Diagnostic imaging approach to gastro-entero-pancreatic carcinomas of neuroendocrine origin – single net center experience in Poland

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Abstract

AIM: The aim of the study was to review the current diagnostic approach, based on the experience of one center performed during a 4-year period, according to WHO criteria of GEP – NET. **MATERIAL AND METHODS**: The study group comprised case records of 134 patients with confirmed GEP-NET carcinomas (WHO groups 2–4). All patients were subjected to clinical, biochemical and imaging examinations performed as routine clinical work-up. The imaging techniques consisted of anatomical (CT, EUS) and functional approaches (SRS, mIBG and FDG PET). **RESULTS**: The clinical classification considered the primary origin of the tumor as follows: 49% – foregut tumors, 44% – midgut, and 7% of tumors of unknown origin. Group of patients with WHO 2 consisted of 98 (73%) subjects. Considering those with foregut tumors EUS followed by CT and SRS were used in each case. SRS and CT imaging was used to assess the extent of the tumor. Patients with midgut tumors had CT and SRS as routine diagnostic imaging examinations. Considering the above-mentioned patients, CT and SRS were used to localize the primary tumor, and assess tumor extent. Overall sensitivity of CT considering the active disease amounted to 96%, while specificity – 75%. Sensitivity of SRS was 97%, while

specificity– 85%.

WHO 3–29 patients, 17 foregut and 9 midgut tumors, and 3 of unknown origin. Diagnostic imaging examinations consisted of CT. Standard SRS (sst2) was negative in most cases. The aggressive behaviour of this type of tumors was detected by means of FDG-PET. Sensitivity of CT amounted to 100%, and that of SRS – 44%. Specificity of CT amounted to 67% and that of SRS – 100%.

WHO 4–7 patients, including 4 foregut and 3 midgut neoplasms. The imaging approach consisted of CT/MR and in 5 cases FDG-PET. Sensitivity of CT amounted to 100%. Only one patient presented with a SRS positive study. FDG-PET sensitivity amounted to 100%.

CONCLUSION: Diagnostic imaging of GEP-NET, consider anatomical and functional techniques, which should be read together. The diagnostic value of CT and SRS were similar in case of WHO 2, while in case of WHO 3 CT had a higher diagnostic accuracy. FDG-PET seems to be a very attractive imaging functional modality in case of patients with WHO 3 and WHO 4.

INTRODUCTION

Neuroendocrine tumors are derived from the diffuse endocrine system and can be found anywhere in the body. This group of tumors is relatively rare, and there is need for robust strategy to establish correct diagnosis and initiate rationale treatment regimens [1–3].

These tumors are usually slow growing, but most of them present with great metastatic potential. If cancer is under control, even in the advanced stages, patients have relatively good prognosis [1–5]. The minority of patients had tumors with very rapid growth and aggressive behaviour, like ordinary metastatic carcinomas. Patients with those tumors had very poor prognosis, despite aggressive chemotherapy, usually surviving less then 12 months [6,7].

Currently, there has to be concerted effort to elaborate the diagnostic and therapeutic algorithm of these tumors. It should be based on the cooperation of many specialists, such as endocrinologists, gastroenterologists, surgeons, oncologists, radiologists, pathologists and nuclear medicine physicians. All should use new technologies and new treatment modalities, in order to quickly establish correct diagnosis and rationale effective treatment [1–3,6,7].

The present WHO classification of endocrine tumors includes neoplasms originating from endocrine glands, such as adrenal pheochromocytomas, pituitary adenomas, nerve elements like paragangliomas, ganglioneuromas and neuroblastomas or from elements of the diffuse endocrine system, such as gastroenteropancreatic endocrine tumors (GEP-NET) [8,9]. Considering pure endocrine tumors (GEP-NET), an uniform scheme of classification is applied for all anatomical sites, identifying 4 categories: (1) well-differentiated endocrine tumors, with benign (1a) or uncertain behaviour (1b) at the time of diagnosis; (2) well-differentiated endocrine carcinomas with low-grade malignant behaviour, (3) poorly differentiated endocrine carcinomas, with high-grade malignant behaviour (4), and mixed neuroendocrine and adenocarcinoma, usually with highly-aggressive malignant behaviour [8,9,10].

From the clinical point of view all GEP-NETs are divided into secretory or non-secretory tumors. The first group is hormonally active and often with the clinical presentation of symptoms and signs suggesting overproduction of agents like bioactive amines, peptides or hormones [2–7]. Those hormonal active tumors are often recognized much easier, due to their specific clinical presentation, in comparison to clinically silent tumors [3–6,7].

Analysis of the biochemistry profile (5HIAA in patients with midgut tumors), another serum hormone, including gut peptides (insulin, gastrin etc. in patients with pancreatic NET tumors) and most important chromogranin A (CgA) measurements are helpful to establish proper diagnosis [2,3,6,7,11,12]. CgA seems to be a good general marker of tumor activity and cancer spread within the body and is detected generally in most of GEP-NET cases [1–7].

The great advantage considering management of GEP-NET is connected with the development of new imaging technologies. Imaging techniques, both functional and anatomical are currently used as routine diagnostic approach in case of patients with GEP-NETs when detecting the primary tumor, and assessing secondary lesions, as well [13–17]. During each case of staging tomographic imaging (both anatomical and functional) techniques should be used. This includes multislice CT or MRI together with somatostatin receptor scintigraphy (SRS), and in some cases mIBG studies [1,2,6,7,10,13–17]. Currently, routine used multidetector computed tomography after contrast enhancement with slice thickness of 1mm provides high quality images in standard axial, coronal and sagittal projections. Additionally, in each case MIP (multi-image projection) and 3D volume rendering reconstruction could be used for better localization. In case of any doubt of the nature of the abdominal lesion seen on CT, or renal insufficiency, MR techniques should be used. Standard algorithm using breath-hold techniques with spin echo T1 and T2 weighted images, biochemical shift, T1 images after gadolinium enhancement could be useful to detect liver lesions [13,16].

The common feature for most NETs is the high density of somatostatin receptor expression (sst2). Some presented with other subtypes of sst receptors expression [1–7]. Considering the group of tumors with high malignancy there is usually lack of sst receptors expression [6,7,15]. Those tumors have poor prognosis and standard SRS is often negative [6,7,17]. Considering the above-mentioned patients with extensive cancer, anatomical CT or MRI are of great value. Currently, imaging techniques using tomographic data sets with final image fusion seem

to be of great value. Additionally, in all patients imaging techniques are very helpful, in order to assess response to treatment, mostly using CT or MRI [1,3,13–19].

