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REVIEW

Nuclear medicine imaging of gastro-entero-pancreatic neuroendocrine tumors. The key role of cellular differentiation and tumor grade: from theory to clinical practice

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Abstract

Nuclear medicine imaging is a powerful diagnostic tool for the management of patients with gastro-entero-pancreatic neuroendocrine tumors, mainly developed considering some cellular characteristics that are specific to the neuroendocrine phenotype. Hence, overexpression of specific trans membrane receptors as well as the cellular ability to take up, accumulate, and decarboxylate amine precursors have been considered for diagnostic radiotracer development. Moreover, the glycolytic metabolism, which is not a specific energetic pathway of neuroendocrine tumors, has been proposed for radionuclide imaging of neuroendocrine tumors. The results of scintigraphic examinations reflect the pathologic features and tumor metabolic properties, allowing the in vivo characterization of the disease. In this article, the influence of both cellular differentiation and tumor grade in the scintigraphic pattern is reviewed according to the literature data. The relationship between nuclear imaging results and prognosis is also discussed. Despite the existence of a relationship between the results of scintigraphic imaging and cellular differentiation, tumor grade and patient outcome, the mechanism explaining the variability of the results needs further investigation.

Keywords: Neuroendocrine tumor; functional imaging; somatostatin receptor scintigraphy; FDG PET; FDOPA PET; differentiation.

Introduction and rationale

Neuroendocrine tumors (NET) are epithelial neoplasms with neuroendocrine differentiation. NETs are a heterogeneous group of rare tumors originating from peptide- and amine-producing cells of the neuroendocrine system. Their incidence is usually reported at between 40 and 50 cases per million, accounting for approximately 0.5% of all malignant neoplasms. Although most NETs originate from the gastrointestinal tract and pancreas, they only make up 2% of all gastro-entero-pancreatic (GEP) malignancies[1].

Only a small proportion of a GEPNET is functional. Flushes and diarrhea are the most reported symptoms related to the tumoral secretion of biologically active peptides and amines[2]. The clinical symptomatology of GEPNET is generally associated with the presence of systemic metastatic spread. However, bowel obstruction or incidental detection of hepatic metastases are common circumstances that lead to diagnosis. Extensive tumor bulk and metastatic disease are the major causes of death. However, long patient survival, which is mainly related to the slow-growing tumor characteristics, is not unusual[3].

Table 1 **Main bibliographic data on GEPNET reporting: functional imaging, tumor grade, tumor differentiation or patient outcome results**

Author	Reference	Patients	Patients with GEPNET	SRS	Somatostatin imaging with PET analogs	FDOPA PET	FDG PET	Tumor grade	Cellular differentiation	Patient outcome
Gabriel et al.	[22]	84	50	+	+					
Buchmann et al.	[23]	27	15	+	+					
Srirajaskanthan et al.	[24]	51	37	+	+			+		
Koopmans et al.	[33]	53	32	+		+				
Montravers et al.	[34]	30	23	+		+				
Ambrosini et al.	[44]	13	11		+	+				
Ambrosini et al.	[35]	13	13	+		+				
Haug et al.	[45]	25	14		+	+				
Campana et al.	[49]	47	41		+			+	+	+
Adams et al.	[50]	15	7	+		+	+	+		
Belhocine et al.	[51]	17	11	+		+	+	+		
Kayani et al.	[52]	38	28		+	+	+	+		
Binderup et al.	[29]	96	81	+		+	+			
Abgral et al.	[54]	18	15	+		+	+		+	+
Garin et al.	[56]	31	23	+		+	+		+	+
Binderup et al.	[57]	98	83			+	+			+
Asnacios et al.	[58]	98	53	+						+

Nowadays, surgery of the primary tumor is the only curative treatment in patients without metastatic disease[4]. Unfortunately, the detection of liver metastases at primary staging generally limits the possibility of complete surgical eradication. Hence, accurate staging is crucial to define the real extent of the disease and to identify patients with inoperable tumors[5,6].

Evidence exists that tumor differentiation and grade are related to the clinical behavior of GEPNETs[7,8]. Differentiation refers to the extent to which the tumor cells resemble their non-neoplastic counterparts. Well-differentiated GEPNETs present a low mitotic activity, and may have punctate necrosis. Cells are uniform and produce neurosecretory granules. Poorly differentiated neuroendocrine carcinomas show fields of necrosis, less cytoplasmic granularity, irregular nuclei, and marked cellular pleomorphism. The distinction between a well-differentiated and a poorly differentiated NET is one of the most important pathologic assessments: the first are rather indolent, whereas the second are likely to be more aggressive. Grade refers to the degree of biological aggressiveness of the tumor, without taking into account the pathologic differentiation. Low-grade NETs are generally considered as the least aggressive in behavior. On the other hand, high-grade tumors tend to grow rapidly and spread faster than tumors with lower grade. Intermediate grade NETs have a less predictable and moderately aggressive course. The proliferative rate can be assessed as the number of mitoses per unit area of tumor or as the percentage of neoplastic cells immunolabeling for the proliferation marker Ki-67. The Ki-67 index is related to the presence of the Ki-67 protein in the active phases of the cell cycle. Ki-67 is a proliferation marker commonly used in all grading systems and it is currently reported in pathology reports[9]. A Ki-67 index less than 2%, between 3% and 20%, and above 20%, is characteristic of low, intermediate, and high-grade GEPNET, respectively. Well-differentiated GEPNETs are classified as either low or intermediate grade, whereas poorly differentiated GEPNETs are classified as high grade in all cases[7,10]. The existence of a high-grade well-differentiated tumor is controversial, and does not figure in any expert recommendation or guideline[11].

Medical imaging is crucial for the management of NET patients. A multidisciplinary morphofunctional approach has been advocated, associating radiologic and nuclear medicine examinations. Nuclear medicine imaging for NET has been mainly developed considering some cellular characteristics that are specific for the neuroendocrine phenotype. Hence, the overexpression of specific trans membrane receptors as well as the cellular ability to take up, accumulate, and decarboxylate amine precursors have been considered for diagnostic radiotracer development[12]. Moreover, the glycolytic metabolism, which is not a specific energetic pathway of NETs, has been proposed for NET radionuclide imaging.

In this article, we briefly review the nuclear medicine diagnostic procedures that are mainly used in clinical practice for NET imaging. The influence of both cellular differentiation and tumor grade in the choice of isotopic examination is examined. The possible relationship between the result of nuclear imaging and patient prognosis is discussed. The main bibliographic data about GEPNETs reported in the article are summarized in Table 1.

Nuclear medicine imaging:
a brief overview

Somatostatin receptor-based imaging

Somatostatin is a peptide produced by both paracrine and endocrine cells in the GEP tract. Somatostatin receptors (sstr) are coupled to cell membrane G-proteins. Five sstr subtypes are known, designated sstr1 to 5. In NETs, sstr2 and sstr5 are particularly abundant[13]. Overexpression of receptors as well as internalization of the hormone–receptor complex are the basis of radiolabeled somatostatin imaging modalities. Octreotide conjugated with diethylene-triamine-pentaacetic acid (DTPA) and labeled with ^{111}In is a radiolabeled somatostatin analog with great affinity for sstr2 and widely used in clinical practice[14,15].

