

# Imaging Features of Non-Small Cell Lung Cancer with Targetable Oncogenic Driver Mutations

Dexter P. Mendoza<sup>1</sup>, Subba R. Digumarthy<sup>1\*</sup>

<sup>1</sup>Department of Radiology, Division of Thoracic Imaging and Intervention, Massachusetts General Hospital, USA

## Article Info

### Article Notes

Received: October 29, 2019

Accepted: November 28, 2019

### \*Correspondence:

Dr. Subba Digumarthy, Department of Radiology,  
Massachusetts General Hospital, Boston, MA U.S.A.  
Email: sdigumarthy@mgh.harvard.edu.

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### Keywords

Non-Small Cell Lung Cancer  
Mutations  
EGFR  
ALK  
ROS1  
Imaging  
Radiology

## Introduction

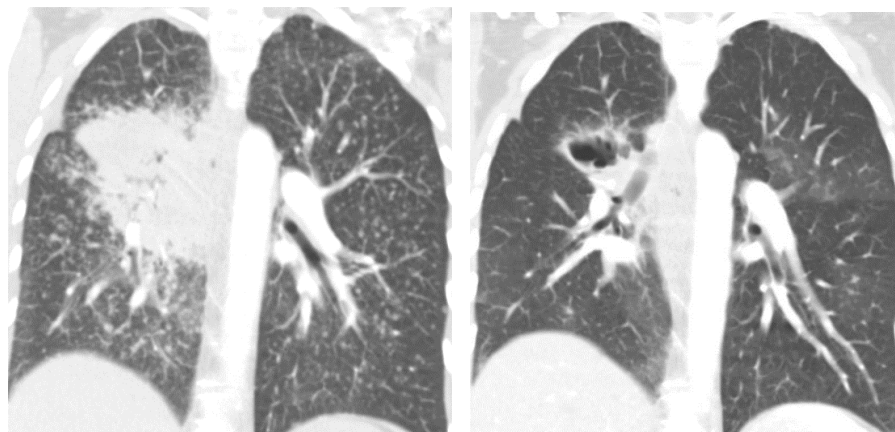
The overall 5-year survival rate and prognosis for advanced non-small lung cancer (NSCLC) continue to be dismal despite significant advances in diagnosis and treatment. In the last decade, however, significant improvements in outcomes have been achieved for a select group of patients with NSCLC harboring certain targetable mutations treated with specific tyrosine kinase inhibitors (TKI)<sup>1-8</sup>. Based on the results of several randomized controlled trials, the National Comprehensive Cancer Network (NCCN) recommends routine testing for targetable mutation in advanced NSCLC<sup>9</sup>. The mutations that are routinely tested include those involving the *EGFR*, *ALK*, and *ROS1* genes that account for approximately 12% of advanced adenocarcinoma of the lung<sup>9,10</sup>. While these mutations have been associated with adenocarcinoma pathology, it is notable that these mutations are typically not seen in cases of mucinous adenocarcinoma, which has been associated with *KRAS* mutations<sup>11</sup>. There are many other targetable mutations such as alterations in the *BRAF*, *RET*, and *MET* genes that can be treated with specific drugs with completed or ongoing clinical trials.

The clinical features of NSCLC that harbor established targetable mutations are distinct and are most commonly seen in non-smokers and in relatively young individuals. The imaging features and distribution of metastases in cancers with targetable mutations can also provide clues to the presence of underlying driver mutations and can help triage patients for molecular testing and selection of mutation panel. The purpose of this review article is to highlight the imaging and clinical features of common driver mutations of NSCLC that can be treated with targeted therapy.

## Epidermal Growth Factor Receptor Mutation

Epidermal growth factor receptor (*EGFR*) mutations are the most common targetable mutation in the treatment of NSCLC<sup>12</sup>. These mutations are more commonly seen in younger patients with little or no smoking history<sup>12</sup>. Several targeted agents, which have been shown to improve survival in this subset of patients, are now FDA-approved as front-line therapy in the treatment of advanced *EGFR*-mutant NSCLC<sup>1,2</sup>.

