68Ga-DOTA-peptides
PET/CT

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NOW: WHAT WE ARE AWARE OF

HETEROGENEOUS

BIOLOGICALLY

METABOLICALLY

GENERALLY → A BETTER PROGNOSIS
as compared to other malignancies

HOWEVER

MORE AGGRESSIVE DISEASE
→ @ diagnosis
→ during the natural course

CLINICAL DIFFERENCES
ACCORDING TO PRIMARY SITES
ENETS GUIDELINES 2016: A SITE SPECIFIC APPROACH

- GEP
  - Pancreatic (F and NF)
  - Ileum/Jejunum
  - Gastric/Duodenal
  - Appendix
  - Colon/Rectal

- Lung

- Metastatic NEN and CUP

- Other
ARE NEN RARE TUMOURS?


PREVALENCE IS ON THE RISE
Adult patients with a NET diagnosis from 1994 to 2009 in Ontario, Canada: 5619 cases were identified.

- **PREVALENCE IS ON THE RISE**

NETs incidence increased from 2.48 to 5.86 per 100,000 per year: 2.36-fold increase vs 1.13 of all cancers.

NM-NEN DIAGNOSIS

**RECEPTOR IMAGING**

- SOMATOSTATIN RECEPTORS
  - 68Ga-DOTA-peptides PET/CT
  - Octreoscan
  - SPECT/CT
  - GLP1-R
    - 68Ga-exendin4

**METABOLIC IMAGING**

- 18F-DOPA PET/CT
- 11C-HTTP
- 18F-FDG PET/CT

Critical Reviews in Oncology/Hematology
71 (2009) 199–213
WHAT PET/CT TRACER?

- **RECEPTOR**
  - 68Ga-DOTA-peptides
  - SR expression
  - tumour grade
  - clinical indication

- **METABOLIC**
  - 18F-DOPA and 18F-FDG
WHAT PET/CT TRACER?

- RECEPTOR
  - Well differentiated, SR expressing tumours

- METABOLIC
  - Low/variable SR-expressing
  - High grade NEN
NEN: GRADING $\rightarrow$ ki67 thresholds

The G2 group

pNEN $\rightarrow$ a cut-off of 5%. G1 vs G2

In G3 $\rightarrow$ cut-off value of 55%
*Milione M et al, Neuroendocrinology. 2016 Mar 5. [Epub ahead of print]*
WHAT PET/CT TRACER?

2010 Who classification

- G1: 68Ga-DOTA-peptides, 18F-DOPA
- G2: 68Ga-DOTA-peptides, 18F-DOPA, 18F-FDG
- G3: 18F-FDG, 68Ga-DOTA-peptides

Grade and SR expression drive the choice of the tracer
68Ga-DOTA-peptides vs 18F-DOPA

Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours

Valentina Ambrosini • Paola Tomassetti • Paolo Castellucci • Davide Campana • Giancarlo Montini • Domenico Rabello • Cristina Nanni • Anna Rizzello • Roberto Franchi • Stefano Fant


Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours

Alexander Haug • Christoph J. Auernhammer • Björn Wängler • Reinhold Tiling • Gerwin Schmidt • Burkhard Göke • Peter Bartenstein • Gabriele Pöppert


A retrospective comparison between 68Ga-DOTA-TOC PET/CT and 18F-DOPA PET/CT in patients with extra-adrenal paraganglioma

Alexander Kroiss • Daniel Putzer • Andreas Frech • Clemens Decristoporo • Christian Uprimny • Rudolf Wolfgang Gasser • Barry Lynn Shulkin • Christoph Url • Gerlin Widmann • Rupert Prommegger • Georg Mathias Sprinzl • Gustav Fraedrich • Irene Johanna Virgolini


- 68Ga-DOTA-peptides: higher accuracy for well diff, SR expressing NEN
SOMATOSTATIN RECEPTOR IMAGING

A milestone in NET diagnosis


SOMATOSTATIN RECEPTOR IMAGING

68Ga-DOTA-peptides PET/CT

- Higher accuracy
- Higher spatial resolution
- Semiquantitative analysis (SUVmax)
- Lower costs
- Patients friendly

- Currently preferable, when available
PET/CT VS SRS: higher accuracy

TATE PERFORMS BETTER THAN SRS

51pts → SRS neg in 35, eq in 16

47pts with radiologically evident disease

PET shows 168/226 lesions vs 27/226 by SRS
PET/CT VS SRS: higher accuracy

pNEN G1
Restaging (after surgery)
Neg SRS
PET/CT VS SRS: higher accuracy
Is accuracy in lesion detection the only issue?

Non functioning pNEN

- CLINICAL PRESENTATION
- BIOLOGY
  - Chromogranin A, PP
- IMAGING
  - CT / MRI
  - EUS (+/- EUS-guided biopsy)
  - STOATOSTATIN RECEPTOR IMAGING
    - Somatostatin receptor scintigraphy (e.g., Octreoscan®) or Gallium-68-Pet/CT

CLINICAL EVALUATION & DIAGNOSTICS

TREATMENT

Tumor = 2 cm

- Option 1. Surveillance:
  - G1, low G2. Asymptomatic, mainly in the head, no radiological signs suspicious for malignancy, patient factors (personal wishes, age, co-morbidities ...).
- Option 2. Surgery
  - G2, symptoms, patient wishes.