Somatostatin receptor scintigraphy (SRS) is routinely indicated for staging purposes and during follow-up in patients with GEPNETs. Good sensitivity and specificity have been reported for SRS, irrespective of tumor site and hormonal secretion[16]. SRS sensitivity is mainly related to the tumoral sstr2 density, decreasing for poorly differentiated tumors[13,16]. The introduction of multiple-head gamma cameras and tomographic acquisition by single photon emission computed tomography (SPECT) has provided three-dimensional imaging, improving sensitivity[17]. Moreover, the latest generation of high-resolution gamma cameras coupled with multidetector computed tomography (SPECT/CT) allows accurate anatomic localization of functional abnormalities[18,19], as well as a reduction in study duration and patient discomfort. Nevertheless, SRS is limited by the unfavorable physical characteristics of ^{111}In, reducing the detection of small lesions, especially in organs with physiologic tracer uptake such as the liver. Accordingly, an inverse relationship between SRS sensitivity and the size of hepatic metastasis has been previously reported[20]. EDDA/HYNIC-Tyr3-octreotide is a ^{99m}Tc-radiolabeled peptide that has been developed in Poland for clinical investigations and intraoperative detection of NETs. According to the results reported by Hubalewska-Dydejczyk et al.[21], the high-quality ^{99m}Tc-EDDA/HYNIC-octreotate images revealed more metastases than ^{111}In-octreotide SRS with better individual lesion separation and seemed more accurate in identifying the site of unknown primary tumors in patients with metastatic NETs.

Both the relatively low spatial resolution of common gamma cameras and the prolonged acquisition time of SRS have led to the development of new somatostatin analogs labeled with ^{68}Ga for positron emission tomography (PET) studies, such as [^{68}Ga-DOTA^0-Tyr^3]octreotide (^{68}Ga-DOTA-TOC), [^{68}Ga-DOTA^0-Tyr^3]octreotate (^{68}Ga-DOTA-TATE) and [^{68}Ga-DOTA^0-1NaI^3]octreotide (^{68}Ga-DOTA-NOC). PET has an increased sensitivity towards SPECT, explained by a two- to threefold higher spatial resolution and a better tumor-to-background ratio. Higher sensitivity than SRS has been reported in most published clinical investigations[22,23], in particular for the detection of small lymph node metastases and secondary bone localizations, providing modification of therapeutic strategy[24]. ^{64}Cu-labeled octreotide conjugates have also been evaluated. In particular, ^{64}Cu-TETA-D-Phe1-octreotide binds to the somatostatin receptor with 5 times the affinity of ^{111}In-octreotide, representing a potential agent for PET imaging of NETs[25]. Unfortunately, the availability of the somatostatin PET analogs is still scarce, whereas SRS is routinely performed in almost all nuclear medicine facilities.

Somatostatin receptor-based functional imaging by SPECT and PET contributed to the development of alternative therapeutic strategies such as radiometabolic therapy with β-emitter labeled somatostatin analogs. One of the most relevant applications of SSR imaging is probably to select patients with well-differentiated and inoperable NETs who are potentially candidates for peptide receptor radionuclide therapy with ^{90}Y and/or ^{177}Lu radiolabeled somatostatin analogs[26,27].

Catecholamine pathway-based imaging

GEPNETs originate from the amine precursor uptake and decarboxylation (APUD) system[12]. Accordingly, the re-uptake of norepinephrine and the uptake of amine substrates such as dihydroxyphenylalanine (DOPA) have been exploited for nuclear medicine radiotracer development.

^{123}I or ^{131}I radiolabeled meta-iodobenzylguanidine (mIBG) is a structural analog of norepinephrine used for clinical imaging. mIBG uses active transport mechanisms to accumulate in the tumor in secretory vesicles. The sensitivity of mIBG scintigraphy for GEPNET has been reported to be about 50%, which is lower than the sensitivity of SRS[28,29]. Although ^{123}I-mIBG is less sensitive for GEPNET detection, it remains useful to predict uptake and response to radionuclide therapy with ^{131}I-labeled mIBG. ^{123}I-mIBG scans remain the first choice in nuclear medicine imaging for the management of patients with pheochromocytoma and neuroblastoma[30].

DOPA is an intermediate product in the synthesis of dopamine. Cellular uptake of DOPA is related to a specific cell membrane transport system. Once internalized, DOPA is decarboxylated to dopamine, and transported into secretory vesicles[31]. For nuclear imaging purposes, DOPA is labeled with ^{18}F (FDOPA) leading to the accumulation of ^{18}F-dopamine in the cell. The high uptake of FDOPA in NETs is the result of the increased synthesis, storage and secretion of biogenic amines[32]. FDOPA PET seems to be superior to morphological imaging and SRS in the localization of both the primary site of the GEPNET and metastatic localizations[33,34]. Moreover, some authors have suggested that FDOPA PET is a valuable imaging tool for the detection of the primary tumor in patients with metastatic GEPNET of
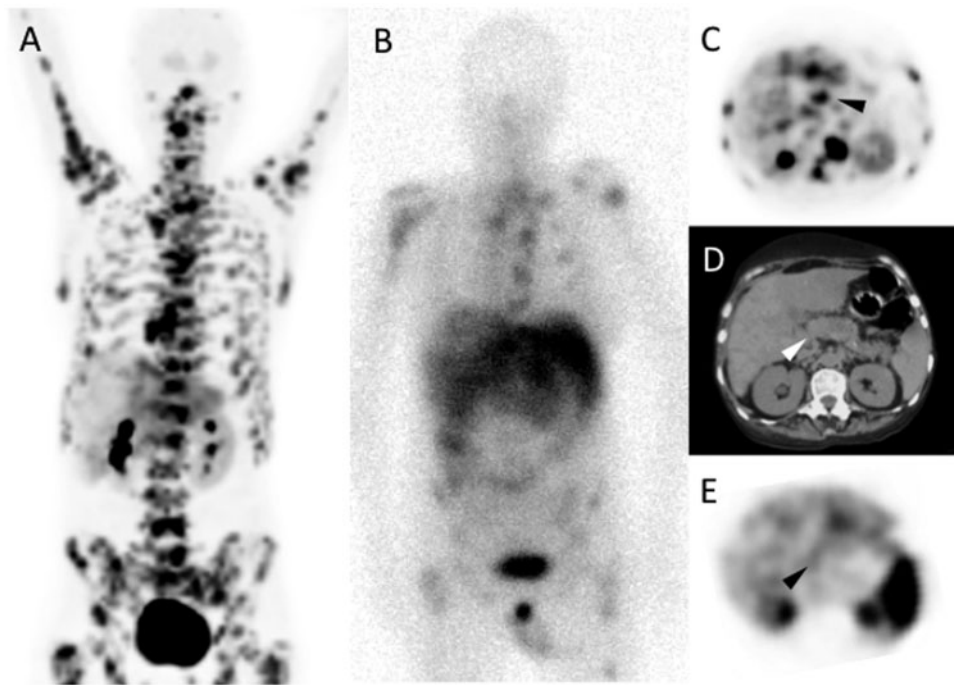
Figure 1   **Results of FDOPA PET (A,C) and SRS (B,E) performed in a 56-year-old patient presenting hepatic metastases (D) of a well-differentiated NET of unknown origin (Ki-67, 5%). SRS allowed the visualization of multiple foci of pathologic uptake in the liver, lymph nodes and bones without evidence of the primary tumor. FDOPA PET confirmed massive bone marrow and skeletal involvement, as well as multiple lymphatic and hepatic metastases. Moreover, FDOPA PET demonstrated intense and focal uptake in the head of pancreas (arrowhead), later confirmed as the primary tumor.**

unknown origin and negative or inconclusive findings at conventional imaging and SRS[35] (Fig. 1). However, its high cost and low availability are still important limiting factors for the routine use of FDOPA in clinical practice.