Several researchers have investigated the imaging features of *EGFR*-mutant NSCLC. Compared to *EGFR*-wild type NSCLC, the primary tumors harboring *EGFR* mutations have been reported to more likely to have groundglass components and more tumoral cavitations and air-bronchograms<sup>13-16</sup>. Several groups have reported



**Figure 1: 54-year-old female non-smoker with EGFR-mutant NSCLC.** (A) Coronal chest CT image shows a consolidative mass with air-bronchograms in the right upper lobe with diffuse lung metastases bilaterally. (B) Follow up chest CT obtained 3 months following initiation of EGFR-targeted tyrosine kinase inhibitor shows marked decrease in extent of the mass with a residual cavitation and marked decrease in bilateral lung metastases. EGFR-mutant NSCLC are associated with increased propensity for diffuse “miliary” lung metastases and are responsive to targeted therapy.

the increased frequency of diffuse “miliary” lung metastases (Figure 1)<sup>17-19</sup>. 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<sup>19</sup>. While diffuse lung metastases are typically associated with worse prognosis, the presence of an *EGFR* mutation can potentially improve outcomes in these patients.

Using 18FDG-PET (18-fluorodeoxyglucose positron emission tomography), Mak *et al.* reported a high maximum standardized uptake value of primary tumor in wild type compared to *EGFR* mutant lung adenocarcinoma<sup>20</sup>. The emerging technique of radiomics identifies the quantitative image parameters that are beyond the resolution of the human eye. Several studies have shown the potential of predicting *EGFR* mutations in NSCLC by using radiomics<sup>21</sup>, although these techniques are not yet fully standardized and have not been validated for routine clinical use.

### Anaplastic Lymphoma Kinase Rearrangement

Anaplastic lymphoma kinase (*ALK*) gene rearrangements, often with fusion of *ALK* to echinoderm microtubule-associated protein-like 4, is the second most common driver mutation with targetable treatment and is reported in approximately 5% of NSCLC<sup>22</sup>. Similar to *EGFR* mutations, *ALK* rearrangements are more common in younger patients with minimal or no smoking history<sup>22,23</sup>. Several *ALK*-targeted TKIs have been shown to be highly effective in treating *ALK*-rearranged NSCLC and are now FDA-approved, with alectinib being the current standard initial therapy in advanced *ALK*-positive<sup>3-7</sup>.

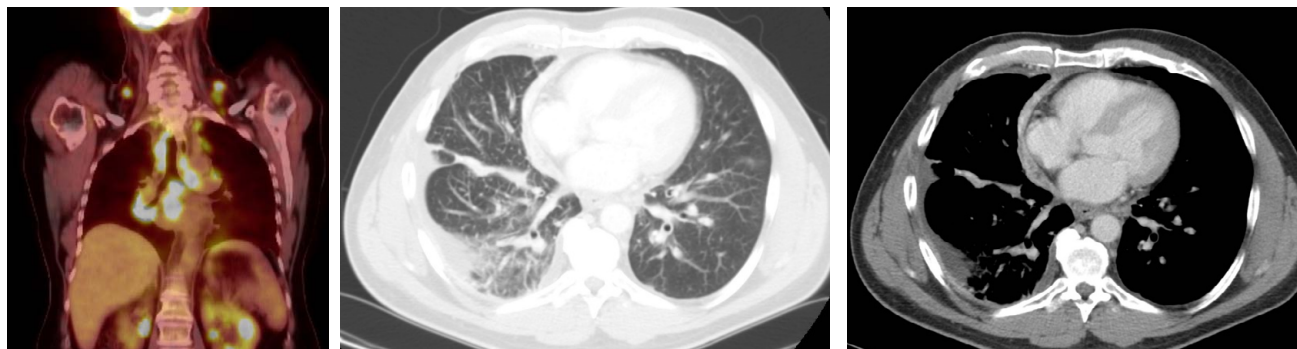
Several authors have also investigated the imaging features of *ALK*-rearranged NSCLC, although most of these studies have been on small sample sizes due to the relative rarity of the mutation<sup>15,24-30</sup>. A recent meta-analysis of these

studies found several common imaging patterns in *ALK*-positive NSCLC<sup>31</sup>. Compared to the primary tumors in *EGFR*-mutant NSCLC, the primary tumors in *ALK*-rearranged NSCLC tend to be more solid and less likely to have air bronchograms or cavitations<sup>31</sup>. More recently, Mendoza *et al.* also reported that the primary tumors tend to occur in the lower lobes in *ALK*-rearranged NSCLC, compared to *EGFR*-wild type and *ALK/EGFR*-negative tumors<sup>32</sup>.