The purpose of the study

The aim of this study was to review the experience of diagnostic imaging approaches in patients with neuroendocrine carcinomas of gastroenteropancreatic origin (GEP-NET), according to the recommendations of The European Neuroendocrine Tumor Society – ENETS.

MATERIAL AND METHODS:

Clinical data

The study group comprised 134 patients initially diagnosed and treated at the Ministry of Internal Affairs and Administration Hospital, Warsaw and patients sent from other clinical centers after initial diagnosis or suspicion of gastroenteropancreatic NET (GEP-NET) during the period between April, 2002 and April, 2006. Mean patient age amounted to 55.3 years (ranging between 19 and 89 years, SD - 13.5 y). The study group comprised 73 female patients.

All presented patients had an established histological diagnosis of GEP-NET carcinoma (WHO groups 2–4). The whole diagnostic approach and further therapy and clinical follow-up were performed by a team of specialists. ENETS guidelines were used in case of standard clinical work-up [6].

All patients were subjected to careful clinical evaluation including history of the disease and physical examination, in order to include or exclude carcinoid syndrome, ZES and other complex cancer syndromes. In every case a family history of neoplastic disease was collected. Management of MEN-1 patients and their families includes screening for endocrine parathyroid and gastroenteropancreatic tumors. Additionally, all patients were evaluated for the presence of secondary endocrine tumors, and possibly for other gut carcinomas.

Laboratory methods

All patients (with symptoms and signs of GEP-NET, and then confirmed histologically, also patients with known GEP-NET tumors, and those with recurrent disease) were subjected to chromogranin A (CgA) level determination using standard laboratory methods [11]. In selected cases (those with midgut tumors) additional measurement of 5-hydroxy indole acetic acid (5-HIAA) during 24 h urine collection, using standard methodology was also performed [1,3,6,11]. Others tests were performed including insulin and peptide C level, gastrin, parathyroid hormone (PTH), calcium, and kalcytonin dependent of clinical suggestion [6,7,11]. In case of NECHM (WHO group 3) and mixed tumors (WHO group 4) α-fetoprotein, carcinoembryonic antigen (CEA), α and β-human chorionic gonadotropin (α-HCG and β-HCG) were determined [11]. All biochemical

analyses were performed using standard commercially available kits, at the laboratory of the Central Clinical Hospital, Ministry of Internal Affairs and Administration, Warsaw.

Diagnostic Imaging

Diagnostic imaging techniques were used for the evaluation the site of origin of the primary tumor, and to detect local and regional involvement, as well as assess tumor extent, in order to detect distant metastases. Detection of the primary tumor, in most cases was based on the anatomical approach. The ultrasound (US) and endoscopic ultrasound (EUS) examinations were performed, considering the detection of foregut tumors localized within the stomach, duodenum and pancreas. Additionally, CT after contrast enhancement was used in case of foregut and midgut tumors. Only several patients, due to previous allergic reactions or poor renal function were subjected to MRI. In the minority of cases the functional approach – SRS – (somatostatin receptor scintigraphy) was used to detect the primary tumor, with the exception of patients with tumor of unknown origin (UNO), and those with clinical signs and symptoms, which were clinically obvious, considering the nature of the disease, such as carcinoid syndrome or ZES. All patients with confirmed GEP-NET had SRS, and in some patients [123]I mIBG (meta-idobenzyl-guanidine) was used. In order to assess the extent of the tumor all patients were subjected to both sets of anatomical and functional imaging approaches. In selected cases, considering patients with tumors confirmed as WHO group 3 and WHO group 4, FDG-PET was performed. In patients with recurrent disease, CT and SRS were used as standard imaging follow-up methods.

Ultrasound (US) and endoscopic ultrasound (EUS)

Standard abdominal ultrasound was performed as the routine, first-line abdominal examination, using standard equipment, (MyLab50, Esaote; I). Convex transducers 2.5–5.5 MHz were used during the abdominal examination. High resolution linear transducers using 6–13 MHz were used, in order to detect superficial lesions of the neck and abdomen, if possible (low attenuation of fat tissue). Color and power Doppler were routinely used, in order to detect the vascular supply of the tumor. In case of foregut tumors EUS was routinely performed using standard equipment (Nemio, Toshiba; J).

CT

CT was used in every case, before and after i.v. contrast enhancement, using multidetector spiral CT (Aquilion 16, Toshiba; J), in order to establish the initial diagnosis, staging and restaging. Every patient received approx. 100-140 ml (1.4 mg/kg) of low ionic contrast medium intravenously, at a rate of 2.7–3.2 ml/s. After injection of the contrast material, three spiral CT acquisitions were obtained during the hepatic arterial phase, the portal venous phase (expanded through the neck and chest and then abdomen and pelvis), and the equilibrium

phase (30, 60, and 240 s respectively), after the initiation of the injection. Scanning was performed at 120 kV and 250–300 mA. Contiguously reconstructed sections (pitch of 1:1). Each spiral CT acquisition through the body was accomplished during a breath-hold moment. A standard 512×512 matrix was used in each case. The slice thickness was 1mm, which was then used to produce reformatting images using the MIP technique and 3D reconstruction. A transverse coronal and sagittal projection were used in every case, considering image analysis. CT examination results were read by an expert with experience in GEP-NET tumors. CT images were interpreted using a dedicated work station (Vitrea, Toshiba), with total freedom for window and level adjustments, and for the magnification of each image at the time of the analysis.

MRI

In selected cases MRI imaging was performed using a 1.5 T whole-body scanner (Eclipse, Marconi Medical Systems; USA). All MRIs were acquired in the axial plane with a phased-array body multicoil. Slice thickness was 7 mm, with a 2 mm intersection gap for all pulse sequences. Fat-suppressed T2-weighted imaging was obtained by means of a respiratory-triggered fast spin-echo sequence. Additional images before contrast enhancement consisted of: T1 SE, T1 SE fat saturation (fat-sat). Further imaging sequence applied T1 GRE and T1 SE after contrast enhancement of Gd-DTPA, at a dose of 0.1mmol/kg. A 256×232 matrix and 256×256 matrix were used in every case. All images were presented as transverse and frontal sections, some as sagittal.

