Genomic Characterization of Lung Cancer and Its Impact on the Use and Timing of PET in Therapeutic Response Assessment

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KEYWORDS

• Genomics • Non–small cell lung cancer (NSCLC) • PET • Therapeutic response assessment

KEY POINTS

- Non–small cell lung cancer (NSCLC) is a heterogeneous disease comprising different histologic and molecular subtypes with distinct clinical characteristics, outcomes, and prognosis.
- PET has an established role in the diagnosis, staging, and monitoring of therapeutic response in patients with NSCLC.
- Early therapeutic response on PET is associated with improved outcomes in patients receiving targeted therapies.
- Newer PET tracers have been developed in hopes of improving the sensitivity and specificity of PET imaging in predicting response to therapeutic targets.

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related mortality, with most patients presenting with locally advanced or metastatic disease.[1] The widespread implementation of ^{18}F-fluorodeoxyglucose (FDG) PET has led to earlier diagnosis of lung cancer with a more accurate assessment of nodal and distant metastatic disease, leading to improvements in treatment planning and selection.[2] Imaging in tumor response assessment is central in determining therapeutic decisions for individual patients as well as quantifying benefit of novel therapies in clinical trials.

In this review article, the authors summarize the genomic landscape of non–small cell lung cancer (NSCLC), highlighting genotypes with available targeted therapies and the implication of clonal evolution and intratumor heterogeneity in the development of drug resistance. They review the impact and timing of PET in therapeutic response assessment in NSCLC, together with limitations of conventional response assessment criteria in the era of targeted therapies and immunotherapies. Also discussed are emerging PET radiotracers that have been developed and evaluated as a noninvasive assessment of biological processes in vivo.

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THE GENOMIC LANDSCAPE OF NON–SMALL CELL LUNG CANCER

NSCLC accounts for 85% of all lung cancer cases and comprises 3 major histologic subtypes with the most common being adenocarcinoma followed by squamous cell carcinoma and less commonly large cell carcinoma.[1] Most cases of lung cancer are related to tobacco smoking; however, approximately 10% to 20% of cases occur in patients who have never smoked, and the declining rates of smoking equals a proportional increase of incidence among never smokers.[3,4] Smoking-related lung cancer has a significantly higher number of mutations and is associated with cytosine to adenine (C > A) nucleotide transversions. Transversions have been associated with different gene mutations in lung cancer; for example, *KRAS* mutations are more frequent in transversion high patients, compared with transversion low patients, who are commonly never smokers and have a higher prevalence of *EGFR* mutations.[3,5]

In the last decade or so, the application of more advanced and accurate high-throughput platform with next-generation sequencing has led to the first genome-wide mutational analyses.[5,6] Lung adenocarcinoma has high rates of somatic mutation, and it is possible to identify oncogenic driver mutations in more than 50% of cases.[7] Driver mutations initiate the transformation of a nonmalignant cell to malignancy and sustain the tumor's survival. This concept of "oncogene addiction," which makes the tumor extremely reliant on downstream growth and survival pathways, provides a potential molecular Achilles heel that may be targeted therapeutically.[8,9]

The most frequent oncogenic driver mutations in lung adenocarcinoma include *KRAS* mutations (33% of tumors), *EGFR* mutations (15%), *ALK* rearrangements (3%–5%), *BRAF* mutations (2%), *ROS1* rearrangements (1%–2%), *PIK3CA* mutations (1%–2%), and *MET* amplifications (1%–2%) (**Fig. 1**). Several other common, but not clinically actionable, loss-of-function mutations and deletions in tumor suppressor genes are as follows: *TP53* (46% of tumors), *STK11* (17%), *RB1* (4%), *NF1* (11%), *CDKN2A* (4%), *SMARCA4* (10%), and *KEAP1* (17%). In recent years, molecular targeted therapies have improved the outcome of patients whose tumors harbor an activating mutation in *EGFR* or *ALK* and *ROS1* gene rearrangement, with other investigational therapies targeting *BRAF*, *MET*, and *RET* currently in clinical trials.[5,7,10]

Squamous cell lung carcinomas are characterized by a high overall mutation rate and marked genomic complexity. Compared with adenocarcinoma, almost all squamous cell lung cancers display somatic mutation of *TP53*, with fewer mutations in genes encoding receptor tyrosine kinase and a higher frequency of loss of tumor suppressor functions affecting genes such as *PTEN*, *NOTCH1*, and *RB1*.[11] Potential therapeutic targets have been identified, such as *FGFR1* amplification, *DDR2* mutation, and *PIK3CA* amplification and mutation, with preliminary activity seen in some early phase trials.[12–14] Although the genomic landscape of NSCLC is illustrated by large numbers of somatic copy number alteration, gene rearrangement, and recurrent alteration in multiple key pathways, most patients lack an actionable driver mutation and are therefore treated with nontargeted therapies, such as chemotherapy or immunotherapy.

At present, structural imaging with computed tomographic (CT) scan is still the standard diagnostic imaging test for assessing therapeutic response, in either the curative setting or more advanced disease. There are, however, several limitations with structural imaging in NSCLC that impede the ability to accurately assess response, including (1) difficulty of CT scan in differentiating between tumor and inflammation or scar tissue after surgery or radiotherapy; (2) difficulty measuring irregular tumor shapes; (3) inaccuracy of lymph node staging; (4) consolidation of the lung obscuring tumors; and (5) poor contrast enhancement between tumor and normal thoracic structures.[15]

PET/CT is becoming the new standard of care in the diagnosis and staging of NSCLC given its high diagnostic accuracy. It provides a more comprehensive assessment of both structural and biological changes[16–18] and is increasingly being used for monitoring treatment response.

Genotypes with Available Targeted Therapies

The discoveries of oncogenic drivers together with the development of targeted therapies have revolutionized the management of advanced NSCLC, improving outcomes for the subgroup of patients with actionable molecular targets. The Lung Cancer Mutation Consortium demonstrated that patients with actionable oncogenic driver mutations who were treated with molecular targeted therapies lived longer.[7] Current guidelines from the College of American Pathologist, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend testing for *EGFR* mutation and *ALK* rearrangement in all patients with advanced stage

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