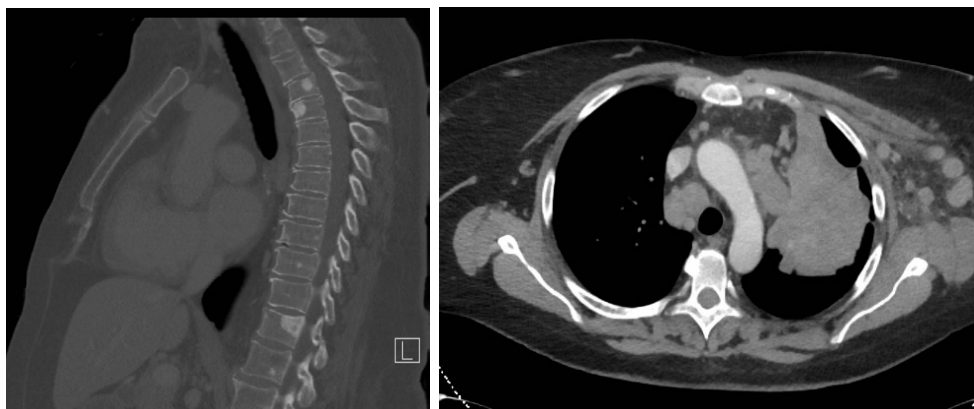
With respect to patterns of metastasis, *ALK*-rearranged NSCLC have a predilection for lymphatic spread, with increased frequencies of intrathoracic lymphadenopathy and lymphangitic carcinomatosis (Figure 2)<sup>31</sup>. The extensive lymphadenopathy seen in *ALK*-rearranged NSCLC can be misinterpreted initially on imaging as representing lymphoma<sup>28,30</sup>. There is also an increased propensity for pleural and pericardial metastases (Figure 2)<sup>31</sup>. The same study by Mendoza, *et al.* reported that osseous metastases, when present, tend to be sclerotic or blastic in nature and may be a useful feature for identifying these mutations<sup>32</sup>. Prior to this report, osseous metastases in NSCLC had been thought to be predominantly lytic in nature. *ALK*-rearranged NSCLC has also been associated with high rates of metastases to the brain, which is also a common site of disease progression<sup>33,34</sup>.

### ROS Proto-Oncogene 1 Rearrangement

ROS proto-oncogene 1 (*ROS1*) rearrangements represent another targetable driver alteration identified in 1-2% of NSCLC<sup>35,36</sup>. Similar to *EGFR* mutations and *ALK* rearrangements, *ROS1* rearrangements are associated with younger age, little to no smoking history, and adenocarcinoma histology<sup>35,36</sup>. Crizotinib is currently the standard first-line treatment for advanced *ROS1*-rearranged NSCLC<sup>8</sup>.



**Figure 2: 46-year-old male non-smoker with ALK-rearranged NSCLC.** (A) Fused FDG-PET/CT image shows extensive FDG-avid mediastinal, hilar, and supraclavicular lymphadenopathy. (B) Axial CT lung window image shows lymphangitic carcinomatosis in the right lower lobe with nodular septal thickening and ground glass opacities. (C) Axial CT mediastinal window shows pleural thickening and a small pleural effusion consistent with pleural metastasis. Extensive lymphadenopathy, lymphangitic carcinomatosis, and pleural metastases are features that have been associated with the presence of an underlying ALK rearrangement in NSCLC.



**Figure 3: 56-year-old female non-smoker with ROS1-rearranged NSCLC.** (A) Sagittal CT image shows sclerotic lesions involving several thoracic vertebral bodies. (B) Axial CT image shows a large left upper lobe mass associated with bilateral mediastinal and left axillary lymphadenopathy. Distant metastatic lymphadenopathy and sclerotic metastases have been associated with underlying ROS1 rearrangements.

