Molecular Imaging and Theranostics in Pancreatic Neuroendocrine Tumours: From a Luminous Present to an Even Brighter Future

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The present thematic “hot topic” issue in Current Radiopharmaceuticals is dedicated to the applications of molecular imaging as major player in the diagnostic scenario of pancreatic neuroendocrine tumours (PanNETs). The therapeutic aspects using radiopharmaceuticals have also been considered.

In the last years, we assisted to a progressive evolution of the available radionuclide imaging techniques dedicated to PanNETs investigation, starting from the conventional Octreoscan© and moving forward to more sophisticated techniques such as 68Ga-DOTA-Peptides PET/CT.

The possibility to provide an accurate characterization both of primary and metastatic disease is of utmost importance in the clinical work-up of PanNETs and molecular imaging has revealed to be a cornerstone for Physicians to support the therapeutic decision process.

The present issue starts with an accurate description of physiopathological premises underlying the mechanisms of uptake of several radiotracers that can be used, with main reference to those characterizing the presence of Somatostatin Receptors (SSTRs), expressed by different subtypes of PanNETs. In this paper, Cuccurullo et al. begins with the explanation of the ancillary role of 18F- Fluorodeoxyglucose (18F-FDG) [1]. In NETs, 18F-FDG may act mainly as a negative prognostic indicator, having capability to reveal dedifferentiated lesions in the restaging of individual patients with a critical clinical evolution. The reason for its infrequent indication is consequently connected with the favorable biological behavior of the majority of PanNETs, which are typically slow growing and express SSTRs according to their degree of differentiation. Therefore, using somatostatin analogs (SSAs) labeled with gamma or positron emitters, SSTRs can be used not only as a target for both diagnosis and therapy, but also for a prognostic evaluation. Currently, the somatostatin theranostic model, based on diagnosis with radiotracers and a Peptide Receptor Radiounclide Therapy (PRRT) performed with a similar molecule radiolabeled with a β- (or α, hopefully in the future) emitter, represents one of the most successful options for the targeted therapy. Although radio-labeled agonists usually provide efficient results, somatostatin antagonists (SS-ANTs) have been recently also proposed, being usable for imaging and therapy. The Cuccurullo’s paper also highlights the reasons why the theranostic model based on SSTRs doesn’t work in insulinoma, which scarcely express SSTR2 and SSTR5, wich are, the most important targets for the routinely used radiolabeled somatostatin analogues. Therefore, in patients with a suspicious of insulinoma, different radiotracers, such as 18F FluoroDOPA (18F-DOPA) or tracers targeting glucagon-like peptide-1 receptor, have to be preferred. However, it has to be pointed out that, although F-DOPA showed interesting results in patients with PanNETs, its role is currently considered secondary compared to somatostatin analogues, especially because of the lack of a theranostic model.

Starting from the classification and physiopathology of PanNETs, the paper by Briganti et al. deeply analyse the currently available gamma-emitters for SSTRs evaluation [2]. A detailed comparison of the diagnostic performance of the available tracers and of hybrid machines compared to the traditional stand-alone tools is also included. In this paper, it is reported that ¹¹¹In-pentetreotide (OctreoScan), successfully applied in well-differentiated (G1-G2) tumors, has lost its primary position because of the better diagnostic accuracy of ⁶⁸Ga DOTA-Peptides PET/CT, maintaining an ancillary role in PanNETs. Briganti et al. also discuss preliminary data obtained with ⁹⁹mTc-EDDA/HYNIC-TOC (Tektrotyd©), labeled with ⁹⁹mTc, having more favorable energy characteristics compared to ¹¹¹Indium, radiolabeling Octreoscan©. To better identify a possible clinical role for Tektrotyd©, in terms of cost/effectiveness, its pharmacokinetics and pharmacodynamics have been compared with respect to those of Octreoscan© and PET DOTA-peptides.

The paper by Carollo et al. is focused on radiochemical issues, providing deep insights of the molecular imaging techniques that can be applied in this setting, including a discussion on the comparison between the different radiotracers; the therapeutic implications that might rise from a precise definition of disease extension and metabolic characterization are also evaluated [3]. This paper shows an overview of the radiopharmaceuticals that have been used so far in the imaging of PanNETs with insights on the potential of new radiopharmaceuticals currently under clinical evaluation.

The implications for therapy of SSTRs imaging are fundamental for PanNETs patients work-up [1]. The expression of SSTRs is a pre-requisite for the success of PRRT, which has been tackled by Alsadik et al. in the current issue [4]. The authors
used a comprehensive literature search strategy of all studies published in English that can be found on SCOPUS and PubMed. The results of PRRT, using $^{177}$Lutetium or $^{90}$Yttrium-DOTA-conjugated peptides in p-NETs, individuated either as a stand-alone entity or as subgroup within the wider category of Gastro-entero-pancreatic neuroendocrine tumours (GEP NETs), have been evaluated. This meta-analysis confirms that PRRT is a well-tolerated and effective treatment option for non-operable and/or metastatic PanNETs. A strong support on a wider diffusion could be achieved from larger randomized controlled trials, comparing PRRT with other treatment modalities.

The radiological aspects regarding the theranostic of PanNETs should not be underestimated neither be allocated on a second level in comparison to molecular imaging. For this reason, this issue also includes an outline on the available conventional radiological techniques that are currently used in PanNETs work-up [5]. In the presence of a primary role of nuclear medicine, either for a whole body analysis or for a molecular characterization, an extensive conventional radiological imaging is however requested, remaining the foundation for the initial diagnosis and staging of these tumors.

