Theranostics in NET

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University Hospital Bonn
University of Bonn
The aim of Theranostics is to provide the right therapy for the right patient at the right time.
NET overexpression of the somatostatin receptors

- Enhanced expression of SSTR on NET compared to normal tissues
- Binding of the SSTR-radiologands to the cell surface
- Internalisation of the SSTR-radiologand-complex
- Uptake of SSTR-radioligand from other cells within the Tumor (such as endothelial cells)
NET overexpression of the somatostatin receptors

- 5 subtypes (SSTR1-5)
- SSTR2 most commonly expressed
- Natural ligand: somatostatin

With courtesy to Dr. Florian Gaertner (University Hospital Bonn)
Theranostics in Neuroendocrine Neoplasia

Theranostics

$^{68}$Ga-DOTATOC PET

$^{177}$Lu-DOTATAE
Theranostics in Neuroendocrine Tumors

Topics

- Neuroendocrine neoplasia (NEN)
- New WHO classification of NEN
- Imaging using radionuclides
- PRRT
  - Evidence
  - Toxicity
  - Combination therapies
Neuroendocrine Neoplasia

- Medullary thyroid cancer
- Thymus-NET
- Neuroblastoma and pheochromocytoma
- Carcinoids of the urogenital tract
- Pulmonary NEN Bronchus-NET
- Typical and atypical
  - SCLC
  - LCNEC
- (GEP-NEN): stomach, duodenum, pancreas, jejunum, ileum, appendix, colon and rectum
- Tumors of the peripheral nervous system
  - Schwannoma
  - Paraganglioma
  - Neuroblastoma
- Merkel cell carcinoma of the skin
• 75 % of all neuroendocrine tumors are in GEP region

• Small intestinal neuroendocrine tumors were first distinguished from other tumors in 1907 by Siegfried Oberndorfer.

• They were named carcinoid tumors because their slow growth was considered to be "cancer-like" rather than truly cancerous.

(Karzinoide Tumoren des Dünndarmes. Frankfurter Zeitschrift für Pathologie, 1907, 1: 426–429)
Incidence of GEP-NEN

Dasari et al., JAMA Internal Medicine 2017
Symptoms

- Behavior: indolent (slow growing) to aggressive
- Symptoms: often non-specific, often late in advanced stages

Vinik Al et al. Pancreas 2009;38:876-889
Small primary and metastases
<table>
<thead>
<tr>
<th>Histological differentiation</th>
<th>WHO-/ENETS- Grade (2017)</th>
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</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td></td>
</tr>
<tr>
<td>Low grade:</td>
<td>G1-NET</td>
</tr>
<tr>
<td>Ki-67 ≤ 3%</td>
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<tr>
<td>Intermediate grade:</td>
<td>G2-NET</td>
</tr>
<tr>
<td>3% &lt; Ki-67 ≤ 20%</td>
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<tr>
<td>High grade:</td>
<td>G3-NET</td>
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<tr>
<td>Ki-67 &gt; 20%</td>
<td></td>
</tr>
<tr>
<td>Poorly-differentiated</td>
<td></td>
</tr>
<tr>
<td>High grade:</td>
<td>G3-NEC</td>
</tr>
<tr>
<td>Ki-67 &gt; 20%</td>
<td>Small cell type</td>
</tr>
<tr>
<td></td>
<td>Large cell type</td>
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<tr>
<td>Histological differentiation</td>
<td>WHO-/ENETS- Grade (2017)</td>
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<tr>
<td>------------------------------</td>
<td>--------------------------</td>
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<tr>
<td>Well-differentiated</td>
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<tr>
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<td>G1-NET Ki-67 ≤ 3%</td>
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<tr>
<td>Intermediate grade:</td>
<td>G2-NET 3% &lt; Ki-67 ≤ 20%</td>
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<tr>
<td>High grade:</td>
<td>G3-NET Ki-67 &gt; 20%</td>
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<tr>
<td>Poorly-differentiated</td>
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<tr>
<td>High grade:</td>
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<tr>
<td>Small cell type</td>
<td></td>
</tr>
<tr>
<td>Large cell type</td>
<td></td>
</tr>
</tbody>
</table>
PET & SPECT Tracers for the detection of NEN