Somatostatin Receptor Scintigraphy (SRS)

The initial SRS study was performed using standard radiolabelled tracer ^{111}In (DTPA-D-Phen^1) OctreoScan™ (185–220 MBq) (Mallinckrodt–Tyco; NL). After direct comparison ^{111}In compound with ^{99m}Tc labelled ligands (data not shown), we routinely used ^{99m}Tc-[HYNIC,Tyr^3]-octreotide [^{99m}Tc TOC] (500–600 MBq), (Polatom; PL), which was approved by the local Ethics Committee of the Central Clinical Hospital of Internal Affairs and Administration, as the diagnostic imaging approach of NET. In case of NECHM or mix NET adeno-carcinoma after negative ^{99m}Tc TOC study we used in selected cases ^{99m}Tc depreotide (NeoSPECT, GE Healthcare; USA), in order to detect those patients with negative sst-2 tumors, and positive SST3 and SST5 tumors. The same imaging protocol was performed using both radiotracers.

The imaging technique mostly consists of the whole body scan and additional tomographic (SPECT – single photon emission computed tomography) abdominal and pelvic scans, but in case of chest deposits the upper part of the body with SPECT was performed using the dual head gamma camera with LEHR collimation (e-cam, Siemens, USA). Images were produced using iterative reconstruction in each case, (OSEM 3D, with 8 subsets and 16 iteration with standard Gaussian filter, commercial software). Routinely, we used 64 projections (128×128 matrix), 24 s per projection. Standard axial, sagittal and coronal planes were used during image analysis. All SRS images were analyzed from the computer screen (e-soft 4.5, Siemens, USA). Any focal or diffuse pathological accumulation observed during the examination was reported as pathology. In doubt of the localization of the pathological uptake we used image fusion with CT or MRI.

mIBG (meta-idobenxyl-guanidine)

Considering the group of midgut tumors, some (12 subjects- our initial experience) underwent the ^{123}I MIBG (AdreView, GE Healthcare; USA) study. After thyroid suppression using Lugol's solution, one day before the study, every patient received an injection of 220–240 MBq of ^{123}I mIBG. Whole body (WB) scan and SPECT study of the abdomen, and in selected cases the chest were acquired after 24h using the dual head gamma camera with LEHR collimation. Images were produced using iterative reconstruction in each case, (OSEM 3D, with 8 subsets and 8 iteration with standard Gaussian filter, commercial software). Routinely, we used 64 projections (128×128 matrix), 24 s per projection. Any focal or diffuse pathological accumulation observed during the examination was reported as pathological.

PET/CT

Some patients with WHO group 3 and 4 carcinomas, and several with WHO group 2 of unknown origin with widespread metastatic disease, were subjected to FDG PET examinations. All examined patients were fasting for at least 6h prior to the PET/CT examination, and then received 370–450 MBq [^{18}F]FDG intravenously followed by a 60-min rest period. In every case acquisition was initiated from the base of the skull to below the groin using a dedicated PET/CT scanner (Biograph LSO PET/CT, Siemens). FDG was produced using a cyclotron (RDS CTI 11 MeV), and the synthesis Fx system (Tracer Lab). No intravenous contrast material was injected for PET/CT scanning. Standard transaxial, coronal, and sagittal sections were interpreted by nuclear medicine physicians.

The SUVmax (standard uptake value) of the tumor for each pixel was automatically calculated by the tomograph software using a region of interest surrounding the tumor. Tumor SUVmax was recorded with the understanding that in these heterogeneous tumors, the highest SUVmax reflected the most metabolically active area of the tumor. The most metabolically active areas are thought to reflect tumor regions with most aggressive tumors. All sites with high activity >2.5 using SUVmax) were representative of the active form of the disease.

Imaging Analysis

Radiologists and nuclear physicians were aware of the clinical stage and examined patients, as to evaluate the presence and extent of cancer. A patient was considered positive for the presence of the disease if there was at least

one single metastatic lesion within the liver or if there was any other pathological lesion anywhere in the body, with suggestion of the active form of the disease during diagnosis. If discordant results were achieved, imaging techniques were correlated with clinical and biochemical data, and final clinical follow-up was performed after at least 6 months.

Histopathological methods

The biopsy samples or surgical specimen material were fixed in 10% buffered formalin and embedded in paraffin. Slides were stained by means of haematoxylin & eosin methods. The immunohistochemical method was used for analysis expression of synaptophysin, chromogranin and Ki67 index – MIB1 antibody (Dako; DK). The histopathological diagnosis was established, according to WHO criteria described elsewhere [8,9].

Statistics

The sensitivity and specificity of CT and SRS in the detection of the active disease were evaluated for each group, considering the WHO classification. The above-mentioned included the detection of the primary lesion and/or extent of the disease. This analysis was performed using the standard formula. Other data were presented as mean values, median in case of follow-up. Comparison between groups was presented as a percentage. The correlation between imaging results and the CgA level was performed for each group of patients with NECLM, NECHM and mixed carcinomas using Kendall tau test. $p < 0.05$ was considered as statistically significant.

RESULTS

All patients were evaluated on the basis of clinical symptoms and signs of neuroendocrine secretory and non-secretory tumors. The primary origin of the tumor, including the foregut, midgut and hindgut was based on the WHO classification of diffuse endocrine tumors of gastro-entero-pancreatic origin. The clinical data presented in this study analysed the heterogeneous group of patients with confirmed GEP-NET carcinomas.

Secretory NECLM tumors (WHO group 2) were found in 38 patients (39%), while non-secretory tumors were diagnosed in 60 patients. Secretory carcinomas of the midgut origin were detected in 25 patients (70%) with primary small bowel tumors, single caecal, appendicical and right colon cancer, all of them presented "carcinoid syndrome".

Additionally, two patients with tumors of unknown origin presented with mild carcinoid syndrome, probably due to midgut origin. Considering foregut bowel tumors there was a single patient with duodenal secretory carcinoid.

Other patients with secretory tumors consisted of 6 patients with ZES and one with malignant insulinoma (insulin over-secretion). Considering patients with ZES there were four with MEN-1, and 2 subjects with pancreatic gastrinoma. The mean CgA level in the whole NECLM group of patients amounted to 290 U/l (ranging between 10–10 200 U/l).

