PRRT: Status and future
PRRT: Mechanism of Action

- Receptor
- Recycling
- Metabolism
- Lysosome
- Endosome
- Radiopeptide
Pathology proven, inoperable tumor

Tumor uptake on octreoscan ≥ normal liver.

No prior therapy with other radiolabelled somatostatin analogues.

Hb ≥ 6 mmol/L; WBC ≥ 2*10⁹/L; Platelets ≥ 80*10⁹/L; serum creatinine ≤ 150 umol/L.

Karnofsky Performance Status ≥ 50.

Signed informed consent
$^{[177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{Octreotate Therapy in practice}$

- IV Aminoacids 4 h
- IV Granisetron 3mg
- IV $^{177}\text{Lu-Octreotate} 30\text{ min}$
- Hospitalization 1 night
## [\textsuperscript{177}Lu-DOTA\textsuperscript{0, Tyr\textsuperscript{3}}]Octreotate Therapy: 504 patients treated according to protocol; Acute Toxicity

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>450</td>
<td>1322</td>
<td>1772</td>
</tr>
<tr>
<td>Vomiting</td>
<td>170</td>
<td>1602</td>
<td>1772</td>
</tr>
<tr>
<td>Pain</td>
<td>173</td>
<td>1599</td>
<td>1772</td>
</tr>
</tbody>
</table>

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Nausea/Vomiting WHO grade 1-2, duration <24h
### [\(^{177}\text{Lu-DOTA}^0,\text{Tyr}^3\)]Octreotate Therapy: 504 patients treated according to protocol; Subacute Toxicity

<table>
<thead>
<tr>
<th>WHO Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>0.4%</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>WBC</td>
<td>1.4%</td>
<td>0.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>PLT</td>
<td>1.9%</td>
<td>0.8%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Percentages are treatment based
Any grade 3/4 toxicity: 3.6%
Any grade 3/4 toxicity patient based: 9.5%

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Hormonal crises, need for special care ± 1 %
[177Lu-DOTA₀,Tyr³]-Octreotate Therapy: Treatment update Patients treated 2000 - 2007 Update up to dec 2009

Number of patients: 613

GEP: 527 patients

Foreign: 225 patients

Dutch: 302 patients

Off-protocol: 23 patients

Protocol: 279 patients
[\text{\textsuperscript{177}Lu-DOTA}^0,\text{Tyr}^3]\text{Octreotate Therapy}

279 Patients / Serious Side-Effects

- 2 Renal insufficiencies
- 2 Leukemias (1 CML, 1 AML)
- 4 cases of MDS
- 1 pancytopenia > 6mo (2 bone marrow biopsies: No MDS)

- \(9/279 = 3\%\)
<table>
<thead>
<tr>
<th>Tumor</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midgut Carcinoid</td>
<td>37</td>
<td>36</td>
<td>41</td>
<td>22</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>NE Pancreas</td>
<td>3</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>NE Unknown Origin</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Gastrinoma/Insulinoma/Vipoma</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Fore &amp; Hindgut Carcinoid</td>
<td>13</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>93</td>
<td>53</td>
<td>68</td>
<td>263</td>
<td></td>
</tr>
</tbody>
</table>

Best responses are listed
[\textsuperscript{177}Lu-DOTA\textsuperscript{0}, Tyr\textsuperscript{3}] Octreotate Therapy:
Liver metastases from a Pancreatic NET

Ongoing regression and change in appearance of liver metastases
$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{Octreotate Therapy:}$

Tumor Uptake and Response (MR, PR, CR)

Tumor Uptake on the OctreoScan
Overall Survival from treatment start:

OS CR/PR/MR 60 mo, SD60 mo, PD 10 mo
Evaluation after $[^{177}\text{Lu}-\text{DOTA}^0,\text{Tyr}^3]\text{octreotate}$ therapy of QoL and symptoms using QLQ scales in the total group

**Improvement of Quality of Life and Symptoms scales**

**Total group N=265**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Before therapy:</th>
<th>Improvement after therapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GHS/QoL &lt; 100</td>
<td>$\geq +10$ in GHS/QoL</td>
</tr>
<tr>
<td></td>
<td>Symptom scales &gt; 0</td>
<td>$\leq -10$ Symptom scales</td>
</tr>
</tbody>
</table>

