

## <sup>18</sup>F-DOPA and Other Radiopharmaceuticals for Imaging Unknown Primary Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a heterogeneous and complex group of neoplasms that have various biologic, chemical, and physical behaviors, mainly depending on the degree of differentiation and the location (1). The simplest clinical classification is between functioning tumors, for which a specific syndrome related to hypersecretion of peptides, biogenic amines, or hormones is observed, and nonfunctioning, for which no specific symptoms related to tumor production are present (2). Although considered relatively rare entities, NETs are increasing in incidence, with about 70% of them deriving from the gastroenteropancreatic system (1,3).

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NETs tend to be generally slow-growing, but approximately two thirds have metastases at diagnosis and so are not amenable to surgery, which remains the treatment mainstay (4). As a matter of fact, clinical presentation is often nonspecific, resulting in delays in diagnosis (up to 5–7 y) (4). Prognosis depends on several variables, including tumor proliferative activity, often evaluated by the Ki-67 index on tumor cells (5).

Nuclear medicine radiopharmaceuticals emitting single photons and positrons allow accurate molecular imaging of NETs, complementary to anatomic–morphologic techniques such as CT and MR (6). In particular, expression of somatostatin receptors by NETs has been exploited for both diagnostic and therapeutic purposes (7).

Because most NETs overexpress somatostatin receptors, they can be successfully visualized in vivo by somatostatin receptor imaging, which has improved their detection, as shown by epidemiologic data indicating a worldwide increase in the prevalence and incidence of these tumors in the past few decades (3). <sup>111</sup>In-pentetreotide is certainly the most used single photon–radiolabeled somatostatin analog (8); the increasing availability of SPECT/CT hybrid devices has led to further improvement in the diagnostic accuracy of this radiopharmaceutical for functional imaging of NETs (9). Nevertheless, despite its good sensitivity in most NETs, the ability of <sup>111</sup>In-pentetreotide to visualize tumor sites is also closely related to their size and is limited in primary and metastatic small lesions (i.e., ≤1 cm) (6). The possibility of labeling somatostatin analogs with <sup>68</sup>Ga has allowed PET to play an important clinical role in diagnosis, staging, and therapy monitoring of patients with receptor-positive NETs, especially in detecting small tumors (6). The most used <sup>68</sup>Ga-DOTA-somatostatin analogs include <sup>68</sup>Ga-DOTATOC, <sup>68</sup>Ga-DOTANOC, and <sup>68</sup>Ga-DOTATATE, with varying affinities for somatostatin receptor subtypes 1–5. In general, among several advantages of <sup>68</sup>Ga-labeled somatostatin analogs over <sup>111</sup>In-pentetreotide imaging, studies comparing the performance of the two kinds of examinations indicate both higher tumor-to-background ratios and higher detection rates for PET, which visualizes also many lesions not identified by CT (6).

However, the somatostatin analogs labeled with <sup>68</sup>Ga are not the only positron-emitting radiopharmaceuticals clinically used for NETs imaging. In this issue of *The Journal of Nuclear Medicine*, Imperiale et al. (10) report their experience with <sup>18</sup>F-3,4-dihydroxyphenylalanine (DOPA) PET/CT in a group of 27 patients with NETs with occult primaries. In fact, not only do NETs overexpress somatostatin receptors but tumor cells take up hormone precursor and transporters and synthesize, store, and release hormones. On the basis of the so-called amine precursor uptake and the

decarboxylation concept, NETs are known to accumulate and decarboxylate L-DOPA; therefore, an increase in the activity of L-DOPA decarboxylase is one of the hallmarks of NETs (6). L-DOPA is an intermediate of the catecholamine synthesis pathway, and its analog <sup>18</sup>F-DOPA is transported into cells by the large neutral amino acid transporter (10).

The location of the primary tumor is an important factor in the management of NETs; the lack of recognition of the primary neoplasm has a negative impact on survival, and despite improvement in the diagnostic work-up of these diseases, there is still a significant percentage of patients in whom, even in the presence of widespread metastatic involvement, the primary tumor remains undetected for a long time after the initial diagnosis (11).

In a series of 36 patients with gastroenteropancreatic NETs in whom no clinical, radiologic, or endoscopic diagnostic modalities had detected the primary neoplasms, the feasibility of <sup>111</sup>In-pentetreotide imaging was evaluated (12). Twenty-nine patients had liver metastases, 1 had skin metastases, 1 had lymph node metastases, 3 had diffuse metastatic involvement, and 2 had carcinoid syndrome. In this study, the primary tumor was visualized by somatostatin receptor scintigraphy (SRS) in 14 of the 36 patients (39%): the site was the pancreas in 3 patients, the midgut in 9, the cecum in 1, and the colon in 1. Identification of the primary lesion by SRS allowed 6 patients to promptly undergo surgery (4 ileal resections, 1 appendectomy, and 1 pancreatoduodenectomy), thus changing their therapeutic management.