Tumor > 2 cm

- Surgery:
  - Limited resection only if conditions favorable to preserve organ function (otherwise, oncological resection).

FOLLOW-UP

- EUS, MRI (or CT) every 6 to 12 months
  - No change, surveillance
  - Increase in size (>0.5 cm) or final Ø>2cm, surgery

- Surveillance depending on final pathology

See section on treatment for advanced disease

a. If low Ki-67 and stability after initial 6 monthly evaluations; b, specific additional tests may be required to accurately stage the tumour (e.g., intra-operative US, intraoperative frozen section)
Is accuracy in lesion detection the only issue?

- PET/CT is preferable, when available

- $^{68}$Ga-DOTATATE PET/CT, $^{99m}$Tc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial

- The Status of Neuroendocrine Tumor Imaging: From Darkness to Light?
Is accuracy in lesion detection the only issue?

- PET/CT is preferable, when available

- In centers without PET/CT, SRS can still provide valuable data...
  ..conscious employment
  ..if SRS negative/equivocal
68Ga-DOTA-peptides are the gold standard for well differentiated NEN

- **Structure:**

  - 68Ga Chelant (DOTA) + Somatostatin Analogue (TOC, NOC, TATE)

  Different affinity for SR subtypes
  No clinically relevant differences (TOC, TATE, NOC)
  SUVmax not directly comparable
Comparison of ⁶⁸Ga-DOTATATE and ⁶⁸Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours

Comparison of ⁶⁸Ga-DOTANOC and ⁶⁸Ga-DOTATATE PET/CT Within Patients with Gastroenteropancreatic Neuroendocrine Tumors

Damian Wild¹,², Jamshed B. Bomanji¹, Pascal Benkert³, Helmut Maecke², Peter J. Ell¹, Jean Claude Reubi⁴, and Martyn E. Caplin⁵
Effect of treatment..


Treatment with Octreotide Does Not Reduce Tumor Uptake of $^{68}$Ga-DOTATATE as Measured by PET/CT in Patients with Neuroendocrine Tumors

Abstract n. I1 ENETS 2016. Aalberg et al. Interim results on the influence of lanreotide on uptake of $^{68}$Ga-DOTATATE in patients with metastatic or unresectable NET: No evidence for discontinuation of lanreotide before $^{68}$Ga-DOTATATE PET/CT.

- 34pts
- PET/CT performed the day before and after PET/CT
- Interim analysis: 17/34 pts:
  - No difference at any disease site
  - Reduced uptake @ physiologic sites
68Ga-DOTA-peptides are the gold standard for well differentiated NEN

- High accuracy for lesions (T,N,M) detection

May 2005-August 2013; 1258 PET/CT scans of 728 pts

68Ga-DOTA-peptides are the gold standard for well differentiated NEN

- High accuracy for lesions (T,N,M) detection

**Overall:**
Sen 90-98%, Spec 92-98%

Performing better than CI, SRS, DOPA and FDG

The Journal of Nuclear Medicine • Vol. 48 • No. 4 • April 2007
68Ga-DOTA-peptides are the gold standard for well differentiated NEN

- High accuracy for lesions (T,N,M) detection
- Uptake correlates with SSTR expression
  (→selection for PRRT)


- Prognostic information

68Ga-DOTA-peptides: impact on management in half the cases.

68Ga-DOTA-NOC $\rightarrow$ 55%

68Ga-DOTA-TATE $\rightarrow$ 50%

The Impact of 68Ga-DOTATATE PET/CT Imaging on Management of Patients with Neuroendocrine Tumors: Experience from a National Referral Center in the United Kingdom


68Ga-DOTANOC PET/CT Clinical Impact in Patients with Neuroendocrine Tumors

Indications to 68Ga-DOTA-peptides PET/CT

- Disease detection
- T, N, M
- CUP
- Detection of relapse
- Selection of PRRT candidates

Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE

Irene Virgolini - Valentina Ambrosini - Jamsheed B. Bomanji - Richard P. Baum - Stefano Fausti - Michael Gabriel - Nikolaos D. Papathanasiou - Giovanna Pepe - Wim Oven - Clemens De Cristoforo - Arturo Chiti


• Monitoring response to/guiding treatment...
• A role in assessment of suspected NET
68Ga-DOTA-peptides PET/CT: high accuracy for T,N,M detection

- G1 pancreatic NEN

CT: neg

68Ga-DOTA-NOC PET/CT: detected a well diff pNEN (tail) G1
68Ga-DOTA-peptides PET/CT: high accuracy for T,N,M detection

- G1 pancreatic NEN and multiple metastatic sites
..UNUSUAL SITES

PARAGANGLIOMA

METASTATIC lung NEN

MULTIFOCAL BREAST NEN
68Ga-DOTA-peptides PET/CT: high accuracy for T,N,M detection

- CUP: PET/CT identifies primary
68Ga-DOTA-peptides PET/CT: detection of relapse

August 2010: surgical resection of ileum NEN (G2) → CT FU

2ys later (2013) CT and PET/CT: liver relapse
68Ga-DOTA-peptides PET/CT: detection of relapse

- August 2010: surgical resection of ileum NEN (G2) → CT FU

- 3ys later (2015): PET/CT detects relapse

FU..how long?
**68Ga-DOTA-peptides PET/CT:** selection of pts for PRRT

Pancreatic metastatic NEN Expressing SR

**Assessment of tp response?**

**Although not ideal**

→ RECIST

68Ga-DOTA-NOC

<table>
<thead>
<tr>
<th>Febb 2013</th>
<th>Sett 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVmax 37</td>
<td>SUVmax 13</td>
</tr>
</tbody>
</table>

PRRT
Is $^{68}$Ga-DOTA-NOC PET/CT indicated in patients with clinical, biochemical or radiological suspicion of neuroendocrine tumour?

