Molecular Imaging of NET

Prof. Dr. Christophe Deroose
Nuclear Medicine - University Hospitals Leuven (UZ Leuven)
Department of Imaging & Pathology – KU Leuven
Leuven Cancer Institute (LKI)
Leuven, Belgium

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For molecular imaging (diagnosis)

Radionuclide:
Emits radiation upon decay.
The radiation can be detected by the nuclear medicine cameras

Vector:
Is responsible for a specific interaction with the target (receptor, transporter, enzyme,…)
Molecular targets for GEP-NET imaging

Receptor-based

- \(^{99m}\text{Tc}\)-DMSA
- \(^{18}\text{F}\)-DOPA
- \(^{11}\text{C}\)-5-HTP
- \(^{123}\text{I}\)-IMT

Metabolic tracers

- \(^{18}\text{F}\)-Dopamine
- \(^{18}\text{F}\)-FDG
- \(^{123}\text{I}\)-MIBG

Phosphate metabolism

- Lysosome

Peptide receptors

- Secretory vesicle

Serotonin pathway

Catecholamine pathway

Glucose metabolism

Adapted from Koopmans, Crit Rev Oncol Hematol, 2009; 71(3):199-213
MOLECULAR IMAGING IN NET SOMATOSTATIN RECEPTOR IMAGING
Peptide Receptors

Receptor-based

Passive diffusion
Active transport
Receptor/ligand internalisation
LAT1 amino acid transporter
Noradrenaline transporter
NaPi co-transporter
GLUT glucose transporter
VMAT transporter

Somatostatin receptor
Bombesin receptor
CCK receptor
VIP receptor
GLP1 receptor

Adapted from Koopmans, Crit Rev Oncol Hematol, 2009; 71(3):199-213
Somatostatin Receptor (SSTR)

- Seven transmembrane G-coupled receptor
- Six human subtypes
  - SSTR1
  - SSTR2 (2A & 2B)
  - SSTR3
  - SSTR4
  - SSTR5
- Function
  - ↓ secretions
    - Endocrine
    - Exocrine
  - ↓ Cell growth
  - ↑ Apoptosis
- Internalise upon agonist binding / recycle

Weckbecker, 2003, Nat Rev Drug Disc; 2(12):999-1017
Overexpression of SSTR subtypes on NET

- Cytoplasmic staining:
  - SSTR1
  - SSTR3
  - SSTR5

- Membrane bound:
  - SSTR2A


NET LN+  NET ileum  pNET

48%
86%
87%
50%
46%

N=34
SSTR overexpressing tumortypes

NET

- Carcinoid:
  - Thymus
  - Bronchus
  - Esophagus
  - Stomach
  - Small bowel
  - Appendix
  - Large bowel
  - Unknown primary

- Pancreatic NET
  - Gastrinoma
  - Insulinoma
  - Glucagonoma
  - VIPoma
  - ACTHoma
  - Somatostatinoma
  - Non-functioning

GEP-NET

Other tumour entities

- Medullary thyroid carcinoma
- Neuroblastoma
- Pheochromocytoma
- Paraganglioma
- Small-cell lung cancer
- Pituitary gland tumours
- Merkel cell tumours
- Menigeoma
- Renal cell carcinoma
- GIST
The somatostatin receptor as a molecular target in NET

- Overexpression correlates with differentiation status
- No correlation with hormonal function of tumor
- SSTR target of pharmacological and radionuclide therapy – SRS as predictive marker
Diagnostic agents for SSR

**Diagnostic Combinations:**

- **Radio-nuclide**
  - $^{111}$In-DTPA-octreotide (pentetreotide) (Octreoscan®)
  - $^{68}$Ga-DOTA, Tyr$^3$-octreotide ($^{68}$Ga-DOTA-TOC)
  - $^{68}$Ga-DOTA, Tyr$^3$-octreotate ($^{68}$Ga-DOTA-TATE)
  - $^{68}$Ga-DOTA, [Phe$^1$-1-Nal$^3$]-octreotide) ($^{68}$Ga-DOTANOC)

- **Chelator**
  - DTPA
  - DOTA
  - NOTA
  - HYNIC

- **Somatostatin analogue**
  - Octreotide
  - Tyr$^3$-octreotide
  - Tyr$^3$-octreotate
  - Naph-octreotide
Vector molecule for SSTR

- Somatostatin: plasma $T_{1/2} \sim 1$ to $3$ min
- Chemical modification needed

Somatostatin (SS14), 14 amino acids

- Tyr$^3$-Octreotide, 8 amino acids (TOC)
  - Tyr-Cys$_D$Phe-H
  - Trp
  - Lys
  - Thr- Cys-Thr(ol)

- Tyroctreotide, 8 amino acids (TATE)
  - Tyr-Cys$_D$Phe-H
  - Trp
  - Lys
  - Thr- Cys-Thr(ol)

- Naphtalene$^3$-Octreotide, 8 amino acids (NOC)
  - Nap-Cys$_D$Phe-H
  - Trp
  - Lys
  - Thr- Cys-Thr(ol)
Radioisotope – Indium-111

- Indium-111 ($^{111}$In)
- Gamma-emitter (also Auger)
- Cyclotron product
  - $p,2n$ reaction of cadmium Cd-112
- Metal
Radioisotope – Gallium-68

- Gallium-68 (\(^{68}\)Ga)
- Positron emitter
- Generator product (germanium-68)
- No cyclotron needed for production (\(\neq ^{18}\)F)
- Metal
## Affinity profiles (IC$_{50}$ in nM) of SS analogues for human SSTR

