

RADIONUCLIDE IMAGING OF NEUROENDOCRINE TUMORS

VIZUALIZACIJA NEUROENDOKRINIH TUMORA METODAMA
NUKLEARNE MEDICINEJelena Šaponjski¹, Đuro Macut^{2,3}, Dragana Šobić Šaranović^{1,3}¹ Clinical center of Serbia, Center for Nuclear Medicine, Belgrade, Serbia² Clinical center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic diseases, Belgrade, Serbia³ University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Correspondence: jelena.saponjski1@gmail.com

Abstract

Neuroendocrine tumors (NETs) are relatively rare and heterogeneous with a variety of clinical expression. They derive from the sensory and secretory neuroendocrine cells mainly within the pulmonary and gastrointestinal tract. They comprise less than 2% of all malignancies. On the basis of clinical behavior, histology, and proliferation rate, they are divided into well differentiated (low grade to intermediate grade) and poorly differentiated (high grade) neuroendocrine carcinoma. Tumor stage and grade have the impact on treatment and prognosis. The treatment of choice is surgery. More than 50% of the patients present metastatic disease at the time of diagnosis, thus the systemic treatment should be considered including somatostatin analogs, chemotherapy, targeted therapy, immunotherapy and peptide receptor radionuclide therapy (PRRT). For the diagnosis and follow-up of these tumors, various radiological methods are used (computed tomography, magnetic resonance imaging, ultrasound) as well as endoscopy. Nuclear medicine methods are used in order to exploit their unique properties mainly amine precursor uptake and decarboxylation system characteristics, as well as the expression of somatostatin receptors. These methods enable whole body examination, staging, selection of patient for PRRT and treatment monitoring as well. Imaging can be performed with gamma camera (SPECT, SPECT/CT) or positron emission tomography (PET/CT). Radiopharmaceuticals used for imaging with gamma camera are usually ^{99m}Tc-(V)-DM-SA, ^{99m}Tc-MIBI, ^{99m}Tc-HYNIC TOC, ¹¹¹In-pentetreotide and ¹³¹I-MIBG/¹²³I-MIBG. Positron emitting radiopharmaceuticals has superior spatial resolution and faster imaging, such as ⁶⁸Ga-DOTA-somatostatin analogues, ¹⁸F-FDG (particularly for high-grade tumors), ¹⁸F-L-DOPA/¹¹C-L-DOPA and ¹¹C-5-hydroxytryptophan that have demonstrated excellent imaging results. The new targeted agents present a challenge in the evaluation procedure of treatment and, therefore, new imaging techniques and an improvement of currently available techniques are mandatory. In this mini-review, the most frequent methods and radiopharmaceuticals are presented, as well as potential development.

Keywords:

neuroendocrine tumors,
positron emission
tomography,
gamma camera,
radiopharmaceuticals

