Imaging and Treatment of Neuroendocrine Tumors with Radiopeptides

Irene A. Burger, MD
Pärnu (Estonia), October 6 – 10, 2014

Radiology and Nuclear Medicine Department
University Hospital Zurich
Switzerland
Ontogenetics

Neuroendocrine tumors consist of cells of the embryonal neural crest.

Nuclear Medicine

Neuroendocrine tumors have distinctive biochemical features, which give us the possibility to image and treat with specific radioligands.
Neuroendocrine Tumors

**Initiation**
- Inactivation of \(\text{MEN1 (1st hit)}\) \(VHL, NF_1, TSC_1, TSC_2, \ ?3q, \ ?1q\)
- Activation of \(\text{RET (MEN-2)}\)

**Transformation Proliferation**
- Hyperplastic cells
- Dysplastic cells
  - Growth factors: \(\? \text{NGF, TGF, bFGF, VEGF} \text{ MEN1 (2nd hit)}\)
  - Activation of oncogenes e.g. \(c-myc, K-ras\)

**Malignant Evolution**
- Well differentiated tumour
- Moderately differentiated tumour
  - Large LOHs
    - 3p-, 1p-, 18q-, 17p-, 8p-
    - Loss of tumour suppressors e.g. \(\text{PTEN}\)
    - Loss of apoptosis gene(s)
    - Chromosomal instability

- Poorly differentiated tumour
  - Loss of adhesion (CD44, NCAMs)
  - Oncogene activation
  - \(\? \text{VEGF induction} \? \text{ineffective nm23 (MEN1)}\)

**Metastasis**
Neuroendocrine Tumors

Carcinoid
Gastrinoma
Glucagonoma
Insulinoma
PPoma
Somatostatinoma
VIPoma
Non-functioning islet cell carcinoma
Corticotrophinoma
Gonadotrophinoma
Somatotrophinoma
Thyrotrophinoma
Prolactinoma
Non-functioning pituitary adenoma
Phaeochromocytoma
Parathyroid adenoma
Ganglioneuroblastoma
Ganglioneuroma
Neuroblastoma
Medulloblastoma
Paraganglioma
Medullary thyroid carcinoma
Prostate tumour with neuroendocrine differentiation
Breast tumour with neuroendocrine differentiation
### Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Site</th>
<th>% of all carcinoids</th>
<th>Regional metastases (%)</th>
<th>Distant metastases (%)</th>
<th>5-year survival with no metastases (%)</th>
<th>5-year survival with regional metastases (%)</th>
<th>5-year survival with distant metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>25.3</td>
<td>5.2</td>
<td>0.5</td>
<td>81.1</td>
<td>76.7</td>
<td>25.6</td>
</tr>
<tr>
<td>Small intestine</td>
<td>28.2</td>
<td>35.9</td>
<td>22.4</td>
<td>59.9</td>
<td>72.8</td>
<td>50</td>
</tr>
<tr>
<td>Appendix</td>
<td>2.4</td>
<td>28.9</td>
<td>9.9</td>
<td>80.8</td>
<td>88.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Colon</td>
<td>7.6</td>
<td>25.8</td>
<td>29.5</td>
<td>76</td>
<td>71.6</td>
<td>30</td>
</tr>
<tr>
<td>Rectum</td>
<td>18.5</td>
<td>2.2</td>
<td>1.7</td>
<td>90.8</td>
<td>48.9</td>
<td>32.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>5.9</td>
<td>3.1</td>
<td>6.5</td>
<td>69.1</td>
<td>N/A</td>
<td>21.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.4</td>
<td>5.2</td>
<td>0.5</td>
<td>90.9</td>
<td>N/A</td>
<td>28.3</td>
</tr>
</tbody>
</table>

### Mitotic count and Ki-67 index

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)a</th>
<th>Ki-67 index (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

---

*a* Mitotic count per high power field (HPF)

*b* Ki-67 index
Precursor

\[ ^{123} \text{I-MIBG} \]
\[ ^{18} \text{F-DOPA PET/CT} \]

SR

Octreo Scan

\[ ^{68} \text{Ga-DOTATATE PET/CT} \]
\[ ^{68} \text{Ga-DOTATOC PET/CT} \]

M

\[ ^{18} \text{F-FDG PET/CT} \]

\[ ^{131} \text{I-MIBG} \]
\[ ^{177} \text{Lu-DOTATATE} \]
\[ ^{90} \text{Y-DOTATOC} \]
\[ ^{90} \text{Y-SIRT (Liver)} \]
Somatostatin is produced in the D – cells of the pancreas, by the hypothalamus and in the gastrointestinal tract. It is an important regulator of the hormonal and neuronal system.

