^{18}F-Fluorodihydroxyphenylalanine in the Diagnosis of Neuroendocrine Tumors

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KEYWORDS

• ^{18}F-Fluorodihydroxyphenylalanine • Neuroendocrine tumor • PET/computed tomography • Pheochromocytoma • Medullary thyroid cancer

KEY POINTS

- ^{18}F-Fluorodihydroxyphenylalanine (FDOPA) shows high sensitivity in detecting catecholaminergic tumors such as pheochromocytomas and paragangliomas, and is the preferred tracer for nuclear medicine imaging of medullary thyroid cancer (MTC).
- The strengths of FDOPA include high tumor-to-background contrast, ability to identify lesions with low somatostatin receptor density, and convenience in assessing patients with MEN-2 syndrome who are at risk of having both MTC and pheochromocytoma owing to their genetic predisposition.
- The triad of FDOPA, ^{18}F-fluorodeoxyglucose, and ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) peptides forms the backbone of all clinical imaging of neuroendocrine tumors in institutions with PET/computed tomography capability.

INTRODUCTION

The current choice of radionuclide techniques for the imaging of neuroendocrine tumors (NETs) has expanded over the last 10 years and requires careful knowledge about the known or presumed characteristics of the disease entity, including genomic features. Tracer selection must take account of subsequent management, for example, whether surgery or another local form of therapy is considered or whether the patient should be a candidate for peptide-based radiotherapy (PBRT). While imaging of somatostatin receptors is preferred in most cases, the use of ^{18}F-fluorodihydroxyphenylalanine (FDOPA) retains its value in 2 important tumor groups: catecholaminergic tumors derived from chromaffin cells of the neural crest (pheochromocytoma, paraganglioma) and medullary thyroid cancer (MTC). Furthermore, FDOPA can be distributed from the site of production to remote hospitals, and is a viable option for general imaging of NETs in institutions that do not have access to ^{68}Ga chemistry.

For radiochemical synthesis of FDOPA, both electrophilic and nucleophilic fluorination methods are applicable. Electrophilic fluorodestannylation[1] is widely used, rapid, and easily automated, but suffers from poor yield and low specific radioactivity.

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Recently the more complicated but higher-yielding nucleophilic approach has been used in commercial synthesis devices[2] with improvement in the availability of FDOPA for human studies. FDOPA has been registered for human use in several European countries since 2006.[3] It may be purchased from the radiopharmaceutical industry, which renders FDOPA PET/computed tomography (CT) the preferred tracer in clinical nuclear medicine departments with limited or absent resources in radiochemistry.

The mechanism of tracer uptake has been established, and is related to capacity of NETs to store and secrete biogenic amines and hormones.[4] However, uptake may not be directly related to the magnitude or presence of hormonal activity, and active transport of neutral amino acids via the sodium-independent system L is an important mechanism of uptake[5] even in the presence of endocrine symptomatology. To enhance signal-to-noise ratio, carbidopa is commonly administered prior to imaging to block decarboxylase activity, which converts FDOPA to ^{18}F-fluorodopamine.[4,6] The experience in the diagnosis of a variety of NETs covers the last 15 years, and is thus longer and wider than that of any of the 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) peptides or ^{11}C-labeled compounds.[3] **Box 1** highlights key information about the practical use of FDOPA among the increased diversity of tracers available for PET and single-photon emission CT.

This article presents the authors' experience of cases whereby FDOPA shows compelling evidence of added value in the management of NETs. Given the heterogeneity of NETs in expression of somatostatin receptors and the variable affinity of different DOTA peptides to 5 subclasses of receptors, it is obvious that patients with unexpected negative findings on peptide-based imaging may benefit from FDOPA, especially if no indication of poor differentiation, oncogenic activation, or other aggressive behavior exists. If the latter 3 features predominate, the authors suggest that ^{18}F-fluorodeoxyglucose (FDG) imaging should be considered. For a comprehensive review of FDOPA imaging in comparison with alternative tracers the reader is referred to the recent article by Balogova and colleagues,[3] which covers all important studies in various forms of NETs. This review also covers studies on those special forms of NETs for which FDOPA is not recommended as the first-line PET tracer, such as Merkel cell carcinoma, small cell lung cancer, and bronchial carcinoids. It must be emphasized, however, that even for these tumors, in sporadic cases FDOPA imaging can be useful as a complementary imaging modality.

Box 1
Pearls, pitfalls, and practical points in the use of FDOPA for the diagnosis of NET

Interpretative Pearls

Wide clinical experience covering 10 to 15 years and all different forms of NET

High specific uptake based on active transport and intracellular storage

Somatostatin receptor density is not directly related to uptake

Low uptake in inflammatory cells

Superior sensitivity compared with somatostatin receptor scintigraphy

Hormonal activity is not necessary for positive uptake, although metabolic and endocrine activity appear to have a relationship

"One-stop-shop" for evaluation of patients with MEN-2 syndrome

Interpretative Pitfalls

Shows fewer lesions than ^{68}Ga-labeled DOTA peptides in the majority of gastroenteropancreatic NETs

Not applicable if peptide-based radiotherapy is considered

Low uptake in paragangliomas of patients harboring mutated succinate dehydrogenase subunit B (SDHB)

Low uptake in medullary thyroid cancer (MTC) in patients having serum calcitonin doubling time less than 24 months

Low uptake in poorly differentiated NETs

Practical Points

Dynamic imaging may be useful in evaluation of pancreatic islet cell tumors and neck in patients with MTC

Preinjection oral carbidopa may mask uptake in islet-cell tumors

On-site radiopharmaceutical production is not mandatory; commercial vendors are available in Europe

IMAGING TECHNIQUE AND ANALYSIS

The whole-body technique used at the authors' institution has been described previously.[7] In brief, the patients fast at least 6 hours before tracer injection, and 150 mg of carbidopa is administered orally 30 minutes before injection to curb amino acid decarboxylase activity peripherally. However, it is controversial as to whether patients with a suspicion of pancreatic islet-cell tumor should receive carbidopa, and experience and institutional guidelines