Sažetak

Neuroendokrini tumori (NET) relativno su retki i sa vrlo heterogenom kliničkom slikom. Potiču iz senzornih i sekretornih neuroendokrinih ćelija, uglavnom unutar plućnog i gastrointestinalnog trakta. Sačinjavaju manje od 2% svih malignih oboljenja. Na osnovu kliničkog ponašanja, histologije i proliferacije, podeljeni su u dobro diferentovane (niski do srednji stepen) i slabo diferentovane (visoki stepen) neuroendokrine tumore. Pripadnost svakoj od ovih kategorija ima uticaj na lečenje i prognozu. Najznačajniji vid lečenja je operativni. S obzirom na to da više od 50% pacijenata u vreme postavljanja dijagnoze već ima metastatsku bolest, mora se razmotriti vid sistemskog lečenja, uključujući analoge somatostatina, hemoterapiju, ciljanu terapiju, imunoterapiju i peptid-receptor radionuklidnu terapiju (PRRT). Za dijagnozu i praćenje ovih tumora koriste se različite radiološke metode (kompjuterizovana tomografija, magnetna rezonanca, ultrazvuk) i endoskopija. Metode nuklearne medicine koriste jedinstvene osobine NET ćelije, uglavnom karakteristike prekursora amina i sistema dekarboksilacije, kao i ekspresije receptora somatostatina. Radionuklidne metode vizualizuju celo telo i mogu lokalizovati i udaljene metastaze u cilju određivanja stadijuma bolesti i praćenja efekta lečenja. Snimanje se može obaviti pomoću gama kamere (SPECT, SPECT/CT) ili pozitronskom emisionom tomografijom (PET/CT). Radiofarmaci koji se koriste za snimanje gama kamerom obično su ^{99m}Tc - (V) -DMSA, ^{99m}Tc -MIBI, ^{99m}Tc -HYNIC TOC, ^{111}In -pentetretid i ^{131}I -MIBG/ ^{123}I -MIBG. Pozitronska emisiona tomografija ima prednost zbog superiorne prostorne rezolucije i brzine snimanja. Najčešće korišćeni pozitronski radiofarmaci su analozi somatostatina, oboježeni pomoću ^{68}Ga , ^{18}F -FDG (naročito za tumore visokog stepena), ^{18}F -L-DOPA/ ^{11}C -L-DOPA i ^{11}C -5-hidroksitriptofan. Dalji razvoj novih radiofarmaka za detekciju neuroendokrinih tumora predstavlja veliki izazov. U ovom radu je dat revijski prikaz najčešće korišćenih tehnologija, kao i trendovi razvoja metoda za otkrivanje neuroendokrinih tumora.

Ključne reči:

neuroendokrini tumori,
pozitronska emisiona
tomografija,
gama kamera,
radiofarmaci

Introduction

Neuroendocrine tumors (NETs) are relatively rare and heterogeneous with diverse clinical expression and progression. They derive from the sensory and secretory neuroendocrine cells mainly within the pulmonary and gastrointestinal tract. For the diagnosis and follow-up of these tumors, various radiological methods are used (computed tomography - CT, magnetic resonance imaging - MR, ultrasound - US) as well as endoscopy. Nuclear medicine methods are based on the physiology of NET cells. Imaging can be performed with gamma camera (SPECT, SPECT/CT) or positron emission tomography with computed tomography (PET/CT). Hybrid systems (SPECT/CT and PET/CT) provide not only functional, but also anatomic images, showing even more precise localization of pathological changes and improved accuracy with semi-quantification of the radiopharmaceutical (RP) accumulation (1). The new targeted agents present a challenge in the evaluation procedure of treatment and, therefore, new imaging techniques and an improvement of currently available techniques are mandatory. In this mini-review, the most frequent methods and radiopharmaceuticals are presented.

Radiopharmaceuticals and methodology of NET detection

The expression of peptide receptors on NET cells is significantly higher, as compared to normal tissue, and these cells were recognized as targets for molecular imaging and therapy (2). Somatostatin and its analogues are proven to inhibit the growth of normal, as well as malignant cells, through one or more of five known NETs cell somatostatin receptor subtypes (3). Somatostatin itself can not be used due to its very short half-life in plasma, where it gets decomposed by proteolytic enzymes (2). A number of peptide-receptor-based RP has been developed and tested (4,5), labelled with gamma or positron emitters. Thus, it is possible to perform somatostatin receptor scintigraphy (SSRS) or positron emission tomography (PET), usually with anatomic localization (PET/CT). Accumulation in NET depends on its affinity for certain types and density of SSR on the tumor cell. Important factor is also the degree of internalization of the whole complex radiopharmaceutical-receptor, which is the highest in somatostatin receptor subtype 2 (SSR2). The most frequently used RP for SSRS are ^{99m}Tc -HYNIC-TOC and ^{111}In -pentetretide (3) (**Figures 1** and **2**). Sensitivity for SSRS for primary and recurrent NET is 91% and 95% for metastases (6), while in abdominal NET imaging it is 76-82% (1). However, the

