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Imaging Features and Metastatic Patterns of Advanced *ALK*-Rearranged Non-Small Cell Lung Cancer

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Abstract

Objective: *ALK* rearrangements are an established targetable oncogenic driver in non-small cell lung cancer (NSCLC). This study's goal was to determine the imaging features of the primary tumor and metastatic patterns in advanced *ALK*-rearranged (*ALK*+) NSCLC that may be different from those in *EGFR*-mutant (*EGFR*+) or *EGFR/ALK*-wild-type (*EGFR-/ALK*-) NSCLC.

Methods: Patients with advanced *ALK*+, *EGFR*+, or *EGFR-/ALK*- NSCLC were retrospectively identified. Two radiologists concurrently assessed the imaging features of the primary tumor and the distribution metastases in these patients.

Results: We identified a cohort of 333 patients with metastatic NSCLC (119 *ALK+*, 116 *EGFR+*, and 98 *EGFR-/ALK*-). Compared to *EGFR*+ and *EGFR-/ALK*- NSCLC, the primary tumor in *ALK*+ NSCLC was more likely to be in the lower lobes (*ALK+*=53%, *EGFR+*=34%,

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EGFR-/ALK-=36%; p<0.05), less likely to be subsolid (*ALK*+=1%, *EGFR+*=11%, *EGFR-/ALK-*=8%; p<0.02), and less likely to have air-bronchograms (*ALK+*=7%, *EGFR+*=28%, *EGFR-/ALK-*=29%; p<0.01). *ALK*+ tumors had higher frequencies of distant nodal metastasis (*ALK+*=20%, *EGFR+*=2%, *EGFR-/ALK-*=9%; p<0.05) and lymphangitic carcinomatosis (*ALK+*=37%, *EGFR+*=12%, *EGFR-/ALK-*=12%; p<0.01) compared to *EGFR*+ and *EGFR-/ALK*- tumors, but lower frequency of brain metastasis compared to *EGFR*+ tumors (*ALK*+=24%, *EGRF*+=41%, p=0.01). Although there was no statistically significant difference in the frequencies of bone metastasis among the three groups, sclerotic bone metastases were more common in the *ALK*+ tumors (*ALK+*=22%, *EGFR+*=7%, *EGFR-/ALK-*=6%; p<0.01).

Conclusion: Advanced *ALK*-positive NSCLC is associated with primary tumor imaging features and patterns of metastasis that are different from those of *EGFR*-mutant or *EGFR*-/*ALK*-wild type NSCLC at the time of initial presentation.

INTRODUCTION

The diagnosis and treatment of advanced non-small cell lung cancer (NSCLC) continue to evolve with advances in molecular testing and targeted therapy. Since the discovery of activating mutations in the epidermal growth factor receptor gene (*EGFR*), which confer sensitivity to EGFR tyrosine kinase inhibitors (TKIs), numerous additional oncogenic driver targets have been identified in NSCLC [1–3]. Occurring in approximately 5% of NSCLC, anaplastic lymphoma kinase (ALK) rearrangements are one of the most common targetable mutations in NSCLC, second only to EGFR mutations [4–6]. Similar to *EGFR* mutations, *ALK* rearrangements are more common in younger patients with minimal or no smoking history and adenocarcinoma histology [7–9]. *ALK* TKIs are highly effective in treating *ALK*-rearranged (*ALK*+) NSCLC, and five distinct *ALK* TKIs have received approval by the United States (US) Food and Drug Administration with alectinib being the current standard initial therapy in advanced *ALK*+ NSCLC [10–17].

On the basis of the robust efficacy of available targeted therapies, the US and European guidelines recommend routine molecular testing for targetable oncogenic alterations including *ALK* rearrangements at the initial diagnosis of advanced NSCLC [18, 19]. Despite these recommendations, the real-world adoption of molecular testing guidelines and the testing performance have remained suboptimal. For example, in one retrospective study, the *ALK* testing rate among advanced nonsquamous NSCLC patients at community practices in the US reached only 66.9% (14,478 of 21,639). Among those patients who did undergo *ALK* testing, 21.5% (3,290 of 15,320) initiated systemic therapy prior to receiving their *ALK* testing results [20]. Given the established efficacy of *ALK* TKIs in *ALK*+ NSCLC and their impact on patient outcomes, improving the rates of implementation and successful completion of molecular testing and the timely initiation of matched targeted therapy is essential.

