Tracer development for detection and characterization of neuroendocrine tumors with PET
Neels, Olivier Christiaan

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 23-06-2019
Chapter 5
Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with $^{18}$F-DOPA and $^{11}$C-5-HTP positron emission tomography

Klaas P. Koopmans¹, Oliver C. Neels¹, Ido P. Kema³, Philip H. Elsinga¹, Wim J. Sluiter⁴, Koen Vanghillewe⁵, Adrienne H. Brouwers¹, Elisabeth G.E. de Vries², Pieter L. Jager¹.

Departments of Nuclear Medicine and Molecular Imaging¹, Medical Oncology², Pathology and Laboratory Medicine³, Endocrinology⁴, University of Groningen and University Medical Center Groningen, The Netherlands.
Department of Radiology⁵, Martini Hospital Groningen, The Netherlands.

In press for J Clin Oncol
Summary

Background
To evaluate and compare diagnostic sensitivity of PET scanning in carcinoid and islet cell tumor patients with a serotonin and a catecholamine precursor as tracers.

Methods
Carcinoid (n=24) or pancreatic islet cell tumor (n=23) patients with at least one lesion on conventional imaging including somatostatin receptor scintigraphy (SRS) and CT scan underwent $^{11}$C-5-hydroxytryptophan ($^{11}$C-5-HTP) PET and $^{18}$F-[F-18]fluoro-L-dihydroxyphenylalanin ($^{18}$F-DOPA) PET. PET findings were compared with a composite reference standard derived from all available imaging, clinical and cytological/histological information.

Findings
In carcinoid tumor patients per patient analysis showed sensitivities for $^{11}$C-5-HTP PET, $^{18}$F-DOPA PET, SRS and CT of 100, 96, 86, 96 % respectively and in islet cell tumors of 100, 89, 78, 87%. In carcinoid patients per-lesion analysis revealed sensitivities for $^{11}$C-5-HTP PET, $^{11}$C-5-HTP PET/CT, $^{18}$F-DOPA PET, $^{18}$F-DOPA PET/CT, SRS, SRS/CT and CT alone of respectively 78, 89, 87, 98, 49, 73 and 63% and in islet cell tumors of 67, 96, 41, 80, 46, 77 and 68%. In all carcinoid patients $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET detected more lesions than SRS (p <0.001). $^{11}$C-5-HTP PET was superior to $^{18}$F-DOPA PET in islet cell tumors (p <0.0001). In all cases CT improved the sensitivity of the nuclear scans.

Interpretation
$^{18}$F-DOPA PET/CT is the optimal imaging modality for staging in carcinoid patients and $^{11}$C-5-HTP PET/CT in islet cell tumor patients.

Introduction
Carcinoid tumors and pancreatic islet cell tumors are relatively indolent tumors. They belong to the group of neuroendocrine tumors that arise from neuroendocrine cells. These tumors can produce and secrete a large variety of products because of their intrinsic ability to take up, accumulate and decarboxylate amine precursors\(^1\). Treatment options for these tumors include curative or debulking surgery, systemic treatment with somatostatin analogues, interferon and chemotherapy\(^2\).

To assess individual treatment options, accurate knowledge of tumor localization, biochemical activity and rate of progression is essential. The initial work-up for patients with carcinoid and islet cell tumors consists of morphological imaging methods such as CT, combined with functional whole body imaging using somatostatin receptor scintigraphy (SRS)\(^3,4\). However, on CT and MR imaging of the abdomen it can be difficult to correctly distinguish tumors and mesenterial metastases from intestinal structures. In addition, CT and MR lesions cannot always be perfectly characterized as being malignant, especially in the pancreas, as frequently benign lesions or cysts may have rather similar or a mixed appearance\(^5,6,7\).
Apart from the advantage of covering the whole body in a single investigation, functional imaging methods also allow characterization of lesions on CT or MR. SRS is often used for this purpose. However, it may produce false negative findings, due to variable affinity and expression levels of somatostatin receptors or small size of lesions because of the limited resolution of the gammacamera and single photon emission tomography (SPECT) methods.