[11]C-5-Hydroxytryptophan (HTP) is a radiolabeled serotonin precursor representing an FDOPA-alternative related radiotracer. HTP is specifically taken up by carcinoid serotonin-producing tumors, decarboxylated by aromatic amino acid decarboxylase (AADC), and stored in vesicles as ^{11}C-serotonin and was shown to be more sensitive in imaging small NET lesions[36–38]. Uptake, decarboxylation, and secretory vesicle transportation rely on the same systems and enzyme as FDOPA. However, the short half-life of ^{11}C requires an on-site cyclotron facility, making HTP not widely available for routine clinical use.

The sensitivity of FDOPA and HTP PET may be reduced for the detection of well-differentiated pancreatic NET due to high physiologic radiotracer uptake and retention in the whole pancreas. As recently reported by Tessonnier et al.[39] in 4 patients with solitary insulinomas, FDOPA PET identified tumor in only one case. The administration of carbidopa, an efficient inhibitor of the peripheral aromatic amino acid decarboxylase (AADC), has been shown to improve image interpretation for FDOPA and HTP PET by increasing tumoral uptake and lowering physiologic pancreatic uptake[32,40]. On the other hand, no final consensus

has been reached about the usefulness of AADC inhibition by carbidopa premedication before an FDOPA PET study in patients with insulinomas or β-cell hyperplasia[41–43].

Nowadays, few comparative studies investigating the diagnostic role of FDOPA and ^{68}Ga-DOTA-NOC or ^{68}Ga-DOTA-TATE PET/CT in GEPNET are available. Ambrosini et al.[44] reported a higher accuracy of ^{68}Ga-DOTA-NOC in the detection of primary tumor and metastatic disease compared with FDOPA in 11 patients with GEPNET. The detection rate of primary tumor with FDOPA was lower than previously reported by the same authors[35]. These results are confirmed by Haug et al.[45], who reported a clear superiority of ^{68}Ga-DOTA-TATE to FDOPA PET in 14 patients. Nevertheless, prospective studies including larger and more homogeneous patient series are necessary to confirm the real superiority of PET/CT with somatostatin analogs towards FDOPA PET/CT in the diagnosis and follow-up of patients with GEPNET.

Glucose metabolism-based imaging

[18]F-Fluoro-2-deoxy-D-glucose (FDG) is a glucose analog labeled with positron-emitting ^{18}F, which is taken up into cells by the glucose molecular transporter. Once internalized, FDG is phosphorylated without entering any

further metabolic processes. Thus, FDG remains trapped within the cell. The widespread clinical use in oncological routine of FDG PET as an imaging tool capable of exploring the differences of glucose metabolic activity between normal and pathologic tissues is justified by its high diagnostic accuracy and therapeutic impact. Nevertheless, limited value of FDG PET/CT is usually reported in the management of NETs, probably because of their low metabolic activity and slow growth. Despite these premises, FDG PET could have a potential value for prognosis stratification in patients with NET, as suggested by Strauss et al.[46] in the early 1990s. Accordingly, NET with increased FDG uptake seem to have a more aggressive behavior with consequent less favorable long-term prognosis[47].

Functional characterization of GEPNET by nuclear medicine imaging

Imaging results according to differentiation and tumor grade

The expression of sstr on the cell surface is a landmark of neuroendocrine differentiation. Well-differentiated NETs are characterized by an important sstr density explaining the good sensitivity of nuclear imaging based on radiolabeled somatostatin analogs[13]. On the other hand, less-differentiated tumors lose their ability to express sstr[48] with consequent reduction in the diagnostic interest of SRS. Campana et al.[49] reported a significant correlation between the scintigraphic results and NET differentiation in 47 patients studied by ^{68}Ga-DOTA-NOC PET/CT. They showed that the intensity of radiotracer uptake was higher in well-differentiated tumors. They also demonstrated the relationship between the degree of radiotracer uptake and the clinical and pathologic features of NET. In the same manner, Srirajaskanthan et al.[24] found a decreased sensitivity of ^{68}Ga-DOTA-TATE PET/CT in patients with poorly differentiated NET.

An inverse relationship between FDG uptake and tumor differentiation has been observed. Increased glycolytic metabolism has been associated with high proliferative and poorly differentiated NETs[50]. Conversely, a higher rate of false-negative results of FDG PET was found comparing FDG PET and SRS in patients with well-differentiated GEPNET[51].

Based on these observations, the mismatch high uptake of somatostatin analogs/low glycolytic metabolism could be considered as the scintigraphic pattern of well-differentiated GEPNETs. Conversely, the scintigraphic pattern low uptake of somatostatin analogs/high glycolytic metabolism could be considered as representative of poorly differentiated tumors.

The potential relationship between the tumor grade and the results of scintigraphic exploration by labeled somatostatin analogs and FDG has still not been completely elucidated. For this purpose, Kayani et al.[52] compared the diagnostic performances of ^{68}Ga-DOTA-TATE and FDG PET/CT in 28 patients with GEPNET and 4 patients with metastatic NET of unknown origin. In this patient cohort, the uptake of ^{68}Ga-DOTA-TATE was globally higher in low-grade NETs (Ki-67 less than 2%) than high-grade tumors. Conversely, lesions with a Ki-67 index above 20% showed a significantly higher FDG uptake. In patients with low-grade NET, only 21 of 123 detected lesions were FDG avid; 120 lesions showed ^{18}Ga-DOTA-TATE uptake. In high-grade NETs, only 5 of 79 detected lesions were positive with ^{68}Ga-DOTA-TATE, whereas 77 were positive for ^{18}F-FDG uptake. Moreover, no lesion exhibited exclusive uptake of either ^{68}Ga-DOTA-TATE in high-grade or FDG in low-grade NETs. In this study, tumor grade was even predictive of scintigraphic pattern. Binderup et al.[29] prospectively performed SRS and FDG PET/CT on 96 consecutive patients with NET including 81 cases of GEPNET. The sensitivity of both techniques was analyzed according to the proliferative index. The authors reported a higher sensitivity of FDG PET in tumors with a proliferative index above 2%. FDG sensitivity was even better when the proliferative rate was above 15%. Conversely, SRS sensitivity was found to be significantly higher for tumors with a proliferation index below 15%. To our knowledge, no published data assessing a potential relationship between FDOPA uptake and either pathologic differentiation or tumor grade are available yet (Figs. 2, 3 and 4).

