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Double tracer PET/CT: what is it and what does it mean?

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ABSTRACT

^{68}Ga-DOTA-peptide PET/CT is a recommended imaging modality in the workup of neuroendocrine neoplasms (NENs), which shows high diagnostic sensitivity and is a strong predictor of successful somatostatin receptor directed treatments. Although not routinely recommended, reliable evidences show that ^{18}F-FDG PET/CT can provide complementary information in this setting with the ability to discriminate slow-proliferating tumors from aggressive, rapidly-proliferating tumors. Further, it has been proposed as an independent prognostic factor for the prediction of either overall survival or progression free survival. In this review, we provide insight into the biologic significance of ^{68}Ga-DOTA-peptides and ^{18}F-FDG uptake, and of the use of double tracer (^{68}Ga-DOTA-peptides plus ^{18}F-FDG) PET/CT in the clinical evaluation of patients affected by NENs.

Key words: ^{68}Ga-DOTATOC PET/CT; ^{18}F-FDG PET/CT; neuroendocrine neoplasms

INTRODUCTION

Neuroendocrine neoplasms (NENs) represent a group of heterogeneous and infrequent tumors, with an estimated incidence of 5.86 per 100,000 per year,[1] that most frequently originate from neuroendocrine cells of the upper airways, the small intestine, the duodenum and the pancreas.[2] NENs are generally asymptomatic in the early, localized stages (with the exception of a small minority of NENs, represented by so-called functioning NENs, which actively secrete bioactive substances and can present with related signs and symptoms, such as flushes and diarrhea). Functioning NENs are often discovered after the development of symptomatic metastases elsewhere in the body,[2,3] which occur most frequently in the lymph nodes, liver, and bones.[4,5] NENs may exhibit a variety of biological behaviors in that they may be aggressive and rapidly growing or indolent[6] and a long survival time (on the order of years) is not uncommon in patients with slowly progressing tumors.[7] The majority of NENs express somatostatin receptors (SSTR) on the cell membrane,[8] which makes them ideal targets for both functional imaging and therapeutic applications with radiolabeled somatostatin analogues (SSAs).[4,9] The level of SSTR expression appears to depend on tumor differentiation, with increased numbers of receptors expressed in well-differentiated NENs compared to poorly-differentiated NENs.[10] Tracers which exploit SSTR expression (^{68}Ga-DOTA-peptide) therefore have been employed in the diagnosis and staging of well-differentiated neuroendocrine tumors (NETs). Poorly-differentiated neuroendocrine carcinomas (NECs), which exhibit a higher proliferative activity and a loss of neuroendocrine features including the expression of SSTRs, are more suited to the use of ^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) imaging.[8] In fact, reported ^{18}F-FDG sensitivity is low in well-differentiated NETs,[11] and significantly improved in poorly-differentiated NECs.[12] Therefore, it has been hypothesized that ^{18}F-FDG-based molecular imaging may differentiate between more biologically aggressive NENs, which exhibit greater ^{18}F-FDG uptake, and more slowly-growing NENs, which exhibit less intense ^{18}F-FDG uptake. However, retrospective reports evaluating the prognostic value of ^{18}F-FDG have provided discordant results.[13,14]

^{18}F-FDG AND ^{68}GA: BIOLOGICAL AND TECHNICAL ASPECTS

^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG)

^{18}F-FDG is the most commonly used radiopharmaceutical tracer for PET imaging in clinical oncology.[15] It is a glucose analogue labeled with positron-emitting 18F. The compound is taken up into cells by glucose transporter

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proteins. Once internalized, ^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate which cannot be further metabolized and remains trapped in the cell.[16]