Valentina Ambrosini · Davide Campana · Cristina Nanni · Silvia Cambioli · Paola Tomassetti · Domenico Rubello · Stefano Fant
68Ga-DOTA-PEPTIDES PITFALLS

- HEAD OF THE PANCREAS

Variable uptake (focal OR diffuse)
68Ga-DOTA-PEPTIDES PITFALLS

HEAD OF THE PANCREAS

February 2009

Transient uptake

June 2009
68Ga-DOTA-PEPTIDES PITFALLS

- ACCESSORY SPLEENS
68Ga-DOTA-PEPTIDES PITFALLS

- LYMPHOCITES ACTIVATION

SARCOIDOSIS

LYMPHOMA

68Ga-DOTA-NOC  18F-FDG

68Ga-DOTA-NOC  18F-FDG
68Ga-DOTA-PEPTIDES ARE NOT THE GOLD STANDARD FOR

- HIGH GRADE NEN
- NEN WITH LOW/VARIABLE SR EXPRESSION
  - pheocromocytoma
  - neuroblastoma
  - medullary thyroid carcinoma
  - benign insulinoma
High grade NEN show preferential FDG uptake

A Comparison of $^{68}$Ga-DOTATATE and $^{18}$F-FDG PET/CT in Pulmonary Neuroendocrine Tumors

Irfan Kayani¹, Brendan G. Connors¹, Ashley M. Growes¹, Thida Win², John Dickson³, Martyn Caplin³, and Jamshed B. Bomanji¹

<table>
<thead>
<tr>
<th>TABLE 2. Tumor Uptake of $^{68}$Ga-DOTATATE and $^{18}$F-FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Low-grade tumors (typical carcinoids)</td>
</tr>
<tr>
<td>Atypical and higher-grade tumors</td>
</tr>
</tbody>
</table>

Values are medians and ranges.

18 pts:
11 typical carcinoid
2 atypical carcinoid
1 small cells NE ca
1 NSLC with NE diff.
2 DIPNECH
FDG: when positive is prognostic

Prospective, 98pts, FU: 1y

**Clin Cancer Res 2010;16:978-985.**

The Journal of Nuclear Medicine • Vol. 50 • No. 6 • June 2009
ENETS: FDG for high grades

Fig. 1 Diagnostic algorithm for neuroendocrine carcinoma and G3 tumours.
When to perform FDG?

Comparison of the prognostic values of $^{68}$Ga-DOTANOC PET/CT and $^{18}$F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor


High Prognostic Value of $^{18}$F-FDG PET for Metastatic Gastroenteropancreatic Neuroendocrine Tumors: A Long-Term Evaluation

*Eur J Nucl Med Mol Imaging*

Favourable outcomes of $^{177}$Lu-octreotide peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours

*N uroendocrinology (DOI:10.1159/000368609)*

The Role of Combined $^{68}$Ga-DOTATOC and $^{18}$FDG PET/CT in the Management of Patients with Pancreatic Neuroendocrine Tumors

Direct comparison of $^{68}$Ga-DOTA-TOC and $^{18}$F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle

*Eur J Nucl Med Mol Imaging*

DOI 10.1007/s00259-016-3328-2
When to perform FDG?

66pts with confirmed NET undergoing PRRT

68Ga-DOTA-peptides scan performed the day before PRRT, @3,6,9mo afterwards

18F-FDG within 2mo of the 68Ga-DOTATOC

Overall 198 combined studies were evaluated
When to perform FDG?

FDG TP in 31% of scans (62/198) and 57% of pts

Group 1
Patients $^{18}$F-FDG-negative initially and during follow-up (28 patients, 42.4 %)

Group 2
Patients $^{18}$F-FDG-positive initially and during follow-up (24 patients, 36.4 %)

Group 3
Patients $^{18}$F-FDG-negative initially but $^{18}$F-FDG-positive during follow-up (9 patients, 13.6 %)

Group 4
Patients $^{18}$F-FDG-positive initially but $^{18}$F-FDG-negative during follow-up (five patients, 7.6 %)

28=5 G1, 23 G2

24=5 G1, 13 G2, 6 G3

9=2 G1, 6 G2, 1 G3

5 G2
When to perform FDG?

15 pts in PD @ study entry
Double tracer imaging: when? How often?

- 68Ga-DOTA-peptides
- 18F-FDG
Double tracer imaging: when/how often?

