Gastro-Entero-Pancreatic Neuroendocrine Tumours

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Disclosures

**NOVARTIS**: advisory board, research grants, educational grants

**IPSEN**: advisory board, research grants, educational grants

**PFIZER**: advisory board, educational grants
**Neuroendocrine cells**

Peptide hormone-producing cells that share a neural-endocrine phenotype

<table>
<thead>
<tr>
<th>Cells that form glands</th>
<th>Cells that are diffusely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Type</strong></td>
<td><strong>Localisation</strong></td>
</tr>
<tr>
<td>D cells</td>
<td>GI tract</td>
</tr>
<tr>
<td>Enterochromaffin</td>
<td>GI tract</td>
</tr>
<tr>
<td>Enterochromaffin-like</td>
<td>GI Tract</td>
</tr>
<tr>
<td>G cells</td>
<td>Stomach &amp; duodenum</td>
</tr>
<tr>
<td>VIP cells</td>
<td>GI Tract</td>
</tr>
<tr>
<td>A cells</td>
<td>Pancreas</td>
</tr>
<tr>
<td>B cells</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Chromaffin</td>
<td>Adrenals</td>
</tr>
<tr>
<td>C cells</td>
<td>Thyroid</td>
</tr>
</tbody>
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NETs

- Rare
- May secrete hormones
- May have somatostatin receptors
- Usually slow growing
- Usually can be treated with more than one option
Incidence of neuroendocrine tumours (NETs) over time, by site and by disease stage
Clinical Classification of NETS

WHO 2002 Solcia et al

- Pancreatic neuroendocrine tumours
  - Functional or Non-functional

- Gastrointestinal neuroendocrine tumours
  - “Carcinoids”
    - foregut
    - midgut
    - hindgut
  - Functional or Non-functional

- Up to 10% associated with adenocarcinoma
Pancreatic Neuro-endocrine Tumours

Sporadic

With MEN-1:
  a. Parathyroid adenomas
  b. Pituitary tumours

With other genetic syndromes
  Von Hippel Lindau (VHL)
  Neurofibromatosis (NF-1)
  Tuberous sclerosis.
Histopathological assessment of NETs

- **Cell morphology**

- **Immunohistochemistry**
  - General markers
    - Chromogranin, Synaptophysin, Cytokeratin
  - Peptide hormones (serotonin)
  - Receptors

- **Ki67** (to assess tumour grading)
  (marker of proliferation, showing how many cells are in cycle)

Histopathological classification of p NETS
WHO 2017 classification

1. **Well-differentiated** neuroendocrine tumours of G1 grade (Ki67 <2%)
2. **Well-differentiated** neuroendocrine tumours of G2 grade (Ki67 3-20%)
3a. Neuroendocrine tumours of G3 grade (Ki67 >20%): well differentiated
3b. Neuroendocrine carcinoma, NEC (Ki67 >20%): poorly differentiated (small or large cell)

+ TNM staging

Intra-tumoural phenotypic heterogeneity is frequently observed in GEP-NETs.

Most primary small bowel NETs are G1 tumours (Ki67<2%).

However, when these tumors metastasize to the liver, they may become highly proliferative.

More than two-thirds of the patients who had G1 primary tumor developed G2 or G3 liver metastases.

Chi et al, Am J Clin Pathol, March 2015
Diagnosis of NETs

- History and clinical examination

- Biochemical tests

- Imaging studies
  (for localization of primary and metastatic lesions)

- Histology - "gold standard"
METASTATIC MIDGUT NETs
(in 30-40%) &
(in 5% of bronchial and 1% of pancreatic NETs)

a. “Carcinoid syndrome”
Flushing, diarrhoea, bronchospasm, Carcinoid heart disease

- 20 – 30 % of patients with liver metastases
- 5% of patients with carcinoid syndrome do not have liver metastases

b. “Carcinoid crisis”
Severe symptoms of carcinoid syndrome + hypotension during procedures that involve GA, as well as in TAE, and when the patient is on inotropes
Carcinoid Heart Disease

- It represents the **development of fibrotic plaques on the heart valves**.
- It **DOES NOT** mean development of myocardial metastases.
- Reported in the past in 40-50% of patients with carcinoid syndrome, **recent prevalence: about 20%**, (midgut NETs with hepatic or retro-peritoneal metastases, ovarian NETs and bronchial NETs).
- Its development is associated with **30–50% reduction in the expected survival** of those patients.
- The median survival improved from 1.5 years in the 1980s to 4.4 years in the late 1990s.