Somatostatin inhibits the secretion of pancreas enzymes, gastrin and pepsin.

It has further a specific roles over the G-protein linked somatostatin receptors (SSTR).

SSTR is overexpressed in various tumors.
Somatostatin Receptors

SSTR is overexpressed in:

- Mengiomas (SSTR 2)
- Neuroendocrine Tumors (SSTR 2)
- Medulloblastomas (SSTR 2)
- Prostate Cancer (SSTR 1)
- Small Cell Lung Cancer
- Thymomas
- Mesenchymal Tumors
  - Osteosarcomas
  - Angiosarcomas
- Breast Cancer
- Melanomas
Somatostatin Receptors
### Ligands to SSTR:

<table>
<thead>
<tr>
<th>Radiopeptide</th>
<th>Abbreviation (Brand Name)</th>
<th>Targeted Receptor Subtype</th>
<th>IC$_{50}$ (nM, mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>SS-28</td>
<td>sst$_1$</td>
<td>5.2 ± 0.3$^4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_2$</td>
<td>2.7 ± 0.3$^4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_3$</td>
<td>7.7 ± 0.9$^4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_4$</td>
<td>5.6 ± 0.4$^4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_5$</td>
<td>4.0 ± 0.3$^4$</td>
</tr>
<tr>
<td><strong>111$^m$In-DTPA-octreotide</strong></td>
<td><strong>111$^m$In-DTPAOC (OctreoScan)</strong></td>
<td>sst$_2$</td>
<td>22 ± 3.6$^4$</td>
</tr>
<tr>
<td><strong>90$^y$Y-DOTA,Tyr$_3$-octreotide</strong></td>
<td><strong>90$^y$Y-DOTATOC (Onalta)</strong></td>
<td>sst$_2$</td>
<td>11 ± 1.7$^4$</td>
</tr>
<tr>
<td>DOTA,Tyr$_3$-octreotate</td>
<td><strong>DOTATATE</strong></td>
<td>sst$_2$</td>
<td>1.5 ± 0.4$^4$</td>
</tr>
<tr>
<td><strong>90$^y$Y-DOTA-lanreotide</strong></td>
<td><strong>90$^y$Y-DOTALAN</strong></td>
<td>sst$_2$</td>
<td>23 ± 54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_5$</td>
<td>16 ± 3.4$^4$</td>
</tr>
<tr>
<td><strong>111$^m$In-DOTA-1-Nal$_3$-octreotide</strong></td>
<td><strong>111$^m$In-DOTANOC</strong></td>
<td>sst$_2$</td>
<td>3.3 ± 0.2$^{38\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_3$</td>
<td>45 ± 3.3$^{38\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_5$</td>
<td>12.2 ± 1.9$^{38\dagger}$</td>
</tr>
<tr>
<td><strong>111$^m$In-DOTA-BzThi$_3$-octreotide</strong></td>
<td><strong>111$^m$In-DOTABOC</strong></td>
<td>sst$_2$</td>
<td>3.1 ± 0.3$^{38\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_3$</td>
<td>21 ± 1.8$^{38\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_5$</td>
<td>7 ± 2.1$^{38\dagger}$</td>
</tr>
<tr>
<td><strong>90$^y$Y-DOTA-cyclo(D-diaminobutyric acid-Arg-Phe-Phe-D-Trp-Lys-Thr-Phe)</strong></td>
<td><strong>90$^y$Y-KE88</strong></td>
<td>sst$_1$</td>
<td>10 ± 2$^{40\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_2$</td>
<td>12 ± 0.5$^{40\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_3$</td>
<td>5.4 ± 1.1$^{40\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_4$</td>
<td>2.8 ± 2.3$^{40\dagger}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sst$_5$</td>
<td>2.8 ± 1.12$^{40\dagger}$</td>
</tr>
<tr>
<td><strong>Antagonist</strong></td>
<td></td>
<td>sst$_2$</td>
<td>11 ± 0.5$^{43\dagger}$</td>
</tr>
</tbody>
</table>

Octreotide Scintigraphy

We can do better than that.... and do we also need it?