<table>
<thead>
<tr>
<th>Peptides</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS-28</td>
<td>$5.2 \pm 0.3$ (19)</td>
<td>$2.7 \pm 0.3$ (19)</td>
<td>$7.7 \pm 0.9$ (15)</td>
<td>$5.6 \pm 0.4$ (19)</td>
<td>$4.0 \pm 0.3$ (19)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>$&gt;10,000$ (5)</td>
<td>$&lt;10,000$ (5)</td>
<td>$187 \pm 55$ (3)</td>
<td>$&gt;10,000$ (4)</td>
<td>$22 \pm 6$ (5)</td>
</tr>
<tr>
<td>CH288</td>
<td>$12 \pm 2$ (5)</td>
<td>$&lt;10,000$ (4)</td>
<td>$376 \pm 84$ (5)</td>
<td>$&gt;10,000$ (3)</td>
<td>$&lt;10,000$ (4)</td>
</tr>
<tr>
<td>DTPA-octreotide</td>
<td>$&gt;10,000$ (6)</td>
<td>$22 \pm 3.6$ (5)</td>
<td>$182 \pm 13$ (5)</td>
<td>$&gt;10,000$ (5)</td>
<td>$237 \pm 52$ (5)</td>
</tr>
<tr>
<td>In-DTPA-octreotide</td>
<td>$2$</td>
<td>$&gt;10,000$ (5)</td>
<td>$22 \pm 3.6$ (5)</td>
<td>$182 \pm 13$ (5)</td>
<td>$&gt;10,000$ (5)</td>
</tr>
<tr>
<td>DOTA-TOC</td>
<td>$14 \pm 2.6$ (6)</td>
<td>$880 \pm 324$ (4)</td>
<td>$743 \pm 190$ (3)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>Y-DOTA-TOC</td>
<td>$11 \pm 1.7$ (6)</td>
<td>$389 \pm 135$ (5)</td>
<td>$73 \pm 12$ (5)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>DOTA-LAN</td>
<td>$26 \pm 3.4$ (6)</td>
<td>$771 \pm 229$ (6)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>Y-DOTA-LAN</td>
<td>$23 \pm 5$ (4)</td>
<td>$290 \pm 105$ (4)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>DOTA-VAP</td>
<td>$29 \pm 7$ (4)</td>
<td>$419 \pm 104$ (4)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>Y-DOTA-VAP</td>
<td>$12 \pm 2$ (5)</td>
<td>$102 \pm 25$ (5)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>DOTA-OC</td>
<td>$14 \pm 3$ (4)</td>
<td>$27 \pm 9$ (4)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>Y-DOTA-OC</td>
<td>$20 \pm 2$ (5)</td>
<td>$27 \pm 8$ (5)</td>
<td>$73 \pm 12$ (6)</td>
<td>$778 \pm 225$ (5)</td>
<td>$73 \pm 12$ (6)</td>
</tr>
<tr>
<td>Ga-DOTA-TOC</td>
<td>$2.5 \pm 0.5$ (7)</td>
<td>$613 \pm 140$ (7)</td>
<td>$&gt;10,000$ (6)</td>
<td>$73 \pm 21$ (6)</td>
<td>$73 \pm 21$ (6)</td>
</tr>
<tr>
<td>Ga-DOTA-OC</td>
<td>$7.3 \pm 1.9$ (4)</td>
<td>$120 \pm 45$ (4)</td>
<td>$&gt;10,000$ (4)</td>
<td>$&gt;10,000$ (4)</td>
<td>$60 \pm 14$ (4)</td>
</tr>
<tr>
<td>DTPA-[Tyr$^3$]-octreotate</td>
<td>$3.9 \pm 1$ (4)</td>
<td>$&gt;10,000$ (4)</td>
<td>$433 \pm 16$ (3)</td>
<td>$&gt;10,000$ (4)</td>
<td>$&gt;10,000$ (4)</td>
</tr>
<tr>
<td>In-DTPA-[Tyr$^3$]-octreotate</td>
<td>$1.3 \pm 0.2$ (3)</td>
<td>$&gt;10,000$ (3)</td>
<td>$433 \pm 16$ (3)</td>
<td>$&gt;10,000$ (4)</td>
<td>$&gt;10,000$ (4)</td>
</tr>
<tr>
<td>DOTA-[Tyr$^3$]-octreotate</td>
<td>$1.5 \pm 0.4$ (3)</td>
<td>$&gt;10,000$ (3)</td>
<td>$433 \pm 16$ (3)</td>
<td>$&gt;10,000$ (4)</td>
<td>$&gt;10,000$ (4)</td>
</tr>
<tr>
<td>Y-DOTA-[Tyr$^3$]-octreotate</td>
<td>$1.6 \pm 0.4$ (3)</td>
<td>$&gt;10,000$ (3)</td>
<td>$433 \pm 16$ (3)</td>
<td>$&gt;10,000$ (4)</td>
<td>$&gt;10,000$ (4)</td>
</tr>
<tr>
<td>Ga-DOTA-[Tyr$^3$]-octreotate</td>
<td>$0.2 \pm 0.04$ (3)</td>
<td>$&gt;10,000$ (3)</td>
<td>$300 \pm 140$ (3)</td>
<td>$300 \pm 140$ (3)</td>
<td>$300 \pm 140$ (3)</td>
</tr>
<tr>
<td>Ga-DOTA-NOC</td>
<td>$1.9 \pm 0.4$</td>
<td>$40 \pm 5.8$</td>
<td>$260 \pm 74$</td>
<td>$7.2 \pm 1.6$</td>
<td>$7.2 \pm 1.6$</td>
</tr>
</tbody>
</table>

**68Ga-DOTATOC: normal biodistribution**

- **High uptake:**
  - Spleen
  - Adrenals
  - Pituitary gland
  - Kidney
  - Bladder

- **Moderate:**
  - Liver
  - Pancreas
    (head/uncinate process)
  - Bowel
  - Inflammatory LN