- Different approaches in different centers and countries
Double tracer imaging: 68Ga-SA+FDG

Setting 1: CUP; pos liver biopsy (NEN G2)

68Ga-DOTA-NOC

Faint/negative
68Ga-DOTA-NOC
Double tracer imaging: $^{68}$Ga-SA+FDG

- Setting 1: CUP; pos liver biopsy (NEN G2)

68Ga-DOTA-NOC 18F-FDG
Double tracer imaging: 68Ga-SA+FDG

- Setting 2: lesions at low-dose CT but negative at 68Ga-DOTA-peptides PET

Pancreatic NEN
Double tracer imaging: 68Ga-SA+FDG

- Setting 3: CT progression, 68Ga-DOTA-peptides cold areas.

68Ga-DOTA-NOC

Ileum NEN
Double tracer imaging: $^{68}$Ga-SA+FDG

- **Setting 3:** CT progression, $^{68}$Ga-DOTA-peptides cold areas.

$^{68}$Ga-DOTA-NOC

*Ileum NEN*
Double tracer imaging: $^{68}$Ga-SA+FDG

- Setting 3: CT progression, $^{68}$Ga-DOTA-peptides cold areas..

$^{68}$Ga-DOTA-NOC

Ileum NEN

18F-FDG
Double tracer imaging: 68Ga-SA+FDG

- Setting 4: high ki67 values..

18F-FDG

- Pt with lung NEC (ki67=70%)
Low/variable SR expression: benign insulinoma

- Clinically challenging
- Conventional imaging: often small sized lesions
- SR-imaging often negative
- DOPA limits: sensitivity low, physiol biodistribution pancreas

- Exendin is a new tracer targeting GLP1-receptor, 68Ga, 111In
Low/variable SR expression: benign insulinoma

- $^{68}$Ga-exendin $\Rightarrow$ targets GLP-1 receptor

Kwadwo Antwi$^1$, Melpomeni Fani$^1$, Guillaume Nicolas$^1$, Christof Rottenburger$^1$, Tobias Heye$^1$, Jean Claude Reubi$^2$, Beat Gloor$^3$, Emanuel Christ$^*$$^4$, and Damian Wild$^*$$^1$

Localization of Hidden Insulinomas with $^{68}$Ga-DOTA-Exendin-4 PET/CT: A Pilot Study

Low/variable SR expression: 18F-DOPA

- high accuracy for well diff NET lesions detection
- Performs better than CI, SRS and FDG (in well differentiated tumours)
- Metabolic: ideal for assessing tp response?

pancreatic NET with multiple metastatic sites
Low/variable SR expression: 18F-DOPA

- technical aspects (so far..)
  → difficult synthesis/high costs/biodistribution
  → preparation: oral carbidopa (not performed by all groups)
  → phys. Biodistribution/NETonset site (liver, pancreas, bowel)

- Lower accuracy vs 68Ga-DOTA-peptides in well diff. SSR-pos NET
Low/variable SR expression: pheocromocytoma

**STAGING**

18F-DOPA

**RELAPSE**

68Ga-DOTA-NOC

18F-DOPA

**References**

J Clin Endocrinol Metab, June 2010, 95(6):2800–2810

6-18F-Fluoro-L-Dihydroxyphenylalanine Positron Emission Tomography Is Superior to 123I-Metaiodobenzyl-Guanidine Scintigraphy in the Detection of Extraadrenal and Hereditary Pheochromocytomas and Paragangliomas: Correlation with Vesicular Monoamine Transporter Expression
Low/variable SR expression: pheocromocytoma

18F-FDG
The value of $^{18}$F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with $^{18}$F-FDG PET-CT

*Eur Radiol (2009) 19: 1425–1434*

PROSPECTIVE: 26pts with increased Ct levels
18F-DOPA and 18F-FDG within 4wks
Standard of reference pathology (17cases) or FU>6mo

<table>
<thead>
<tr>
<th>Tumor localization</th>
<th>DOPA PET</th>
<th>FDG PET</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>15</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>20</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Organ metastases (liver)</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total lesions (%)</td>
<td>50/53 (94%)</td>
<td>33/53 (62%)</td>
<td>34/53 (64%)</td>
</tr>
</tbody>
</table>
Low/variable SR expression: medullary thyroid carcinoma

Fig. 5 Preoperative staging of a 53-year-old female (no. 26) MTC patient with a DOPA positive but FDG negative PET-CT tumor in the right thyroid lobe (pT2 N1)
Low/variable SR expression: medullary thyroid carcinoma

Comparison of $^{18}$F-DOPA, $^{18}$F-FDG and $^{68}$Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma

18 pts_MTC

Elevated calcitonin levels after initial surgery

Reference: cytohistological diagnosis or FU of at least 12 months
DOPA detected a higher number of lesions (141 vs 88 of 156 TP NB localizations)

Bone marrow/bone recurrence/metastases

18F-Dopa PET/CT: higher sensitivity than 123I-MIBG (96 vs 71%, p<0.001)
NM- therapy: PRRT

- Goal: to deliver citotoxic radiation to the tumour

- Early studies ➔ Lack of standardisation
  - Inclusion criteria
  - Dose/dose scheme
  - Response evaluation criteria
The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

