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Review article

Theranostics and Precision Medicine in Neuroendocrine Tumors

Filip Veličković[1,2], Marina Vlajković[1,2], Miloš Stević[1,2], Nina Topić[1], Tamara Anđelković[1,2], Đuro Macut[3]

[1]*University Clinical Center Niš, Center of Nuclear Medicine, Niš, Serbia*
[2]*University of Niš, Faculty of Medicine, Niš, Serbia*
[3]*University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia*

SUMMARY

Introduction. Neuroendocrine tumors (NETs) have increased expression of somatostatin receptors (SSTR), where subtype 2 and 5 are the most common. Overexpression of the SSTR is an outstanding molecular target for inoperable and metastatic NETs that enables a unique approach of targeted diagnosis and treatment. In addition to SSTRs, neuroendocrine tumors also express other receptors that can be suitable targets for visualization by nuclear medicine methods.
Aim. This review paper is focused on the most common radiopharmaceuticals and their molecular targets that are used today based on theranostic approach in NETs.
Results. In conventional nuclear medicine, the most important diagnostic radiopharmaceuticals are somatostatin analogs (SSA) labeled with ^{111}In and ^{99m}Tc, however ^{99m}Tc has advantages over ^{111}In based on better physical characteristics and better performance. In recent years, highly potent theranostic pairs have been created for the imaging and treatment of NETs, which can strongly bind SSTR. Derivatives of ^{68}Ga-labeled octreotide are recommended for diagnostics and follow-up of NENs. The great advantage of ^{68}Ga radiopharmaceuticals is that identical compounds can be labeled with therapeutic radionuclides ^{90}Y and ^{177}Lu.
Conclusion. Peptide receptor radionuclide therapy is a systemic molecular target therapy that has proven to be safe and very effective in controlling the disease and prolonging the survival of patients with advanced and inoperable NETs. With a negligible number of adverse events, this therapy is safe and should be administered to all patients who meet the necessary criterias, primarily overexpression of the somatostatin receptor type 2.

Keywords: **neuroendocrine tumours, somatostatin receptor, scintigraphy, radionuclide therapy**

Corresponding author:
Filip Veličković
e-mail: velickovicfilip@yahoo.com

INTRODUCTION

Theranostics involves obtaining pre-therapeutic imaging and radionuclide therapy using the same or similar molecule, whereby nuclear medical imaging labeling is done with radionuclides that are gamma or beta plus emitters, while beta minus or alpha emitters are used for the therapy (1).

Theranostics includes diagnostic methods that are used for the prediction of effectiveness of specific therapeutic interventions on an individual basis as well as for the monitoring a response to treatment. Radiolabeled compounds used for this purpose are focused on specific biological processes representing a kind of targeted imaging. Targeted imaging in oncology enables non-invasive tumor-specific diagnostics, precise localization of tumors and metastases, and has the potential for pre-therapeutic quantification of the receptor status and dosimetry. This enables precise selection and planning of therapy, as well as monitoring a response to therapy, resulting in personalized medicine (1, 2).

Ideally, pretherapeutic imaging and radionuclide therapy should be performed using radionuclides of the same chemical element as iodine-123/124 for imaging and iodine-131 for therapy (3).

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that arise from diffuse, pluripotent neuroendocrine cell systems and can originate from very different places in the body, but the most common places of origin are the digestive tract and lungs. According to the embryological origin, they are divided into tumors of the foregut (lung, stomach, pancreas, gallbladder and duodenum), midgut (jejunum, ileum, appendix and ascending colon) and hindgut (descending colon and rectum) (4). According to the degree of differentiation, neuroendocrine neoplasms include distinct disease categories: neuroendocrine tumors (NETs), which represent well-differentiated tumors, and neuroendocrine carcinomas (NECs), which are poorly differentiated and represented in a smaller percentage of all NENs (5). These classification guidelines were issued in 2010 by the World Health Organization and are based on the histopathological characteristics of NEN (6).

Today, NENs are classified according to the primary site of origin, degree of spread and hormonal activity. Functional NENs represent neoplasms that are accompanied by the symptoms of hormonal hypersecretion, while in non-functional NENs, the symptoms of the disease arise due to the mere presence of the tumor mass, without hormonal activity. In about 20% of cases, NENs can be accompanied by carcinoid syndrome, which includes the appearance of a typical triad - redness of the facial skin, diarrhea and abdominal pain. Carcinoid syndrome occurs as a result of excessive secretion of serotonin by the tumor, as well as other mediators that enter the circulation and lead to these symptoms (7). These tumors were formerly called "carcinoids", however, this term is no longer in use.