- **Low:**
  - Lung
  - Brain
  - Muscle
$^{68}$Ga-DOTATOC normal biodistribution: adrenal
$^{68}$Ga-DOTATOC PET/CT is highly sensitive for small tumors

MEN 1
Smallest lesion is 10 mm, but it is hotter than the spleen!
$^{68}$Ga-DOTATATE: detection of small lesions

LN: SUV$_{\text{max}}$ 8.5 – 7 mm

LN: SUV$_{\text{max}}$ 4.5 – 4 mm
**Contribution of SSTR radionuclide imaging**

- **Sensitive and specific** detection of tumoral lesions, including very small lesions (G1&G2):
  - Diagnosis of NET in cases of clinical suspicion
    - lesion on morphological imaging
    - hormonal symptoms
    - ↑ serum chromogranin A
  - Pre-operative staging
  - Post-operative staging
  - Suspicion of recurrence
  - Advanced therapy planning: liver surgery, debulking, SIRT, liver Tx, …

- **Molecular characterization** of tumoral lesions:
  - **Predictive** biomarker for cold somatostatin analogue (SSA) treatment
  - **Predictive** biomarker for peptide receptor radionuclide therapy (PRRT)
2012 ESMO guidelines for NET management

Table 10. Summary of recommendations

- The diagnosis of NET should be confirmed by histopathology (CgA, synaptophysin Ki-67).
- The current classification and staging systems should be applied in the clinic.
- **Somatostatin receptor imaging besides standard imaging (CT and MRI)** is part of standard of care.
- Resection of locoregional disease in patients with small intestinal NET (carcinoids) is recommended.
- Somatostatin analog therapy is first-line therapy in all functional NET and small intestinal NET G1/G2.
- Everolimus and sunitinib are registered for pancreatic NETs based on two phase III randomized trials.
- Temozolomide alone or in combination with capecitabine is promising for treatment of pancreatic NETs.

ENETS Guidelines Si-NET: SRS only if gallium-68 not available!

In the search for a primary tumor, cross-sectional imaging with CT and/or MRI should be followed by $^{68}$Ga-DOTATOC PET in combination with native or preferably 3-phase contrast-enhanced CT (functional imaging) or if not available SRS SPECT/CT.

SRS (\(^{111}\)In-Pentetreotide) detects more NET lesions than FDG or MIBG

SRS ($^{111}$In-Pentetretotide) has higher sensitivity for NET than FDG or MIBG

N=96  All NET subtypes, except colonic (FDG>$^{111}$In-Pentetretotide)

**TABLE 5. Sensitivity of Functional Imaging Results Based on Origin of Tumor**

<table>
<thead>
<tr>
<th>Origin of tumor</th>
<th>SRS</th>
<th>$^{123}$I-MIBG</th>
<th>$^{18}$F-FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal neuroendocrine (n = 45)</td>
<td>91% (41)</td>
<td>71% (32)</td>
<td>36% (16)</td>
</tr>
<tr>
<td>Pancreaticoduodenal neuroendocrine (n = 29)</td>
<td>90% (26)</td>
<td>31% (9)</td>
<td>79% (23)</td>
</tr>
<tr>
<td>Neuroendocrine of lung (n = 7)</td>
<td>86% (6)</td>
<td>57% (4)</td>
<td>71% (5)</td>
</tr>
<tr>
<td>Colonic neuroendocrine (n = 6)</td>
<td>67% (4)</td>
<td>17% (1)</td>
<td>83% (5)</td>
</tr>
<tr>
<td>Unknown or rare origin (n = 9)</td>
<td>89% (8)</td>
<td>44% (4)</td>
<td>78% (7)</td>
</tr>
<tr>
<td>Total</td>
<td>89% (85)</td>
<td>52% (50)</td>
<td>58% (56)</td>
</tr>
</tbody>
</table>

Data in parentheses are numbers of patients.

**TABLE 6. Functional Imaging Results Based on Proliferation Index**

<table>
<thead>
<tr>
<th>Ki67 value</th>
<th>Positive</th>
<th>SRS</th>
<th>Negative</th>
<th>SRS</th>
<th>Positive</th>
<th>$^{123}$I-MIBG</th>
<th>Negative</th>
<th>$^{123}$I-MIBG</th>
<th>Positive</th>
<th>$^{18}$F-FDG</th>
<th>Negative</th>
<th>$^{18}$F-FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2%</td>
<td>87% (40)</td>
<td>13% (6)</td>
<td></td>
<td></td>
<td>48% (22)</td>
<td>52% (24)</td>
<td></td>
<td></td>
<td>41% (19)</td>
<td>59% (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%–15%</td>
<td>96% (25)</td>
<td>4% (1)</td>
<td></td>
<td></td>
<td>73% (19)</td>
<td>27% (7)</td>
<td></td>
<td></td>
<td>73% (19)</td>
<td>27% (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15%</td>
<td>69% (9)</td>
<td>31% (4)</td>
<td></td>
<td></td>
<td>46% (6)</td>
<td>54% (7)</td>
<td></td>
<td></td>
<td>92% (12)</td>
<td>8% (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data in parentheses are numbers of patients.

For Ki67 >2% and 2%-15%, but not for >15% (FDG>$^{111}$In-Pentetretotide)

41% of grade 1 patients are positive on FDG!