- **Global Health Status/QoL**: 83/233 = 36%
- **Fatigue**: 110/223 = 49%
- **Nausea and vomiting**: 47/67 = 70%
- **Pain**: 82/154 = 53%
- **Dyspnnoea**: 47/107 = 44%
- **Insomnia**: 72/123 = 59%
- **Appetite loss**: 57/90 = 63%
- **Constipation**: 28/47 = 60%
- **Diarrhoea**: 86/129 = 67%
### PRRT in GEPNET Patients: Tumor Response

<table>
<thead>
<tr>
<th>Center</th>
<th>Ligand</th>
<th>Patients</th>
<th>CR+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam (Valkema 2002)</td>
<td>$[^{111}\text{In-DTPA}^0]\text{octreotide}$</td>
<td>26</td>
<td>0%</td>
</tr>
<tr>
<td>New Orleans (Anthony 2002)</td>
<td>$[^{111}\text{In-DTPA}^0]\text{octreotide}$</td>
<td>26</td>
<td>8%</td>
</tr>
<tr>
<td>Milan (Bodei 2003)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>21</td>
<td>29%</td>
</tr>
<tr>
<td>Basel (Waldherr 2001/2)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>74</td>
<td>24%</td>
</tr>
<tr>
<td>Basel (Waldherr 2002)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>33</td>
<td>33%</td>
</tr>
<tr>
<td>Multicenter (Valkema 2006)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>58</td>
<td>9%</td>
</tr>
<tr>
<td>Multicenter (Bushnell 2010)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>90</td>
<td>4%</td>
</tr>
<tr>
<td>Copenhagen (Pfeifer 2011)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>53</td>
<td>23%</td>
</tr>
<tr>
<td>Warsaw (Cwikla 2010)</td>
<td>$[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]\text{octreotide}$</td>
<td>58</td>
<td>23%</td>
</tr>
<tr>
<td>Rotterdam (Kwekkeboom 2008)</td>
<td>$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{octreoate}$</td>
<td>310</td>
<td>29%</td>
</tr>
<tr>
<td>Gothenburg (Sward 2010)</td>
<td>$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{octreoate}$</td>
<td>26</td>
<td>38%</td>
</tr>
<tr>
<td>Lund (Garkavij 2010)</td>
<td>$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{octreoate}$</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>Milan (Bodei 2011)</td>
<td>$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{octreoate}$</td>
<td>42</td>
<td>31%</td>
</tr>
<tr>
<td>Center</td>
<td>Ligand</td>
<td>Patients</td>
<td>Liver Mets</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Multicenter (Valkema 2006)</td>
<td>$^{90}\text{Y-DOTATOC}$</td>
<td>58</td>
<td>-</td>
</tr>
<tr>
<td>Multicenter (Bushnell 2010)</td>
<td>$^{90}\text{Y-DOTATOC}$</td>
<td>90</td>
<td>72%</td>
</tr>
<tr>
<td>Copenhagen (Pfeifer 2011)</td>
<td>$^{90}\text{Y-DOTATOC}$</td>
<td>53</td>
<td>87%</td>
</tr>
<tr>
<td>Warsaw (Cwikla 2010)</td>
<td>$^{90}\text{Y-DOTATOC}$</td>
<td>58</td>
<td>85%</td>
</tr>
<tr>
<td>Rotterdam (Kwekkeboom 2008)</td>
<td>$^{177}\text{Lu-octreotate}$</td>
<td>310</td>
<td>89%</td>
</tr>
</tbody>
</table>
PRRT: Adverse events

• $^{90}$Y-DOTATOC: Renal insufficiency in 1-3.5% (3 studies); MDS in 2% of patients (1 study).

• $^{90}$Y-DOTATOC: Renal insufficiency in 9% in 1 study; not all had amino acid protection; poor baseline kidney function not excluded.

• $^{177}$Lu-DOTA-Octreotide: Renal insufficiency in 0.5%; MDS in 1% in 1 study.

