Functional imaging and therapy for endocrine tumours

David Pattison
Nuclear Medicine Physician (& Endocrinologist)
Deputy Director, Department of Nuclear Medicine & Specialised PET Services
Royal Brisbane & Women’s Hospital
Diffuse (Neuro)Endocrine System

- Thyroid
- Lung
- Pancreas (non-carcinoid)
- Adrenal
- Small Intestine
- Rectum/Colon
- Other
  - Thyroid / MTC
  - Adrenal / Pheo / Parag
  - Cervix / Ovary
Functional NETs - overview

• Diagnosis is often delayed
  • Rare presentation may mimic more common conditions

• Requirements
  • Clinical evidence of hormone secretion / syndrome
  • Elevated plasma hormone level
  • Tumour localisation / staging

• Endocrinologist role
  • Initial diagnostic evaluation / work-up (incl confirmatory testing, eg 72 hr fast)
  • Localisation (eg dynamic testing, molecular imaging)
  • Management of hormonal syndrome
  • Surveillance of patients with familial endocrine syndromes
Overview

• **Background**
  • GEP-NET (insulinoma), Phaeo & paraganglioma (PPGL)

• **Molecular Imaging**
  • $^{68}$Ga-DOTATATE PET/CT
  • $^{68}$Ga-exendin-4 PET/CT
  • FDG PET/CT
  • FDOPA PET/CT

• **Radionuclide Therapy**
  • RCT: NETTER-1 Trial (midgut NETs)
  • GEP-NETs / PPGL

• **Future directions**
  • Next generation SSTR imaging: SSTR2-antagonists & $^{64/67}$Cu-SARTATE
  • Australian radionuclide therapy trials
Overview

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• Radionuclide Therapy
  • RCT: NETTER-1 Trial (midgut NETs)
  • GEP-NETs / PPGL

• Future directions
  • Next generation SSTR imaging: SSTR2-antagonists & $^{64/67}$Cu-SARTATE
  • Australian radionuclide therapy trials
NET cell-specific characteristics currently used for their localization

Adapted from co-author, Karel Pacak, with permission
Evolution of SSTR Imaging

Planar

SPECT

SPECT/CT

PET/CT

\[ {}^{111}\text{In-Octreotide} \]

\[ {}^{68}\text{Ga-Octreotate} \]

radionuclide

Linker (chelator)

peptide

target
## Management Impact of SSTR PET/CT

<table>
<thead>
<tr>
<th>Study</th>
<th>No pt</th>
<th>Tracer</th>
<th>Management Impact</th>
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<tbody>
<tr>
<td>Ambrosini 2010</td>
<td>90</td>
<td>DOTA-NOC</td>
<td>50% △ stage or therapy modification</td>
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<tr>
<td>Srirajaskanthan R 2010</td>
<td>41</td>
<td>DOTA-TATE</td>
<td>Inter-modality △ 71%</td>
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<tr>
<td>Frilling A 2010</td>
<td>52</td>
<td>DOTA-TOC</td>
<td>△ treatment decision 60%</td>
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<tr>
<td>Haswa N 2011</td>
<td>109</td>
<td>DOTA-NOC</td>
<td>Inter-modality △ 19%</td>
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<tr>
<td>Ruf J 2011</td>
<td>64</td>
<td>DOTA-TOC</td>
<td>Inter-modality △ 38%</td>
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<tr>
<td>Hofman MS 2012</td>
<td>59</td>
<td>DOTA-TATE</td>
<td>Inter-modality △ 47%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Intra-modality △ 10%</td>
</tr>
</tbody>
</table>

✓ High management impact similar in patients with negative or positive Octreotide SPECT/CT, suggesting redundancy of this technique

Hofman MS, J Med Imaging Rad Onc 2012;56(1)-40-7.
NET indications for $^{68}$Ga-DOTATATE PET/CT

- **STAGING**
  - prior to resection of apparently localised disease

- **LOCALISATION**
  - primary site in patients with biochemical suspicion of NET
    - Insulinoma *J Clin Endocrinol Metab* 2017; 102: 195-199
    - Ectopic ACTH *J Clin Endocrinol Metab* 2012; 97: 2207-2208
    - Oncogenic osteomalacia *J Clin Endocrinol Metab* 2013; 98: 687-694
  - unknown primary with metastatic NET