Semi-quantitative determination of SSR expression with $^{111}$In-pentetreotide

Krenning scale

Visual comparison of uptake in tumor versus normal organs

Cold somatostatin analogues can slow tumor growth... in SSTR scintigraphy + patients

in 73/85 patients (86%)

- **Positive**: 63/85 (74%; 86% w. scan)
- **Negative**: 10/85 (12%; 14% w. scan)
- **Unknown**: 12/85 (14%)

**Inclusion criterium**: target lesion grade 2 or higher on SSTR scintigraphy (Krenning scale)

100% SSTR positive

HR: 0.34

PFS

HR: 0.47

PFS

Placebo, 40 events; median, 6.0 months

Octreotide LAR, 26 events; median, 14.3 months

Lanreotide 120 mg
32 events, 101 patients
Median not reached

Placebo
60 events, 103 patients
Median, 18.0 mo (95% CI, 12.1–24.0)

P<0.001 for the comparison of progression-free survival
Hazard ratio for progression or death, 0.47 (95% CI, 0.30–0.73)

Rinke, 2009, J Clin Oncol; 2009;27:4656-4663

SUV of $^{68}$Ga-DOTATOC predicts probability of PRRT response in NETs

$\text{SUV}_{\text{max}}: 26.4$

$\text{SUV}_{\text{max}}: 16.5$

Responding Lesions

Non-Responding Lesions

Sens: 68%
Spec: 95%

Sens: 95%
Spec: 60%
Metastatic NET (midgut)
- RECIST progression on fixed dose SSA
- Ki67 <20% (Gr 1/2)
- SRS + (G2-4) all lesions
- Adequate GFR, blood, liver
- No prior PRRT

Stratification
- Fixed dose SSA: <6 months vs >6 months
- SRS uptake score

PRRT $^{177}$Lu-DOTATATE
- 4 x 7.4GBq; interval 8±1w
- 30 mg Octreotide LAR/4w

1 ary end: PFS
2 ary end: ORR, TTP, OS, DoR, PFS$_2$
NETTER-1: Prespecified subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrahepatic metastases</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.20 (0.12–0.35)</td>
</tr>
<tr>
<td>No</td>
<td>0.15 (0.04–0.50)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>&gt; ULN</td>
<td>0.21 (0.09–0.49)</td>
</tr>
<tr>
<td>≤ ULN</td>
<td>0.19 (0.11–0.35)</td>
</tr>
<tr>
<td>Somatostatin receptor expression</td>
<td></td>
</tr>
<tr>
<td>Grade &lt; 4</td>
<td>0.23 (0.12–0.41)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0.18 (0.08–0.39)</td>
</tr>
<tr>
<td>S-HIAA</td>
<td></td>
</tr>
<tr>
<td>&gt; 2x ULN</td>
<td>0.15 (0.08–0.29)</td>
</tr>
<tr>
<td>≤ 2x ULN</td>
<td>0.19 (0.06–0.55)</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td></td>
</tr>
<tr>
<td>&gt; 2x ULN</td>
<td>0.19 (0.09–0.27)</td>
</tr>
<tr>
<td>≤ 2x ULN</td>
<td>0.11 (0.01–0.87)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>ENETS Grade 2</td>
<td>0.15 (0.07–0.34)</td>
</tr>
<tr>
<td>ENETS Grade 1</td>
<td>0.24 (0.13–0.44)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.24 (0.12–0.45)</td>
</tr>
<tr>
<td>Female</td>
<td>0.17 (0.08–0.35)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>0.24 (0.12–0.48)</td>
</tr>
<tr>
<td>≤ 65 yr</td>
<td>0.20 (0.10–0.38)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.21 (0.13–0.33)</td>
</tr>
</tbody>
</table>

**SRS**: $^{68}$Ga-peptide PET is superior to conventional scintigraphy ($^{111}$In-Pentetretotide)

**Comparison** $^{111}$In-Pentetretotide, $^{68}$Ga-DOTATOC, CT (n=84)

- **Sensitivity:**
  - $^{68}$Ga-DOTATOC 97%
  - $^{111}$In-Pentetretotide 52%
  - CT 61%

- **Better performance for small lesions in LN and bone**
  

**Comparison** $^{111}$In-Pentetretotide, $^{68}$Ga-DOTATOC, CT (n=27)

- **Sensitivity:**
  - $^{68}$Ga-DOTATOC 100%
  - $^{111}$In-Pentetretotide 66%
  - CT or MRI 73%

- **$^{68}$Ga-DOTATOC finds more lesions in lung and bones**
  
## Comparison of $^{68}$Ga-DOTA-peptide PET vs. $^{111}$In-pentetreotide

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>$^{68}$Ga-Peptide</th>
<th>Level (Patient/lesion)</th>
<th>Sensitivity $^{111}$In-pentetreotide</th>
<th>Sensitivity $^{68}$Ga-peptide</th>
<th>Δ Sens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriel</td>
<td>2007</td>
<td>84</td>
<td>-TOC</td>
<td>Patient</td>
<td>52.0%</td>
<td>97.0%</td>
<td>45.0%</td>
</tr>
<tr>
<td>Buchmann</td>
<td>2007</td>
<td>27</td>
<td>-TOC</td>
<td>Region</td>
<td>66.0%</td>
<td>100.0%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Srirajaskanthan</td>
<td>2010</td>
<td>51</td>
<td>-TATE</td>
<td>Lesion</td>
<td>11.9%</td>
<td>74.3%</td>
<td>62.4%</td>
</tr>
<tr>
<td>Van Binnebeek</td>
<td>2016</td>
<td>53</td>
<td>-TOC</td>
<td>Lesion</td>
<td>60.0%</td>
<td>99.9%</td>
<td>39.9%</td>
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<tr>
<td>Deppen</td>
<td>2016</td>
<td>78</td>
<td>-TATE</td>
<td>Patient</td>
<td>72.0%</td>
<td>96.0%</td>
<td>24.0%</td>
</tr>
<tr>
<td>Sadowski</td>
<td>2016</td>
<td>131</td>
<td>-TATE</td>
<td>Lesion</td>
<td>30.9%</td>
<td>95.1%</td>
<td>64.2%</td>
</tr>
<tr>
<td>Morgat*</td>
<td>2016</td>
<td>19</td>
<td>-TOC</td>
<td>Lesion</td>
<td>20.0%</td>
<td>76.0%</td>
<td>56.0%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>443</td>
<td></td>
<td></td>
<td>Range</td>
<td>12-72%</td>
<td>74-100%</td>
</tr>
</tbody>
</table>