High rates of glycolysis are found in many malignant tumor cells.[17] Compared with normal cells, malignant cells have an increased number of cell surface glucose transporter proteins and increased intracellular glycolytic enzyme levels, including hexokinase and phosphofructokinase.[15,16] In clinical practice, therefore, ^{18}F-FDG is often used to distinguish malignant from normal tissues, to stage many types of neoplasms, and to detect recurrence after treatment.[18] Moreover, ^{18}F-FDG uptake, reflecting glucose metabolism, has been associated with higher cellular proliferative activity, increased tumor aggressiveness, and a less favorable prognosis. However, it should be noted that the uptake of ^{18}F-FDG varies greatly for different tumor types and increased ^{18}F-FDG uptake is not necessarily specific for neoplasms. Increased ^{18}F-FDG uptake may also be due to inflammatory processes, muscle contraction and brown fat activation.[8,15] From the technical point of view,^{18}F-FDG is administered via intravenous injection (standard doses: 10-20 mCi of ^{18}F-FDG, 0.14-0.21 mCi/kg of body weight)[19] and images are acquired approximately 60 min after injection to allow ^{18}F-FDG clearance from the blood pool and sufficient ^{18}F-FDG uptake in the target tissues (^{18}F-FDG half-life is 109 min).[15] In order to minimize competitive inhibition of ^{18}F-FDG uptake by glucose, patients should be fasted for at least 6 h prior to ^{18}F-FDG injection. Blood glucose levels are routinely assessed before starting the imaging, and 200 mg/dL is considered the maximum cutoff point.[16] Adequate pre-hydration is important to reduce ^{18}F-FDG concentration in urine and to reduce radiation dose to the patient.[16]

^{68}Ga-DOTA-peptides

^{68}Ga-DOTA-peptides are radiolabeled SSAs capable of specifically binding to SSTR, which are overexpressed on the surface of NET cells,[16] thus permitting functional imaging and therapeutic targeting of NETs.[20] Five different SSTR subtypes have been identified (SSTR1 to SSTR5), but SSTR2 is the predominant receptor subtype in NETs.[21] Many ^{68}Ga-DOTA-peptides have been developed for PET imaging of NETs.[8] The most widely employed in the clinical setting are ^{68}Ga-DOTANOC ([DOTA0,1-Nal3]-octreotide), ^{68}Ga-DOTATATE ([DOTA0,Tyr3,Thr8]-octreotide), and ^{68}Ga-DOTATOC ([DOTA0,Tyr3]-octreotide).[8] The major difference among these compounds relies on a slightly different affinity to SSTR subtypes. Although all ^{68}Ga-DOTA-peptides can bind to SSTR2, ^{68}Ga-DOTATOC and ^{68}Ga DOTANOC also bind to SSTR5, and ^{68}Ga-DOTANOC has additional affinity for SSTR3.[22] Physiological ^{68}Ga-DOTA-peptides uptake is evident in liver, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall, intestine, and pancreas.[23] In particular, a physiological focal location of uptake is in the pancreatic uncinate process, which must be considered in imaging interpretation.[8] Moreover, as SSTRs are also expressed in peritumoral vessels and in inflammatory and immune cells, false-positive findings may be constituted by non-NETs and inflammatory diseases.[8] That being stated, the reported sensitivity and specificity of PET/CT with ^{68}Ga-DOTA-peptides in the diagnosis of NETs are 96% and 100%, respectively.[24] Such outcomes are superior to that obtained with somatostatin receptor scintigraphy (SRS) and CT in NENs diagnosis, staging, and restaging.[25] The synthesis of ^{68}Ga-DOTA-peptides is relatively easy and does not require an on-site cyclotron. ^{68}Ga (physical half-life 68.3 min) is eluted from an in-house ^{68}Ga generator (physical half-life 270.8 days by electron capture) that allows a continuous tracer production.[8] ^{68}Ga-DOTA-peptides are administered via intravenous injection and images are acquired between 45 and 90 min after injection.[8] The activity administered in adults is 1.5-3 MBq per kg (100-200 MBq).[8] To avoid possible SSTR blockade, patients undergoing PET/CT with ^{68}Ga-DOTA-peptides should stop SSAs treatment, with an interval time depending on the type of drug used (1 day for short-acting SSAs and 3-4 weeks for long-acting SSAs).[8] No fasting before the injection of radiolabeled SSAs is needed.[8]

FOCUS ON ^{18}F-FDG AND ^{68}GA PET/CT IN NENs

At present, ^{18}F-FDG PET/CT is not routinely recommended for NENs imaging. The generally slow-growing behavior of this tumor type led to the hypothesis of a lower glycolytic activity compared with many other malignancies, and accordingly, of a lower sensitivity for ^{18}F-FDG PET in this setting. This notwithstanding, ^{18}F-FDG PET/CT shows a positive result in about 60% of NEN patients.

