Computed Tomography Imaging Characteristics of Non–Small-Cell Lung Cancer With Anaplastic Lymphoma Kinase Rearrangements: A Systematic Review and Meta-Analysis

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Abstract

We analyzed all published research and compared the imaging features of anaplastic lymphoma kinase (ALK)-rearranged non–small-cell lung cancer (NSCLC) patients with those without ALK rearrangements. This meta-analysis included 12 studies with 2210 NSCLC patients, 456 of whom had ALK rearrangement. We found that ALK-rearranged NSCLC patients have distinct clinical and imaging features, which might assist in selecting patients who might benefit from expedited or repeat molecular testing when necessary.

Introduction: Several studies have suggested that non–small-cell lung cancer (NSCLC) patients who harbor anaplastic lymphoma kinase (ALK) rearrangement might have different imaging features compared with those without the rearrangement. The goal of this work was to systematically investigate the computed tomography (CT) imaging features of ALK-rearranged NSCLC. **Materials and Methods:** We searched published studies that investigated CT imaging features of ALK-rearranged NSCLC compared with ALK-negative, including epidermal growth factor receptor (EGFR)-mutant and ALK/EGFR-negative, NSCLC. We extracted clinicopathologic characteristics and CT imaging features of patients in the included studies. Features were compared and tested in the form of odds ratios (ORs) or weighted mean differences at a 95% confidence interval. **Results:** Twelve studies with 2210 patients with NSCLC were included. Compared with ALK-negative NSCLC, ALK-rearranged NSCLC was more likely to be solid (OR, 2.37; $P < .001$) and less likely to have cavitation (OR, 0.45; $P = .002$). In advanced stages, patients with ALK-rearranged NSCLC, compared with EGFR-mutant NSCLC, were more likely to have lymphadenopathy (OR, 3.47; $P < .001$), pericardial metastasis (OR, 2.18; $P = .04$), pleural metastasis (OR, 2.07; $P = .004$), and lymphangitic carcinomatosis (OR, 3.41; $P = .02$), but less likely to have lung metastasis (OR, 0.52; $P = .003$). Compared with ALK/EGFR-negative NSCLC, ALK-rearranged NSCLC was more likely to have lymphangitic carcinomatosis (OR, 3.88; $P = .03$), pleural metastasis (OR, 1.89; $P = .02$), and pleural effusion (OR, 2.94; $P = .003$). **Conclusion:** ALK-rearranged NSCLC has imaging features that are different compared with EGFR-mutant and ALK/EGFR-negative NSCLC. These imaging features might provide clues as to the presence of ALK rearrangement and help in the selection of patients who might benefit from expedited molecular testing or repeat testing after a negative assay.

Clinical Lung Cancer, Vol. 20, No. 5, 339-49
Keywords: Epidermal growth factor receptor mutation, Metastasis, Mutation, Radiogenomics, Radiology

Introduction

The discovery of actionable oncogenic mutations and rearrangements in non–small-cell lung cancer (NSCLC) ushered in an era of personalized or precision oncology, dramatically altering the diagnostic and therapeutic landscape of NSCLC.[1] One key oncogenic driver in NSCLC is chromosomal rearrangements involving

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Submitted: Feb 5, 2019; Revised: Apr 14, 2019; Accepted: May 2, 2019; Epub: May 11, 2019

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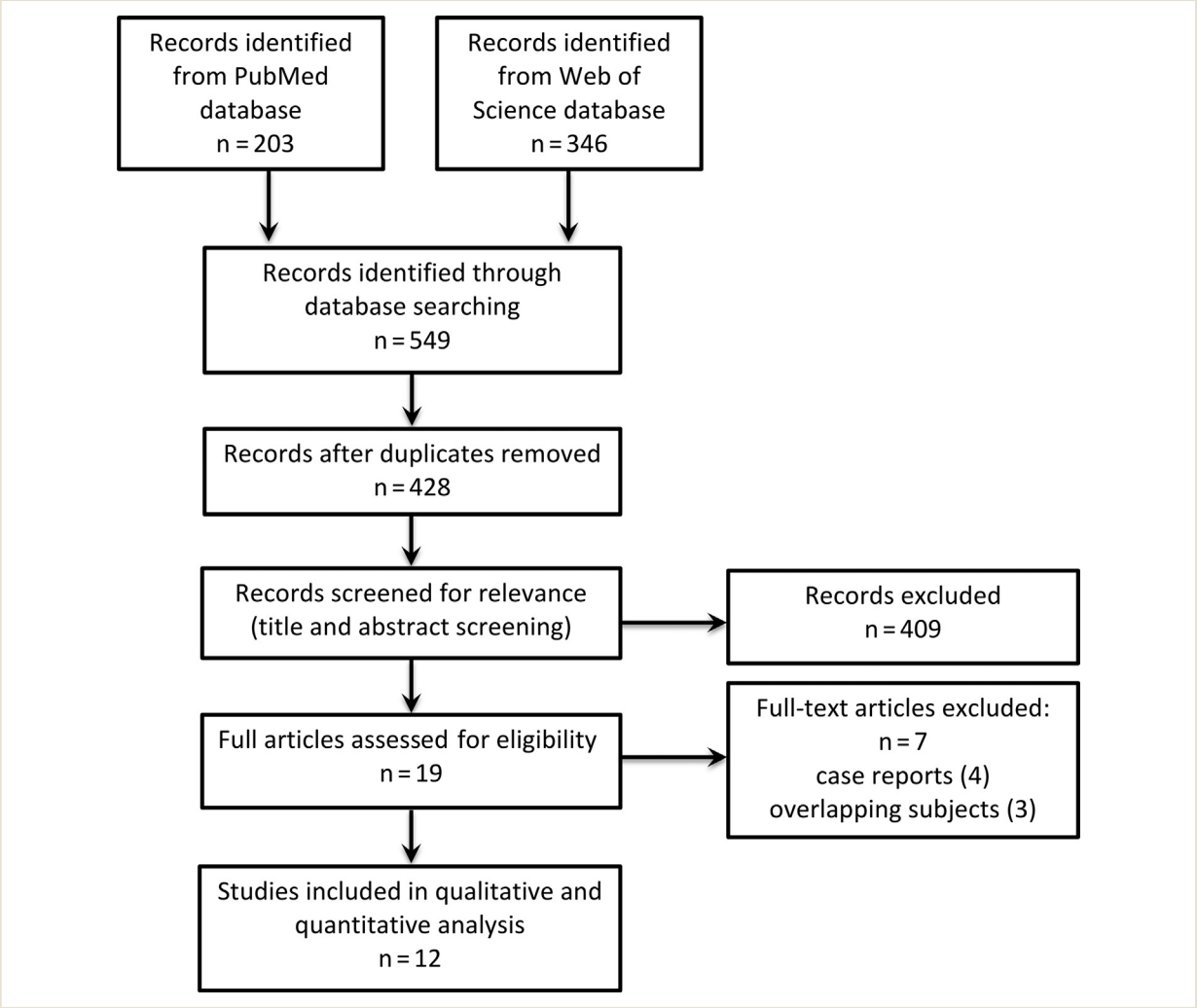
1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2019.05.006