*Battacharyya S, et al, AJC 2008
Davar et al, JACC 2017*
**Insulinoma**
- Fasting hypoglycaemia, low blood glucose, and improvement after administration of glucose (Whipple’s triad)

**Gastrinoma**
- Recurrent/resistant to treatment peptic ulcers, not related to *H. pylori* & NSAIDs
- Chronic diarrhoea responding to PPIs

**VIPoma**
- Chronic diarrhoea, hypokalaemia, and dehydration

**Glucagonoma**
- New onset of DM, weight loss, and “migratory necrolytic erythema”
CLINICAL PRESENTATION (2)

Non-specific symptoms

- Dyspepsia
- Chronic abdominal pain
- Weight loss
- Symptoms compatible with IBS
- Etc, etc. So…

Tumours are diagnosed incidentally:

a. During surgery
b. During endoscopy
c. On imaging studies and guided biopsy of tumour lesions.
Biochemical tests (biomarkers): Non-specific - Chromogranin-A (CgA)

- **Sensitivity**: 60-90%
- Correlate with tumour burden
- Early decrease of its levels may predict PFS and OS
- Independent factor of survival in midgut NETs

**Not raised in:**
- Small volume disease
- Rectal NETs
- Insulinomas
- Poorly differentiated NECs

**May be raised in non-NETs situations:**
- Chronic PPI use
- Atrophic gastritis
  - IBD
- Renal failure
- Cirrhosis
- Other cancers

**Specificity**: 10 – 35%

Modlin et al, Am J Gastroenterology 2015
Kidd et al, Curr Opin Endocrinol Diabetes Obes 2016

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Biochemical tests (biomarkers) : Specific

SPECIFIC

a. 24hour urinary 5-HIAA  
(metastatic midgut NETs)

Please note that: certain foods like bananas, avocados, aubergine, pinepapple, plums, walnuts and some drugs like paracetamol, fluorouracil, methysergide, naproxen and caffeine, may cause false positive results, whilst other drugs like levodopa or phenothiazines may cause false negative results.

b. Fasting gut hormones  
(functioning pancreatic NETs)

(gastrin, VIP, somatostatin, insulin, glucagon)

c. Role of Gastrin in differentiation of types of Gastric NETs
MAAA PCR-based test (NETest)

- Multianalyte with Algorithm Analysis Assay.
- Using gene microarray-based approaches of both malignant NET tissue and blood, a PCR-based 51 marker signature (multigene test) was developed.
- High sensitivity (85–98%) and specificity (93–97%) for the detection of bowel and pancreatic NETs in circulating blood.
- Not affected by age, gender, ethnicity, fasting or medications.

Modlin et al, Am J Gastroenterol 2015
Conventional imaging in NETs

**Spiral CT και MRI**: can reveal the primary site in ~30-70% and distal metastases in 90% of patients.

**CT enterography**: can detect the primary small bowel NET with sensitivity 85% and specificity 97%.

*Ricke et al, European J Radiol 2001*
*Paulsen et al, Radiographics 2006*
Carcinoid Tumours:
\[ \text{sst2} > \text{sst5} > \text{sst1} > \text{sst3} & \text{sst4} \]

Gastrinomas:
\[ \text{sst2} > \text{sst5} = \text{sst1} > \text{sst3} > \text{sst4} \]

Insulinomas:
\[ \text{sst5} > \text{sst3} > \text{sst2} > \text{sst4} > \text{sst1} \]

NFPETS:
\[ \text{sst2} > \text{sst3} > \text{sst1} > \text{sst5} > \text{sst4} \]

Glucagonomas/MCT/phaeo:
\[ \text{sst2} > \text{sst1} > \text{sst5} = \text{sst4} > \text{sst3} \]
In-111-DTPA-Octreotide (OCTREOSCAN)

- Reveals the primary in 50-80% and the metastases 95% of patients.
- Can predict the response to treatment with somatostatin analogues.
- Lower sensitivity in NETs with Ki67>15%, tumour size < 10mm and insulinomas.

