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Role of imaging biomarkers in mutation-driven non-small cell lung cancer

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Abstract

Lung cancer remains the leading cause of cancer-related deaths worldwide. The treatment of non-small cell lung cancer (NSCLC), which accounts for a vast majority of lung cancers, has shifted to personalized, targeted therapy following discoveries of several targetable oncogenic mutations. Targeting of specific mutations has improved outcomes in many patients. This success has led to several target-specific agents replacing chemotherapy as first-line treatment in certain mutated NSCLC. Several researchers have reported that there may be imaging biomarkers that may be predictive of the presence of these mutations. These features, when present, have the potential in triaging patients into the most appropriate diagnostic and treatment algorithms. Distinct imaging features and patterns of metastases that have been associated with NSCLC with various targetable oncogenic mutations are presented in this review.

Key words: Non-small cell lung cancer; Imaging biomarker; Targeted therapy; Oncogenic mutations; Radiomics; Metastatic pattern

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Core tip: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related deaths worldwide. Targeted therapy has improved outcomes in subsets of patients with certain targetable mutations. Several researchers have reported imaging biomarkers, which may predict the presence of these mutations. In this review, we present the primary tumor

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imaging features and patterns of metastases in NSCLC with oncogenic mutations.

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INTRODUCTION

Lung cancer results in millions of deaths annually and is the leading cause of cancer-related deaths worldwide^[1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers, and more than half of NSCLC are metastatic at the time of diagnosis^[2]. The prognosis in cases of metastatic NSCLC remains dismal despite advances in treatment, with five-year survival rates of approximately 5%^[3].

Genotyping studies have revealed genetic heterogeneity in NSCLC and identified several key driver mutations, many of which have been found to be targetable or potentially targetable^[3]. Mutations with currently approved targeted therapies (Table 1) include *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, *BRAF* mutations, and *NTRK* gene fusions^[4]. There are other driver mutations in NSCLC for which targeted therapies are under investigation in clinical trials or available as off-label use of agents approved for other indications. These include mutations involving rearranged during transfection proto-oncogene (*RET*), *MET*, human epidermal growth factor receptor 2 (*HER2*), and *KRAS* genes.

In certain patient subgroups, targeted therapy can improve outcomes, making the detection of these mutations an important step in developing personalized treatment strategies. Several (phenotypic) biomarkers have been reported to suggest the presence of specific mutations in NSCLC and to predict responsiveness to certain targeted therapies. The fundamental principle of these biomarkers is that their presence may be indicative of a specific underlying driver mutation in NSCLC and these biomarkers include clinical, pathologic, as well as imaging features.

MOLECULAR TESTING PLATFORMS

Given the success of targeted therapy in certain molecular subsets of patients, screening for driver mutations has become an essential step in the evaluation of patients with newly diagnosed NSCLCs. Current guidelines, including those from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association of Molecular Pathologists, now recommend assessment for the presence of driver mutations in patients with advanced NSCLC, specifically in those with adenocarcinoma^[4,5].

While screening for driver mutations has been widely adopted in clinical practice, no standard screening platform has been established. The optimal testing platform would be accurate, cost-effective, and with a fast turnaround time. The methods currently available offer these features to varying degrees. Their sensitivities may also depend on the mutation being assessed. As such, no single platform has emerged as the optimal testing method for all (Table 2).

The techniques most commonly employed in molecular analysis of tumor tissue include direct gene sequencing, allele-specific sequencing by polymerase chain reaction (PCR), next generation sequencing (NGS), fluorescence in situ hybridization (FISH) and evaluation of protein expression by immunohistochemistry (IHC). All of these techniques require tissue samples. Direct gene sequencing (*i.e.*, Sanger sequencing) was one of the first methods used to perform genotyping but has largely been replaced since by the other methods as it requires a higher tumor cellularity in tissue samples and is more prone to false negative results.

In allele-specific tissue testing, raw DNA is amplified using PCR and is then analyzed for specific abnormalities. Amplification with PCR allows for greater sensitivity and allows for testing of more than one abnormality at a time (*i.e.*, multiplex testing). Its main drawback is that it can only test for predefined abnormalities and is unable to detect new mutations.

FISH testing can be used to detect gene rearrangements, amplifications, or deletions.

Table 1 Targetable genotypes in non-small cell lung cancer with Food and Drug Administration-approved targeted therapies

Molecular alteration	Approved targeted therapies
EGFR	Afatinib
	Dacomitinib
	Erlotinib
	Gefitinib
	Osimertinib
ALK	Alectinib
	Brigatinib
	Ceritinib
	Crizotinib
	Lorlatinib
ROS1	Crizotinib
	Entrectinib
BRAF	Dabrafenib + trametinib
NTRK	Larotrectinib
	Entrectinib

EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; ROS1: c-ROS oncogene 1; NTRK: Neurotrophic receptor tyrosine kinase.