Buchmann et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. EJNM 2007
Gallium-68

Physical half-life about 68 min, decays in 89% via positron emission of 1.92 MeV

It is a generator product of Germanium 68
Physical half-life is 270.8 days

The 68Ge/68Ga generator system is available since the seventies. However, the right chemistry and increased need to image endocrine tumors led to a GMP production of the generators in the last 10 years.
Buchmann et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. EJNM 2007
Especially in bony lesions, Ga68 based PET Imaging has a higher sensitivity than either Octreotide SPECT or CT.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PET (%)</th>
<th>SPECT (%)</th>
<th>CT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97 (69/71)</td>
<td>52 (37/71)</td>
<td>61 (41/67)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (12/13)</td>
<td>92 (12/13)</td>
<td>71 (12/17)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>96 (81/84)</td>
<td>58 (49/84)</td>
<td>63 (53/84)</td>
</tr>
</tbody>
</table>

Gabriel et al. 68Ga-DOTA-Tyr3-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT. JNM 2007
### Octreo-SPECT vs $^{68}$Ga DOTATOC

<table>
<thead>
<tr>
<th>PET/CT</th>
<th>Octreotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 – 150MBq Ga68 (generator)</td>
<td>2 day protocol</td>
</tr>
<tr>
<td>60 minutes resting time</td>
<td>110Mbq Indium-111 (expensive !)</td>
</tr>
<tr>
<td>15’ scanning time</td>
<td>long scanning time (40 min 1 FOV))</td>
</tr>
<tr>
<td>3.47mSv</td>
<td>About 8 – 12 mSv</td>
</tr>
</tbody>
</table>

Gabriel et al. $^{68}$Ga-DOTA-Tyr3-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT. JNM 2007
Octreo-SPECT vs $^{68}$Ga DOTATOC
Patients with Neuroendocrine Tumors (6 Pulmonary NET, 28 Gastroenteropancreatic (GEP) NET, 4 metastatic NET with unknown primary)

All patients received Ga68 DOTATATE PET/CT and FDG – PET/CT

24 Low Grade (Ki67 < 2%)
14 Intermediate Grade (Ki67 2 – 20%) oder High Grade (> 20%)
Patient with Low Grade bronchial carcinoid

Pneumonectomy:

Histology shows a carcinoid close to the hilus of the lung and poststenotic pneumonia.
55 year old patient with NET of unknown primary.

FDG – PET/CT shows histology proven hilar and mediastinal metastases.

Histology revealed Intermediate Grade (Ki67 15%).

FDG in this patient is superior to Gallium DOTATATE.
### Numbers of Patients Showing Predominant Uptake of $^{68}$Ga-DOTATATE or $^{18}$F-FDG According to Tumor Grade

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>Predominant uptake of $^{68}$Ga-DOTATATE</th>
<th>Predominant uptake of $^{18}$F-FDG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/intermediate-grade NET</td>
<td>3</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Low-grade NET</td>
<td>21</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>11</td>
<td>35</td>
</tr>
</tbody>
</table>

Two-tailed $P<.0001$. Fisher exact T-test.

NET indicates neuroendocrine tumors; $^{68}$Ga-DOTATATE, $^{68}$Ga-DOTA-[SCAP][D(R)Phe$^1$,Tyr$^3$]-octreotate; $^{18}$F-FDG, $^{18}$F-Fluorodeoxyglucose.
$^{68}$Ga-DOTATATE at USZ

High grad NET of pancreatic tail (G3).
Left pancreatic resection and splenectomy.

CT- Follow up:

FDG PET/CT:
Heterogeneous lesion of the pancreatic head with central necrosis:

FDG PET/CT with high activity (SUV_{max} 32)

NET of the pancreatic head, G2, Mib-Index 3-5%
18F-FDG vs 68Ga-DOTATATE

Warburg Effect

Ki – 67

DOTATATE  

FDG

Irfan Kayani et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008
$^{68}$Ga-DOTATATE at USZ
Submucosal polyp with well differentiated neuroendocrine tumor (0.6 cm)
### Nebennierenrinde

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>ng/l</td>
<td>&lt; 46</td>
</tr>
<tr>
<td>Cortisol</td>
<td>nmol/l</td>
<td>958</td>
</tr>
</tbody>
</table>

*values in normal range* 176, 114, 1067
Wedge resection left upper lobe:
Well differentiated NET of the lung (Carcinoid),
T1, N0, L1, G1, Mib-1:1%

<table>
<thead>
<tr>
<th></th>
<th>ng/1</th>
<th>mmol/1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>&lt; 46</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Cortisol</td>
<td>54</td>
<td>58</td>
<td>9</td>
</tr>
</tbody>
</table>
$^{68}$Ga-DOTATATE - Further indications?