In addition to conventional radiology, functional, molecular imaging is of particular importance in the diagnosis, staging and treatment of well-differentiated NETs. A large percentage of NETs tend to retain the properties of neuroendocrine cells and express five different subtypes of somatostatin receptors (SSTRs) on their surfaces. One of them, subtype 2 (sstr2) is especially overexpressed by neuroedocrine tumor cells providing a basis for molecular imaging and targeted therapy (8, 9). This overexpression of the somatostatin receptor represents the most common molecular target for both imaging and therapy of NETs. In addition to SSTRs, neuroendocrine tumors also express other receptors that can be suitable targets for visualization by nuclear medicine methods. Therefore, the aim of this review was to show the most common radiopharmaceuticals and their molecular targets that are used today in the diagnosis of neuroendocrine tumors and to present treatment modalities based on theranostic approach.

Epidemiology of neuroendocrine tumors

Gastroenteropancreatic NENs (GEP-NEN) constitute a heterogeneous group of malignant diseases with a neuronal phenotype and the ability to secrete hormones and amines. They show remarkable similarity with the neuroendocrine cells of the embryonic intestine (5). The frequency of GEP-NEN recorded an increase of more than six times for the period 1997 - 2012 (10). An increase in the incidence of localized and NENs with regional spread is more pronounced than that of NENs with distant metastases. The prediction of the incidence of GEP-NEN in the USA, based on the updated Surveillance and Epidemiology Database (SEER), estimates 3.56/100,000 affected population per year (10). In Europe, the frequency of GEP-NEN is also high, ranging between 1.33 - 2.33/100,000 inhabitants; how-

ever, the data come from national and regional registers and are heterogeneous and mostly retrospective (11, 12).

Men get sick slightly more often than women, and in them the course of the disease is in a higher percentage with an unfavorable outcome (5). Most NENs are well-differentiated NETs that occur sporadically. GEP-NEN of pancreas, duodenum, stomach and, less often, thymus and lungs can also arise as part of multiple endocrine neoplasia type 1 (MEN1) syndrome. Pancreatic neuroendocrine neoplasm (Pan-NET) can occur as part of von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC), and neurofibromatosis (5). In these hereditary diseases, NEN is most often multifocal, and the onset of the disease occurs one to two decades earlier than in sporadic tumors. In hereditary syndromes, NEN is most often detected in the early stages of the disease. The frequency of NEN in hereditary syndromes (MEN1, VHL disease) is around 5% (11). Recently, the whole genome sequencing revealed 17% of apparently sporadic Pan-NETs to carry germline mutations that also involve DNA repair genes (e.g, MUTYH, CHEK2, BRCA2), so the percentage of NENs in different syndromes is likely higher (12). Although most NENs are sporadic, the hereditary form must be considered when diagnosing, especially in Pan-Net (13). Genetic testing is also recommended in the presence of the MEN syndrome (hyperparathyroidism and pituitary adenoma), in the familial form of NEN or diseases suspected of being hereditary, as well as in patients younger than 40 years in whom the presence of gastrinoma has been proven (14).

Molecular biology of nuroendocrine neoplasms

Histological confirmation of NENs is mandatory in all patients, performed on resection samples or tumor biopsy in advanced disease. Suspicion of NENs is already present after the evaluation of the histomorphological pattern of cell growth and cytological evaluation of hematoxylin-eosin stained tissue.

A precise assessment of the place of origin or prediction of the biological behavior of NENs is based on a detailed analysis of the architecture of cell growth, immunohistochemical, genetic and molecular profile of the neoplasm (15).

