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Editorial

The NETPET Score: Combining FDG and Somatostatin Receptor Imaging for Optimal Management of Patients with Metastatic Well-Differentiated Neuroendocrine Tumors

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Abstract

Neuroendocrine tumors (NET) are often metastatic at the time of diagnosis. Metastatic well-differentiated (G1/G2) NET may display a wide range of behaviors, ranging from indolent to aggressive, even within apparently homogeneous categories. Thus, selecting the optimal treatment strategy is a challenging task. Somatostatin receptor imaging (SRI) is the standard molecular imaging technique for well-differentiated NET. When performed with ^{68}Ga-labeled somatostatin analogs (SRI-PET), it offers exquisite sensitivity for disease staging. SRI is also a prerequisite for using targeted radionuclide therapy (e.g. ^{177}Lu-DOTATATE). 18F-FDG imaging has traditionally been reserved for staging poorly-differentiated G3 neuroendocrine carcinomas. However, recent data showed that FDG imaging has prognostic value in patients with well-differentiated NET: high uptake was associated with an increased risk of early progression while low uptake suggested an indolent tumor.

In this issue of the Journal, Chan and colleagues propose a grading system where the results from the combined reading of SRI-PET and FDG-PET are reported as a single parameter, the "NETPET" score. While the scoring system still needs validation, it is clear that time has come to think about FDG and SRI in metastatic NET not as competitors but as complementary imaging modalities. Dual-tracer imaging can be viewed as a way to characterize disease phenotype in the whole-body. Moving from the prognostic value of dual-tracer imaging to a tool that allows for individualized management would require prospective trials. This editorial will argue that dual-tracer FDG-PET and SRI-PET might influence management of patients with well-differentiated metastatic NET and help selecting between different therapy options.

Key words: Neuroendocrine tumors, NET, GEP-NET, PET/CT, Prognosis, ^{18}F-FDG, Somatostatin analogs, Gallium-68, ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, Somatostatin receptor, Radionuclide therapy, ^{177}Lu-DOTATATE.

The annual incidence of neuroendocrine tumors (NET), including gastrointestinal NET, pancreatic NET, pulmonary carcinoids and other rare NET, was estimated as 5 per 100.000 in the US population in the years 2000-2004 [1]. About one-third of NET exhibit symptoms related to the secretion of bioamines and peptides (e.g. carcinoid syndrome in serotonin-secreting tumors, hypoglycemia in insulin-producing pancreatic NET), while the majority are non-functioning. Even when they are

well-differentiated, NET are often diagnosed at advanced stages. Distant metastases, mainly to the liver, are present at diagnosis in about 40–45% of pancreatic, small intestinal, and colonic NET, and in about 5–15% of appendiceal, gastric, and rectal NET [2].

For patients with well-differentiated metastatic NET, with unresectable disease, optimal selection of palliative treatment options (timing and method) is crucial to maintain or improve quality of life and to prolong survival [2,3]. Adequate management is based on the likelihood of disease progression and the most important prognostic parameters are the site of the primary tumor and the tumor grade. In the 2010 WHO/ENETS classification, well-differentiated NET are graded G1 (≤2% Ki67 immunostaining and <2 mitoses) or G2 (3–20% Ki67 or 2-20 mitoses), while NEC G3 (>20% Ki67 or >20 mitoses) represent small-cell or large-cell neuroendocrine carcinomas [4]. However, even within similar categories, tumor behavior of metastatic well-differentiated NET can vary widely [2,3]. Grade determination often relies on a previously resected primary tumor, or on biopsy of a single metastatic lesion that may not reflect tumor heterogeneity [5]. Identifying better predictors of progression in well-differentiated NET is thus required to guide treatment strategies.

Somatostatin receptor imaging (SRI) is widely used in well-differentiated NET for diagnosis, staging, follow-up, as well as for deciding upon the suitability of peptide receptor radionuclide therapy (PRRT) [6,7]. In many centers, SRI is now performed with positron emission tomography/computed tomography (SRI-PET) and ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC or ^{64}Cu-DOTATATE, resulting in improved sensitivity compared to conventional ^{111}In-octreotide imaging [6,8,9]. On the other hand, ^{18}F-FDG imaging (FDG-PET) has traditionally been used for staging poorly-differentiated G3 tumors, or to complement SRI in well-differentiated NET when Ki67 exceeds 10% [6]. However, there are arguments for a wider use of dual-tracer imaging (SRI-PET + FDG-PET) in well-differentiated NET, as recent studies underscored the prognostic value of FDG-PET in these patients [10-15].

In this issue of the Journal, Chan and colleagues propose a grading system where results from the combined reading of SRI-PET and FDG-PET in patients with metastatic NET are reported as a single parameter, the NETPET score [16]. This proposal is interesting and timely. In this editorial, I will discuss the value of FDG imaging in patients with well-differentiated metastatic NET and offer some perspectives on how dual-tracer imaging may influence current management strategies.