It is highly sensitive in detecting rearrangements in the *ALK*, *ROS1*, and *RET* genes as well as *MET* amplification and *NTRK* fusion^[6,7]. Tissue IHC has also been found to be highly sensitive and specific in detecting *ALK* and *ROS1* rearrangements by detecting expression of abnormal proteins, but it has not been as helpful in the detection of other mutations^[8,9]. It is also routinely used in determining *PD-L1* expressivity in tumor cells^[10].

Finally, NGS is an automated platform that, like allele-specific sequencing, can simultaneously test for multiple genetic abnormalities. It is highly sensitive in the detection of *EGFR*, *HER2*, *MET*_{ex14}, *BRAF*, and *KRAS* mutations^[6,11]. It can also detect *ALK*, *ROS1*, and *RET* rearrangements, but with lower sensitivity^[6,11], and identify novel mutations. The main drawback is cost, as NGS demands advanced bioinformatics systems, fast and complex data processing, and large data storage requirements. Another potential challenge of NGS is the detection of novel variants and mutations of indeterminate significance.

CLINICOPATHOLOGIC BIOMARKERS IN MUTATED NSCLC

Although testing for several driver mutations is now standard of care in the management of advanced NSCLC, significant disparities in compliance with recommended exist around the world, and even within the United States^[12,13]. The identification of clinical, pathologic, and imaging biomarkers has the potential to improve compliance and mitigate these disparities. Moreover, identification of these biomarkers has the potential to lower cost by helping to identify the patients who may benefit the most from molecular testing and by assisting in the selection of the most appropriate testing algorithm.

Several clinicopathologic features have been associated with the presence of certain mutations (Table 3). *EGFR* mutations are the first molecular alterations in lung cancer shown to confer sensitivity to specific targeted therapies. *EGFR* mutations are identified in approximately 15% of lung adenocarcinomas in the United States but have been reported in up to approximately 60% of Asian cases^[14]. Affected patients tend to be younger with minimal or absent history of smoking^[15]. Several generations of tyrosine kinase inhibitors (TKI) have been approved as first-line treatment in advanced *EGFR*-mutant NSCLC^[16-22].

ALK gene rearrangements, most commonly resulting in fusion of *ALK* to

Table 2 Commonly used platforms for detection of mutations in non-small cell lung cancer

Testing technique	High sensitivity in detecting	Lower sensitivity in detecting
Direct gene sequencing		<i>BRAF</i>
Requires high tumor cellularity		<i>EGFR</i>
Largely replaced by newer techniques		<i>HER2</i>
		<i>KRAS</i>
Allele specific sequencing	<i>BRAF</i>	
Detects predefined abnormalities	<i>EGFR</i>	
Allows for multiplex testing	<i>HER2</i>	
	<i>KRAS</i>	
	<i>MET</i> ex14 skipping	
Next Generation sequencing	<i>BRAF</i>	<i>ALK</i>
Can detect novel mutations	<i>EGFR</i>	<i>RET</i>
Allows for multiplex testing	<i>HER2</i>	<i>ROS1</i>
Can be costly and time consuming	<i>KRAS</i>	<i>NTRK</i>
	<i>MET</i> ex14 skipping	<i>MET</i> amplification
Fluorescent in situ hybridization	<i>ALK</i>	
	<i>RET</i>	
	<i>ROS1</i>	
	<i>NTRK</i>	
	<i>MET</i> amplification	
Immunohistochemistry Also used to detect PD-L1 protein expression	<i>ALK</i> <i>ROS1</i>	<i>NTRK</i> fusion

Table 3 Summary of reported clinicopathologic biomarkers in select molecular genotypes in non-small cell lung cancer¹

Clinicopathologic features	<i>EGFR</i> -mutant	<i>ALK</i> -rearranged	<i>ROS1</i> -rearranged	<i>BRAF</i> V600E-mutant	<i>MET</i> exon 14 skipping
Age	Younger	Younger	Younger	No specific age predilection	Older compared to another mutated NSCLC
Race	More common in Asian populations	More common in Caucasian populations	No specific racial predilection	No specific racial predilection	No specific racial predilection
Smoking history	Minimal to no smoking history	Minimal to no smoking history	Minimal to no smoking history	Minimal to no smoking history; positive smoking history in non-V600E mutation	Both smokers and non-smokers
Tumor histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Increased incidence of <i>MET</i> ex14 skipping with sarcomatoid histology

¹Data collected from several sources^[40,54,63,65,66,71].

echinoderm microtubule-associated protein-like 4 (EML4), are reported in approximately 5% of NSCLC^[23,24]. Similar to *EGFR*-mutant NSCLC, *ALK*-positive NSCLCs are more common in younger patients with minimal or no smoking history^[25,26]. Several *ALK*-targeted TKIs have been shown to be highly effective in treating *ALK*-positive NSCLC and are now Food and Drug Administration-approved^[27-32].