- $^{111}$In-Octreotid (OctreoScan®)
  - Available since 1989
  - Planar Scintigraphy / SPECT
  - Low sensitivity, long protocol (2 days), relatively high radiation exposure

- $^{68}$Ga-DOTA-TOC / -NOC / -TATE
  - PET tracers
  - Higher sensitivity, higher resolution
  - Shorter protocols (2 hours), lower radiation exposure
PET & SPECT Tracers
SSTR-Imaging

Sensitivity 97%

$^{68}$Ga-DOTATOC PET/CT
limited availability
Investigation time: $< 2$ h
Radiation exposure: 3 mSv

Sensitivity 65%

$^{111}$In-Octreotide
Investigation time: $> 24$ h
Radiation exposure: 9 mSv
SSTR-Imaging

Indications

- Staging
  - Metastasis detection / exclusion
  - Primary tumor localization

- Re-Staging
  - Tumor residuals
  - Recurrence

- Determination of receptor status
  - Biotherapy
  - PRRT

- Therapy-Monitoring
• **Staging**
  - SSTR PET "method of choice"
  - should generally be used in all patients preoperatively for staging
  - Exception: insulinomas, since sensitivity is only about 25%

• **Follow-Up**
  - **G1 > 2 cm, limited to pancreas, N0:**
    - US/CT/MR 6 - 12 months post-op, then annually
    - SSTR PET at diagnosis, then every 2 years
  - **G2 > 2 cm or locally invasive or N1:**
    - US/CT/MR every 3 months post-op
    - SSTR PET 3 months post-op, then annually

• **Zollinger-Ellison Syndrome:**
  - SSTR PET preoperatively recommended for gastrinoma localization (duodenum)

• **MEN1-Syndrome without detectable tumor:**
  - Routine use of SSTR PET still unclear
Indications for FDG PET

- Poorly differentiated neuroendocrine carcinomas (NEC G3)
- Evaluation of dedifferentiated tumor cells in NET G1 / G2 /G3
## NEN classification according to histopathology

<table>
<thead>
<tr>
<th>Histological differentiation</th>
<th>WHO-/ENETS- Grade (2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td></td>
</tr>
</tbody>
</table>
| Low grade:                   | G1-NET  
Ki-67 ≤ 3%            |
| Intermediate grade:          | G2-NET  
3% < Ki-67 ≤ 20%       |
| High grade:                  | G3-NET  
Ki-67 > 20%            |
| Poorly-differentiated        |                          |
| High grade:                  | G3-NEC  
Ki-67 > 20%  
Small cell type  
Large cell type |
Scan instead of Biopsy?

Ileum NET, G1 (<2% MIB-1)

With courtesy to Prof. Dr. Kristiansen, Department of Pathology, University Hospital Bonn
FDG PET + SSTR PET

Therapy planning

CUP-NET, Ki67: 17%

P-NET, Ki67: 1-10%

P-NET, Ki67: 10-15%
FDG PET + SSTR PET
PET-assisted biopsy

P-NET Ki67: 5%

• <55% less responsive to platinum based chemo

• >55% more responsive (but still recurred quicker and worse survival)

DOTATOC-PET

FDG-PET

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study


1Department of Oncology, Haukeland University Hospital, Bergen, Norway; 2Department of Medical Sciences, Upstate University, Upstate, Sweden; 3Department of Surgery, Rikshospitalet University Hospital, Oslo, Norway; 4Department of Oncology, University Hospital of Bergen, Bergen, Norway; 5Department of Oncology, University of Oslo, Oslo, Norway.
PET imaging in NEN
FDG PET + SSTR PET

Indications for FDG PET
- Poorly differentiated neuroendocrine carcinomas (NEC G3)
- Evaluation of dedifferentiated tumor cells in NET G1 / G2 /G3

What is the frequency of FDG-positive scans in G1/G2 NET?
13 % - 70 %

What is the impact of FDG-positive scans on prognosis in G1/G2 NET?
FDG-positivity is a significant prognostic factor

PET imaging in NEN
FDG PET + SSTR PET

GEP-NEN Therapies

different ways to treat
Biotherapy
Octreotide & Lanreotide

Figure 1. Progression-free Survival (Intention-to-Treat Population).

