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Neuroendocrine Tumors (NET) and Nuclear Medicine

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EDITORIAL

Neuroendocrine tumors, most commonly shortened in NET, are rare diseases: every year are diagnosed less than 5 new cases per 100 thousand people1.

The term NET groups together different types of cancer that develop in various regions of the human body. They are born, in fact, by cells with characteristics partly similar to nerve cells ("neuro") partly similar to the endocrine ones, scattered almost everywhere in the human organism. So, some NET develop in endocrine glands (such as adrenals, pituitary gland and pancreas), while others affect other organs, such as bowel and lungs. The most frequent forms are born in the digestive tract that is the so-called GEP (gastro-entero-pancreatic) [2]. In the majority of cases, these tumors evolve slowly, but a minority of NET is very aggressive, as in the case of pheochromocytoma, paraganglioma or medullary thyroid cancer[3].

A neuroendocrine tumor is often discovered accidentally, during the execution of diagnostic tests performed for other reasons. Other times it is suspected from symptoms; blood tests can in these cases reveal increased levels of hormones (such as just insulin, gastrin, etc.) or other substances produced by the tumor, particularly chromogranin A (a protein generally produced by endocrine tumors)[4].

In order to confirm the suspected diagnosis, identify the exact location of the tumor and its overall dimensions, check if it is already widespread to other organs and if it is surgically removable, it is essential to use imaging techniques[5, 6].

Computed tomography (CT) is established as the primary modality, although subsequent technologies such as RMI are currently competing with the CT in the recognition of these diseases. Endoscopic ultrasound has an important role in the preoperative assessment of the pancreas where a small functioning tumor or the possibility of multiple tumors is suspected[7].

As it is well known, these techniques show mostly the morphological aspect of the lesions, while the best technical research of these tumors is to study their functional behavior.

Functional imaging modalities – such as somatostatin receptor scintigraphy (SRS) [8] – have great impact on patient management by providing tools for diagnosing, better staging of the disease, visualization of occult tumor, and evaluation of eligibility for somatostatin analogue treatment[9]. In fact, various tumors, classically specified as either neuroendocrine or non-neuroendocrine, contain high numbers of somatostatin receptors, which enable in vivo localization of the primary tumor and its metastases by scintigraphy with the radiolabelled somatostatin analogue octreotide. In many instances a positive scintigram predicts a favorable response to treatment with octreotide[10]. It is now well known that octreotide or other somatostatin analogues labeled with an appropriate radionuclide such as beta-emitters Yttrium-90 or Lutetium-177 are used in cancer therapy[11, 12].

The cited SRS by means of 111-Indium labeled octreotide is in fact capable of magnify the 5 receptor subtypes of somatostatin present on the cell surface of these tumors, allowing to identify also small neoplastic agglomerates, whose definition is often difficult by conventional imaging techniques[13]. This method also allows a prognostic evaluation in relation to receptor density in vivo[14], also enabling to consider the analogues also for the therapy of these tumors in the case of positive results[15] and finally, thanks to its particular sensitivity (58-100%) is able to modify the therapeutic approach in over 50% of cases[16].

Recently, spatial resolution has come to represent the main limiting factor in the use of 111-Indium labeled octreotide in the diagnostic

