with subsolid morphology were classified as having an *EGFR* mutation based on next-generation sequencing, which is more sensitive than PNA clamping or direct sequencing (35). In addition, wild type in this study could have included other driver mutations, such as ROS protooncogene 1 (*ROS1*) rearrangements or B-Raf protooncogene (*BRAF*) point mutations.

Our observations indicate that lymph node metastasis was a risk factor for recurrence, which is consistent with previous studies (36,37). We also demonstrated that ALK IHC positivity was independently associated with poor disease-free survival. ALK IHC positivity was associated with more distant metastasis during follow-up (*Table 3*). Even in patients with stage IA or IB disease, recurrence occurred in 50% (2/4) of those positive for ALK IHC. Therefore, the benefits of adjuvant chemotherapy according to genomic alterations should be evaluated for patients with pathologic stage I lung adenocarcinoma in future studies. To the best of our knowledge, this is the first study to show differences in disease-free survival according to genomic alterations in patients with resected lung adenocarcinoma. Not only for metastatic lung cancer, but genomic evaluation in early-stage lung cancer may help in predicting prognosis, such as disease-free survival.

This study has several limitations. First, it was a retrospective single-center study in a population of 100% Asian patients with a relatively small sample size. As we included only patients for whom *EGFR* mutation, ALK IHC, and *KRAS* mutation results were available, the possibility of potential selection bias should be considered. Therefore, the results of our study should be interpreted conservatively. Second, chest CT was performed at various institutions with different protocols or thicknesses. However, experienced radiologists independently reviewed each CT scan for quality control. Third, only early-stage lung adenocarcinoma was included in the study; it is unclear whether the results of this study would be applicable to advanced lung adenocarcinoma.

Conclusions

Genomic alterations are associated with clinicoradiopathologic features in patients with resected lung adenocarcinoma. Identifying genomic alterations could help to predict the prognosis of early-stage lung adenocarcinoma.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Samsung Medical Center approved this retrospective study (IRB No. SMC 2018-03-125) and individual consent for this retrospective analysis was waived.

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