According to these results, it seems possible to predict in vivo and with good accuracy both tumor grade and cellular differentiation from the analysis of nuclear medicine examinations. Moreover, the 2 scintigraphic patterns previously reported for tumor differentiation (i.e. high uptake of somatostatin analogs/low glycolytic metabolism versus low uptake of somatostatin analogs/high glycolytic metabolism) could also be appropriate for the grade[53].

Although well-differentiated NETs are often low-grade lesions, the finding of a well-differentiated endocrine carcinoma with a high Ki-67 index is of importance, increasing the interest for proliferative index estimation as a powerful prognostic tool. Currently, the choice of scintigraphic examination is mainly guided by tumor differentiation. Nevertheless, evidence exists about the important role played by tumor aggressiveness independently of the degree of cellular differentiation. For this purpose, Abgral et al.[54] recently investigated the performances of SRS and FDG PET/CT in a rare subgroup of 18 patients with stage IV well-differentiated endocrine carcinoma characterized by a Ki-67 index above or equal to 10%. On a per patient analysis, SRS and FDG PET sensitivity was 83% and 100%, respectively. Taking as a standard the highest number of distinct lesions visualized by at least one imaging method (per lesion analysis), the sensitivities of SRS and FDG PET were 43% and 77%,
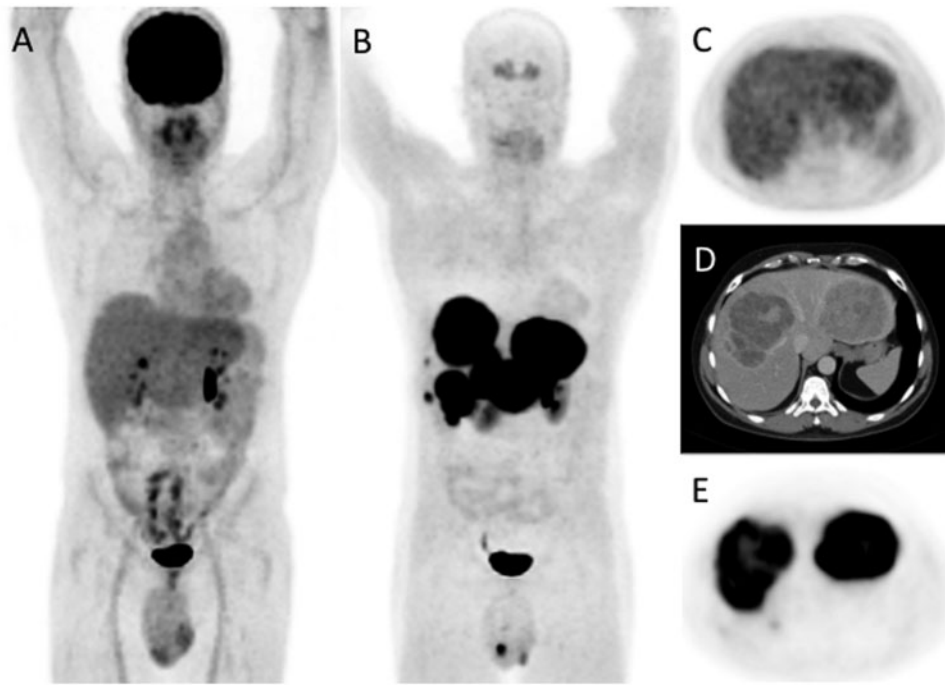
Figure 2   FDG (A,C) and FDOPA PET/CT (B,E) results performed before liver transplantation in a 49-year-old patient with a history of well-differentiated ileal NET surgically treated (Ki-67, 1%). Intense uptake of FDOPA was observed in multiple and voluminous hepatic metastases. FDG PET showed no or minimal uptake in the liver lesions.

respectively, with a statistically significant superiority of FDG PET for detection of lymph node involvement. According to these results, the authors proposed FDG PET as the first choice scintigraphic method for staging of metastatic well-differentiated endocrine carcinoma with Ki-67 of 10% or higher.

All this evidence suggests that an intimate relationship between tumor differentiation and grade could explain the variability in the results of nuclear medicine examinations. Nevertheless, the exact influence of one on the another has still not been completely elucidated.

Nuclear imaging results for patient outcome prediction

There is a growing body of evidence suggesting the potentiality of FDG PET/CT in the prediction of long-term prognosis in patients with NET. A correlation between the intensity of tumoral radiotracer uptake and survival has been reported. Pasquali et al.[55] first reported the accuracy of FDG PET for identifying NETs with rapidly growing or aggressive behavior, supporting the evidence that an increased glycolytic rate reveals a worse prognosis. More recently, Garin et al.[56] evaluated the prognostic value of FDG PET/CT in a prospective study enrolling 38 patients with metastatic well-differentiated NET. The pancreas or small intestine was the site of the primary tumor in 20 of 38 patients. Histologically,

4 patients had a high-grade tumor and 34 had a low-grade tumor. Overall positive and negative predictive value of FDG PET/CT for the detection of disease progression within the first 6 months of follow-up was 93% and 91%, respectively. FDG PET/CT was found to be more sensitive than pathologic differentiation and Ki-67 in the early prediction of rapidly progressive disease. In 4 cases, there was a discrepancy between the pathologic examination (showing a well-differentiated tumor) and the Ki-67 immunostaining diagnosing a high-grade phenotype.

These results are consistent with the recent work of Binderup et al.[57] based on a population of 98 patients with NET including 83 GEPNETs, 8 bronchopulmonary carcinoid tumors and 7 primary tumors of unknown origin. In this study, the prognostic value of FDG uptake, the proliferation index, chromogranin A, and liver metastases were assessed. During the 1-year follow-up, 13 of 14 dead patients were FDG PET positive and only one was FDG PET negative. Five of 13 lethal tumors showed a proliferation index below 2%, among which 4 showed FDG uptake. In this study, the positive prognostic value of FDG PET for the prediction of patient outcome was better than the Ki-67 index.