- **THERANOSTIC**
  - ‘Assess suitability & response to THERApy with a diagNOSTIC test’
  - SSTR density/distribution to guide suitability for SSA therapy or PRRT

- **RESTAGING**
  - Therapeutic response assessment
  - Post operatively (rising CgA)
25 year history of non-localised insulinoma
Insulinoma: Peptide Receptor Expression

- **Incidence & density** of 10 peptide receptors assessed by *in vitro* receptor autoradiography

- **2/27 cases** had –ve GLP-1R expression but **very high SSTR2 expression** = ‘flip-flop’

25 year history of non-localised insulinoma

$^{68}$Ga-DOTA-exendin-4 PET/CT
GLP-1 plays a diverse role in glucose homeostasis

- **incretin effect**: glucose-dependent insulin secretion by pancreatic beta cells

**GLP-1 receptors**

- widespread within GI tract
- overexpressed in various NETs (esp insulinomas)

**Exendin-4 (exenatide, Byetta™)**

- long-acting GLP-1 analogue originally isolated from saliva of Gila monster
- radiolabelling with $^{68}$Ga or $^{111}$In
  - $^{111}$In-DOTA-exendin-4 SPECT/CT (Basel)
  - $^{68}$Ga-DOTA-exendin-4 PET/CT (Basel)
  - $^{68}$Ga-NOTA-exendin-4 PET/CT (NIH/Beijing)

*J Nucl Med* 2010; 51: 1059-1067
Prospective cohort study of 53 patients with endogenous hyperinsulinism

1 negative case: 46mm G2 lesion, +ve on SSTR, CT, MRI & FDG avid

9 non-surgical cases: 3 focal lesions declined surgery, 2 congenital hyperinsulinism, 2 clinical nesidioblastosis, 2 uncertain diagnosis

Comparison of GLP-1R PET/CT and Conventional Imaging in Patients with Insulinoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GLP-1R PET/CT (n = 43)</th>
<th>CT (n = 43)</th>
<th>MR (n = 25)</th>
<th>EUS (n = 25)</th>
<th>SRS (n = 25)</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97.7%</td>
<td>74.4%</td>
<td>56.0%</td>
<td>84.0%</td>
<td>19.5%</td>
</tr>
<tr>
<td>95% CI</td>
<td>87.7–99.9</td>
<td>58.8–86.5</td>
<td>34.9–75.6</td>
<td>63.9–95.5</td>
<td>8.8–34.9</td>
</tr>
<tr>
<td>P</td>
<td>NA</td>
<td>0.006</td>
<td>0.006</td>
<td>0.125</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPV</td>
<td>100%</td>
<td>94.3%</td>
<td>93.3%</td>
<td>95.7%</td>
<td>100%</td>
</tr>
<tr>
<td>95% CI</td>
<td>92.0–100</td>
<td>80.8–99.3</td>
<td>68.1–99.8</td>
<td>78.1–99.9</td>
<td>59.0–100</td>
</tr>
<tr>
<td>P</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI = confidence interval; NA = not applicable.


68Ga-exendin-4 PET/CT
Extra-pancreatic insulinoma

Insulinoma  Diffuse uptake
Adjacent renal uptake

**Delayed imaging at 2-3 hours recommended in negative cases**

Pattison & Hicks, *Endocr Relat Cancer* 2017; 24: R203-R221
False negative – SSTR+ve / GLP1R-ve

Benign vs Metastatic Insulinoma

- 11 patients with metastatic insulinoma imaged with both GLP-1R & SSTR\(^1\)
  - \(^{111}\)In-DTPA-Exendin-4 SPECT/CT +ve: 4/11
  - \(^{68}\)Ga DOTATATE PET/CT +ve: 8/11

- ‘Flip-flop’ phenomenon:
  - Both tracers positive in only 1 patient

- Conceptual explanation due to pathologic role of GLP-1R and hypoglycaemia

Metastatic Insulinoma: ‘triple flop’
FDG predicts survival

- Multivariate analysis: SUVmax > 3 only significant predictor of PFS (HR: 8.4)
  - No difference in survival: presence or number of hepatic metastasis on CT, CgA
  - Ki,67 not significant in multivariate analysis
- 40% of patients with Ki,67% < 2% were FDG positive