Recently, two positron emission tomography (PET) tracers have emerged as potential functional imaging modalities in neuroendocrine tumors. In combination with the high resolution of PET this may lead to a clinically relevant improvement in detection, characterization and staging of these tumors. The first new tracer method is 18F-DOPA PET, employing the catecholamine precursor 6-[F-18]fluoro-L-dihydroxyphenylalanin (18F-DOPA) whose uptake is based on the property of neuroendocrine tumors to take up amine precursors. For the detection of carcinoid disease, its superiority over presently used modalities has been shown, but this advantage is less clear for islet cell tumors. The second metabolic PET tracer 11C-5-hydroxytryptophan (11C-5-HTP) is a direct precursor for the serotonin pathway and therefore a potentially sensitive universal method for neuroendocrine tumor detection. However, availability and experience with 11C-5-HTP is limited due to its complex production. Currently, there are no head-to-head studies available in which 18F-DOPA is compared to 11C-5-HTP PET in their ability to detect neuroendocrine tumors.

Therefore, the aim of this study was to evaluate the diagnostic sensitivity of 11C-5-HTP in comparison with 18F-DOPA PET in a large population of patients with a carcinoid or islet cell tumor.

**Methods**

**Patients**

Patients eligible for this prospective single-centre diagnostic accuracy study were: new patients referred to our centre with a carcinoid or pancreatic islet cell tumor, based on clinical, histological and/or biochemical findings and at least one abnormal lesion detected on CT, MRI, sonography or SRS, and patients known to have a histopathologically proven neuroendocrine tumor, who had a clinical indication for (re)staging and who had at least one abnormal lesion on conventional imaging studies. We excluded patients under 18 years of age, pregnant patients and those with an additional non-neuroendocrine tumor. Each consecutive patient underwent 11C-5-HTP PET, 18F-DOPA PET, SRS, CT of the abdomen and also the chest, when indicated, within a short interval, and in random order. Biochemical analysis for relevant tumor markers in blood and urine was performed. All patients were allowed to continue their medication.

The local medical ethics committee approved the study and all patients gave written informed consent.

**Procedures**

**11C-5-HTP PET and 18F-DOPA PET**

For the reduction of tracer decarboxylation and subsequent renal clearance all patients received 2 mg/kg carbidopa orally as pre-treatment 1 h prior to the 11C-5-HTP and 18F-DOPA injection to increase tracer uptake in tumor cells. 11C-5-HTP was produced using
a multi-enzymatic synthesis of enantiomerically pure $^{11}$C-5-HTP on a Zymark robotic system$^{14}$. Patients fasted for 2 h before the examination. Whole body 2D-PET images were acquired 10 min after the intravenous (IV) administration of $^{11}$C-5-HTP (200 ± 50 MBq, with an estimated mean radiation dose of 0.67 mSv) on a Siemens ECAT HR+ positron camera (Siemens, Knoxville, TN, USA) with attenuation correction (7-10 bed positions of 5 min emission and 3 min transmission scan).

$^{18}$F-DOPA was produced as described earlier$^{17}$. Patients fasted for 6 h before the examination. Whole body 2D-PET images were acquired as described for $^{11}$C-5-HTP PET 60 min after the IV administration of $^{18}$F-DOPA (180 ± 50 MBq, with mean radiation dose of 4 mSv)$^{18}$. Two nuclear medicine physicians (KPK, PLJ) blinded for the results of other imaging examinations and clinical information interpreted the sets of $^{11}$C-5-HTP and $^{18}$F-DOPA PET images independently. Discrepant cases were reviewed in a multidisciplinary team and a consensus was reached. Only lesions with an unequivocal visibility clearly above normal activity in that body region were considered abnormal.

**Somatostatin receptor scintigraphy**

According to Dutch standards, 24 h after IV administration of 200 MBq $^{111}$In-octreotide (Octreoscan; Mallinckrodt, Petten, The Netherlands – with an estimated mean radiation dose of 10 mSv$^{19}$), planar total-body and SPECT images were obtained using standard methods. (Siemens Multispect 2 gammacamera, medium energy collimator, 10 min spotviews, 64 projections of 30 s). If interfering bowel activity was observed, 48 h images were recorded$^{20}$. SRS scans were subsequently independently reread by a nuclear medicine physician (PLJ) blinded for the results of other imaging examinations and clinical information.