Warner, Gastroenterology 2005
Toumpanakis et al, Neuroendocrinology 2014
**Ga-68 DOTATATE PET**

- Improved sensitivity, resolution of PET
- Increased tumoural affinity (10x to SSR-2)
- Reduced radiation dose (less than ½: 4-5 vs. 12 mSv)
- Study duration 2-3 hours (vs. 24-48 hours)

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The role of $^{18}$F-FDG-PET in NETs

- $^{18}$F- FDG – PET is useful for evaluation of extent of disease:
  
  a) In poorly-differentiated G3 tumours
  
  b) In tumours with high Ki67 > 10%, and no Octreoscan uptake

- It seems that intense $^{18}$F-FDG uptake by tumour lesions predicts survival (one study)

Binderup T et al, Clin Cancer Res. 2010
Abgral et al, Clin Endocrinol Metabol 2011
Hepatic metastases from NET (68Ga-octreotate PET, left) and from colorectal cancer (FDG-PET, right) in the same patient.

Use of Molecular Imaging to Differentiate Liver Metastasis of Colorectal Cancer Metastasis From Neuroendocrine Tumor Origin.

Desai et al, J Clin Gastroenterology 2010
Combination of PETs for NET heterogeneity

Metastatic pancreatic NET, G1 (based on histology from the pancreatic primary) was referred to our Unit for PRRT.

A few of the hepatic lesions were non-avid on Ga-68 PET (blue arrows)

An FDG PET was then performed and showed avid uptake in those non-avid lesions on Ga-68 PET (orange arrows)

A US-guided biopsy of one of those FDG avid (Ga-68 non-avid) lesions revealed G3 NET (Ki67: 30%) and the patient received chemotherapy instead of PRRT.
Diagnostic algorithm

**History – clinical examination**
- Chromogranin-A
- Fasting gut hormones
  - 5-HIAA
  - NT-pro BNP

**Triple phase CT c/a/p**
- Or MRI

**Somatostatin Receptor Imaging**

- (Ga-68 PET OctreoScan)

- Commencement of treatment
  - Clinical, biochemical & radiological follow-up

**Cardiac ECHO**
- MRI liver
- MRI spine
- GLP-1 scan
- I-123 MIBG

**FDG-PET scan**
- High-grade tumours
- Suspected tumour heterogeneity
- Suspected second malignancy

**GLP-1 receptor imaging**
For localization of benign insulinomas

**Tissue diagnosis**
Treatment of NETs

A) Medical control of patient’s symptoms.
B) Resection of tumor primary and if possible, metastatic lesions.
C) Control of tumor growth in cases of advanced disease.
D) Improvement and maintenance of patient’s quality of life.
Somatostatin Analogues

Octreotide LAR

Lanreotide Autogel
In addition to SSA, **Telotristat Ethyl** inhibits serotonin production and alleviates symptoms.

5-HIAA: 5-hydroxyindole acetic acid

SSA: somatostatin analogue

SSTR: somatostatin receptor

5-HIAA: 5-hydroxyindole acetic acid

Urine

Serotonin

hormonal syndrome
flushing, diarrhoea....

5-HIAA

Tryptophan

Serotonin

SSTR

SSA
**TELESTAR results:**
Reduction in Mean Daily Bowel Movement Frequency at Baseline and Week 12

Mild nausea: 15%
Mild depression: 15-20%
Other medications for symptom control in pNETs

- High doses of Proton Pump Inhibitors (PPIs) in Gastrinomas
- Diazoxide, Corticosteroids and Everolimus in Insulinomas
- Corticosteroids in life-threatening diarrhoea in VIPomas
- Prophylactic aspirin in glucagonomas

*UKI-NETS Guidelines for NETs, Gut 2011*
Surgical treatment in pNETs

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>Local Metastases</th>
<th>Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical treatment</td>
<td>114 months</td>
<td>129 months</td>
<td>60 months</td>
</tr>
<tr>
<td>No surgical treatment</td>
<td>35 months</td>
<td>64 months</td>
<td>31 months</td>
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</tbody>
</table>

- Curative surgery (even in presence of hepatic metastases) and debulking of hepatic metastases seem to increase survival, especially in patients < 55 years old.
- Controversial data for MEN-1 gastrinomas.
- Palliative resections.