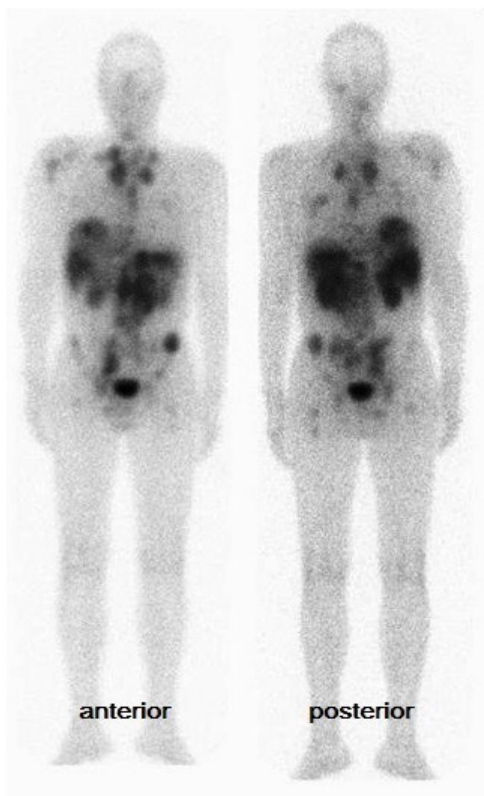


Figure 1. Whole body scintigram with ^{111}In -pentetreotide in the patient with multiple NET metastases (mediastinum, liver, retroperitoneum, bones) of unknown origin

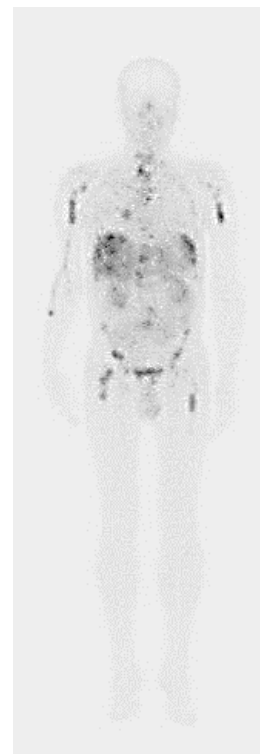


Figure 2. Whole body scintigram with $^{99\text{m}}\text{Tc}$ -HYNIC-TOC in the patient with NET of unknown primary with lesions in lung, bone and liver metastases

question raised recently was if the internalization is a necessary condition for visualization of SR. Recent studies point out that analogues of somatostatin have more binding sites on the cell and that radiolabelled antagonists have the possibility to include even inactive receptors on the cell surface (7). Thus, antagonists labelled with gamma emitting radionuclides, such as ^{111}In -DOTA-BASS vs. ^{111}In -pentetreotide in the preclinical study showed better contrast and revealed significantly more metastatic lesions (25 vs. 17), although both ligands have almost identical affinity for SR. Also, tumor uptake and prolonged accumulation in tumor tissue, until 24 h, significantly improves diagnostic possibilities (8,9). In clinical studies, imaging with ^{111}In -DOTA-BASS was much more effective than with ^{111}In -DTPA-octreotide, because of the 4 times higher tumor uptake, two times higher tumor/liver ratio which resulted in much more detected lesions (5). However, ^{111}In -DOTA-JR 11 was proved to be the most superior antagonist (9, 10) since 24 hours after injection showed higher tumor uptake and revealed more tumor lesions in comparison to both ^{111}In -DOTA-BASS and ^{111}In -pentetreotide (10).

The best results are obtained in well differentiated tumors. The results of SSRS can be used for estimation of prognosis, since higher accumulation of somatostatin analogue/ antagonist reflects better tumor differentiation, better prognosis and better response to treatment with somatostatin. Thus, visualization can fail in low differentiated tumors. The scan interpretation should be performed carefully because non-tumor accumulation can be seen physiologically in urogenital and digestive system, as well as in infections, inflammations and autoimmune diseases (11).

