THE ROLE OF SOMATOSTATIN RECEPTOR SCINTIGRAPHY IN THE DIAGNOSIS AND FOLLOW-UP OF THE PANCREATIC NEUROENDOCRINE NEOPLASMS

by

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The aim of investigation was to assess the role of somatostatin receptor scintigraphy in diagnosis and follow-up of pancreatic neuroendocrine neoplasms. Somatostatin receptor scintigraphy was performed with 740 MBq ^{99m}Tc-EDDA/HYNIC TOC for diagnosis of primary tumors and follow-up after the therapy. There were 63 true positive, 24 true negative, 4 false positive, and 6 false negative findings. Sensitivity was 91.3 %, specificity 85.7 %, positive predictive value 94.0 %, negative predictive value 80.0 %, accuracy 89.7 %. The SPECT contributed diagnosis in 28 true positive findings. In 32 patients (33 %) somatostatin receptor scintigraphy significantly changed the management of the patients (10 had surgery, in 17 somatostatin analogues, and in 5 peptide receptor radionuclide therapy was introduced). Mean Ki-67 index in true positive patients was 13.8 5.0 % while in true negative 7.1 3.4 % which is significantly lower at $p < 0.05$. There was significantly ($p < 0.01$) higher number of increased chromogranin A values in true positive than in true negative patients ($p = 0.000857$). Our results confirmed the value of SRS in the diagnosis and follow-up of the patients with pancreatic neuroendocrine neoplasms PanNEN if primary tumors, recurrences or metastases are suspected, as well as for appropriate choice of the therapy.

Key words: somatostatin receptor scintigraphy, neuroendocrine tumor, pancreas, follow-up, nuclear medicine, radionuclide

INTRODUCTION

Since the discovery of X-rays by the end of the 19th century by William Roentgen [1], clinical practice has been significantly changed, developed and improved. It offered for the first time possibility to discover changes in the body of the patient without surgical procedures. Using sealed and opened sources of radiation in medicine through diagnostic radiology, nuclear medicine, and radiation therapy became routine clinical practice, advancing rapidly during time, and are considered as essential tools in diagnosis and in therapy for the majority of clinical conditions. However, apart for obvious and irreplaceable clinical benefits, application of radiation in medicine caries a certain risk. Thus, in application of these procedures overall tendency is risk to benefit ratio, *i. e*. the minimization of risk balanced against the need for appropriate and adequate results. It is very difficult to achieve and standardize the use of radiation procedures in medicine, bearing in mind variety of equipment, different education, standard of healthcare *etc*., throughout of the world. In some developed countries, nearly 50 % of radiation exposure originates from medical sources. For the sake of protection of the patients, it is necessary that procedures should seek to achieve diagnostic information of satisfactory clinical quality using the lowest reasonably achievable dose [2]. One of the procedures that brings the crucial clinical information in diagnosis, staging, follow-up after the therapy, choice of the biopsy sites and putting indication for radionuclide therapy is somatostatin receptor scintigraphy (SRS), based on the fact that somatostatin

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analogues bind to cells of neuroendocrine tumors which express somatostatin receptors. This method accomplishes results and provides necessary information for the management of the patients with neuroendocrine tumors.

Pancreatic neuroendocrine neoplasms (PanNEN) are a heterogeneous group of tumors with different clinical but similar imaging possibilities and characteristics. If they are diagnosed early, in general, their overall survival is good [3]. Curative surgery is the best treatment but many patients may have small lesions that are difficult to detect, or wide spread disease by the time of diagnosis. After clinical investigation with laboratory analysis, imaging is necessary to establish the diagnosis. Ultrasound (US), endoscopic US, computed tomography (CT), and magnetic resonance imaging (MRI), play a major role in the initial assessment [4], but very often they do not confirm small lesions or distant metastases. Inclusion of nuclear medicine imaging in diagnostic algorithm is usually necessary for primary tumor visualization, staging and evaluation of treatment. In specific cases, for diagnosis of occult insulinomas [5, 6], sampling procedures can be performed.

According to the current World Health Organization grading system 2017, PanNEN can be classified, according to their Ki-67 proliferation index, into well differentiated neuroendocrine tumors (PanNET) grade (G) 1 (G1), with a Ki-67 index amounting to, or <2 %, G2 with a Ki-67 index between 2 % and 20 % and poorly differentiated PanNET and pancreatic neuroendocrine carcinomas (PanNEC) G3 with a Ki-67 index higher than 20 %. The PanNET and PanNEC (small and large cell types), have different genetic aberrations [6]. Grading, primary localization, the hormone and peptide secretion as well as the metastatic spread correlates well with the clinical features and prognosis [5, 6].