ENETS Guidelines for NETs, Neuroendocrinology 2016
Auernhammer & Goke, Gut 2011
Fendrich & Bartsch, Langenbecks Arch Surg 2011
Control of tumour growth for advanced inoperable GEP-NETs

**Medical therapy**
- Somatostatin analogues (SSAs)
  - Interferon-α
- Molecular targeted therapies
  - Everolimus
  - Sunitinib
- Systemic chemotherapy

**Loco-regional therapy**
- Radiofrequency ablation (RFA)
- Embolization/chemoembolization/radioembolization

**Nuclear medicine and radiation**
- Tumour-targeted, radioactive therapy:
  - PRRT using:
    - $^{177}$Lu –DOTATATE
- External radiation (for bone/brain metastases)
Median time to progression in LAR group: 14.3 m vs 6 months in placebo.

After 6 m of treatment: stable disease in 66.7% of LAR vs 37.2% of placebo.

Most favorable effect in patients with low-hepatic tumour load and resected primary tumour.
Progression-free survival and tumor growth with Lanreotide Autogel in patients with enteropancreatic NETs: Results from CLARINET, a randomized, double-blind, placebo-controlled study

Primary endpoint: PFS (ITT, N=204)

Lanreotide Autogel 120 mg
32 events / 101 patients
median, not reached

Placebo
60 events / 103 patients
median, 18.0 months [95% CI: 12.1, 24.0]

Lanreotide Autogel vs. placebo
p=0.0002 HR=0.47 [95% CI: 0.30, 0.73]

Patients alive and with no progression (%)

Time (months)

P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

Caplin et al, NEJM 2014
1. Platinum-based chemotherapy is the treatment of first choice in GEP-NECs with good RR but short PFS.

2. A 55% cut-off level of Ki67 seems promising predictive factor of response in NECs.

3. Streptozocin-based regimens induce responses in 30-40% well-differentiated pNETs and 15% carcinoids.

4. Temozolomide combinations are promising but direct comparison with streptozocin is required.

5. More studies are needed to assess the response in functional NETs and carcinoids.


7. Chemotherapy seems to be the preferred option in pNETs with rapid symptomatic and radiological progression, however prospective studies are needed.

Toumpanakis et al. Best Pract Res Clin End Metab 2007
Sorbye et al: the NORDIC NEC study, Ann Oncol 2013
Sunitinib

Everolimus

D.Metz & R.Jensen, Gastroenterology 2008
Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors


- Double blind randomized study
- 171 patients
- Progression within 12 months
- Ki67 < 20%
- 69% had chemotherapy before
- Sunitinib 37.5mg vs placebo

<table>
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<tr>
<th></th>
<th>PFS</th>
<th>OR</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Sunitinib</td>
<td>11.4</td>
<td>9.3%</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5</td>
<td>0%</td>
<td>21 (25%)</td>
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Learning point from Sunitinib trial

Oral Sunitinib can control tumour growth in G1/G2 advanced & progressive pancreatic NETs with potential favorable implications to OS

- 30% : diarrhoea, nausea, vomiting, fatigue
- 10-20% : Hypertension, neutropenia

Five years after study closure, **median OS was 38.6** (25.6-56.4) months for sunitinib and 29.1 (16.4-36.8) months for placebo (P = 0.094), with 69% of placebo patients having crossed over to sunitinib

*Faivre et al, Ann Oncol 2016*
Everolimus for Advanced Pancreatic Neuroendocrine Tumours (RADIANT-3)