ROS1 rearrangements, most commonly genetic translocations between *ROS1* and *CD74*, represent another targetable driver alteration identified in 1%-2% of NSCLC^[33,34]. Similar to *EGFR* mutations and *ALK* rearrangements, *ROS1* rearrangements are also associated with younger age, little to no smoking history, and

adenocarcinoma cell type^[33,34]. *ALK* and *ROS* tyrosine kinase domains share a high degree of homology, making *ROS1*-positive NSCLC highly sensitive to crizotinib^[33]. Entrectinib, a tropomyosin receptor kinase (TRK)/*ROS1* inhibitor, has also been found to be effective and has been approved for the treatment of advanced *ROS1*-positive NSCLC^[4].

Mutations in the *BRAF* gene, which are present in 2%-4% of NSCLC, have emerged as another possible target in the treatment of NSCLC^[35,36]. *BRAF* is a protein kinase, which, when constitutively activated by a mutation, can lead to increased cell proliferation and survival, decreased cell death, and oncogenesis through the RAS/MAPK pathway^[36,37]. Several subtypes of *BRAF* mutations exist and are typically classified as either V600E or non-V600E^[36-38]. Unlike mutations involving *EGFR*, *ALK*, and *ROS1*, those with activating non-V600E *BRAF* mutations are typically current or previous smokers, although those with V600E mutations are typically also less likely to have a history of smoking^[36,39,40]. Combination treatment with *BRAF* and *MEK* inhibitors, dabrafenib and trametinib, has been approved for advanced NSCLC with *BRAF* V600E mutations^[41].

Fusions involving one of three TRK (*NTRK* fusions) are seen in less than 1% of NSCLC and has not been shown to have a predilection based on gender, age, smoking history, or histology^[42]. Two TRK inhibitors, larotrectinib and entrectinib, have shown efficacy against NSCLC harboring *NTRK* fusions and have been approved in advanced cases^[43,44].

RET fusions are detected in 1%-2% of NSCLC and are more commonly seen in patients with no significant smoking history^[45,46]. Multi-targeted TKIs such as cabozantinib and vandetanib have been found to have anti-*RET* activity^[47,48]. Subsequently, highly potent, *RET*-selective TKIs, pralsetinib (BLU-667) and selpercatinib (LOXO-292), have shown promising preliminary safety and efficacy profiles in patients with advanced solid tumors harboring *RET* alterations and are under investigation in the treatment of *RET*-positive NSCLC^[49,50].

The *MET* proto-oncogene encodes a receptor tyrosine kinase, which plays a role in the RAS/MAPK, Rac/Rho, and PI3K/Akt signaling pathways, which mediate cellular growth, anti-apoptosis, and metastasis^[51]. *MET* amplification and overexpression have been found in a wide variety of malignancies including lung cancer, both as a primary driving mutation and as an acquired resistance mechanism in *EGFR*-mutated NSCLC^[52,53]. *MET* exon 14 (*METex14*) skipping represents a distinct subset of *MET* mutations seen in up to 4% of NSCLC and is mutually exclusive of other driver mutations, including *EGFR*, *ALK*, and *ROS1*^[3,53]. *METex14* skipping mutations tend to affect older patients compared to *EGFR* and *ALK*^[53-55]. Although most tumors with *METex14* skipping mutations are adenocarcinomas, there is increased incidence of the mutation in those with sarcomatoid histology^[54]. Crizotinib and cabozantinib have shown promise in treating the treatment of NSCLC harboring *METex14* skipping mutations, and several clinical trials are currently underway investigating novel *MET*-targeted TKIs, including tepotinib and capmatinib^[56,57].

HER2 encodes an *EGFR* family receptor tyrosine kinase, with mutations in *HER2* gene detected in approximately 1%-3% of NSCLC^[58,59]. These mutations are more commonly seen in lung adenocarcinoma and are more common in nonsmokers and women^[59]. There is evidence showing that *HER2*-mutated NSCLC may respond to trastuzumab-based regimens and ado-trastuzumab emtansine^[58-60], and several clinical trials of novel TKIs targeting *HER2* are currently underway including poziotinib, TAK-788, pyrotinib and others.

