

Whole-body ^{11}C -5-hydroxytryptophan positron
emission tomography as a universal imaging
technique for neuroendocrine tumors – comparison
with somatostatin receptor scintigraphy and
computed tomography

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Abstract

Neuroendocrine tumors (NET's) can be small and situated almost anywhere throughout the body. Our objective was to investigate if whole body (WB) positron emission tomography (PET) with ^{11}C -5-hydroxytryptophan (5-HTP) can be used as a universal imaging technique for NET's and to compare this technique with established imaging methods. Forty two consecutive patients with evidence of NET and a detected lesion on any conventional imaging (6 bronchial-, 2 foregut-, 16 midgut-, and 2 thymic carcinoids, 1 ectopic Cushing's syndrome, 4 gastrinomas, 1 insulinoma, 6 non-functioning endocrine pancreatic tumors, 1 gastric carcinoid, 1 paraganglioma and 2 endocrine differentiated pancreatic carcinomas) were studied. The WB- ^{11}C -5-HTP-PET examinations were compared with WB-computed tomography (CT) and somatostatin receptor scintigraphy (SRS). Tumor lesions were imaged with PET in 95 % of the patients. In 58 % of the patients PET could detect more lesions than SRS and CT, equal numbers in 34 % whereas in 3 cases SRS or CT showed more lesions. In 84% (16/19 patients) PET could visualize the primary tumor compared to 47 % and 42% for SRS and CT respectively. The surgically removed PET-positive primary tumor sizes were 6-30 mm. To conclude, this study indicates that WB- ^{11}C -5-HTP-PET can be used as a universal imaging method for detection of NET's. This study also shows that WB- ^{11}C -5-HTP-PET is sensitive in imaging small NET-lesions, such as primary tumors, and can in a majority of cases image significantly more tumor lesions than SRS and CT.

Introduction

Neuroendocrine tumors (NET's) are relatively slow growing tumors with a malignant potential. Endocrine related symptoms are common and distant metastases are in many cases present at the time of diagnosis (1). NET's belong to the so called *amine precursor uptake and decarboxylation* (APUD)-omas, ie, they have the capacity for uptake and decarboxylation of amine precursors like 5-hydroxytryptophan (5-HTP) or L-dihydroxyphenylalanine (L-DOPA), and subsequent storage or release of serotonin (5-HT) and dopamine (2, 3). Carcinoid tumors of midgut origin, midgut carcinoids (MGC) produce serotonin via the precursors tryptophan and 5-hydroxytryptophan. Serotonin is metabolized to 5-hydroxyindole acetic acid (5-HIAA) and excreted in the urine (Fig. 1). For midgut carcinoids serotonin, urinary-5-HIAA and chromogranin A (CgA) are the main tumor markers (4), whereas in foregut carcinoids (bronchial carcinoids and endocrine pancreatic tumors (EPT)) and hindgut carcinoids serotonin production is rare and therefore 5-HIAA is seldom increased. Still production of 5-HTP can occur also in these groups therefore, immunohistochemical staining for serotonin may be positive (1).

The initial workup in NET-visualization is often performed with conventional imaging methods like computed tomography (CT) or magnetic resonance imaging (MRI) due to their advantages in both diagnosis, routine tumor staging and for monitoring of therapy. Abdominal sonography can be an additional option mainly for liver lesions while endosonography is preferably used in the workup of EPT (5, 6). Endoscopy should be performed in patients with suspected gastrinoma to identify eventual peptic ulcers but also to rule out lesions in the duodenum, especially in patients with multiple endocrine neoplasia type 1 (MEN-1) -associated gastrinomas

(7). In the last decade somatostatin receptor scintigraphy (SRS) has emerged as the functional imaging technique of choice for diagnostic workup of NET's (5, 8-10), as well as for evaluation of receptor status prior to treatment with unlabeled somatostatin analogues or peptide receptor targeted radionuclide therapy (PRRT) (11, 12).

Drawbacks with SRS are related to the somewhat limited spatial resolution and tumor-to-background ratio that might hamper visualization of small tumor lesions.

There are also NET's that lack or express a different subset of somatostatin receptors, thereby not imaged by SRS. Tumor-detection-rates of NET's in the range of 60 - 100 % have been reported with SRS and also inflammatory processes, lymphomas and thyroid abnormalities can be imaged with this technique (9, 13).

The standard PET-tracer in oncology, ^{18}F -fluorodeoxyglucose (FDG), have shown to be of limited value in the imaging of NET's (14, 15). In contrast, with PET using the ^{11}C -labeled serotonin precursor 5-HTP as tracer we have previously demonstrated a high tracer uptake in a limited amount of patients, where the change of transport rate constant indicated PET also to be useful in therapy monitoring of NET's (16).