^{18}F-FDG and ^{68}Ga PET/CT and primary tumor site

NENs which arise in the thoracic region have a higher proportion of high-grade versus low-grade NENs (18-23.0% *vs.* 1-2.0% of all lung neoplasms), as has been reported in a review by Fisseler-Eckhoff and Demes.[26] In this context it should be observed that poorly differentiated NENs are usually ^{18}F-FDG-avid and demonstrate less ^{68}Ga-DOTA-peptide uptake. Among indolent, low-grade thoracic NETs, i.e. typical bronchial carcinoids, a low glucose turnover is common.[27] In these histotypes, ^{68}Ga-DOTA-peptide PET/CT demonstrates a superior diagnostic power over ^{18}F-FDG PET/CT, being able to correctly discriminate endobronchial neoplasms from adjacent atelectasis. The good correlation of ^{18}F-FDG and ^{68}Ga-DOTATATE uptake with tumor grade in pulmonary NETs justifies their clinical use as an aid in the identification, both at initial staging and during follow-up and evaluation of treatment results, of the presence of aggressive tumors or dedifferentiated areas within a low grade neoplasm.[28]

NENs which arise in the gastro-entero-pancreatic (GEP)

area show a higher proportion of low-grade versus high-grade malignant neoplasia.[29] Among GEP-NENs, midgut NENs are low-grade in more than half of cases (G1), whereas pancreatic NENs are more evenly distributed with regard to Ki-67 labeling index and consequently tumor grade.[30] It should be noted that higher grade NENs tend to show a significant uptake of ^{68}Ga-DOTA peptides and, conversely, significantly lower ^{18}F-FDG avidity.

^{18}F-FDG PET/CT is positive in 97% of patients with high-grade thoracic NENs (SCLC),[31] in 75% of patients with low-grade thoracic NENs (carcinoids),[32] in 53-57% of patients with pancreatic NENs and in 29% of gastrointestinal low-grade NENs (carcinoids).[33]

^{18}F-FDG and ^{68}Ga-DOTA-peptide PET/CT and tumor grade

The WHO grading system defines 3 categories of NENs based on mitotic count and Ki-67 proliferative index (G1, mitotic count < 2 cells/10 high-power fields (HPF) and Ki-67 index ≤ 2%; G2, mitotic count 2-20 cells/10 HPF or Ki-67 index 3-20%; and G3, mitotic count > 20 cells/10 HPF or Ki-67 index > 20%).[34,35] Tumors with higher Ki-67 expression display an increased proliferative activity and are associated with a less favorable prognosis.[36] ^{18}F-FDG PET/CT gives an index of cellular glycolytic activity, but it has also been hypothesized that it may reflect also tumor proliferation, based on correlations of ^{18}F-FDG uptake with the number of S-phase cells.[37] As expected, the proportion of patients with a positive ^{18}F-FDG PET scan was found to be markedly higher in patients harboring high-grade, highly-proliferating NECs compared with patients with well-differentiated, slowly-proliferating NETs (83% *vs.* 12,5%).[12] In a surgical series of pancreatic NENs, ^{18}F-FDG PET SUV max (maximum standardized uptake value) significantly correlated with tumor grade (Spearman rank correlation 0.584; P = 0.0018), and the sensitivity, specificity, and accuracy of differentiating G3 tumors from G1/G2 tumors were 100.0%, 62.5%, and 66.7%, respectively.[34] When well/moderately and poorly differentiated NENs are considered together, both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT positivity seem to correlate with tumor grade: a higher uptake of ^{68}Ga-DOTATATE has been described in low-grade compared with high-grade tumors (P = 0.019) and, conversely, a higher uptake in high-grade compared with low-grade NENs (P = 0.029).[38] When considering only intermediate and low-grade tumors, only ^{18}F-FDG PET/CT maintained a significant correlation with tumor grade, showing higher tracer uptake in intermediate versus low-grade NENs. On the contrary, ^{68}Ga-DOTATATE PET/CT showed similar uptake values in G1 and G2 NENs.[38] That notwithstanding, even in G1 NETs the rate of ^{18}F-FDG PET/CT positivity may be high. For example, in a prospective series of 98 patients with NENs, ^{18}F-FDG PET/CT was positive in 40% of patients with G1 NETs (Ki-67 labeling index < 2%), 70% of patients with Ki-67 labeling index 2-15% and 93% of patients with Ki-67 labeling index > 15%.[39] Although some studies fail to demonstrate such a relationship,[11,14] these observations suggest overall that ^{18}F-FDG PET/CT may provide information on tumor grade in NENs, showing a high accuracy in the distinction of NECs from NETs, and promising outcomes in the stratification of well-/moderately-differentiated NETs.[40]