**CT**

CT (4-16 slice, Siemens Somatom Sensation, Siemens Medical Systems, Erlangen, Germany – with an estimated mean radiation dose of 8-20 mSv)$^{21}$ was performed using oral contrast and IV contrast (Visipaque 270, 120 ml, 2.5 ml/s) enhancement. The reconstruction interval was 0.75-5 mm. All patients underwent an abdominal CT, 42 patients also a chest CT. CT scans were interpreted as part of routine patient care and were reread by an experienced radiologist (KV) blinded for the clinical information. In discrepant cases consensus was reached after multidisciplinary discussion.

**Composite Reference standard**

As a composite reference standard for presence of tumor lesions, all available cytological, histological, follow-up findings and all imaging findings were used. This is considered the optimal gold standard, as cytological or histological verification of every lesion is not feasible and not justifiable in these patients$^{5}$. Whenever possible, new findings on PET were verified with additional investigations.
Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with $^{18}$F-DOPA and $^{11}$C-5-HTP positron emission tomography

Biochemical analysis
As markers for serotonin metabolism we measured serotonin levels in platelets and urinary 5-hydroxy indole acetic acid (5-HIAA) in a 24 h urine collection (upper reference limits 5.4 nmol/10$^9$ platelets and 3.8 mmol/mol creatinine, respectively)\textsuperscript{22,23,24,25}. Serum chromogranin A was determined using a radioimmunoassay (Cga-React, Cis Bio International, Gif-sur-Yvette, France) as a marker for general neuroendocrine tumor activity (reference interval 20-100 mg/L).

Data and statistical analysis
The STARD checklist was used during design and writing of this report\textsuperscript{26}. Based on earlier studies, $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET are both accurate techniques for staging of neuroendocrine tumors, but results may differ in subgroups\textsuperscript{5,6,14}. Therefore we aimed to study approximately 25 carcinoid and 25 islet cell tumor patients to make a statistically meaningful comparison between both diagnostic methods. We wanted to be able to document an increase in sensitivity from 65\% (average value, for islet cell tumor patients for conventional imaging) to 90\% with $^{11}$C-5-HTP PET, using McNemar’s test for comparison with 80\% power and 5\% two-sided significance levels. Analyses were performed at the level of individual patients and individual lesions. When the number of lesions in one organ (e.g. liver) was higher than 10, the number of lesions was truncated at 10 for that region to avoid bias.

PET and SRS are whole body modalities, while CT only covers the most relevant parts of the body. In order to eliminate bias towards total body imaging methods, only body areas for which all four imaging modalities were available have been evaluated.

Sensitivities were calculated using the composite reference standard, and were compared using paired observations and McNemar’s test. Patient based sensitivity was calculated as number of patients with a positive test (at least one lesion detected) by total number of patients. Per lesion sensitivity of a modality was calculated by dividing the number of positive lesions detected with that modality by the total number of positive lesions. Significance level was 0.05, two-sided. The statistical tests were carried out using the SPSS package version 12.0.

Results
Patients
Between February 2005 and February 2007, 50 consecutive patients were recruited, of which 3 patients declined one or more of the imaging procedures leaving full data of 24 patients with a carcinoid tumor and 23 patients with an islet cell tumor for analysis, as presented in the flow diagram (figure 1). Patient characteristics are presented in table 1.
All carcinoid patients and 39% of islet cell tumor patients had biochemical proof of increased serotonin metabolism. CT, SRS, $^{11}$C-5-HTP PET, $^{18}$F-DOPA PET were carried out within a median of 55 days. In 29 patients both PET scans were performed on the same day. The mean interval between both PET scans was 18 days. Newly detected lesions were confirmed with MRI (n=2), bone scintigraphy (n=2), planar X-ray (n=3) and sonography (n=3), surgery (n=3) or biopsy (n=1). Results in a representative patient are shown in figure 2.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n of patients) Male/Female</td>
<td>29/18</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>56 (18-79)</td>
</tr>
<tr>
<td>New patients vs. patients with known disease (no patients)</td>
<td>11/36</td>
</tr>
<tr>
<td><strong>Patients with abdominal carcinoid (n patients)</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with carcinoid syndrome</td>
<td>12</td>
</tr>
<tr>
<td>Treatment during scan</td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogues (n)</td>
<td>17</td>
</tr>
<tr>
<td>Somatostatin analogues + interferon (n)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Patients with islet cell tumors (n patients)</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment during scan</td>
<td>23</td>
</tr>
<tr>
<td>Somatostatin analogues (n)</td>
<td>4</td>
</tr>
<tr>
<td>Somatostatin analogues + interferon (n)</td>
<td>1</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1</td>
</tr>
<tr>
<td>Radiotherapy on bone metastases</td>
<td>1</td>
</tr>
</tbody>
</table>
Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with $^{18}$F-DOPA and $^{11}$C-5-HTP positron emission tomography

