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
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[17].

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 is 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, METex14, BRAF, and KRAS mutations\([11,12]\). It can also detect ALK, ROS1, and RET rearrangements, but with lower sensitivity\([6,13]\), 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 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\([10]\). Affected patients tend to be younger with minimal or absent history of smoking\([10]\). Several generations of tyrosine kinase inhibitors (TKI) have been approved as first-line treatment in advanced EGFR-mutant NSCLC\([10,11]\).

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                    |                                | BRAF                          |
| Requires high tumor cellularity           |                                | EGFR                          |
| Largely replaced by newer techniques      |                                | HER2                          |
|                                           |                                | KRAS                          |
| Allele specific sequencing                | BRAF                          |                                |
| Detects predefined abnormalities          | EGFR                          |                                |
| Allows for multiplex testing              | HER2                          |                                |
|                                           | KRAS                          |                                |
| Next Generation sequencing                | BRAF                          | ALK                           |
| Can detect novel mutations                | EGFR                          | RET                           |
| Allows for multiplex testing              | HER2                          | ROS1                          |
| Can be costly and time consuming          | KRAS                          | NTRK                          |
|                                           | MET exon 14 skipping          | MET amplification              |
| Fluorescent in situ hybridization         | ALK                           | RET                           |
|                                           | RET                           | ROS1                          |
|                                           | NTRK                          | MET amplification              |
| Immunohistochemistry                      | ALK/ROS1                      | NTRK fusion                   |

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

| Clinicopathologic features | EGFR-mutant | ALK-rearranged | ROS1-rearranged | BRAF V600E-mutant | MET 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; positive smoking history in non-V600E mutation | Both smokers and non-smokers |
| Tumor histology            | Adenocarcinoma | Adenocarcinoma | Adenocarcinoma | Adenocarcinoma | Increased incidence of METex14 skipping with sarcomatoid histology |

1 Data 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.\textsuperscript{35,39} ALK and ROS tyrosine kinase domains share a high degree of homology, making ROS1-positive NSCLC highly sensitive to crizotinib.\textsuperscript{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.\textsuperscript{46}

Mutations in the BRAF gene, which are present in 2%-4% of NSCLC, have emerged as another possible target in the treatment of NSCLC.\textsuperscript{35,39} 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.\textsuperscript{46,47} Several subtypes of BRAF mutations exist and are typically classified as either V600E or non-V600E.\textsuperscript{48,49} 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 less likely to have a history of smoking.\textsuperscript{46,49,50} Combination treatment with BRAF and MEK inhibitors, dabrafenib and trametinib, has been approved for advanced NSCLC with BRAF V600E mutations.\textsuperscript{51}

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.\textsuperscript{51} Two TRK inhibitors, larotrectinib and entrectinib, have shown efficacy against NSCLC harboring NTRK fusions and have been approved in advanced cases.\textsuperscript{52,53}

RET fusions are detected in 1%-2% of NSCLC and are more commonly seen in patients with no significant smoking history.\textsuperscript{54,55} Multi-targeted TKIs such as cabozantinib and vandetanib have been found to have anti-RET activity.\textsuperscript{56,57} 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.\textsuperscript{58,59}

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.\textsuperscript{60} 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.\textsuperscript{61} 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.\textsuperscript{62,63} METex14 skipping mutations tend to affect older patients compared to EGFR and ALK.\textsuperscript{61,64} Although most tumors with METex14 skipping mutations are adenocarcinomas, there is increased incidence of the mutation in those with sarcomatoid histology.\textsuperscript{64} 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.\textsuperscript{65,66}

HER2 encodes an EGFR family receptor tyrosine kinase, with mutations in HER2 gene detected in approximately 1%-3% of NSCLC.\textsuperscript{67,68} These mutations are more commonly seen in lung adenocarcinoma and are more common in nonsmokers and women.\textsuperscript{69} There is evidence showing that HER2-mutated NSCLC may respond to trastuzumab-based regimens and ado-trastuzumab emtansine, 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.\textsuperscript{70} 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.\textsuperscript{71}

**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 cancer

| Imaging feature | EGFR mutation | ALK rearrangement | ROS1 rearrangement | METex14 skipping mutation |
|-----------------|---------------|-------------------|--------------------|----------------------------|
| Primary tumor   | Increased ground-glass components | Purely solid lesion | Purely solid lesion | Multifocal primary lung cancers |
| Presence of air bronchograms (pneumonic appearance) | Peripheral predilection | Peripheral predilection | Peripheral predilection |
| Metastatic patterns | 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, 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-raneg NSCLC

![CT imaging features and distribution of metastases in ROS1-ranged NSCLC](image)

**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\[^{[G12S]}\]. 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\[^{[8,10,14]}\] 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)\(^{65,66}\), RET rearrangements\(^{77,78}\) and METex14 skipping mutations\(^{65}\). Two small studies have also suggested that the primary tumors in ROS1-positive NSCLC tend to be peripheral\(^{71}\), although a subsequent larger study failed to support these findings\(^{75}\).

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\(^{69}\). 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\(^{69}\). 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\(^{65,69}\). 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)\(^{65,67,77}\). More recently, a similar predilection for intrathoracic and distant nodal metastases have been associated with ROS1-positive NSCLC\(^{69}\). 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\(^{66,71}\).

#### 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\(^{69}\). 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\(^{69}\).

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\(^{69}\). While it may appear intuitive to 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\(^{80}\). 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
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\[^{[86,89]}\]. 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\[^{[86,89]}\]. 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\[^{[86,89]}\]. Reported frequencies of brain metastasis at time of diagnosis of advanced disease range from 23%-41% in EGFR-mutant NSCLC\[^{[86,89]}\], 23%-42% in ALK-positive NSCLC\[^{[86,89]}\], and 9%-36% in ROS1-positive NSCLC\[^{[86,89]}\]. 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\[^{[86,89]}\] and HER2-mutant NSCLC\[^{[86,89]}\], 21% for NSCLC with METex14 skipping mutations\[^{[86,89]}\], 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\[^{[66]}\]. 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 or osteoblastic 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\[^{[90]}\].

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\[^{[90]}\]. More recently, a different study comparing the imaging features of ROSI-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 ROSI-positive NSCLC.

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**Figure 5** Lymphangitic carcinomatosis and pleural metastases in 26-year old male non-smoker with ROSI-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) consistent 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).
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\textsuperscript{[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 \textit{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 \textit{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 \textit{ROS1} or \textit{ALK} positive NSCLC, which tend to be more sclerotic at presentation. Sclerosis of previously lytic lesion is often seen after treatment.

and \textit{ALK}-positive NSCLC compared to \textit{EGFR}-mutant NSCLC\textsuperscript{[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\textsuperscript{[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 \textit{BRAF} mutation in NSCLC\textsuperscript{[40,96]}. It has been suggested, however, that at the time of presentation, patients with lung cancer harboring the V600E \textit{BRAF} mutation may be more likely to have intrathoracic metastases, particularly pleural metastases, while those with non-V600E \textit{BRAF} mutations may be more likely to have intra-abdominal metastases\textsuperscript{[40]}.

Finally, METex14 skipping mutations in NSCLC have recently been associated with increased incidence of oligometastatic disease\textsuperscript{[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\textsuperscript{[54]}. Several studies, however, have reported better outcomes in patients with limited metastatic burden when managed with radical treatment with curative intent\textsuperscript{[54]}.
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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