Medullary thyroid cancer with lymph nodes metastases
Histology: Metastasis of an anaplastic Meningeoma WHO Grad III
Mengiomas have high SSTR2 Expressions. Gallium 68 DOTATOC PET/CT does alter IMRT field in over 50% of the patients.

Gehler et al. [68Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. Rad Oncol. 2009
$^{68}\text{Ga-DOTATATE}$ is not only very sensitive for meningeomas, it can also be used to quantify the expected dose of each lesion in case of a $^{177}\text{Lu}$-therapy.

For this lesion a dose of 11.7 Gy would be expected with 3.7 GBq $^{177}\text{Lu}$-DOTATATE.
$^{68}$Ga-DOTATATE – Further indications?

Prostate Cancer hormonal resistant with new rise in PSA
$^{68}$Ga-DOTATATE – pitfalls:

- hypophysis
- adrenals
- spleen
$^{68}$Ga-DOTATATE – pitfalls:

Pancreatic head
Retrospective review of $^{68}$Ga-DOTANOC PET/CT studies of 100 patients:

<table>
<thead>
<tr>
<th>$^{68}$Ga-DOTANOC uptake in pancreas</th>
<th>Patients ($n$)</th>
<th>PET scans ($n$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal or intense</td>
<td>8</td>
<td>16 (6.5%)</td>
</tr>
<tr>
<td>Diffuse or faint</td>
<td>23</td>
<td>66 (26.9%)</td>
</tr>
<tr>
<td>None</td>
<td>69</td>
<td>163 (66.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>245</td>
</tr>
</tbody>
</table>

Incidence of Increased $^{68}$Ga-DOTANOC Uptake in the Pancreatic Head in a Large Series of Extrapancreatic NET Patients Studied with Sequential PET/CT. JNM 2011, Castellucci et al
Indications:

- Gastro-entero-pancreatic tumours (GEP) (e.g.: carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.), functioning and non functioning
- Sympatho-adrenal system tumours (phaeochromocytoma, paraganglioma, neuroblastoma and ganglioneuroma)
- Medullary thyroid carcinoma
- Pituitary adenoma
- Merkel cell carcinoma
- Small cell lung cancer
- Meningioma
Metaiodobenzylguanidine (MIBG) is a structural analog to Guanethidin and is closely related to Norepinephrin.

MIBG is internalized via the Norpepinephrine Transporter and is stored in the neurosecretory granula via the Monoamine transporter.

MIBG scan is positive in Pheochromocytomes, Neurblastosmas, Ganglioneuroblastomas, Ganglioneurmas, Paragangiosmas, Carcinoids, Medullary Thyreoid Cancer, Merkelcell Carcinomas.

However, we want to go beyond these images
NETs accumulate and decarboxylate L-DOPA. Increased activity of L-DOPA decarboxylase was found to be a hallmark of Neuroendocrine Tumors.

23 patients with carcinoids prospectively enrolled. All patients received SRS and DOPA PET/CT.

DOPA PET is more accurate especially in bone lesions (Sens. 100%, Spec. 91%) but insufficient in lung (Sens. 20%, Spec. 94%)

CT fails in 40% to detect bone lesions.

33 patients with low grade NET prospectively enrolled. All patients received SRS and DOPA PET/CT.

DOPA-PET: Sensitivity of 93% vs. 25% for detection of carcinoid (Ki-67 <5% and containing serotonin) vs. noncarcinoid tumors

SRS: Sensitivity of 81% vs. 75% for detection of carcinoid tumors vs. noncarcinoid tumors

DOPA-PET vs. SRS:
Carcinoids: more accurate staging with DOPA
Noncarcinoids: more accurate staging with SRS

25 Patients, well differentiated NET (9 midgut, 5 pancreatic, 6 lung, 1 paranasal, 4 unknown primary)

Ga 68 DOTATATE PET/CT positive in 54/55 suspected tumor regions. DOPA PET/CT positive in 29/55 regions.

