

Can PET/CT Guide the Personalized Treatment of Patients with Gastroenteropancreatic Neuroendocrine Neoplasms?

Gastroenteropancreatic neuroendocrine neoplasms (GEPs) arise from the diffuse neuroendocrine system. Their incidence has markedly increased over the past 3 decades, probably as a result of the improvement in imaging and biochemical methods of detection (1). They are a heterogeneous group of neoplasms with varying clinical expressions, presenting as either functioning or nonfunctioning, with an indolent clinical course in most patients. Functioning tumors are commonly associated with a typical hormonal syndrome directly related to a hormone secreted by the neoplasm; nevertheless, patients may have symptoms for many years before the correct diagnosis is made, because symptoms are often nonspecific and can be due to hormonal excess, local tumor growth, or metastatic spread (2).

Tumor grading and staging represent the main prognostic factors of these neoplasms. Apart from location, GEPs are graded according to proliferation activity, usually evaluated by the Ki67 index on tumor cells, which can have a strong impact on prognosis and therapy (3). The well-differentiated neoplasms, regardless of their benign or malignant behavior, are named neuroendocrine

up of GEPs. In this issue of *The Journal of Nuclear Medicine*, Has Simsek et al. (7) propose the complementary use of ^{67}Ga -DOTATATE and ^{18}F -FDG PET/CT in patients with GEPs for assessing the relationship between *in vivo* uptake of the two radiopharmaceuticals and Ki67 indices in the management of therapy. Previous studies had reported that high ^{18}F -FDG uptake is usually associated with more aggressive GEPs and a less benign prognosis, whereas higher uptake of ^{67}Ga -DOTATATE is characteristic of low-grade neoplasms versus high-grade ones (3,9).

In the series of Has Simsek et al. (7), 27 patients were prospectively evaluated and classified as having NETs (10 G1 and 15 G2) or neuroendocrine carcinoma (2 G3). The patients with G2 NETs were then divided into two groups: 2a (Ki67 of 3%–9%) and 2b (Ki67 of 10%–20%). According to the PET/CT findings, GEPs were further dichotomized as showing either predominantly ^{67}Ga -DOTATATE uptake or predominantly ^{18}F -FDG uptake, considering both the number of detected lesions and the maximum standardized uptake value of the radiopharmaceutical. On a lesion basis, the overall sensitivity of ^{67}Ga -DOTATATE and ^{18}F -FDG PET/CT was 95% and 37%, respectively. Concordant findings were considered to have predominantly ^{67}Ga -DOTATATE uptake if the Ki67 index was lower and predominantly ^{18}F -FDG uptake if the Ki67 index was higher. Taking into account a cutoff value of 9% for Ki67, 19 of the 27 patients showed concordant findings and 8 showed discordant ones. ^{67}Ga -DOTATATE uptake was predominant in 5 patients with a Ki67 index of more than 9%, and ^{18}F -FDG uptake was predominant in 3 patients with a Ki67 index of 9% or less; these last 3 patients had G2a disease. The combined PET/CT assessment led to a change in treatment options in 59% of patients (16/27).

Kayani et al. (5), in studying a group of 38 patients with neuroendocrine neoplasms, including 28 GEPs, found that 3 patients lacked uptake of both ^{67}Ga -DOTATATE and ^{18}F -FDG (1 G1, 1 G2, and 1 G3). In the remaining 35 patients, predominantly ^{67}Ga -DOTATATE uptake was observed in all 21 G1 neoplasms and predominantly ^{18}F -FDG uptake in all 6 G3 neoplasms; of the 6 G2 neoplasms, 3 had predominantly ^{67}Ga -DOTATATE uptake and the other 3 predominantly ^{18}F -FDG uptake. The combined use of the two radiopharmaceuticals caused the choice of therapy to be changed from radionuclide to systemic chemotherapy in 25% of the patients with intermediate- or high-grade neoplasms (4/16: 1 G2 and 3 G3). The conclusions of this retrospective study were that tumor grade influenced tracer avidity but that it was difficult to establish a full link between radiopharmaceutical uptake and histopathologic indices of tumor proliferation, mainly because of the large number of lesions in several patients, but also taking into account that percutaneous biopsy may not reliably reflect *in vivo* tumor heterogeneity.

The clinically useful complementary role of ^{18}F -FDG to somatostatin receptor imaging has been subsequently confirmed in a large prospective study enrolling 96 patients with neuroendocrine neoplasms (82 GEPs, 7 in the lungs and 7 with liver metastases of unknown primary) (10). The sensitivity of ^{18}F -FDG PET was significantly higher for neoplasms with a Ki67 index of 2% or more (80%

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tumors (NETs) and graded G1 (Ki67 < 2%) or G2 (Ki67 of 2%–20%); the poorly differentiated neoplasms are named neuroendocrine carcinomas and graded G3 (Ki67 > 20%) (4). Both NETs and neuroendocrine carcinomas are also further classified according to the TNM staging system of the European Neuroendocrine Tumor Society and the American Joint Committee on Cancer/Union for International Cancer Control, to stratify them regarding prognosis (5). The recent advances in molecular biology have led to an increase in treatment options for these patients, but their management has become more complex, requiring a multidisciplinary approach.

Nuclear medicine has for several years played an important clinical role in imaging and treating GEPs. A well-known characteristic of most GEPs is overexpression of somatostatin receptors, which can successfully be visualized *in vivo* by somatostatin receptor imaging, using radiopharmaceuticals emitting single photons or positrons. Moreover, somatostatin analogs labeled with β -emitting radionuclides are target therapy for inoperable or metastasized GEPs (6).

In the current decade, PET/CT using ^{67}Ga -DOTA-labeled somatostatin analogs has been introduced for the diagnostic work-

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