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart. Study Identification, Screening, and Selection on the Basis of PRISMA Guidelines



anaplastic lymphoma kinase (ALK), often with fusion of a portion of ALK to echinoderm microtubule associated protein-like 4 (EML4). Several small-molecule tyrosine kinase inhibitors (TKIs) have been developed to target ALK fusions and have led to improved survival of this subset of patients.[1-3] Consequently, current guidelines recommend testing for actionable genetic alterations in the setting of advanced NSCLC. In patients with identified targets, target-specific TKIs have replaced chemotherapy as first-line treatment.[2-4]

Although several studies have investigated the imaging features of NSCLC harboring ALK fusions (ie, ALK-rearranged NSCLC) compared with those without the fusion, most have small cohorts, because of the mutation's relative rarity.[5-16] In this work, we systematically reviewed and analyzed the current medical literature to examine the imaging features of patients with ALK-rearranged NSCLC compared with those without ALK rearrangements.

Materials and Methods

This meta-analysis was carried out in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17,18] The primary procedures were as outlined in the following sections.

Search Strategy

We searched PubMed and Web of Science databases for all articles about imaging features of NSCLC with ALK rearrangements published between January 1, 2007 and February 1, 2019. The medical subject terms and key words used for search were "ALK," "anaplastic lymphoma kinase," "lung cancer," "lung carcinoma," "adenocarcinoma," "NSCLC," "CT," "imaging," "radiologic," and "radiogenomic."

Inclusion and Exclusion Criteria for Study Selection

Studies were included if they satisfied the following criteria: (1) subjects have NSCLC on the basis of pathological or cytological

Table 1 Characteristics of Included Studies

Reference	Country of Origin	Blinded	Treatment-Naive	Number of Included Patients and Mutation Type				Stage
				ALK	EGFR	Other	Total	
Choi et al[11]	Korea	Yes	Yes	68	130	0	198	IV
Halpenny et al[15]	United States	Yes	Yes	30	97	0	127	I-IV
Jeong et al[12]	Korea	Unknown	Yes	41	Unknown	180[a]	221	IIIB-IV
Kim et al[10]	Korea	Unknown	Yes	25	101	72[b]	198	I-IV
Miao et al[5]	China	Yes	Yes	27	112	6[c]	139	IIIB-IV
Nakada et al[14]	Japan	Unknown	Unknown	27	115	94[a]	236	I-IV
Park et al[9]	Japan	Unknown	Yes	51	159	55[d]	265	I-IV
Rizzo et al[7]	Italy	Yes	Yes	31	60	64[d]	155	IV
Wang et al[8]	China	Yes	Yes	41	66	0	107	I-IV
Yamamoto et al[16]	United States	Yes	Yes	47	0	125[b]	172	I-IV
Zhang et al[6]	China	Unknown	Yes	20	Unknown	20[b]	40	IV
Zhou et al[13]	China	Yes	Yes	48	166	132[a]	346	I-IV
Total				456	1006	748	2210	

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; NSCLC = non–small-cell lung cancer.
[a]Wild type.
[b]ALK⁻.
[c]ALK and EGFR.
[d]KRAS.

results; (2) ALK rearrangements were identified using fluorescence in situ hybridization (FISH) analysis, immunohistochemistry (IHC), or reverse transcription polymerase chain reaction; and (3) computed tomography (CT) features of ALK-rearranged tumors were studied and compared with those without ALK rearrangements. A publication was excluded if: (1) it had insufficient data; (2) it included subjects that overlapped with those from a previously published study from the same authors or institution; (3) it was an abstract, case report, comment, narrative review, or editorial; or (4) the full-text article was not available.

After the database search, 2 investigators (D.P.M. and J.S.) independently performed title and abstract screen and subsequent full article review of the records resulting from the database search. Discrepancies were resolved by full article review and consensus between the 2 investigators. Finally, 12 articles were included in the qualitative and quantitative analysis (Figure 1).[5-16]

Data Extraction

The following information was extracted from the included articles: first author's last name, year of publication, country of origin, and the number and clinicopathological characteristics of included patients. The primary tumor imaging features extracted from the studies included: size, location (central vs. peripheral), density (solid vs. subsolid), and the presence or absence of spiculation, lobulation, calcification, air bronchograms, cavitation or "bubble-like lucencies" (BLL). Of note, 3 studies[5,8,10] reported "bubble lucency" or BLL instead of cavitation and another[13] reported cavitation and BLL together. On the basis of the definitions and examples the investigators provided, we included BLL with cavitation for the purpose of our analysis.

The presence or absence of pleural effusions, lymphangitic carcinomatosis, lymphadenopathy, and distant metastases were also recorded for those with advanced disease (stages III and IV). Data were extracted from each article independently by 2 investigators (D.P.M. and J.S.). For 1 study, which provided 2 readers' separate image interpretations, we extracted data provided by reader 1.[15] Any discrepancies between the independent extractions of data were resolved by consensus after concurrent review of the original articles.

Statistical Analysis

All statistical analyses were performed using the Review Manager 5 software (The Cochrane Collaboration).[19] Clinicopathologic characteristics and imaging findings in ALK-rearranged NSCLC were compared with those without ALK rearrangements (ie, ALK-negative) and were tested in the form of an odds ratio (OR) or weighted mean difference at a 95% confidence interval (CI) using forest plots. All statistical tests were 2-sided, and the significance level was set at .05. Subanalyses were performed to compare ALK-rearranged NSCLC with those with epidermal growth factor receptor (EGFR) mutations (ie, EGFR-mutant NSCLC) and with those without known ALK rearrangement or EGFR mutation (ie, ALK/EGFR-negative NSCLC).