Binderup et al, *Clin Cancer Res* 2010, 16(3)
Adapted from Michael Hofman, PMCC
‘A single biopsy, the standard of tumour diagnosis and the cornerstone of personalised medicine decisions, cannot be considered representative of the landscape of genomic abnormalities in a tumour’
Metastatic Insulinoma

*In-vivo disease characterisation*

*In-vivo* whole body disease characterisation facilitates personalised, targeted therapy

Adapted from Michael Hofman, PMCC
Metastatic Insulinoma
Symptomatic treatment with TACE

Baseline + 6 months + 12 months

INTRACTABLE HYPOGLYCAEMIA

46 yo woman
Inpatient
IV Dextrose infusion
Enteral feeding
Diazoxide
Dexamethasone
Octreotide
Characterisation of insulinoma phenotype with molecular imaging

<table>
<thead>
<tr>
<th>ENETS Grade</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67 index, %</td>
<td>≤2</td>
<td>3-20</td>
<td>&gt;20 &gt;60</td>
</tr>
</tbody>
</table>

- **Well differentiated** (slowly growing)
- **Poorly differentiated** (aggressive, poorer prognosis)

- **DOTATATE**: SSTR expression
- **FDG**: glycolytic activity
- **Exendin**: GLP-1R expression

Adapted from Hofman MS, Hicks RJ *Discov Med* 2012; 14(74):71-81
18F-FDOPA Imaging

- Well established role in localisation of congenital hyperinsulinism (CHI), but insulinoma controversial

1st paper – localised 9/10 (90%) cases¹ 😊
- included 1 metastatic, 2 nesidioblastosis

2nd paper – localised 1/6 (17%) cases² ❌

3rd paper – localised 8/11 (73%) cases³ 😐
- Carbidopa pre-medication to inhibit AADC in background physiologic pancreatic tissue
- improved target : background ratio

Carbidopa improves $^{18}$F-FDOPA localisation
Approach to molecular imaging for insulinoma

Hyperinsulinaemic Hypoglycaemia

Arterial-phase contrast-enhanced CT (+/- MRI)

No

LOCALISATION?

Yes

68Ga-exendin-4 PET/CT
Endoscopic US
? Localisation

(68Ga-DOTATATE PET/CT or 18F-FDOPA PET/CT)

68Ga-DOTATATE PET/CT
? Metastatic disease
? Suitability for PRRT

Selective Arterial Calcium Stimulation Test

18F-FDG PET/CT:
? Discordant SSTR-ve / FDG+ve disease

1. Ki67 > 5%
2. Disease progression < 6 months
3. SSTR -ve lesions

Pattison & Hicks, *Endocr Relat Cancer* 2017; 24:203-221
Phaeochromocytoma & Paraganglioma (PPGL)

Genetics

Cluster 1: ‘Pseudohypoxia’ group

- SDHA / B / C / D
- SDHAF2
- FH
- VHL
- HIF2A / EPAS1

Induction of anaerobic glycolysis → Warburg effect
Intense FDG avidity ≠ poorly differentiated disease
In vivo disease characterisation #1 ‘Undifferentiated NET’

46yo ♂ with left mandibular pain.

OPG demonstrates mass.

Biopsy: “undifferentiated NET”

? primary site of disease

FDG

Activated brown fat

Organ of zuckerkandl primary & jaw metastasis

Pl Normetadrenaline 18000
### Patient Information Sheet

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had Chemotherapy?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>When did you last receive this treatment?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had Radiotherapy?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>If yes, where on the body?</td>
<td></td>
</tr>
<tr>
<td>When did you last receive this treatment?</td>
<td></td>
</tr>
<tr>
<td>Are you taking any hormone therapy?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Are you taking any Anti-Hypertensives?</td>
<td>High Blood Pressure</td>
</tr>
<tr>
<td>Do you have any allergies e.g. Penicillin, Latex?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Please list:</td>
<td></td>
</tr>
<tr>
<td>Are you claustrophobic?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Are you or were you ever a smoker?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Female patients: - Are you pregnant?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>- Last noted menstrual period?</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

- Scan Length: 505.7 to 1,076.48 cm
- Number of Steps: 189
- Scan Start Time: 6:38 PM
- Uptake Time: 6:38 PM
- Technologist's initials: [Redacted]
- Patient Height: 157 cm
- Patient Weight: 93 kg
- Injection site: [Redacted]

