Non small cell lung cancer with targetable driver alterations: Imaging perspective

Eric W Zhang and Subba R Digumarthy*
Department of Radiology, Division of Thoracic Imaging and Intervention, Massachusetts General Hospital, USA

Abstract

The discovery of targetable driver alterations has transformed the treatment paradigm in advanced non-small cell lung cancer (NSCLC). Small molecule tyrosine kinase inhibitors have increased survival in the treatment of metastatic NSCLC, and it is now standard of care to screen for targetable driver mutations. The knowledge of imaging findings that are characteristic of specific driver alterations will help to identify, triage, and initiate early treatment in patients. This review will explore the most common driver alterations in NSCLC, the recent advances in targeted therapy, and the characteristic clinical and imaging features.

Introduction

The treatment of advanced non-small cell lung cancer (NSCLC) has dramatically changed with the discovery of driver oncogenes and the development of small molecule tyrosine kinase inhibitors (TKIs) that impede signaling pathways. The change started with discovery of the effectiveness of the TKI gefitinib in the treatment of epidermal growth factor receptor (EGFR)-mutant advanced NSCLC [1,2]. This has sparked the hunt for other oncogene driver alterations and therapeutic agents, and led to discovery of activating chromosomal rearrangements of the anaplastic lymphoma kinase (ALK), receptor tyrosine kinase 1 (ROS1), and rearranged-during-transfection (RET) genes as well as somatic variations in the V-raf murine sarcoma viral oncogene homolog B (BRAF) and mesenchymal-epithelial transition (MET) genes [3-11]. These discoveries coupled with encouraging results from multiple controlled trials using targeted therapy have led to a paradigm shift in the diagnosis and treatment of advanced NSCLC, whereby it is now routinely recommended to test for actionable driver alterations [12,13]. This combination of therapeutics and diagnostics, aptly termed *theranostics*, represents the progression towards personalized medicine in modern oncology [14,15].

Despite recommendations for routine molecular testing for NSCLC driver oncogenes from both US and European guidelines [12,16], the real-world clinical practice remains suboptimal. A recent multinational study looking into the rates of molecular testing in advanced NSCLC showed substantial variability in percentage of patients undergoing EGFR mutation testing ranging from 41% in Germany to 97% in Taiwan, and ALK rearrangement testing was even less, ranging from 23% in Germany to 3% in Taiwan [17]. In the United States a recent study demonstrated only 66.9% of patients underwent ALK testing for advanced NSCLC in community hospitals [18]. This heterogeneity in practice is the result of local differences in drug approval timelines, reimbursement policies, and test panels [17]. Furthermore, testing for NSCLC driver alterations is continuously evolving with no standardized testing platform [19]. Given these roadblocks, it is not surprising that parallelizing the rise of precision medicine is an increased interest in radiogenomics, which attempts to define relationships between molecular genomic markers and imaging features [20,21]. By leveraging known clinical and imaging features, the triaging of patients with advanced NSCLC for specific molecular testing and treatment selection can potentially be facilitated [22]. The purpose of this review is to outline the current NSCLC driver alterations, the latest advances in approved and off-label targeted therapies, and most recent developments in NSCLC radiogenomics.

Targeted oncogene therapy

Underlying the concept of targeted therapy is the idea of oncogenic addiction [23], whereby cancer cells become dependent on specific oncogenes for proliferation and survival. In healthy cells, multiple redundant genes serve similar functions, whereas, in cancer cells, these same genes are often inactivated [23]. As shown in in-vitro studies, inactivation of critical driver oncogenes in cancer cells leads to cellular death due to dysregulated pro-survival and pro-apoptotic signals [24]. The small molecule TKIs and monoclonal antibodies can exploit this intrinsic weakness and are therefore effective in specific oncogene-driven NSCLCs [25].

Epidermal growth factor receptor gene (EGFR)

Epidermal growth factor receptor (EGFR) is part of tyrosine kinase receptor families responsible for cellular differentiation, proliferation, and anti-apoptosis pathways [26,27]. EGFR is implicated in the activation of ERK MAPK, AKT-PI3K, and PLC-γ1-PKC molecular pathways, which allows for unregulated growth and survival of cancer cells [27]. Though EGFR is overexpressed in up to 80% of NSCLC [28], only the activating mutations in the EGFR gene are the frequent targets...
for therapy and include TKIs such as erlotinib, gefitinib, and afatinib. The two most prevalent driver mutations of the EGFR gene are L858R missense substitutions and exon 19 deletions [29,30].