ROLE OF DOUBLE TRACER PET/CT AT DIAGNOSIS

Diagnostic workup and staging

^{68}Ga-DOTA-peptide PET/CT is considered fundamental in the diagnostic workup in patients with suspected thoracic and/or GEP NETs.[41]

SSTR-based PET studies with ^{68}Ga-labeled SSAs (^{68}Ga-DOTA-peptides) represent the evolution of SRS with ^{111}In-pentreotide which emerged in the late eighties as the gold standard in diagnosing, staging and follow-up of patients with NET,[4,42] with reported sensitivity and specificity ranging between 60-99% (except only for insulinomas which show a low SSTR2 expression)[8] and 85-98%, respectively.[4,43,44] Despite these encouraging results, which were superior to those achieved by CT or MRI,[4,45,46] SRS was limited by a low spatial resolution and an inability to precisely localize neoplastic lesions, especially prior to the introduction of SPECT/CT hybrid systems.[8] These shortcomings have been overcome by the development of ^{68}Ga-labeled SSAs suitable for PET imaging. PET studies with ^{68}Ga-labeled SSAs have several advantages over SRS including better diagnostic accuracy for the detection of lung and bone lesions, higher affinity for SSTR2, higher spatial resolution, lower radiation exposure, better patient comfort, and faster reporting. Results are typically available within a few hours rather than 24 or even 48 h for SRS with 111In-pentreotide. Results also have the possibility of quantifying radionuclide biodistribution which includes the potential to use data for monitoring the response to anticancer agents.[4,47,48] Combining PET and CT scans additionally increased the diagnostic accuracy, as CT provides complementary anatomic information.[25] Among the various ^{68}Ga-labeled SSAs, ^{68}Ga-DOTATOC shows a particularly high affinity for SSTR2 which permits even the detection of small lesions with lower SSTR expression.[4,49] ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC are also clinically useful because of their high affinity to SSTR2 and, of particular importance, to SSTR3 and SSTR5 for ^{68}Ga-DOTANOC.[4,50,51] In a meta-analysis on the diagnostic performance of SSTR-based PET or PET/CT in patients with suspicious thoracic and/or GEP NETs, sensitivity and specificity of PET or PET/CT with ^{68}Ga-DOTA-peptides in detecting NETs on a per patient-based analysis ranged from 72% to 100% and from 67% to 100%, with pooled estimates of 93% (95% CI: 91-95%) and 91% (95% CI: 82-97%), respectively. The area under the ROC curve was found to be 0.96, demonstrating that SSTR-based PET or PET/CT with ^{68}Ga-DOTA-peptides are accurate diagnostic methods in NET diagnosis.[41] Being able to detect NET

lesions at a significantly higher rate than conventional imaging with CT and/or MRI, ^{68}Ga-DOTA-peptides PET/CT is particularly useful in "difficult" situations, such as the identification of the primary tumor in metastatic patients after failure of conventional imaging,[4,8,52] the detection of small metastases not always detectable by CT or MRI,[4,52] or the characterization of lesions of uncertain nature after conventional imaging. For these reasons, it is generally required, for example, to guide the selection of patients towards those who are potential candidates for radical surgery or for liver resection with curative intent.[4,22] In the preoperative staging, ^{68}Ga-DOTATOC PET provides additional information that significantly influences surgical management in around 20% of patients.[53,54]