approach in neuroendocrine tumors. In this scenario the receptor PET with 68Ga-DOTA-octreotide is playing an increasingly important role[17]. Currently, 68Ga-DOTA-peptides mostly used are 68Ga-DOTA-TOC, 68Ga-DOTA-NOC and 68Ga-DOTA-TATE[18]. The rationale for their use as in the case of indium-labeled octreotide is due to the ability of the NET to over-express the somatostatin receptors on the cell membranes. In literature[19], PET with 68Ga-DOTA-peptides is reported as a reference method for the diagnosis and staging of neuroendocrine tumours, with sensitivity and specificity respectively of 97% and 96%, well above that of CT and Octreoscan. PET with 68Ga- DOTA-peptides provides additional information compared to other radiological surveys in 21.4% of cases and leads to a change in therapeutic management in 51% of patients. 18F-DiOxyPhenylAlanine (DOPA) is an amino acid precursor of dopamine, which being a precursor of catecholamines can also be used in the study of neuroendocrine tumors. The rationale for use in the imaging of the NET is based on the ability of these tumors to accumulate and decarboxilate the amine precursors, including the dioxy-phenylalanine through the amino acid enzyme decarboxylase which has significantly increased levels in neuroendocrine tumors. The main use of this method is in the NET with high release of catecholamines such as Pheochromocytoma and Paraganglioma, where the methodology achieves the best sensitivity and specificity (90% and 100% respectively). The indication of 18F-DOPA for the study of both adrenal and extra-adrenal Pheochromocytoma is reported in both the presentation of the disease and the suspicion of recurrence (sensitivity 91%, specificity 95%). In addition, PET with 18F-DOPA is a highly sensitive method of identifying paragangliomas in the head-to-neck district, even those with small dimensions, due to its high target/background ratio. Furthermore generator-derived radionuclides for PET/CT imaging are promising for optimizing targeted radiotherapy by an individual patient-based approach, applying pre-therapeutic evaluation, as well as dosimetric calculations, and for measuring treatment response after radionuclide therapy[20]. In this way molecular targeting vectors could be used for both diagnoses (molecular imaging) and therapy (molecular targeted treatment), which is reflected in the acronym THERANOSTICS[21].

The combination of structural images (CT or MRI) with functional SPECT or PET images of the same sections of the body can provide complementary anatomical and physiological information that is of great importance to diagnosis and treatment[22]. From the clinical point of view the application of such an imaging system is particularly used for those performances which involve a radio pharmaceutical distribution hard to be attributed to a specific anatomical region. The data obtained from the CT component also make it possible to obtain attenuation-corrected scintigraphic data, thus improving on the quality of the SPECT or PET image alone[23].

In conclusion, the management of neuro endocrine tumors requires a fairly accurate diagnostic phase in which nuclear medicine plays a predominant role. Somatostatin analogues for SPECT (111In-Octreoscan and the more recent ^{99m}Tc-EDDA/HYNIC-TOC)[24] or PET (68Ga-DOTA-peptides) offer better staging of the disease, visualization of occult tumour, and evaluation of eligibility for somatostatin analogue treatment.

The subsequent therapy is based on the surgical approach for the more localized and affordable forms. In presence of metastases and/or generalized forms, can be used medical treatments based on chemotherapeutics, but generally the standard of care for metastatic NETs is somatostatin analog therapy with octreotide (available in both short- and long-acting formulations) or a depot formulation of lanreotide[25]. But nuclear medicine, as reported, is becoming essential for radioreceptor therapy with somatostatin analogues labeled with beta emitters. The basic principle is to replace the gamma-emitting radionuclide that marks the diagnostic radiopharmaceutical with a beta emitters radionuclides. At the present time, the most commonly used somatostatin analogues are radiopharmaceuticals 90Y- DOTA-TOC and 177Lu-DOTA-TATE. All these compounds with peptides have as a critical organ the kidney for glomerular filtration and their tubular resorption, therefore the exposure threshold of this organ should not exceed the share of 25 Gy. Appropriate pre-therapy dosing estimates are therefore necessary, which in the case of Radiopharmaceutical 90Y-DOTATOC (which does not emit γ-rays) are based on a diagnostic examination with Octrescan, whereas in the case of 177lu-DOTA-TATE are based on the scintigraphic detection of the γ emission of the therapeutic radiopharmaceutical itself. Therapy with radiolabelled somatostatin analogues with 90y-DOTA-TOC or 177lu-DOTA-TATE is

significantly effective in NET with response rates up to 30%. In particular a study with 177Lu-DOTA-TATE (Lu-PRRT) showed this to be a viable option of targeted therapy in the pancreatic neuroendocrine tumors G1-G2 (PNET) with positive results also in terms of survival with passage from 40 to 72 months of survival from diagnosis, compared to a similar control group[26].