The landmark Iressa Pan-Asian Study (IPASS) heralded the use of the TKI gefitinib as first-line treatment in the management of EGFR-mutant advanced NSCLC [31]. At the same time, patients with EGFR wild-type fared better with standard chemotherapy than gefitinib [HR 2.85; P <0.001], a finding that underlines the importance of early and accurate molecular testing in the treatment of advanced NSCLC [31]. Subsequent clinical trials comparing gefitinib [32-34] as well as other TKIs such as erlotinib [35,36], afatinib [37,38], and osimertinib [39] to chemotherapy as first-line treatment in EGFR-mutated NSCLC have all confirmed findings of improved PFS and superior quality of life.

EGFR mutations are among the most prevalent actionable driver mutations in NSCLC ranging from up to 15% in Europe, 24% in the United States, and 47% in Asia [40,41] and are seen more frequently in Asians, younger populations, and females with minimal smoking history [42-45]. Investigations into imaging features of EGFR-mutant NSCLC have demonstrated several distinguishing features from wild-type EGFR NSCLC, including tumors with more internal cavitations, increased prevalence of air-bronchograms, and increased ground-glass component on computed tomography imaging [46-49]. An important differentiating feature of EGFR mutation adenocarcinomas is the increased frequency of diffuse “miliary-like” lung metastases (Figure 1), an association that has been reported in multiple studies [47,50-52] In the setting of advanced NSCLC with mild or no smoking history, the presence of diffuse lung metastases should raise the index of suspicion for an underlying EGFR mutation and potentially more rapid triaging for molecular testing [52]. In the realm of functional imaging, 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) have demonstrated lower maximum standardized uptake value in EGFR-mutated NSCLC when compared to EGFR wild-type NSCLC [53]. Additionally, preliminary radiomic studies have shown potential in predicting EGFR mutations in NSCLC, although more research is necessary as such techniques have not been standardized in routine clinical practice [53,54].

**Anaplastic lymphoma kinase (ALK)**

ALK rearrangements were initially discovered in non-Hodgkin lymphoma in 1994 [55]. In 2007, Soda et al. identified similar ALK rearrangements fusing ALK gene to the echinoderm microtubule-associated protein-like 4 gene (EML4) on chromosome 2. The expression of this EML-ALK fusion protein aberrantly activates multiple signaling pathways, including PI3K/Akt and Ras/Mek/Erk cascades, involved in cellular survival and proliferation [56].

Multiple trials demonstrated the efficacy of TKIs in treating ALK-positive NSCLC. The earliest clinical trials demonstrated improved outcomes using crizotinib as first-line and second-line treatment for ALK-positive advanced NSCLC [57-59]. Subsequent randomized clinical trials demonstrated the superiority of alectinib to crizotinib [60]. Alectinib is now the preferred first-line targeted therapy of advanced EML-ALK lung cancer [61]. The other agents that are approved include ceritinib, brigatinib, and lorlatinib [62-64]. Lorlatinib is the latest third-generation TKI with potent ALK-mutation coverage and CNS penetration [65].

ALK-positive NSCLC is found in up to 5% of lung adenocarcinomas [66]. ALK-positive NSCLC has an earlier age of onset with a median age of 52 years compared to 64 years in wild-type NSCLC [67]. It is interesting to note that ALK rearrangement in other cancers such as anaplastic large cell lymphomas also have early disease onset in children and young adults [56]. There is a strong association between ALK-positive NSCLC and light- or never-smoking history. Histologically, the vast majority of EML4-ALK mutations are adenocarcinomas and is more likely than other mutations to be solid tumors containing signet ring cells [68]. Importantly, it has been noted that ALK rearrangements occur largely exclusive from EGFR or KRAS mutations [67,69,70], perhaps related to underlying oncogene addiction.

