Non–small Cell Lung Cancer PET Imaging Beyond F18 Flurodeoxyglucose

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KEYWORDS

• Lung cancer • PET/CT • Carcinoid • Proliferation • Hypoxia • Angiogenesis • Personalized therapy

KEY POINTS

- Non–small cell lung cancer (NSCLC) has significant heterogeneity histologically, biologically, and molecularly.
- F18 Flurodeoxyglucose (FDG) is a nonspecific PET tracer. Although useful, FDG PET is not able to define the entire complexity of NSCLC heterogeneity.
- Gallium-68 (^{68}Ga)-somatostatin analog PET imaging has significantly improved diagnosis of well-differentiated pulmonary carcinoid tumors.
- PET tracers targeting tumor proliferation, hypoxia, and angiogenesis are promising for improving the sensitivity and specificity of PET imaging for better lesion characterization, treatment stratification, and therapeutic monitoring.
- PET tracers designed to characterize driver genes and pathway-specific targets could provide noninvasive key information in tumor genetic characterization for personalized therapy in NSCLC patients.

INTRODUCTION

F18 Flurodeoxyglucose (FDG) PET/CT is now widely used clinically and has revolutionized tumor staging, restaging, treatment planning, and prognosis assessment in lung cancer and many other malignancies. The interpretation of FDG PET is dependent, however, on tissue glucose metabolism, which is not malignancy specific. Not all malignancies are FDG avid. Many benign etiologies, especially inflammatory/infectious changes, may cause increased FDG activity. It is not rare to have false-positive and false-negative findings on an FDG PET scan.[1,2] Furthermore, all histologic subtypes of lung cancer have significant heterogeneity—histologically, biologically, and molecularly.[3] In addition to energy metabolism, multiple microenvironmental factors, including hypoxia and angiogenesis, may affect tumor progression and treatment response. Tumor heterogeneity may present in different tumor masses within the same person, and even within the same tumor mass. The presence of significant tumor heterogeneity may affect treatment outcome. FDG PET, although useful, is not able to define the entire complexity of NSCLC heterogeneity. As a result, more specific PET imaging probes are extremely valuable for accurate tumor staging studies and to determine response to treatment.

Traditionally, histologic findings serve as the most important findings guiding treatment decisions in non–small cell lung cancer (NSCLC) and other malignancies. This has changed significantly in the past decade, because molecular diagnostics may provide critical information of driver mutations in lung cancer patients to help selecting the best

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targeted agent for personalized patient care. NSCLC subtypes are divided not only by histology criteria but also by molecular characteristics. Many oncogene mutations, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), have been identified as important tumor markers and critical targets in NSCLC therapy. Much progress has been made recently for lung cancer in recent years to develop new PET tracers to improve the sensitivity and specificity of PET imaging for better lesion characterization, treatment stratification, and therapeutic monitoring. Especially, recent development in molecular diagnostics and targeting agents for genomically defined lung cancer patients have brought in a new era in the diagnosis and treatment of lung cancer. Although most of these new tracers are in the early stages of development or are still under research, they represent the future of PET imaging with unlimited potential clinical value. This article reviews some of current progresses of PET imaging other than FDG in development, clinical practice, and potential future applications.

TRACERS IN PULMONARY NEUROENDOCRINE TUMORS

Pulmonary neuroendocrine tumors are a heterogeneous group of malignancies that arise from neuroendocrine cells (Kulchitsky cells), including low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), and high-grade malignancies (large cell neuroendocrine carcinoma and small cell lung cancer).[4,5] High-grade pulmonary neuroendocrine tumors tend to have high FDG activity. A well-differentiated typical carcinoid (accounting for 2% of primary lung neoplasms), however, often with intense enhancement in contrast-enhanced CT study, generally has low uptake on FDG PET/CT imaging, (see Yiyan Liu's article, "Lung Neoplasms with Low F18-Fluorodeoxyglucose Avidity," in this issue).

The development of ^{68}Ga-1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid-d-Phe1,Tyr3-octreotate (^{68}Ga-DOTATATE) (Food and Drug Administration approved) and other somatostatin-based PET tracers (^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC) have significantly improved diagnosis of neuroendocrine tumors including pulmonary carcinoid. All 3 (DOTATOC, DOTANOC, and DOTATATE) PET tracers bind specifically to subtypes 2 of somatostatin receptor (SSTR). DOTANOC also presents a good affinity for subtypes 2, 3, and 5 of SSTR. ^{68}Ga–DOTA-peptides PET imaging offers multiple advantages over traditional SSTR scintigraphy (indium ^{111}In–pentetreotide), including a much higher affinity for SSTRs, superior resolution and contrast, and shorter examination times, making it superior to ^{111}In–DTPA-pentetreotide single-photon emission CT (SPECT) or SPECT/CT imaging in the diagnosis of pulmonary and gastroenteropancreatic neuroendocrine tumors.[6]

For patients with suspected pulmonary carcinoid tumors, somatostatin-based PET significantly outperformed FDG PET. Venkitaraman and colleagues[7] performed a prospective study, including 32 patients with clinical suspicion of bronchopulmonary carcinoid. These patients were evaluated with ^{68}Ga-DOTATOC PET/CT and FDG PET/CT. Using tissue diagnosis as the reference standard (confirmed 21 typical carcinoid tumors, 5 atypical carcinoids, and 6 noncarcinoid tumors), the sensitivity, specificity, and accuracy of ^{68}Ga-DOTATOC PET/CT in the diagnosis of pulmonary carcinoid tumor were 96.15, 100%, and 96.87%, respectively, whereas those of FDG PET/CT were 78.26, 11.1% and 59.37%, respectively. More recently, Walker and colleagues[8] also demonstrated that ^{68}Ga-DOTATATE PET is more specific than FDG PET in the evaluation of indeterminate pulmonary nodules.

Incorporating ^{111}In–DTPA-octreotide[9] or ^{68}Ga-DOTATATE[10] ^{68}Ga-DOTATOC[11,12] imaging to FDG PET could improve sensitivity and specificity in the diagnosis of pulmonary carcinoid tumors. Indolent tumors, such as typical well-differentiated bronchial carcinoids, have low FDG uptake (therefore, FDG PET is of limited use at discriminating tumors from scars and distal atelectasis in these patients) but have high uptake on ^{68}Ga-DOTATATE PET imaging (which makes differential diagnosis easy and simple), whereas atypical and higher-grade carcinoids have less ^{68}Ga-DOTATATE avidity but are more FDG avid.[10] There is strong evidence indicating that PET imaging with ^{68}Ga-somatostatin analogs and FDG PET may provide complementary information for evaluating pulmonary neuroendocrine tumors. It has been recommended that PET imaging with ^{68}Ga-somatostatin analogs should be the first choice and performed first in the initial evaluation of patients with clinical suspicion of pulmonary carcinoid, and, if negative, FDG PET/CT could be performed subsequently.[13] Large prospective studies analyses are needed to validate this diagnostic strategy.

PET IMAGING OF TUMOR PROLIFERATION

Uncontrolled cell proliferation is a key feature of malignancy. Increased cell division activity is an important prognosticator of various malignancies and an important target of anticancer treatment.

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