Conversely, positive findings with NET-specific radiotracers seem to be associated with a less aggressive disease and a better patient outcome. Asnacios et al.[58] recently evaluated the correlation between SRS, sstr expression, and prognosis. Consecutive patients with
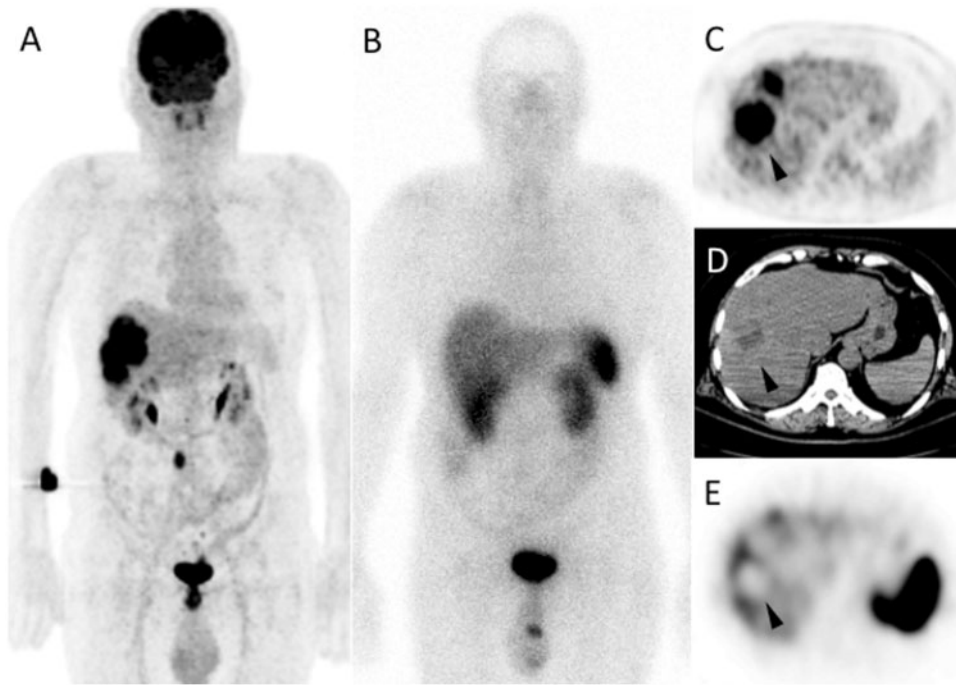
Figure 3 **Results of FDG PET (A,C), SRS-SPECT (B,E) and corresponding non-enhanced CT slice (D) performed in a 63-year-old patient with poorly differentiated rectal NET (Ki-67, 11%). FDG PET allowed the detection of the primary tumor and both lymphatic para-aortic and right-lobe hepatic metastases. On the other hand, SRS showed no pathologic uptake, particularly in the liver (arrowheads).**
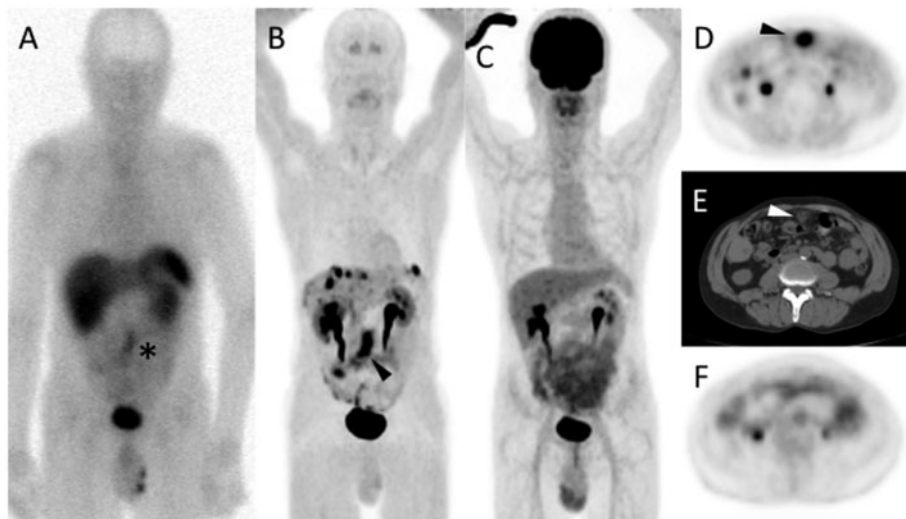

Figure 4 **SRS (A), FDOPA (B,D) and FDG PET/CT (C,F) results performed for restaging purposes in a 66-year-old patient with a history of well-differentiated colic NET (Ki-67, 2%) previously treated by surgery. SRS only showed faint uptake concerning a peritoneal relapse (*). FDOPA PET showed a clear multifocal peritoneal carcinomatosis (arrow-head) and multiple hepatic metastases. Despite the absence of focal FDG uptake, diffuse and moderate uptake was observed in the pelvic cavity suggesting the shield sign, in keeping with peritoneal carcinomatosis.**

a well-differentiated NET and negative (48 patients) or positive (50 patients) findings at SRS, were compared.

The authors reported a better overall survival at 60 months when SRS was positive. Even in the absence of any treatment, SRS proved to be a valuable prognostic tool. Similar results were shown by Campana et al.[49] investigating 47 patients with NET by ^{68}Ga-DOTA-NOC PET/CT.
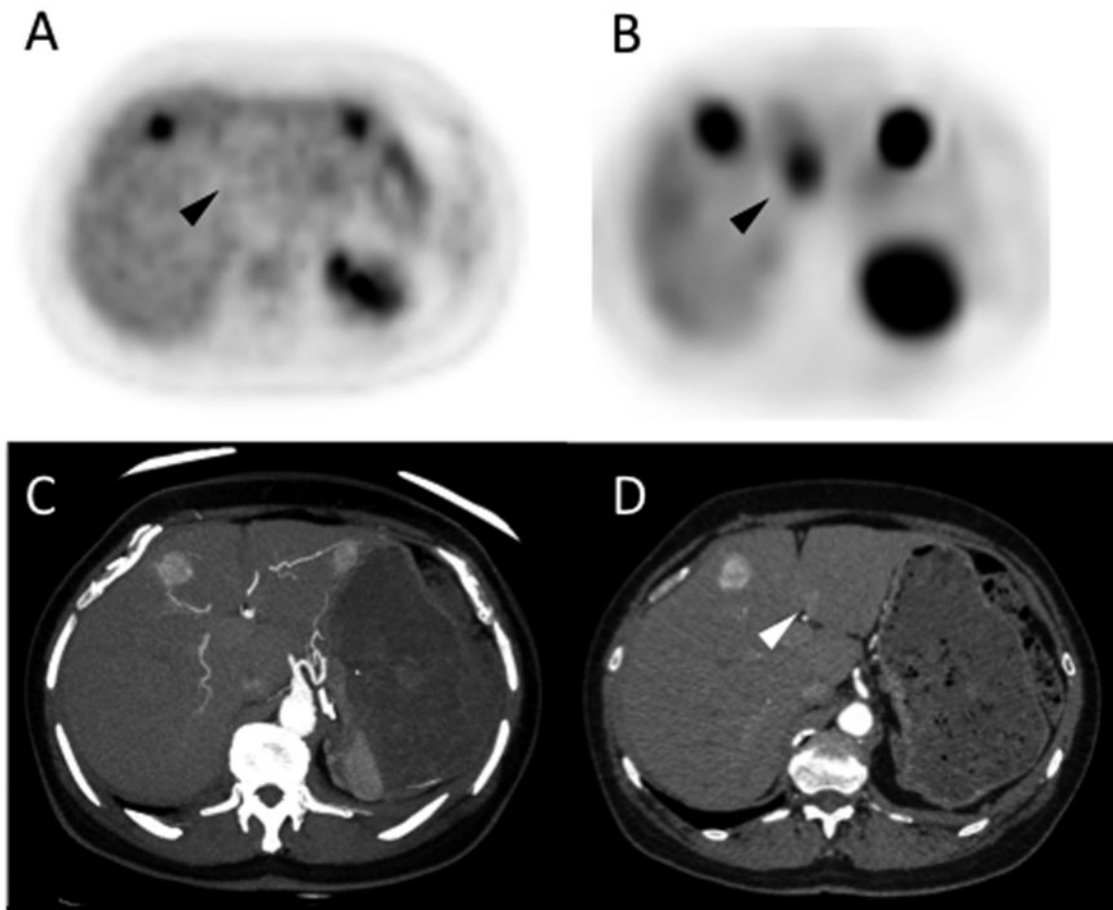
Figure 5 **Multiple hepatic metastases (C,D, contrast-enhanced CT maximum projection intensity and axial slice performed some days after the scintigraphic examinations) in a 57-year-old patient with poorly differentiated pancreatic NET previously treated by surgery. Biopsy confirmed the neuroendocrine nature of one hepatic lesion. The pathologic report showed a well-differentiated NET (Ki-67, <3%). Several hepatic foci of pathologic uptake were detected by FDG PET (A) and SRS (B). Some lesions showed both radiotracer uptake and other exclusive uptake of FDG or labeled somatostatin analogs (arrowhead). The discrepancy between the results of pathologic reports and isotopic procedures strongly suggests different degrees of tumor differentiation in the same patient.**