The dopamine-precursor L-DOPA, labeled with ^{11}C or ^{18}F , has also been used for PET imaging of NET's (17, 18). In the former of these studies 3 patients were co-examined with ^{11}C -5-HTP and in these patients higher standardized uptake values (SUV) were seen for 5-HTP than for DOPA (unpublished data), indicating that 5-HTP might be preferable for the amine-uptake system of NET's. On the other hand, since these tracers are actively internalized and rapidly decarboxylated intracellularly (19, 20), a functionally inactive or necrotic tumor can be overlooked with these imaging techniques. In the study by Hoegerle et al (18), using ^{18}F -DOPA-PET in 17 patients

with gastrointestinal carcinoids, the highest sensitivity was seen for the combination of non-functional techniques including both CT and MRI.

For the diagnostic imaging of pheochromocytomas, PET with ^{18}F -dopamine has been shown to be very sensitive and recent publications indicate that this imaging modality is superior to both SRS and ^{131}I -metaiodobenzylguanidine (MIBG) scintigraphy (21, 22).

Our hypothesis was that the system for uptake and internalization of an amine-precursor might be expressed to a certain degree in all APUD-omas. Therefore, by using a radio labeled amine-precursor as PET-tracer, our objective was to investigate if this method can be used as a universal imaging technique for visualization of all tumors histopathologically characterized as being of neuroendocrine differentiation. We chose ^{11}C labeled 5-HTP as the tracer based on previous observations (see above) and aimed at including a mixture of different NET's for diagnostic imaging, of both primary tumors and metastases, with PET in comparison with SRS (Octreoscan®) and CT.

Materials and Methods

Patients

Forty-two consecutive patients with neuroendocrine tumors, referred to the Dept of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden, were included in the study (6 bronchial- 16 midgut-, 2 foregut-, and 2 thymic carcinoids, 1 ectopic Cushing's syndrome, 4 gastrinomas, 1 insulinoma, 1 gastric carcinoid (ECL-oma), 6 non-functioning EPT's, 2 endocrine differentiated pancreatic carcinomas and 1 paraganglioma), including 3 patients with MEN-1.

Inclusion criteria were either: a) histopathological diagnosis of NET *and* detected lesion on *any* conventional radiology (CT, abdominal- or endosonography) *or* on SRS, or b) biochemical evidence of NET *and* detected lesion on any conventional radiology *or* on SRS.

In all patients biopsy or surgery was performed for histopathological diagnosis. Patient characteristics together with tumor markers and ongoing tumor treatment are shown in Table 1. Nineteen patients had been submitted to previous tumor surgery and 17 patients were operated after the biochemical and imaging workup, allowing surgical comparison of the imaging results in this subgroup of patients.

All patients granted informed consent and the study was approved by the local Ethics Committee.

Positron emission tomography

^{11}C was produced using a Scanditronix 17 MeV cyclotron (General Electrics Medical Systems, Milwaukee, WI, USA) and ^{11}C -5-HTP was produced in a multienzymatic reaction according to previously described procedures (23, 24). The patients were

examined using a Siemens ECAT HR+ PET-scanner (Siemens, Germany) with 4-5 bed positions, each with a 13.6 cm axial field of view providing 2.5 mm slices with a resolution of approximately 5.5 mm. The emission times were typically 5, 6.7, 10, 10 and 15 minutes at bed positions 1-5, respectively. A 5 minutes segmented WB-transmission scan was acquired at all bed positions using externally rotating ^{68}Ge -pins. The images were corrected for scatter and attenuation, then reconstructed in a 128 x 128 matrix to represent radioactivity concentration using an iterative reconstruction algorithm utilizing 6 iterations, 16 subsets and a 8 mm ramp filter. WB-PET scanning was started 20 minutes post intravenous injection (PI) of ^{11}C -5-HTP at a dose of 140-521 MBq (mean 381 MBq). To reduce tracer decarboxylation by blocking the enzyme aromatic amino acid decarboxylase (AADC), all patients received 200 mg of carbidopa as pretreatment 1 hour prior to the PET-examination as described in a recent communication (25).

Somatostatin receptor scintigraphy

Somatostatin receptor scintigraphy was performed using ^{111}In -DTPA-D-Phe1-octreotide, labeled as previously described (26) and delivered by Mallinckrodt Medical (Petten, Netherlands). Patients were injected with one kit, 6 mCi (222 MBq), as recommended by the producer and planar antero-posterior as well as lateral scintigrams were collected after 24 h with a large field of view gamma camera and a medium-energy collimator. Static WB-images were obtained and single photon emission computed tomography (SPECT) was additionally performed after 24 hours using a single headed γ -scintillation camera (Nuclear Diagnostics, Hagersten, Sweden and London, UK) and the data collection was performed using a 64-step rotation of 360° in a 64 x 64 word matrix and 40 second acquisition per projection. Images were

iteratively reconstructed in 4 subsets, 4 iterations and no postfiltering (HOSEM, Hermes Ordered Subset Expectation Maximization: Hermes, Stockholm, Sweden). In one patient a regular filtered back-projection was used (No. 14).