The major indications for SSRS are tumors with high expression of somatostatin receptors such as NETs in gastroenteropancreatic, urogenital and sympatico-adrenal system, lungs, thyroid and Merkel cell carcinoma of the skin. It can be also performed in some tumors with weaker expression of somatostatin receptors such as breast, non-small cell and prostate cancer, melanoma, lymphoma and meningioma. Somatostatin receptor scintigraphy is indicated for the localization of primary and metastatic NETs, differentiation of NETs from other tumors, selection of patients for (radionuclide) therapy with somatostatin analogues and monitoring the treatment effect after surgery, radiotherapy, chemoembolization, somatostatin analogues treatment and chemotherapy.

High sensitivity of PET/CT allow better visualization and quantification of somatostatin analogues by calculation of the standardized uptake value (SUV). It is the index of RP accumulation, in proportion with the injected dose and body area, and it is used as the criteria for clinical decision making. A significant progress has been made in NET diagnosis by introduction of gallium-68 (^{68}Ga) labeled somatostatin analogues. This radionuclide is obtained from generator, which allows production of RP on the place of imaging. Better visualization of NET is allowed by ^{68}Ga -labeled somatostatin analogs, than those labelled with gamma emitting radionuclides due to significantly better resolution of PET. Thus, sensitivity and specificity of ^{68}Ga -DOTANOC PET/CT in primary gastroenteropancreatic NET were 78.3% and 92.5%, and for metastases 97.4% and 100%