**Figure 2.** Full-color in appendix. Fused $^{18}$F-DOPA – PET CT scan (A), SRS (B), $^{18}$F-DOPA PET (C) and $^{11}$C-5-HTP PET (D) of a 80 year old male patient with metastatic carcinoid tumor. The CT scan shows a mesenterial mass and two smaller lesions in the upper mediastinum. On SRS (both planar and SPECT, not shown here) only the larger mediastinal mass, the large mesenterial mass and a small lesion on the left cranial side of the urinary bladder could be found. Both $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET showed a number of smaller lesions in the upper mediastinum and upper lobes of both right and left lung, with $^{18}$F-DOPA yielding the best contrast. Note that the small lung lesions show less $^{11}$C-5-HTP uptake than $^{18}$F-DOPA uptake.

**Patient based analysis**

Based on our selection criteria, all patients were considered positive for tumor. In a per patient analysis in carcinoid tumor patients, $^{11}$C-5-HTP PET detected one or more tumor lesions in all 24 patients (sensitivity 100%, table 2), whereas $^{18}$F-DOPA PET and CT detected one or more tumor lesions in 23 of 24 patients (sensitivity 96%) and SRS detected one or more tumor lesions in 18 of 21 patients (sensitivity 86%).

In a per patient analysis in patients with islet cell tumors, $^{11}$C-5-HTP detected one or more tumor lesions in 23 of a total of 23 patients (sensitivity 100%) CT detected one or more tumor lesions in 20 of 23 patients (sensitivity 87%), SRS in 14 of 19 patients (sensitivity 78%) and $^{18}$F-DOPA PET 16 of 23 patients (sensitivity 89). However, there were no statistically significant differences.

**Lesion based analysis**

In patients with a carcinoid tumor, 371 tumor lesions were detected based on the composite reference standard (table 3). The largest number of lesions was present in liver and abdomen (75% of all). $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET had the highest sensitivity for the detection of these lesions compared to the other imaging modalities. The smallest lesion size that could be detected with $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET was approximately 5 mm, as measured and confirmed on the PET-CT fused images. Overall $^{18}$F-DOPA PET found most lesions, followed by $^{11}$C-5-HTP PET. However, this difference was not statistically significant. $^{18}$F-DOPA PET and $^{11}$C-5-HTP PET were both significantly better in detecting tumor lesions than SRS ($^{18}$F-DOPA PET: p=0.001 for $^{11}$C-5-HTP PET: p=0.008). The combination $^{18}$F-DOPA PET with CT had the highest sensitivity for
detection of carcinoid lesions (98%), as CT detected lesions missed by nuclear medicine techniques, and vice versa. Therefore, combining nuclear medicine techniques with CT yielded more lesions. When SRS would have been left out, not a single lesion would have been missed.

In patients with islet cell tumors, a total of 294 tumor lesions were detected. Most lesions (71%) were found in the liver and abdomen. In these patients $^{11}$C-5-HTP PET and CT performed equally well, and were both better than the other imaging modalities, although not statistically significant. Both SRS and $^{18}$F-DOPA PET had a relatively poor performance for islet cell tumor detection. Again, combining SRS and PET with CT led to an increased number of detected islet cell tumor lesions and therefore increased sensitivity (table 3) The combination of $^{11}$C-5-HTP PET with CT had the highest sensitivity. When SRS would have been left out, only 8% of all lesions would have been missed. These PET negative lesions were found in two patients.

There was no statistical relationship between elevation of biochemical parameters and imaging results of $^{18}$F-DOPA PET, $^{11}$C-5-HTP PET, SRS, or CT.