Computed Tomography (CT)

Whole body CT was performed, using two different scanners (Somatom Plus 4 and Somatom Plus S, Siemens, Germany), over the thorax and abdomen in all patients before PET-scanning. CT was performed before and during intravenous contrast-enhancement using 8 mm slice thickness and increment. For CT of the pancreas 3 mm slice thickness and 4.5 mm increment were additionally used in the arterial contrast enhancement phase.

The image findings were assigned to the following categories: liver metastases (l.m.), abdominal lymph node metastases (a.lgl.m.), lung metastases (lung.m.), mediastinal lymph node metastases (m.lgl.m.) and bone metastases (bone.m.). When more than 5 lesions were detected in one of these categories this was described as > 5 lesions. The images were interpreted by radiologists (CT) and nuclear medicine physicians (SRS) who were blinded for the results of the other imaging modalities. Comparison between imaging techniques was made by two of the authors (H.O. and A.S). All examinations in each patient were performed during a maximum period of 8 weeks (mean 3.2 weeks \pm 2.8 SD).

Results

The results of the different imaging modalities are shown in Table 1.

Four patients (3 MGC and 1 EPT) had to be excluded from the study. For 2 of these patients there was a change in the medical therapy between the examinations that altered the baseline conditions and made comparison of modalities unreliable. One patient did not want to continue the study after performing 2 of the 3 imaging modalities and the last subject was excluded after one examination due to severe pain.

Overall comparison

The greatest number of lesions was visualized with ^{11}C -5-HTP-PET. In 95 % (36/38) of the patients PET could visualize positive lesions. Two patients (No. 20 and 37, see below) were negative on PET. In 58 % (22/38) of the patients more lesions were detected with PET than with SRS and CT. In 34 % (13/38) of the patients imaging with PET visualized equal number of lesions as SRS and/or CT. In 3 cases (patients No. 20, 35 and 37) SRS or CT showed more lesions than PET. Patient No. 20 had a recurrence of a non functioning EPT, visible solely on SRS as a lymph node metastasis (Table 1). Patient No. 35, with a diagnosis of multiple endocrine neoplasia type 1 (MEN-1), displayed liver metastases and mediastinal lymph node metastases of a thymic carcinoid as well as a primary tumor in the thymus on CT. Both SRS and PET could image the primary tumor but not the metastases. In patient No. 37 disseminated tumor disease of a pancreatic carcinoma, with some endocrine differentiation on immunohistochemistry, was detected on CT. Two lesions were slightly positive on SRS, whereas PET only showed areas as totally devoid of activity

in the thymus and liver. These 3 patients will be discussed further in the Discussion section.

SRS could detect more lesions than CT in 37 % (14/38) whereas in 21 % (8/38) of the patients CT showed more lesions than SRS.

PET-positive tumor lesions in 33 out of 36 PET-positive patients (92 %), a total of 51 lesions, were histopathologically confirmed as tumor with biopsy or surgery (Fig 2) and no false positive PET-lesions were found among the examined samples. In patient No. 12, with suspected residual disease after primary surgery, the lesions were not large enough to be transabdominally biopsied and surgery was clinically not indicated. In patient No. 27 and 34, with residual or recurrent disease after primary tumor surgery, it was not technically possible to perform diagnostic biopsies at the time of the study. There was a discussion about if this could represent post operative changes. However, based on the functional information of the positive PET-images, active treatment intervention was suggested in both cases.

PET could visualize the primary tumor lesion in 84 % (16/19) of the patients with remaining primary tumor, compared to 58 % (11/19) for SRS and 47 % (9/19) for CT (Fig 3). The primary tumors not visualized on PET were 2 MGC's (No. 5 and 9) and one endocrine pancreatic cancer (no 37). For 3 of the MGC-patients the area of the primary tumor was included in a larger PET-positive tumor mass.

In all cases there was a better spatial resolution and a higher tumor-to-background ratio at PET than on SRS (Fig 4) and the contrast in the images was higher on PET than on CT.

A subgroup of seventeen patients underwent surgery after the biochemical- and imaging work-up (Table 1). Sixteen of these patients displayed PET-positive lesions (patient No. 20 was negative on PET) and in 15 of those cases surgery could confirm tumor findings. In patient No. 23, with a non functioning EPT, surgery could not verify the PET findings except for the liver lesion that was radio-frequency ablated during operation. In this patient, who had been submitted to previous abdominal surgery, radical surgery was planned. However, on a new PET-scan performed postoperatively, the intra abdominal PET-positive tracer uptakes were still present. Twelve of the operated patients had a remaining primary tumor. Nine of these primary tumors were confirmed surgically and all of them were positive on PET. In two patients with MGC the operation was not directed toward the primary gut tumor and this lesion was therefore not verified. In patient No. 31 only the lymph node metastasis could be removed at reoperation. The sizes of the surgically removed PET-positive primary tumors were in the range of 6 mm to 30 mm. Additionally, biopsy could confirm 4 of the non-operated PET-positive primary tumors (patients No. 15, 24, 30 and 35), whereas the final patient with liver metastases from a foregut carcinoid and a previously unknown primary tumor (No. 32), now displaying a positive PET-image over the pancreas, has not yet been confirmed and could therefore not be accounted for.