Summary and conclusion

Nuclear medicine is a valuable non-invasive diagnostic modality for the staging and follow-up of patients with GEPNET. The results of scintigraphic examinations reflect the pathologic features and metabolic properties of the tumors, making the in vivo characterization of tumor differentiation and grade possible. The 2 scintigraphic patterns previously described (i.e. high uptake of somatostatin analogs/low glycolytic metabolism versus low uptake of somatostatin analogs/high glycolytic metabolism) could be considered as the extremes of all possible results. However, this binary-like classification is not applicable in all situations. A continuum of results combining a variable uptake degree of specific (radiolabeled somatostatin analogs, FDOPA) and non-specific (FDG) radiotracers is usually encountered in daily practice. The uptake intensity of radiolabeled analogs of somatostatin, FDOPA and FDG can vary in different lesions in the same patient mainly reflecting the tumor heterogeneity but also a possible variable degree of tumor differentiation (Fig. 5).

Even if cellular differentiation is commonly related to tumor grade, some exceptions exist, making both assessments necessary[54,57]. The association of multitracer nuclear investigations could play a role in the assessment of tumor differentiation and grade in a non-invasive manner, increasing the diagnostic accuracy and orienting therapeutic strategies[29,52,54,56]. In particular, the assessment of glycolytic metabolism by FDG PET seems to be potentially useful in identifying high-risk patients with more aggressive tumors, especially in those cases where there is disagreement between the pathologic results obtained from the biopsy of a metastatic location and the primary tumor after surgical debulking (Fig. 6).
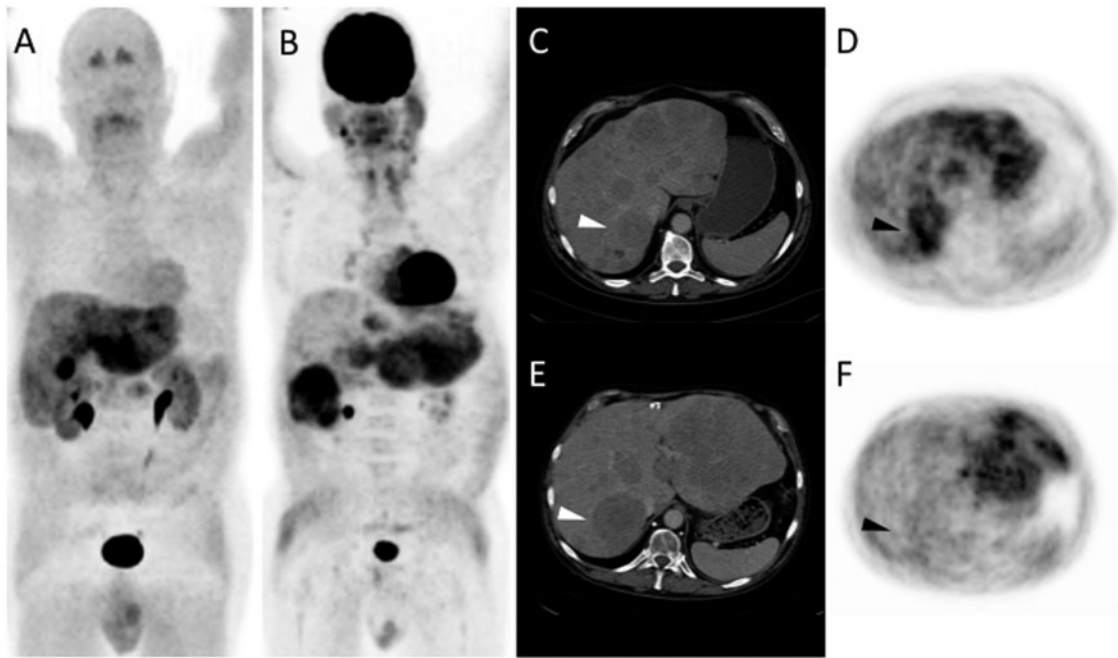
Figure 6   FDOPA PET (A,D), FDG PET (B,F) and enhanced CT (C,E) results of a 65-year-old patient with a duodenal NET and liver metastatic involvement. Biopsy of one hepatic localization showed a well-differentiated carcinoma with Ki-67 index of 10%. The pathologic examination of the primary tumor showed poorly differentiated carcinoma with a Ki-67 index of 10%. Both FDG PET and FDOPA PET showed multiple non-concordant foci of pathologic uptake in the liver (arrowheads).
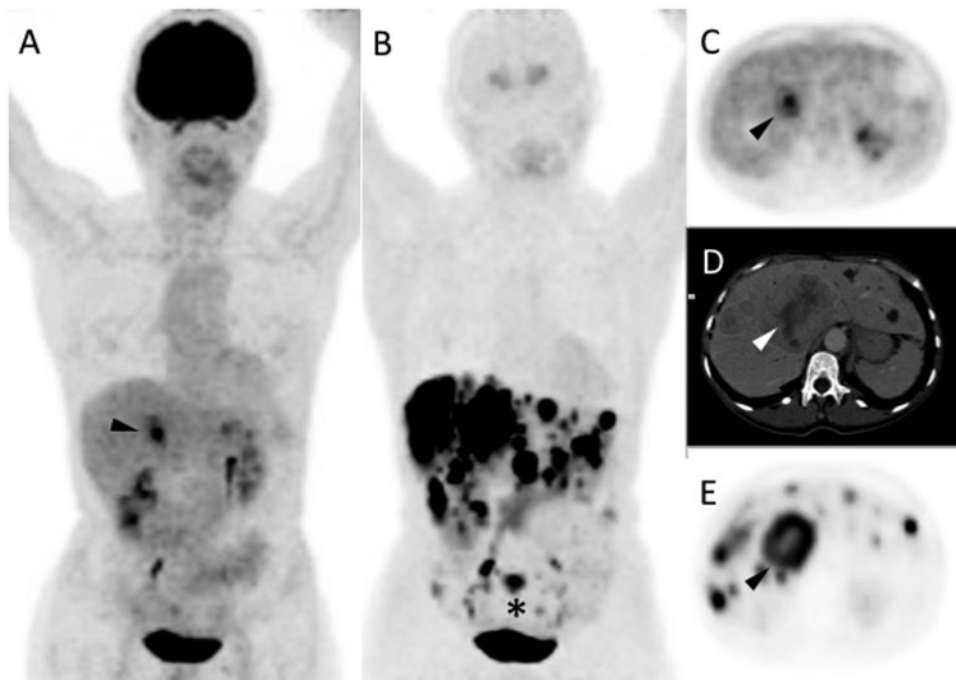