Table 2. Patient based analysis.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Number of patients with positive lesions</th>
<th>Sensitivity (95%CI)</th>
<th>Mean and median number of lesions per patient (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid tumor (n=24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>23</td>
<td>96% (78 -100)</td>
<td>7.5; 9.7 (0 – 30)</td>
</tr>
<tr>
<td>SRS</td>
<td>18</td>
<td>86% (62 – 95)</td>
<td>5.5; 6.9 (0 – 30)</td>
</tr>
<tr>
<td>$^{18}$F-DOPA PET</td>
<td>23</td>
<td>96% (73 – 100)</td>
<td>11.0; 13.4 (0 – 33)</td>
</tr>
<tr>
<td>$^{11}$C-5-HTP PET</td>
<td>24</td>
<td>100% (85 – 100)</td>
<td>10.0; 12.1 (0 – 33)</td>
</tr>
<tr>
<td>Islet cell tumor (n=23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>20</td>
<td>87% (66 – 97)</td>
<td>7.0; 8.7 (0 – 41)</td>
</tr>
<tr>
<td>SRS</td>
<td>14</td>
<td>78% (56 – 97)</td>
<td>1.0; 5.1 (0 – 40)</td>
</tr>
<tr>
<td>$^{18}$F-DOPA PET</td>
<td>16</td>
<td>89% (66 – 97)</td>
<td>1.0; 5.2 (0 – 40)</td>
</tr>
<tr>
<td>$^{11}$C-5-HTP PET</td>
<td>23</td>
<td>100% (84 – 100)</td>
<td>3.0; 8.7 (1 – 40)</td>
</tr>
</tbody>
</table>

The results for the patient based analysis are presented with the number of tumor positive patients, patient based sensitivity with 95%CI and the mean and median number of lesions per patient.
Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with 18F-DOPA and 11C-5-HTP positron emission tomography

Table 3. Lesion based analysis.

<table>
<thead>
<tr>
<th></th>
<th>CT Sensitivity (95%CI)</th>
<th>SRS Sensitivity (95%CI)</th>
<th>SRS + CT Sensitivity (95%CI)</th>
<th>¹⁸F-DOPA PET Sensitivity (95%CI)</th>
<th>¹⁸F-DOPA PET + CT Sensitivity (95%CI)</th>
<th>¹¹C-5-HTP PET Sensitivity (95%CI)</th>
<th>¹¹C-5-HTP PET + CT Sensitivity (95%CI)</th>
<th>Number of positive regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carcinoid tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>46% (19-75)</td>
<td>31% (87-62)</td>
<td>69% (38-91)</td>
<td>85% (54-99)</td>
<td>92% (63-100)</td>
<td>85% (54-99)</td>
<td>92% (63-100)</td>
<td>13</td>
</tr>
<tr>
<td>Mediastinal*</td>
<td>75% (53-90)</td>
<td>25% (10-47)</td>
<td>91% (67-98)</td>
<td>58% (36-78)</td>
<td>100% (84-100)</td>
<td>54% (32-75)</td>
<td>54% (32-75)</td>
<td>24</td>
</tr>
<tr>
<td>Lung*</td>
<td>60% (34-84)</td>
<td>50% (21-74)</td>
<td>90% (59-99)</td>
<td>40% (16-68)</td>
<td>73% (44-93)</td>
<td>13% (1-41)</td>
<td>73% (44-93)</td>
<td>15</td>
</tr>
<tr>
<td>Liver</td>
<td>67% (59-74)</td>
<td>62% (54-70)*</td>
<td>78% (71-85)</td>
<td>93% (88-96)</td>
<td>100% (98-100)</td>
<td>84% (78-90)</td>
<td>91% (86-95)</td>
<td>158</td>
</tr>
<tr>
<td>Pancreas</td>
<td>50% (0-100)</td>
<td>0% (0-88)</td>
<td>50% (0-100)</td>
<td>50% (0-100)</td>
<td>100% (12-100)</td>
<td>50% (0-100)</td>
<td>100% (12-100)</td>
<td>2</td>
</tr>
<tr>
<td>Abdomen / pelvis</td>
<td>68% (59-76)</td>
<td>50% (41-59)</td>
<td>83% (75-89)</td>
<td>87% (79-92)</td>
<td>99% (95-100)</td>
<td>81% (73-87)</td>
<td>95% (89-98)</td>
<td>122</td>
</tr>
<tr>
<td>Bone</td>
<td>28% (14-45)</td>
<td>69% (52-84)</td>
<td>69% (52-84)</td>
<td>100% (89-100)</td>
<td>100% (89-100)</td>
<td>92% (77-98)</td>
<td>92% (77-98)</td>
<td>36</td>
</tr>
<tr>
<td>Extremities</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>63% (58-68)</td>
<td>49% (44-54)*</td>
<td>73% (68-78)</td>
<td>87% (84-91)</td>
<td>98% (96-99)</td>
<td>78% (74-83)</td>
<td>89% (86-92)</td>
<td>371</td>
</tr>
</tbody>
</table>