PET and anatomical imaging (CT)

No tumor could be imaged with CT in 8 patients (Table 1). Two patients expressed no tracer uptake and could therefore not be imaged on the PET-scans (No. 20 and 37). In patients with MGC (No. 1-13), PET imaged abdominal lymph node metastases (lgll.m) in all 13 patients, liver metastases were imaged in 10/13 patients, mediastinal

Igll.m in 7/13 and bone metastases in 3/13 patients. The corresponding numbers for imaging with CT were 6/13, 6/13, 4/13 and 1/13 patients.

In the group of EPT's (No. 14-23) four patients had a remaining primary tumor (No, 14, 15, 17 and 19). All of these tumors were visualized by PET, whereas CT could visualize solely one (No. 15). Abdominal Igll.m were imaged with PET in 6/10, liver metastases in 5/10 and lung metastases in 1/10 patients, compared to 3/10, 4/10 and 1/10 respectively for CT.

In bronchial carcinoids (No. 25-31) PET detected the primary tumor in 4/4 cases, liver metastases in 2/7, bone metastases in 1/7 and mediastinal Igll.m in 3/7 patients.

Corresponding numbers for CT were 3/4, 1/7, 1/7 and 1/7 patients.

Both modalities imaged the ECL-oma (No. 24), whereas the paraganglioma (No. 36) only was positive on PET. For tumors initially classified as forgut carcinoids (No. 32 and 33), later specified as EPT and duodenal carcinoid, PET could image the primary as well as the liver metastases in both cases, whereas only the liver metastases could be imaged by CT. The primary thymic carcinoid of patient No. 35 was imaged by both modalities as well as the mediastinal Igll.m of the second pat with thymic carcinoid (No. 34), but the liver- and lymph node metastases of this patient could only be imaged by CT. These liver metastases were rapidly progressive and expressed a high proliferation index (Ki 67).

In the two patients with pancreatic cancers with endocrine differentiation on immunohistochemistry and a high proliferation index (Ki 67), PET was totally negative in patient No. 37, whereas CT imaged extensive disease, and in patient No. 38 PET could image liver metastases that were not visible on CT. Both these cases are tumors with a lower differentiation than what is common in NET's.

PET and SRS

In MGC's, SRS imaged abdominal Igll.m in 10/13, liver metastases in 4/13, mediastinal Igll.m in 7/13 and bone metastases in 2/13 patients. Corresponding numbers for PET were, as seen above, 13/13, 10/13, 7/13 and 3/13 patients.

Primary EPT's could be visualized in 2/4 cases with SRS, whereas PET imaged all 4. Abdominal Igll.m were imaged with SRS in 3/10 of EPT's, liver metastases in 3/10 and lung metastases in 0/10 patients. This is to be compared with 6/10, 5/10 and 1/10 patients respectively for PET. However, bone metastases were seen in one patient (No. 18) on SRS but non PET.

Regarding bronchial carcinoids SRS imaged the primary tumor in 2/4 patients, compared to 4/4 patients with PET. Liver-, bone- and mediastinal Igll metastases were visualized by SRS in 1/5, 1/5 and 3/5 patients respectively. Corresponding figures for PET were 2/5, 1/5 and 3/5 respectively.

Both techniques imaged the ECL-oma, the paraganglioma and the primary thymic carcinoids, whereas in the patients initially classified as foregut carcinoids (No. 32 and 33), PET could image lesions at more sites than SRS in both cases. Two lesions in patient No. 37 were seen on SRS, but not on PET, whereas in patient No. 38 PET could image both primary and liver metastases while only liver lesions were seen on SRS.

Tumor subgroup results

All four gastrinomas were readily imaged with ¹¹C-5-HTP-PET. Two of these patients displayed tumors that were found to be less than 2 cm in diameter at surgery (No. 14 and 17, Fig 3 and 4). Their peptide hormone production was markedly elevated. In contrast, 4 out of 5 non functioning EPT's, i.e. tumors that cause no hormonal

symptoms, revealed nevertheless elevated 5-HTP uptake and consequently were imaged by PET.

All seven bronchial carcinoids were depicted by PET, including the patient with Cushing's syndrome due to ectopic ACTH-production (No. 29). This tumor was surgically removed and measured approximately 2 cm in diameter. This is interesting since ectopic ACTH- producing tumors are known to be difficult to image (27, 28). Further studies are needed to support this observation. However, the residual/recurrent tumor of a patient that previously had been operated for an ACTH-producing bronchial carcinoid causing a Cushing's syndrome (No. 31), but now with normal ACTH and cortisol levels, could also clearly be visualized by PET.