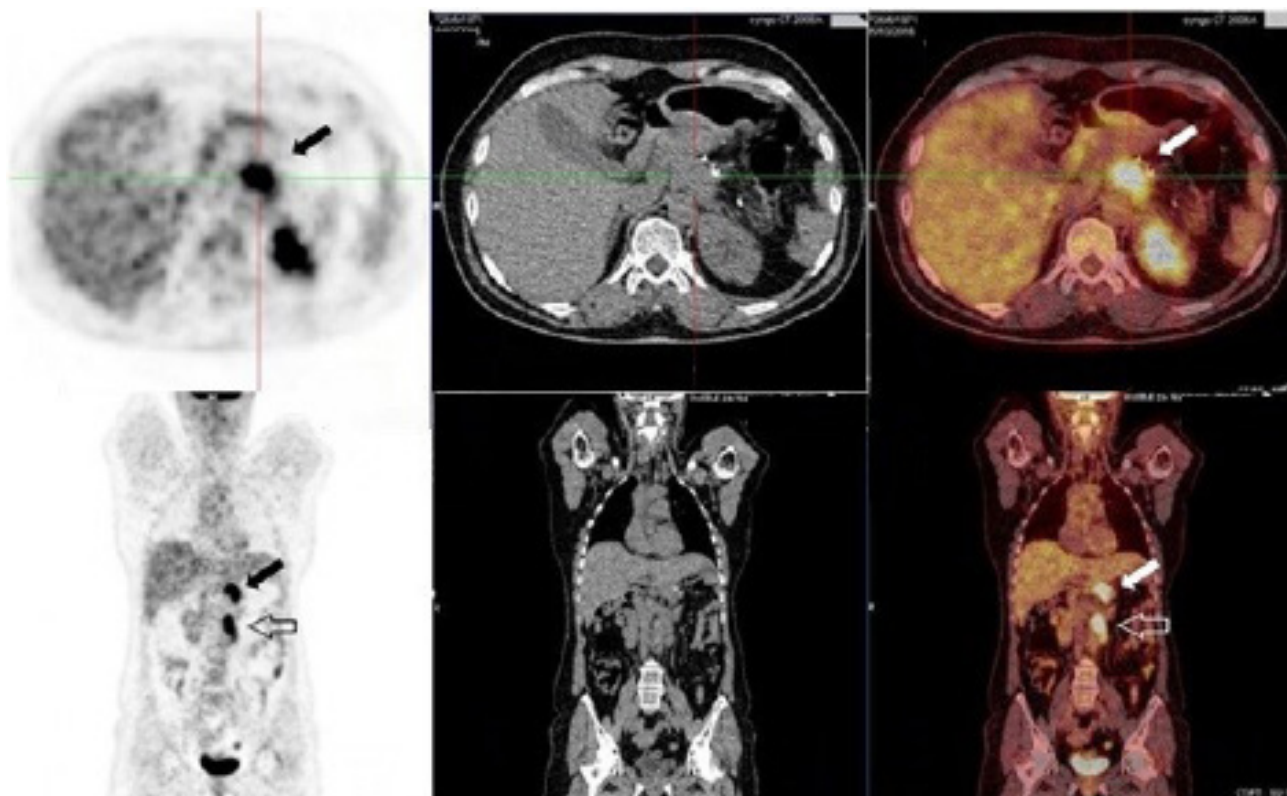


Figure 3. ^{18}F -FDG PET/CT in the patient after partial pancreatectomy because of pancreatic NET. Recurrence in pancreas with secondary deposits in retroperitoneal lymph nodes

(12). In some studies of pancreatic NETs, sensitivity of ^{18}F -FDG was 60-92% and ^{68}Ga -DOTA RP 82-100% (13,14). Antagonists can also be labelled with ^{68}Ga . Thus, ^{68}Ga -NODAGA-JR11 vs ^{68}Ga -DOTATOC showed lower uptake in liver, spleen, pancreas and digestive system which enables detection of small metastases in these organs, which is important - especially in liver. Radiation doses for the patients with antagonists are lower than those calculated for analogues (15,16). However, in clinical studies, uptake of ^{68}Ga -NODAGA-JR11 in NETs was not higher in comparison to ^{68}Ga -DOTATATE. Also, more liver metastases were revealed with ^{68}Ga -NODAGA-JR11 vs. ^{68}Ga ^{68}Ga -DOTATOC, because of lower liver background (sensitivity 94% vs. 59%). Positive predictive values for ^{68}Ga -DOTATOC and ^{68}Ga -NODAGA-JR11 PET/CT were similarly high (95%) (15,16). Recent advances in the diagnosis of NETs are made with the use of somatostatin analogues and antagonists labelled with copper-64 (^{64}Cu). It has half life of 12.7 h, which allows delayed imaging with higher target to background ratio. A special advantage is the possibility of performing radionuclide therapy with analogue or antagonist labelled with beta emitting radionuclide ^{67}Cu . It is produced in cyclotron, but because of long half life, it can be transported at long distance which is the advantage. Due to the higher expression of copper transporter on the tumor cell, the ^{64}Cu itself is being accumulated in the tumor cells for the key role that copper ions have in DNA replication. About 60-70% of ^{64}Cu absorbed from malignant cell remains in nucleus, allowing effective possibility of radionuclide therapy. Analogues of somatostatin labelled with ^{64}Cu , such as ^{64}Cu -DOTATATE and ^{64}Cu -TETATOC allows better resolution, higher

sensitivity and more favorable dosimetry even after therapeutic application. However, the ^{64}Cu -DOTATATE is more sensitive than ^{68}Ga -DOTATATE for NET diagnostics. Effective radiation dose is similar to that of other positron emitting radiopharmaceuticals (17,18). The newest investigation of radiopharmaceuticals, ^{64}Cu -SarTATE vs. ^{64}Cu -DOTATATE, showed excellent uptake in tumors 2 h after injection for both of them. However, tumor uptake of ^{64}Cu -DOTATATE was significantly lower after 24 h, while ^{64}Cu -SarTATE persisted in tumor, increasing contrast in the late phase. At the same time, ^{64}Cu -SarTATE accumulated less in comparison to ^{64}Cu -DOTATATE in non target organs (liver, lungs). Uptake of ^{64}Cu -SarTATE in kidneys was very high at 2 h, while dramatically decreased after 24 h (19). Unlike promising antagonists explained previously, antagonists labeled with ^{64}Cu did not show better performance than analogues (20).