Immunohistochemical analysis is used to characterize the aggressiveness of NENs, by evaluating the Ki-67 proliferation index, as well as neuroendocrine differentiation by evaluating chromogranin A and CD56. Unraveling the genetic and molecular mechanisms of the pathogenesis of NENs, together with the elucidation of the molecular heterogeneity of neoplasms and the unique features of molecular structures, may provide new possibilities for diagnosis and therapy. Molecular targeted therapies (MTTs) such as everolimus and sunitinib were the first examples of molecularly targeted therapies that can be used in the treatment of NEN and were subsequently approved for this purpose (15). Innovative drugs being developed in conjunction with genetic tests are expected to identify specific subgroups of patients who will respond positively to each individual molecular target. Multiparametric molecular and genetic analysis, such as NETest and MASTER, are already in research that attempts to elucidate neuroendocrine neoplasms from the aspect of enabling not only the selection of an appropriate therapeutic option, but also the identification of response to treatment or early recurrence. Such an approach would also aim at an early change in the strategic approach to treatment (15).

Immunohistochemical markers of neuroendocrine neoplasms

Chromogranin A (CgA) and synaptophysin are considered the most specific immunohistochemical markers for confirming neuroendocrine neoplasms. CgA is an acid glycoprotein of the granin family expressed in well-to-moderately differentiated neuroendocrine neoplasms. In poorly differentiated NENs, CgA is only focally positive. Chromogranin A may have limited sensitivity in hindgut carcinoids originating from the left side of the transverse colon, rectum, and anus (16).

Synaptophysin is a membrane glycoprotein, which is a good marker of neuroendocrine cells and NENs with diffuse cytoplasmic immunostaining (17). Immunolabeling for CgA and synaptophysin characterizes "pure" NENs. However, certain tumor types designated as "impure" NENs, which are composed of cells of different origins such as NEN-like solid pseudopapillary neoplasms of the pancreas or mixed acinar NECs, can also stain focally with these markers (18).

The World Health Organization classification of endocrine tumors of the digestive tract classifies as mixed neuroendocrine non-NEN (MiNEN) tumors, all those in which any staining component is represented in at least 30% of the lesions. Even in cases where one of the two components is represented in only a small part of the tumor, such as adenocarcinomas or other non-NECs with interspersed expression of CgA or synaptophysin in less than 30% of tumor cells, it represents a diagnosis of a neoplasm with a neuroendocrine component. This arbitrarily determined threshold value of 30% was proposed because it was established that even a lower value of the neuroendocrine component of the tumor does not affect the biological characteristics of these tumors (19).

Neural cell adhesion molecule (NCAM) or CD56 is a membrane glycoprotein responsible for neuromuscular and interneuron interaction. It is frequently expressed in several types of non-NEN tumors such as small cell lung cancer (20).

Molecular imaging of neuroendocrine tumors

Neuroendocrine neoplasms represent tremendous diagnostic challenge because their clinical presentation occurs relatively late (with the early appearance of liver metastases) and it is treatment non-specific and variable. When suspecting the presence of NEN, it is necessary to identify the presence of a tumor and the primary localization of the tumor as well as to assess the presence of regional and distant metastases. When functional tumors release vasoactive products that bypass first-pass metabolism, as in the case of liver metastases, carcinoid syndrome may occur (21). This syndrome occurs most often in small intestinal NENs and less frequently in unknown primary NENs. The symptoms include palpitations, flushing, sweating, and diarrhea (22). Bronchial NENs occasionally produce adrenocorticotropic hormones, resulting in Cushing's syndrome.

For this purpose, the determination of serum biomarkers as well as different modalities of visualization techniques are routinely used today (21). The most often ET biomarkers are serum CgA and urinary 5-hydroxyindoleacetic acid, the breakdown product of serotonin.

Different visualization techniques have a key role in the diagnosis, staging, choice of therapy and monitoring of NEN. Radiological visualization procedures are usually the first diagnostic line for the detection of these tumors. They include morphological modalities such as abdominal echosonography, computed tomography (CT), magnetic resonance (MR), transabdominal ultrasound, endoscopic ultrasound (EUZ) and intraoperative ultrasound examination (IOUZ).

Somatostatin receptor scintigraphy

The molecular basis for the *in vivo* localization and clinical application of somatostatin analogs in diagnosis and treatment is the fact that the largest number of NETs show overexpression of somatostatin receptors.

Out of five known somatostatin receptor subtypes (sstr1-sstr5) on differentiated NETs cells surface, sstr2 is the most prominently present, which is also the primary target of therapy with unlabeled somatostatin analogs (23). Radiopharmaceuticals for imaging the expression of somatostatin receptors utilize either single photon computerized tomography (SPECT) or positron emission tomography (PET) techniques, of which the PET technique is increasingly being used for diagnosing, staging and prediction of effectivess of treating patients with NETs. Image fusion of PET or SPECT with CT provide additional anatomical localization of lesions.