John J. Zakenun · L. Bodei · J. Mueller-Brand · M. E. Pavel · R. P. Baum · D. Hörsch · M. S. O’Dorisio · T. M. O’Dorisiol · J. R. Howe · M. Cremonesi · D. J. Kwekkeboom
NM- therapy: PRRT

- **Indications**: SR-expressing tumours or metastatic or inoperable NEN, ideally G1 and G2 (WHO 2010), high SR-expression @ SRI (SRS or PET/CT)

- **Contraindications**
  - absolute: pregnancy, severe concomitant illnesses
  - Relative: severe renal or bone marrow
Treatment regimens for the noncompromised patient

\(^{90}\)Y-DOTATATE / \(^{90}\)Y-DOTATOC
- Administered activity: 3.7 GBq (100 mCi)/m\(^2\) body surface
- Number of cycles: two
- Time interval between cycles: 6–12 weeks or
- Administered activity: 2.78–4.44 GBq (75–120 mCi)
- Number of cycles: two to four
- Time interval between cycles: 6–12 weeks

\(^{177}\)Lu-DOTATATE / \(^{177}\)Lu-DOTATOC
- Administered activity: 5.55–7.4 GBq (150–200 mCi)
- Number of cycles: three to five
- Time interval between cycles: 6–12 weeks

Combination \(^{90}\)Y/\(^{177}\)Lu peptides: Combination therapies with \(^{90}\)Y and \(^{177}\)Lu peptides are being actively investigated and may prove to be of additional therapeutic benefit. However, such combination treatments should be performed in centres with sufficient competence and extensive experience. In this case administered activities should be adjusted on an individual basis.

Sequential administration:
- \(^{90}\)Y administered activity: 2.5–5.0 GBq (68–135 mCi)
- \(^{177}\)Lu administered activity: 5.55–7.4 GBq (150–200 mCi)
- Number of cycles: two to six
- Time interval between cycles: 6–16 weeks

Concurrent therapies, administering a cocktail of \(^{177}\)Lu and \(^{90}\)Y peptides are also emerging.
Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [\(^{90}\text{Y-DOTA}\)]-TOC in Metastasized Neuroendocrine Cancers

Anna Imhof, Philippe Brunner, Nicolas Marinecek, Matthias Briel, Christian Schindler, Helmut Rasch, Helmut R. Mücke, Christoph Rochlitz, Jan Müller-Brand, and Martin A. Walter

\(^{177}\text{Lu-DOTATATE Molecular Radiotherapy for Childhood Neuroblastoma}

Jennifer E. Gains\(^1\), Jamshed B. Bomanji\(^2\), Naomi L. Fersht\(^1\), Tracy Sullivan\(^3\), Derek D’Souza\(^3\), Kevin P. Sullivan\(^1\), Matthew Aldridge\(^2\), Wendy Waddington\(^2\), and Mark N. Gaze\(^1\)

Cohort Study of Somatostatin-Based Radiopeptide Therapy With \[^{90}\text{Y-DOTA}\]-TOC Versus \[^{90}\text{Y-DOTA}\]-TOC Plus \[^{177}\text{Lu-DOTA}\]-TOC in Neuroendocrine Cancers

Linda Villard, Anna Romer, Nicolas Marinecek, Philippe Brunner, Michael T. Koller, Christian Schindler, Quinn K.T. Ng, Helmut R. Mücke, Jan Müller-Brand, Christoph Rochlitz, Matthias Briel, and Martin A. Walter

Somatostatin-based radiopeptide therapy with \[^{177}\text{Lu-DOTA}\]-TOC versus \[^{90}\text{Y-DOTA}\]-TOC in neuroendocrine tumours

A. Romer • D. Seiler • N. Marinecek • P. Brunner • M. T. Koller • Q. K. T. Ng • H. R. Maecke • J. Müller-Brand • C. Rochlitz • M. Briel • C. Schindler • M. A. Walter


J Nucl Med 2011; 52:1041–1047


Treatment With the Radiolabeled Somatostatin Analog
$[^{177}\text{Lu-DOTA}^{0},\text{Tyr}^{3}]\text{Octreotate}$: 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. Kremming

J Clin Oncol 26:2124-2130. © 2008 by American Society of Clinical Oncology

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
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<tr>
<td>Carcinoid</td>
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<tr>
<td>Nonfunctioning pancreatic</td>
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<tr>
<td>Gastrinoma</td>
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<tr>
<td>Insulinoma</td>
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<td>1</td>
<td>20</td>
<td>1</td>
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<td>VIPoma</td>
<td>1</td>
<td>50</td>
<td>51</td>
<td>107</td>
<td>61</td>
</tr>
</tbody>
</table>

Total                     | 5  | 86  | 51   | 107  | 61   | 310 |

Abbreviations: GEPNETs, gastroenteropancreatic neuroendocrine tumors; CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; VIPoma, vasoactive intestinal peptide-secreting tumor.