Several studies have reported imaging features that can potentially predict the presence of EGFR mutations [21–23]. Whether there are distinct radiologic features associated with *ALK*+ NSCLC that may help distinguish this subset *a priori*—potentially helping select patients in whom molecular testing should be prioritized or repeated if initial testing is

unsuccessful or inconclusive—remains unknown. Published reports thus far have suggested that *ALK*+ NSCLC may be associated with solid density of the primary tumor, the presence of lymphangitic carcinomatosis, lymphadenopathy, and increased propensity for metastasis to the pleura and pericardium, but these studies were limited by small cohorts of *ALK*+ patients [24–30]. Here, we evaluated the pre-treatment imaging of 119 patients with advanced *ALK*+ NSCLC in order to determine and compare the radiologic features to those of *EGFR*-mutant (*EGFR*+) and *EGFR/ALK*-wild-type (*EGFR-/ALK*-) NSCLC.

SUBJECTS AND METHODS

Patients

This study was performed under an institutional review board-approved protocol. From a prospectively maintained database of patient with *ALK*+ NSCLC, we assessed all patients who presented with *ALK*+ NSCLC to the thoracic oncology clinic of Massachusetts General Hospital (MGH) between January 2013 and December 2018 for eligibility. We included all patients with a) metastatic NSCLC at presentation; b) known *ALK* rearrangement as determined per local testing using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and/or next-generation sequencing (NGS); and c) with pre-treatment imaging available for review. As control groups, we selected a subset of 150 consecutive patients with known metastatic *EGFR*+ NSCLC and another subset of 150 consecutive patients who were negative for both *ALK* and *EGFR* mutations from separate internal databases. We excluded patients 1) without metastatic disease at initial presentation; and 2) those who had any local or systemic therapy prior to the earliest imaging study available. Patient inclusion and exclusion process is summarized in Figure 1. Electronic medical records were retrospectively reviewed to extract clinical and pathologic data, including age, sex, race, smoking history, tumor histology, and disease stage at initial based on 7th edition of the American Joint Committee on Cancer TNM Classification of Malignant Tumors.

Imaging review and analysis

Initial imaging studies performed prior to the initiation of cancer treatment were selected for analyses for each patient. Imaging studies reviewed for each patient included CT of the chest, abdomen, and pelvis with or without concurrent fluorodeoxyglucose (FDG)-positron emission tomography (PET) images, and CT and/or MRI of the brain. All imaging was performed at our institution or at another facility with images uploaded into our picture archiving and communications system (PACS; AGFA Impax 6, Mortsel, Belgium). A board-certified radiologist specializing in lung cancer imaging (SRD) and a cardiothoracic imaging fellow (DPM) retrospectively reviewed all imaging concurrently. Findings were determined and recorded by consensus.

The primary tumor, when identifiable, was evaluated for the following features: size, location, solid versus subsolid density, and the presence of other features including air bronchograms, cavities, calcifications, or lymphangitic carcinomatosis. Malignant lymph nodes were confirmed to be malignant with at least one of the following: positive histology, increased uptake on FDG-PET imaging, or malignant behavior based on follow

up imaging and were recorded as ipsilateral or contralateral, and as hilar, mediastinal, supraclavicular, or distant (e.g. cervical, axillary, intra-abdominal). All indeterminate lymph nodes were presumed to be benign. Sites examined for metastases included the lungs, pleura, pericardium, liver, adrenals, other visceral organs (e.g. spleen, kidney, etc.), bones, subcutaneous soft tissues, and brain. Brain metastases were identified using CT or magnetic resonance imaging (MRI) of the brain. Other sites of metastases were identified using CT with or without concurrent FDG-PET images. Bone metastases, when present, were further classified as either predominantly lytic versus predominantly blastic or sclerotic. The assessment of bone metastasis was done at a site without fracture.

