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EDITORIAL

The future of nuclear medicine imaging of neuroendocrine tumors: on a clear day one might see forever…

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Introduction

Early identification of neuroendocrine tumors (NETs) is a critical prerequisite to establishing effective treatment. While substantial advances have occurred in the last two decades, there is little progress regarding the identification of small subcentimeter lesions and the determination of tumor proliferative rates and metabolic characteristics. At this time, delineation of lesions mainly utilizes various combinations of somatostatin receptor (SSR) density, glucose metabolism and Hounsfield units.

This editorial addresses unmet needs in nuclear medicine (molecular) imaging with a view to identifying areas that require amplification. The principal goal is to amplify and extend the diagnostic and prognostic role of imaging. Specific focus is required to validate and standardize current techniques while introducing strategies that will resolve currently unmet needs.

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The current status of nuclear medicine imaging of neuroendocrine tumors

A correct and timely diagnosis is crucial in NET management to establish the most effective treatment [1]. Nuclear medicine techniques, particularly positron emission tomography (PET) scan/ computed tomography (CT), exhibit optimal diagnostic sensitivity for primary and metastatic gastro-entero-pancreatic (GEP) NETs. They are usually combined with anatomic techniques to maximize the acquisition of clinically relevant spatial information [2]. In broader terms, a combination of morphological and molecular imaging with radiolabeled probes enables characterization of a lesion in terms of its structural location, anatomical relation, disease extent and its functional status. Overall, the role of nuclear medicine imaging is diagnosis of primary and secondary lesions, assessment of the efficacy of therapy, and to provide information regarding the metabolic and secretory properties of the neoplasia. However, it is evident from published data that there exists a wide variation in diagnostic accuracy. At this time, the most accurate and reproducible (robust) methodology in terms of technology and optimal radioisotope selection is undefined.

Integral components of the techniques

Nuclear medicine imaging consists of conventional scintigraphy and PET/CT. Scintigraphy is classically carried out with ^{111}In-pentetreotide (or OctreoScan®), or, more rarely, with ^{99m}Tc-labeled peptides, like ^{99m}Tc-HYNIC-TOC, while PET techniques utilize ^{68}Ga-DOTA-peptides (DOTA-NOC, −TOC and –TATE - ^{68}Ga-SMS-R-PET), and the amine precursors ^{18}F-DOPA, and ^{11}C-5-hydroxytryptophan (^{11}C-5HTP) [3–6].

In nuclear medicine, radiolabeled somatostatin analogs (SSA) are the most utilized, since they represent an optimal

paradigm of theranostics [7]. Currently, ^{68}Ga-SMS-R-PET is regarded as the ideal nuclear medicine NET imaging tool and has, for all practical purposes, displaced OctreoScan®. Alternative PET techniques using ^{18}F-DOPA and ^{11}C-5HTP are effective, but have been supplanted by the increased availability and better performance of ^{68}Ga-SMS-R-PET [8, 9].

Strength of each technique

NET functional imaging comprises a set of tools that facilitates tumor characterization by localization, staging and restaging of both primary and metastatic tumors. In addition, it provides lesion characterization (SSR density, indirect quantification of proliferative activity and tumor heterogeneity through the measurement of glucose metabolism and assessment of substrate metabolism), as well as guiding the selection of therapy (cold or radiolabeled SSAs).

A key clinical impact of functional imaging is provided by its ability to modify therapeutic strategy and prognosis. Thus, somatostatin receptor imaging (SRI), particularly with ^{68}Ga-SMS-R-PET, alters management in >50 % and successfully predicts response to cold or radiolabeled analogues [10, 11]. Although conventional ^{18}fludeoxyglucose (FDG) PET is not a primary diagnostic tool in NETs, standardized uptake value (SUV) assessment can provide predictive information in terms of progression-free survival and response to peptide receptor radiotherapy (PRRT) [12, 13].