Heterogeneity was evaluated using the inconsistency index (I^2) with values >50% indicating significant heterogeneity. A random effects model was adopted if I^2 was 50% or greater and a fixed effect model was used if I^2 was ≤50%.

Pooled analysis of continuous data (ie, patient age and tumor size) was performed using the means and SDs reported. When medians and ranges were reported by a study, means and SDs were estimated using methods described by Hozo and colleagues.[20]

Results

Eligible Studies

A total of 12 studies were included in this study and are summarized in Table 1.[5-16] Most of the studies (9/12) were from Asia, 2 were from the United States, and 1 was from Italy. Seven studies

Table 2 Comparison of Patient Clinical Characteristics Among the Different Molecular Subsets

Patient Characteristic	ALK^+ vs. All ALK^-			ALK^+ vs. $EGFR^+$			ALK^+ vs. $ALK/EGFR^-$		
	Studies (Patients) Included	OR (95% CI)[a]	*P*	Studies (Patients) Included	OR (95% CI)[a]	*P*	Studies (Patients) Included	OR (95% CI)[a]	*P*
Age[b]	12 (2204)	−8.59 (−10.51 to −6.68)	**<.001**	9 (1771)	−8.41 (−10.86 to −5.97)	**<.001**	8 (1032)	−8.16 (−10.70 to −5.61)	**<.001**
Sex (Female vs. Male)	12 (2204)	0.88 (0.71-1.09)	.19	9 (1354)	0.58 (0.45-0.75)	**<.001**	8 (1025)	1.85 (1.12-3.05)	**.02**
Smoking Status (Never vs. Ever Smoker)	10 (1882)	0.71 (0.42-1.20)	.2	8 (1144)	1.31 (0.92-1.86)	.13	6 (869)	0.44 (0.32-0.61)	**<.001**

Statistically significant *P* values are shown in bold.
Abbreviations: ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor; NSCLC = non–small-cell lung cancer; OR = odds ratio.
[a]Odds ratio >1 favors increased prevalence in ALK-rearranged NSCLC.
[b]Means and variances were estimated from reported medians and ranges using methods described by Hozo et al.[20] Comparisons are reported as weighted mean differences or odds ratios.

explicitly stated that the readers were blinded to the mutation status, and 11 studies explicitly stated that the CT scans evaluated were before treatment.

Patient Characteristics

The 12 included studies investigated a total of 2210 patients with NSCLC. Of these, 456 had tumors harboring an ALK rearrangement (ALK-rearranged). The most common ALK-negative group consisted of patients with EGFR-mutant NSCLC (n = 1006). Other ALK-negative patients included those with Kirsten rat sarcoma viral oncogene homolog mutations (n = 119), those who were negative for ALK and/or EGFR mutations (n = 623), or those positive for ALK and EGFR mutations (n = 6). These 6 patients were excluded from the meta-analysis.

Comparisons of clinical characteristics among molecular subsets are summarized in Table 2.[20] The ALK-rearranged group was on average more than 8 years younger than the ALK-negative, the EGFR-mutant, and the ALK/EGFR-negative groups. Of the 2204 included patients, 1246 (56.5%) were women, 948 (43%) were men, and 10 (0.5%) were unknown. Those with ALK-rearranged NSCLC were less likely to be female compared with those with EGFR-mutant NSCLC (OR, 0.58; 95% CI, 0.45-0.75; $P < .001$), but more likely to be female compared with those with ALK/EGFR-negative NSCLC (OR, 1.85; 95% CI, 1.12-3.05; $P = .02$).

Ten of the 12 studies reported smoking status. Of the patients included in these studies (n = 1882), 716 (38%) were smokers and 1166 (62%) were nonsmokers. Those with ALK-rearranged NSCLC were more likely to be nonsmokers compared with the ALK/EGFR-negative group (OR, 0.44; 95% CI, 0.32-0.61; $P < .001$). There was no significant difference in smoking status between the ALK-rearranged and EGFR-mutant groups.

Imaging Characteristics

Primary Tumor Features. Comparisons of imaging features of the primary tumors among the molecular subsets are summarized in Table 3.[5,8,10,12,13,20] ALK-rearranged tumors were more likely to be solid (OR, 2.37; 95% CI, 1.64-3.43; $P < .001$) and less likely to have cavitation or BLL (OR, 0.45; 95% CI, 0.26-0.75; $P = .002$) compared with ALK-negative tumors (Figures 2 and 3). Patients with ALK-rearranged tumors were also less likely to have air bronchograms compared with those with EGFR-mutant tumors (OR, 0.57; 95% CI, 0.41-0.81; $P = .002$; Figure 2). There was no statistically significant difference among the groups with regard to size and presence or absence of spiculation, lobulation, calcification, or necrosis.