In patient no. 28 who previously had undergone primary surgery for a bronchial carcinoid and now had a recurrence of the disease in thorax, PET could, apart from the positive mediastinal lesion (also seen on SRS, but only retrospect at CT), visualize a multiple of liver metastases (Fig 5). After repeated ultrasonography examinations, tumor spread to the liver was confirmed with biopsy and the patient was subjected to medical treatment instead of surgery.

All of the MGC's were readily visualized with ^{11}C -5-HTP-PET, probably facilitated by the fact that HTP is the precursor of serotonin, which is produced by a majority of patients in this subgroup of NET's. In patients with MGC very small lesions could be detected due to a high tracer uptake. Liver lesions of approximately 0.5 cm (the resolution of the PET-camera is 5.5 mm), hardly detectable on US or CT, were readily imaged by PET (Fig. 4), as well as several small intraabdominal lesions. In retrospect, however, by rereading of the CT images with knowledge of the PET findings, many of these previously overlooked lesions could be detected.

In contrast, also the less common NET's, such as a gastric carcinoid (No. 24), a cervical non functioning paraganglioma (No. 36) and 2 thymic carcinoids (No. 34 and 35), were clearly depicted by ^{11}C -5-HTP-PET. For patient No. 36, with a recurrence of a paraganglioma, the PET images were very supportive in the clinical management since both CT and MRI initially were negative. In this case SRS also clearly imaged the lesion in the neck (Fig 6).

Discussion

In this study we have consecutively included an unselected material of tumors classified as NET's. The results from this study confirm the presence of the APUD concept in NET's and that this specific characteristic can be used for diagnostic visualization using the carbon-11 labeled serotonin precursor 5-HTP. Tumors in all patients, but two, did take up the amine-precursor and could therefore be imaged with PET. For a majority of the patients, PET could image several previously undiagnosed lesions, most in the 0.5-1.5 cm range and therefore easily overlooked at CT. The PET-data adds functional information of a lesion, thereby making it possible to determine its nature. PET could also contribute substantially in visualization of the primary tumors. These tumors are often small and can therefore be difficult to detect. In this sense the high tumor-to-background ratio and spatial resolution of PET compared to SRS, as well as the high image contrast compared to CT, was of great importance. Regarding primary MGC's, usually very tiny lesions in the intestinal lumen, these lesions can not be expected to be identified by PET but rather with an endoscopic approach.

The two patients in whom PET not could visualize any tumor (patient No. 20 and 37) had a recurrence of a non functioning EPT and an endocrine pancreatic carcinoma with poor differentiation and high proliferation index (Ki 67 > 40%). In one other case PET displayed less tumor lesions than SRS and CT. This was in patient No. 35, with a thymic carcinoid and liver metastases with a high proliferation rate. In common for these three cases is a low peptide hormone production and therefore almost normal biochemical markers. This might indicate that the amine precursor uptake system is not as well expressed in these tumors, as also in necrotic tumor lesions, resulting in a

low uptake of the radio labelled amine precursor 5-HTP and thereby a poor tumor imaging. In these patients FDG would most likely have been a better choice of PET tracer for tumor visualization. Since ^{11}C -5-HTP is incorporated in a biochemical pathway, PET imaging with this tracer reflects the metabolic activity of a tumor concerning processing of biogenic amines. Consequently, some lesions show lower tracer uptake and occasional lesions such as necrotic tumors were shown to lack tracer accumulation. Also tumors with very low peptide production, i.e. non-functioning tumors or poorly differentiated tumors can be difficult to detect using this concept. This was illustrated by patient no 19, with multiple EPT's as part of a MEN-1 syndrome. The patient only showed a slight elevation of PP-levels and CgA, and consequently the 5-HTP uptake was only slightly increased in 2 pancreatic lesions, although sufficient for visualization by PET. On the other hand, when surgery was performed in this patient 3 EPT-lesions were found and the smallest tumor measured 4 mm in diameter.

A drawback in this study is the fact that surgical confirmation of the imaging results only could be achieved in 17 out of 38 patients. For the remaining 19 patients there was no clinical indication to perform surgery. In this sub-group of seventeen patients the sensitivity and specificity of ^{11}C -5-HTP-PET was shown to well surpass that of both SRS and CT.

For all patients, except 3 (No. 12, 27 and 34) biopsies from lesions that were positive on the PET-scans were performed and found to represent tumor, indicating that the uptake seen on PET truly represents tumor. Indeed surgery is gold standard for verification of tumor lesions. However, this study was not designed to compare PET to surgery and a full surgical lesion mapping was therefore not performed.

When ^{11}C -5-HTP-PET was compared to SRS and CT, more tumor lesions were detected in a majority of cases. SRS, however, still defends its place as the nuclear imaging method of choice for NET's due to its availability and capacity to reflect the tumor expression of somatostatin receptors, which forms the basis for therapy with non radioactive- and beta-emitting labeled (Peptide Receptor Radionuclide Therapy, PRRT) somatostatin analogues. In combination with conventional radiology SRS probably is sufficient as workup in a majority of patients with NET's (5), but as this study indicates, ^{11}C -5-HTP-PET contributes in a majority of cases, especially with regard to small tumor lesions. This new and fairly expensive technology is probably most beneficial in selected patients such as those with biochemical evidence of an endocrine tumor or recurrence of a tumor but a negative imaging work up, as well as to map possible metastases in patients where aiming at curative surgery. Another situation when ^{11}C -5-HTP-PET can contribute to the workup is when considering liver transplantation in a patient with solely liver metastases of a NET. In that case it is crucial to exclude extra hepatic tumor sites before introducing potent immunosuppressive treatment.