Limitations of nuclear medicine techniques

Despite the efficacy of ^{68}Ga-SMS-R-PET, it is as yet not completely integrated into clinical guidelines [14]. Similarly, functional imaging has not been incorporated into response assessment criteria, which currently rely solely on anatomic information [15]. Despite the high level of awareness of clinicians, the lack of homogeneity regarding the techniques has dampened initial enthusiasm, since comparability has become an issue.

Some of the current limitations of NET functional imaging represent complexities relating to regulatory aspects of isotope/carrier usage as well as to standardization issues. From the regulatory perspective, only ^{111}In-pentetreotide has U.S. Food and Drug Administration (FDA) / European Medicines Agency (EMA) approval for NET imaging.

Thus, for ^{68}Ga-SMS-R-PET, although four peptides are currently in use (DOTATOC, DOTANOC, DOTATATE and HA-DOTATATE), no marketing authorization for Ge/Ga generators or ^{68}Ga-DOTA-peptides exists [16]. These peptides are therefore prepared according to the Good Radiopharmacy Practice. Although a European pharmacopeia monograph on ^{68}Ga-DOTATOC was implemented in 2013 (http://www.edqm.eu/medias/fichiers/index_english1.pdf), the EANM guidelines only regulate the general aspects of the procedure. Specific items such as acquisition parameters, administered activity and SUV measurement have been delegated to individual centers [16].

Overall, the methodological limitations of functional imaging include the lack of consensus regarding the optimal agents and techniques (numerous radiopharmaceuticals and scanning techniques, viz. SPECT vs. PET, and for PET, the numerous radiopharmaceuticals available). Furthermore, there is a lack of a fully validated comparison between a state-of-the-art OctreoScan® and ^{68}Ga-SMS-R-PET, and no full validation of the ^{68}Ga-SMS-R-PET technique.

Areas that require advance

^{68}Ga-SMS-R-PET validation The requirements are threefold and include: the choice of peptide, the type of radiopharmaceutical preparation, and the reproducibility of the PET technique.

1) Preferred peptide: None of the three peptides currently in use demonstrate a clear diagnostic superiority over the others [17, 18].
2) Preparation: Apart from DOTATOC, which has a European Pharmacopeia monograph, radiopharmaceuticals are prepared according to non-standardized local procedures. Furthermore, no standardized toxicity and sterility data exist.
3) PET technique reproducibility: Current protocols are not uniformly consistent in the acquisition time point or the optimal preparation of patients, i.e., the time interval between cold SSA injection and imaging. The semi-quantitative parameter to quantify uptake, i.e. the SUV, is intrinsically variable and varies significantly among individual PET scanners and between centers. Moreover, its reproducibility may be altered by the use of different peptides (with different receptor affinities), by different scanning times (resulting in different phases of tumor uptake), by the degree of receptor saturation in normal tissue due to the co-administration of cold analogues [19] and by splenectomy [20].

^{18}FDG uptake Increased ^{18}FDG uptake as a prognostic marker for NET aggression requires rigorous clinical validation. In parallel, its correlation with the tumor Ki67 index, the transcript proliferome or other indices of proliferation have not been adequately delineated. For example, ^{18}FDG is positive in a substantial percentage of slow-proliferating low grade (G1) tumors, confounding the generally accepted notion that it is

only useful in the identification of rapidly proliferating and poorly differentiated tumors [13].

Biologic information There is a need to integrate the biological information of NET pathophysiology with nuclear medicine diagnostic and therapeutic strategies. Thus, the relationship between the intrinsic variability of individual NET cells (EC, beta, ECL, D, Clara etc.) that comprise the different tumor types and nuclear medicine strategies requires investigation. This should include a delineation of histopathological indices, high-throughput molecular analyses, receptor subtyping and characterization as well as the definition of metabolic parameters that delineate function and proliferation. Aggregation of such information will provide added value in the interpretation of diagnostic scans and further inform the efficacy of therapeutic strategies.