Much progress has been made recently in the realm of radiogenomics in terms of imaging characteristics of ALK-positive NSCLC. The latter is more likely to be solid tumors with fewer propensities for air bronchograms when compared with EGFR-positive tumors. These findings have been reiterated in multiple past studies [71-73] and confirmed on a recently published meta-analysis [74]. The largest study to date on the imaging features of ALK-positive NSCLC have also recently demonstrated that these tumors are more likely to be found in the lower lobes and have increased association with sclerotic bone metastases (Figure 2) when compared to EGFR-positive NSCLC. Furthermore, ALK-positive tumors have been found to be more likely associated with distant nodal metastases and lymphangitic spread when compared to EGFR positive tumors [75,76]. These novel discoveries have the potential to change management in the care of advanced NSCLC. Although imaging alone will not replace molecular genetic testing, imaging and clinical features of NSCLC can potentially help in the prioritization of testing or re-testing following an inconclusive initial result and expedite initiation of targeted TKIs in patients with ALK-positive NSCLCs [75].

**ROS1 rearrangements**

Rearrangement of the receptor tyrosine kinase 1 (ROS1) gene on chromosome 6q22.1 was first implicated in NSCLC in 2007 [3]. Prior to this discovery, ROS translocation had been implicated in glioblastoma [77], with simultaneous discovery of the same genetic alteration in multiple other malignancies such as cholangiocarcinoma, ovarian cancer, and angiosarcoma [78]. Similar to other driver oncogenes, increased ROS signaling has been associated with cellular proliferation and survival with the involvement of the PI3K/AKT, MAPK/ERK, SHP1/2, and JAK/STAT3 signaling pathways [79-81]. Interestingly, the ROS1 gene has been found to be related to ALK on phylogenetic analysis, and this genetic homology likely explains the cross-inhibitory

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**Figure 1.** CT image of the chest in lung windows demonstrating presence of diffuse (miliary) lung metastases in EGFR-positive NSCLC. Note the primary lung mass in the posterior right upper lobe (arrow) and small right malignant pleural effusion (arrowhead).
activity of several ALK-mutation tyrosine kinase inhibitors in ROSI-mutation NSCLC [78].

Crizotinib was the first TKI to be approved by the FDA [82] in the treatment of ROSI-rearranged NSCLC in 2016, following the results of the phase I PROFILE 1001 study, which demonstrated a disease control rate (DCR) of 90% and a median progression-free survival (PFS) of 19.2 months [83]. Entrectinib has recently been approved by the FDA [84] for the treatment of ROSI-rearranged NSCLC based on part in results from three clinical trials, demonstrating median PFS of 19.3 months and objective response rate (ORR) of 72 percent [85]. Although not yet approved by the FDA, lorlatinib has also demonstrated efficacy in the treatment of ROSI-mutant NSCLC, with favorable preliminary results [86]. Additional TKIs under research with potential utility in ROSI-positive NSCLC include ceritinib [87], cabozantinib [88], and repotrectinib [89].

ROS-I rearrangement is found in approximately 1-2% of NSCLC [90,91]. Comparable to ALK-rearranged NSCLC, ROSI rearrangement NSCLC is associated with a younger age of onset and is found in predominantly minimal-to-never smokers. Adenocarcinoma histology is also found in the vast majority of cases [7,90]. However, despite these clinicopathologic similarities to ALK-rearranged NSCLC, ROSI-rearranged NSCLC has been found to have significantly lower rates of extrathoracic metastases and a lower incidence of brain metastases [92]. These results were recently corroborated in a radiogenic analysis of ROSI versus EGFR and ALK mutation NSCLC [93]. Also, ROSI NSCLC was found to be more associated with lymphangitic carcinomatosis (Figure 3) and sclerotic bone metastases than EGFR-mutant NSCLC [93]. Additional studies on the imaging features of ROSI-rearranged NSCLC have noted that primary cancers tend to be located at the periphery of the lungs [94,95].

**BRAF mutation**

Mutations in the V-raf murine sarcoma viral oncogene homolog B (BRAF) gene are relatively uncommon, seen in less than 5% of NSCLC [11]. BRAF is an effector of the RAS-RAF-MEK-ERK pathway, which regulates cellular survival, growth, and proliferation and is first described in melanoma [96,97]. Approximately half of BRAF mutations in NSCLC are the result of substitution of valine for glutamic acid at codon 600 (V600E) [98]. While historically, BRAF mutations were classified according to the presence or absence of this point mutation, new research has subdivided BRAF mutations into three functional classes related to the degree of RAF kinase activation. Class I mutations are V600-positive and function through monomorphic kinase-independent signaling. Class II and III mutations are both V600-negative and with increased kinase signaling in class II mutations or impaired kinase signaling in class III mutations [99,100].