**DOB:** 26/10/1967
**Phnsw:** [Redacted]
**Wt:** 93 kg
**99mTc MBq of 90 Gy checked 26 06 22 870 hrs**
**IV 86.1% 0 840 hrs**
**DC 460 MBq**
**PMC / Buil - No:** 1

**BSL:** 8.9 mmol/L

**Authorised by:** [Redacted]

*Authorised by Dr. Eddie Lee April 2011*
Question

• What is the best staging investigation for this case?
  A. Repeat $^{18}$F-FDG PET/CT with propranolol to suppress brown fat uptake
  B. $^{123}$I-MIBG SPECT/CT
  C. CT & MRI
  D. $^{68}$Ga-DOTATATE PET/CT
  E. $^{18}$F-FDOPA PET/CT
Prospective evaluation of 17 patients (289 lesions) with SDHB-related metastatic PHEO/PGL

Lesion based detection rate:

- \(^{68}\text{Ga}\)-DOTATATE PET/CT: 98.6% (CI 96.5-99.5%)
- \(^{18}\text{F}\)-FDG PET/CT: 85.8% (CI 81.3-89.4%, p<0.01)
- \(^{18}\text{F}\)-FDOPA PET/CT: 61.4% (CI 55.6-66.9%, p<0.01)
- \(^{18}\text{F}\)-FDA PET/CT: 51.9% (CI 46.1-57.7%, p<0.01)
- CT/MRI: 84.8% (CI 80.0-88.5%, p<0.01)

Theranostic role for radionuclide therapy

- \(^{68}\text{Ga}\)-DOTATATE (PRRT) & \(^{123}\text{I}\) or \(^{124}\text{I}\)-MIBG (\(^{131}\text{I}\)-MIBG)

Clin Cancer Res 2015; 21: 3888-3895
FDG vs GaTate vs MIBG

Brown fat activation
? Paraganglioma

Intense FDG avidity
• SDHx or VHL mutation
• Mets $\rightarrow$ SDHB

Intense GaTate avidity
• Suitable for PRRT

Negative MIBG
• $\downarrow$ sensitivity (57%) in metastatic/SDHB disease
• Use to assess suitability for $^{131}$I-MIBG therapy
PPGL: Molecular imaging by indication

Adrenal
? laterisation
Adrenergic

Paraganglioma
? metastatic (>4cm adrenal)
Noradrenergic

Surveillance:
As per genotype (DOTATATE)

Theranostic:

$^{18}$F-FDOPA PET/CT or $^{123}$I-MIBG SPECT/CT (funded)
$^{68}$Ga-DOTATATE PET/CT

$^{68}$Ga/$^{177}$Lu-DOTATATE PET/CT
$^{123}$I/$^{131}$I-MIBG SPECT/CT
In vivo disease characterisation #2
‘Metastatic phaeochromocytoma’

‘4cm R adrenal nodule & multiple metastases on CT’

FDG –ve adrenal mass → Non SDH/VHL

GaTate & MIBG avid bilateral adrenal masses → Bilateral phaeo
**In vivo disease characterisation #2**

‘Metastatic phaeochromocytoma’

FDG avid locally invasive thyroid mass with regional metastases

→ Medullary thyroid cancer

→ ? MEN 2
In vivo disease characterisation #2

‘Metastatic phaeochromocytoma’

FDG avid hepatic and extensive bony metastases → Metastatic MTC (‘metabolic signature’)

Summary:
1. Bilateral phaeo
2. Metastatic MTC
3. MEN2A phenotype → likely RET mutation
In vivo disease characterisation #3

‘Metastatic phaeochromocytoma’

44M
JAK2 –ve polycythaemia
Rising catecholamines
? Recurrent / metastatic phaeo

Metastatic & progressive

FDOPA & MIBG >
DOTATATE avidity
→ Consider I-131 MIBG therapy
→ ?HIF2A mutation (Pacak-Zhuang syndrome)
Overview

• **Background**
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• **Molecular Imaging**
  • $^{68}$Ga-DOTATATE PET/CT
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• **Radionuclide Therapy**
  • RCT: NETTER-1 Trial (midgut NETs)
  • GEP-NETs / PPGL