- Patients at risk
  - Octreotide LAR: 42 patients/22 events; median, 84.7 months
  - Placebo: 43 patients/26 events; median, 83.71 months

Caplin NEJM 371;3 July 17, 2014
Rinke A et al. Neuroendocrinology 2015
GEP-NEN Therapies

- PRRT
- CTX
- OP
- RTX
- TACE/TARE
- Bio-TX
- Targeted Therapy
<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>half time</th>
<th>$E_\beta$ [keV]</th>
<th>Distance [mm]</th>
<th>$E_\gamma$ [keV]</th>
<th>Pro/Cons</th>
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</thead>
<tbody>
<tr>
<td>$^{90}\text{Y}$</td>
<td>2.7 d</td>
<td>935</td>
<td>2270</td>
<td>-</td>
<td>pro: cross-fire cons: toxicity</td>
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<tr>
<td>$^{177}\text{Lu}$</td>
<td>6.7 d</td>
<td>149</td>
<td>497</td>
<td>208, 113</td>
<td>Best therapeutic</td>
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</tbody>
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Radionuclide Therapy of NEN using $^{177}$Lu-DOTATATE

**NETTER 1 - study**

G1 and G2 MIDGUT-NET, progressive under biotherapy, in each arm 115 patients

- **PRRT + Octreotide LAR 30mg**
  - PFS (median): not reached

- **Octreotide LAR 60mg**
  - PFS (median): 8.4 months

HR [95% CI]: 0.209 [0.129 – 0.338]

$P < 0.0001$

**Overall survival**

FDA approves new treatment for certain digestive tract cancers

For Immediate Release

January 26, 2018

The U.S. Food and Drug Administration today approved Lutathera (lutetium Lu 177 dotate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs.

“GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing,” said Richard Pazdur, M.D., director of the FDA’s Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research. “This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies
Treatment With the Radiolabeled Somatostatin Analog $^{177}$Lu-DOTATAT$_0$Tyr$_3$ Octreotate: Toxicity, Efficacy, and Survival

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Kremning

**Abstract**

Patients and Methods
Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8-29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients, and efficacy analysis in 310 patients.

Results
An overall complete response was 2%, a partial response after 2-8% of administration, a minor response after 20%, a stable disease after 35%, and a progressive disease after 20%.

- Better responses in pancreatic NETs than carcinoids
- Disease-specific survival:
  - 11 months for progressive disease
  - >48 months for stable disease or remission
- Global survival gain estimate: 23-69 months (vs. historical controls)
<table>
<thead>
<tr>
<th>Paper</th>
<th>Year Type*</th>
<th>Radioligand</th>
<th>n</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
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<tbody>
<tr>
<td>Kwekkeboom J Clin Oncol</td>
<td>2008 RS</td>
<td>$^{177}\text{Lu-DOTATATE}$</td>
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<td>NA (≈46)</td>
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<tr>
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<td>2010 PS</td>
<td>$^{90}\text{Y-DOTATOC}$ all with refractory carcinoid syndrome</td>
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<td>Year Type</td>
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<td>ORR (%)</td>
<td>DCR (%)</td>
<td>PFS (mo)</td>
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<td>Imhof J Clin Oncol</td>
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<tr>
<td>Sansovini Neuroendocrinol</td>
<td>2013 PS</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>26 (FD)</td>
<td>39</td>
<td>85</td>
<td>29+</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>26 (RD)</td>
<td>18</td>
<td>77</td>
<td>20</td>
<td>NR</td>
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<tr>
<td>Ezziddin Eur J Nucl Med</td>
<td>2014 RS</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>68</td>
<td>60</td>
<td>85</td>
<td>34</td>
<td>53</td>
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</tbody>
</table>
Patient with Midgut NET, progressive under bio-therapy, Ki67: 5 %
Case example

Patient with Midgut NET, progress under bio-therapy

03/2014  1. Lu-DOTATATE Therapy with 6.0 GBq

06/2014  2. Lu-DOTATATE Therapy with 6.6 GBq

09/2014  3. Lu-DOTATATE Therapy with 6.7 GBq

12/2014  4. Lu-DOTATATE Therapy with 6.0 GBq
Case example
Toxicities

• Nephrotoxicity
  – $^{177}$Lu-based PRRT $< 2\%$ (3-4° CTCAE)
  – $^{90}$Y-based PRRT $5-10\%$ (3-4° CTCAE)