In case of those with WHO group 3 and WHO group 4 there were no clear secretory tumors. None of these patients presented with a specific clinical syndrome. Considering both groups, non-specific signs and symptoms of cancer involvement, dominated. Mean CgA in the second group was 42 U/l (ranging between 11 and 173), and in the third – 47 U/l (ranging between 11 and 170).

According to the embryological origin of tumors, 66 (49%) patients were diagnosed with foregut tumors, 59 (44%) patients with midgut cancer, while others had tumors of unknown origin. None of the above-mentioned had evidence of hindgut carcinoma. There were 6 subjects with cancer of unknown origin within NECLM (WHO 2), and 3 subjects with NECHM (WHO 3).

According to the WHO classification histopathological results showed 98 patients with NECLM (73%), 29 with NECHM (22%), and 7 (5%) patients with mixed neuroendocrine carcinomas and adenocarcinomas (Figure 1). Mean patient age with NECLM was 53.5 years, NECHM – 52.2 years and mixed cancer type – 61.7 years. There were 82 patients alive during a median of 17.6 months of follow-up, considering the NECLM group.

Only three (31%) subjects remain alive in the NECHM group during a median 7 months follow-up period. Considering the third group of patients (WHO group 4) three (43%) subjects were alive during a median 17 months of clinical follow-up. All clinical data, according to histopathological results (WHO) were presented in Table 1.

Table 1. Clinical data according to histopathological results (WHO) of patients with neuroendocrine carcinomas, considering the presented groups.

Cancer type	Number of subjects	mean age (years)	range	female/male ratio	median follow-up	alive	death
NECLM (WHO 2)	98	53.5	21–75	57/41	17.6	82 (84%)	16 (16%)
NECHM (WHO 3)	29	52.2	28–76	14/15	7	9 (31%)	20 (69%)
NEC-Adenoca (WHO 4)	7	61.7	43–89	2/5	17	3 (43%)	4 (57%)
Total	134	53.7	21–89	73/61	17.0	94	40

(NECLM neuroendocrine carcinoma low malignancy; NECHM – neuroendocrine carcinoma high malignancy; NEC-Adenoca – mixed form neuroendocrine carcinoma and adenocarcinoma)
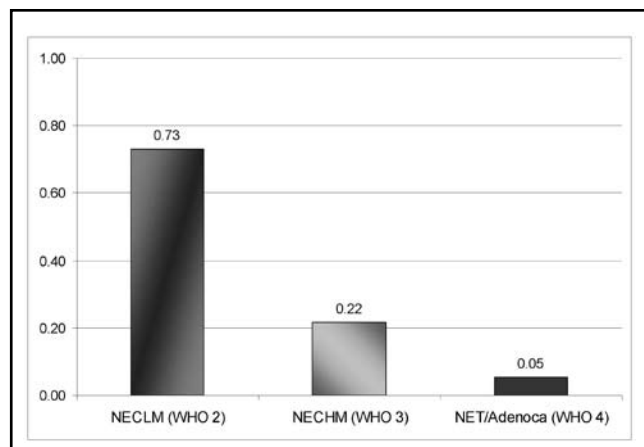
Figure 1. Graphic presentation of the distribution of neuroendocrine carcinomas in case of 134 patients, according to WHO criteria.

Patients with NECLM (WHO group 2) constituted 98 subjects (57 females). There were 43 cases of foregut tumors (44%) and 55 cases (56%) of midgut carcinomas, including patients with carcinomas of unknown origin (7 cases), who were probably classified to midgut tumors, due to the clinical course.

Foregut tumors comprised the stomach – 3 subjects, duodenum – 2 subjects, single Vaters' papilla, and 37 patients with pancreatic cancer. Midgut tumors were localized as follows: small bowel carcinomas – 37 subjects, caecal – 2 subjects, appendicical – 4 subjects and right colon – 5 patients. There were 87 subjects (89%) with primary cancer and 11 with recurrences (11%).

The second group of patients with NECHM (WHO group 3) consisted of 29 subjects (14 female). There were 17 cases of foregut tumors (59%) and 9 cases (31%) of midgut cancers, while the remaining three patients were diagnosed with cancer of unknown origin. Foregut tumors consisted of oesophageal – single case, stomach – 2 subjects, single Vaters' papilla, and 13 subjects with

pancreatic cancer. The WHO 3 midgut tumors consisted of small bowel tumors found in 5 subjects, right colon cancer found in 3 subjects, and one caecal neuroendocrine carcinoma.

The third group of patients with mixed type of tumors (WHO group 4) consisted of 7 subjects (2 female). There were 4 cases of foregut and 3 cases of midgut tumors. Foregut tumors were found in the stomach – 2 subjects, and in two 2 patients within the pancreas. Midgut cancers were observed in 3 patients, including the small bowel, cecum and right colon. Table 2 presented data concerning the primary origin of every type of carcinoma.

Imaging results

All patients with NECLM were subjected to anatomical (CT after i.v. contrast enhancement and/or US) and additional functional imaging (SRS) examinations (93 subjects). Most of them had ultrasonography as the initial study including trans-abdominal US and EUS in case of foregut cancers, in those with confirmed GEP-NET or with high expectancy of GEP-NET. In case of secretor tumors (carcinoid syndrome or ZES), SRS examinations were also initially performed. Due to the lack of standard US or/and EUS examination results and common underestimation of the presence and extent of cancer, no further analysis of sensitivity and specificity of US were performed in this study.

The preferred method of anatomical imaging was CT, which was used as standard morphological imaging, in order to establish the initial diagnosis (Figure 2), during the staging or restaging process (Figure 3). Every patient had at least a single CT scan after i.v. contrast enhancement. Sensitivity of CT in this group of patients amounted to 96%, while specificity – 75%. Only several subjects had MRI scans and most of them had CT as well. Thus, no further analysis of results of this technique will be presented.

In order to evaluate the presence of active disease, almost all patients with NECLM were subjected to at least

Figure 2A and B. Primary non-secretor pancreatic NECLM (WHO group 2) in a 42-old male patient with history of non-specific abdominal pain – standard CT after i.v contrast enhancement- transverse (**A**) and coronal (**B**) view of this patient, large tumor mass of the pancreatic body and tail involving the spleen and posterior wall of the abdomen, additional liver deposits.

one SRS examination (Figure 4). High-quality images were obtained in all cases using ^{99m}Tc TOC, and only a few patients had ^{111}In (DTPA-D-Phen^1) OctreoScan™ (16 subjects, all of them had repeated ^{99m}Tc TOC as follow-up study as well). No side-effects were observed after ^{99m}Tc TOC injection. There were 73 subjects with active disease confirmed by means of other imaging modalities, biochemistry (CgA) and clinical follow-up. Diagnostic sensitivity of SRS amounted to 97%, while specificity – 85%.