**CR+PR=30%, MR=16%**
NM- therapy: PRRT

**Table 3. Significant Factors Predicting Disease-Specific Survival in Patients (n = 310)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>Survival (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>61</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>107</td>
<td>&gt; 48</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Remission</td>
<td>142</td>
<td>&gt; 48</td>
<td></td>
</tr>
<tr>
<td>Liver involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>85</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>191</td>
<td>&gt; 48</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>None</td>
<td>34</td>
<td>&gt; 48</td>
<td></td>
</tr>
<tr>
<td>KPS ≤ 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>271</td>
<td>&gt; 48</td>
<td>.001</td>
</tr>
<tr>
<td>Baseline weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>235</td>
<td>&gt; 48</td>
<td>.001</td>
</tr>
<tr>
<td>Presence of bone metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>242</td>
<td>&gt; 48</td>
<td>.004</td>
</tr>
<tr>
<td>Tumor type gastrinoma/insulinoma/VIPoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>33</td>
<td>.04</td>
</tr>
<tr>
<td>No</td>
<td>291</td>
<td>&gt; 48</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Significance levels pertain to Cox regression analysis of more factors than are listed in the Table, and which are listed in Table 1 and are marked with an asterisk.

Abbreviations: PD, progressive disease; SD, stable disease; KPS, Karnofsky performance status; VIPoma, vasoactive intestinal peptide-secreting tumor.
NM-therapy: PRRT

Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors

Table 5 Tumor responses in patients with gastroenteropancreatic neuroendocrine tumors, treated with different radiolabeled somatostatin analogs (adapted with permission from Kwekkeboom et al. (2005a) copyright 2005 Society of Nuclear Medicine, Inc.)

<table>
<thead>
<tr>
<th>Center (reference)</th>
<th>Ligand</th>
<th>Patient number</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>CR + PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam (Valkema et al. 2002)</td>
<td>$[^{111}\text{In-}]$DTPA$_0^0$ octreotide</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>5 (19%)</td>
<td>11 (42%)</td>
<td>10 (38%)</td>
<td>0</td>
</tr>
<tr>
<td>New Orleans (Anthony et al. 2002)</td>
<td>$[^{111}\text{In-}]$DTPA$_0^0$ octreotide</td>
<td>26</td>
<td>0</td>
<td>2 (8%)</td>
<td>NA</td>
<td>21 (81%)</td>
<td>3 (12%)</td>
<td>8</td>
</tr>
<tr>
<td>Milan (Bodei et al. 2003)</td>
<td>$[^{90}\text{Y-}]$DOTA$_0^0$Tyr$_3^3$ octreotide</td>
<td>21</td>
<td>0</td>
<td>6 (29%)</td>
<td>NA</td>
<td>11 (52%)</td>
<td>4 (19%)</td>
<td>29</td>
</tr>
<tr>
<td>Basel (Waldherr et al. 2001, 2002a)</td>
<td>$[^{90}\text{Y-}]$DOTA$_0^0$Tyr$_3^3$ octreotide</td>
<td>74</td>
<td>3 (4%)</td>
<td>15 (20%)</td>
<td>NA</td>
<td>48 (65%)</td>
<td>8 (11%)</td>
<td>24</td>
</tr>
<tr>
<td>Basel (Waldherr et al. 2002b)</td>
<td>$[^{90}\text{Y-}]$DOTA$_0^0$Tyr$_3^3$ octreotide</td>
<td>33</td>
<td>2 (6%)</td>
<td>9 (27%)</td>
<td>NA</td>
<td>19 (57%)</td>
<td>3 (9%)</td>
<td>33</td>
</tr>
<tr>
<td>Rotterdam (Valkema et al. 2006)</td>
<td>$[^{90}\text{Y-}]$DOTA$_0^0$Tyr$_3^3$ octreotide</td>
<td>58</td>
<td>0</td>
<td>5 (9%)</td>
<td>7 (12%)</td>
<td>33 (61%)</td>
<td>10 (19%)</td>
<td>9</td>
</tr>
<tr>
<td>Rotterdam (Kwekkeboom et al. 2008)</td>
<td>$[^{177}\text{Lu-}]$DOTA$_0^0$,-Tyr$_3^3$octreotate</td>
<td>310</td>
<td>5 (2%)</td>
<td>86 (28%)</td>
<td>51 (16%)</td>
<td>107 (35%)</td>
<td>61 (20%)</td>
<td>29</td>
</tr>
</tbody>
</table>

Endocrine-Related Cancer (2010) 17 R53–R73
NM-therapy: PRRT

Table 7 Results of recent chemotherapy reports compared to treatment with \[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3\]octreotate