• Hematotoxicity (reversible)
  – $^{177}$Lu-based PRRT $5-10\%$ (3-4° CTCAE)
  – $^{90}$Y-based PRRT $8-13\%$ (3-4° CTCAE)
Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide therapy assessed by EORTC QLQ-C30

Milka Marinova¹ · Martin Mücke²,³,⁴ · Lukas Mahlberg⁵ · Markus Essler⁵ · Henning Cuhls² · Lukas Radbruch² · Rupert Conrad⁶ · Hojjat Ahmadzadehfar⁵

Excluded from the analysis
n=63
- 47 patients did not fill the EORTC QLQ-C30 questionnaire or the form was incomplete
- 11 patients were missed to FU³ or less than 3-months FU
- 5 patients were still under PRRT therapy

*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [0-100] ³ follow-up
IMPROVED QUALITY OF LIFE: P-NET under PRRT

Marinova et al. EJNMMI 2017
Quality of life in patients with midgut NET following peptide receptor radionuclide therapy

Milka Marinova¹ • Martin Mücke²,³,⁴ • Felix Fischer⁵ • Markus Essler⁵ • Henning Cuhls² • Lukas Radbruch² • Shiwa Ghaei¹ • Rupert Conrad⁶ • Hojjat Ahmadzadehfar⁵
PRRT
mono- or combination therapy

PRRT as monotherapy or in combination with biotherapy

PRRT + Temozolomide
PRRT + Temozolomide /Capecitabine

18F-FDG PET  68Ga-DOTATOC PET  68Ga-DOTATOC PET  18F-FDG PET
GEP-NET Therapies

- OP
- CTX
- PRRT
- Bio-TX
- RTX
- TACE/TARE
- Targeted Therapy

PRRT + Biotherapy
Is there a survival benefit of adding SSA to PRRT as a combination therapy or maintenance therapy?
## PRRT + Biotherapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All pts n (%)</th>
<th>Group 1 n (%)</th>
<th>Group 2 n (%)</th>
<th>( P(\chi^2) )</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>89 (53.0)</td>
<td>40 (49.4)</td>
<td>49 (56.3)</td>
<td>n.s.</td>
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<tr>
<td>Female</td>
<td>79 (47.0)</td>
<td>41 (50.6)</td>
<td>38 (43.7)</td>
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</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.1</td>
<td>63.1</td>
<td>63.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Patients &lt;65</td>
<td>92 (54.8)</td>
<td>43 (53.1)</td>
<td>49 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Patients &gt;65</td>
<td>76 (45.2)</td>
<td>38 (46.9)</td>
<td>38 (43.7)</td>
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<tr>
<td><strong>EGOG-index</strong></td>
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<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>n.s.</td>
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<tr>
<td>ECOG 0</td>
<td>34 (20.2)</td>
<td>11 (13.6)</td>
<td>23 (26.4)</td>
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<tr>
<td>ECOG 1</td>
<td>114 (67.9)</td>
<td>60 (74.1)</td>
<td>54 (62.1)</td>
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<tr>
<td>ECOG 2</td>
<td>20 (11.9)</td>
<td>10 (12.3)</td>
<td>10 (11.5)</td>
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<td><strong>Type of GEP-NET</strong></td>
<td></td>
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<tr>
<td>Pancreas</td>
<td>84 (50)</td>
<td>48 (59.3)</td>
<td>36 (41.4)</td>
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<tr>
<td>Midgut</td>
<td>46 (27.4)</td>
<td>18 (22.2)</td>
<td>28 (32.2)</td>
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<tr>
<td>Others</td>
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<td>15 (18.5)</td>
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<td><strong>Tumor functionality</strong></td>
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<tr>
<td>Functioning</td>
<td>99 (58.9)</td>
<td>44 (54.3)</td>
<td>55 (63.2)</td>
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<td>Nonfunctioning</td>
<td>69 (41.1)</td>
<td>37 (45.7)</td>
<td>32 (36.8)</td>
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<td><strong>Ki67</strong></td>
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<tr>
<td>Mean</td>
<td>5.6</td>
<td>5.8</td>
<td>5.4</td>
<td>n.s.</td>
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<tr>
<td>&lt;10%</td>
<td>113 (76.9)</td>
<td>54 (76.1)</td>
<td>59 (77.6)</td>
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<tr>
<td>≥10 to ≤20%</td>
<td>34 (23.1)</td>
<td>17 (23.9)</td>
<td>17 (22.4)</td>
<td></td>
</tr>
</tbody>
</table>
**PRRT + Biotherapy**