Considering the NECHM group (WHO group 3) all 29 patients were subjected to CT after i.v. contrast enhancement. Computed tomography estimated the presence of cancer, considering those with active disease confirmed by other methods with sensitivity amounting to 100%, and specificity, due to the overestimation of disease presence in a single patient – 67%.

SRS using a standard SST2 receptor avid tracer was performed in 28 subjects. The sensitivity of standard SST2 scintigraphy amounted to 44%; an additional 6 patients were subjected to the ^{99m}Tc NeoSPECT study, which was positive in 3 patients (sensitivity 75%) (Figure 5), in one case- false negative and an additional subject had TN and other FP results. This patient with FP was also positive with a one year follow-up period of clinically-free disease. Another patient with a false negative study using ^{99m}Tc NeoSPECT was positive in standard SRS using SST2 avid tracers. Overall sensitivity and specificity of ^{99m}Tc NeoSPECT in detection of NECHM is of limited value, due to the sample size.

In this group of patients standard FDG PET was performed in 8 patients, 6 of them were true positive and the remaining two were true negative. Sensitivity and specificity of FDG PET in this selected group of patients amounted to 100%.

The following group of 7 patients with mixed cancers (WHO group 4) had positive CT scans. Five of them also had SRS, only one with the expression of the SST2

Table 2. Primary origin of all carcinomas in the presented groups.

| PRIMARY	NECLM	NECHM	NEC-Adenoca
appendix	0.04		
caecum	0.02	0.03	0.14
colon	0.05	0.1	0.14
duodenum	0.02		
esophagus		0.03	
ileum	0.38	0.17	0.14
pancreas	0.38	0.46	0.29
papilla Vatery	0.01	0.03	
rectum			
stomach	0.03	0.08	0.29
UNO*	0.07	0.1	

* UNO – unknown origin
(NECLM neuroendocrine carcinoma low malignancy; NECHM – neuroendocrine carcinoma high malignancy; NEC-Adenoca – mixed form neuroendocrine carcinoma and adenocarcinoma)

receptor, which was positive during standard SRS. The FDG-PET study was performed in five patients, proving positive in 4 cases.

Only one patient had no active disease during 12 months of clinical and imaging follow up, CT and PET were negative. In patients with the active disease CT and PET were positive, sensitivity amounting to 100%.

The comparison of metastatic involvement considering all three groups of patients, based on imaging results, clinical data, final histology and clinical follow-up was presented in Table 3.

The correlation between imaging results and CgA at the time of the diagnosis/staging or restaging process was
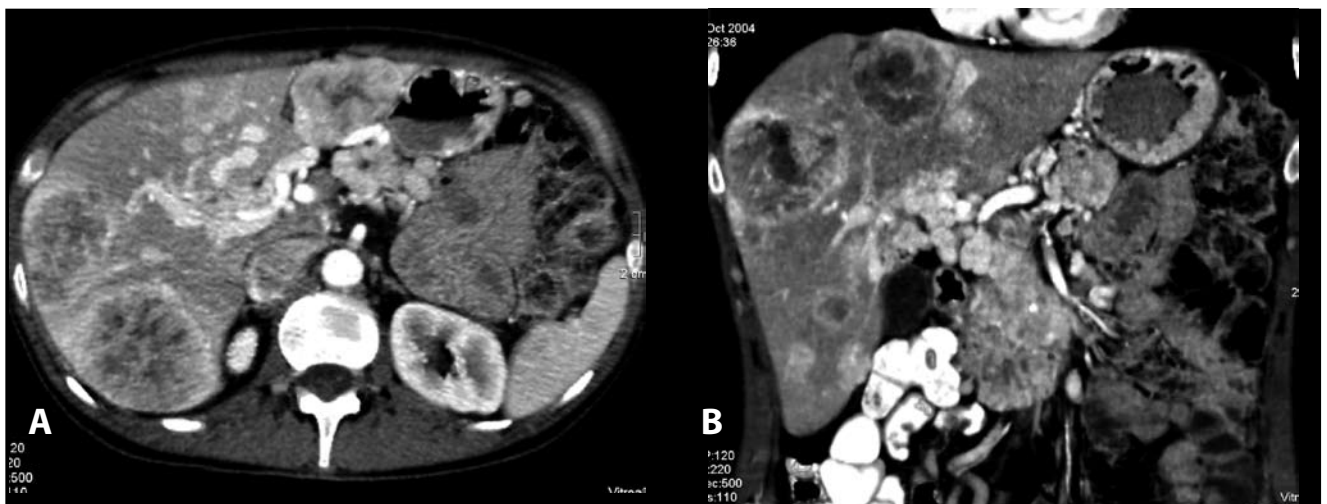
Figure 3A and B. Primary secretor pancreatic (gastrinoma) NECLM (WHO group 2) in a 50- year old female patient- clinically ZES. Previous chemotherapy (streptozotocin and 5FU 10x), restaging. A standard CT before 90Y DOTA TATE treatment, transverse (**A**) and coronal (**B**) view.

Table 3. Comparison of metastatic involvement considering all three patient groups, based on imaging results, clinical data, final histology in selected sites and clinical follow-up.
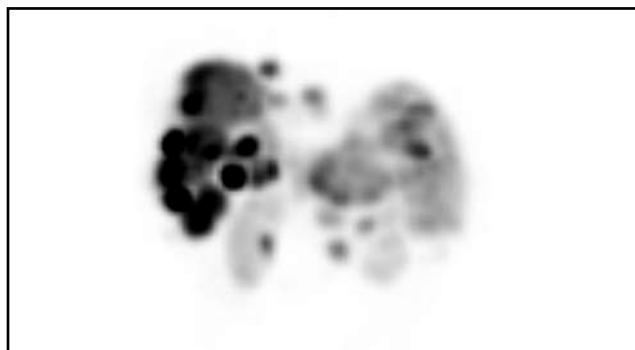
MTS	NECLM	NECHM	NEC-Adenoca
Liver (isolated)	0.08	0.07	
liver, lymph nodes	0.56	0.59	0.71
lymph nodes	0.25	0.24	0.29
others	0.22	0.07	
No metastatic deposits	0.11	0.07	