On the other hand, ^{18}F-FDG PET is not routinely used in NENs imaging,[39] on the assumption that, due to the low proliferation rate and low metabolic activity generally seen in NETs, ^{18}F-FDG PET would have a low sensitivity and would not provide additional information to conventional CT and SSTR-based imaging.[11,38] Indeed, ^{18}F-FDG-based functional imaging demonstrates a low overall diagnostic sensitivity for NENs (58% for ^{18}F-FDG PET,[39] 66% for ^{18}F-FDG PET/CT),[38] and in general, SSTR-based functional imaging with ^{68}Ga-DOTA-peptides has superior accuracy in NENs diagnosis and staging compared with ^{18}F-FDG PET/CT. Nonetheless, it is known that one of the main limitations of SSTR-based PET/CT with ^{68}Ga-DOTA-peptides lies in the detection of poorly differentiated NECs, which frequently show a low expression of SSTRs on cell membrane. Such limitation can be overcome by combining the use of ^{18}F-FDG with ^{68}Ga-DOTA-peptides. The combination of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT improves the diagnostic accuracy over single tracer-PET/CT. Indeed, Kayani *et al*.[38] reported a sensitivity of 82% for ^{68}Ga-DOTATATE PET/CT alone and of 66% for ^{18}F-FDG PET/CT alone compared with 92% for double tracer (^{68}Ga-DOTATATE plus ^{18}F-FDG) PET/CT.

Prognostic relevance

Combining ^{18}F-FDG PET/CT with ^{68}Ga-DOTA-peptides PET/CT can provide additional prognostic information.

A high SSTR expression does not represent per se a prognostic parameter in terms of PFS.[55] ^{18}F-FDG uptake, conversely, seems to be related to higher Ki-67 index, higher proliferation rate and worse prognosis.[12,14]

In a first study by Pasquali *et al*.,[12] a positive ^{18}F-FDG PET scan was associated with early progression and a shorter survival. Ninty-three percent of patients with a positive ^{18}F-FDG PET scan had a progressive disease within 6 months *vs.* 8,7% of patients with a negative ^{18}F-FDG PET scan. Similarly, 95% of patients with a positive ^{18}F-FDG PET scan were alive at 2 years *vs.* 42% of patients with a negative ^{18}F-FDG PET scan. These observations were confirmed by Binderup *et al*.[39] in their prospective study conducted on 98 NEN patients. ^{18}F-FDG PET/CT positivity (both in terms of positive/negative and quantified by SUVmax) was an independent prognostic factor for the prediction of overall survival (OS) for NEN patients. With a hazard ratio (HR) of 10 for risk-of-death for patients with FDG-positive compared with FDG-negative foci, this test exceeded the prognostic value of "conventional" parameters such as Ki-67 labeling index and the presence of liver metastases. Similarly, a statistically significant difference in PFS between the ^{18}F-FDG-positive and the ^{18}F-FDG-negative group was found. Additionally, comparable results were obtained in another study with long-term follow-up, demonstrating an overall 4 year survival rate of 0% in patients with a positive ^{18}F-FDG PET scan versus 87% in patients with a negative ^{18}F-FDG PET scan.[56] These findings have been confirmed by a prospective study of patients with metastatic NENs in which a correlation was noted between ^{18}F-FDG PET positivity and worse prognosis in terms of shorter OS and PFS. OS was 95% and 95% at 1 and 2 years, respectively, for patients with a negative ^{18}F-FDG PET scan, versus 72% and 42% at 1 and 2 years, respectively, for patients with a positive ^{18}F-FDG PET scan. PFS was 87% and 75% at 1 and 2 years, respectively, for patients with a negative ^{18}F-FDG PET scan, versus 7% and 0% at 1 and 2 years, respectively, for patients with a positive ^{18}F-FDG PET scan.[2]

^{18}F-FDG PET may be useful even in a non-metastatic setting, to predict the prognosis in surgical patients. In a study conducted on patients with pancreatic NENs ^{18}F-FDG PET SUVmax correlated with tumor grade and also appeared to be significantly related to postoperative disease-free survival ($P = 0.0463$).[34]

Predictive relevance

Predicting the course of a metastatic NEN is difficult. Aggressive treatment should be proposed to all patients in good overall health with high-grade NECs because of their rapidly progressive behavior. Different therapeutic strategies may instead be proposed to patients with well-differentiated NETs, which may show a variable range of malignant behavior. Due to the fact that available treatments may have significant long-term toxicity, it is important to distinguish between rapidly progressive NENs, for which active treatment is necessary and relatively indolent NENs, which may be treated more conservatively.

