The role of positron emission tomography (PET) in diagnostics of gastroenteropancreatic neuroendocrine tumours (GEP NET)

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Abstract

PET is a successful modality to detect cancer and in recent years has demonstrated a great diagnostic value in large series of tumour types. PET combines high sensitivity and reasonable resolution, and offers the ability to perform whole body scans. ^{18}F-deoxyglucose (FDG)-PET has also been used to diagnose tumours of neuroendocrine origin. Even if ^{18}F-FDG has been successfully and widely employed in oncology, it has not demonstrated a significant uptake in well differentiated neuroendocrine tissues. Thus ^{18}F-FDG is not a good tracer for neuroendocrine tumours, as FDG-PET imaging of number of GEP tumours revealed increased glucose metabolism only in less differentiated GEP tumours with high proliferative activity and in metastatising MTC associated with rapidly increasing CEA levels. In such a situation, additional ^{18}F-FDG PET should be performed only if somatostatin receptor scintigraphy (alone or with ^{99m}Tc-DMSA) is negative. On the contrary, other positron emitter tracers seem to be more promising. ^{68}Ga-DOTA-NOC (tetraazycyclododecanetetraacetic acid-[1--Nal^3]-octreotide) has been used as a positron emitter tracer for the detection of NETs in preliminary studies. A serotonin precursor 5-hydroxytryptophan (5-HTP) labelled with ^{11}C has shown an increased uptake in carcinoids. This uptake seems to be selective and some clinical evidence has demonstrated that it allows the detection of more lesions with PET than with CT or octreotide scintigraphy. Another radiopharmaceutical in the development for PET is ^{11}C-L-DOPA, which seems to be useful in imaging endocrine pancreatic tumours.

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Neuroendocrine gastroenteropancreatic tumours belong to the so called APUD-cell system (amine precursor uptake and decarboxylation) and are consequently capable of producing and processing amines and bioactive peptides [1,2]. Clinical symptoms can be reduced by the use of somatostatin analogs and in vitro the combination of octreotide and dexamethasone has shown additive effects in reducing serotonin release from midgut tumours cells [3]. Malignant neuroendocrine tumours (NETs) constitute a rare and heterogeneous group of tumours including the neuroendocrine adrenal, as well as endocrine islets within glandular tissue (thyroid or pancreatic) and cells dispersed between exocrine cells, such as endocrine cells of the digestive and respiratory tracts, known as carcinoid tumours [4]. They have traditionally been classified further according to the anatomical site of origin: foregut, midgut and hindgut [5]. Whithin these subgroups the biological and clinical characteristics of them vary considerably [6]. NETs can either be sporadic or occur as part of familiar syndromes, mainly Multiple Endocrine Neoplasia (MEN) I and II, von Hippel Lindau (VHL) syndrome and neurofibromatosis (NF)-I, and have multipotent secretory capacities producing distinct clinical syndromes [7-9].

In Poland the availability of PET-CT diagnostic is low. There are only a few PET study centers, e.g. in Bydgoszcz. Positron emission tomography (PET) imaging is based on the individual characteristics of cancer tissue (proliferative activity, viability, other biological parameters). PET is a successful modality to detect cancer and in recent years, it has demonstrated a great diagnostic value in large series of tumour types [10]. PET combines high sensitivity and reasonable resolution, and offers the ability to perform whole body scans. Positron emission tomography (PET) supplies a range of labeled compounds to be used for the characterization of tumour biochemistry. In PET, to diagnose neuroendocrine tumours, radiopharmaceutics like fluorine-18--fluorodeoxyglucose (^{18}F-FDG), ^{11}C-harmine, nuclear antigen Ki-67, tetraazycyclododecanetetraacetic acid-[1-Nal^3]-octreotide

(^{68}Ga-DOTA-NOC), ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP), ^{11}C-L-DOPA are usually used. The PET-technique provides visualization, but also the assessment of tumour biological characteristics such as substrate transport, metabolism, receptor expression and enzyme activity [3].

The metabolism of tumour cells is characterized predominantly by enhanced glycolysis [11]. The first routinely used PET tracer in oncology, ^{18}F-labeled deoxyglucose (FDG), was successfully used for diagnosis of cancer, reflecting increased expression of glucose transporter in cancerous tissue. Cancer cells demonstrate increased glucose metabolism, due in part to an increased number of glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, among others, both of which promote glycolysis [12]. Fast FDG uptake in physiologic glucose utilization reduces serum insuline levels to near basal levels, and thus diminishes FDG uptake in such organs as heart. This tracer, however, usually does not show sufficient uptake in well-differentiated tumours such as neuroendocrine tumours. Fluorine-^{18}F-deoxyglucose (^{18}F-FDG), a glucose analogue, is a marker of tumour viability, based upon the increased glycolysis that is associated with malignancy in comparison with most normal tissue [13]. ^{18}F-FDG is not a good tracer for neuroendocrine tumours, as FDG-PET imaging of a number of GEP tumours revealed that increased glucose metabolism can only be seen in less differented GEP tumours without somatostatin receptors and with high proliferative activity and in metastasing medullary thyroid cancer associated with rapidly increasing CEA levels [14].