(NECLM neuroendocrine carcinoma low malignancy; NECHM – neuroendocrine carcinoma high malignancy; NEC-Adenoca – mixed form neuroendocrine carcinoma and adenocarcinoma)

Figure 4. SRS (somatostatin receptor scintigraphy) 99mTc-[HYNIC, Tyr3]-octreotide [99mTc TOC] in the patient presented in Figure 2, SPECT coronal view, multiple liver deposits with very high uptake of tracer additional non-homogenous uptake within the pancreas, also non-homogenous liver uptake.

very high in case of NECLM, Kendall tau 0.537, (p<0.001). Considering the second group of patients with NECHM there was no correlation between imaging results and CgA Kendall tau 0.179, (p=0.256). Considering the third group of patients with mixed type of carcinomas, due to sample size, correlation was not performed.

DISCUSSION

This comprehensive data set, which was build during 4 years, considered the same diagnostic approach based on ENETS and UK-NET recommendations, proving helpful during clinical practice [6,7]. Most of our patients had previous detected disease but now, all had restaging consider disease extend and in some case rename of disease base on a new WHO classification of the GEP-NET tumor. A new histological WHO classification seems to be very helpful, in order to select patients towards the best treatment modality and further follow-up [8,9]. The population of GEP-NET patients presented in this study could not be representative for all GEP-NET, considering epidemiological data [6,7]. This is due to the large number of subjects with extensive disease, progression

or widespread of cancer, which were sent to our team and therefore, our data seem to be preselected. Most of the NETWD tumors, which are commonly resectable were cured after initial diagnosis, with no need to expand treatment after surgical removal of the benign lesion.

The embryologic traditional classification of foregut, midgut and hindgut tumors remains in use by clinicians, helping select treatment and determining prognosis [1,3,4–7]. The results of this study indicated that practical indication of rational treatment and prognosis of patients with GEP-NET had careful evaluation of the presence of the active disease and also carcinoma extent.

These should be achieved using diagnostic imaging techniques. The GEP-NET classification, based on secretory or non-secretory conditions, embryological origin and WHO classification which was used in every case was based on ENETS recommendations [6]. In general the imaging approach depended on primary tumor localization.

In case of tumors originating from the foregut and hindgut the endoscopic technique including the most sensitive EUS seems to be the best choice. Considering the group of patients with foregut cancer the endoscopic
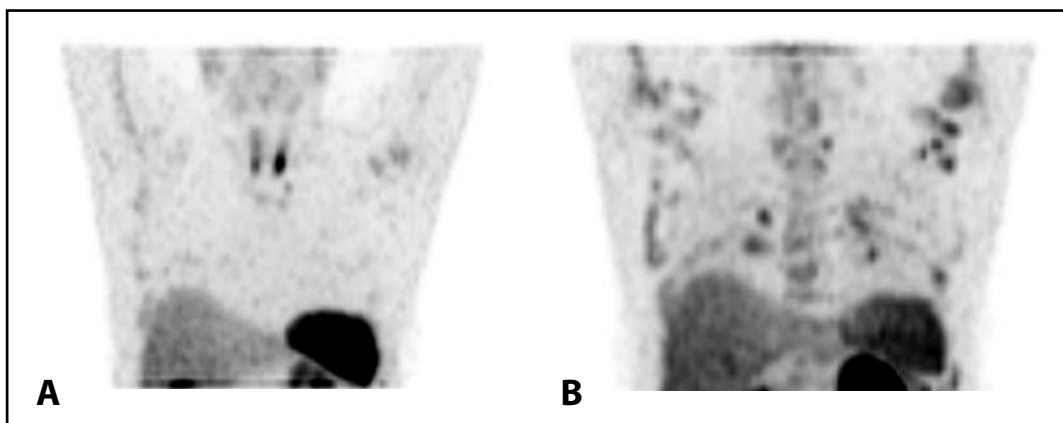
Figure 5A and B. Somatostatin receptor scintigraphy - SRS 99mTc-[HYNIC,Tyr3]-octreotide [99mTc TOC] – (**A**) and 99mTc [depreotide – NeoSPECT] – (**B**) in the 46 year- old female, with NECHM (WHO group 3) of unknown origin, SPECT coronal view, multiple deposits within the chest including bone meta and mediastinal lymph nodes involvement.

approach could underestimate the extent of cancer, therefore, evaluation using tomography should be performed in every case [1,3,6,7,14–20]. These techniques include the anatomical and scintigraphic imaging approach, as well. In all neuroendocrine midgut tumors, especially NECLM, CT and SRS have the best diagnostic accuracy. Using [99mTc] labelled ligands of somatostatin receptors we have good tumor localization and extent of the disease, as compared to [111In] Octreoscan™. Technetium labelled tracers present great advantage, described elsewhere [20–22]. Additional SPECT and anatomical tomography is of great value in combination with the fusion image [20, 23]. The new tracer, such as [99mTc]-[HYNIC,Tyr^3,Thr^8]-octreotide ([99mTc] TATE) [20] or [99mTc]-[HYNIC,Tyr^3]-octreotide ([99mTc] TOC) [21] with conjunction of a modern mutidetector CT is probably an attractive option for users of the SPECT technology [17,19,20,23], even in case of recent PET-CT success, using [68Ga] DOTA-NOC or [68Ga] DOTA TOC in the diagnosis of somatostatin receptor positive tumors [24,25]. The sensitivity of SPECT using technetium labelled compounds and software with new iterative reconstruction is slightly worse than the [68Ga] DOTA-NOC or [68Ga] DOTA TOC PET technology, but is cheap and clinically useful, due to the large number of patients examined during a single day. Reading together the images of SPECT and modern CT as image fusion, even in case of disease underestimation, as compared to PET-CT, the differences between both techniques have probably no significant clinical impact on patient management. Other PET tracers like C-5-hydroxy-L-tryptophan show very high sensitivity in the detection of GEP-NET [26], even higher than for somatostatin receptor scintigraphy, without significant clinical impact considering the change of management and therapy. Another limitation of PET examinations is the small number of centers with this PET technology.