Finally, activating *KRAS* mutations are the most commonly identified alterations in NSCLC, seen in up to 25% of lung adenocarcinomas^[61]. Unlike *EGFR* and *ALK* alterations, *KRAS* mutations are generally seen in smokers. Several previous efforts to identify RAS-specific inhibitors have been unsuccessful. Currently, several agents are under investigation in the treatment of NSCLC with *KRAS*-G12C mutations, which accounts for approximately 12% of *KRAS* mutations in NSCLC^[62].

IMAGING BIOMARKERS IN MUTATED NSCLC

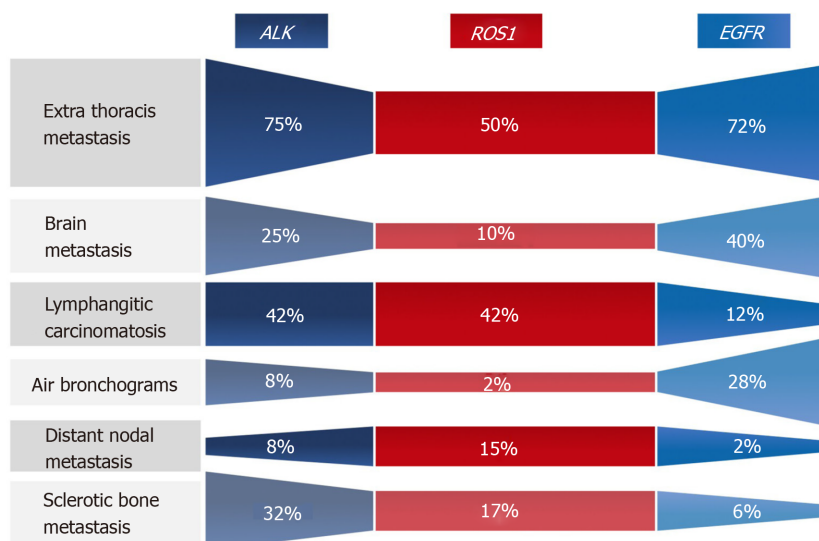
There has been increasing awareness of the clinical features (*e.g.*, minimal to no history of smoking, Asian descent, *etc.*) that are associated with certain mutations in NSCLC, but the association of the imaging features and underlying driver mutations in NSCLC remains under-recognized. Emerging data suggest that there are differences among NSCLC harboring different targetable oncogenic driver mutations with respect to the imaging features of the primary tumor and patterns of metastases (Table 4, Figure 1).

Table 4 Summary of reported imaging biomarkers in select molecular genotypes in non-small cell lung cancer¹

Imaging feature	EGFR mutation	ALK rearrangement	ROS1 rearrangement	METex14 skipping mutation
Primary tumor	Increased ground-glass components Presence of air bronchograms (pneumonic appearance)	Purely solid lesion	Purely solid lesion	Multifocal primary lung cancers
Metastatic patterns		Peripheral predilection	Peripheral predilection	Peripheral predilection
	Diffuse lung metastases	Lymphangitic carcinomatosis	Lymphangitic carcinomatosis	Oligometastatic disease
		Pleural and pericardial metastasis	Pleural metastases	
		Intrathoracic and distant lymphadenopathy	Intrathoracic and distant lymphadenopathy	
	Lytic bone metastases	Sclerotic bone metastases	Sclerotic bone metastases	Lytic bone metastases
	High rates of brain metastases	High rates of brain metastases	High rates of brain metastases, but lower compared to EGFR and ALK	High rates of brain metastases, but lower compared to EGFR and ALK

¹Data collected from several sources^[54,63,65,66,71]. EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase.

CT imaging features and distribution of metastases in ROS1-rearranged NSCLC



Lennerz, drawn using data from Digumarthy *et al.*, 2019 *Clin Lung Cancer*

Figure 1 Comparison of select primary tumor features and metastatic patterns among patients with non-small cell lung cancer with ALK, ROS1, or EGFR alterations^[71].

These features, when present, can potentially point to certain mutations.

PRIMARY TUMOR FEATURES

Several researchers have investigated the imaging features of the primary tumors in those with mutation-driven NSCLC. The most commonly investigated features are the tumor density, morphology, and location.