Somatostatin receptor (sstr) scintigraphy was introduced into clinical practice by Reubi and Krenning in 1991 after synthesizing ^{111}In-DTPA0-D-Phe-octreotide (OctreoScan), which is still used today for the detection of NEN despite the unfavorable physical characteristics of Indium (24). The disadvantages of this method of medical imaging are related to the unfavorable physical characteristics of ^{111}In, which has a long half-life of 67 h and suboptimal gamma energy (173 keV and 247 keV), which limits the applied radioactivity to 110 – 220 MBq in order to reduce the radiation exposure of patients affecting the sensitivity of the findings. The first synthesized radiopharmaceutical for commercial use was ^{111}In-DTPA-D-Phe1-octreotide which shows binding affinity for subtype 2 sstr. The properties of this radiopharmaceutical were later improved by synthesizing ^{111}In-DOTA-D-Phe1-Tyr3-octreotide (^{111}In-DOTA-TOC) which had a similar binding capacity in *in vitro* and *in vivo* assays but had a higher affinity and higher internalization potential (25). In this radiopharmaceutical, Phe was

replaced by Tyr, which increased the hydrophilicity of the radiolabeled peptide and enabled better stability of labeling compounds with ^{90}Y and ^{177}Lu, which are used as peptide radiopharmaceuticals for radionuclide therapy (26 - 28).

DOTA is a universal ligand that enabled the development of ^{68}Ga-DOTA-Tyr3-octreotide (^{68}Ga-DOTA-TOC), a radiopharmaceutical for PET (29). By replacing ^{111}In with the radionuclide ^{68}Ga, it was possible to improve the biodistribution characteristics and increase the uptake of this radiopharmaceutical for PET (30). After this, several more somatostatin analogs were synthesized, DOTA-Tyr3-octreotate (DOTA-TATE) with increased binding affinity exclusively for the sstr2 subtype, as well as a series of other compounds with an increased degree of binding for different sstr subtypes such as: DOTA-lanreotide (DOTA-LAN), DOTA-1-NaI3-octreotide (DOTA-NOC) and DOTA-1-NaI3-octreotate (DOTA-NOC-ATE) (31, 32).

The diagnostic specificity and accuracy of Octreoscan is around 90%, although this radiopharmaceutical has a lower sensitivity in detecting liver metastases compared to MRI and CT scan (33). This radiopharmaceutical does not have diagnostic significance as before due to the introduction of newer PET radiopharmaceuticals that more accurately and reliably detect even smaller lesions. However, it is still used especially from the aspect of dosimetry studies because the half-life of Indium-111 is similar to the half-life of 90-yttrium.

DOTA-NOC is a compound that shows a 3 - 4 times higher binding affinity for sstr2 than DOTA-TOC, but also shows a preference for binding to sstr3 and sstr5 subtypes, so administration of this radiolabeled compound resulted in increased tumor uptake and improved kidney-tumor activity ratio (34 - 36). For diagnostic purposes, these ligands are labeled with ^{111}In and ^{68}Ga, or with ^{90}Y and ^{177}Lu for therapeutic purposes (36). Furthermore, ^{99m}Tc-.