For the performance of nuclear medicine procedure, it is necessary to insert/inject radionuclide in the body of the patient. Radionuclides, in their tendency to achieve stability, during disintegration emit electromagnetic radiation, which can be detected, localized, and quantitated from out of the body by sophisticated radiation detectors, either using gamma camera without or with computed tomography (SPECT, SPECT/CT) or, positron emission tomography with computed tomography (PET/CT). Radionuclides can be used alone, or, more often, they are chemically bound to a stable molecule or a compound, in the form of radiopharmaceutical which has avidity for the specific organ, system or the tissue. Thus, nuclear medicine methods, provide functional imaging by exploiting specific tumor cell properties and processes, and enabling whole-body imaging [7]. Apart of diagnosis, imaging, according to the increased accumulation of radiopharmaceuticals in a tumor, can provide data for selection of the patients for radionuclide therapies and prediction of the efficacy of such treatment.

One of the most frequent radiopharmaceuticals for PanNEN diagnosis is SRS, using somatostatin analogues (or, recently antagonists) labelled with indium-111 or technetium-99m (^{111}In or ^{99m}Tc), targeting somatostatin receptors on the cell surface using SPECT or SPECT/CT. An improvement has been made by PET/CT somatostatin receptor imaging with somatostatin analogues labelled with gallium-68 (^{68}Ga-SSA). The SRS as well as PET/CT with SSA can provide the basis for radionuclide treatment with yttrium-90 or lutetium-177 (^{90}Y or ^{177}Lu) labelled somatostatin analogues [8]. Thus, tumor imaging and follow-up can be specific for every PanNET patient [5, 9, 10].

Other radiopharmaceuticals can also be used for the detection of PanNEN such as rdiolabeled metaiodobenzylguanidine (^{123}I-MIBG or ^{131}I-MIBG) [11], fluorine-18-l-3,4-dihydroxyphenylalanine (^{18}F-DOPA), fluorodeoxyglucose (^{18}F- FDG), Carbon-11-5-hydroxitriptophane (^{11}C-5-HTP) as well as several cholecystokinin (CCK2) receptor-binding radiopeptides labelled with ^{99m}Tc, ^{111}In or ^{68}Ga.

The aim of our investigation was to assess SRS role in diagnosis and follow-up of PanNEN based on our results from the single center and the patients from Serbia.

MATERIAL AND METHODS

Among 97 patients with PanNEN, 21 were primary tumors while 76 were recurrences and metastases. There were 7 insulinomas, 2 gastrinomas while 88 had neuroendocrine pancreatic tumors. In total there were 12 G1, 76 G2 and 9 G3 tumors. Number and grades of pancreatic NET, investigated with SRS, are shown in tab. 1. All the patients gave the informed consent for the investigation and the study according to the decision of Ethical Committee of the Clinical Center of Serbia (668/6 from 19.04.2018). The study was approved by Ethical Committee of the Faculty of Medicine, University of Belgrade (1550/V-9 from 31.05.2019). All the radiation safety measures regarding patient doses, quality control of radio- pharmaceuticals and equipment as well as radiation monitoring have been conducted [12].

The SRS was performed for diagnosis and follow-up of the patients with PanNEN. Initially, laboratory diagnostics was performed following US, CT, MRI, as well as endoscopy. The SRS findings were confirmed by surgery, biopsy and clinical follow-up of 5 years. The histopathological diagnosis included

Table 1. Number and findings in different types of pancreatic NET investigated with SRS

NET	*n*	TP	TN	FP	FN
Insulinoma	7	3 G2	4 G2	0	0
Gastrinoma	2	1 G20	0	1 G2	0
Pancreatic NET	88	59 (5 G1, 45 G2, 9 G3)	20 (6 G1, 14 G2)	3 (1G1, 2G2)	6 G2
Total	97	63	24	4	6

immunohi-stochemical profile of the tumor in regard to chromogranin A (CgA), as well as the Ki-67 index.