Overwhelmingly, most primary tumors in both mutated and non-mutated NSCLC are solid in density, including those with mutations involving *KRAS*, *EGFR*, *ALK*, *ROS1*, *RET*, *MET*, *BRAF*, *HER2*, and *KRAS*^[40,54,63-71]. To date, the imaging features of NSCLC with *NTRK* fusions have not been studied, likely owing to their rarity. While most lung tumors are typically solid, several studies^[63,64,66] have reported increased propensity of primary tumors in *EGFR*-mutant NSCLC to have a

consolidative “pneumonic” appearance with ground-glass components, cavitations, and air-bronchograms (Figure 2A and 4A). This highlights the need for vigilance in the setting of non-resolving consolidations to prevent missed or delayed diagnosis in these patients.

Primary tumor location, particularly the tumor’s axial location (*i.e.*, central versus peripheral location), is another commonly investigated imaging feature. Increased tendency for peripheral rather than central locations has been reported in NSCLC with *ALK* rearrangements (Figure 3A)^[66], *RET* rearrangements^[70,72] and METex14 skipping mutations^[54]. Two small studies have also suggested that the primary tumors in *ROS1*-positive NSCLC tend to be peripheral^[70,73], although a subsequent larger study failed to support these findings^[71].

More recently, it has been reported that the primary tumors in *ALK*-positive NSCLC are more likely to occur in the lower lobes, compared to *EGFR*-wild type and *ALK/EGFR*-negative tumors^[66]. Most lung cancers develop in the upper lobes. Propensity for lung cancer development in the lower lobes has been reported in lung cancers developing in nonsmokers, although the presence or absence of an underlying driver mutation was not included in the study^[74]. It has also been suggested that lower lobe tumors may be associated with a worse prognosis, but the studies did not include NSCLC with targetable mutations^[75,76]. Tumor location may have implications with respect to accessibility for biopsy, surgery, or radiation therapy.

PATTERNS OF NODAL AND DISTANT METASTASES

Nodal metastasis

Nodal status is an important prognostic factor and determinant of treatment offered to patients with lung cancer. A number of studies have suggested that certain driver mutations may have increased predisposition for both intrathoracic and distant nodal metastases. In particular, several studies have reported increased frequency for extensive lymphadenopathy in *ALK*-positive NSCLC (Figure 3C)^[65,66,71,77]. More recently, a similar predilection for intrathoracic and distant nodal metastases have been associated with *ROS1*-positive NSCLC^[71]. The extensive lymphadenopathy seen in *ALK*-positive and *ROS1*-positive NSCLC can potentially be misinterpreted initially on imaging as either lymphoma or small cell lung cancer^[65,71].

Lung metastases

Several studies have reported that there is increased frequency of diffuse “miliary” (*i.e.*, widespread disseminated) lung metastases in *EGFR*-mutant NSCLC (Figure 2A and 4A). Our group has previously reported up to a six-fold increased incidence of diffuse lung metastases in *EGFR*-mutant NSCLC compared to *EGFR*-wild type NSCLC^[63]. While diffuse lung metastases are typically associated with worse prognosis, the presence of an *EGFR* mutation and increased responsiveness to targeted therapy (Figure 2B) can potentially improve outcomes in these patients. In the setting of a dominant lung mass and diffuse “miliary” lung metastases, *EGFR*-mutant NSCLC should be suspected^[63].

ALK-positive NSCLC, on the other hand, has been associated with lymphangitic carcinomatosis (Figure 3B and 4B) in comparison to *EGFR*-mutant NSCLC^[65-67,78]. More recently, *ROS1*-positive NSCLC has also been associated with predilection for lymphangitic carcinomatosis (Figure 5A)^[71]. On imaging, lymphangitic carcinomatosis is characterized by nodular thickening of the axial and peripheral, subpleural interstitium, with relative sparing of the intralobular interstitium^[79]. Lymphangitic carcinomatosis is associated with worse prognosis in various extrapulmonary malignancies, but its prognostic impact in the setting of primary lung malignancies remains unclear due to paucity of data^[80]. While it may appear intuitive that lymphangitic carcinomatosis is suggestive of more advanced disease, a concurrent targetable mutation with either *ALK* or *ROS1* may improve outcomes in these patients (Figure 5C).

More recently, it has been suggested that NSCLC with METex14 skipping mutations may have increased frequency of multifocal, synchronous primary lung cancer at presentation (Figure 4C), which was observed in approximately 1 in 5 patients^[54]. The authors suggested that this multifocality may be secondary to synchronous adenocarcinomas with distinct splice site mutations, which has been previously described for METex14-mutated primary lung adenocarcinomas^[81].