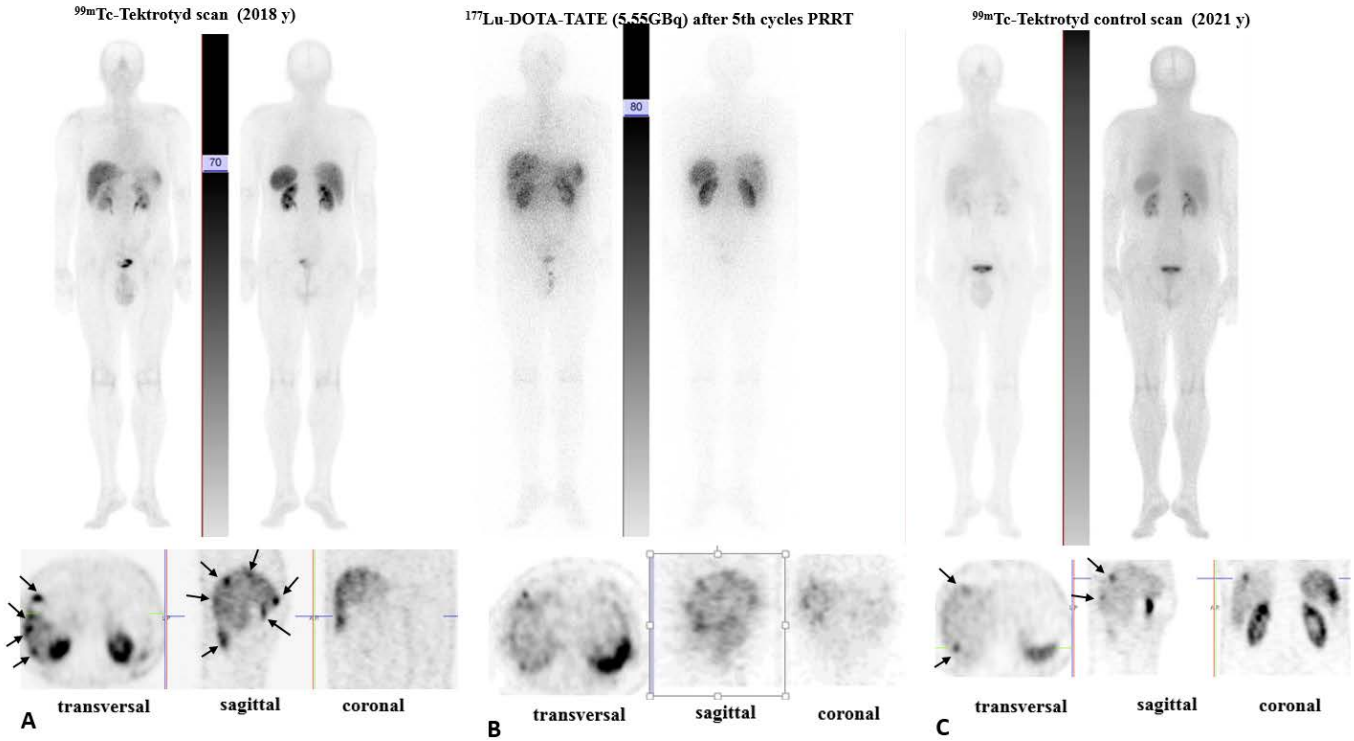

Figure 1. *Patient K.LJ. (62 years of age) admitted to the Center of Nuclear Medicine, University Clinical Center Niš, after hemicolectomy and bowel resection p; p multicentric carcinoid of the intestine ileum and appendix and metastatic regional lymph nodes - NET-G1 in the year 2016. A: Pretreatment somatostatin receptor scintigraphy with 99mTc-Tektrotyd showing multiple metastases in the liver, with excellent radiopharmaceutical accumulation. B: 177Lu-DOTA-TATE post-therapy scan after the 5th cycle. C: 99mTc-Tektrotyd control scan 2 years after five cycles of PRRT therapy with 177Lu-DOTA-TATE and 177Lu/90Y showing only the remaining low activity liver lesions (partial remission)*