- Median progression-free survival: 48 months
- Median overall survival: 91 months

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- Median progression-free survival: 27 months
- Median overall survival: 47 months

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- Median progression-free survival: 27 months
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- Median overall survival: 47 months

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- Median progression-free survival: 27 months
- Median overall survival: 47 months

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**Overall survival**

- **Ki67 < 10%**
  - Median: 90 months

- **Ki67 ≥ 10%**
  - Median: 32 months

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**Yordanova et al. Clin Cancer Res. 2018 Jun 27.**
GEP-NET Therapies

PRRT + Chemotherapy

CTX
PRRT
Bio-TX
OP
RTX
TACE/TARE
Targeted Therapy
1- Radiosensitizing 5-FU is administered as a continuous infusion at a dose of 200 mg/m²/day from the second cycle of PRRT starting 4 days prior to radionuclide administration and continuing for up to 3 weeks.

*During the period of this study, 5-FU is omitted from the first cycle to minimize flare as a result of hormone secretion*

2- Chemotherapy with oral 1,650 mg/m² capecitabine (Xeloda, Roche Products) for 14 consecutive days is commenced on the morning of radionuclide therapy. Cycles of capecitabine are repeated every 8 weeks at the time of each subsequent radiopeptide infusion.

3- Chemotherapy commences 5 days prior to PRRT with oral capecitabine 1,650 mg/m² for 14 days in patients not receiving temozolomide.
The capecitabine dose is fixed at 1,500 mg/m² for 14 days in all patients receiving temozolomide.
Oral temozolomide is given in the last 5 days of each 14-day capecitabine period.


median OS: was not achieved
Later reported: median OS: 55 months

median PFS: 48 months
Safety:

Leucopenia: in 42 % (no G3/4)

Anemia: 38 % (no G3/4)

Thrombocytopenia: in 38 % (G3/4: 6%)

we need more data


From August 1999 to May 2017, 149 patients with GEP NEN G3 received PRRT at 12 centers.

### Tumor differentiation
- **Well**: 60 (40)
- **Intermediate**: 9 (6)
- **Poor**: 62 (42)
- **Not specified**: 18 (12)

**Percentage Ki-67**
- **21–54%**: 125 (84)
- **≥55%**: 23 (15)
- **Not specified**: 1 (1)

### Ki-67 and differentiation
- **NET G3**: 58 (39)
- **NEC; Ki-67 21–54%**: 44 (30)
- **NEC; Ki-67 ≥55%**: 17 (11)
- **Not specified**: 30 (20)

### Number of prior lines of medical treatment
- **0**: 30 (20)
- **1**: 62 (42)
- **2**: 31 (21)
- **>2**: 26 (18)

### Prior treatment
- **Primary tumor resected**: 58 (39)
- **Somatostatin analog**: 74 (50)

### Chemotherapy/targeted therapy
- **In total**: 88 (59)
  - **Cisplatin**: 31 (21)
  - **Carboplatin**: 26 (17)
  - **Etoposide**: 46 (31)
  - **Capecitabine/5-fluorouracil**: 38 (26)
  - **Temozolomide**: 19 (13)
  - **Streptozotocin**: 13 (9)
  - **Everolimus**: 9 (6)
  - **Doxorubicin**: 5 (3)
  - **Sunitinib**: 4 (3)
  - **Oxaliplatin**: 4 (3)
  - **Interferon**: 2 (1)
## Table 3  PRRT response (n = 114) and outcomes (n = 149) in GEP NEN G3.