It is effective therapy in over 80% of cases. Overall it is well tolerated, with mild and reversible bone marrow and renal toxicity, in particular fractioning the total dose of radiopharmaceutical[27]. Another very recent study showed that peptide receptor radionuclide therapy is a valuable treatment option in patients with advanced NETs, especially in small bowel[28].

Alpha emitters have significantly more potent effects and various advantages compared to beta emitters[29]. Although a limited number of studies have been performed with alpha emitters, only a few have targeted NETs. But there is a rationale for alpha emitters, existing clinical use of alpha emitters (Bi-213, Ac-225, Pb-212, At-211, Ra-223) in various clinical applications (non-NET), and review existing literature on the preclinical and clinical use of alpha emitters in NETs[30].

REFERENCES

[1] O Hauso, BI Gustafsson,a M Kidd, HL Waldum, I Drozdov, AKC Chan, IM Modlin: Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* 113(1015): 2655, 2008

[2] R Arnold: Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. *Best Pract Res Clin Gastroenterol* 19:491, 2005

[3] H Chen, RS Sippel, K Pacak:The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma & Medullary Thyroid Cancer. *Pancreas* 39 (6) : 775, 2010

[4] LJ Deftos: Chromogranin A: It's Role in Endocrine Function and as an Endocrine and Neuroendocrine Tumor Marker. *Endocr Rev* 12 (2): 181, 1991

[5] B Wiedenmann, R Jensen, M Mignon, CI Modlin, B Skogseid, G Doherty, K Öberg: Preoperative Diagnosis and Surgical Management of Neuroendocrine Gastroentero - pancreatic Tumors : General Recommendations by a Consensus Workshop. *World J Surg* 22: 309, 1998

[6] MH Mullan, PG Gauger, NW Thompson: Endocrine tumours of the pancreas: Review and recent advances. *ANZ J Surg* 71: 475, 2001

[7] AG Rockall, RH Reznek: Imaging of neuroendocrine tumours (CT/MR/US). *Best Practice & Research Clinical Endocrinology & Metabolis*m 21(1): 48, 2007

[8] SWJ Lamberts, WH Bakker, J-C Reubi, EP Krenning: Somatostatin-receptor imaging in the localozation of endocrine tumors. *N Engl J Med* 323:1246, 1990

[9] AG Rockall, RH.Reznek: Nuclear imaging of neuroendocrine tumours. *Best Practice & Research Clinical Endocrinology & Metabolis*m 21(1): 69, 2007

[10] EP Krenning, DJ Kwekkeboom, WEA Bakker, WAP Breeman, PPM Kooij, HY Oei, M van Hagen, PTE Postema, M de Jong, JC Reubi, TJ Visser, AEM Reijs, LJ Hofland, JW Koper, SWJ Lamberts: Somatostatin receptor scintigraphy with [111 In-DTPA-D-Phe 1]-and [123 I-Tyr 3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 20(8):716, 1993

[11] M de Jong, WAP Breeman, R Valkema, BF Bernard, EP Krenning: Combination Radionuclide Therapy Using ^{177}Lu- and ^{90}Y-Labeled Somatostatin Analogs. *J Nucl Med* 46(1- supp l):13S, 2005

[12] I Virgolini, K Britton, J Buscombe, R Moncayo, G Paganelli, P Riva: In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. *Seminars in Nuclear Medicine* 32: 148, 2002

[13] D Ferone, MP van Hagen, DJ Kwekkeboom, PM van Koetsveld, DM Mooy, E Lichtenauer-Kaligis, A Schönbrunn, A Colao, SWJ Lamberts, LJ Hofland: Somatostatin Receptor Subtypes in Human Thymoma and Inhibition of Cell Proliferation by Octreotide in Vitro. *J Clin Endocrinol Metab* 85 (4): 1719, 2000

[14] A Asnacios, F Courbon, P Rochaix, E Bauvin, V Cances-Lauwers, C Susini, S Schulz, A Boneu, R Guimbaud, L Buscail: Indium-111–Pentetreotide Scintigraphy and Somatostatin Receptor Subtype 2 Expression: New Prognostic Factors for Malignant Well-Differentiated Endocrine Tumors. *J Clin Oncol* 26(6): 963, 2008