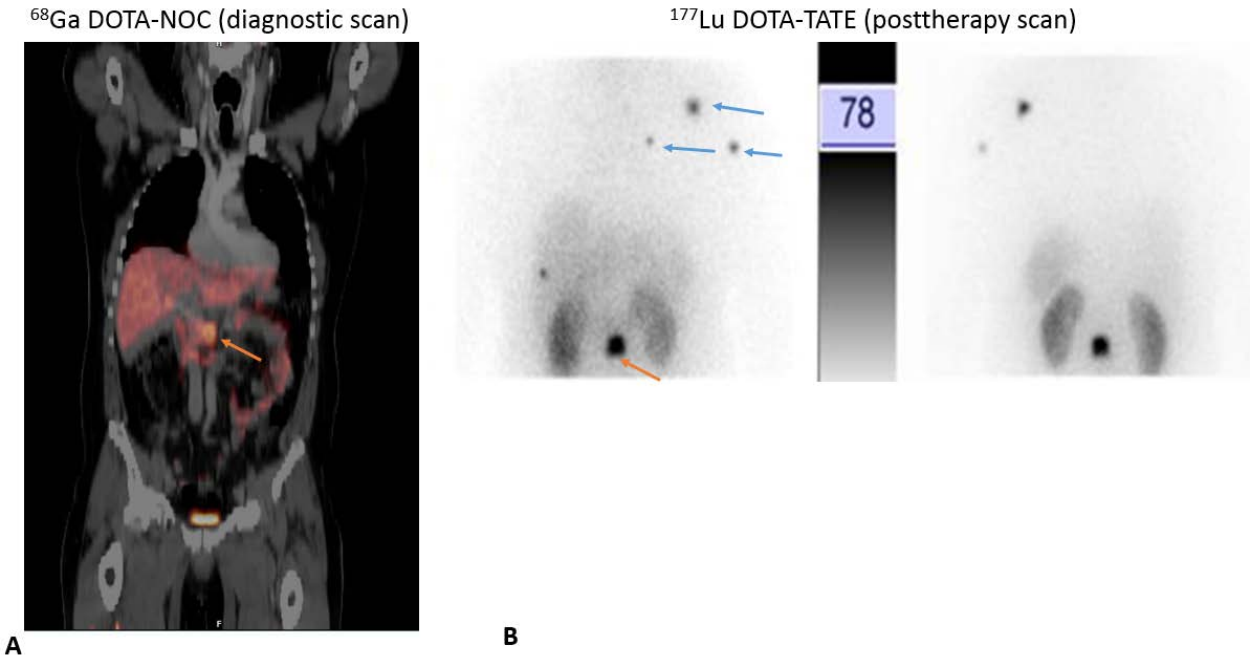

Figure 2. *Patient J.B. (32 years of age) admitted to the Center of Nuclear Medicine, University Clinical Center Niš, for the PRRT treatment of metastatic paraganglioma. A: Pretherapy diagnostic 68Ga-DOTA-NOC PET/CT scan showing mesenterial lesion and one liver lesion on the coronal section (orange arrows). B: 177Lu-DOTA_TATE post-therapy coronal section showing additional lung lesions (blue arrows)*

pertechnetate-labelable octreotide derivatives have been synthesized, of which ^{99m}Tc-Na-(hydrazinonicotyloyl)-Tyr3-octreotide (HYNIC-TOC, Tectrotyd) shows excellent image quality in NET patients (37 - 39) (Figure 1)

Somatostatin analogs labeled with technetium-99m providing high-resolution images have advantages over ^{111}In because scintigraphy is performed on the same day. The most commonly used are ^{99m}Tc-EDDA/HYNIC-octreotate, or ^{99m}Tc-EDDA/HYNIC-octreotide (40, 41).

In recent years, ^{68}Ga-labeled the following octreotide derivatives have been recommended for -diagnostics and follow-up of NENs: [^{68}Ga-DOTA,Tyr3]octreotide (^{68}Ga-DOTA-TOC), [^{68}Ga-DOTA, Tyr3, Thr8]octreotate (^{68}Ga -DOTA-TATE) or [^{68}Ga - DOTA, 1-Nal3]octreotide (^{68}Ga -DOTA-NOC) (28, 29). There is no significant difference between these three radiopharmaceuticals in terms of the quality of the obtained image, although there are variations and differences in binding affinity for individual somatostatin receptor subtypes (42, 43). The great advantage of these radiopharmaceuticals is that identical compounds can be labeled with therapeutic radionuclides ^{90}Y and ^{177}Lu and used for peptide receptor radionuclide therapy (Figure 2).

Other peptide cell receptors have also been identified in last decades: vasoactive intestinal peptide -VIP (44 - 46), bombesin (47, 48), substance P (49), gastrin, gastrin-releasing peptide-GRP, cholecystokinin-CCK (50,51), neurotensin (52, 53) and others, but still without appropriate theranostic therapeutic radiopharmaceutical.

Peptide receptor radionuclide therapy is a targeted molecular therapy that involves the systemic application of radiopharmaceuticals with high affinity for receptors that are overexpressed on neuroendocrine tumors. Radionuclide-labeled somatostatin receptor agonists ^{90}Y-DOTA-TOC (Y-90-DOTA0, Tyr3-octreotide) or ^{177}Lu-DOTA-TATE (Lu-177-DOTA0, Tyr3, Thr8-octreotide or Lu-177-DOTA0, Tyr3-octreotide) have been successfully used for the past 20 years in the treatment of metastatic or inoperable neuroendocrine neoplasms expressing subtype 2 somatostatin receptors.