- Double blind randomized trial
- 410 patients
- 50% chemo-naive
- Ki67 < 20%
- Progression within 12 months
- Everolimus 10 mg vs placebo

<table>
<thead>
<tr>
<th>Effect</th>
<th>Everolimus</th>
<th>Placebo</th>
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<tr>
<td>PFS OR</td>
<td>11 months</td>
<td>4.6 months</td>
</tr>
<tr>
<td>5%</td>
<td>2%</td>
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Adverse effects:
- 30% : aphthous ulcers, rash, diarrhoea, fatigue
- 10 – 30% : lower respiratory infections, interstitial pneumonitis
- < 10% : cytopenias, hyperglycaemia

Learning point from RADIANT-3 trial

Oral Everolimus can control tumour growth in G1/G2 advanced & progressive pancreatic NETs

Everolimus prolonged PFS regardless of prior chemotherapy

*Lombard-Bohas C et al, Pancreas 2015*
Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)
- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

Endpoints:
- Primary: PFS (central)
- Key Secondary: OS
- Secondary: ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:
- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.
Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.
Primary Endpoint: PFS by Central Review

52% reduction in the relative risk of progression or death with everolimus vs placebo

\[ \text{HR} = 0.48 \ (95\% \ CI, 0.35-0.67); \ P < 0.00001 \]

\[ P\text{-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.} \]
Transarterial Hepatic Embolization and Chemoembolization

- Symptomatic benefit (40-80%)
- Partial response: ~ 50%
- ? Survival benefit


- Morbidity (carcinoid crisis, fever, pain, hepatic failure, intestinal ischaemia)
- Mortality
- i.v. octreotide infusion pre- and post therapy in midgut carcinoids

**Careful selection of patients**

Toumpanakis et al, Best Pract Res Clin End Metab 2007
The β−-emitter labelled somatostatin analogue delivers a lethal radiation dose to the tumour cell.
Computed tomography scans in a patient with a metastasized nonfunctioning endocrine pancreatic tumor before treatment (left) and 3 months after the last treatment (right).

131 pts
CR 2%; PR 26%; MR 19%; SD 35%; PD 18%

Radiolabelled Somatostatin Analogue LU-177-DOTA, Tyr3 Octreotate in patients with endocrine gastroenteropancreatic tumours

Kwekkeboom et al JCO 2005; 23: 2754-2762
NETTER-1 Study Objectives and Design

Evaluate the efficacy and safety of LUTATHERA® + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)

International, multicentre, randomized, comparator-controlled, parallel-group

Treatment and Assessments
Progression-free survival (RECIST criteria) every 12 weeks

- **n = 116**
  - 4 administrations of 7.4 GBq of LUTATHERA® every 8 weeks + SSAs (symptom control)

- **n = 113**
  - Octreotide LAR (high dose - 60mg every 4 weeks)

5 Years follow up

Baseline progression according to RECIST 1.1 criteria
The median time between the oldest pre-baseline and the baseline scans (used to determine the progression at enrolment) was 11.4 months for patients in the LUTATHERA® arm and 11.7 months for the control arm

N = 229 (ITT)
Number of events: 90
• $^{177}$Lu-Dotatate: 23
• Oct 60 mg LAR: 67

Hazard ratio: 0.21 [0.129 – 0.338] p < 0.0001

79% reduction in the risk of disease progression/death

Estimated Median PFS in the $^{177}$Lu-Dotatate arm ≈ 40 months

Octreotide LAR 60 mg
Median PFS: 8.4 months

All progressions centrally confirmed and independently reviewed for eligibility (SAP)
Which treatment and for Whom

- Patient’s clinical status, comorbidities and preferences
- Tumour Histology
- Location of primary
- Positive uptake in Octreoscan or Ga-68 PET
- Tumour burden
- Tumour status
- Presence of carcinoid heart disease and/or mesenteric fibrosis
- Predictive molecular markers?
- Cost??
Multi-Disciplinary Team (MDT) approach for NETs

- Accurate diagnosis & staging
- Evaluation of performance status & quality of life
- Consensus agreement on treatment plan
- Continuous reassessment, discussion and peer review of the individualized treatment plan
Thank you