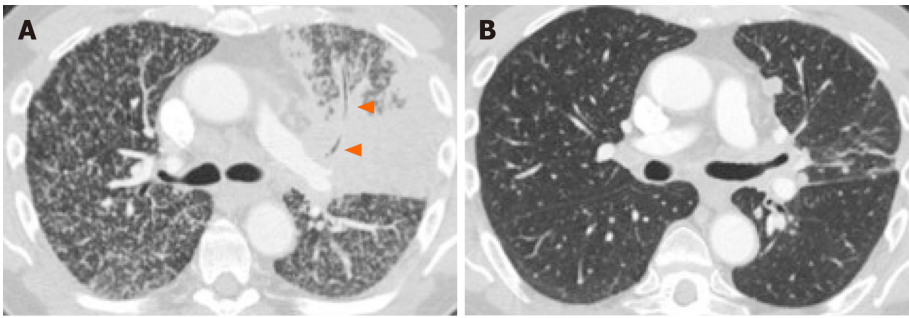


Figure 2 Primary tumor features and “miliary” type metastases in 66-year-old male non-smoker with *EGFR*-mutant non-small cell lung cancer. A: Pretreatment computed tomography (CT) shows a mass-like consolidation in the left upper lobe with internal air bronchograms (arrowheads) and diffuse 1-2 mm nodules bilaterally consistent with “miliary” metastases. Consolidative, “pneumonic”, appearance of the primary tumor is associated with *EGFR* mutations in non-small cell lung cancer; B: Post-treatment CT shows marked treatment response to targeted therapy with mild residual scarring and nodularity in the left upper lobe and near-complete resolution of diffuse metastases.



Figure 3 Lymphangitic carcinomatosis, pleural metastasis and, extensive lymphadenopathy in 64-year old female non-smoker with *ALK*-positive non-small cell lung cancer. A: Pretreatment computed tomography (CT) shows a right upper lobe nodule (arrow) corresponding to the primary lung tumor; B: CT slice at the level of the carina shows extensive right sided nodular septal thickening consistent with lymphangitic carcinomatosis; C: CT (mediastinal window) shows extensive right hilar and subcarinal lymphadenopathy (arrowheads) consistent with nodal metastases. A pleural effusion, later proven to be malignant by cytology, is also noted. These features have been associated with *ALK*-positive non-small cell lung cancer (NSCLC). Similar features have also been described in *ROS1*-positive NSCLC (Figure 5).

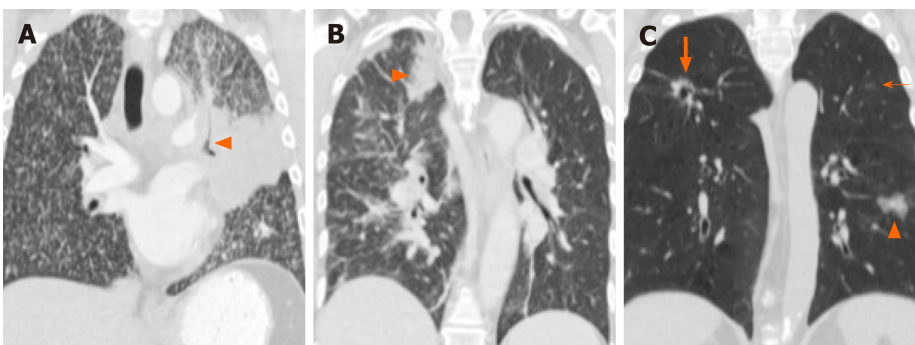


Figure 4 Imaging features of the primary lung tumor and patterns of lung metastases in non-small cell lung cancer with driver mutations. A: Computed tomography (CT) of a patient with *EGFR*-mutant non-small cell lung cancer (NSCLC) shows a dominant central left upper lobe mass with diffuse “miliary” type metastases bilaterally. Note the “consolidative” appearance of the dominant mass with air bronchograms (arrowhead), which have also been associated with *EGFR*-mutant NSCLC; B: CT of a patient with *ALK*-rearranged NSCLC shows a solid dominant peripheral right upper lobe mass (arrowhead) with nodular thickening of interstitium and ground glass opacities consistent with lymphangitic carcinomatosis, which have been associated with NSCLC with either *ALK* or *ROS1* rearrangements; C: CT of a patient with NSCLC with *MET* exon 14 skipping mutation shows a part-cystic, part-solid nodule in the right upper lobe (thick arrow) with an additional ground glass nodule in the left lower lobe (arrowhead) and a smaller ground glass nodule in the left upper lobe (thin arrow), consistent with synchronous multifocal lung cancers.