*: MEN-1

---

Comparison of $^{68}$Ga-DOTATATE PET/CT vs. $^{111}$In-pentetretotide SPECT: largest series on record

<table>
<thead>
<tr>
<th>Comparison  $^{111}$In-Pentetretotide, $^{68}$Ga-DOTATATE, CT (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity:</strong></td>
</tr>
<tr>
<td>– $^{68}$Ga-DOTATATE</td>
</tr>
<tr>
<td>– $^{111}$In-Pentetretotide SPEC/CT</td>
</tr>
<tr>
<td>– CT</td>
</tr>
<tr>
<td><strong>$^{68}$Ga-DOTATATE PET/CT induced change in management</strong></td>
</tr>
<tr>
<td>in 43 of 131 patients (32.8%)</td>
</tr>
<tr>
<td><strong>In patients with carcinoid symptoms and negative biochemical testing:</strong></td>
</tr>
<tr>
<td>– $^{68}$Ga-DOTATATE PET/CT: positive in 65.2%</td>
</tr>
<tr>
<td>– 40% of these were anatomic imaging and $^{111}$In-pentetretotide SPECT/CT negative</td>
</tr>
</tbody>
</table>

Sadowski, 2016, J Clin Oncol; 34(6): 588-96
$^{68}$Ga-DOTATOC ≈ $^{68}$Ga-DOTATATE

- n=40
- Lesions detected:
  - $^{68}$Ga-DOTATOC: 262
  - $^{68}$Ga-DOTATATE: 254 (97%)

SUV$_{\text{max}}$

20.4 ± 14.7
16.0 ± 10.8

**TABLE 2**
Tumor Uptake

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>$^{68}$Ga-DOTATATE</th>
<th>$^{68}$Ga-DOTATOC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Native SUV$_{\text{max}}$</td>
<td>Normalized SUV$_{\text{max}}$ for liver</td>
<td>Normalized SUV$_{\text{max}}$ for muscle</td>
</tr>
<tr>
<td>All</td>
<td>40</td>
<td>16.0 ± 10.8</td>
<td>2.0 ± 2.2</td>
</tr>
<tr>
<td>Hepatic metastases</td>
<td>34</td>
<td>19.2 ± 11.3</td>
<td>2.4 ± 2.7</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>17</td>
<td>10.6 ± 8.7</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>Lymphatic metastases</td>
<td>24</td>
<td>15.4 ± 9.6</td>
<td>1.8 ± 1.8</td>
</tr>
<tr>
<td>Pulmonary metastases</td>
<td>5</td>
<td>9.8 ± 5.5</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>11</td>
<td>18.4 ± 12.3</td>
<td>2.5 ± 2.3</td>
</tr>
</tbody>
</table>

Very similar findings in $^{68}$Ga-DOTATOC vs $^{68}$Ga-DOTATATE

68Ga-DOTANOC vs 68Ga-DOTATATE

Normal Biodistribution

Metastatic NET

Clinical impact of $^{68}$Ga-DOTA-peptide PET/CT vs $^{111}$In-Pentretretotide

- Detection of **smaller** lesions
- Detection of lesions with only **light to moderate** SSR expression
- Detection of **more** lesions
  - $\Rightarrow$ No change in therapy
  - $\Rightarrow$ Change in therapy in substantial fraction of patients e.g.:
    - Additional liver metastases $\Rightarrow$ change in liver directed therapy
    - Extra-hepatic metastases (refrain from SIRS, refrain from liverTx)
- “One stop shop” – **90 minutes** door to door, including diagnostic CT ($^{111}$In-pentetreotide: 2 day procedure)
- Be **careful** with **direct comparison** between $^{111}$In-pentetreotide and $^{68}$Ga-DOTA-peptide PET
  - More lesions does not necessarily mean clinical progression!
Differential binding of SSTR agonists and antagonists

SSTR Agonist

Activated receptor state
Bound to GDP

Inactivated receptor state
Bound to GTP

Based on Ginj, 2006, Proc Natl Acad Sci U S A.; 103(44): 16436-41
Differential binding of SSTR agonists and antagonists

**SSTR Agonist**
- **Activated** receptor state
- Bound to GDP

**SSTR Antagonist**
- **Inactivated** receptor state
- Bound to GTP

Based on Ginj, 2006, Proc Natl Acad Sci U S A.;103(44):16436-41
Differential binding of SSTR agonists and antagonists

SSTR Agonist

Activated receptor state

Internalisation

SSTR Antagonist

Inactivated receptor state

No Internalisation

Based on Ginj, 2006, Proc Natl Acad Sci U S A.; 103(44):16436-41
Imaging somatostatin receptor expression with SSTR antagonists

$^{111}$In-pentetreotide (Octreoscan®) (Agonist)

$^{111}$In-DOTA-BASS (Antagonist)

Pitfall: increased **physiological** uptake in pancreatic head and uncinate process

No Whipple without cytological or morphological imaging confirmation
Pitfall: SSR expression on meningeoma ($^{68}$Ga-DOTATATE)
Pitfall: inflammatory uptake in degenerative osteoarthritis ($^{68}$Ga-DOTATATE)
Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on $^{68}$Ga-DOTATOC
Peptide Receptors – Glucagon-like peptide 1 receptor (GLP-1R)

**Receptor-based**

- **99mTc-DMSA**
- **18F-DOPA**
- **11C-5-HP**
- **123I-IMT**
- **18F-Dopamine**
- **123I-MIBG**
- **18F-FDG**