Statistical analysis

Patient characteristics and imaging features were summarized descriptively. Continuous data were described as median with range, and categorical data were described as frequencies with percentages. The Wilcoxon rank-sum test and Fisher's exact test were performed to compare continuous and categorical features, respectively. All tests were two-sided. P-values less than 0.05 were considered significant. In order to determine the radiologic predictors of *ALK* rearrangements as compared to *EGFR* mutations or lack of *EGFR*/*ALK* alterations, multivariable logistic regression models were built with oncogenic driver types as the outcome. The criteria for choosing candidate predictors were p-value <0.05 based on univariate analyses.

RESULTS

Patient characteristics

A total of 333 patients were included in this study (*ALK*+: 119, *EGFR*+: 116, *EGFR-/ALK-*: 98). Table 1 summarizes patient characteristics for all three cohorts. Patients with *ALK*+ NSCLC were younger at initial diagnosis than patients with *EGFR*+ or *EGFR-/ALK-* NSCLC. In this study, *ALK*+ patients were more likely to be female (56% vs 41%, p=0.03) and more likely to be non-smokers (72% vs 16%, p<0.01) compared to *EGFR-/ALK-* patients.

Primary tumor features

Table 2 summarizes comparison among the three genotype groups with respect to the CT imaging features of the primary tumor. There was no significant difference in the size of the primary tumor (median largest dimension: *ALK+:* 45 mm, *EGFR*+: 48 mm, *EGFR-/ALK-:* 52 mm; p>0.05). *ALK*+ tumors were more likely to be in the lower lobes compared to *EGFR*+ and *EGFR-/ALK-* tumors (52% vs 34% vs 36%, p<0.05), and less likely to be subsolid in density (1% vs 11% vs 8%, p<0.02) or have air bronchograms (7% vs 28% vs 29%, p<0.01). Cavitation was less common among *ALK*+ tumors than *EGFR-/ALK-* tumors (4% vs 12%, p=0.04).

Lymphadenopathy and Metastatic Patterns

Comparison of metastatic patterns among the three tumor genotypes are summarized in Table 3. *ALK*+ NSCLC were more likely to have intrathoracic nodal disease compared to *EGFR*+ NSCLC (93% vs 83%; p=0.02) and more likely to have distant nodal metastasis

compared to both *EGFR+* and *EGFR-/ALK-* NSCLC (20% vs 2% vs 9%, p<0.05) (Figure 2). *ALK*+ tumors were more likely to exhibit lymphangitic carcinomatosis than the *EGFR*+ and *EGFR-/ALK-* groups (37% vs 12% vs 12%, p<0.01) and less likely to have lung metastases than both groups (19% vs 66% vs 68%, p<0.01) (Figure 3). Compared to *EGFR*+ tumors, *ALK*+ tumors were associated with lower frequency of brain metastases (24% vs 41%, p=0.01) and higher frequency of pleural (46% vs 27%, p<0.01) and soft tissue metastases (6% vs 0%, p=0.01) at the time of diagnosis prior to any treatment. Compared to *EGFR-/ALK-* tumors, *ALK*+ tumors had lower frequency of adrenal metastases (7% vs 32%, p<0.01) but higher frequency of liver metastases (22% vs 6%, <0.01). While there was no significant difference in the frequencies of bone metastases, *ALK*+ NSCLC were more likely than *EGFR*+ and *EGFR-/ALK-* NSCLC to have sclerotic bone metastases (24% vs 7% vs 6%, p<0.01).

Multivariable logistic regression models

Based on multivariate analysis, younger age at diagnosis, the absence of air bronchograms in the primary tumor, the absence of lung metastasis, the absence of brain metastasis, and the presence of lymphangitic carcinomatosis, pleural metastasis, sclerotic bone metastasis, or distant lymph node metastasis were significant predictors of whether patients had *ALK+* vs *EGFR*+ NSCLC (Table 4; Figure 4A). Younger age at diagnosis, non-smoking history, the absence of air bronchograms, the absence of lung metastasis, the absence of adrenal metastasis, and the presence of lymphangitic carcinomatosis, liver metastasis, or sclerotic bone metastasis were significant predictors of whether patients had *ALK*+ vs *EGFR-/ALK-* NSCLC (Table 4; Figure 4B).