Overall DOTATE PET/CT better in 13 patients. In 11/13 patients with augmented serotonin levels with positive DOPA PET/CT. Serotonin correlates with DOPA SUVmax.
$^{68}$Ga-DOTATATE vs $^{18}$F-DOPA:

Patient with pancreatic NET and normal Serotonin
Patient with metastatic carcinoid and elevated serotonin

68Ga-DOTATATE vs 18F-DOPA:
Indications:

- Carcinoid Tumors (WHO 2000)
- Gastroenteropancreatic tumors
- Glomus tumors
- **Medullary thyroid cancer**
- Small cell lung cancer
- Pheochromocytoma
### Tracer selection:

1. **Is it Well differentiated?**
   - 1. Low Grade  
     - Receptor Imaging
   - 2. Intermediate Grade  
     - FDG or Receptor Imaging
   - 3. High Grade  
     - FDG

2. **Carcinoid/Functional?**
   - 1. Yes  
     - DOPA PET/CT
   - 2. No  
     - Receptor Imaging

3. **Do I want to Treat?**
   - 1. Yes  
     - Receptor Imaging
   - 2. No  
     - See 1/2
Diagnostik und Therapie

$^{123}$I-MIBG
Octreo Scan

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

$^{68}$Ga-DOTATATE PET/CT

$^{68}$Ga-DOTATOC PET/CT

$^{18}$F-FDG PET/CT

$^{131}$I-MIBG

$^{177}$Lu-DOTATATE

$^{90}$Y-DOTATOC

$^{90}$Y-SIRT (Liver)
Cohort Study 2 x 58 patients with carcinoid tumor. Patient either received standard of care (surgery, chemotherapy, external beam) or standard of care and MIBG treatment.
131I-MIBG Therapy:

![Graph showing survival rates over time for two groups (A and B). The graph includes survival curves for different follow-up periods (3 years, 5 years, and 10 years).]

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>% Surviving in group A (95% CI)</th>
<th>% Surviving in group B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>77 (63–86)</td>
<td>56 (43–68)</td>
</tr>
<tr>
<td>5 years</td>
<td>63 (47–75)</td>
<td>47 (34–59)</td>
</tr>
<tr>
<td>10 years</td>
<td>38 (23–53)</td>
<td>33 (21–46)</td>
</tr>
</tbody>
</table>
Image & Treat:

68Gallium – DOTATATE

Lu177 – DOTATATE

Image

Treat
Radiopeptide Therapy: $^{177}$Lu or $^{90}$Y

$^{90}$Y is a high-energy $\beta$ emitter that has a maximum range of 12 mm. $^{177}$Lu has a low energy – with an emission range of 2 mm.

-> Energy deposition within small lesions of 1 cm: $^{90}$Y = 63% $^{177}$Lu = 81%

Therefore $^{90}$Y is supposed to be better for large lesions, while $^{177}$Lu seems to be better for smaller lesions.
Radiopeptide Therapy: $^{177}$Lu or $^{90}$Y

Comparative study with 910 patients with $^{90}$Y DOTA-TOC and 141 patients with $^{177}$Lu DOTA-TOC:

Better overall survival for $^{177}$Lu

Decreased haematotoxicity for $^{177}$Lu
Results
A total of 486 patients completed three or more treatment cycles; 237 patients received \([^{90}\text{Y}-\text{DOTA}]-\text{TOC}\) and 249 patients receiving \([^{90}\text{Y}-\text{DOTA}]-\text{TOC} + [^{177}\text{Lu}-\text{DOTA}]-\text{TOC}\). The rates of severe hematologic toxicity (8.9% vs 11.2%; \(P = .47\)) were comparable.

Conclusion
\([^{90}\text{Y}-\text{DOTA}]-\text{TOC} + [^{177}\text{Lu}-\text{DOTA}]-\text{TOC}\) was superior to \([^{90}\text{Y}-\text{DOTA}]-\text{TOC}\) in patients with \([^{90}\text{Y}-\text{DOTA}]-\text{TOC}\) alone in patients compared with the current practice in radiopeptide therapy with the combination of radioisotopes.
Toxicity:

504 patients accessible, within 24h nausea (25%), vomiting (10%), abdominal discomfort or pain (10%). 1% hormone-related crisis.

Subacute, hematological toxicity, occurred in 3.6% after 4 to 8 weeks Two cases of renal insufficiency (both had pre-existent kidney function deterioration).
ALT/AST increase in patients with extensive liver metastasis. 3 patients with MDS (after 3 years).
Take home:

- FDG is not sensitive in well differentiated NET

- Always keep Ki-67 in mind if you select a tracer:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)a</th>
<th>Ki-67 index (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

- For not hormonal active NET DOTATATE is superior to DOPA

- For smaller lesions use rather $^{177}$Lu – also if you have low blood values.
The Network of USZ – PSI – ETH