^{18}F-deoxyglucose (FDG)-PET has also been used to diagnose tumours of neuroendocrine origin. Therefore, this examination provides opposite information to that from ^{111}In-pentetreotide or $^{123/131}$I-MIBG, which is related to the tissue differentiation. The most clinically aggressive neuroendocrine tumours have shown an intense uptake of FDG. The sensitivity of FDG-PET in these malignancies with a poor prognosis seems to be higher than in SST receptor scintigraphy. To detect some metastatic lesions, that are not revealed by other conventional modality techniques, ^{18}F-FDG diagnostics staged and monitored medullary thyroid carcinomas, phaeochromocytomas and paraganglioma [15-18]. Using [^{111}In-DTPA-D-Phe]-pentetreotide for in vivo somatostatin receptors imaging, no malignant lesions could be visualized. Primary tumours and all metastases showed an increased FDG uptake, suggesting high glucose tumour metabolism. The use of ^{11}C-harmine-PET enables diagnostic visualization of the tumour cells, mainly in subpopulations of neuroendocrine GEP-tumours such as non-functioning endocrine pancreatic tumours (EPT), small tumour lesions and somatostatin receptor negative tumours [19]. The number of specific neuroendocrine markers and hormones expressed by these tumours, or the amount of biologically active neurohormones secreted, is not prognostically indicative of malignant behaviour. Ki-67 is a nuclear antigen expressed in proliferating cells (G1, S, G2 and M phases) but not in resting cells (G0 phase). Well-differentiated gastroenteropancreatic tumours demonstrated inverse relationships between cell proliferation (GEP tumour tissue low profilerative activity – low Ki-67 expression), in vivo in somatostatin receptors expression and FDG uptake (normal biodistribution). High levels of Ki-67 immunoreactivity were observed in all primary tumours and metastases of less well-differentiated GEP tumours (no in vivo somatostatin receptor expression), in a direct proportion to the increased FDG uptake [11].

^{11}In-DTPA-octreotide (Octreoscan) is the diagnostic agent classically used in preliminary phase to assess the biodistribution of the therapeutic compound, based on binding to the SST_2 receptor subtype. For PET studies, ^{68}Ga-DOTA-TOC has been used as a positron emitter tracer. ^{68}Ga-DOTA-NOC (tetraazycyclododecanetetraacetic acid-[1-Nal^3]-octreotide) has been synthesised by Wild and co-workers. This compound for PET imaging has high affinity for SST_2 and SST_5 and has been used for the detection of NETs in preliminary studies. As ^{68}Ga-DOTA-NOC binds to NETs via a receptor mechanism, the sensitivity of this compound could be lower than of ^{18}F-DOPA, which accumulates via a metabolic mechanism, in some histological types expressing a low number of somatostatin receptors. The overall sensitivity and specificity of ^{68}Ga-DOTA-NOC as compared to those of ^{18}F-DOPA have still to be assessed, but it may be realistic to predict a complementary role for the two tracers, as they explore different features of NETs [20].

On the contrary, other positron emitter tracers seem to be more promising. New radiopharmaceuticals base on different precursors, namely 5-hydroxytryptophan (5-HTP) and L-DOPA labelled with ^{11}C [21,22]. A serotonin precursor 5-hydroxytryptophan (5-HTP) labeled with ^{11}C has proved successful with neuroendocrine GEP tumours: increased uptake in carcinoids and demonstrated increased uptake and irreversible trapping of this tracer in carcinoid tumours, the tracer was shown both in primary tumours and in metastases [10,22]. The uptake was so selective and the resolution was so high that one could detect more liver and lymph node metastases with PET than with CT or octreotide scintigraphy. Another radiopharmaceutical in the development for PET is ^{11}C-L-DOPA, which seems to be useful in imaging of endocrine pancreatic tumours [10]. ^{11}C-L-DOPA was applied as a tracer for dopamine synthesis, and it was successfully used to detect both functioning and non-functioning endocrine pancreatic tumours [22]. PET can detect small lesions in the thorax and the abdomen not detected by other methods. It detects more lesions in the liver and lymph nodes than other methods and furthermore, it can be used to monitor treatment effects.

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