Pleura and pericardial metastases

In addition to increased frequency of lymphangitic carcinomatosis, *ALK*-positive NSCLC has also been associated with increased frequencies of both pleural (Figure 3C) and pericardial metastases^[65], and *ROS1*-positive NSCLC has also been associated with pleural metastases (Figure 5B)^[71]. The mechanism behind these potential differences in



Figure 5 Lymphangitic carcinomatosis and pleural metastases in 26-year old male non-smoker with *ROS1*-positive non-small cell lung cancer. A: Pre-treatment computed tomography (CT) shows a dominant right lower lobe mass with diffuse bilateral, right greater than left, lymphangitic carcinomatosis characterized by nodular interstitial thickening and ground glass opacities; B: Pre-treatment CT (mediastinal window) shows right pleural nodular thickening and pleural effusion (arrowheads) consisted with pleural metastasis; C: Initial post-treatment CT shows marked interval response to targeted therapy with near complete resolution of right lower lobe mass and of lymphangitic carcinomatosis. Increased frequencies of lymphangitic carcinomatosis and pleural metastases have also been described in *ALK*-positive non-small cell lung cancer (Figure 2).

metastatic tropisms among the different genotypes remains to be determined.

Brain metastases

The brain is a common site of metastasis in NSCLC, with over 20% of patients with advanced NSCLC having brain metastases at the time of diagnosis, and up to approximately 50% developing them within three years^[82-84]. Brain metastases present a unique challenge, as their treatment requires agents that can cross and can remain active beyond the blood-brain barrier.

Several studies have suggested potential differences in the frequencies of brain metastases across the different oncogenic drivers in NSCLC^[85]. NSCLC harboring alterations in *EGFR*, *ALK*, or *ROS1* have been associated with increased frequencies of brain metastases^[86-89]. Some reports, however, show that there is significant overlap in the frequencies of brain metastases among the different mutation groups^[90]. Reported frequencies of brain metastasis at time of diagnosis of advanced disease range from 23%-41% in *EGFR*-mutant NSCLC^[66,86,87], 23%-42% in *ALK*-positive NSCLC^[66,86], and 9%-36% in *ROS1*-positive NSCLC^[71,88,90]. Less data is available with respect to the frequencies of brain metastases in the other mutational subgroups. Incidence of 25% have been reported for both *RET*-positive^[91] and *HER2*-mutant NSCLC^[92], 21% for NSCLC with METex14 skipping mutations^[54], and 10% for *BRAF*-mutant NSCLC. Ranges of reported incidences of brain metastases in the more common molecular subtypes are presented on Figure 6. Further investigation is necessary to determine if differences in tropism to the brain truly exist across the different oncogenic subsets in NSCLC and to determine the underlying mechanism resulting in differences. Nevertheless, the high incidences of brain metastases across several of these mutated tumors underscore the need for targeted agents that have robust CNS activity.

Bone metastases

The bones are a common site of metastasis in NSCLC and osseous metastases are seen in up to 40% of patients with advanced lung cancer^[93]. Bone metastases are a significant cause of morbidity in cancer patients as they can predispose to pathologic fractures, cause debilitating pain and severely reduce quality of life.

Osseous metastases from a variety of malignancies can be either predominantly lytic or predominantly sclerotic in appearance. Many lytic lesions may also become sclerotic with treatment. Malignancies classically associated with sclerotic bone metastases are prostate cancer and small cell lung cancer. In general, bone metastases in NSCLC usually present as lytic lesions, with sclerotic metastases rarely seen prior to treatment^[94,95].

A number of studies, however, have reported that there may be a predisposition to either lytic or sclerotic bone metastasis based on the presence of an underlying driver mutation in NSCLC. *ALK*-positive NSCLC, for instance, has been associated with sclerotic metastases (Figure 7). In a study comparing the imaging findings of *ALK*-positive NSCLC to those of *EGFR*-mutant NSCLC, more than half of the patients with bone metastases in the setting of *ALK*-positive NSCLC had sclerotic bone metastases prior to any treatment. In contrast, sclerotic bone metastases were seen in only 1 of 6 patients with *EGFR*-mutant NSCLC^[66]. More recently, a different study comparing the imaging features of *ROS1*-positive NSCLC to those with *ALK* or *EGFR* alterations, showed similar frequencies of bone metastases among the three mutational subgroups, but an increased frequency of sclerotic bone metastases in both *ROS1*-positive NSCLC

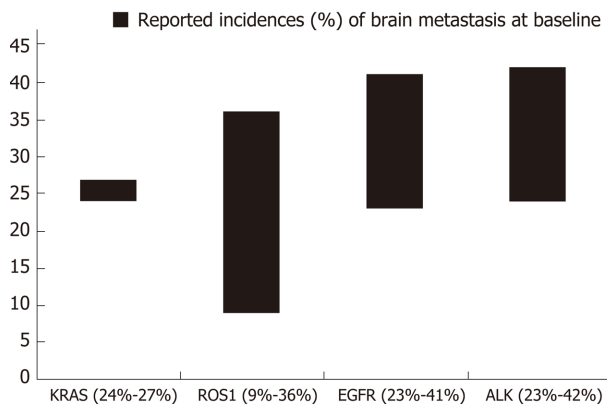


Figure 6 Range of reported incidences (%) of brain metastases in advanced mutated non-small cell lung cancer with driver mutation.