So far ^{11}C -5-HTP-PET can only be performed at centers with access to a cyclotron for synthesis of the radionuclide ^{11}C due to its short half life (20min). On the other hand, with the use of ^{11}C a molecule remains structurally and biologically intact, which is important when working with endocrine pathways and small molecules such as 5-HTP. Nevertheless, a labeling with e.g. ^{18}F is needed to facilitate the spread of this imaging technique.

To conclude; this study indicates that ^{11}C -5-HTP-PET is a sensitive method for detection of NET's and it exceeds both SRS and CT in tumor visualization. The contribution of patient tumor status with this technique is considerable. With the exception for poorly differentiated NET's and possibly non functioning tumors, we believe that ^{11}C -5-HTP can be used as a universal technique for imaging of NET's, with the greatest benefit in imaging of small tumor lesions e.g. primary tumors. This study also reflects that many different NET's process biogenic amines to some degree regardless of functionality and endocrine syndrome.

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Figure Legends

Figure 1. Synthesis of serotonin. Thick arrow indicating the carbon atom which is substituted for a carbon-11 atom, whereby the 5-HTP molecule is kept structurally and biologically intact.

Figure 2. PET-examination with ^{11}C -5-HTP in patient no 17 (A and B, different coronal views) with a MEN-1 syndrome and multiple gastrinomas in the pancreas. Thin arrows indicating two high, and one more discrete, pathological intrapancreatic tracer uptakes. Bent arrow indicating liver. Somatostatin receptor scintigraphy of the same patient (C). Thin arrow indicating the sole pancreatic lesion that was imaged, bent arrow indicating liver and thick arrow spleen. At surgery 3 endocrine pancreatic tumors were found, corresponding to the PET findings.

Figure 3. Patient no 14 with biochemical evidence of a gastrinoma and where endoscopic ultrasonography indicated a pathological intraabdominal lesion. PET clearly images the lesion that later can be verified as a duodenal gastrinoma and surgically removed. Both SRS and CT were negative. Thick arrow indicating liver.

Figure 4. PET-scan with ^{11}C -5-HTP (A, axial view) in patient no 5 with a midgut carcinoid, displaying several pathological tracer uptakes in the liver. Corresponding somatostatin receptor scintigraphy image (B) showing the pathological uptakes in the liver with lower spatial resolution and

tumor-to-background ratio. Corresponding CT-image (C). Thin arrow indicating tumor, bent arrow kidney and thick arrow spleen in all images.

Figure 5. Patient no 28 with a bronchial carcinoid and a recurrence in the thorax. PET-scan (A) with thin arrow indicating mediastinal tumor and thick arrow indicating liver metastasis (several liver lesions were imaged on different views). Somatostatin receptor scintigraphy (B, static view) could image one intra thoracic lesion (thin arrow). Curved arrow indicating non-malignant thyroid uptake and thick arrow indicating sinusitis. Corresponding CT (C) where the lesion (arrow) in thorax clearly could be spotted in a retrospect analysis.

Figure 6 PET-image of patient no 36 (A) with a recurrence of a cervical paraganglioma (carotid body tumor) where both CT and MRI initially were evaluated as being negative. Somatostatin receptor scintigraphy was also positive (B). Thin arrow indicating tumor in both images. Thick arrow indicating liver.