^{68}Ga-DOTA-peptide PET/CT, depicting the amount of SSTR expression on NEN cells, has been proposed as a predictive tool for both SSAs treatment and PRRT.[22,57] While SSTR-based functional imaging positivity is not required before the start of SSAs therapy, it is a basic requirement for PRRT with beta-emitting radiolabeled SSAs.[3,8,22,58] Due to its pharmacokinetics, PRRT is effective only in SSTR-expressing lesions.[59] SUVmax measured on PET imaging with ^{68}Ga-DOTA-peptides exactly correlates with the number of SSTR on tumor

cells and a higher SSTR expression is a rough predictor of response to PRRT.[55,60] Clinical studies demonstrated higher tumor remission rates after PRRT in patients with a high baseline SUVmax on ^{68}Ga-DOTA-peptide PET/CT versus patients with a lower baseline SUVmax on ^{68}Ga-DOTA-peptide PET/CT.[59]

Therefore, patients with positive ^{18}F-FDG PET/CT but negative ^{68}Ga-DOTA-peptide PET/CT cannot be effectively targeted with PRRT, as the negative ^{68}Ga-DOTA-peptide PET/CT indicates that the obligatory target is not expressed. Such patients, who frequently harbor high-grade NECs, may benefit instead from conventional chemotherapy[61] or, in selected cases, from biologic agents such as everolimus or sunitinib.[62,63] Conversely, if patients have ^{18}F-FDG-avid lesions which retain sufficient SSTR expression as evidenced by concordant ^{18}F-FDG and ^{68}Ga-DOTA-peptides uptake, these sites of aggressive disease can potentially be targeted with PRRT.[64] Indeed, it has been reported that many such patients, including those who have failed conventional therapies,[64] have remarkable responses to PRRT, although with shorter PFS[55] compared to patients without a positive ^{18}F-FDG PET/CT scan. In a study conducted on patients with metastatic, well differentiated (G1-G2) NETs, undergoing 177Lu-DOTATATE PRRT, the disease control rate was significantly higher in patients who had a negative ^{18}F-FDG PET/CT scan after ^{177}Lu-DOTATATE PRRT (100%) versus patients who had a positive PET scan after 177Lu-DOTATATE PRRT (76%).[55] Moreover, PFS was significantly lower in patients who had a positive ^{18}F-FDG PET/CT scan, of whom 48% had progressive disease (PD) after a median follow-up of 20 months, versus patients who had a negative ^{18}F-FDG PET/CT scan, of whom 26% had PD after the same follow-up time.[55] In a study on patients with metastatic well-differentiated NETs,[65] of the 42 patients who had pretreatment ^{18}F-FDG PET imaging, 31 patients had a positive ^{18}F-FDG PET scan (SUVmax > 2.5) with an average survival time of 18.9 months (range 1.4-45.8 months) and 11 patients had a negative ^{18}F-FDG PET scan (SUVmax ≤ 2.5) with an average survival time of 31.8 months (range 7.4-42.9 months). Survival in patients with a negative ^{18}F-FDG PET scan was significantly longer than in patients with a positive ^{18}F-FDG PET scan (P = 0.001 with 95% confidence interval).[65]

It has been proposed that these patients could benefit from the adjunct of radiosensitizing chemotherapy with 5-FU to PRRT[66] and trials are ongoing to assess this hypothesis.

Heterogeneity description

The histopathological classification of NENs is limited by an intrinsic bias when applied to patients with metastatic disease. The tissue obtained from needle biopsy of a single lesion is not necessarily representative of the all the cells in that tumor, or all the tumor lesions in all tumor sites[38,39,55] given that NENs display a particularly high heterogeneity.[34] Accurate tumor grading for prognostication and risk stratification would theoretically require multiple biopsies from different tumor sites and in different moments over time through the evolution of the disease, but obviously this is not always possible.[34,55]