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>PFS (m) (95% CI)</th>
<th>OS (m) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1 (1)</td>
<td>47 (41)</td>
<td>43 (38)</td>
<td>23 (20)</td>
<td>14 (10.4–17.6)</td>
<td>29 (23.3–34.7)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2)</td>
<td>21 (36)</td>
<td>26 (45)</td>
<td>10 (17)</td>
<td>16 (11.0–21.0)</td>
<td>39 (28.1–49.9)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>17 (53)</td>
<td>8 (25)</td>
<td>7 (22)</td>
<td>14 (8.2–19.8)</td>
<td>23 (16.2–29.8)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>3 (38)</td>
<td>2 (25)</td>
<td>3 (38)</td>
<td>3 (0–6.2)</td>
<td>4 (0–12.6)</td>
</tr>
<tr>
<td>SRI tumor uptake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Liver</td>
<td>1 (9)</td>
<td>3 (27)</td>
<td>4 (36)</td>
<td>3 (27)</td>
<td>16 (7.9–24.1)</td>
<td>25 (8.6–41.4)</td>
</tr>
<tr>
<td>&gt;Liver</td>
<td>0</td>
<td>44 (43)</td>
<td>38 (37)</td>
<td>20 (20)</td>
<td>14 (10.0–18.0)</td>
<td>29 (21.6–36.4)</td>
</tr>
<tr>
<td>Primary tumor site</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Pancreas</td>
<td>0</td>
<td>32 (48)</td>
<td>23 (34)</td>
<td>12 (18)</td>
<td>14 (10.4–17.6)</td>
<td>29 (21.7–36.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>11 (42)</td>
<td>9 (35)</td>
<td>6 (23)</td>
<td>10 (0–21.2)</td>
<td>31 (7.5–54.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>11 (52)</td>
<td>5 (24)</td>
<td>16 (8.4–23.6)</td>
<td>29 (11.4–46.6)</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>0</td>
<td>19 (42)</td>
<td>23 (51)</td>
<td>3 (7)</td>
<td>19 (13.9–24.1)</td>
<td>44 (25.2–62.8)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (2)</td>
<td>21 (41)</td>
<td>13 (25)</td>
<td>16 (31)</td>
<td>8 (3.3–12.7)</td>
<td>19 (11.7–26.3)</td>
</tr>
<tr>
<td>Proliferation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 21–54%</td>
<td>1 (1)</td>
<td>41 (41)</td>
<td>41 (41)</td>
<td>16 (16)</td>
<td>16 (12.7–19.3)</td>
<td>31 (24.2–37.8)</td>
</tr>
<tr>
<td>Ki-67 ≥55%</td>
<td>0</td>
<td>6 (43)</td>
<td>2 (14)</td>
<td>6 (43)</td>
<td>6 (3.0–9.0)</td>
<td>9 (4.5–13.5)</td>
</tr>
<tr>
<td>Differentiation and proliferation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET G3</td>
<td>0</td>
<td>18 (42)</td>
<td>22 (51)</td>
<td>3 (7)</td>
<td>19 (14.4–23.6)</td>
<td>44 (25.3–62.7)</td>
</tr>
<tr>
<td>NEC; Ki-67 21–54%</td>
<td>1 (3)</td>
<td>16 (41)</td>
<td>12 (31)</td>
<td>10 (26)</td>
<td>11 (5.4–16.6)</td>
<td>22 (16.0–28.0)</td>
</tr>
<tr>
<td>NEC; Ki-67 ≥55%</td>
<td>0</td>
<td>5 (45)</td>
<td>1 (9)</td>
<td>5 (45)</td>
<td>4 (0.8–7.2)</td>
<td>9 (1.6–16.4)</td>
</tr>
</tbody>
</table>
PRRT in NET G3

Take-home message

- Both SSTR PET and FDG PET are important modalities in NEN
  - Treatment Planning / Biopsy

- PRRT is one of the most efficacious systemic therapies for inoperable NETS
  - Objective response
  - PFS and OS
  - Quality of life

- PRRT is well tolerated
  - Serious toxicity is rare with $^{177}$Lu-DOTATATE
Take-home message

PRRT is an essential modality in the multidisciplinary management of NET patients

PRRT for NET G3

PRRT may be combined with biotherapy

PRRT should be combined with chemotherapy in specific cases
Prof. Dr. med. Hojjat Ahmadzadehfar, MSc
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