Radiochemical purity of ^{99m}Tc-Tektrotyd performed using thin-layer chromatography in all the doses applied to the patients was minimum 90 %. Every dose administered to a patient was assayed in a properly functioning radioisotope dose calibrator, and is within 20 % of the prescribed dose. Dose calibrators were regularly tested for accuracy, constancy, linearity, and geometry. Gamma camera was regularly tested and set for energy level centered over photopeak, uniformity, resolution, linearity, SPECT Center of rotation, SPECT phantom and with preventive maintenance. Whole body scintigraphy was performed with ECAM gamma camera and computer (ESOFT), with high resolution collimator and one photopeak activity (140 keV 20 %), 2 and 24 hours after *i.v.* application of 370-740 MBq ^{99m}Tc-EDDA/HYNIC TOC (^{99m}Tc-Tektrotyd, Polatom), approximately 550 MBq for the patient weighing 70 kg. Afterwards, SPECT was performed using 360º orbit, 30 s/view, step and shoot). The data were stored in computer matrix 128 128 and reconstructed with filtered back-projections (Butterworth filter, cut-off 0.6 cycles/pixel, order 5) and iterative reconstruction. Before the study, the therapy with somatostatin analogs was withdrawn. The results were interpreted by one specialist of nuclear medicine and one resident, only by qualitative analysis, which implied visibly increased focal accumulation of radiopharmaceutical beyond the places of physiological accumulation.

The results were presented as mean standard error (SE). Diagnostic performance of SRS was determined by calculating sensitivity, specificity, positive and negative predictive values (PPV, NPV) and accuracy. Student T test was used to determine statistically significant difference between Ki-67 in true positive and true negative patients (TP, TN). Chi- quadrat test was used to estimate the difference in the increased/decreased CgA values between TP and TN patients.

RESULTS

There were 63 true positive (TP) figs. 1-3, 24 true negative (TN), 4 false positive (FP), and 6 false negative (FN) SRS results. Sensitivity of the method was 91.3 %, specificity was 85.7 %, positive predictive value was 94.0 %, negative predictive value was 80.0 % and accuracy 89.7 %. Detailed numbers and findings in different types of pancreatic NET investigated with SRS are shown in tabs. 1 and 2.

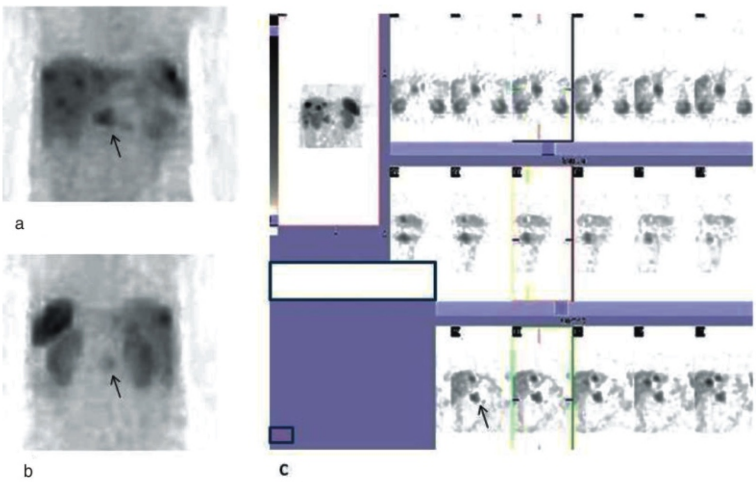

Figure 1. Somatostatin receptor scintigraphy with ^{99m}Tc-EDDA-HYNIC TOC: (a) anterior planar view (b) posterior planar view (c) SPECT. Focal accumulation of radiopharmaceutical in abdomen and in a few places in liver. Recurrence of PanNEN with liver metastases after surgery

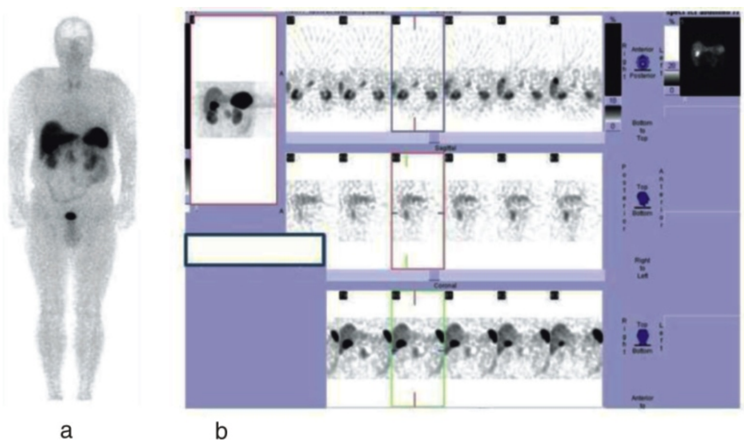

Figure 2. Somatostatin receptor scintigraphy with ^{99m}Tc-EDDA-HYNIC TOC: (a) anterior whole body scintigram (b) SPECT. Discreet diffuse and partly focal accumulation of radiopharmaceutical in abdomen. Fluid collection after surgery, false positive finding