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor types</th>
<th>Patient number</th>
<th>PR/CR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
<th>Study (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STZ + doxorubicin</td>
<td>PNET</td>
<td>16</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>Cheng &amp; Saltz (1999)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Carc</td>
<td>56</td>
<td>16</td>
<td>NA</td>
<td>20</td>
<td>Bukowski et al. (1994)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Carc</td>
<td>7</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>Ritzel et al. (1995)</td>
</tr>
<tr>
<td>FU + IF-A</td>
<td>Carc/PNET</td>
<td>24</td>
<td>21</td>
<td>NA</td>
<td>8</td>
<td>Andreyev et al. (1995)</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Carc/PNET</td>
<td>30</td>
<td>7</td>
<td>NA</td>
<td>16</td>
<td>Neijt et al. (1995)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Carc/PNET</td>
<td>24</td>
<td>4</td>
<td>3</td>
<td>18</td>
<td>Ansell et al. (2001)</td>
</tr>
<tr>
<td>STZ + FU + doxorubicin</td>
<td>PNET</td>
<td>84</td>
<td>39</td>
<td>18</td>
<td>37</td>
<td>Kouvaraki et al. (2004)</td>
</tr>
<tr>
<td>Doxorubicin + FU</td>
<td>Carc</td>
<td>85</td>
<td>13</td>
<td>5</td>
<td>16</td>
<td>Sun et al. (2005)</td>
</tr>
<tr>
<td>STZ + FU</td>
<td>Carc</td>
<td>78</td>
<td>15</td>
<td>5</td>
<td>24</td>
<td>Sun et al. (2005)</td>
</tr>
<tr>
<td>Irinotecan + FU</td>
<td>Carc/PNET</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>15</td>
<td>Dureux et al. (2006)</td>
</tr>
<tr>
<td>Oxaliplatin + capecitabine</td>
<td>Well-differentiated NET</td>
<td>27</td>
<td>30</td>
<td>NA</td>
<td>40</td>
<td>Bajetta et al. (2007)</td>
</tr>
<tr>
<td>[^{177}\text{Lu-octreotide}</td>
<td>Carc/PNET</td>
<td>310</td>
<td>30</td>
<td>32</td>
<td>46</td>
<td>Kweekkeboom et al. (2008)</td>
</tr>
</tbody>
</table>

STZ, streptozotocin; FU, 5-fluorouracil; IF-A, interferon-α; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available (adapted with permission from Kweekkeboom et al. (2008) copyright 2008 American Society of Clinical Oncology. All rights reserved).

- PRRT \(\rightarrow\) longer median PFS

*Endocrine-Related Cancer (2010) 17 R53–R73*
177Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumours: Results of the Phase III NETTER-1 Trial

Jonathan Strosberg¹, Edward Wolin², Beth Chasen³, Matthew Kulke⁴, David Bushnell⁵, Martyn Caplin⁶, Richard P. Baum⁷, Erik Mittra⁸, Timothy Hobday⁹, Andrew Hendifar¹⁰, Kjell Oberg¹¹, Maribel Lopera Sierra¹², Philippe Ruszniewski¹³, Dik Kwekkeboom¹⁴ On behalf of the NETTER-1 study group

first phase 3 multicenter stratified open controlled randomised parallel-group study comparing 177Lu-DOTATATE with octreotide LAR in pts with inoperable progressive SR-positive midgut tumours
### Netter-1 study: aim and design

<table>
<thead>
<tr>
<th>Aim</th>
<th>Evaluate the efficacy and safety of $^{177}$Lu-Dotatate plus Octreotide 30 mg compared to Octreotide LAR 60 mg (off-label use)(^1) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30 mg (label use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>International multicenter, randomized comparator-controlled, parallel-group</td>
</tr>
</tbody>
</table>

#### Treatment and Assessments

- Tumour burden assessment (RECIST criteria) every 12 weeks

#### Baseline and Randomization

- **Dose 1**: 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + Octreotide 30 mg
- **Dose 2**: Octreotide LAR 60 mg every 4 weeks
- **Dose 3**: 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + Octreotide 30 mg
- **Dose 4**: Octreotide LAR 60 mg every 4 weeks

- n = 115

---

1. FDA and EMA recommendation

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna
Netter-1 study: objectives

Primary objective

Compare Progression Free Survival (PFS) after treatment with $^{177}$Lu-Dotatate plus 30 mg octreotide LAR vs treatment with high dose (60 mg) octreotide LAR

Secondary objectives

- Compare the Objective Response Rate between study arms
- Compare the Overall Survival between study arms
- Compare the Time to Progression between study arms
- Evaluate the safety and tolerability of $^{177}$Lu-Dotatate
- Evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire
Netter-1 study results

- 36 European and 15 USA centers involved
Netter-1 study: results

N = 229 (ITT)
Number of events: 90

• $^{177}$Lu-Dotatate: 23
• Octreotide LAR 60 mg: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001
PFS: PRRT vs other tp

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Condition</th>
<th>1st Line</th>
<th>2nd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMID</td>
<td>octreo</td>
<td>placebo</td>
<td>metastatic MID-gut</td>
<td>14.3mo</td>
<td>6mo</td>
</tr>
<tr>
<td>RADIANT 2</td>
<td>EVE+octreo</td>
<td>placebo+octreo</td>
<td>carcinoid</td>
<td>16mo</td>
<td>11.3mo</td>
</tr>
<tr>
<td>RADIANT 3</td>
<td>EVE+bsc</td>
<td>placebo+bsc</td>
<td>pNET</td>
<td>11mo</td>
<td>4.6mo</td>
</tr>
<tr>
<td>RADIANT 4</td>
<td>EVE+bsc</td>
<td>placebo+bsc</td>
<td>GI and LUNG NEN</td>
<td>11mo</td>
<td>3.9mo</td>
</tr>
<tr>
<td>SUNITINIB</td>
<td>SUNITINIB</td>
<td>placebo</td>
<td>pNET</td>
<td>11.4mo</td>
<td>5.5mo</td>
</tr>
</tbody>
</table>
## Netter-1 study: results