The role of <sup>68</sup>Ga-DOTANOC PET/CT in the detection of undiagnosed primary sites of NETs was assessed in a study including 59 patients, on whom physical examination and conventional imaging (multislice CT, MR, ultrasound, and endosonography) had been performed within 3 wk before PET/CT (13). Most of the patients had low-grade NETs (Ki-67 < 5%). <sup>68</sup>Ga-DOTANOC imaging detected the primary tumor in 35 of

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59 cases (59%), at the following locations: 16 pancreas, 2 lungs, 2 rectum/colon, 14 small intestines (duodenum/ileum/jejunum), and 1 paraganglioma. On retrospective analysis, CT alone confirmed the findings of PET/CT in 12 patients. PET alone in many cases was not sufficiently precise to identify the anatomic site of the primary neoplasm, and only PET/CT allowed the correct diagnosis. On the basis of somatostatin receptor PET/CT findings, 6 patients underwent surgery and the primary lesion was removed (4 pancreatic, 1 ileal, and 1 rectal tumor), resulting in a management change in approximately 10% of the subjects. In the remaining 29 patients, because of the advanced stage of the disease, the primary lesions were not resected.

These data were recently confirmed in 20 patients with histopathologically proven metastatic NETs and no localization of primary tumor on conventional imaging (14). <sup>68</sup>Ga-DOTANOC PET/CT detected the unknown primary lesion in 12 cases (60%): 4 in the duodenum, 4 in the ileum, and 1 each in the pancreas, stomach, colon, and lung, with a change in management in 3 of 20 patients (15%), who underwent surgery.

In the study of Imperiale et al. (10) <sup>18</sup>F-DOPA PET/CT was able to localize the primary neoplasm in 12 of 27 patients (44%), who underwent SRS, liver ultrasound, CT, and abdominal MR in the previous 3 mo; in particular, all 12 primary tumors were detected in patients examined at initial staging and none were detected in the 4 patients evaluated during follow-up. Of the primary lesions visualized by <sup>18</sup>F-DOPA, 7 were in the ileum, 2 in the terminal ileum, 1 in the duodenum, 1 in the pancreas, and 1 in the gallbladder (the only one poorly differentiated). The most important result of detecting these 12 tumors was certainly that their identification led to surgical resection in all cases. Moreover, the primary neoplasm remained occult in 13 patients during follow-up (mean, 21 mo). More patients with positive PET/CT results than patients with negative results had clinical symptoms and higher values of serotonin secretion.

The finding of a relationship between <sup>18</sup>F-DOPA positivity and functioning of NETs has been previously reported for a group of 71 carcinoid patients (15). The whole-body metabolic tumor burden calculated by means of <sup>18</sup>F-DOPA imaging correlated with the metabolic endocrine tumor activity measured by biochemical tumor markers of the serotonin and

catecholamine pathway in plasma and urine. The strongest correlation was found with urinary levels of 5-hydroxyindoleacetic acid, which is mostly excreted by midgut carcinoids.

In a paper evaluating the impact of <sup>18</sup>F-DOPA PET on the management of adult patients with documented or occult digestive NETs, a subgroup of 16 patients with abdominal metastases but the primary tumor unknown was investigated (16). <sup>18</sup>F-DOPA imaging detected the primary neoplasm in 6 patients (38%) and in 5 other patients upstaged the disease. These results support the data of Imperiale et al. (10), indicating that <sup>18</sup>F-DOPA PET/CT can play a clinical role in visualizing the occult primary lesions in patients with metastatic NETs.

Medical imaging is of the utmost importance for the management of patients with NETs, and different nuclear medicine procedures can assess the pathologic features and metabolic properties of NETs, thus allowing the in vivo characterization of these diseases (6). Therefore, in this clinical scenario, <sup>18</sup>F-DOPA has to be comparable to other radiopharmaceuticals used for imaging NETs, and the choice of the best one depends mainly on the most probable primary neoplasm and its aggressiveness. A recent review on this topic reported that, currently, <sup>18</sup>F-DOPA seems to have better diagnostic accuracy than other radiopharmaceuticals in some precise NET subtypes: medullary thyroid cancer, catecholamine-producing tumors with low aggressiveness, and well-differentiated carcinoid tumors of the midgut, as well as in congenital hyperinsulinism (17). Nevertheless, for correct image interpretation, it is mandatory that the interpreter be well aware of <sup>18</sup>F-DOPA physiologic biodistribution and normal variants, including possible pitfalls that may lead to PET/CT misinterpretations in various clinical settings (18).

With respect to detection of an occult primary NET, both immunohistochemistry and biochemical markers may guide the choice of the radiopharmaceutical. <sup>18</sup>F-FDG has a role for imaging poorly differentiated NETs with biologically more aggressive behavior and could be tried first in neoplasms with a high proliferation index, that is, a Ki-67 of more than 15% (19). In tumors with a lower proliferation index, high levels of serotonin, urinary 5-hydroxyindoleacetic acid, catecholamine derivatives, or calcitonin suggest the selection of <sup>18</sup>F-DOPA, which is indi-

cated also if CDX-2 is present in metastases (elevated probability of a midgut primary NET) (20). For tumors with a lower proliferation index, the presence in metastases of TTF-1 (NETs of pulmonary origin) or PDX-1 (gastroduodenal or pancreatic NETs) (21) favors the use of SRS or <sup>68</sup>Ga-DOTA peptide PET/CT, which should also be preferred for nonfunctioning NETs and gastroenteropancreatic NETs of hindgut origin.

It may be concluded that, although comparative studies including larger series are needed to better elucidate the diagnostic role of these various radiopharmaceuticals in detecting primary unknown NETs, the preliminary published data suggest that <sup>18</sup>F-DOPA is able to accurately localize occult primary lesions better than SRS, especially in well-differentiated and functioning midgut carcinoid tumors, and could be the first imaging choice in this clinical context.

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