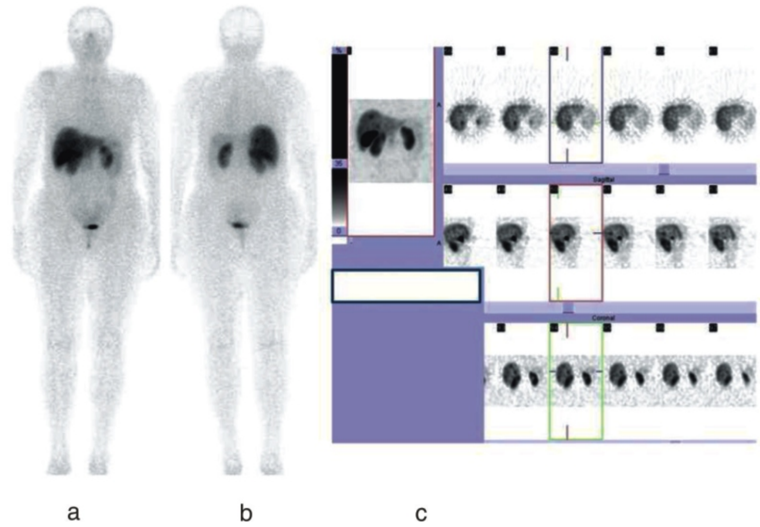

Figure 3. Somatostatin receptor scintigraphy with ^{99m}Tc-EDDA-HYNIC TOC: (a) anterior whole body scintigram (b) posterior whole body scintigram (c) SPECT. Focal accumulation of radiopharmaceutical in two places in liver. Liver metastases of PanNEN after surgery

Table 2. Statistical parameters of SRS in diagnosis and follow up of all the investigated neuroendocrine pancreatic tumors

Parameter	Value [%]	95 % Confidence interval CI
Sensitivity	91.3	82.03 % to 96.74 %
Specificity	85.7	67.33 % to 95.97 %
Positive predictive value	94.0	86.37 % to 97.51 %
Negative predictive value	80.0	64.72 % to 89.71 %
Accuracy	89.7	81.86 % to 94.94 %

The SPECT contributed diagnosis in 28 TP findings. In 32 patients (33 %) SRS significantly changed the management of the patients (in 10, surgery was repeated while in 17 somatostatin analogues and in 5 peptide receptor radionuclide therapy was introduced).

Mean Ki-67 value in TP patients was 13.8 5.0 %, while in TN patients it was 7.1 3.4, which is significantly lower at $p < 0.05$ (the t-value is 1.76829, the p-value is 0.04144). There was significantly ($p < 0.01$) higher number of increased CgA values in individual TP patients than in TN patients (the chi-square statistic is 11.1144, the p-value is 0.000857).

DISCUSSION

Our results (3TP and 4 TN) of SRS scintigraphy in insulinomas without FP and FN findings can be explained by very small group and very good choice of the patients. However, other authors recommend other radiopharmaceuticals for this indication. Thus, Medina-García *et al*. [13] suggested that benign insulinomas express mostly the glucagon-like peptide-1 receptor (GLP-1R) and low levels of somatostatin receptors, while malignant insulinomas over-express somatostatin receptors or GLP-1R in low levels. Thus they recommended a combined kit, containing radiolabeled GLP-1R (exendin) and somatostatin analogue. Sun *et al*. [14] confirmed the value of both ^{99m}Tc-HYNIC-TOC SPECT/CT and ^{68}Ga-Exendin-4 PET/CT, emphasizing the value of ^{68}Ga-Exendin-4 PET/CT. Antwi *et al*. [15] and Brom *et al*. [16] also emphasized the clinical value of PET/CT with ^{68}Ga labelled exendin.

In our study we had one TP and one FP SRS findings in patients with gastrinomas. One FP finding was due to postoperative local inflammation because of the recent surgery. In addition to the SRS, which proved to be half-useful as in our study, Gotthardt *et al*. [17] obtained in 54.5 % of patients with negative SRS, positive results of gastrin receptor scintigraphy and recommended it for selected patients as it may provide additional information in patients with equivocal or absent somatostatin uptake. With ^{68}Ga-DOTA-minigastrin PET the results were even better.