DISCUSSION

This is the largest study to date to systematically assess the imaging features and metastatic patterns of *ALK*+ NSCLC. We found that *ALK*+ NSCLC has some imaging features and patterns of metastasis that are distinct compared to those of *EGFR*+ and *EGFR-/ALK-* NSCLC. In our cohort, *ALK*+ tumors were more likely be in the lower lobes compared to *EGFR+* or *EGFR-/ALK-* tumors, and were less likely to be subsolid in density or have air bronchograms. Additionally, *ALK*+ tumors were more likely to be associated with absence of lung metastases and presence of lymphangitic carcinomatosis, distant nodal metastases, and sclerotic bone metastasis compared to *EGFR*+ or *EGFR-/ALK-* tumors.

Of note, virtually all of the primary tumors in *ALK*+ NSCLC evaluated in this study presented as solid masses or nodules. While most of the primary tumors in *EGFR*+ and *EGFR-/ALK-* NSCLC were also solid in density, there were increased frequencies of subsolid density and presence of air-bronchograms in these molecular subsets of tumors. The association between *EGFR*+ tumors and subsolid density and air bronchograms has been reported [23, 31, 32], although the mechanism behind these differences is unclear. *ALK*+ tumors in our study were also more likely to be in the lower lobes compared to the *EGFR*+ or *EGFR-/ALK-* tumors. While the propensity for the lower lobe location has been suggested for nonsmokers (vs upper lobe location for smokers) [33], the impact of the driver oncogene on the primary tumor location has not previously been reported. It has been

suggested that lower lobe tumors may be associated with poorer prognoses; however, these studies did not include oncogene-driven tumors treated with targeted therapy [34, 35].

Prior smaller studies have suggested the propensity of *ALK*+ NSCLC for lymphangitic carcinomatosis [28, 30]. Its association with sclerotic bone metastases observed in our cohort, however, is a novel finding. Historically, sclerotic metastases have been considered relatively rare compared to lytic metastases in treatment-naïve NSCLC [36, 37]. It is also noteworthy that *ALK*+ NSCLC had decreased frequency of lung metastases compared to *EGFR*+ or *EGFR-/ALK*- NSCLC. *EGFR*+ NSCLC can be associated with an increased frequency of "miliary" lung metastases [38, 39], which may partially account for this difference. These differences may potentially have larger prognostic implications in patients, as metastases are the primary determinants of mortality in NSCLC [40, 41].

Current guidelines recommend testing for the most common targetable molecular alterations in NSCLC including *ALK* rearrangements, and treatment with targeted TKIs is only indicated in those who test positive for the targetable mutations [18, 19]. Without further study and validation, imaging cannot replace molecular testing in determining the presence of *ALK* rearrangements in NSCLC, the distinct radiologic features described herein may potentially help identify patients who may benefit from prioritized testing or re-testing following an initial non-diagnostic or inconclusive result. Available assays for *ALK* rearrangement detection include IHC, FISH, and NGS. The latter two, especially NGS, can be time-consuming. There are diagnostic pathways that have been suggested to reduce time to diagnosis and to expedite initiation of targeted TKIs when appropriate [42–44]. Patients with clinical and imaging findings that suggest the presence of an ALK rearrangement (or other oncogene subsets such as *EGFR*+ NSCLC) could benefit from being triaged towards these expedited pathways. Additionally, conflicting *ALK* testing results can be seen using different diagnostic methods; for example, a patient with a negative *ALK* FISH result may then be found to have an *ALK*+ tumor by IHC or NGS testing and go on to benefit from ALK TKIs [45–49]. The presence of compelling clinical and radiologic features may help determine which patients should be re-tested using an alternative diagnostic method.

This study had several limitations. Due to its retrospective, single-institution nature, the findings herein may not be generalizable. While this study evaluated the largest cohort of patients with *ALK*+ NSCLC, the sample size still remained relatively small. Other oncogene subsets such as *ROS1*- or *RET*-rearranged lung cancer or *BRAF*-mutant lung cancer were not examined in this study. In addition, the EGFR-/ALK- cohort may be heterogeneous as it may include many different other mutational subsets other than *ALK* or *EGFR*. Due to these limitations, it remains unknown if there are imaging features of *ALK*-rearranged NSCLC that overlap with those of other mutational subgroups other than *EGFR*, and further study may be helpful in defining these features. Finally, while our findings suggested distinct imaging features that may be helpful in distinguishing *ALK*+ NSCLC from *EGFR*+ or *EGFR-/ALK*- NSCLC, we were not able to elucidate the biologic mechanisms underlying these differences, and further study is needed to explore why certain oncogenes exhibit particular metastatic tropism or primary tumor characteristics.