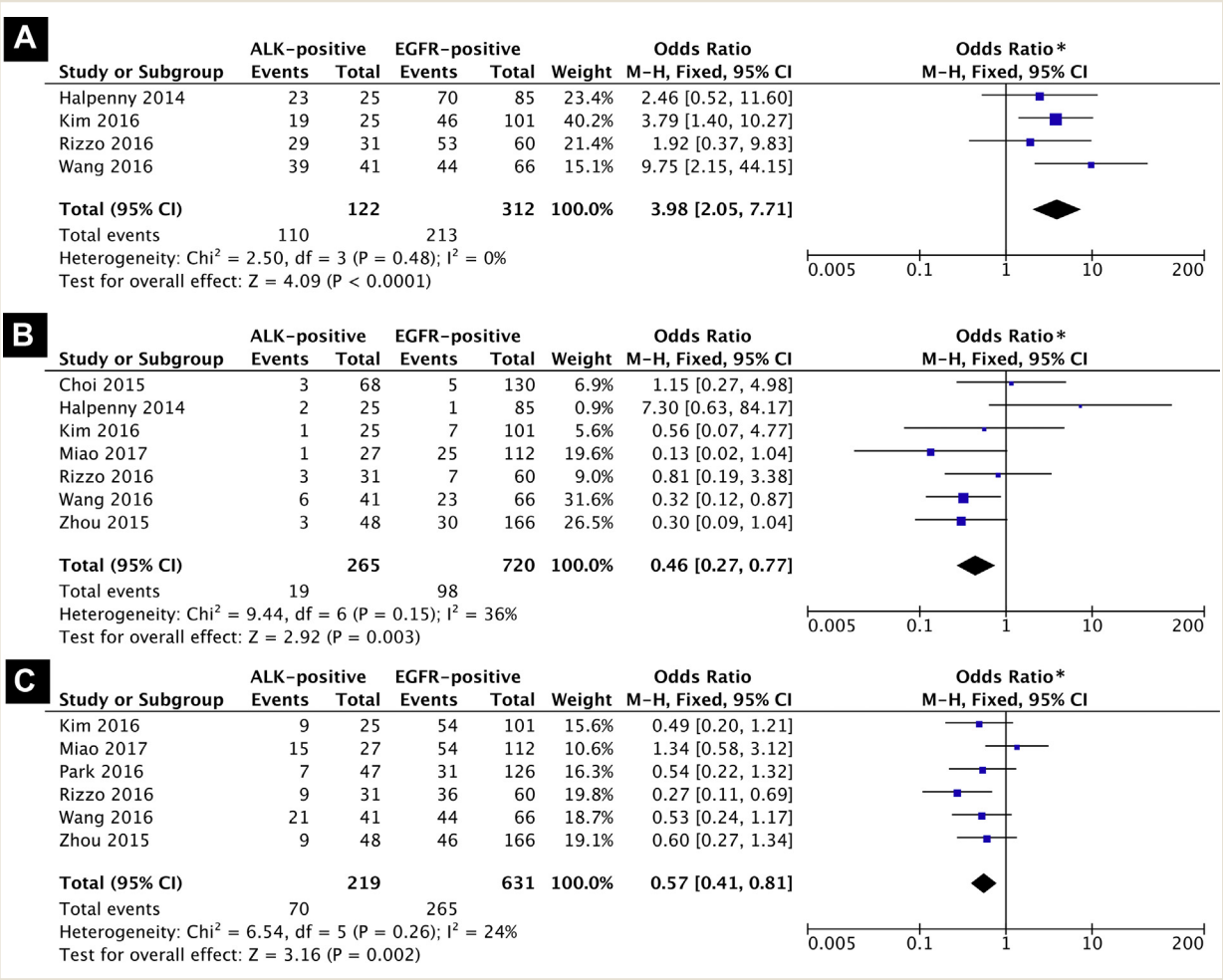
Pattern of Metastasis and Other Ancillary Findings. Table 4 shows a summary of the prevalence of metastases according to site and comparison among the molecular groups in the setting of advanced NSCLC. Compared with patients with advanced EGFR-mutant NSCLC, those with advanced ALK-rearranged NSCLC were more likely to have lymphadenopathy (OR, 3.47; 95% CI, 2.06-5.85; $P < .001$), lymphangitic carcinomatosis (OR, 3.41; 95% CI, 1.25-9.34; $P = .01$), and metastases to the pericardium (OR, 2.18; 95% CI, 1.05-4.56; $P = .04$), and pleura (OR, 2.07; 95% CI,

Table 3 Comparison of Primary Tumor Features Among the Different Molecular Subsets

Tumor Feature/Ancillary Finding	ALK$^+$ vs. All ALK$^-$			ALK$^+$ vs. EGFR$^+$			ALK$^+$ vs. ALK$^-$ and EGFR$^-$/Unknown		
	Studies (Patients) Included	OR (95% CI)[a]	*P*	Studies (Patients) Included	OR (95% CI)[a]	*P*	Studies (Patients) Included	OR (95% CI)[a]	*P*
Mean Diameter, cm[b]	8 (1501)	−1.47 (−4.49 to 2.0)	.41	6 (878)	0.88 (−3.32 to 4.89)	.67	5 (633)	2.70 (−6.03 to 0.94)	.15
Central (vs. Peripheral)[c]	5 (667)	1.64 (0.94-2.89)	.08	2 (198)	1.39 (0.50-3.84)	.53	4 (500)	1.56 (0.79-3.07)	.20
Solid (vs. Subsolid or Other)	8 (1265)	2.37 (1.64-3.43)	**<.001**	4 (434)	3.98 (2.05-7.71)	**<.001**	4 (453)	2.28 (1.18-4.41)	**.01**
Spiculation (Present vs. Absent)	8 (1571)	0.70 (0.39-1.25)	.23	6 (846)	0.83 (0.34-2.00)	.68	4 (593)	0.75 (0.27-2.05)	.58
Lobulation (Present vs. Absent)	7 (1352)	1.42 (0.64-3.14)	.38	6 (846)	1.13 (0.38-3.41)	.83	4 (593)	1.25 (0.40-3.86)	.7
Calcification (Present vs. Absent)	4 (570)	1.21 (0.57-2.54)	.62	4 (434)	1.15 (0.53-2.49)	.72	2 (192)	1.16 (0.35-3.91)	.81
Air Bronchograms (Present vs. Absent)	7 (1389)	0.67 (0.49-0.91)	**.01**	6 (850)	0.57 (0.41-0.81)	**.002**	4 (514)	1.13 (0.70-1.82)	.61
Cavitation or BLL (Present vs. Absent)[d]	7 (1253)	0.45 (0.26-0.75)	**.002**	7 (985)	0.46 (0.27-0.77)	**.003**	3 (372)	0.42 (0.18-0.97)	**.04**
Necrosis (Present vs. Absent)	4 (806)	1.16 (0.70-1.93)	.56	4 (610)	1.31 (0.77-2.22)	.32	2 (275)	0.69 (0.30-1.61)	.4

Statistically significant *P* values are shown in bold.
Abbreviations: ALK = anaplastic lymphoma kinase; BLL = bubble-like lucencies; CI = confidence interval; EGFR = epidermal growth factor; NSCLC = non–small-cell lung cancer; OR = odds ratio.
[a]Odds ratio >1 favors increased prevalence in ALK-rearranged NSCLC.
[b]Means and variances were estimated from reported medians and ranges using methods described by Hozo et al.[20] Comparisons are reported as weighted mean differences instead or odds ratios.
[c]Jeong et al reported tumor location as peribronchovascular, subpleural, or both.[12] We considered peribronchovascular as central and subpleural as peripheral and excluded "both" in our analysis.
[d]Kim et al,[10] Miao et al,[5] and Wang et al[8] reported "bubble lucency" or "bubble-like lucencies" instead of cavitation. Zhou et al[13] reported cavitation and BLL together. For the purpose of our analysis, BLLs were considered as cavitations.