The future

1) Strategies to advance current techniques

   The development of an efficient and reproducible SSR-based molecular imaging procedure is a strategic necessity to ensure clinical acceptance of current and future techniques. The recent assignment by FDA/EMA of orphan drug designation to ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE is, hopefully, a step towards uniformity.

   A critical issue is the need to validate ^{68}Ga-SMS-R-PET, especially by assuring SUV objectivity and comparability. Options include correction of the tumor maximum SUV (SUV_{max}) with background [21], the correction of the tumor SUV_{max} with the spleen [22], and the calculation of molecular tumor volume [23]. Finally, in order to be predictive, the apocryphal "Rotterdam scale" needs to be objectified and adapted to PET. The collaboration of clinical and nuclear medicine societies in the process of standardization is necessary to assure adoption of a uniform process.

2) Introduction of novel techniques and strategies

   Improvements in current techniques that utilize Ga-68 are worthy of consideration. Thus, SSAs labeled with Cu-64 are of considerable interest, due to the excellent image quality and the spatial resolution [24]. The 12.5-hour half-life allows later imaging compared to Ga-peptides, with stable tumor to background ratios at least 3 h after injection, thus matching more closely the tumor uptake kinetics, and the possibility of imaging at 24 h.

   An additional area is the development of alternative fusion imagery. Preliminary studies with fused ^{68}Ga-SMS-R-PET and magnetic resonance imaging (MRI) scan, both as diffusion-weighted and gadoxetate-enhanced images, have demonstrated similar high per-region (98.9 and 97.7 %, respectively) and per-organ (95.7 and 91.3 %, respectively) sensitivity, with comparable high specificity (99.6–99.7 %) [25]. The PET and MRI techniques provide complementary information, regarding both the anatomical detail and the functional characterization of the tissue, including the diffusion-weighted imaging (DWI) parameters and the receptor-mediated uptake of the ^{68}Ga-DOTA-peptide.

   SSAs have been the workhorse of imagery for two decades, and alternative radiopharmaceuticals that provide increased diagnostic accuracy should be identified. In this respect, the use of SSR antagonists appears to represent a highly promising strategy [26]. The lack of internalization and the recognition of increased binding sites represent an inversion of the current paradigm of agonists. Agents such as ^{111}In-DOTA-BASS [^{177}Lu-DOTA-pNO_2-Phe-c (dCys-Tyr-dTrp-Lys-Thr-Cys) dTyrNH_2] or ^{111}In-DOTA-JR11 (DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH2) exhibit higher levels and longer retention rates, thereby providing a higher sensitivity compared to ^{111}In-pentetreotide [27]. In terms of therapeutic application, in vitro studies indicate a significantly greater binding of ^{177}Lu-DOTA-BASS on neuroendocrine tumor cells than the current best agonist ^{177}Lu-DOTATATE [28]. The clinical translation of this observation suggests a higher tumor accumulation with increased irradiation, while the lower normal tissue accumulation implies diminished exposure [29]. Of note, however, is the observation that the somatostatin receptor affinity of such compounds can be diminished by binding to radiometals, such as Ga-68. To retain optimal SSTr binding of the JR11 antagonist, a specific 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (NODAGA) chelator was required [27].

   The development of novel receptor targets utilizing innovative radiopharmaceuticals needs identification. In particular, specific agents that identify a particular tumor or one with a specific secretory product need to be investigated. A number of peptides have been tested in preclinical and clinical trials. Among these, the GLP-1 receptor (GLP-R) peptides, such as ^{111}In-exendin-4 (localization of occult insulinomas), are the most advanced for clinical application [30]. ^{111}In-exendin-4 specifically addresses the paucity of SSRs in benign insulinomas. In this respect, GLP-R and SSR imaging demonstrate the biologically mutable aspect of insulinomas, which may be GLP-R positive and SSR negative or vice-versa, a reflection of their malignant phenotype [31]. A ^{68}Ga-labeled exendin-4 is the logical next step and has been tested in clinical trials [32, 33].