• **Future directions**
  • Next generation SSTR imaging: SSTR2-antagonists & $^{64/67}$Cu-SARTATE
  • Australian radionuclide therapy trials
Theranostics

Prediction of response to **THERApy** using a diag**NOSTIC** test = Personalised medicine
Peptide Receptor Radionuclide Therapy (PRRT)

- **111Indium (InTate)**
  - Auger 10 μm (ultra short range)
  - t½ 2.8d

- **90Yttrium (Y-tate)**
  - Long range beta 1cm
  - t½ 2.6d

- **177Lutetium (LuTate)**
  - Short range beta 1-3mm
  - t½ 6.7d

Adapted from A/Prof Michael Hofman, PMCC
• Open label, multicentre randomised controlled trial, 229 pts (Europe & USA)
  • Lu177-DOTATATE 7.4GBq x4 + Octreotide LAR 30mg monthly vs Octreotide LAR 60mg monthly
• Inclusion criteria:
  • Metastatic / inoperable midgut well-differentiated (Ki,67 <20%) NET
  • Disease progression (RECIST v1.1) prior 3 years despite Octreotide LAR 20-30mg
  • Karnovsky performance index >60
  • SSTR expression on all tumour sites (Octreotide scan)
• Exclusion criteria:
  • Cr clearance < 50ml/min, Hb <80, WCC <2, Platelets <75, Bili > 3xULN
  • Any prior PRRT
  • Any surgery, liver-directed transarterial therapy or chemo within 12 weeks
Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors


---

**A Progression-free Survival**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>$^{177}$Lu-DOTATE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 months</td>
<td>116</td>
<td>113</td>
</tr>
<tr>
<td>27 months</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>24 months</td>
<td>76</td>
<td>47</td>
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<tr>
<td>21 months</td>
<td>59</td>
<td>28</td>
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<td>18 months</td>
<td>42</td>
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<td>15 months</td>
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<td>12 months</td>
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<td>6 months</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>0 months</td>
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$P<0.001$

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**B Overall Survival (Interim Analysis)**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>$^{177}$Lu-DOTATE</th>
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</tr>
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<tbody>
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<td>30 months</td>
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<td>24 months</td>
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<tr>
<td>0 months</td>
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</table>

$P<0.004$
# PRRT: Indications & AE’s

## Criteria for treatment with PRRT at Peter MacCallum Cancer Centre:

- **Unresectable** locally advanced or metastatic neuroendocrine tumor (NET); and
- Somatostatin receptor (SSTR) scan **uptake > liver** (i.e. Krenning score 3 or 4); and
- No evidence of macroscopic SSTR –ve / FDG +ve disease; and
- Either:
  - uncontrolled symptoms due to hormone secretion / tumour burden; or
  - radiologic, scintigraphic or biochemical evidence of **progression in prior 12 months**; or
  - G2 or G3 disease with significant tumor burden or impaired performance status

## Contraindications:

- Hypoalbuminaemia (< 25g/L), GFR < 30ml/min, platelet count < 50,000 or pancytopenia
- ECOG Performance score =4 or expected survival < 3 months.

## Adverse events:

- Generally very well tolerated compared to other therapies
  - Transient nausea, discomfort, fatigue
- Major risks:
  - Myelodysplasia 1-2%
  - Hormonal flare; esp. insulinoma, phaeochromocytoma & VIPoma
# Metastatic NETS treatment comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of patients</th>
<th>Grade</th>
<th>Therapy</th>
<th>Median PFS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMID(^1)</td>
<td>RCT – midgut</td>
<td>85</td>
<td>G1 (95%)</td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Octreotide LAR</td>
<td>14.3</td>
</tr>
<tr>
<td>CLARINET(^2)</td>
<td>RCT – pancreas, midgut, hindgut, UKP</td>
<td>204</td>
<td>G1 or G2 (Ki,67 &lt; 10%)</td>
<td>Placebo</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lanreotide</td>
<td>&gt;24</td>
</tr>
<tr>
<td>RADIANT(^3)</td>
<td>RCT – progressive PNETS</td>
<td>410</td>
<td>G1 or G2</td>
<td>Placebo</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>(NB: RADIANT 4 included lung &amp; midgut NETs)</td>
<td></td>
<td></td>
<td>Everolimus</td>
<td>11</td>
</tr>
<tr>
<td>Raymond, et al(^4)</td>
<td>RCT – progressive PNETS</td>
<td>171</td>
<td>G1 or G2</td>
<td>Placebo</td>
<td>5.5</td>
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<td></td>
<td>Sunitinib</td>
<td>11.4</td>
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<tr>
<td>Eziddin, et al(^5)</td>
<td>Single centre series PNETS</td>
<td>68</td>
<td>G1, G2</td>
<td>LuTate</td>
<td>34</td>
</tr>
<tr>
<td>Kwekkeboom(^6)</td>
<td>Single centre series PNETS &lt; midgut</td>
<td>310</td>
<td>G1, G2 &amp; G3</td>
<td>LuTate</td>
<td>32</td>
</tr>
<tr>
<td>Kashyap, et al(^7)</td>
<td>Single centre series PNETS &gt; midgut</td>
<td>52</td>
<td>G2 &amp; G3</td>
<td>LuTate + 5FU</td>
<td>48</td>
</tr>
</tbody>
</table>