Our results in PanNEN point out very high sensitivity of 91.30 % and PPV 94.03 %, as well as very good specificity 85.71 % and accuracy 89.69 % while NPV is a bit lower 80.00 %, because of the fact that some PanNEN do not express somatostatin receptors, and are in accordance to our previous results [18, 19] obtained in NET in general. Rubenthaler *et al*. [20] obtained for primary tumor staging sensitivity of 80.0 % and a specificity of 88.4 % of PET/CT with SSA. In comparison to our findings, where change of patient management was obtained in 33 % of the cases, the application of PET/CT with SSA led to a change in patient management in 44 % of all cases. In favor of our findings, Briganti *et al*. [21], in evaluation of literature data concluded that in spite of a higher affinity and resolution of PET technology, Tektrotyd could be used in the daily practice of NEN, either pancreatic or not, at least in centers without a PET/CT or a ^{68}Ga generator. However, because of wider availability, a lower cost, and a longer decay, in comparison to peptides labeled with ^{68}Ga, SRS is more suitable for dosimetry calculations in the patients predicted for peptide receptor radionuclide therapy. Al-Chalabi *et al*. [22], emphasized the role of SPECT/CT especially in eliminated places of physiological activity, thus decreasing FP and FN results. Hasegawa *et al*. [23] found in NET (including pancreas) that SRS showed positive findings in 3 (100 %) of grade 1 (G1) and in 12 (92.3 %) of grade 2 (G2) lesions with high concordance rate with SSTR2 expression (93.8 % in the whole body and 92.9 % in the liver). Etchebehere *et al*. [24] obtained a significant difference in detectability of PanNEN between ^{68}Ga-SSA, SRS SPECT/CT, and diffusion-weighted whole body MRI (respectively, sensitivities of 0.96, 0.60, and 0.72; specificities of 0.97, 0.99, and 1.00; PPV of 0.94, 0.96, and 1.00; NPV values of 0.98, 0.83, and 0.88; and accuracies of 0.97, 0.86, and 0.91). Similar results were obtained by Dromain *et al*., [25] who concluded that PET/CT using ^{68}Ga-SSA is superior to SRS SPECT/CT, showing higher sensitivities for GEP-NET lesion detection (more than 90 %), particularly due to a better special resolution or better receptor affinities, emphasizing its drawback that these techniques are not available in every center. Similar to our results, Ilhan *et al*. [26] proved that imaging results altered surgical management in 33 % patients with PanNEN. He also concluded that apart of this, somatostatin receptor imaging still provided additional information for surgery planning in more than 95 % of the cases. Virgolini *et al*. [27] concluded that ^{68}Ga- SSA PET/CT has significant implications for the management of NET patients in about one-third of patients. However, she emphasized possibility of FP findings because of its accumulation in the head of pancreas. Similar observation, but with ^{99m}Tc-HYNIC-TOC in 19.4 % of the patients was observed by Yamaga *et al*. [28] although our results do not confirm that.

For this purpose, other radiopharmaceuticals can also be used. High ^{18}F-FDG uptake is usually associated with more aggressive tumors and a less favorable prognosis. The value of this imaging modality in most grades 1 and 2 GEP-NET is limited, because of their slow growth and consequently low glucose utilization [5, 29]. However, in grade 3 NEC, it might have additional value, especially in those cases where SRS is negative [30]. Sunden *et al.* [29] suggested that ^{11}C-5-HTP PET showed the highest sensitivity (96 %) for the detection of PanNEN as compared with CT, SRS and ^{18}F-DOPA PET. However, it is not widely available because of the short half-life and a complex synthesis. Scintigraphy with radiopharmaceuticals based on catecholamine metabolism like ^{123}I-MIBG (or ^{131}I-MIBG) has lower sensitivity for the imaging of PanNEN (<10 %), but have potential application in the choice of the radionuclide therapy with ^{131}I-MIBG [31]. Similarly, ^{18}F-DOPA PET did not show high sensitivity for the detection of PanNEN, but can have an important role in the diagnosis of congenital hyperinsulinism [32]. However, estimated effective dose per scan in all other radiopharmaceuticals was higher. Thus, it was the highest for ^{18}F-FDG (7.0 mSv), lower for ^{68}Ga-DOTATATE (4.8 mSv), ^{68}Ga-DOTATOC (4.3 mSv), ^{68}Ga-DOTANOC (3.1 mSv) and ^{111}In-DTPA-octreotide (5.9 mSv) [33], while it was the lowest for ^{99m}Tc – HYNIC TOC (3.8 mSv) [34].

In our study, mean Ki-67 value in TP patients was 13.8 % 5.0 %, while in TN patients it was 7.1 % 3.4%, which is significantly lower at $p < 0.05$, pointing out that tumors with higher Ki-67 are more often prone to recurrences and metastases than those with lower Ki-67. It is in accordance with the results of Mihalache *et al*. [35] who proved the value of SRS in locating the tumor, but he emphasized that tumor grading based on the mitotic count and Ki-67 index must be established for every case. According to Fujimori *et al*. [36], Ki-67 index of >10 % is one of the significant unfavorable predictors for survival of these patients.