Figure 2 Primary Tumor Characteristics of Anaplastic Lymphoma Kinase (ALK)-Rearranged Non–Small-Cell Lung Cancer (NSCLC) Compared With Epidermal Growth Factor Receptor (EGFR)-Mutant NSCLC. Forest Plots Show a Comparison of ALK-Rearranged NSCLC With EGFR-Mutant NSCLC With Respect to: (A) Solid Density; (B) Presence of Cavitation; and (C) Presence of Air Bronchograms. * Odds Ratio >1 Favors Increased Incidence of the Imaging Feature in ALK-Rearranged NSCLC



1.26-3.40; $P = .004$), but less likely to have lung metastases (OR, 0.52; 95% CI, 0.11-1.11; $P < .001$; Figure 4).

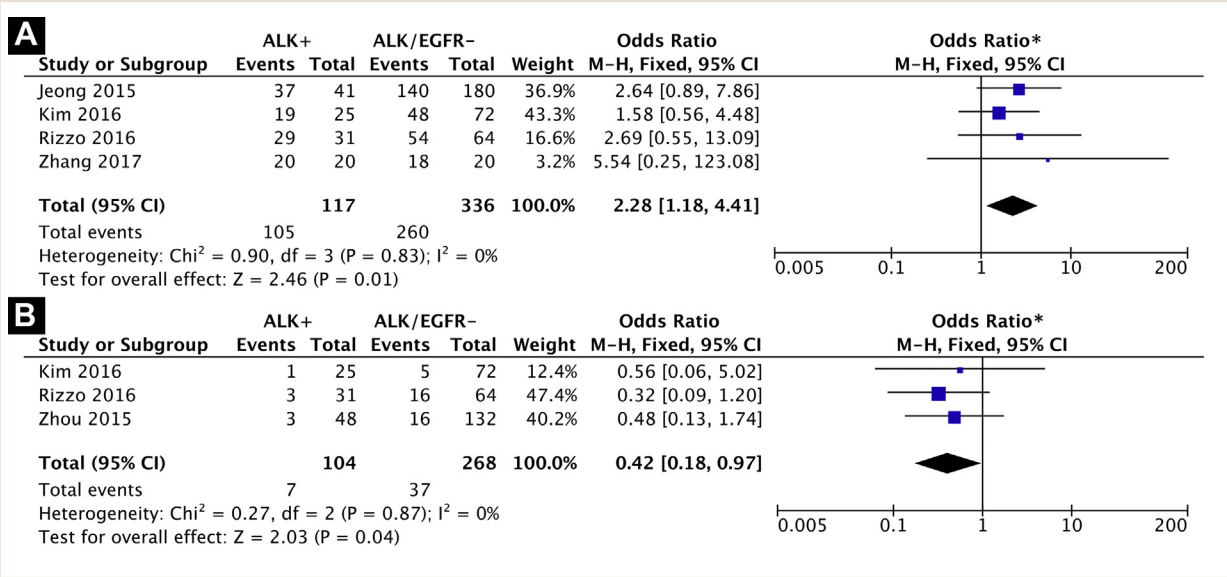
Compared with patients with advanced ALK/EGFR-negative NSCLC, those with advanced ALK-rearranged NSCLC were also more likely to have lymphangitic carcinomatosis (OR, 3.88; 95% CI, 1.11-13.57; $P = .03$), pleural metastasis (OR, 1.89; 95% CI, 1.09-3.27; $P = .02$), and pleural effusion (OR, 2.94; 95% CI, 1.45-5.98; $P = .003$; Figure 5).

Discussion

In this meta-analysis we integrated all available published data regarding the imaging features of ALK-rearranged NSCLC compared with ALK-negative NSCLC. The findings suggest that ALK-rearranged NSCLC has distinct clinicopathologic and radiologic characteristics compared with EGFR-mutant NSCLC and ALK/EGFR-negative NSCLC. Compared with all ALK-negative NSCLC, tumors with ALK rearrangements have a higher tendency to affect younger patients, who might have little or no significant history of smoking. On imaging, ALK-rearranged NSCLC tends to be solid and less likely to have cavitation compared with ALK-negative NSCLC. Advanced stage ALK-rearranged NSCLCs are more likely to be associated with lymphadenopathy, lymphangitic carcinomatosis, and pleural effusions, and are more likely to metastasize to the pleura and pericardium.

Our findings are consistent with reports that ALK-rearranged NSCLC is more common in younger patients with minimal or no history of smoking.[21-24] In our meta-analysis, those with ALK-rearranged NSCLC were on average approximately 8 years younger than those with EGFR-mutant NSCLC and those with ALK/EGFR-negative NSCLC. A large proportion of the ALK-rearranged patients were nonsmokers, at a frequency more than that of ALK/EGFR-negative NSCLC. Not surprisingly, smoking status was not significantly different compared with those with EGFR mutations, which are also common among nonsmokers and light smokers.[25,26]

Figure 3 Primary Tumor Characteristics of Anaplastic Lymphoma Kinase (ALK)-Rearranged Non–Small-Cell Lung Cancer (NSCLC) Compared With ALK/Epidermal Growth Factor Receptor (EGFR)-Negative NSCLC. Forest Plots Show a Comparison of ALK-Rearranged NSCLC With ALK/EGFR-Negative NSCLC With Respect to: (A) Solid Density; and (B) Presence of Cavitation. * Odds Ratio >1 Favors Increased Incidence of the Imaging Feature in ALK-Rearranged NSCLC



Anaplastic lymphoma kinase-rearranged NSCLCs most commonly present as solid tumors and has almost a fourfold and more than twofold higher odds of being solid compared with EGFR-mutant and ALK/EGFR-negative tumors, respectively. However, ALK-rearranged tumors had approximately a 50% lower odds of having air bronchograms compared with EGFR-mutant NSCLC and 50% lower odds of having cavitation compared with EGFR-mutant and ALK/EGFR-negative tumors. These findings may, at least in part, be because EGFR-mutant tumors have been associated with greater propensity for ground glass components and air bronchograms.[27,28] The underlying mechanisms leading to these differences, however, are unclear. Notably, there was no significant difference between the groups with regard to size of the primary tumor and presence or absence of spiculation, lobulation, calcification, and necrosis.