What is the frequency of FDG-positive scans in well-differentiated G1/G2 NET and what is the impact of this finding on prognosis?

Three prospective studies showed that FDG positivity is not rare in metastatic well-differentiated G1/G2 NET and is a stronger predictor of progression and prognosis than the existing WHO groups [10,11,14]. In the study by Garin and colleagues, 30 patients with documented well-differentiated metastatic NET were offered a period of wait-and-watch before treatment [10,13]. FDG-PET was positive on visual analysis in 7 patients and progression within six months occurred in 6, while only 2 of 23 PET-negative patients showed early progression ($p < 0.001$) [10]. When considering only the subgroup of patients with G1/G2 tumors and positive SRI, FDG-positivity was present in 3/23 cases and was correlated with significantly decreased progression-free survival (PFS) and overall survival (OS) [13]. Binderup et al. investigated 98 patients with advanced NET [11]. FDG was positive (focal uptake) in 40% of G1, 70% of G2 and 93% of G3 patients. Among the fourteen patients who died, 13 had a positive FDG scan (hazard ratio of 10.3). Five of 47 patients in the G1 group died, four of whom had a positive FDG-PET [11]. In the study recently reported by Johnbeck et al., 88 patients had well-differentiated advanced NET [14]. Treatment strategies were based on standard of care. FDG was positive in 39% of G1 and 50% of G2 patients. In these patients with well-differentiated NET, only FDG-positivity was a significant prognostic factor with a hazard ratio of 2.4 for PFS ($P = 0.003$) and 5.3 for OS ($P = 0.001$) [14].

In a retrospective analysis, Ezziddin and colleagues reviewed data from 89 patients with metastatic NET and identified three prognostic groups based on the ratio of SUV_{max} of the lesion with the highest FDG uptake to that of normal liver parenchyma (ratio ≤ 1; >1 to 2.3; >2.3). These groups were associated with significant differences in overall survival (median OS not reached after 114 months *vs*. 55 months *vs*. 13 months) [12].

Are results of SRI-PET and FDG-PET complementary?

A positive SRI is a favorable prognostic factor as it signals that the metastatic NET expresses somatostatin receptors and is well differentiated [17]. SRI-PET has also an important predictive value [18-20]. For example, Kratochwil et al. investigated the ability of ^{68}Ga-DOTATOC PET to predict response of liver metastases to PRRT in 30 patients. Significant

differences were observed in SUVmax at baseline between responding and non-responding lesions [20]. This is in line with studies showing an association between the radiation dose received by the tumors and therapeutic response [21].

Some authors found that FDG has a higher prognostic value than SRI [10,13], while others found that SRI is better than FDG regarding its prognostic value [22] or its global impact on management [23]. However, many authors now see SRI and FDG not as competitors but as complementary diagnostic tools [24-28]. For example, Nilica and colleagues used dual-tracer imaging in the setting of PRRT in 66 patients with metastatic NET. All patients were ^{68}Ga-DOTATOC PET-positive initially and at follow-up. FDG-PET showed more and/or larger metastases than ^{68}Ga-DOTATOC PET in five patients at baseline and in four patients during follow-up. In all nine patients the disease progressed [25]. Some teams are investigating dual-tracer imaging for preoperative prognostication and risk stratification in pancreatic tumors or pulmonary carcinoid [27,28]. Lococo et al. showed that a ratio of ≥1.19 between the SUVmax on SRI-PET and the SUVmax on FDG-PET can differentiate between a typical or atypical carcinoid [28]. Preoperative biopsy has difficulty in distinguishing between these entities [29].

In total, somatostatin receptor expression and differentiation status (SRI-PET) and glycolytic activity and metabolic reprogramming (FDG-PET) are both important prognostic factors.

The dual-tracer NETPET score

The strategy adopted by Chan and colleagues was first to identify the lesion that is the *most* FDG-avid, relative to its uptake on SRI, as this is likely to represent the most aggressive phenotype [16]. Once this lesion was defined it provides the primary categorization of the subject, and subcategories are then provided based on the number of lesions that exhibit this high-risk trait. In the NETPET scoring system, a grade P1 indicates purely somatostatin receptor-positive lesions without FDG uptake above background and P5 the presence of significant FDG-positive/somatostatin receptor-negative disease. In the intermediate categories P2 to P4, the "target" lesion exhibits positivity on both scans, with progressive increase in FDG uptake (relative to uptake on SRI) as we move from P2 to P4. Finally, P0 indicates a normal scan on both FDG and SRI (e.g., in case of completely resected disease) [16].

The authors retrospectively investigated the prognostic value of the NETPET score in 62 subjects with metastatic NET who received ^{68}Ga-DOTATATE and FDG-PET within 31 days of each other. Due to limitations imposed by the number of patients, the authors used only three groups: P1 (11 patients; SRI+ve/FDG-ve disease); P2-4 grouped together (n=33; SRI+ve/FDG+ve disease); P5 (n=18; SRI-ve/FDG+ve disease). Overall survival was significantly associated with NETPET grade (log-rank test, p=0.0018) [16].