• $^{177}$Lu-DOTA-Octreotide update in 279 Dutch patients (long follow-up): 2 renal insufficiencies; 2 Leukemias (1 CML, 1 AML); 4 MDS; 1 pancytopenia > 6mo (2 bone marrow biopsies: no MDS). 9/279 = 3%
PRRT and established therapies

- Except for Sandostatin LAR in midgut carcinoids no proof of efficacy with prospective randomised trials for any treatment.
- Streptozotocin + Doxorubicin, Everolimus, and Sunitinib were proven effective with randomised trials in Pancreatic NETs.
- Many other studies are RETROspective.
- Available retrospective data favour PRRT in terms of PFS.
[¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate Therapy: Randomised Registration Trial

Prospective randomised trial started 2012

Randomisation

¹⁷⁷Lu-Octreotate 4*200 mCi
Sandostatin LAR 30 mg

High Dose Sandostatin LAR
(60 mg/4 wks)

• Midgut carcinoid patients, progressive under Sandostatin LAR
• Primary endpoint: PFS
[\textsuperscript{177}Lu-DOTA\textsuperscript{0},Tyr\textsuperscript{3}]Octreotate Therapy: Expected Next Randomised Trial

- Randomisation

- \textsuperscript{177}Lu-Octreotate 4*200 mCi
- Everolimus or Sunitinib

- Pancreatic NET patients, metastatic, inoperable disease, baseline progressive
- Primary endpoint: PFS
Additional treatment cycles with $^{177}$Lu-octreotate in patients with gastroenteropancreatic neuroendocrine tumours who developed progressive disease after an initial tumour response

Martijn van Essen, Eric P Krenning, Boen L Kam, Dik J Kwekkeboom
Additional treatment with $^{177}\text{Lu}$-octreotate after relapse

Anti-tumour effects:

- Renewed tumour regression
  - 7 / 24 patients (29%)
  - 2 partial remissions
  - 5 minor responses

- Stable disease
  - 6 / 24 patients (25%)

- Progressive disease
  - 11 / 24 patients (46%)
Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with $^{[177}\text{Lu-DOTA}^0,\text{Tyr}^3]$Octreotide


1Department of Nuclear Medicine, 2Department of Surgery, 3Department of Pathology, 4Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands, 5Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, 6Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands.
[177Lu-DOTA⁰,Tyr³]Octreotate Therapy: Inoperable Tumor of the Head of the Pancreas

- Initially inoperable tumor. CT before (May 2004) and 3 months after the last treatment (March 2005). Identical scaling. PR.
- Increase in bodyweight: 14 kg.
Conclusions

- Successful surgery after $^{177}\text{Lu}$-octreotate in an encouraging rate of 9/29 neoadjuvant treated patients (31%)
- Surgery after $^{177}\text{Lu}$-octreotate seems to be associated with improved PFS
- Surgery after $^{177}\text{Lu}$-octreotate could be safely performed in all patients
- Prospective study on the neoadjuvant use of $^{177}\text{Lu}$-octreotate in patients with nonfunctioning pancreatic NETs should be initiated, in which predefined criteria of tumor resectability should be incorporated
PRRT: variants

• Combined $^{90}$Y- and $^{177}$Lu DOTATOC/TATE: 3 retrospective human studies reporting better PFS (No RCT)

• Intraarterial PRRT: Better response rate livermetastases several studies (No RCT)

• Chemosensitisation (Capecitabine): RCT ongoing

• Neoadjuvant PRRT pNETs: several case reports (No RCT)

• Adjuvant PRRT: No Studies
RANDOMISED, PROSPECTIVE TRIALS ARE NEEDED
Combination of PRRT and other treatments promising?

YES

BUT:
• Combination of PRRT and other treatments:
• **Objective Response Rate is not indicative of success,** because a percentage of patients that does not respond to one therapy will respond to the alternative.

• PFS is the outcome parameter to be used
PRRT combined with other Treatments

Considerations

• The question is whether combination within a short timeframe gives better PFS than use the treatments sequentially when there is (renewed) tumor progression

• The control arm for the combination should not be one of the components (PRRT or the treatment with which it is combined) but sequential treatment when there is (renewed) tumor progression

• PRRT + Tx → PFS1
• PRRT → PD → TX → PFS2
[\textsuperscript{177}Lu-DOTA^0, Tyr^3]\textit{Octreotate} Therapy

Conclusions

- PRRT holds great promise
- High tumor response rate
- Limited side-effects
- Good quality of life
- Long progression free period
- Variants, (neo)adjuvant use
- Randomised prospective trial started in carcinoids
- Trial in Pancreatic NETs expected to follow soon