Great value of modern CT and MRI has been documented by recent data. The CT acquisition time covering the neck, chest, abdomen and pelvis is very attractive, due to excellent spatial resolution using MIP and volume enabling to produce 3D images including virtual colonoscopy [13,16–19,27,28,29]. Great value of details seen during CT is used by the surgeon to plan an operation [6,7,13]. Also CT and/or MRI are of great value, when assessing tumor response towards treatment, which is routinely used by most NET teams worldwide. The most popular are RECIST and WHO criteria [1,6,7]. Currently, the new CT technology seems to very useful in the detection of primary and metastatic carcinomas of neuroendocrine origin.

Direct comparison between SRS and CT, which was presented and published thus far in literature data, demonstrated differences between the diagnostic accuracy of both approaches [20, 29,30]. Additional recent data suggested the great value of MRI over SRS and CT, especially in liver deposits [31]. Our study indicated that today in case of patients with NECLM the difference between both SRS and CT could be insignificant. The relative difference previously reported and in recent articles is probably dependent on the experience of radiologists and nuclear medicine physicians who read images, as well as patient selection [20,29–31]. Considering our group of patients with NECLM most were sent to assess the staging of the disease. Thus, the high accuracy of CT in our study could overestimate the real diagnostic accuracy of CT [20]. Considering those with suspicion of NET, SRS seems to be a simple method of localizing
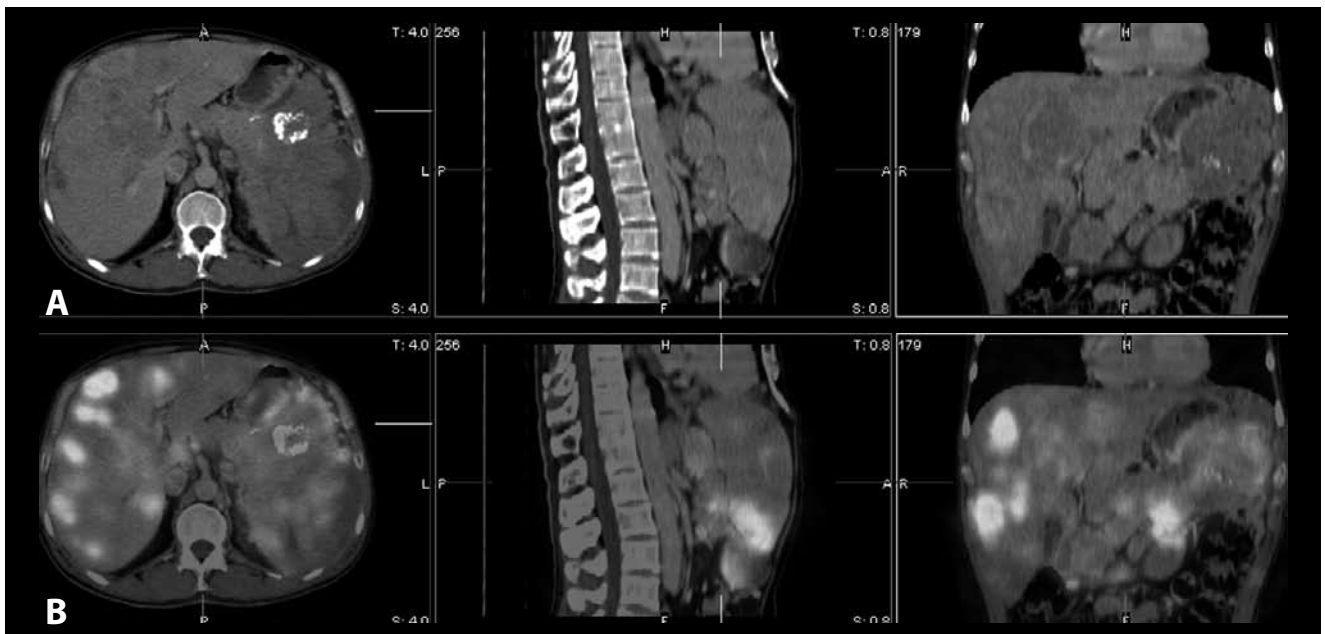
Figure 6A and B. Primary non-secretor NECLM in a 42-year old patient with small bowel NECLM (WHO group 2) – midgut carcinoid). Standard CT after i.v contrast enhancement, transverse sagittal and coronal views (**A**). Image fusion of somatostatin receptor scintigraphy (SRS) using [99mTc]-[HYNIC,Tyr^3]-octreotide [[99mTc] TOC], and CT (**B**).

the primary tumor, also in those patients with extensive tumor involvement [1,3–7,13]. The great advantage of nuclear medicine images consists in the relatively simple identification of pathological uptake through the body, which is more complex to that of CT. Current msCT examinations consist of hundreds of images before and after contrast enhancement, which renders difficult and time consuming the localization of the primary tumor, and to correctly assess the extent of the disease [13,17–19].

The advantage of current SRS technology using [99mTc] tracers over [111In] Octreoscan™ mentioned before consists in the high quality of images, due to better statistics (higher activity of [99mTc] tracer), better spatial resolution of images, better patient dosimeter, and single day examination with both whole body scan and tomography (SPECT). Additionally, a new iterative reconstruction algorithm used by current modern software significantly improved the quality of images [17,19]. If there is any doubt of the nature of lesions detected during standard SRS using [99mTc] labelled agent, some of the authors suggested additional acquisition of images after 24h [20–22], but in our opinion image fusion seems to be a more suitable approach (standard SRS together with CT) (Figure 6). We observed that image quality using [99mTc] radiotracers after 24h is very poor and only spot images are available with no value of SPECT, due to the low count rate.

Very high diagnostic accuracy of standard SRS in the detection of the extent of the tumor is of course the method of choice during diagnostics, although in patients with low expression or even inactive SST2 receptor standard SRS could underestimate the extent of the disease [1,6,7,13]. This is uncommon in the group of patients suffering from NECLM [1,3,6,7,15].

An additional feature commonly observed consists in the non-homogenous distribution of sst2 receptor within the tumor and therefore, underestimation of its size [14,15]. In such cases, better morphological image for the surgeon planning an operation can be obtained through CT or MRI images. Careful visual examination of CT should cover the whole body including neck, chest, abdomen and pelvis, using the dedicated window for every part of the body including careful skeletal analysis, due to often skeletal metastasis in patients with foregut tumors [3,6,7,13,17,19,20,28]. Therefore, both techniques particularly in case of NECLM should be routinely performed in every case. If there is any clinical suggestion of brain involvement MRI of the head is the best choice.