Our study showed significantly ($p < 0.01$) higher number of increased CgA values in individual TP patients than in TN patients, but some other authors [37] found in GEP NET patients only a weak association between a change in plasma CgA and changes in tumor burden, concluding that CgA as a single biomarker was inadequate to predict tumor progression. However, some other authors [38] confirmed our findings concluding that in 112 patients with PanNEN, CgA values correlated well with TP findings on ^{68}Ga-SSA PET/CT. Rossi *et al*. [39] concluded that CgA seems to have predictive value six months prior to radiological progression for PanNEN.

Finally, some recent recommendations [7] for detection of PanNEN are as follows: for well-differentiated (G1, G2) clinically non-functioning NET of the pancreas, SRS and HTP PET can be used, in patients with insulinoma HTP PET, GLP1R imaging and SRS, while with those with gastrinomas and other functioning pancreatic tumors SRS and HTP PET are recommended. In patients with poorly differentiated (G3) GEP-NEC, ^{18}F- FDG PET is recommended.

CONCLUSION

Our results confirmed good correlation between SRS results and Ki-67 and CgA values. Also, SRS proved to be valuable method in the diagnosis, follow-up and assessment of the choice of therapy in the patients with PanNEN, especially if recurrences or metastases are suspected.

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AUTHORS' CONTRIBUTIONS

V. M. Artiko, D. P. Šobić Šaranović and Dj. P. Macut conceptualized the research, designed and prepared the research plan, supervised the research, text writing and revised the manuscript. Additionally, V. M. Artiko interpreted the findings. T. V. Isailović selected patients and provided clinical advice.

J. M. Šaponjski collected data, selected patients, performed radionuclide studies in the patients, interpreted findings, analyzed the data and, wrote the paper.

D. D. Jovanović and N. M. Bogosavljević prepared data for analysis, analyzed the data and made statistical analysis.

All the authors have contributed to article preparation.

REFERENCES

[1] Goodman, P. C., The New Light: Discovery and Introduction of the X-Ray, *American Journal of Roentgenology, 165* (1995), pp. 1041-1045

[2] Donya, M., *et al*., Radiation in Medicine: Origins, Risks and Aspirations, *Global Cardiology Science and Practice, 57* (2014):57 http://dx.doi.org/10.5339/ gcsp.2014.57

[3] Zamir, M. A., *et al*., Imaging of Pancreatic-Neuroendocrine Tumours: An Outline of Conventional Radiological Techniques, *Curr Radiopharm, 12* (2019), 2, pp. 135-155

[4] Bhate, K., *et al*., Functional Assessment in the Multimodality Imaging of Pancreatic Neuro-Endocrine Tumours, *Minerva Endocrinol, 35* (2010), 1, pp. 17-25

[5] De Herder, W., GEP-NETs Update: Functional Localisation and Scintigraphy in Neuroendocrine Tumours of the Gastrointestinal Tract and Pancreas (GEP-NET), *Eur J Endocrinol, 170* (2014), 2, pp. 173-183

[6] Hofland., J., *et al*., Advances in the Diagnosis and Management of Well-Differentiated Neuroendocrine Neoplasms, *Endocr Rev, 41* (2020), 2, pp. 371-403

[7] Signore, A., Artiko, V., Hybrid Fusion Images in Diagnostic and Therapeutic Procedures, *Q J Nucl Med Mol Imaging, 62* (2018), 1, pp. 1-2

[8] Jeremić, M., *et al*., Calculation of Absorbed Dose Die to the ^{90}Y-DOTATOC Peptide Receptor Radionuclide Therapy by MCNP5/X, *Nucl Technol Radiat, 33* (2018), 4, pp. 325-417

[9] Todorović-Tirnanić, M., *et al*., Contemporary Nuclear Medicine Diagnostics of Neuroendocrine Tumors, *Serbian Archives of Medicine (Srpski arhiv za celokupno lekarstvo), 143* (2015), 2, pp. 108-115

[10] Šobić-Saranović, D. P., *et al*., The Utility of Two Somatostatin Analog Radiopharmaceuticals in Assessment of Radiologically Indeterminate Pulmonary Lesions, *Clin Nucl Med, 37* (2012), 2, pp. 14-20

[11] Radović, B., *et al*., Evaluation of the SIOPEN Semi-Quantitative Scoring System in Planar Simpatico-Adrenal MIBG Scintigraphy in Children with Neuroblastoma, *Neoplasma, 62* (2015), 3, pp. 449-455