CONCLUSIONS

This is the largest study to date to assess the imaging features and metastatic patterns of advanced *ALK*+ NSCLC. Our findings suggest that *ALK*+ tumors have certain imaging features and patterns of metastasis that are distinct compared to *EGFR*+ or *EGFR-/ALK-* NSCLC. Although these radiologic features cannot substitute for appropriate molecular testing to detect oncogenic driver gene alterations such as *ALK* rearrangements, they may nevertheless assist in selecting those patients who are most likely to benefit from expedited genotyping, or from repeat testing following an initial non-diagnostic result.

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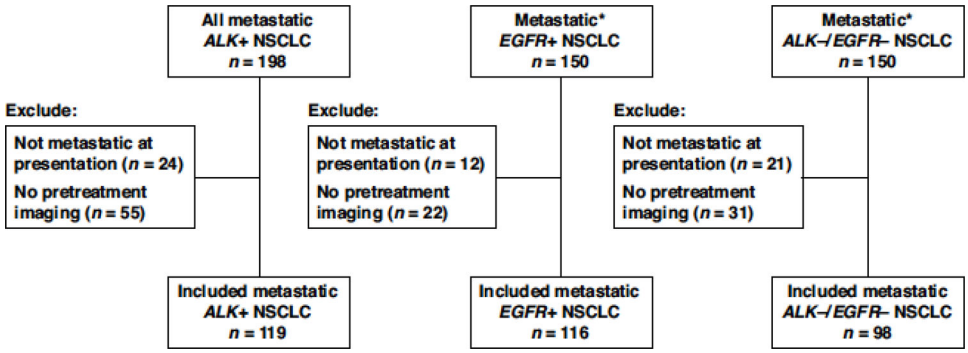

Figure 1. Selection of patients with ALK+, EGFR+, and ALK-/EGFR- NSCLC.

*A subset of 150 consecutive patients with metastatic EGFR+ NSCLC and 150 consecutive patients with metastatic ALK-/EGFR- NSCLC were selected from separate databases as control groups.

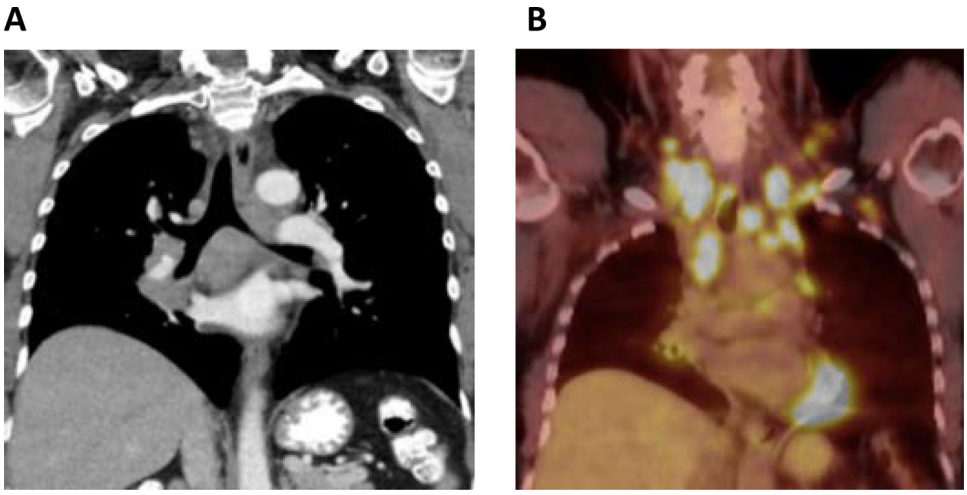

Figure 2. Extensive lymphadenopathy associated with *ALK*+ lung cancer.

A 61-year-old female never smoker presented with a solid right lower lobe mass associated with extensive mediastinal, hilar, supraclavicular, cervical, and left axillary lymphadenopathy, and was later found to have *ALK*+ NSCLC. Representative coronal slices of (A) CT and (B) PET imaging are shown.