**Peptide receptors**

- Lysosome
- Nucleus
- Secretory vesicle
- Secretory vesicle

**Pathways**

- **Phosphate metabolism**
- **Serotonin pathway**
- **Catecholamine pathway**
- **Glucose metabolism**

**Transporters**

- LAT1 amino acid transporter
- Noradrenaline transporter
- NaPi co-transporter
- GLUT glucose transporter
- VMAT transporter

**Radiotracers**

- Somatostatin receptor
- Bombesin receptor
- CCK receptor
- VIP receptor
- GLP1 receptor

Adapted from Koopmans, Crit Rev Oncol Hematol, 2009; 71(3):199-213
Glucagon-like peptide 1 receptor (GLP-1R) ligands for SPECT

- Receptors for glucagon-like peptide 1 (GLP-1) are highly overexpressed in almost all insulinomas
  

- \([\text{Lys}^{40}(\text{Ahx-DTPA}^{111}\text{In})\text{NH}_2]\)exendin-4 pre-clinically validated tracer (RIP-Tag mouse model)
  

---

Mouse SPECT/CT

- HE
- Autoradiography

---

Pancreas
Tu

Liver
Tumor

Bladder

D1: distance = 3.8 mm
Glucagon-like peptide 1 receptor (GLP-1R) ligands for SPECT

Man, 64 year
Neuroglycopenia
Endogenous hyperinsulinism

SPECT/CT: small nodule between the duodenum and the superior mesenteric artery

Glucagon-like peptide 1 receptors (GLP-1R) ligands for PET ($^{68}$Ga-DOTA-exendin-4)
MOLECULAR IMAGING IN NET
$^{18}$F-FDG
Differentiation

Ki67 index

Mitoses

Biological aggressiveness

Patient prognosis

SSTR expression

$^{18}$F-FDG

INDOLENT

AGRESSIVE
2-$^{18}$Ffluoro-2-deoxy-D-glucose vs. D-Glucose

- **FDG = Glucose**
  - Transported by GLUT receptors
    - Brain
    - Myocardium – Skeletal muscle
    - Tumoral cells
    - Inflammatory cells (activated neutrophils, macrophages)
    - Bowel (small intestine, colon)
  - Phosphorylation by hexokinase
- **FDG ≠ Glucose**
  - No isomerisation by phosphohexose isomerase
  - No substrate for SGLT (active renal tubular transporter) \( \Rightarrow \) renal clearance
Contribution of $^{18}$F-FDG PET(CT) imaging for GEP-NETs

- **Sensitive** detection of tumoral lesions, including small lesions (G3):
  - Staging
  - Suspicion of recurrence
  - Restaging
  - Therapy monitoring

- **Molecular characterization** of tumoral lesions:
  - **Prognostic** biomaker
  - **Guidance** for (re-)biopsy incase of clinical/morphological progression.
SRS ($^{111}$In-Pentetreotide) has higher sensitivity for NET than FDG or MIBG

N=96  All NET subtypes, except colonic (FDG>$^{111}$In-Pentetreotide)

For Ki67 >2% and 2%-15%, but not for >15% (FDG>$^{111}$In-Pentetreotide)

41% of grade 1 patients are positive on FDG!

18F-FDG PET detects patients with poor prognosis.

- **Progression-free survival (PFS)**:
  - FDG +: Lower progression-free survival probability.
  - FDG -: Higher progression-free survival probability.
  - Hazard Ratio: 9.4
  - 95% CI: 2.9 - 30.8

- **Overall survival (OS)**:
  - FDG +: Lower overall survival proportion.
  - FDG -: Higher overall survival proportion.
  - Hazard Ratio: 10.3
  - 95% CI: 1.3 - 78.7

- Sensitivity for FDG: 58%

Metabolic grading of NET with $^{18}\text{F}$-FDG

Prognostic Stratification of Metastatic Gastroenteropancreatic Neuroendocrine Neoplasms by $^{18}\text{F}$-FDG PET: Feasibility of a Metabolic Grading System

Samer Ezziddin$^1$, Linda Adler$^1$, Amir Sabet$^1$, Thorsten Dirk Pöppel$^2$, Florian Grabellus$^3$, Ali Yüce$^4$, Hans-Peter Fischer$^5$, Birgit Simon$^6$, Tobias Höller$^7$, Hans-Jürgen Biersack$^1$, and James Nagarajah$^2$

**TABLE 3**

<table>
<thead>
<tr>
<th>Pathologic Grade</th>
<th>Pathologic Ki-67 index</th>
<th>Metabolic Grade</th>
<th>T/L SUV ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>pG1</td>
<td>$\leq 2%$</td>
<td>mG1</td>
<td>$&lt; 1$</td>
</tr>
<tr>
<td>pG2</td>
<td>3–20%</td>
<td>mG2</td>
<td>1–2.3</td>
</tr>
<tr>
<td>pG3</td>
<td>$&gt; 20%$</td>
<td>mG3</td>
<td>$&gt; 2.3$</td>
</tr>
</tbody>
</table>

T/L: Tumor/Liver

Metabolic grading of NET with $^{18}$F-FDG

Prognostic Stratification of Metastatic Gastroenteropancreatic Neuroendocrine Neoplasms by $^{18}$F-FDG PET: Feasibility of a Metabolic Grading System

Samer Ezziddin¹, Linda Adler¹, Amir Sabet¹, Thorsten Dirk Pöppel², Florian Grabellus³, Ali Yüce⁴, Hans-Peter Fischer⁵, Birgit Simon⁶, Tobias Höller⁷, Hans-Jürgen Biersack¹, and James Nagarajah²