| **Islet cell tumors** |                        |                         |                             |                               |                                    |                                  |                                    |                          |
| Head and neck        | 0% (0-63)              | 100% (36-100)           | 100% (36-100)               | 25% (0-82)                    | 25% (0-82)                        | 50% (5-95)                       | 50% (5-94)                       | 4                         |
| Mediastinal*         | 61% (40-79)            | 37% (18-56)             | 63% (40-79)                 | 43% (24-63)                   | 68% (47-84)                       | 79% (59-92)                      | 93% (76-99)                      | 28                        |
| Lung*               | 0                      | 0                      | 0                            | 0                             | 0                                  | 0                                | 0                                  | 0                         |
| Liver                | 77% (69-84)            | 57% (48-65)             | 85% (78-91)                 | 39% (31-48)                   | 86% (79-92)                       | 67% (59-75)                      | 96% (91-99)                      | 132                       |
| Pancreas             | 50% (26-74)            | 50% (26-74)             | 86% (58-97)                 | 56% (30-79)                   | 83% (58-97)                       | 79% (52-94)                      | 94% (72-100)                     | 18                        |
| Abdomen / pelvis     | 80% (68-89)            | 31% (20-42)             | 81% (69-89)                 | 29% (19-41)                   | 83% (72-91)                       | 50% (38-62)                      | 100% (95-100)                    | 76                        |
| Bone                 | 32% (17-51)            | 46% (27-62)             | 46% (27-62)                 | 68% (49-83)                   | 68% (49-83)                       | 97% (84-100)                     | 97% (84-100)                     | 34                        |
| Extremities          | 50% (0-100)            | 0% (0-89)               | 0% (0-89)                   | 50% (0-100)                   | 100% (12-100)                     | 50% (0-100)                      | 50% (0-100)                      | 2                         |
| **Total**            | 68% (63-74)            | 46% (40-52)             | 77% (72-82)                 | 41% (36-47)                   | 80% (75-85)                       | 67% (62-73)                      | 96% (93-98)                      | 294                       |

The sensitivities for the combination SRS with CT, ¹⁸F-DOPA PET with CT and ¹¹C-5-HTP PET with CT are shown. To illustrate the additional value of combining these scans with each other, the results for the combination of nuclear imaging methods with CT are shown. * p = 0.007 for the comparison of SRS with ¹⁸F-DOPA PET; § p=0.001 for the comparison of SRS with ¹¹C-5-HTP PET and p=0.008 for the comparison of SRS with ¹¹C-5-HTP PET.
Chapter 5

Discussion

This study demonstrates that both $^{11}$C-5-HTP PET and $^{18}$F-DOPA PET have excellent sensitivity to detect carcinoid and islet cell tumors lesions. $^{11}$C-5-HTP PET was the only imaging method, which was able to detect tumor lesions in all carcinoid and islet cell tumor patients. In carcinoid patients $^{18}$F-DOPA PET was the best modality as it detected more lesions compared to all other modalities including $^{11}$C-5-HTP PET, CT and SRS. In islet cells tumors $^{11}$C-5-HTP PET detected more tumor positive patients and lesions than $^{18}$F-DOPA PET and SRS (figure 3). Adding CT to both PET techniques resulted in a slight further improvement in sensitivity (table 3). Therefore $^{18}$F-DOPA PET-CT is considered the optimal technique for staging of patients with carcinoid tumors, and $^{11}$C-5-HTP PET-CT for islet cell tumor patients. In patients with carcinoid tumors, SRS scanning can be omitted without missing any lesions.

For islet cell tumors, this is less clear-cut. $^{11}$C-5-HTP PET combined with CT gives the best tumor detection for most patients. However, in a minority, namely 8% of patients, SRS performs equal or better than metabolic PET imaging methods. Therefore, in patients with islet cell tumors SRS remains of additional value.