In terms of technological advances, a significant improvement has been obtained with the advent of new hybrid machines that could potentially improve the management of these patients [6]. Hybrid PET/MRI systems are currently available in few Centres world-wide, providing excellent results derived from the combination of PET with MRI, which is better for soft tissue characterization and for reducing radiation exposure compared to CT [7]. Furthermore, Diffusion-Weighted Imaging (DWI) is an invaluable tool to depict small liver lesions undetectable by PET or CT; a further improvement allowed by MR in detecting small hepatic metastases may be achieved combining 3-Tesla and DWI together with the administration of liver specific contrast media. Hence, the best candidates to be imaged with SSTR PET/MRI are patients selected for hepatic de-bulking or having liver predominant disease. In the perspective by Mapelli and Picchio, the capability of PET/MRI to better evaluate tumor response to treatment difficult to be analyzed using traditional RECIST criteria is also discussed. The better evaluation of anatomic changes and enhancement characteristics allowed by MRI may significantly implement SSTR PET, defining a more reliable procedure to be used in place of CT and MRI alone or of PET/CT. In this context, SSTR-RADS Version 1.0 response criteria have been recently introduced as a promising alternative and valuable tool for response assessment in NETs [8]. To better define the clinical role of PET/MRI in patients with p-NETs, it has to be pointed out that at present, this tool doesn’t show, using a standard approach, the same diagnostic accuracy in detecting small lung lesions with respect to PET/CT. Therefore, in presence of a negative or dubious pattern at pulmonary level, a chest CT scan would be recommended additionally to PET/MRI [9, 10]. Moreover, MRI has a lower sensitivity in identifying hypersclerotic bone lesions compared to other imaging modalities and SUV quantification with attenuation correction is still suboptimal [11]. At present, these limitations, although scarcely significant for a clinical utilization in PanNETs, have to be taken in account, looking forward to technological improvements, allowing to obtain similar accuracies as for PET/CT.

Based on the contents reported in the present issue, it can be concluded that in patients with PanNETs, a protean disease often presenting with liver metastases, many topics have to be considered to understand the role of molecular imaging in the different clinical scenarios.

At first diagnosis, it is mandatory to detect primary tumour, more frequently identified using radiological techniques, and to define whole body diffusion and molecular characterization. In the latter field, nuclear medicine techniques are determinant. Being the major role actually played by PET/CT with 68Ga-DOTA peptides, the use of Octreoscan$^{®}$ is considered to be a second choice, while the clinical position of Tektrotyd$^{®}$ is still to be fully defined. In patients with insuloma, waiting for radiopharmaceuticals having a better diagnostic accuracy, $^{18}$F-DOPA has to be preferred compared to radiolabeled somatostatin analogues. Interesting perspectives seem to be related to a wider evaluation of innovative radiotracers, including GLP-1 Receptor Peptides, as exendin, GRP receptor ligands, as bombesin agonists and antagonists, and gastrin/cholecystokinin analogs, as minigastrin. Nevertheless, further studies, also better evaluating radiochemistry and pharmacokinetics, are needed before their possible clinical application. Similarly, new approaches capable to early predict the efficacy of anti-angiogenesis treatments could be defined through a research based on radiolabeled new drugs, such as bevacizumab. Conversely, it is currently too early to predict the clinical impact of a technological revolution associated with fully digital PET scanners or with the use of alternative radionuclides, with main reference to Cu-64.

This means that in the near future, the primacy of somatostatin analogues labelled with 68Ga will remain unquestionable in the general evaluation of PanNETs, also because of the theranostic model associated with PRRT. Regarding innovative radiopharmaceuticals, neither radiolabeled somatostatin antagonists nor $^{11}$C-5-hydroxy-tryptophan (HTP), negatively affected by the labelling with the short life radionuclide C-11, may actually cover a clinical role. Conversely, 18F-FDG may find a clinical utility in restaging patients in whom a dedifferentiation is suspected, in order to better define therapeutic strategies.

Future developments will be based on a wider diffusion of more performing technologies, such as PET/MRI or digital PET, in the clinical application of new radiopharmaceuticals and a more comprehensive multilevel integration of biologic information pertaining to a specific tumor and single patient. This approach, possibly encompassing genomic considerations, is currently evolving as a new entity denoted ‘precision medicine’ [12]. In this context, together with nonspecific biomarkers, such as chromogranin-A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA), the evaluation of proliferative activity (Ki67) should be considered. In the future, the clinical application of specific NET transcripts in whole blood could potentially conduct to an earlier diagnosis, also providing information useful for prognostic stratification and a better definition of therapeutic strategies [11]. A further improvement is also required for an improved monitoring of tumor response. In PanNETs, radiological procedures based on RECIST are unsatisfactory while newer radiological criteria are not yet consolidated; therefore, validated tech-
niques utilizing molecular imaging, supported by the morpho-structural information allowed by CT or MRI should be implemented. In this direction, more reliable results could be obtained through the development of new criteria, eventually including the adoption of functional MRI, of more precise hematocrit biomarkers, of quantitative methods not only based on SUV.

In conclusion, a multidisciplinary approach is mandatory in clinical practice in order to reach the best consensus on treatment approach for each patient. In this context, together with the major role of nuclear medicine physicians and radiologists, of oncologists, endocrinologists and surgeons, the contribution of experts in epidemiology, laboratory medicine and genomics is advocated. Therefore, in agreement with L. Bodei, we can conclude that “a fusion product of molecular and genomic information with tumor imaging is likely to be the quintessence of future NET diagnosis and define the progress from darkness to light” [13].

REFERENCES


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