[15] G Paganelli, L Bodei, D Handkiewicz Junak, P Rocca, S Papi, M Lopera Sierra, M Gatti, M Chinol, M Bartolomei, M Fiorenza , C Grana : ^{90}Y–DOTA– D - Phe^{1} –Try^{3}–octreotide in therapy of neuroendocrine malignancies. *Biopolymers (Pept Sci)* 66:393, 2002

[16] M Van Essen, EP Krenning, M De Jong, R Valkema, DJ Kwekkeboom: Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with

somatostatin receptor positive tumours. *Acta Oncol* 46(6): 723, 2007

[17] G Riccabona, C Decristoforo: Peptide Targeted Imaging of Cancer. *Cancer Biother Radiopharm* 18(5): 675, 2004

[18] I Virgolini, V Ambrosini, JB Bomanji, RP Baum, S Fanti, M Gabriel, ND Papathanasiou, G Pepe, W Oyen, C De Cristoforo, A Chiti: Procedure guidelines for PET/CT tumour imaging with 68Ga-dota-conjugated peptides: 68Ga-dota-toc, 68Ga-dota-noc, 68Ga-dota-tate. *Eur J Nucl Med* 37(10): 2004, 2010

[19] DJ Kwekkeboom, WW de Herder, BL Kam, CH van Eijck, M van Essen, PP Kooij, RA Feelders, MO van Aken, EP Krenning: Treatment with radiolabeled somatostatin analog (177Lu-DOTA0, Tyr3) octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 26:2124, 2008

[20] F Rösch, RP Baum: Generator-based PET radiopharmaceuticals for molecular imaging of tumours: on the way to THERANOSTICS. *Dalton transactions* 40(23): 6104, 2011

[21] L Mango: Theranostics: A Unique Concept to Nuclear Medicine. *Highpubs J of Cancer Sci Res* 1:001, 2017

[22] O Schillaci: Functional–Anatomical image fusion in neuroendocrine tumors. *Cancer Biother Radiopharm* 19(1): 129, 2004

[23] L Mango, G Ventroni: Hybrid Technology: From Cars to Diagnosis. *ARC Journal of Radiology and Medical Imaging* 2(1):1, 2017

[24] M Gabriel, C Decristoforo, E Donnemiller, H Ulmer, C Watfah Rychlinski, S.J. Mather, R Moncayo: An Intrapatient Comparison of 99mTc-EDDA/HYNIC-TOC with111In-DTPA Octreotide for Diagnosis of Somatostatin Receptor–Expressing Tumors. *J Nucl Med* 44:708, 2003

[25] C Chung: Management of neuroendocrine tumors. *Am J Health Syst Pharm* 73:21, 2016

[26] M Cremonesi, M Ferrari, L Bodei, G Tosi, G Paganelli: Dosimetry in peptide radionuclide receptor therapy: a review. *J Nucl Med* 47:1467, 2006

[27] S Nicolini, M Sansovini, S Severi, M Monti, A Ianniello, F Matteucci, G Paganelli: Terapia radiorecettoriale dei tumori neuroendocrini pancreatici. *L'Endocrinologo* 17(1): 21, 2016

[28] N Sharma, BG Naraev, EG Engelman, MB Zimmerman, DL Bushnell Jr, TM O'dorisio, TR Halfdanarson: Peptide receptor radionuclide therapy outcomes in a North American cohort with metastatic well-differentiated neuroendocrine tumors. *Pancreas*, *46* (2) : 151, 2017

[29] L Mango, M Pacilio: Therapy with Alpha Rays. *ARC Journal of Radiology and Medical Imaging* 1(1):1, 2016

[30] J A Carrasquillo: Alpha Radionuclide Therapy: Principles and Applications to NETs. In: *Diagnostic and Therapeutic Nuclear Medicine for Neuroendocrine Tumors*, Springer International Publishing, p. 429, 2017.

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