Therapy with labeled somatostatin analogs shows enormous potential in the treatment of patients with advanced and inoperable NEN. A re-

cent meta-analysis including 22 published studies of 1,758 unresectable or metastatic NENs treated with ^{177}Lu-labeled peptides, aimed to examine the efficacy of this treatment modality with Recist and Recist 1.1. criteria, showed a response to treatment in 33% of patients, while disease control was recorded in as many as 79% (recist criteria) i.e 83% (recist 1.1 criteria) (54).

CONCLUSION

Overexpression of the somatostatin receptor is an outstanding molecular target for inoperable and metastatic NENs that enables a unique approach of targeted diagnosis and treatment with the same molecule that has an affinity for these receptors labeled either with a diagnostic or therapeutic radionuclide. The theranostic approach enables a personalized approach to each patient based on a previous diagnostic molecular evaluation of the somatostatin receptor in order to hit the same molecular targets with the appropriate therapeutic radionuclide for the purpose of treatment. Previous reports have shown that the therapy with labeled somatostatin analogs shows enormous potential in the treatment of patients with advanced and inoperable NEN. Peptide receptor radionuclide therapy is a systemic molecular target therapy that has proven to be safe and very effective in controlling the disease and prolonging the survival of patients with advanced and inoperable neuroendocrine neoplasms. With a negligible number of adverse events, this therapy is safe and should be administered to all patients who meet the necessary criteria, primarily overexpression of the somatostatin receptor type 2.

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Teranostika i precizna medicina u neuroendokrinim tumorima

Filip Veličković[1,2], Marina Vlajković[1,2], Miloš Stević[1,2], Nina Topić[1], Tamara Anđelković[1,2], Đuro Macut[3]

[1]*Univerzitetski klinički centar Niš, Centar za nuklearnu medicinu, Niš, Srbija*
[2]*Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija*
[3]*Univerzitetski klinički centar Srbije, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Beograd, Srbija*

S A Ž E T A K

Uvod. Neuroendokrini tumori (NET) imaju povećanu ekspresiju somatostatinskih receptora (SSTR), a najčešći su podtipovi 2 i 5. Prekomerna ekspresija SSTR-a je izvanredna molekularna meta za neoperabilne i metastatske NET-ove koja omogućava jedinstven pristup ciljanoj dijagnostici i terapiji. Pored SSTR-a, neuroendokrini tumori eksprimiraju i druge receptore koji mogu biti pogodne mete za vizuelizaciju metodama nuklearne medicine.
Cilj. Ovaj pregledni rad je fokusiran na najčešće radiofarmaceutike i njihove molekularne mete koje se danas koriste na osnovu teranostičkog pristupa u NET-ovima.
Rezultati. U konvencionalnoj nuklearnoj medicini najvažniji dijagnostički radiofarmaceutici su analozi somatostatina (SSA) obeleženi ^{111}In i ^{99m}Tc; međutim, ^{99m}Tc ima prednost u odnosu na ^{111}In na osnovu boljih fizičkih karakteristika i lakšeg izvođenja. Poslednjih godina stvoreni su veoma moćni teranostički parovi za snimanje i lečenje NET-ova, koji se mogu snažno vezati za SSTR. Derivati ^{68}Ga obeleženih oktreotidom preporučuju se za dijagnostiku i praćenje NEN-a. Velika prednost ^{68}Ga radiofarmaceutika ogleda se u tome što se identična jedinjenja mogu obeležiti terapeutskim radionuklidima ^{90}Y i ^{177}Lu.
Zaključak. Radionuklidna terapija usmerena na peptidne receptore je sistemska molekularna ciljna terapija koja se pokazala bezbednom i veoma efikasnom u kontroli bolesti i dužem preživljavanju bolesnika sa uznapredovalim i neoperabilnim NET-ovima. Uz zanemariv broj neželjenih efekata, ova terapija je bezbedna i treba je primeniti kod svih bolesnika koji ispunjavaju neophodne kriterijume, pre svega prekomernu ekspresiju somatostatinskih receptora tipa 2.

Ključne reči: **neuroendokrini tumori, somatostatinski receptori, scintigrafija, radionuklidna terapija**