The most commonly used RP for PET/CT in oncology is fluorine-18 labeled analog of D-glucose (2-deoxy-2- ^{18}F fluorglucose (FDG). It is transported into the cell using glucose transporter molecules in the cell membrane (GLUT1). The first step of glucose phosphorylation is glycolysis, enzyme degradation process in which is released the energy required for physiological processes. However, FDG is not subject of degradation because of the modified second carbon atom configuration that prevents the next enzyme reaction. Once it is phosphorylated, FDG cannot go out of the cell, causing the progressive accumulation. As malignant tumors have increased glycolysis, density and GLUT's phosphokinase activity, FDG accumulation is more intense than in healthy tissue (Figure 3). The

prolonged retention in tumors - due to metabolic trapping of FDG in cells - gives enough time for imaging. Accumulation in inflammatory zones decreases specificity of this diagnostic method. However, NETs do not have high glycolysis and those which show a high uptake are characterized by a more aggressive behaviour (21). Uptake correlates with the tumors' proliferative index. This is the reason why it is preferred radiopharmaceutical for low differentiated tumors. It can be predictive factor since more intense FDG accumulation in NET indicates worse prognosis (13). However, sometimes FDG PET investigation can accomplish results obtained with other radiopharmaceuticals, especially radiolabelled analogues of somatostatin (14).

NETs can be also visualized using guanidine analogues labelled with iodine radioisotopes (^{123}I , ^{124}I , ^{131}I). Metaiodobenzylguanidine (mIBG) is structurally similar to noradrenaline. It is using the same membrane transporters as noradrenaline thus entering the cell of sympathetic system. It is accumulated in paraganglioma, pheochromocytoma, neuroblastoma, ganglioneuroblastoma, ganglioneurinoma, medullary thyroid carcinoma and in some other NETs. It is retained in the neuroblastoma cytoplasm, and in pheochromocytoma and paraganglioma secretory vesicles. The mostly used RP in clinical practice is ^{123}I -mIBG imaged with gamma camera or SPECT/CT. In spite of superior resolution the use of ^{124}I -mIBG PET/CT is limited by availability. The sensitivity of ^{123}I -mIBG scintigraphy of paraganglioma is 83-100% and specificity 95-100% (22). However, ^{131}I -mIBG is frequently used for targeted therapy or as an imaging agent prior to therapeutic dose administration (Figure 4). Semiquantification of tumors' uptake is used as a parameter for therapeutic dose determination. Due to its long half-life, beta radiation and high-energy gamma radiation which is unfavorable for SPECT, the ^{131}I -mIBG is not suitable for diagnostic purpose. Sensitivity of ^{123}I -mIBG scintigraphy for detection of pheochromocytoma is 68-82%, paraganglioma 58-78% and neuroblastoma 79-89% (2). In pancreatic, gastrointestinal and lung NETs, sensitivity of ^{123}I -mIBG scintigraphy is 54-72%, which is lower than SRS. In prospective research of 96 NET patients, the results of SSRS, ^{123}I -mIBG and ^{18}F FDG PET were directly compared. While mIBG was positive only in half of the patients who had positive SSRS, the opposite happened in three patients (30). At the same time, FDG PET findings were positive in all patients with positive findings of two other methods. Thus, mIBG scintigraphy is the imaging method of choice for neuroblastoma and pheochromocytomas and mIBG scintigraphy may therefore be used when other imaging modalities fail to localize the NETs and mIBG therapy is considered.

Technetium labelled pentavalent dimercaptosuccinil acid ($^{99\text{m}}\text{Tc}$ -DMSA-V) is transported into the cell with sodium phosphate cotransporter due to its similarity to phosphate anion (24). It accumulates in metabolically active tumor cells, including thyroid carcinoma