Ki67:10%  Ki67:1%  Ki67:20%

Metabolic grading of NET with $^{18}$F-FDG

Pathological grading

Metabolic grading

Radiolabelled Neurotransmitter Precursors

- **99mTc-DMSA**
- **18F-DOPA**
- **11C-5-HTP**
- **123I-IMT**
- **18F-Dopamine**
- **123I-MIBG**
- **18F-FDG**

**Pathways:**
- **Phosphate metabolism**
- **Secretory vesicle**
- **Nucleus**
- **Peptide receptors**
- **Catecholamine pathway**
- **Serotonin pathway**

**Transporters:**
- **LAT1 amino acid transporter**
- **Noradrenaline transporter**
- **NaPi co-transporter**
- **GLUT glucose transporter**
- **VMAT transporter**
- **Somatostatin receptor**
- **Bombesin receptor**
- **CCK receptor**
- **VIP receptor**
- **GLP1 receptor**

**Receptor/Ligand Internalisation:**
- **Passive diffusion**
- **Active transport**
- **Receptor/ligand internalisation**

Adapted from Koopmans, Crit Rev Oncol Hematol, 2009; 71(3):199-213
$^{18}$F-FDOPA: 6-L-$^{18}$F-Fluorodihydroxyphenylalanine

Jager, JNM 2008
$^{18}$F-DOPA metabolism

**Diagram:**
- $^{18}$F-FDOPA in plasma
- L-type amino acid transporter
- L-amino acid decarboxylase
- $^{18}$F-Fluorodopamine
- Vesicular monoamine transporter
- $^{18}$F-Fluorodopamine
- Dopamine-ß-hydroxylase
- $^{18}$F-Fluoronorepinephrine

*Inhibited by carbidopa both peripherally and intracellularly*
Diagnostic accuracy of $^{18}$F-DOPA

$^{18}$F-DOPA Planar SRS  PET/CT

$^{18}$F-DOPA biodistribution: striatum, kidney, ureter, bladder

<table>
<thead>
<tr>
<th>Table 1: Patients’ characteristics (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (male/female)</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Newly diagnosed patients vs known disease</td>
</tr>
<tr>
<td>Histological vs biochemical diagnosis</td>
</tr>
<tr>
<td><strong>Primary localisation</strong></td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Duodenum</td>
</tr>
<tr>
<td>Jejunum</td>
</tr>
<tr>
<td>Ileum</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td><strong>Treatment during scan</strong></td>
</tr>
<tr>
<td>Somatostatin analogues only</td>
</tr>
<tr>
<td>Somatostatin analogues and interferon</td>
</tr>
<tr>
<td><strong>Biochemical variables</strong></td>
</tr>
<tr>
<td>Platelet serotonin &gt; 5.4 nmol/10^9 platelets</td>
</tr>
<tr>
<td>Urinary 5-HIAA &gt; 3.8 mmol/mol creatinine</td>
</tr>
<tr>
<td>Urinary metanephrine &gt; 9.9 μmol/mol creatinine</td>
</tr>
<tr>
<td>Urinary normetanephrine &gt; 260 μmol/mol creatinine</td>
</tr>
<tr>
<td>Urinary 3-methoxytyramine &gt; 197 μmol/mol creatinine</td>
</tr>
<tr>
<td>Serum chromogranin A &gt; 100 mg/L</td>
</tr>
</tbody>
</table>

Data are number of patients or median (range).

Koopmans, Lancet Oncol, 2006
Diagnostic accuracy of $^{18}$F-DOPA in patients with carcinoid tumors: lesion base

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$^{18}$F-DOPA</th>
<th>SRS</th>
<th>CT</th>
<th>SRS+CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>46%</td>
<td>54%</td>
<td>65%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(95-98%)</td>
<td>(43-50%)</td>
<td>(51-58%)</td>
<td>(62-69%)</td>
</tr>
</tbody>
</table>

Sensitivity for all studied sites is better for $^{18}$F-DOPA than SRS or than CT, except for lung (55% vs. 64% SRS+CT)

Table 3: Sensitivity of imaging methods in patients with carcinoid tumours

Koopmans, Lancet Oncol, 2006
$^{18}$F-DOPA: normal biodistribution

- Carbidopa pretreatment
- Major uptake in
  - kidneys
  - ureter
  - bladder
- Minor uptake in
  - striatum
  - myocardium
  - liver
  - muscles
- Note absence of pancreatic uptake
\( ^{18} \text{F-DOPA}: \) pathological uptake in NET

- Carbidopa pretreatment
- Carcinoid in several locations
  - abdomen
  - liver
  - mediastinum
- Intense uptake
- Detection of small lesions
- Absence of pancreatic uptake.

Jager, JNM 2008
$^{18}$F-DOPA: pathological uptake in pancreatic islet NET

- Carbidopa pretreatment
- Primary malignant islet cell tumor located in tail of pancreas (blue arrow)
- Several liver metastases (red arrows)

Jager, JNM 2008
$^{11}$C-5-HTP, a serotonergic metabolic tracer for NET

CT  SRS  $^{18}$F-DOPA  $^{11}$C-5-HTP

$^{18}$F-DOPA PET/CT  SRS  $^{18}$F-DOPA  $^{11}$C-5-HTP

$^{11}$C-5-HTP = $^{18}$F-DOPA > SRS

Koopmans, JCO 2008
# 11C-5-HTP, a serotonergic metabolic tracer for NET

**N=294 lesions**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>68%</td>
<td>63 - 74</td>
</tr>
<tr>
<td>SRS (111In-Octreotide)</td>
<td>46%</td>
<td>40 - 52</td>
</tr>
<tr>
<td>SRS + CT</td>
<td>77%</td>
<td>72 - 82</td>
</tr>
<tr>
<td>18F-DOPA</td>
<td>41%</td>
<td>36 - 47</td>
</tr>
<tr>
<td>18F-DOPA + CT</td>
<td>80%</td>
<td>75 - 85</td>
</tr>
<tr>
<td>11C-5-HTP</td>
<td>67%</td>
<td>62 - 73</td>
</tr>
<tr>
<td>11C-5-HTP + CT</td>
<td>96%</td>
<td>93 - 98</td>
</tr>
</tbody>
</table>