Our meta-analysis showed that ALK-rearranged NSCLC might have a predilection for lymphatic spread. Lymphatic involvement in ALK-rearranged NSCLC is reported by investigators as lymphadenopathy and/or lymphangitic carcinomatosis.[8,9,11,15] Several authors noted that this extensive lymph node involvement in ALK-rearranged NSCLC has often been misinterpreted initially as representing lymphoma or small-cell lung cancer on CT images.[11,15] Of note, Miao and colleagues reported a greater tendency for the presence of lymphadenopathy and less tendency for the presence of lymphangitic carcinomatosis in ALK-rearranged NSCLC, although neither observation reached statistical significance.[5] This discrepancy might be related to the study's relatively smaller sample size compared with the other studies.

Pleural disease was reported in 8 studies of ALK-rearranged NSCLC, most commonly reported as pleural effusion[5,7,9,15,16] or pleural metastases.[5,6,8,11,15] Although some investigators reported adjacent pleural thickening, retraction, or attachment, these rates failed to reach statistical significance.[5,7,8,13] It is important to note that the investigators who reported pleural effusion and pleural thickening, retraction, or attachment did not specify if these findings represented pathologically proven pleural involvement by the tumor (ie, malignant effusion and direct tumor extension). Overall, there appears to be increased propensity for pleural metastases in ALK-rearranged NSCLC.

Two studies reported the presence or absence of pericardial metastasis.[5,11] Although the presence of pericardial metastasis remains rare in both groups, with pooled incidences of 15.8% in ALK-rearranged NSCLC and 8.3% in ALK-negative NSCLC, our analysis shows that there is a twofold higher odds of pericardial metastasis in ALK-rearranged NSCLC over ALK-negative NSCLC. As such, the presence of a pericardial effusion in a patient with known ALK-rearranged NSCLC should increase the suspicion for the presence of pericardial metastasis.

Although patients with ALK-rearranged NSCLC had higher odds of having lymphatic, pleural, and pericardial metastases, they had almost 50% lower odds of having lung metastases compared with those with EGFR-mutant NSCLC.[5,6,9,11] EGFR-mutant NSCLC, however, has previously been associated with diffuse "miliary" lung metastases.[29,30] Other metastatic sites reported include the brain,[5,6] liver,[5,6] and adrenal glands,[6] but the pooled number of patients and incidences of the metastases were too small to draw any meaningful conclusions. It is important to note, however, that several studies have reported higher incidences of brain metastases in patients with ALK-rearranged NSCLC, with incidences of 45% to 70% in those who have previously received ALK-targeted TKIs.[31-33] The mechanism for differences in metastatic tropism between ALK-rearranged and ALK-negative groups is unclear, but distinctive patterns of

Table 4 Comparison of Metastatic Sites and Other Ancillary Findings Among the Different Molecular Subsets in Advanced Stage (III or IV) NSCLC

Metastatic Site/Other Findings	ALK^+ vs. All ALK^-			ALK^+ vs. $EGFR^+$			ALK^+ vs. ALK^- and $EGFR^-$/Unknown		
	Studies (Patients) Included	Odds Ratio[a]	*P*	Studies (Patients) Included	Odds Ratio[a]	*P*	Studies (Patients) Included	Odds Ratio[a]	*P*
Bone	3 (377)	0.50 (0.18-1.41)	.19	2 (337)	0.35 (0.11-1.11)	.08	1 (40)	1.22 (0.35-4.24)	.75
Lung	4 (642)	0.60 (0.41-0.88)	**.01**	3 (510)	0.52 (0.34-0.80)	**.003**	2 (122)	1.03 (0.48-2.18)	.95
Lymph Nodes	3 (545)	1.30 (1.96-5.55)	**<.001**	3 (510)	3.47 (2.06-5.85)	**<.001**	1 (82)	1.71 (0.52-5.62)	.38
Pericardium	2 (337)	2.18 (1.05-4.56)	**.04**	2 (337)	2.18 (1.05-4.56)	**.04**	0 (0)	NA	NA
Pleura	3 (377)	1.92 (1.21-3.05)	**.005**	2 (337)	2.07 (1.26-3.40)	**.004**	2 (238)	1.89 (1.09-3.27)	**.02**
Pleural Effusion	3 (503)	1.44 (0.92-2.27)	.11	3 (403)	1.27 (0.86-6.56)	.31	2 (177)	2.94 (1.45-5.98)	**.003**
Lymphangitic Carcinomatosis	5 (689)	3.58 (1.61-7.98)	**.001**	4 (614)	3.41 (1.25-9.34)	**.02**	2 (122)	3.88 (1.11-13.57)	**.03**

Statistically significant *P* values are shown in bold.
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor; NSCLC = non–small-cell lung cancer.
[a]Odds ratio >1 favors increased prevalence in ALK-rearranged NSCLC.

spread have also been reported in other mutation-positive subsets.[34,35] These differences in patterns might have larger prognostic implications because metastasis is the primary determinant of mortality in NSCLC.

These distinct imaging features and metastatic tropisms also have the potential to help guide the management of NSCLC. Although the presence or absence of these features in a patient cannot replace molecular testing, it might help guide in determining which patients might benefit from expedited screening and those who might benefit from repeat alternative testing after an unexpectedly negative or discordant results from assays.