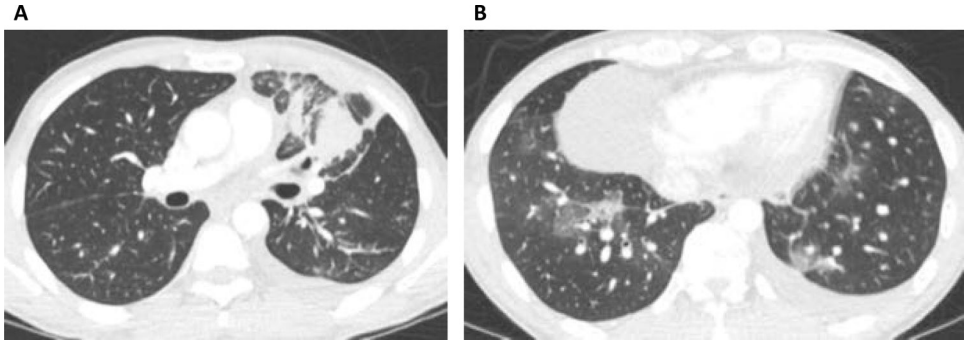

Figure 3. Lymphangitic carcinomatosis associated with *ALK*+ lung cancer.

Representative axial CT images are taken from a 43-year-old male never smoker who presented with (A) dominant left upper lobe mass with surrounding lymphangitic carcinomatosis and (B) additional areas of lymphangitic carcinomatosis in the lower lobes.

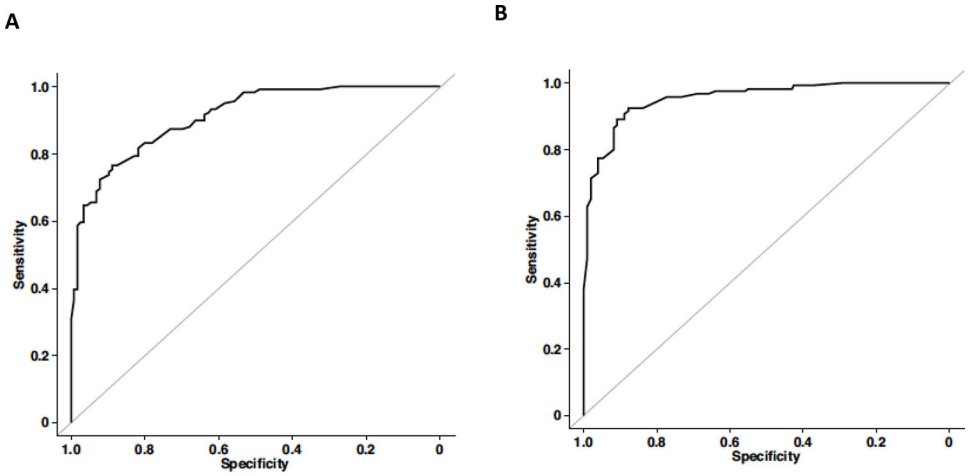

Figure 4.

(A) ROC curve for the multivariable logistic regression model for *ALK*+ vs *EGFR*+ NSCLC. (B) ROC curve for the multivariable logistic regression model for *ALK*+ vs *EGFR-/ALK*- NSCLC.

Table 1.

Patient characteristics.

		Driver alteration, n(%)			P-value	
Patient Characteristic	**All (N=333)**	***ALK*+ (N=119)**	***EGFR*+ (N=116)**	***EGFR-/ALK*- (N=98)**	***ALK*+ vs. *EGFR*+**	***ALK*+ vs/ *EGFR-/ALK*-**
Age, median (range)	61 (19–90)	51 (19–84)	63 (26–90)	68 (42–84)	<0.01	<0.01
Age						
≤60	162 (49%)	90 (76%)	51 (44%)	21 (21%)	<0.01	<0.01
>60	171 (51%)	29 (24%)	65 (56%)	77 (79%)		
Ethnicity						
Asian	31 (9%)	14 (12%)	15 (13%)	2 (2%)	0.46	<0.01
Caucasian	273 (82%)	91 (76%)	93 (80%)	89 (91%)		
Others	29 (9%)	14 (12%)	8 (7%)	7 (7%)		
Gender						
Female	187 (56%)	67 (56%)	80 (69%)	40 (41%)	0.06	0.03
Male	146 (44%)	52 (44%)	36 (31%)	58 (59%)		
Smoking						
Ever	159 (48%)	33 (28%)	44 (38%)	82 (84%)	0.13	<0.01
Never	174 (52%)	86 (72%)	72 (62%)	16 (16%)		

Table 2.