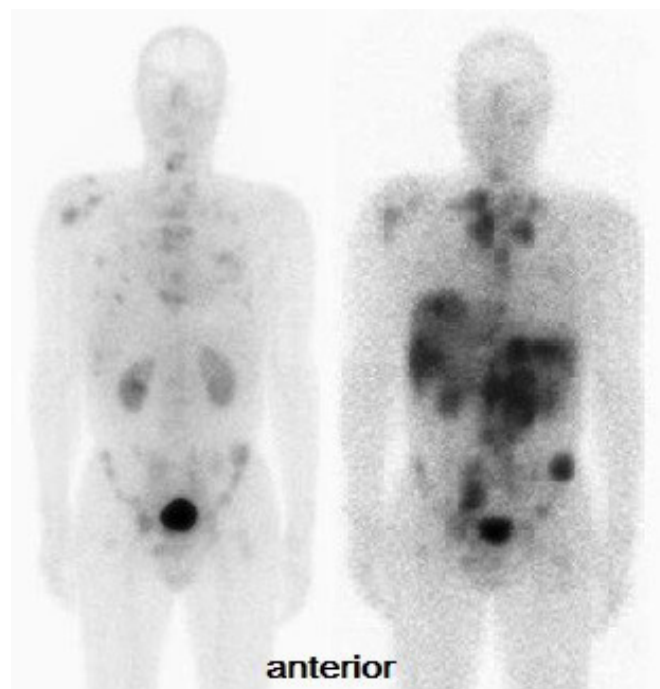


Figure 4. Whole body scintigram with $^{99\text{m}}\text{Tc}$ -DMSA(V) (left) and ^{111}In -pentetreotide (right) in the patient with metastases of NET of unknown origin

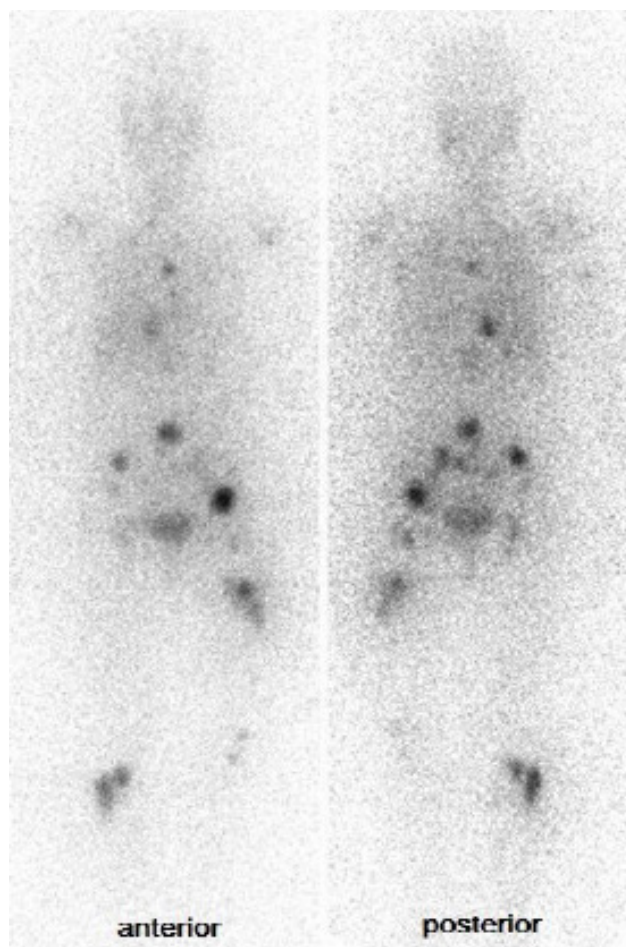


Figure 5. Whole body scintigram with ^{131}I -mIBG in the patient with metastatic paraganglioma, after surgery of primary mediastinal tumor

because of the higher activity in tissue due to the accumulation of lactic acid. Some studies showed that the sensitivity of DMSA (V) scintigraphy for medullary thyroid cancer is 89%, but the results of other studies are controversial (25) (**Figure 5**). The greatest sensitivity, in studies where DMSA, SRS, and FDG are compared, was achieved with FDG. The mIBG imaging is indicated only for metastatic medullary carcinoma, when therapy using ^{131}I -mIBG (26) is indicated. The sensitivity of FDG PET for metastatic MTC is 78% in patients with calcitonin values more than 1,000 pg/ml, and only 20% in patients with a lower concentrations of tumor marker. Slightly higher sensitivity of 81% for medullary carcinoma was achieved with ^{18}F -DOPA PET/CT (dihydroxyphenylalanine), than with ^{18}F -FDG (58 and 78%) and ^{68}Ga -DOTATOC (72%) of (27).