   Following the same principle of the paradigm shift from agonist to antagonists, it was recently demonstrated that the ^{125}I-BH-exendin(9–39) GLP-1 antagonist has

excellent binding properties and constitutes a promising imaging agent [34].

Similar evaluation of the multi-receptor expression of neuroendocrine cells has demonstrated that the cholecystokinin/gastrin ligands, such as CCK_8 and minigastrin analogs labeled with ^{111}In or ^{99m}Tc, may also have clinical utility [35].

Other targets that have been explored for NET imaging include the bombesin receptor family, which include GRP (gastrin-releasing peptide), NMB (neuromedin B), and BB_3 (bombesin receptor subtype 3) receptors [36]. In vitro usage to identify prostate cancer indicates positive identification in 60–100 % [35–39]. Similarly, GRP and BB_3 receptors have been identified in 7/10 and 2/10 gastrinomas, respectively, NMB receptors have been found in 11/27 ileal, while BB3 receptors were the predominant receptors described in 10/29 bronchial NETs [36]. More than 40 different bombesin analogs, agonists and antagonists labeled with ^{99m}Tc or with ^{68}Ga have been evaluated in vitro. They comprise an additional potential class of radiopharmaceuticals for NET imaging [37].

The low plasma stability and high kidney retention have limited the application of these alternative peptides as theranostics [40]. Nevertheless, newer, more stable molecules and the co-administration of specific enzyme inhibitors, such as the neutral endopeptidase inhibitor phosphoramidon, can be utilized to increase the bioavailability of these compounds [41]. Adjunctive strategies of this type are likely to herald a new era in the application of receptor peptides and supplant the model of somatostatin analogs in the study of neuroendocrine tumors.

Assessment of alternative components of NET biology such as angiogenesis has led to the development of promising strategies utilizing radiolabeled antibodies such as the Zr-89-labeled bevacizumab. This concept has been applied to the evaluation of a variety of NETs treated with everolimus. A decrease in the SUV led to the proposal that this technique could be of value as an early predictor of anti-angiogenetic therapeutic efficacy [42].

3) Utilization of other biologic information to amplify accuracy

It is clear that monoanalyte-derived information can never be as effective as the product of multianalyte parameters. Thus, an image alone is, by definition, limited only by the lack of additional, relevant parameters that can be integrated into an amplifiable diagnostic quotient. Inclusion of such additional material, in a mathematical probability index, or in a matrix or via a nomogram has proved of considerable added prognostic value in other disciplines [43]. The multi-level parallel assessment of different forms of tumor/patient relevant information is mandatory to strengthen diagnostic and prognostic accuracy. To optimally increase information gained from nuclear medicine techniques, NET images will likely require integration of tumor and blood biomarkers and the development of prognostic nomograms. A particularly informative source of information would be the integration of circulating tumor genomic data obtained from blood (simultaneous liquid biopsy) at the time of nuclear medicine image acquisition. Thus, receptor determined tumor characteristics could be combined with tumor transcript profiles, allowing for the development of a personalized predictive assessment of tumor status before, during and after treatment [44].

Coda

The integration of functional and anatomic imaging optimizes the delineation of the status of a NET. PET, particularly with ^{68}Ga-DOTA-peptides, is supplanting OctreoScan®. Emerging strategies include the use of SSR-antagonists and GLP1-R peptides. However, the present lack of homogeneity and validation has limited the clinical acceptance of novel techniques. A robust and standardized basis to objectify nuclear medicine procedures is a critical requirement.

The future development of multi-dimensional-algorithmic data quotients (tissue, blood and imaging) for each patient, as opposed to a mono-dimensional image-based procedure, is likely to generate information that is far more accurate than the current strategy. In this respect, the combination of a simultaneous gene transcript blood signature from the tumor as well as a functional image may provide an informative mechanism for capturing knowledge of both the biology of an individual tumor, as well as its current and future behavior.

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