[12] Surić Mihić, M., *et al*., Hand Monitoring in Nuclear Medicine Departments in Croatia – First Results, *Nucl Technol Radiat, 35* (2020), 1, pp. 82-86

[13] Medina-García, V., *et al*., A Freeze-Dried Kit Formulation for the Preparation of Lys(27) (^{99m}Tc-EDDA/HYNIC)-Exendin(9-39)/^{99m}Tc-EDDA/HYNIC-Tyr3-O ctreotide to Detect Benign and Malignant Insulinomas, *Nucl Med Biol, 42* (2015), 12, pp. 911-9166

[14] Sun, M., *et al*., Ectopic Insulinoma: Case Report, *BMC Surg, 19* (2019), 1, p. 197

[15] Antwi, K., *et al*., Volume Replacement Fluid Demarks Benign Insulinoma With 68Ga-DOTA-Exendin-4 PET/CT, *Clin Nucl Med, 44* (2019), 5, pp. e347-e348

[16] Brom, M., *et al*., ^{68}Ga-Labelled Exendin-3, a New Agent for the Detection of Insulinomas with PET, *Eur J Nucl Med Mol Imaging, 37* (2010), 7, pp. 1345-1355

[17] Gotthardt, M., *et al*., Added Value of Gastrin Receptor Scintigraphy in Comparison to Somatostatin Receptor Scintigraphy in Patients with Carcinoids and Other Neuroendocrine Tumours, *Endocr Relat Cancer, 13* (2006), 4, pp. 1203-1211

[18] Artiko, V., *et al*., Evaluation of Neuroendocrine Tumors with ^{99m}Tc-EDDA/HYNIC TOC, *Nucl Med Rev Cent East Eur, 19* (2016), 2, pp. 99-103

[19] Artiko, V., *et al*., The Clinical Value of Scintigraphy of Neuroendocrine Tumors Using (^{99m})Tc-HYNIC-TOC, *J BUON, 17* (2012), 3, pp. 537-542

[20] Rubenthaler, J., *et al*., Neuroendocrine Tumors of the Stomach, Duodenum and Pancreas: Value of (Hybrid) Radiological Diagnostics, *Radiologe, 59* (2019), 11, pp. 961-967

[21] Briganti, V., *et al*., Gamma Emitters in Pancreatic Endocrine Tumors Imaging in the PET Era: Is there a Clinical Space for ^{99m}Tc-peptides?, *Curr Radiopharm, 12* (2019), 2, pp. 156-170

[22] Al-Chalabi, H., *et al*., Feasibility of a Streamlined Imaging Protocol in Technetium-99m-Tektrotyd Somatostatin Receptor SPECT/CT, *Clin Radiol, 73* (2018), 6, pp. 527-534

[23] Hasegawa, S., *et al*., Clinical Usefulness of Somatostatin Receptor Scintigraphy in Japanese Patients with Gastroenteropancreatic Neuroendocrine Tumors, *Digestion, 96* (2017), 1, pp. 13-20

[24] Etchebehere, E. C., *et al*., ^{68}Ga-DOTATATE PET/CT, ^{99m}Tc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial, *J Nucl Med, 55* (2014), 10, pp. 1598-1604

[25] Dromain, C., *et al*., Imaging of Neuroendocrine Tumors of the Pancreas, *Diagn Interv Imaging, 97* (2016), 12, pp. 1241-1257

[26] Ilhan, H., *et al*., Impact of (68)Ga-DOTATATE PET/CT on the Surgical Management of Primary Neuroendocrine Tumors of the Pancreas or Ileum, *Ann Surg Oncol, 22* (2015), 1, pp. 164-171

[27] Virgolini, I., *et al*., Location of a VIPoma by Iodine-123-Vasoactive Intestinal Peptide Scintigraphy, *J Nucl Med, 39* (1998), 9, pp. 1575-1579

[28] Yamaga, L. Y., *et al*., ^{99m}Tc-HYNIC-TOC Increased Uptake Can Mimic Malignancy in the Pancreas Uncinate Process at Somatostatin Receptor SPECT/CT, *Radiol Med, 121* (2016), 3, pp. 225-228

[29] Sundin, A., Radiological and Nuclear Medicine Imaging of Gastroenteropancreatic Neuroendocrine Tumours, *Best Pract Res Clin Gastroenterol, 26* (2012), 6, pp. 803-818