Figure 7   FDG PET (A,C) and FDOPA PET (B,E) results for a 68-year-old patient with clinical and biological suspicion of NET. FDG PET showed an exclusive pathologic uptake in hepatic segment IV−VIII, corresponding to a metastatic lesion on enhanced CT (D). Biopsy of hepatic metastasis (arrowheads) showed a well-differentiated NET of unknown origin with a Ki-67 index of 3%. FDOPA PET showed the ileal primary tumor (*) and multiple hepatic and lymph node metastases.

The management of patients with NET largely depends on the results of pathologic examination, which allows differentiation of aggressive malignancies from low-grade tumors. Generally, grade and differentiation are determined from a limited tissue sample obtained from biopsy or from partial surgical resection, which might be not truly representative of the whole tumor burden. On the other hand, nuclear medicine provides whole-body imaging, allowing extensive in vivo characterization of the tumor that is potentially useful for guiding biopsy, in particular of FDG-avid lesions that are not clearly detectable on CT or are largely necrotized or are avid in only a part (Fig. 7).

The prediction of patient outcome is a real challenge in clinical routine. Recently, the usefulness of nuclear medicine imaging for predicting patient prognosis has been advocated. Particularly, examinations based on FDG PET and radiolabeled somatostatin analogs may provide prognostic information independently from the pathologic indexes that are commonly accepted and used in daily routine. Moreover, tumor FDG uptake seems to be associated with a worse patient outcome even in well-differentiated or low-grade tumors. Despite the existence of a relationship between the tumor scintigraphic pattern, cellular differentiation, tumor grade and patient outcome, the intimate mechanism explaining the variability of the results has not been completely elucidated[59].

In conclusion, we emphasize the emerging role of nuclear medicine imaging in the management of NET. Hence, a better understanding of tumor biology and pathophysiology seems necessary to improve patient outcome. Prospective studies including larger and homogeneous patient series taking into account both cellular differentiation and tumor grade are necessary to confirm the real place for nuclear medicine in the diagnosis and follow-up of patients with NET.

Conflict of interest statement

References

[1] Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 2004; 80: 394–424. doi:10.1159/000085237.

[2] Warner RR, Mani S, Profeta J, Grunstein E. Octreotide treatment of carcinoid hypertensive crisis. Mt Sinai J Med 1994; 61: 349–355.

[3] Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008; 247: 490–500. doi:10.1097/SLA.0b013e31815b9cae.

[4] Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004; 25: 458–511. doi:10.1210/er.2003-0014.

[5] Landry CS, Scoggins CR, McMasters KM, Martin RC 2nd. Management of hepatic metastasis of gastrointestinal carcinoid tumors. J Surg Oncol 2008; 97: 253–258. doi:10.1002/jso.20957.

[6] Kocha W, Maroun J, Kennecke H, et al. Consensus recommendations for the diagnosis and management of well-differentiated gastroenterohepatic neuroendocrine tumours: a revised statement from a Canadian National Expert Group. Curr Oncol 2010; 17: 49–64.

[7] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010; 39: 707–712. doi:10.1097/MPA.0b013e3181ec124e.

[8] Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev 2011; 30(Suppl 1): 3–7. doi:10.1007/s10555-011-9292-1.

[9] Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol 2000; 182: 311–322. doi:10.1002/(SICI)1097-4652(200003)182:3<311::AID-JCP1>3.0.CO;2-9.

[10] Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 2010; 39: 735–752. doi:10.1097/MPA.0b013e3181ebb168.

[11] Tang LH, Shia J, Vakiani E, Dhall D, Klimstra DS. High grade transformation of differentiated neuroendocrine neoplasms (NENs) of the enteropancreatic system : a unique entity distinct from de novo high grade neuroendocrine carcinoma (HGNECa) in pathogenesis and clinical behavior. Lab Invest 2008; 88(Suppl 1): 137A.

[12] Pearse AG. The APUD cell concept and its implications in pathology. Pathol Annu 1974; 9: 27–41.

[13] Papotti M, Bongiovanni M, Volante M, et al. Expression of somatostatin receptor types 1–5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch 2002; 440: 461–475. doi: 10.1007/s00428-002-0609-x.

[14] Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001; 28: 836–846. doi:10.1007/s002590100541.

[15] Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993; 20: 716–731.

[16] Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: somatostatin receptor imaging with (111)In-pentetreotide. Neuroendocrinology 2009; 90: 184–189. doi:10.1159/000225946.

[17] Schillaci O, Spanu A, Scopinaro F, et al. Somatostatin receptor scintigraphy in liver metastasis detection from gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2003; 44: 359–368.

[18] Krausz Y, Keidar Z, Kogan I, et al. SPECT/CT hybrid imaging with 111In-pentetreotide in assessment of neuroendocrine tumours. Clin Endocrinol (Oxf) 2003; 59: 565–573. doi:10.1046/j.1365-2265.2003.01885.x.

[19] Wong KK, Cahill JM, Frey KA, Avram AM. Incremental value of 111-In pentetreotide SPECT/CT fusion imaging of neuroendocrine tumors. Acad Radiol 2009; 17: 291–297. doi:10.1016/j.acra.2009.08.015.

[20] Dromain C, de Baere T, Lumbroso J, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol 2005; 23: 70–78. doi:10.1200/JCO.2005.01.013.

[21] Hubalewska-Dydejczyk A, Fross-Baron K, Mikolajczak R, et al. 99mTc-EDDA/HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results

of 3 years' experience. Eur J Nucl Med Mol Imaging 2006; 33: 1123–1133. doi:10.1007/s00259-006-0113-7.

[22] Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007; 48: 508–518. doi:10.2967/jnumed.106.035667.

[23] Buchmann I, Henze M, Engelbrecht S, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2007; 34: 1617–1626. doi:10.1007/s00259-007-0450-1.

[24] Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. J Nucl Med 2010; 51: 875–882. doi:10.2967/jnumed.109.066134.

[25] Anderson CJ, Pajeau TS, Edwards WB, Sherman EL, Rogers BE, Welch MJ. In vitro and in vivo evaluation of copper-64-octreotide conjugates. J Nucl Med 1995; 36: 2315–2325.

[26] Gabriel M, Oberauer A, Dobrozemsky G, et al. 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. J Nucl Med 2009; 50: 1427–1434. doi:10.2967/jnumed.108.053421.