Koopmans, JCO 2008
Radiolabeled Catecholamines

- $^{18}$F-DOPA
- $^{11}$C-5-HTP
- $^{123}$I-IMT
- $^{123}$I-MIBG
- $^{18}$F-Dopamine
- $^{18}$F-FDG

**Peptide receptors**

**Phosphate metabolism**

**Secretory vesicle**

**Catecholamine pathway**

**Serotonin pathway**

**Noradrenaline transporter**

**LAT1 amino acid transporter**

**NaPi co-transporter**

**GLUT glucose transporter**

**VMAT transporter**

**Somatostatin receptor**

**Bombesin receptor**

**CCK receptor**

**VIP receptor**

**GLP1 receptor**

**Glucose metabolism**

**Passive diffusion**

**Active transport**

**Receptor/ligand internalisation**

Adapted from Koopmans, Crit Rev Oncol Hematol, 2009; 71(3):199-213
meta-IodoBenzylGuanidine

University of Michigan Medical School, 1980
Guanethidine derivative – Mimicks Norepinephrine (NE)
$^{131}$I or $^{123}$I label
Uptake: (a) Active (type I)
(b) Passive
neuroendocrine tumors
Catecholamine radiopharmaceuticals

- $^{131}$I-MIBG:
  - Low specific activity
  - Physically infavourable characteristics for imaging

- $^{123}$I-MIBG:
  - High specific activity
  - Physically more favourable
    - Photon energy: 159 keV vs 364 keV
    - $T_1/2$: 13 hours vs 192 hours
  - No beta emission
  - $\rightarrow$ reduced dosimetry, increased sensitivity, allows SPECT
  - Negative: Cost

- $^{124}$I-MIBG:
  - PET imaging
Cellular uptake of MIBG - General

1. Uptake 1
2. Passive diffusion
3. Intracellular transport
4. Storage in granules
5. Release from cell.
Cellular uptake of MIBG - NET

Norepinephrin transporter (abbreviation: NET)

Cytoplasmic structures

1: Uptake 1, 2: Passive diffusion, 3: Intracellular transport
4: Storage in granules, 5: Release from cell.
Sensitivity of MIBG for NET

Koopmans, Crit Rev Oncol/Hem, 2009
Binderup, JNM, 2010
Long-Term Outcome and Toxicity After Dose-Intensified Treatment with $^{131}$I-MIBG for Advanced Metastatic Carcinoid Tumors

Samer Ezziddin$^1$, Amir Sabet$^1$, Timur Logvinski$^2$, Khaled Alkawaldeh$^1$, Charlotte J. Yong-Hing$^3$, Hojjat Ahmadzadehfar$^1$, Frank Grünwald$^4$, and Hans-Jürgen Biersack$^1$

**Outcome**

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Treatment Outcomes in Patients with Carcinoid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td><strong>Value</strong></td>
</tr>
<tr>
<td>Radiologic</td>
<td></td>
</tr>
<tr>
<td>Complete or partial remission</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Minor remission</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
</tr>
<tr>
<td>Evaluable (symptomatic)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Complete resolution</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>6 (55)</td>
</tr>
<tr>
<td>No significant change</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival (95% CI)</td>
<td>34 mo (13–55)</td>
</tr>
<tr>
<td>Median overall survival (95% CI)</td>
<td>47 mo (32–62)</td>
</tr>
<tr>
<td>5-y survival (95% CI)</td>
<td>31% (9–54)</td>
</tr>
</tbody>
</table>

Values are reported as number (percentage) unless otherwise indicated.

**Toxicity**

N=31

Take Home Messages

• **SSTR scintigraphy or PET**
  - Sensitivity > 90% compared to conventional techniques
  - Is part of standard management in a large fraction of NET patients
    - Time of diagnosis
    - During follow-up
  - First choice in patients with grade 1 or 2 NET
  - Can be useful in isolated tumor marker rise (chromogranin, 5-HIAA)
  - $^{111}$In-Pentetreotide: not gold standard (use of SPECT/CT strongly advised)
  - $^{68}$Ga-DOTA-peptides are the best tracers, should be used when available
  - Pitfalls: uncinate process, other tumors (e.g. meningeoma), spleen, inflammation
  - Antagonists next step

• **$^{18}$F-FDG**
  - First choice in patients with grade 3 NET for determination of tumor extent
  - Offers prognostic information in patients with grade 1 or 2 NET
  - Metabolic grading in metastatic patients?

• **$^{18}$F-DOPA/$^{11}$C-5-HTP/$^{18}$F-Dopamine**: other techniques inconclusive
Take Home messages
SSR as theranostastic target

FDG is gold standard for NET G3 and has prognostic value in G1/2

SSR imaging, preferentially with PET, is current gold standard for NET (G1/2) imaging

SSR expression can be (semi-)quantitatively scored

Predictive value for cold SSA treatment (Clarinet > Promid)

Very strong predictive value for SSR-targeting radionuclide treatment (PRRT)

GLP-1 PET ligands best imaging agents for benign insulinoma

Other tracers (18F-DOPA/11C-5-HTP/18F-Dopamine) can be considered to localize (biochemically) suspected NET (e.g. ACTH producing tumor)
Henry N. Wagner Jr
1927 - 2012
“Forefather of Nuclear Medicine”

“The future of nuclear medicine is PET….

…and Therapy”
Questions?

Leuven City Hall