Imaging features of the primary tumor.

Tumor Feature	All (N=333)	Driver alteration, n(%)			P-value	
		ALK+ (N=119)	*EGFR*+ (N=116)	*EGFR-/ALK-* (N=98)	*ALK*+ vs. *EGFR*+	*ALK*+ vs *EGFR-/ALK-*
Tumor size largest diameter, median (range)	49 (2–134)	45 (5–115)	48 (11–134)	52 (2–115)	0.09	0.18
Tumor size						
≥3cm	259 (78%)	89 (75%)	95 (82%)	75 (77%)	0.21	0.87
<3cm	74 (22%)	30 (25%)	21 (18%)	23 (23%)		
Upper vs lower lobe						
Upper lobe	196 (59%)	56 (47%)	77 (66%)	63 (64%)	<0.01	0.01
Lower Lobe	137 (41%)	63 (53%)	39 (34%)	35 (36%)		
Central vs peripheral						
Central	200 (60%)	66 (55%)	83 (72%)	51 (52%)	0.01	0.68
Peripheral	133 (40%)	53 (45%)	33 (28%)	47 (48%)		
Solid or not						
Solid	311 (93%)	118 (99%)	103 (89%)	90 (92%)	<0.01	0.01
Subsolid	22 (7%)	1 (1%)	13 (11%)	8 (8%)		
Air bronchograms						
No	264 (79%)	111 (93%)	83 (72%)	70 (71%)	<0.01	<0.01
Yes	69 (21%)	8 (7%)	33 (28%)	28 (29%)		
Cavitation						
No	310 (93%)	114 (96%)	110 (95%)	86 (88%)	0.77	0.04
Yes	23 (7%)	5 (4%)	6 (5%)	12 (12%)		
Tumor calcification						
No	327 (98%)	119 (100%)	111 (96%)	97 (99%)	0.03	0.45
Yes	6 (2%)	0 (0%)	5 (4%)	1 (1%)		

Table 3.

Sites of metastasis.

Metastatic Site	All (N=333)	Driver alteration, n(%)			P-value	
		ALK+ (N=119)	*EGFR*+ (N=116)	*EGFR*-/*ALK*- (N=98)	*ALK*+ vs. *EGFR*+	*ALK*+ vs/ *EGFR*-/*ALK*-
Thoracic Node						
No	32 (10%)	8 (7%)	20 (17%)	4 (4%)	0.02	0.55
Yes	301 (90%)	111 (93%)	96 (83%)	94 (96%)		
Intrathoracic						
No	76 (23%)	34 (29%)	28 (24%)	14 (14%)	0.46	0.01
Yes	257 (77%)	85 (71%)	88 (76%)	84 (86%)		
Lung						
No	166 (50%)	96 (81%)	39 (34%)	31 (32%)	<0.01	<0.01
Yes	167 (50%)	23 (19%)	77 (66%)	67 (68%)		
Pleural mets						
No	192 (58%)	64 (54%)	85 (73%)	43 (44%)	<0.01	0.17
Yes	141 (42%)	55 (46%)	31 (27%)	55 (56%)		
Lymphangitic carcinomatosis						
No	263 (79%)	75 (63%)	102 (88%)	86 (88%)	<0.01	<0.01
Yes	70 (21%)	44 (37%)	14 (12%)	12 (12%)		
Pericardium						
No	329 (99%)	116 (97%)	116 (100%)	97 (99%)	0.25	0.63
Yes	4 (1%)	3 (3%)	0 (0%)	1 (1%)		
Extra-thoracic						
No	95 (29%)	33 (28%)	32 (28%)	30 (31%)	>0.99	0.66
Yes	238 (71%)	86 (72%)	84 (72%)	68 (69%)		
Intra-abdominal						
No	233 (70%)	87 (73%)	81 (70%)	65 (66%)	0.66	0.30
Yes	100 (30%)	32 (27%)	35 (30%)	33 (34%)		
Adrenal						
No	278 (83%)	111 (93%)	100 (86%)	67 (68%)	0.09	<0.01
Yes	55 (17%)	8 (7%)	16 (14%)	31 (32%)		
Liver						
No	277 (83%)	93 (78%)	92 (79%)	92 (94%)	0.87	<0.01
Yes	56 (17%)	26 (22%)	24 (21%)	6 (6%)		
Spleen						
No	328 (98%)	114 (96%)	116 (100%)	98 (100%)	0.06	0.07
Yes	5 (2%)	5 (4%)	0 (0%)	0 (0%)		
Bone						
No	195 (59%)	65 (55%)	67 (58%)	63 (64%)	0.69	0.17
Yes	138 (41%)	54 (45%)	49 (42%)	35 (36%)		