[27] Bodei L, Pepe G, Paganelli G. Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors with somatostatin analogues. Eur Rev Med Pharmacol Sci 2010; 14: 347–351.

[28] Quigley AM, Buscombe JR, Shah T, et al. Intertumoural variability in functional imaging within patients suffering from neuroendocrine tumours. An observational, cross-sectional study. Neuroendocrinology 2005; 82: 215–220. doi:10.1159/000092522.

[29] Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med 2010; 51: 704–712. doi:10.2967/jnumed.109.069765.

[30] Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med 2006; 36: 228–247. doi:10.1053/j.semnuclmed.2006.03.007.

[31] Koopmans KP, Neels ON, Kema IP, et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. Crit Rev Oncol Hematol 2009; 71: 199–213. doi:10.1016/j.critrevonc.2009.02.009.

[32] Neels OC, Koopmans KP, Jager PL, et al. Manipulation of [11C]-5-hydroxytryptophan and 6-[18F]fluoro-3,4-dihydroxy-L-phenylalanine accumulation in neuroendocrine tumor cells. Cancer Res 2008; 68: 7183–7190. doi:10.1158/0008-5472.CAN-08-0095.

[33] Koopmans KP, de Vries EG, Kema IP, et al. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. Lancet Oncol 2006; 7: 728–734. doi:10.1016/S1470-2045(06)70801-4.

[34] Montravers F, Grahek D, Kerrou K, et al. Can fluorodihydroxyphenylalanine PET replace somatostatin receptor scintigraphy in patients with digestive endocrine tumors? J Nucl Med 2006; 47: 1455–1462. doi: 47/9/1455 [pii].

[35] Ambrosini V, Tomassetti P, Rubello D, et al. Role of 18F-dopa PET/CT imaging in the management of patients with 111In-pentetreotide negative GEP tumours. Nucl Med Commun 2007; 28: 473–477. doi:10.1097/MNM.0b013e328182d606.

[36] Ahlstrom H, Eriksson B, Bergstrom M, Bjurling P, Langstrom B, Oberg K. Pancreatic neuroendocrine tumors: diagnosis with PET. Radiology 1995; 195: 333–337.

[37] Orlefors H, Sundin A, Ahlstrom H, et al. Positron emission tomography with 5-hydroxytryprophan in neuroendocrine tumors. J Clin Oncol 1998; 16: 2534–2541.

[38] Orlefors H, Sundin A, Garske U, et al. Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography.

J Clin Endocrinol Metab 2005; 90: 3392–3400. doi:10.1210/jc.2004-1938.

[39] Tessonnier L, Sebag F, Ghander C, et al. Limited value of 18F-F-DOPA PET to localize pancreatic insulin-secreting tumors in adults with hyperinsulinemic hypoglycemia. J Clin Endocrinol Metab 2010; 95: 303–307. doi:10.1210/jc.2009-1357.

[40] Orlefors H, Sundin A, Lu L, et al. Carbidopa pretreatment improves image interpretation and visualisation of carcinoid tumours with 11C-5-hydroxytryptophan positron emission tomography. Eur J Nucl Med Mol Imaging 2006; 33: 60–65. doi:10.1007/s00259-005-1891-z.

[41] Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxyphenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol 2008; 26: 1489–1495. doi:10.1200/JCO.2007.15.1126.

[42] Kauhanen S, Seppanen M, Nuutila P. Premedication with carbidopa masks positive finding of insulinoma and beta-cell hyperplasia in [(18)F]-dihydroxy-phenyl-alanine positron emission tomography. J Clin Oncol 2008; 26: 5307–5308. doi:10.1200/JCO.2008.18.8581.

[43] Kauhanen S, Seppanen M, Minn H, Nuutila P. Clinical PET imaging of insulinoma and beta-cell hyperplasia. Curr Pharm Des 2010; 16: 1550–1560. doi:10.2174/138161210791164090.

[44] Ambrosini V, Tomassetti P, Castellucci P, et al. Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. Eur J Nucl Med Mol Imaging 2008; 35: 1431–1438. doi:10.1007/s00259-008-0769-2.

[45] Haug A, Auernhammer CJ, Wangler B, et al. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2009; 36: 765–770. doi:10.1007/s00259-008-1030-8.

[46] Strauss LG CP. The application of PET in clinical oncology. J Nucl Med 1991; 32: 25.

[47] Hicks RJ. Use of molecular targeted agents for the diagnosis, staging and therapy of neuroendocrine malignancy. Cancer Imaging 2010; 10 (Spec no. A): S83–S91. doi: 10.1102/1470-7330.2010.9007.

[48] Ezziddin S, Logvinski T, Yong-Hing C, et al. Factors predicting tracer uptake in somatostatin receptor and MIBG scintigraphy of metastatic gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2006; 47: 223–233. doi: 47/2/223 [pii].

[49] Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. J Nucl Med 2010; 51: 353–359. doi:10.2967/jnumed.109.066662.

[50] Adams S, Baum R, Rink T, Schumm-Drager PM, Usadel KH, Hor G. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. Eur J Nucl Med 1998; 25: 79–83. doi:10.1007/s002590050197.

[51] Belhocine T, Foidart J, Rigo P, et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl Med Commun 2002; 23: 727–734. doi:10.1097/00006231-200208000-00005.

[52] Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008; 112: 2447–2455. doi:10.1002/cncr.23469.

[53] Fuccio C, Musto A, Cambioli S, et al. When should F-18 FDG PET/CT be used instead of 68Ga-DOTA-peptides to investigate metastatic neuroendocrine tumors? Clin Nucl Med 2011; 36: 1109–1111. doi:10.1097/RLU.0b013e31823361f7.

[54] Abgral R, Leboulleux S, Deandreis D, et al. Performance of 18Fluorodeoxyglucose-positron emission tomography and

somatostatin receptor scintigraphy for high Ki67 (>=10%) well-differentiated endocrine carcinoma staging. J Clin Endocrinol Metab 2011; 96: 665–671. doi:10.1210/jc.2010-2022.

[55] Pasquali C, Rubello D, Sperti C, et al. Neuroendocrine tumor imaging: can ^{18}F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? World J Surg 1998; 22: 588–592. doi:10.1007/s002689900439.

[56] Garin E, Le Jeune F, Devillers A, et al. Predictive value of ^{18}F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J Nucl Med 2009; 50: 858–864. doi:10.2967/jnumed.108.057505.

[57] Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res 2010; 16: 978–85. doi:10.1158/1078-0432.CCR-09-1759.

[58] Asnacios A, Courbon F, Rochaix P, et al. Indium-111-pentetreotide scintigraphy and somatostatin receptor subtype 2 expression: new prognostic factors for malignant well-differentiated endocrine tumors. J Clin Oncol 2008; 26: 963–970. doi:10.1200/JCO.2007.12.7431.

[59] Alexandraki KI, Kaltas G. Gastroenteropancreatic neuroendocrine rumors: new insights in the diagnosis and therapy. Endocrine 2012; 41: 40–52. doi:10.1007/s12020-011-9562-2.