Fluorine-18 labeled DOPA- (^{18}F -DOPA) follows the path of catecholamine synthesis and it is accumulated by the NET cells. It enters the cytoplasm through amino acid transporters on the cell membrane and decarboxylates (converts) to dopamine (^{18}F -fluorodopamin, FDA). Further, dopamine is converted to norepinephrine in secretory vesicles. Thus, accumulation of the RP in the NET cell is dependent on the expression of amino acid transporter and decarboxylase activity. Main clinical indications for ^{18}F -DOPA PET are pheochromocytoma, paraganglioma, medullary thyroid carcinoma, congenital hyperinsulinism and Parkinsonism. However, due to still limited availability of this RP indication for ^{18}F -DOPA PET is only in cases when ^{68}Ga and/or ^{18}F FDG PET is negative. Although the ^{18}F production depends on cyclotron, a relatively long half-life of this radionuclide is convenient (as well as in case of ^{18}F FDG) for wide distribution. The sensitivities in malignant pheochromocytoma / paraganglioma using ^{18}F -DOPA, ^{18}F FDG PET and ^{131}I -mIBG scintigraphy are 100%, 89% and 75% respectively (28). In a similar study (in which ^{123}I -mIBG was used, sensitivity was calculated in relation to a total number of a lesion, not the patients), the results were: 45%, 74% and 57% respectively (29). Timmers and all, directly compared PET/CT with the FDA's, F-DOPA, FDG and ^{123}I -mIBG SPECT. They obtained the following sensitivities for metastatic paraganglioma: FDA 76%, FDG 74%, mIBG 57% and DOPA 45% (29).

Imaging of other molecular targets is also the subject of investigation. Thus, carbon-11-5-hydroxytryptophan (^{11}C -5-HTP), radiolabeled precursor in the serotonin synthesis is recommended, particularly for detecting small pancreatic NETs and early recurrences (30). Also, several cholecystokinin (CCK2) receptor-binding radiopeptides have been developed for scintigraphy of these tumors, such as ^{111}In -DOTA-CCK, $^{99\text{m}}\text{Tc}$ -demogastrin and ^{111}In -DOTA-MG11 (30). For detection of insulinomas promising results show glucagon-like-peptide (GLP1R), labelled with $^{99\text{m}}\text{Tc}$, ^{111}In or ^{68}Ga . However, ^{123}I -labelled vasoactive intestinal peptide (VIP) receptor, can be also used for various NETs (30).

The theranostic approach in nuclear medicine couples diagnostic imaging and therapy using the same molecule or at least very similar molecules, which are either radiolabelled differently or given in different dosages (31). It would be ideal to use the same carrier molecule labeled with radioisotopes of the same chemical element for radionuclide diagnostic and therapeutic purpose (for diagnoses gamma or positron-emitter, beta minus and alpha emitter for therapy) (32,33). For therapeutic purposes in NET patients, the peptides DOTATATE, DOTANOC and DOTATOC can be labelled either with ^{90}Y or ^{177}Lu (31).

Radioguided surgery of NETs comprises intraoperative localization of NETs tissue using a probe detector and has been successfully applied in many areas of minimal invasive surgery in order to increase the efficiency of surgery, discovering even very small lesions, such as 5 mm in diameter (34). Radioguided surgery proved to be the most sensitive method for NET localization, compared to preoperative imaging methods (CT, MRI, SPECT), intra-operative surgical palpation and intra-operative ultrasonography (34).

Conclusion

Further progress can be expected in wider application of contemporary hybrid systems (SPECT/CT and PET/CT), as well as development of the new radiopharmaceuticals for imaging, therapy and radioguided surgery. It will also have an impact on clinical decision-making and treatment results.

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