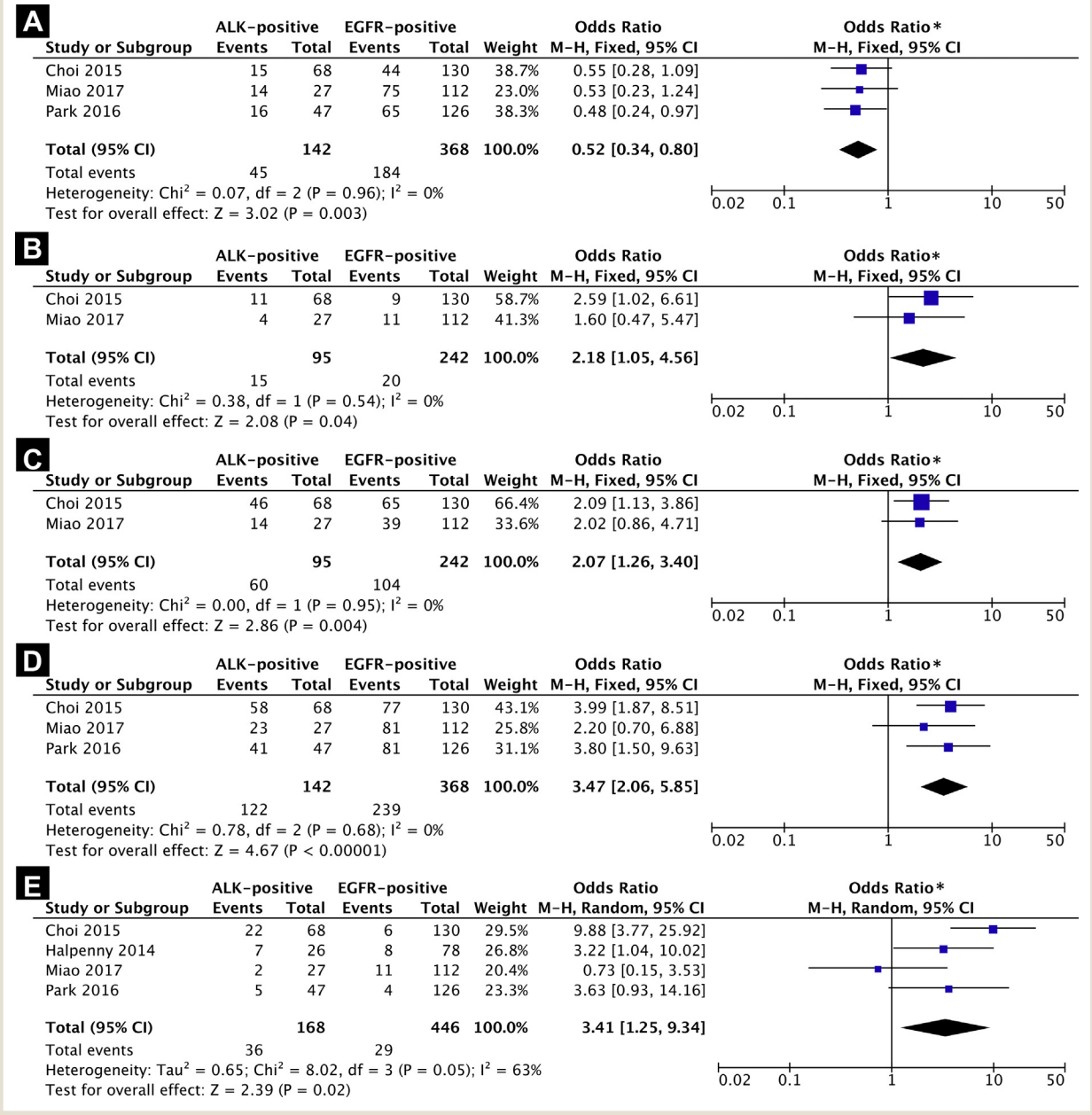
Fluorescence in situ hybridization remains the gold standard assay for the diagnosis of ALK rearrangements.[36,37] FISH, however, is costly, time- and labor-intensive, and its interpretation can be challenging, which requires specialized training and technical expertise. Other assays alternative to FISH have emerged, including IHC and next-generation sequencing (NGS). IHC is more accessible, is less operator-dependent, and has shorter turnaround times, with sensitivity and specificity exceeding 90% with FISH as the reference standard.[38,39] Although NGS requires more tissue and more time for analysis, it has the advantage of simultaneous evaluation for multiple alterations.[40,41] Although all 3 assays are highly accurate in the detection of ALK rearrangements, they require adequate tissue sampling and processing, which take time and might delay treatment.[42,43] More rapid pathways have been proposed to reduce time to diagnosis and facilitate earlier initiation of directed therapies.[44-46] Patients with clinical and imaging features suggestive of the presence of ALK rearrangements might benefit from expedited testing pathways. In addition, although FISH remains the gold standard assay for the detection of ALK rearrangements, several researchers have reported patients with NSCLC who were ALK-negative on FISH analysis, but positive on either IHC or NGS, and who had dramatic response to treatment with crizotinib.[47-51] The presence of compelling clinical and imaging features might help clinicians in selecting patients who might benefit from repeat or alternative testing.

Limitations of this meta-analysis include the retrospective nature of all of the included studies. Although the comparison group consisted of patients with different underlying oncogenic mutations or without known mutation, a large proportion had EGFR mutations, which limits the generalizability of the findings. However, because ALK and EGFR mutations are common in younger patients with minimal or no history of smoking, differentiating between the 2 groups might, in fact, be more clinically relevant.

Conclusion

The findings of this meta-analysis suggest that patients with ALK-rearranged NSCLC have imaging features that are different compared with those with EGFR-mutant NSCLC and ALK/EGFR-negative NSCLC. ALK-rearranged NSCLCs are more likely to be solid and less likely to have air bronchograms or cavitation. In advanced cases, ALK-rearranged NSCLCs are also more likely to be associated with lymphadenopathy, lymphangitic carcinomatosis, pleural effusions, and pleural and pericardial metastases. These distinct radiologic patterns might suggest differences in pathogenesis related to ALK rearrangements and might provide clues as to the presence of these genetic alterations. Although these features are not a substitute for

Figure 4 Patterns of Metastasis in Anaplastic Lymphoma Kinase (ALK)-Rearranged Non–Small-Cell Lung Cancer (NSCLC) Compared With Epidermal Growth Factor Receptor (EGFR)-Mutant NSCLC. Forest Plots Show a Comparison of Advanced ALK-Rearranged NSCLC With Advanced EGFR-Mutant NSCLC With Respect to: (A) Lung Metastases; (B) Pericardial Metastases; (C) Pleural Metastases; (D) Lymphadenopathy; and (E) Lymphangitic Carcinomatosis. *Odds Ratio >1 Favors Increased Incidence of the Imaging Feature in ALK-rearranged NSCLC