Less data is available regarding the imaging features of *ROS1*-rearranged NSCLC. Two small studies have previously reported that the primary tumors in *ROS1*-rearranged NSCLC tend to be peripheral rather than central in location<sup>37,38</sup>. A larger, more recent study, however, did not support these findings and suggested that *ROS1*-rearranged NSCLC share several imaging features to those of *ALK*-rearranged NSCLC, including increased propensity for lymphangitic carcinomatosis and distant lymphadenopathy and tendency to have sclerotic rather than lytic bone metastases (Figure 3)<sup>39</sup>. Similar to the primary tumors in *ALK*-rearranged NSCLC, the primary tumors in *ROS1*-rearranged NSCLC were also less likely to air bronchograms compared to *EGFR*-mutant NSCLC<sup>39</sup>.

### Other potentially targetable mutations

Other oncogenic driver mutations have emerged as promising targets in the treatment of NSCLC. These, among others, include rearranged during transfection proto-

oncogene (*RET*), mesenchymal-epithelial transition gene exon 14 (*ME*Tex14) skipping, and *BRAF* gene mutations. Less data is available regarding the imaging features of NSCLC harboring these mutations.

*RET* fusions are seen in 1-2% of NSCLC and are also more commonly seen in younger patients with minimal to no smoking history and adenocarcinoma histologic subtype<sup>40,41</sup>. Recently, two highly potent, *RET*-selective TKIs have demonstrated promising preliminary safety and efficacy profiles in patients with advanced NSCLC harboring *RET* alterations<sup>42-44</sup>. Small studies investigating the imaging features of *RET*-rearranged NSCLC have reported the increased tendency of the primary tumors *RET*-rearranged NSCLC to be more peripheral rather than central in location<sup>38,45</sup>. In addition, *RET*-rearranged NSCLC has been associated with a higher frequency of brain metastases<sup>46</sup>. This underscores the importance of developing therapies that can cross the blood-brain barrier and that have robust CNS activity.

This high propensity for brain metastases has also been reported in NSCLC harboring METex14 skipping mutations<sup>47</sup>. These mutations are reported in up to 4% of NSCLC and are typically encountered in slightly older patients compared to the other common targetable driver mutations<sup>48,49</sup>. At this time, the imaging features and metastatic patterns in METex14-positive NSCLC have not been extensively studied.

Finally, *BRAF* mutations are another promising target in NSCLC<sup>50</sup>. *BRAF* mutations have historically been classified as either V600-mutant or non-V600-mutant, but emerging evidence regarding biological differences among those with non-v600 mutations has allowed for further stratification into functional classes, which have been shown to have differences in clinical outcomes<sup>51</sup>. Previous studies, including one by our group, failed to show differences in the imaging features of the primary tumor among these functional classes, with tumors from all groups typically presenting as solid masses or nodules<sup>30,52</sup>. We did find, however, that V600-mutant NSCLC may be more likely to have intrathoracic metastases while non-V600-mutant NSCLC may have more intra-abdominal metastases at the time of presentation<sup>52</sup>.

## Conclusions

Current evidence supports that there are differences in the imaging features and patterns of metastases among NSCLC harboring different targetable oncogenic driver mutations. The mechanism behind the morphological differences of the primary tumor and the differences in metastatic tropisms among these molecular subgroups remain unclear, but they suggest differences in their respective underlying biology.

While these imaging features and metastatic patterns may suggest the presence of specific targetable mutations, they are unlikely to replace molecular genotyping in identifying these mutations and guiding therapy. They may, however, assist in selecting patients who may benefit from expedited pathways for molecular testing or repeat testing when the initial genotyping results are discordant with the clinical and imaging presentation. More study is necessary to elucidate the mechanism behind these differences and their implication to treatment and prognosis.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest related to this work. Other disclosures (not related to this work) are below:

**DPM:** No relevant disclosures.

**SRD:** Provides independent image analysis for hospital contracted clinical research trials programs for Merck, Pfizer, Bristol Mayer Squibb, Novartis, Roche, Polaris, Cascadian, Abbvie, Gradalis, Clinical Bay, Zai laboratories. Received honorarium from: Siemens, not related to work.

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