Data presented are obtained from several sources^[66,71,86-88,90].

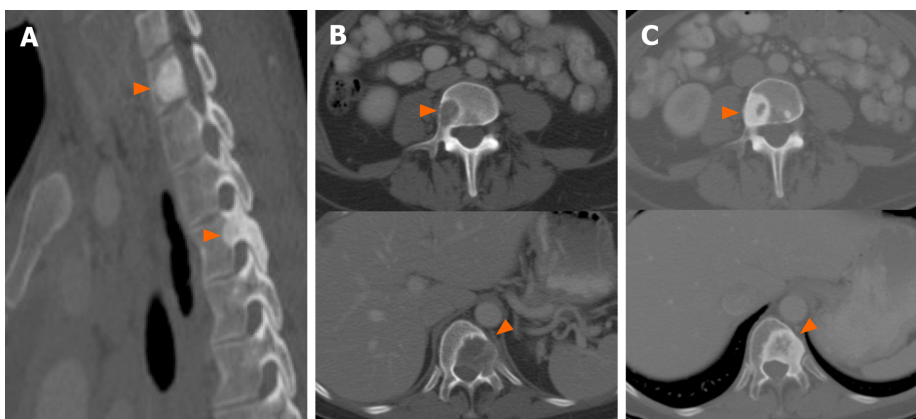


Figure 7 Patterns of bone metastases in non-small cell lung cancer with driver mutations. A: Pretreatment computed tomography (CT) images (sagittal, bone window) show sclerotic lesions involving the cervicothoracic spine (arrowheads) consistent with osseous metastases in *ROS1*-positive non-small cell lung cancer (NSCLC); B: Pretreatment CT images (sagittal, bone window) show lytic lesions involving thoracic and lumbar vertebral bodies (arrowheads) in patient with *EGFR*-mutant NSCLC; C: Post-treatment CT of the same patient as **Figure 7B** shows interval sclerosis of previously lytic osseous metastases (arrowheads). In general, most NSCLC tend to have lytic lesions in contrast to those with *ROS1* or *ALK* positive NSCLC, which tend to be more sclerotic at presentation. Sclerosis of previously lytic lesion is often seen after treatment.

and *ALK*-positive NSCLC compared to *EGFR*-mutant NSCLC^[71]. In contrast, a series presenting the clinicopathologic and imaging features of NSCLC with METex14 skipping mutations reported the bone metastases to be predominantly lytic in these patients^[76]. The morphology of bone metastases in the other molecular subgroups has yet to be reported.

Other metastatic patterns

No specific imaging biomarker has yet to be identified to suggest the presence of an underlying *BRAF* mutation in NSCLC^[40,96]. It has been suggested, however, that at the time of presentation, patients with lung cancer harboring the V600E *BRAF* mutation may be more likely to have intrathoracic metastases, particularly pleural metastases, while those with non-V600E *BRAF* mutations may be more likely to have intra-abdominal metastases^[40].

Finally, METex14 skipping mutations in NSCLC have recently been associated with increased incidence of oligometastatic disease^[54]. In the case series, the authors reported 4 patients that had only a single site of metastases (3 with adrenal metastasis and 1 one with soft tissue metastasis), although the findings have yet to be validated^[54]. Several studies, however, have reported better outcomes in patients with limited metastatic burden when managed with radical treatment with curative intent^[97].

CONCLUSION

The mechanism behind the morphological differences of the primary tumor and the differences in metastatic tropisms among the molecular subgroups of NSCLC remain unclear. While none of the imaging features and metastatic tropisms we discussed can reliably predict the presence of specific genetic alterations in isolation and they are unlikely to replace molecular genotyping in directing the need for targeted therapy, these imaging biomarkers can indicate the presence of specific targetable mutations and can play an adjunctive role. These features can assist in the selection patients who may benefit from expedited pathways for molecular testing or repeat testing when the initial genotyping results are equivocal or discordant with the clinical and imaging presentation. Given the importance of initiating targeted therapy in patients with targetable mutations, it is imperative to use all biomarkers available – clinical, histopathologic, and radiologic – in detecting these mutations.

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