This approach is clinically suitable for cancers originating from every organ, such as foregut (stomach, duodenum and pancreas) and midgut cancers, which was reported before and confirmed in our study [13–20]. Additionally, there is a very high correlation between the presence of active disease observed during the diagnostic imaging approach and CgA level. The above-mentioned was noted in our study, which is well-known and reported by others [1,10–13].

Considering patients with NECHM and mixed carcinomas, standard SRS in most cases underestimated the presence and extent of the disease, due to dedifferentiation of cancer cells, lack or low expression of active SST2 receptors, and/or expression of other types of sst receptors, such as sst3 and sst5 [1–7]. In those patients, routine examinations using standard SRS should be performed in every case, due to potential SST2 expression. Another therapeutic option considered the use of "cold" or radiolabelled somatostatin analogues [31–34].

Great advantage of morphological imaging over standard SRS in both patient groups is obvious [1,3,13]. Other functional imaging techniques, such as [99mTc] NeoSPECT could be used in patients with negative standard SRS, in order to assess the expression of other subtypes of SST receptors or other receptors, which are commonly seen in neuroendocrine cancer cells [6,9,11,13].

In our series we began using [99mTc] NeoSPECT recently and thus far, no conclusive results exist, considering our group of patients. There are few reports of the potential use of this tracer, when selecting patients with negative standard SRS scans ([90Y] DOTA LAN), considering the treatment of patients without SST2 receptor expression [35].

In selected cases routine anatomical imaging approach in patients with confirmed NECHM or mixed cancers, should be repeated for a period of three months, due to the often aggressive behaviour of these tumors [1,3,6–9,13]. This should be used in both foregut and midgut cancers, as well.

Considering patients with NECHM and mixed tumors we found in our initial group of 13 patients that, standard [18FDG]-PET seems to be a very good diagnostic technique. In case of active disease, especially after treatment, we observed that standard [18FDG] PET is very useful, with high diagnostic accuracy. It is well-known that in the NECLM group, old fashion carcinoids or islet tumors of the pancreas FDG PET underestimated the presence or extent of the disease, and was of little clinical value [36,37]. Thus far, there are no clear reports considering the assessment of [18FDG] PET in case of GEP-NET within groups WHO 3 and 4. Our initial results using FDG PET in patients with both WHO groups 3 and 4, are very promising, with high sensitivity and specificity (13 patients, 10 of them had active disease and 3 were free of disease for at least 6 months). Additionally, our initial experience suggested the high value of FDG-PET, when assessing cancer activity, spread of the disease and response to treatment, as well in particular types of carcinomas. Further studies are required, in order to assess the real value of this technology in the GEP-NET groups WHO 3 and 4.

Considering our results, previous reports and based on ENETS guidelines, we elaborated the diagnostic algorithm for foregut and midgut cancers. Because foregut tumours were of different origin including the stomach, duodenum and pancreas we presented a separate diagnostic approach for every organ.

Foregut cancers – stomach
- WHO group 2
  – Endoscopy and/or EUS (with biopsy, if diagnosis is established); CT with i.v. contrast enhancement (3-phase), other investigations only required if proof of metastatic or residual disease after biopsy, including standard SRS, and MR of the spine or bone scan (often bone meta);
- WHO group 3 and 4
  – Endoscopy and/or EUS (with biopsy, if diagnosis is established); CT with i.v. contrast enhancement (3-phase), FDG PET; SRS (99mTc depreotide), standard SRS?, and MR of the spine or standard bone scan (bone mets);

Duodenum
- WHO group 2
  – Endoscopy and/or EUS (with biopsy, if diagnosis is established); CT with i.v. contrast enhancement (3-phase), standard SRS, intraoperative SRS (often very small volume of cancer), other investigations only required if proof of metastatic or residual disease after biopsy, like MR of the spine or bone scan (bone meta);
- WHO group 3 and 4
  – Very rare, diagnostic imaging approach like stomach;

Pancreas
- WHO group 2
  – EUS (with biopsy, if diagnosis is established); CT with i.v. contrast enhancement (3-phase), standard SRS, intraoperative SRS (if very small volume of cancer), FDG PET in case of "gastrinoma, VIP-oma and insulinoma – usually SRS (–), abdominal US (?), 123I MIBG (?) and MR of the spine or standard bone scan (bone meta);
- WHO group 3 and 4
  – EUS (with bx, if diagnosis is established); CT with i.v. contrast enhancement (3-phase), FDG PET, SRS (depreotide), standard SRS, abdominal US(?) and MR of the spine or standard bone scan (bone meta);

Midgut cancers (including small bowel, appendix, caecum and right colon)
- WHO group 2
  – CT with i.v. contrast enhancement (3-phase), standard SRS, 123I MIBG, colonoscopy, abdominal US (?);
- WHO group 3
  – CT with i.v. contrast enhancement (3-phase), FDG PET; SRS (99mTc depreotide), standard SRS, colonoscopy, abdominal US (?);
- WHO group 4
  – CT with i.v. contrast enhancement (3-phase), FDG PET; SRS (99mTc depreotide), colonoscopy; MR (spine), abdominal US (?);

Hindgut cancers (very rare-none in our group of patients, based on literature data [6,7])
- WHO group 2, 3 and 4
  – Colonoscopy, CT with i.v. contrast enhancement (3-phase), MR pelvis, FDG PET, SRS (99mTc depreotide), standard SRS (?), abdominal US (?);

CONCLUSIONS

Diagnostic imaging of GEP-NET considered the anatomical and functional techniques, which should be read together.

The diagnostic value of CT and SRS match in case of NECLM (WHO group 2), but in the group of NECHM (WHO 3) CT had significant higher diagnostic accuracy. FDG-PET seems to be a very attractive imaging functional modality in patients with NECHM and mixed carcinomas (WHO group 3 and 4).

The interpretation of anatomical and functional images in patients with GEP-NET, considering the primary tumor and extent of the disease are different, in comparison to standard cancer, due to the nature of neuroendocrine tumors.

In conclusion, imaging results should be connected with the hormonal condition of the tumor, site of primary tumor origin and current histological WHO classification.

The overall diagnostic approach including the clinical examination, biochemistry and imaging should be performed in centers with special interest in GEP-NET tumors.

ACKNOWLEDGEMENTS:

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