Overactivity of the serotonin and most likely also the catecholamine pathway appears to be the key factor that determines the intracellular tracer concentration. Increased activity of transmembrane amino acid transporters results in high entry of both tracers in cells. In the tumoral cytoplasm $^{11}$C-5-HTP and $^{18}$F-DOPA PET are metabolized via the abundantly present enzyme aromatic amino acid decarboxylase (AADC) to hormonal products which can be stored in pathway specific secretory vesicles. In contrast to islet cell tumors, most patients with carcinoid tumors the serotonin pathway is highly active. In these cells, the storage capability for the $^{11}$C-5-HTP metabolites is relatively saturated by endogenous serotonin. The $^{11}$C-5-HTP metabolites are therefore rapidly degraded via mono amino oxidase activity and subsequently excreted from the cell. This may explain the superior diagnostic performance for $^{18}$F-DOPA PET in carcinoid and $^{11}$C-5-HTP in islet cell tumors.

The intracellular tracer concentration is directly related to the probability of visualization using the PET scanner. These high tracer concentrations allow the detection of smaller lesions, up to 5 mm in diameter.

In both patient groups CT detected additional lesions and was therefore complementary to the PET techniques. The combination of $^{11}$C-5-HTP PET with CT proved to be the best method to detect islet cell tumor lesions, whereas the combination $^{18}$F-DOPA PET with CT detected most tumor lesions in patients with carcinoid disease. Both PET combinations performed better than the combination of SRS with CT in both tumor types. Although difficult to quantify, another advantage of combining CT with $^{11}$C-5-HTP or $^{18}$F-DOPA PET is the ability to characterize neuroendocrine origin of lesions of lesions found on CT.

Both PET methods allow better staging and estimation of the total body tumor load. The addition of $^{11}$C-5-HTP PET to CT in islet cell tumor patients clearly helps to provide a better understanding of the number of lesions and their distribution. This will support treatment decisions. In addition, better estimation of the total body tumor load and the detection of metastases in unknown regions may refine clinical management. Finally, the recent development of combined PET-CT scanning gives superior diagnostic information in
Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with $^{18}$F-DOPA and $^{11}$C-5-TP positron emission tomography

a single session, largely obviates the need for SRS, and reduces the burden of multiple diagnostic tests. All other published data regarding $^{11}$C-5-TP are from the group of Uppsala, Sweden. They studied 42 patients with a mixture of neuroendocrine and non-endocrine tumor patients. They concluded that $^{11}$C-5-TP PET was superior to SRS and CT for neuroendocrine tumor lesions and could be regarded as a universal imaging agent for these tumours$^{13}$. No head to head comparison of $^{18}$F-DOPA and $^{11}$C-5-TP versus CT and SRS was performed. Recent data also point to the utility of $^{18}$F-DOPA PET in assessing pancreatic lesions in infants and adults with hyperinsulinism$^{28}$.

![Figure 3. Full-color in appendix. CT scan (A), SRS (B), $^{18}$F-DOPA PET (C) and $^{11}$C-5-TP PET (D) of a 54 year old male patient with metastatic islet cell tumor. The CT scan shows a large mass in the pancreatic head region (arrow), SRS shows equivocal (arrow) and $^{18}$F-DOPA PET shows low uptake in the pancreatic region and minor uptake in the upper chest and in two thoracic vertebrae. $^{11}$C-5-TP PET, however, shows numerous bone, liver and abdominal lesions, including the pancreatic region with much higher contrast.](image-url)

In our study in both patient groups $^{11}$C-5-TP PET was far superior to SRS and in islet cell tumor patients $^{11}$C-5-TP PET performed even better than $^{18}$F-DOPA PET. Therefore, $^{11}$C-5-TP PET could indeed be seen as a universal imaging agent for carcinoid and islet cell tumors. However, the synthesis of $^{11}$C-5-TP PET is complex. For efficient use of available resources and time it seems logical to use $^{18}$F-DOPA PET for all patients with non-islet cell tumors and $^{11}$C-5-TP PET only for those with a proven or a suspected islet cell tumor. As PET is now in general performed in combination with CT, this even further improves the lesion detection and characterization properties of both PET scans and provides anatomical information all in a single and rapid session.

**Acknowledgements**

Supported by grant 2003-2936 from the Dutch Cancer Society.
Chapter 5

References


Improved staging and characterization of lesions in patients with carcinoid and islet cell tumors with $^{18}$F-DOPA and $^{11}$C-5-HTP positron emission tomography