The NETPET scoring system is quite appealing as it summarizes the results of both scans in a single parameter [16]. As this is a retrospective analysis, the reasons that led to dual-tracer imaging, the kind of treatment received and how it impacted the outcome could not be analyzed. Thus, these findings need to be validated prospectively.

The authors visually compared the SRI-PET and the FDG-PET uptake, by using a SUVmax scale from 0 to 15 for ^{68}Ga-DOTATATE and from 0 to 7 for ^{18}F-FDG [16]. Thus, the reproducibility of visual scoring will be an important parameter to assess. It will also be helpful to compare visual scoring versus scoring based on quantitative methods of image analysis, such as the ratio of SUVmax between the two tracers or the tumor-to-liver ratio for each tracer.

Importantly, the NETPET score was designed to discriminate the subjects in the intermediate groups (P2 to P4), i.e. those who exhibit uptake on both FDG and SRI [16]. Unfortunately, because the number of patients was limited, these intermediate categories were merged. So, how the individual intermediate classifications impact the prognosis and decision making is matter for future studies.

How dual-imaging with FDG-PET and SRI-PET might influence management of patients with well-differentiated metastatic NET?

The variable clinical outcome of patients with well-differentiated metastatic NET, even within apparently homogeneous patient categories, makes the selection of an optimal treatment strategy challenging [2,3,30]. In many situations, dual-tracer imaging might prove useful.

Initial management in metastatic well-differentiated intestinal (midgut) NET: Despite their proven antiproliferative activity, it remains controversial whether somatostatin analogs should be started at diagnosis in all patients. In the CLARINET trial (nonfunctioning metastatic NET with Ki67 <10%), a high percentage of patients on the placebo arm remained stable for a long time, especially so in small intestinal NET (median PFS in small intestinal NET 21 months, in pancreatic NET 12 months) [31]. In the absence of extensive tumor burden, a watch-and-wait strategy may thus be justified in a

subgroup of patients that still needs to be defined [3]. Dual-tracer imaging can help identifying these subgroups, as patients with SRI-positive/FDG-PET negative metastatic NET display a long PFS [13]. On the other hand, the CLARINET trial did not include patients with Ki67 above 10% and there is no consensus on the upper cut-off value of Ki67 for using somatostatin analogs rather than more aggressive treatments [3]. High uptake on ^{68}Ga-DOTATATE has been associated with longer stability under somatostatin analogs [18]. Three different scores of FDG uptake were associated with highly different prognoses [12]. Thus, dual-tracer imaging associated with an appropriate scoring system might help deciding which patients can be observed and monitored, which should be started on somatostatin analogs and which might need more aggressive therapy. The NETPET score may help in this sense.

Initial management in advanced/metastatic well-differentiated pancreatic NET: The ENETS consensus suggests using somatostatin analogs or chemotherapy as first choice [3], although there is no consensus on the upper cut-off value of Ki67 for using somatostatin analogs [3]. Using dual-tracer imaging, a high uptake on SRI with low FDG uptake would favor the use of somatostatin analogs, while the opposite suggests the use of chemotherapy. Some authors have already used high FDG uptake as a basis for choosing chemotherapy [23,24].

PRRT in well-differentiated metastatic NET: In the NETTER-1 trial, patients with midgut NET who had disease progression during first-line somatostatin analogue therapy were randomly assigned to receive ^{177}Lu-Dotatate or high dose octreotide LAR alone [7]. The estimated rate of PFS at month 20 was 65.2% in the ^{177}Lu-Dotatate group and 10.8% in the control group [7]. For intestinal NET, either PRRT or the mTOR inhibitor everolimus may be used as 2nd line if somatostatin analogs fail [3,7,32]. PRRT also offers high response rates in pancreatic NET [33,34] and pulmonary carcinoid [35]. Given the importance now gained with PRRT in metastatic NET, adequate patient selection will be an important issue in the coming years. The SUVmax on SRI is predictive of response to PRRT [20]. On the other hand, high FDG uptake has been associated with shorter PFS [15]. By consequence, a scoring system based on dual-tracer imaging that takes into account the uptake on both SRI-PET and FDG-PET would be helpful for patient selection. High uptake on SRI compared to FDG would favor PRRT [25], while a high ratio of FDG to SRI uptake would predict resistance to PRRT [25]. Some teams have combined PRRT with chemotherapy [36,37], for example in patients with SRI-positive but FDG-avid disease [37].

Guiding biopsies: When the disease does not fit into the WHO grading, or if the disease changes its pattern or the expression of its biomarkers [30], dual-tracer imaging may guide a novel biopsy [16,25].

Conclusion: the NETPET scoring system based on dual-tracer imaging devised by Chan and colleagues may help better characterizing well-differentiated metastatic NET lesions. This may positively impact the management of these patients and help selecting between different therapeutic options. Its potential should be investigated within prospective trials.

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