Table 1. Patient Characteristics and Lesion detection

Pat No	Sex	Diagnosis	Peripheral tumor marker	Tumor treatment	CT	Tumor lesions according to:		Lesion detection, comparison	Biopsy/ Operation
						SRS	PET		
1	M	MGC (pt -)	U-5HIAA 2.2 CgA 4.5	none	m.lgll.m.(2) l.m.(3)	m.lgll.m.(2)	m.lgll.m.(2) l.m.(5), a.lgll.m.(2)	PET > CT > SRS	B
2	M	MGC (pt -)	U-5HIAA 4.1 CgA 5.4	none	0 (retro +)	m.lgll.m.(2) a.lgll.m.(2), bone(1)	m.lgll.m.(2) a.lgll.m.(3), bone(2)	PET > SRS > CT	B
3	F	MGC (pt -)	U-5HIAA 21.6 CgA 6.8	α -IFN 9MU/w	l.m.(1-2)	a.lgll.m.(3)	l.m.(1) a.lgll.m.(2)	PET = SRS > CT*	B
4	F	MGC	U-5HIAA 2.8 CgA 6.0	none	m.lgll.m.(1)	m.lgll.m.(2) a.lgll.m.(1)	m.lgll.m.(2), l.m.(4) a.lgll.m./p.t.(>5)	PET > SRS > CT	O
5	M	MGC	U-5HIAA 5.2 CgA 29	none	l.m.(5)	l.m.(3)	l.m.(>5) a.lgll.m.(2)	PET > CT > SRS	O
6	F	MGC (pt -)	U-5HIAA 43.6 CgA 47	Sandostatin LAR 30 mg / 4w	bone(1) l.m.(>5) a.lgll.m.(2)	bone(1), l.m.(>5) m.lgll.m.(1) a.lgll.m.(2)	bone(2), l.m.(>5) m.lgll.m.(2) a.lgll.m.(2)	PET > SRS > CT	B
7	F	MGC (pt -)	U-5HIAA 28,2	α -IFN 15MU/w	a.lgll.m.(1)	a.lgll.m.(1)	a.lgll.m.(1), l.m.(3)	PET > SRS = CT	B
8	M	MGC (pt -)	U-5HIAA 45,8 CgA 152	Sandostatin 500 mikrog x 2	l.m.(>5)	l.m.(>5)	l.m.(>5), bone(1) a.lgll.m.(1)	PET > SRS > CT	B
9	M	MGC	U-5HIAA 10.6 CgA 55	none	m.lgll.m.(2) a.lgll.m.(1)	m.lgll.m.(4) a.lgll.m.(1)	m.lgll.m.(>5), l.m.(>5) a.lgll.m.(>5)	PET > SRS > CT	O
10	F	MGC	U-5HIAA 42.6 CgA 134	Sandostatin LAR 30 mg / 4 w	a.lgll.m.(1) l.m.(>5)	a.lgll.m./p.t.?(1) l.m.(>5)	a.lgll.m./p.t.?(3) l.m.(>5)	PET > SRS = CT	B
11	F	MGC	U-5HIAA 2.7 CgA 12.1	none	a.lgll.m.(2) m.lgll.m.(2)	a.lgll.m./p.t.?(2) m.lgll.m.(2)	a.lgll.m./p.t.(5) m.lgll.m.(2), l.m.(5)	PET > SRS = CT	O
12	F	MGC (pt -)	U-5HIAA 0.9 CgA 6.1	α -IFN 15MU/w	0	a.lgll.m.(2)	a.lgll.m.(2)	PET = SRS > CT	-
13	M	MGC (pt -)	U-5HIAA 24.7 CgA 7.7	α -IFN 15MU/w Sandostatin LAR 30mg/4w	m.lgll.m.(2) a.lgll.m.(>5)	m.lgll.m.(2) a.lgll.m.(>5)	m.lgll.m.(3) a.lgll.m.(>5) lung(3)	PET > SRS > CT	B
14	M	Gastrinoma	Gastrin 1587 CgA 50	none	0 (1 a.lgll.m. on endo US)	0	panc.t.(1) <i>or</i> a.lgll.m.(1)	PET > SRS = CT	O
15	M	Gastrinoma (inoperable)	Gastrin 361 CgA 1258	none	panc.t.(1) (>10cm)	panc.t.(1)	panc.t.(1)	PET = SRS = CT	B
16	M	Gastrinoma (pt -)	Gastrin 26600 CgA 2609	Strepto 2g/3w 5-FU 400mg/m ² /3w	l.m.(>5)	l.m.(<5)	l.m.(>5), a.lgll.m.(3)	PET > SRS > CT	B
17	F	Gastrinoma (MEN-1)	Gastrin 12200° CgA 485°	none	l.m.(3)	panc.t.(1), l.m.(2?)	l.m.(3), panc.t.(2)	PET > SRS > CT	O
18	F	Insulinoma (pt -)	Ins 20, CgA 218 Proinsulin 514	Strepto 2g/3w Caelyx 30mg/m ² /4w	lung(>5 "dots") m.lgll.m.(>5) l.m.(>5) a.lgll.m.(>5)	bone(>5) m.lgll.m.(>5) l.m.(>5) a.lgll.m.(>5)	lung(>5) m.lgll.m.(>5) l.m.(>5) a.lgll.m.(>5)	PET = SRS = CT*	B
19	M	EPT (non f, MEN-1)	PP 127 CgA 3,8	none	0 (1 panc.t on US)	0	panc.t.(2)	PET > SRS = CT	O
20	F	EPT (non f) (pt -)	PP 149	none	0 (1 a.lgll.m on US)	a.lgll.m.(1)	0	SRS > CT = PET	O