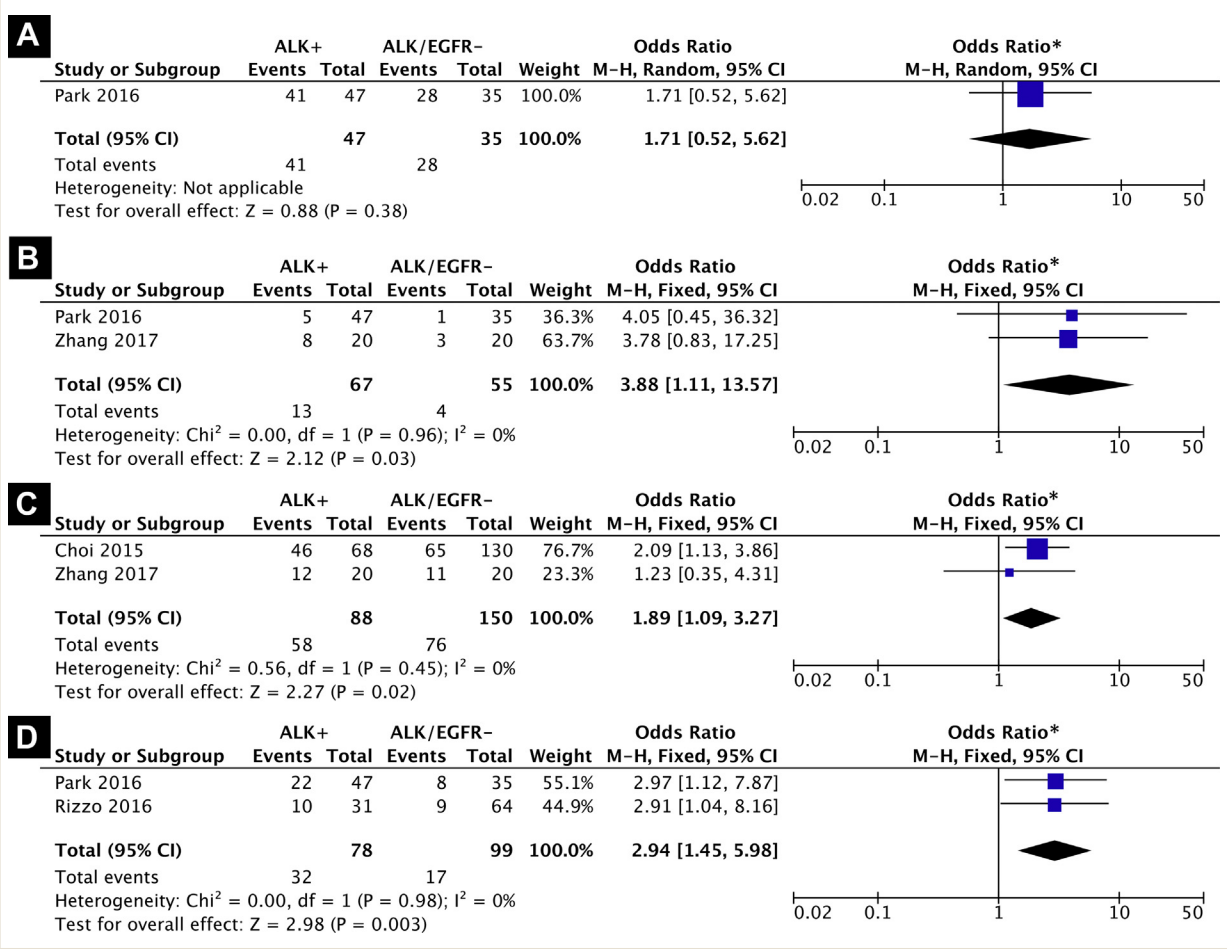


genetic testing, they might help in the selection of patients who might benefit from expedited molecular testing or repeat testing after an unexpected negative assay result.

Clinical Practice Points

- Anaplastic lymphoma kinase rearrangements are a known targetable mutation in the treatment of NSCLCs.
- Several TKIs have been developed to treat patient with NSCLC who harbor these rearrangements.
- These TKIs have improved survival of this molecular subset of patients.
- Several studies have investigated the imaging features of these tumors, but most of these studies had small cohorts because of the relative rarity of the mutation.

Figure 5 Patterns of Metastasis in Anaplastic Lymphoma Kinase (ALK)-Rearranged Non–Small-Cell Lung Cancer (NSCLC) Compared With ALK/Epidermal Growth Factor Receptor (EGFR)-Negative NSCLC. Forest Plots Show a Comparison of Advanced ALK-Rearranged NSCLC With Advanced EGFR-Mutant NSCLC With Respect to: (A) Lymphadenopathy; (B) Lymphangitic Carcinomatosis; (C) Pleural Metastases; and (D) Pleural Effusion. * Odds Ratio >1 Favors Increased Incidence of the Imaging Feature in ALK-Rearranged NSCLC



- In our meta-analysis we combined all available data and showed that NSCLCs harboring these mutations have distinct features that might help distinguish it from those without the mutation.
- Compared with NSCLC without ALK rearrangements, these tumors are more likely to be associated with extensive lymphadenopathy, lymphangitic carcinomatosis, and pleural effusions, and more likely to metastasize to the pleura and pericardium.
- Although these features are not a substitute for genetic testing, they might help guide in the selection of patients who might benefit from expedited molecular testing or repeat testing after an unexpected negative assay result.

Disclosure

Alice T. Shaw is a compensated consultant or received honoraria from: ARIAD, Bayer, Blueprint Medicines, Chugai, Daiichi Sankyo, EMD Serono, Foundation Medicine, Genentech/Roche, Guardant, Ignyta, KSQ Therapeutics, Natera, Novartis, Pfizer, Taiho Pharmaceutical, Takeda, and TP Therapeutics; and has received research funding (institutional) from: Daiichi Sankyo, Ignyta, Novartis, Pfizer, Roche/Genentech, and TP Therapeutics. The remaining authors have stated that they have no conflicts of interest.

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