Metastatic Site	All (N=333)	Driver alteration, n(%)			P-value	
		ALK+ (N=119)	*EGFR*+ (N=116)	*EGFR-/ALK-* (N=98)	*ALK*+ vs. *EGFR*+	*ALK*+ vs/ *EGFR-/ALK-*
Bone type						
None	198 (59%)	65 (55%)	68 (59%)	65 (66%)	<0.01	<0.01
Lytic	93 (28%)	26 (22%)	40 (34%)	27 (28%)		
Sclerotic	42 (13%)	28 (24%)	8 (7%)	6 (6%)		
Brain						
No	227 (68%)	90 (76%)	69 (59%)	68 (69%)	0.01	0.36
Yes	106 (32%)	29 (24%)	47 (41%)	30 (31%)		
Distant lymph node						
No	298 (89%)	95 (80%)	114 (98%)	89 (91%)	<0.01	0.04
Yes	35 (11%)	24 (20%)	2 (2%)	9 (9%)		
Soft tissue						
No	316 (95%)	112 (94%)	116 (100%)	88 (90%)	0.01	0.31
Yes	17 (5%)	7 (6%)	0 (0%)	10 (10%)		

Table 4.

Multivariable models for *ALK*+ vs. *EGFR*+ NSCLC and vs. *EGFR-/ALK*- NSCLC.

Predictor (vs. EGFR+)		**OR (95% CI)**	**P-value**
Age at diagnosis	>60 vs ≤60	0.19 (0.08 – 0.43)	<0.01
Air bronchograms	Yes vs No	0.11 (0.03 – 0.42)	<0.01
Lung metastasis	Yes vs No	0.08 (0.03 – 0.19)	<0.01
Pleural metastasis	Yes vs No	2.99 (1.31 – 6.83)	0.01
Lymphangitic carcinomatosis	Yes vs No	5.63 (2.06 – 15.35)	<0.01
Bone metastasis	Lytic vs None	1 (0.42 – 2.39)	>0.99
	Sclerotic vs None	4.04 (1.27 – 12.87)	0.02
Brain metastasis	Yes vs No	0.34 (0.15 – 0.76)	0.01
Distant lymphadenopathy	Yes vs No	18.43 (3.53 – 96.13)	<0.01
Predictor (vs. EGFR-/ALK-)		**OR (95% CI)**	**P-value**
Age at diagnosis	>60 vs <=60	0.16 (0.06 – 0.43)	<0.01
Smoke status	Never vs Ever	12.15 (4.24 – 34.81)	<0.01
Air bronchograms	Yes vs No	0.07 (0.02 – 0.34)	<0.01
Lung metastasis	Yes vs No	0.07 (0.02 – 0.21)	<0.01
Lymphangitic carcinomatosis	Yes vs No	5.22 (1.5 – 18.23)	0.01
Adrenal metastasis	Yes vs No	0.13 (0.03 – 0.56)	0.01
Liver metastasis	Yes vs No	8.26 (1.79 – 38.15)	0.01
Bone metastasis	Lytic vs None	1.58 (0.49 – 5.15)	0.45
	Sclerotic vs None	10.84 (1.67 – 70.28)	0.01

Abbreviations: OR, odds ratio; CI, confidence interval