Metastatic insulin/gastrin secreting pancreatic NET

• 77yo man admitted with unconscious collapse & intractable hypoglycaemia despite:
  • Diazoxide 50 mg tid
  • IV Dextrose 20% via PICC
  • Glucagon sc 1 mg qid
  • Chlorothiazide
  • Dexamethasone 8 mg/day
  • Dextrose 50% via NGT/PEG tube

• Prolonged admission complicated by:
  • 30 kg weight gain/fluid overload
  • Steroid-induced myopathy
  • Severe hyponatraemia (Na+ 114 mmol/L; N>135)
  • Deconditioning (ECOG 4)
  • Venous-access associated DVT
Gastrin (N < 55 pmol/L)
Chromogranin A (N < 21.8 U/L)

CgA
Gastrin

Hyperglycaemia therapy
Hypoglycaemia

PRRT (177Lu-DOTA-octreotate)
Current status

• Asymptomatic
• Ongoing complete resolution of hypoglycaemia
• No hyperglycaemic medications
• 26 patients with progressive, bulky metastatic GEP-NET treated sequentially with 1-2 cycles $^{90}$Y-DOTATATE & 2-3 cycles $^{177}$Lu-DOTATATE PRRT
  • Bulky disease (>4cm lesions) = worse prognosis
  • $^{90}$Y vs $^{177}$Lu = ↑dosimetry in large lesions but ↑ toxicity

• Outcomes:
  • Partial response 42%, stable disease 58%
  • Symptomatic relief in all, resolution 4/7 patients
  • Median progression-free survival 33 months
  • Adverse events: 8 grade 3/4 lymphopaenia, 2 grade 3/4 thrombocytopaenia
High clinical and morphologic response using $^{90}$Y-DOTA-octreotate sequenced with $^{177}$Lu-DOTA-octreotate induction peptide receptor chemoradiation therapy (PRCRT) for bulky neuroendocrine tumours

Grace Kong $^1$, Jason Callahan $^1$, Michael S. Hofman $^1$$^2$, David A. Pattison $^1$, Tim Akhurst $^1$, Michael Michael $^3$$^4$, Peter Eu $^1$, Rodney J. Hicks $^1$,$^4$

**DOTATATE**

Progressive metastatic pancreatic NET

Despite 3 cycles chemotherapy

**EXCELLENT RESPONSE**

Excellent response to 1 cycle Ytate & 3 cycles LuTate with radiosensitising 5FU

Response maintained > 6 months

**FDG**

60 M

*J Nucl Med Mol Imaging* 2017; 44: 476-489
20 patients with metastatic PPGL treated with PRRT for following indications:

- 14 for uncontrolled hypertension
- 6 for progressive/symptomatic metastatic disease

Outcomes:

- Partial response 29%, stable disease 57%
- 8/14 reduced antihypertensive requirement
- Median progression-free survival 39 months
- Adverse events: 4 grade 3 lymphopaenia, 2 grade 3 thrombocytopenia
- Logistic and radiation safety advantages vs I131 MIBG

Efficacy of Peptide Receptor Radionuclide Therapy (PRRT) for Functional Metastatic Paraganglioma and Phaeochromocytoma