21	F	EPT(non f) (pt -)	CgA 5.7 PP 594	Strepto 2g/3w 5-FU 400mg/m ² /3w	l.m.(4)	l.m.(2 <i>tracer negative</i>)	l.m.(>5) a.lgll.m.(2)	PET > CT > SRS	O
22	M	EPT(non f) (pt -)	CgA 10	α-IFN 9MU/w	a.lgll.m.(1)	a.lgll.m.(1)	a.lgll.m.(1)	PET = SRS = CT	O
23	M	EPT (non f) (pt -)	CgA 4.2	none	a.lgll.m.(2)	0	a.lgll.m.(3) l.m.(1)	PET > CT > SRS	O
24	F	ECL-oma	CgA 70	none	stomach(1)	stomach(1)	stomach(1)	PET = SRS =CT	B
25	M	Bronchial carc (pt -)	Gastrin 903 CgA 377	Strepto 2g/3w 5-FU 400mg/m ² /3w	l.m.(>5) bone(>5)	l.m.(>5) bone(>5)	l.m.(>5) bone(>5)	PET = SRS = CT	B
26	F	Bronchial carc	normal	none	lung(1)	lung(1)	lung(1)	PET = SRS = CT	O
27	F	Bronchial carc (pt -)	CgA 4.4	none	m.lgll.m.(1) (post op changes?)	m.lgll.m.(1)	m.lgll.m.(2)	PET > SRS = CT	-
28	F	Bronchial carc (pt -)	CgA 4.5	none	0 (retro +)	m.lgll.m.(1)	m.lgll.m.(2), l.m.(>5)	PET > SRS > CT	B
29	F	Bronchial carc Mb Cushing	ACTH 340 U-cortisol 136	none	lung(3) (2 antrakosis at op)	0	lung(1)	PET = CT > SRS	O
30	F	Bronchial carc (Adenocarc?)	CgA 8.8	none	lung(1)	0	lung(1)	PET = CT > SRS	B
31	F	Bronchial carc (St post Mb Cushing, m.lgll.m.-)	normal	none	0	lung(1) m.lgll.m.(1)	lung(1) m.lgll.m.(1)	PET = SRS > CT	O
32	F	Forgut carc (EPT? non f)	CgA 10.5	none	l.m.(>5)	l.m.(>5)	l.m.(>5), panc.t.(1-2)	PET > SRS = CT	B
33	M	Foregut carc/ duodenal carc (a.lgll.m.-)	Proinsulin 45 PP 185	none	0	a.lgll.m./duodenal t.(1)	duodenal t.(1) a.lgll.m.(1), l.m.(4)	PET > SRS > CT	O
34	M	Thymic carc (pt -)	Calcitonin 12.3	none	m.lgll.m.(1)	m.lgll.m.(1)	m.lgll.m.(1)	PET = SRS = CT	-
35	M	Thymic carc (MEN-1)	Proinsulin 34 PP 259	none	thymus(1) l.m.(5), m.lgll.m.(4)	thymus(1)	thymus(1) l.m.(multiple <i>tracer neg</i>)	CT > PET = SRS	B
36	M	Paraganlioma (pt -)	Calcitonin 24	none	0 (CT+MRT retro +)	m.lgll.m.(1)	m.lgll.m.(1)	PET = SRS > CT	O
37	M	E Panc ca	CgA 5.5	none	panc.t.(1) m.lgll.m.(1) l.m. (>5) a.lgll.m.(>5)	m.lgll.m.(1) a.lgll.m.(1)	0 (panc.t. <i>tracer neg</i>) l.m.(3 <i>tracer neg</i>)	CT > SRS > PET	B
38	F	E Panc ca	CgA 5.0	none	panc.t.(1)	l.m.(2)	panc.t.(1), l.m.(4)	PET > SRS >= CT	O

Abbreviations: M, male; F, female; MGC, midgut carcinoid; EPT, endocrine pancreatic tumor; non F, non functioning; MEN-1, multiple endocrine neoplasia type 1; carc, carcinoid; ECL-oma, Entero Chromaffine Like-oma (= gastric carcinoid); E Panc ca, endocrine differentiated pancreatic cancer (with high proliferation index); pt, primary tumor; pt -, primary tumor resected; m/a.lgll.m.-, mediastinal/abdominal lymph node metastasis resected; l.m., liver metastases; a.lgll.m., abdominal lymph node metastases; m.lgll.m., mediastinal lymph node metastases; panc.t., pancreatic tumor; U-5HIAA, urinary-5 hydroxy indole acetic acid (ref range < 2.1 pmol/h); CgA, chromogranin A (ref range < 4 nmol/L); PP, Pancreatic polypeptide (ref range < 100 pmol/L); Gastrin (ref range < 60 pmol/L); Calcitonin (ref range < 10 ng/L); Insulin (ref range < 14 mU/L); Proinsulin (ref range < 16 pmol/L); ACTH, adrenocoticotropin (ref range < 60 ng/L); u-cortisol (ref range 3.8 - 15 nmol/h); ° possibly interfered by markedly reduced kidney function. * same number but different lesion sites. Strepto, Streptozotocin; 5-FU, 5-Fluorouracil; IFN, Interferon; MU, million units; US, abdominal sonography; Endo US, Endosonography; Number of lesions in parenthesis. If more than 5 lesions are seen, this is referred to as > 5. Retro+ = retrospect positive (with knowledge of OS and/or PET-data).