Functional imaging can non-invasively and simultaneously visualize in real-time all metabolically active tumor sites in the whole body.[39,55] While ^{68}Ga-DOTA-peptides avidity is a feature of well-differentiated disease, ^{18}F-FDG avidity tends to be associated with more aggressive, de-differentiated disease.[66] Variable tracer uptake at different lesion sites within the same patient is a relatively common finding, and reflects the wide spectrum of differentiation of some NENs, where heterogeneity of cellular differentiation may be present even within one single tumor lesion.[12,38]

This observation, while suggesting caution in the interpretation of Ki-67 indexes obtained from biopsy samples, on the other hand reflects the potential ability of PET/CT to map cellular heterogeneity. Consistently, the prognostic value of ^{18}F-FDG PET/CT positivity exceeded that of "conventional" parameters such as Ki-67 labeling index and presence of liver metastases in the study of Binderup *et al*.[39] Similarly, ^{18}F-FDG PET/CT was found to be more sensitive than pathologic differentiation and Ki-67 labeling index in the early prediction of rapidly progressive disease in the report of Garin *et al*.[2] A total tumor population characterization using a combination of ^{18}F-FDG PET/CT and ^{68}Ga-DOTA-peptides PET/CT seems a clinically useful approach,[52] being able to map the entire degree of tumor differentiation in the same patient at different time points throughout the natural course of disease.[22,38,52]

ROLE OF MOLECULAR IMAGING IN THE EVALUATION OF RESPONSE AFTER TREATMENT

Early prediction of therapy response in cancer patients is essential to guide therapy and avoid the side effects and costs of ineffective therapies.

^{68}Ga-DOTATOC PET/CT was found to be superior to standard imaging with CT and/or MRI in the detection of primary tumor recurrence in pretreated patients in whom tumor recurrence was suspected during the follow-up period (8/40 *vs.* 2/40, $P < 0.001$).[4]

The role of ^{68}Ga-DOTATOC PET/CT in evaluating treatment response after PRRT is debated. Some authors reported that decreased ^{68}Ga-DOTATATE uptake after finishing the first cycle of PRRT significantly correlated with symptom improvement and a longer TTP in patients harboring well-differentiated NETs.[67,68] In other studies, ^{68}Ga-DOTATOC PET was not found to be superior to CT in the assessment of response to SSTR-targeted PRRT.[69] For this reason, early variations in SUVmax of ^{68}Ga-DOTATOC PET actually cannot be used as a surrogate

marker of response. However, the persistence of high levels of ^{68}Ga-DOTATATE uptake during treatment with SSAs can suggest the continuation of cold SSAs treatment in patients with stable disease and/or to switch to PRRT in patients with signs of clinical/radiological worsening.[52]

^{18}F-FDG PET/CT may be useful, instead, in the evaluation of patients with dedifferentiated tumor recurrences[69] and of patients who had ^{18}F-FDG-avid lesions at diagnosis in whom changes in ^{18}F-FDG SUV between pre-therapy baseline and intratherapy follow-up scans may be an indicator of response to treatment. In this context it may be useful to refer to a standardized set of rules which can be employed to objectively assess tumor response to treatment such as PERCIST criteria which were developed for quantitative PET evaluation of changes in tumor metabolic activity induced by anticancer treatments.[70] For instance, the use of these criteria has shown to be clinically useful in the evaluation of patients with SCLC.[71]

CONCLUSION

Double-tracer PET/CT is a useful tool in the management of NENs.

Parameters that may influence the decision of the clinician to request a double-tracer PET/CT study are include tumor grading, primary tumor site and clinical setting (i.e. resectable *vs.* advanced disease, *etc.*).

^{68}Ga-DOTA-peptide PET/CT is routinely employed in the setting of low- and intermediate-grade NENs; ^{18}F-FDG PET/CT has a more debated role in the management of NENs. Besides its established role in the management of highly proliferating neoplasms, it can be a useful tool even in more indolent tumors.

Double-tracer PET/CT may have not only diagnostic, but also predictive and prognostic applications. Double-tracer staging shows a higher overall accuracy than conventional imaging and can provide prognostic information. A possible predictive role of nuclear medical imaging has been suggested, but has not yet been fully validated. Although ^{68}Ga-DOTA-peptide PET/CT has been found in several studies to be a strong predictor of response to PRRT, the role of 18F-FDG PET/CT as a predictive factor is still under investigation.

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