<table>
<thead>
<tr>
<th></th>
<th>177-Lu-Dotatate (n=111)</th>
<th>Octreotide LAR 60mg (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td>106 (96%)</td>
<td>95 (86%)</td>
</tr>
<tr>
<td><strong>Related to treatment</strong></td>
<td>95 (86%)</td>
<td>34 (31%)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>29 (26%)</td>
<td>26 (24%)</td>
</tr>
<tr>
<td><strong>Related to treatment</strong></td>
<td>10 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events</strong></td>
<td>7 (6%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td><strong>Related to treatment</strong></td>
<td>5 (5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna
**ENETS 2016**

**PANCREATIC NEN**

**Advanced locally-resectable disease or distant metastases**

- **Functional Activity**
  - Diazoxide (insulinoma) or PPI (gastrinoma) or Octreotide or Lanreotide or IFN–alpha 2b (if SSTR–) → Consider Debulking surgery of LM (Fig 1)
  - Consider loco-regional*/ablative therapies (Fig 1) or SSA dose increase or add-on IFN–alpha 2b (if not already receiving) or Everolimus (insulinoma) or PRRT

- **Complete resection if feasible (G1/G2)**
  - Resect primary and metastases (Fig 1)

- **Non-functional (G1, low G2, low tumor burden, SD or initial diagnosis, no symptoms)**
  - Lanreotide (Octreotide) or Watch & Wait → PD → Everolimus or Sunitinib or Cytotoxic chemotherapy or loco-regional therapies or Lanreotide (Octreotide) (if prior Watch & Wait)

- **Non-functional (G2, high tumor burden, and/or PD or symptoms)**
  - Cytotoxic chemotherapy → PD → Everolimus or Sunitinib → PD → PRRT** or 2nd line CTX or Clinical trial

- **NEN G3**
  - Cisplatin + Etoposide or STZ/5-FU or TEM/CAP → PD → FOLFOX or FOLFIRI or Clinical trial
Conclusions

PET/CT → gold standard for imaging

$^{68}$Ga-DOTA-peptides → well differentiated, SR-pos

$^{18}$F-DOPA → in well diff, low/variable SR-expression

$^{18}$F-FDG → in high grade NEN and to assess aggressiveness

$^{68}$Ga-exendin → benign insulinoma
Conclusions

- Increasing prevalence of NEN
- Higher percentage of atypical cases
  - Improvements in diagnosis and therapy
  - Require a multidisciplinary discussion
THANK YOU FOR YOUR ATTENTION! ANY QUESTIONS?
Back-up slides
Netter-1 study: inclusion criteria

INCLUSION CRITERIA

• Patients ≥18 years of age
• Metastatic or locally advanced, inoperable, histologically proven, well-differentiated midgut NET, functioning or not
• Ki67 index ≤ 20% (Grade 1-2)
• Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of octreotide LAR (20-30 mg every 3-4 weeks)
• Somatostatin receptor positive disease
• Karnofsky Performance Score ≥ 60
**Netter-1 study: results**

<table>
<thead>
<tr>
<th></th>
<th>(^{177}\text{Lu-Dotatate (n=116)})</th>
<th>Octreotide LAR 60mg (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (46%)</td>
<td>60 (53%)</td>
</tr>
<tr>
<td>Female</td>
<td>63 (54%)</td>
<td>53 (47%)</td>
</tr>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>63 (±9)</td>
<td>64 (±10)</td>
</tr>
<tr>
<td><strong>BMI (Kg/sqm), mean (SD)</strong></td>
<td>25 (±5)</td>
<td>26 (±7)</td>
</tr>
<tr>
<td><strong>Primary tumour site, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>6 (5%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Ileum</td>
<td>86 (74%)</td>
<td>82 (73%)</td>
</tr>
<tr>
<td>Appendix</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Right colon</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (17%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td><strong>Site of metastasis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>97 (84%)</td>
<td>94 (83%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>77 (66%)</td>
<td>65 (58%)</td>
</tr>
<tr>
<td>Bone</td>
<td>13 (11%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Lungs</td>
<td>11 (10%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>40 (35%)</td>
<td>37 (33%)</td>
</tr>
</tbody>
</table>
**TABLE 3. Systems of Nomenclature for Neuroendocrine Tumors**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lung and Thymus (WHO)&lt;sup&gt;34&lt;/sup&gt;</th>
<th>GEP-NETs (ENETS)&lt;sup&gt;28,29&lt;/sup&gt;</th>
<th>GEP-NETs (WHO 2010)&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Lung and Thymus (Moran et al)&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Pancreas (Hochwald et al)&lt;sup&gt;14&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>Carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 1 (G1)</td>
<td>Neuroendocrine neoplasm, grade 1</td>
<td>Neuroendocrine carcinoma, grade 1</td>
<td>Well-differentiated pancreatic endocrine neoplasm, low grade</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>Atypical carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 2 (G2)</td>
<td>Neuroendocrine neoplasm, grade 2</td>
<td>Neuroendocrine carcinoma, grade 2</td>
<td>Well-differentiated pancreatic endocrine neoplasm, intermediate grade</td>
</tr>
<tr>
<td>High grade</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, large cell neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

The grade of the tumor MUST be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as *neuroendocrine tumor* or *neuroendocrine carcinoma* without reference to grade do not provide adequate pathology information.

*(Pancreas 2010;39: 707–712)*