J Clin Endocrinol Metab 2017; 102: 3278-3287
Chromogranin A (ug/L)

Plasma Normetanephrine (pmol/L)

PRRT

$^{177}$Lu-DOTA-octreotate

SABR

Surgery

EBRT
Overview

• **Background**
  • GEP-NET (insulinoma), Phaeo & paraganglioma (PPGL)

• **Molecular Imaging**
  • $^{68}$Ga-DOTATATE PET/CT
  • $^{68}$Ga-exendin-4 PET/CT
  • FDG PET/CT
  • FDOPA PET/CT

• **Radionuclide Therapy**
  • RCT: NETTER-1 Trial (midgut NETs)
  • GEP-NETs / PPGL

• **Future directions**
  • Next generation SSTR imaging: SSTR2-antagonists & $^{64/67}$Cu-SARTATE
  • Australian radionuclide therapy trials
The next generation – SSTR ANTAGONISTS

• Promising new theranostic agents
  • $^{68}$Ga/$^{177}$Lu-DOTA-JR11
  • $^{68}$Ga-OPS202

• Up to 10x tumour dose compared with $^{177}$Lu-DOTATATE in human dosimetry pilot study

• Clinical trials ongoing

64CuSARTATE - First-Time in Human Trial

- Completed phase I trial in 10 patients at Peter Mac
- Sarcophagine leads to stable Cu-64 binding and high retention in tumour sites
  - Clearance of liver activity enhances lesion definition with most intense lesion to liver ratio more than doubling by 24 hours
- Acceptable radiation dosimetry for diagnostic use (3.1 mSv/200 MBq administered)
- Offers prospective dosimetry and theranostic pair with Cu-67 for PRRT
- Distribution from centralised GMP radiopharmacy is feasible
$^{64}$CuSARTATE - First-Time-in-Human Trial

Pt #9- pNET

Major impact on definition of small intra-hepatic metastases

CONTROL-NETs Trial

- Pancreatic NET:
  - LuTate vs CAPTEM chemotherapy
- Mid-gut NET:
  - LuTate + CAPTEM vs LuTate alone
- Recruitment completed end of 2018

LuCAT Trial

Patients with G3 NEN with Ki67 of 21.55%
SSTR positive on GaTate PET/CT
No Spatially discordant FDG-avid disease

Lu-177 PRRT
PRRT up to 4 cycles
Restage with CT 10 and 20 weeks after first cycle;
GaTate, FDG, CT 30 weeks

CAPTEM chemotherapy
Oral capcitabine Day 1-14, Temozolomide Day 10-14, 4 weekly
until unacceptable toxicity or patient intolerance
Restage with CT 10 and 20 weeks after first cycle;
GaTate, FDG, CT 30 weeks

Follow up every 3 months with CT
If evidence of RECIST 1.1 progression, restage with GaTate and FDG

Upon progression for PRRT arm:
2 cycles PRRT – if disease SSTR+, no discordant FDG+ lesions,
AND prior response
Cross over to CAPTEM – if discordant FDG+, SSTR- disease

Upon progression for CAPTEM arm:
Cross over to PRRT arm— if disease SSTR+, no discordant FDG+ lesions
Salvage chemotherapy/best supportive care – if discordant FDG+, SSTR-
disease

Follow up for minimum 24 months from start of treatment

Response rate
Safety/Toxicity
Quality of life
PFS, Overall survival
Predictive and prognostic factors
Tissue banking

Supported by ARTnet, ENETs, Unicorn Foundation, ITM
Conclusion

- Molecular imaging plays important role in NET management
  - DOTATATE PET/CT: staging, localization, theranostic
  - FDG PET/CT: prognostic, guide biopsy, theranostic
  - $^{68}$Ga-exendin 4 PET/CT: insulinoma
  - FDOPA PET/CT: phaeo (paraganglioma), MTC, congenital hyperinsulinism

- Detailed *in vivo* disease characterisation is possible using multiple molecular imaging tracers to guide individualised treatment

- Radionuclide therapy:
  - $^{177}$Lu-DOTATATE is highly effective for progressive metastatic midgut NETs
  - increasing evidence base for other SSTR-avid NET, including PPGL

- Emerging ‘next generation’ SSTR-antagonists and SSTR-analogue ($^{64}$Cu-SARTATE)