The classification of BRAF-mutation NSCLCs has significant clinicopathologic and prognostic implications. Class I BRAF V600 mutation NSCLC have demonstrated superior progression-free survival when treated with standard chemotherapy agents carboplatin and pemetrexed [101]. Similarly, studies of BRAF V600 mutation small-molecule TKIs have had the most success, due in part to prior clinical trials on the treatment of melanoma [102]. Dabrafenib [103], vemurafenib [104], and combination therapy involving dabrafenib and trametinib [105,106] have all shown promise in class I V600-positive mutation NSCLC. Currently, dabrafenib plus trametinib is approved by the FDA for BRAF V600E mutation NSCLC patients who have progressed on chemotherapy. Conversely, the research on BRAF non-V600 mutation NSCLC has been less encouraging with insufficient data to draw any major conclusions [107]. Unsurprisingly, the prognosis of non-V600 mutation NSCLC is significantly worse than V600 mutation NSCLC with a three-year survival of 24 percent in V600 mutation NSCLC versus 0 percent in non-V600 mutation [108]. From a clinical perspective, V600 mutation patients are more likely to be minimal- or never-smokers when compared to non-V600 mutation patients [108]. A recent study on the imaging features of BRAF showed that the majority of such tumors were solid

**Figure 2.** Sagittal and axial CT images of the chest on bone and lung windows in a patient with genotype-proven ALK-positive NSCLC. (a) Multiple sclerotic metastases are noted in the vertebral bodies and manubrium (arrowheads). (b) The primary mass is noted in the right inferior hilum (arrow).

**Figure 3.** Axial CT images of the chest in lung windows at the lung bases and at the level of the midlung in a patient with genotype-proven ROSI-positive NSCLC. (a) Increased nodular interlobular septal thickening at the lung bases in keeping with worsening lymphangitic carcinomatosis (arrows). (b) The primary mass is seen in the superior segment of the left lower lobe (arrowhead).

**Figure 4.** Axial CT images of the chest and abdomen on soft-tissue windows and accompanying 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) images in two different patients with genotype-proven BRAF-positive NSCLC. (a) Images of V600-negative BRAF NSCLC demonstrating solitary right adrenal metastasis with increased uptake on FDG-PET (arrows). (b) Images of V600-positive BRAF NSCLC demonstrating multiple intrathoracic metastases along the right mediastinal pleura (arrowheads) and in multiple mediastinal lymph nodes, with increased uptake on FDG-PET.
and mass-like. The authors demonstrated no significant difference in imaging features between the three functional classes of BRAF-mutation. Intrathoracic metastases and pleural involvement was found to be more common in class I mutation tumors compared to class II or III, whereas the latter had an increased propensity for intra-abdominal spread (Figure 4) [109].

Other targetable mutations

While TKIs have all been approved by the FDA in the front-line treatment of EGFR, ALK, ROS1, and BRAF-positive NSCLCs [12], there exist many other potentially targetable driver mutations in NSCLC, with much ongoing research in this domain. The most promising of oncogenic drivers include amplification of the mesenchymal-epithelial transition (MET) factor, rearrangement of the rearranged during transfection (RET), and mutations of the human epidermal growth factor 2 (HER2) genes. Current clinical trials involving these driver alterations have been either inconclusive or negative to date, with off-label usage of tyrosine kinase inhibitors and immunomodulators [15,110]. Similarly, there is currently a paucity of radiogenomic research on the imaging features of these particular driver mutations.

Conclusion

The groundbreaking discovery of specific driver alterations in NSCLC also lead to the discovery and adoption of small-molecule tyrosine kinase inhibitors for the treatment of advanced NSCLC. The clinicopathologic and radiogenomic studies documented significant differences in clinical presentation, patterns of metastases, and imaging features among the different driver mutations in NSCLC. Although not as specific as molecular genotyping, these clinical and radiogenomic characteristics can help in triaging patients for appropriate test selection, expedited diagnosis and therapy, and repeat genotyping in the event of discordant results. The emergence of a multitude of new driver oncogenes means that more research is needed on all fronts.

Conflict of interest

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