[30] Severi, S., *et al*., Role of 18FDG PET/CT in Patients Treated with ^{177}Lu-DOTATATE for Advanced Differentiated Neuroendocrine Tumours, *Eur J Nucl Med Mol Imaging, 40* (2013), 6, pp. 881-888

[31] Buscombe, J. R., *et al*., Long-Term Efficacy of Low Activity Meta-(^{131}I)Iodobenzylguanidine Therapy in Patients with Disseminated Neuroendocrine Tumours Depends on Initial Response, *Nucl Med Commun, 26* (2005), 11, pp. 969-976

[32] Zani, A., *et al*., The Predictive Value of Preoperative Fluorine-18-L-3,4-Dihydroxyphenylalanine Positron

Emission Tomography-Computed Tomography Scans in Children with Congenital Hyperinsulinism of Infancy, *J Pediatr Surg, 46* (2011), 1, pp. 204-208

[33] Walker, R. C., *et al*., Measured Human Dosimetry of 68Ga-DOTATATE, *J Nucl Med, 54* (2013), 6, pp. 855-860

[34] Grimes, J., *et al*., Patient-Specific Radiation Dosimetry of ^{99m}Tc-HYNIC-Tyr3-Octreotide in Neuroendocrine Tumours, *J Nucl Med, 52* (2011), 9, pp. 1474-1481

[35] Mihalache, O., *et al*., Pancreatic Neuroendocrine Tumors – Case Series and Literature Review, *Chirurgia (Bucur), 114* (2019), 5, pp. 630-638

[36] Fujimori, N., *et al*., Natural History and Clinical Outcomes of Pancreatic Neuroendocrine Neoplasms Based on the WHO 2017 Classification; A Single-Center Experience of 30 Years, *Pancreatology, 20* (2020), 4, pp. 709-715

[37] Dam, G., *et al*., Prospective Study of Chromogranin A as a Predictor of Progression in Patients with Pancreatic, Small-Intestinal, and Unknown Primary Neuroendocrine Tumors, *Neuroendocrinol, 110* (2020), 2, 217-224

[38] Tirosh, A., *et al*., Association Between Neuroendocrine Tumors Biomarkers and Primary Tumor Site and Disease Type Based on Total ^{68}Ga-DOTATATE-Avid Tumor Volume Measurements, *Eur J Endocrinol, 176* (2017), 5, pp. 575-582

[39] Rossi, R. E., *et al*., Chromogranin A as a Predictor of Radiological Disease Progression in Neuroendocrine Tumours, *Ann Transl Med, 9* (2015), 3, p. 118

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УЛОГА СЦИНТИГРАФИЈЕ СОМАТОСТАТИНСКИХ РЕЦЕПТОРА У ДИЈАГНОСТИЦИ И ПРАЋЕЊУ НЕУРОЕНДОКРИНИХ НЕОПЛАЗМИ ПАНКРЕАСА

Циљ испитивања био је процена улоге сцинтиграфије соматостатинских рецептора у дијагнози и праћењу неуроендокриних неоплазми панкреаса. Сцинтиграфија соматостатинских рецептора рађена је помоћу 740 MBq ^{99m}Tc-EDDA/HYNIC TOC ради дијагностике и праћења неуроендокриних неоплазми панкреаса. Тачно позитивних резултата је било 63, тачно негативних 24, лажно позитивних 4 и лажно негативних 6. Сензитивност је била 91.3 %, специфичност 85.7 %, позитивна предиктивна вредност 94.0 %, негативна предиктивна вредност 80.0 %, а тачност 89.7 %. SPECT је допринео дијагнози у 28 тачно позитивних налаза. У 32 пацијента (33 %) резултати сцинтиграфије соматостатинских рецептора значајно су променили лечење пацијената (у 10 је поновљена хирушка интервенција, у 17 примењени аналози соматостатина, а у 5 индикована радионуклидна терапија пептидима). Средња вредност индекса Ki-67 у тачно позитивних пацијената била је 13.8 5.0 % док је у тачно негативних била 7.0 3.4 %, што је значајно ниже, $p < 0.05$. Био је значајно већи број ($p < 0.01$) повишених вредности хромогранина А у пацијената са тачно позитивним у односу на оне са тачно негативним вредностима ($p = 0.000857$). Наши резултати потврђују вредност сцинтиграфије соматостатинских рецептора у дијагностици и праћењу пацијената са неуроендокриним неоплазмама панкреаса уколико постоји сумња на присуство примарних тумора, рецидива или метастаза, као и у избору одговарајуће терапије.

Кључне речи: сцинтиграфија соматостатинских рецептора, неуроендокрини тумор, панкреас, праћење, нуклеарна медицина, радионуклиди