Management of Neuroendocrine Tumors

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Diagnostic Challenges in NET

- Heterogeneous group of tumours
- Wide variety of clinical presentations
- Late presentation
- Different terminology and classifications
- Histologic diagnosis may be difficult
NET Vary by Primary Tumour Site

- Generally characterized by their ability to produce peptides that may lead to associated syndromes\(^1,2\)
- Historically classified based on embryonic origin\(^3\)
  - Foregut tumours
  - Midgut tumours
  - Hindgut tumours
- Today, primary tumour location is recommended for NET classification\(^4\)
- "Karzinoide", Oberndorfer 1907

Clinical syndromes associated with endocrine pancreatic tumors

- Functioning (70 → 30%)
  - insulinoma: 1-3 per million (17%)
  - gastrinoma: 0.5-3 per million (15%)
  - VIP-oma: 0.05-0.2 per million (2%)
  - glucagonoma: 0.01-0.1 per million (1%)
  - somatostatinoma
  - ACTH-oma, GRF-oma <10%
  - calcitonin-, serotonin-
  - PTH-rp producing

- Non-functioning (30-70%) 0.2-2 per million
Classification of NET

• Functional versus non-functional

• Classification by site of origin
  – Nearly identical characteristics on routine histologic evaluation, but different responses to therapeutic agents

• Classification by tumour stage: TNM
  – AJCC
  – ENETS

• Histologic classification
  – Well differentiated, poorly differentiated
  – Tumours with a high grade (grade 3), a mitotic count >20 per 10 high powered fields, or a Ki-67 proliferation index of >20% represent highly aggressive malignancies

• Molecular Classification
  – MEN 1 & 2, Tuberosis Sclerosis, Von Hippel Lindau disease
Incidence of NET is Increasing*

*Approximate 5-fold increase between 1975 and 2004
Approximate 7-fold increase also evident in Norwegian registry

SEER = Surveillance, Epidemiology, and End Results (for malignant NET)

NET are the Second Most Prevalent Type of Gastrointestinal Malignancy

Prevalence in SEER Database

Colorectal\(^1\)  |  GEP-NET\(^2\)  |  Stomach\(^1\)  |  Pancreas\(^1\)  |  Esophagus\(^1\)  |  Hepatobiliary\(^1\)  

2 times more prevalent than pancreatic cancer

GEP = gastroenteropancreatic

33-Month Median Survival for Patients with Metastatic NET

Tumours with well- and moderately differentiated histology

![Graph showing survival probabilities over time with different colors for localized, regional, and distant stages.]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>223</td>
</tr>
<tr>
<td>Regional</td>
<td>111</td>
</tr>
<tr>
<td>Distant</td>
<td>33</td>
</tr>
<tr>
<td>95% CI</td>
<td>208-238</td>
</tr>
<tr>
<td>104-118</td>
<td>31-35</td>
</tr>
</tbody>
</table>

- SEER: 5-year survival, SI-NET: 54%; pNET 27%
- Survival rates are 3 times higher in specialized centres in Europe and US

CI = confidence interval

Correlation of Primary Tumour Site with Survival

Known prognostic factors include:
- Location of primary tumour
- Extent of disease
- Tumour stage
- Degree of differentiation/proliferative index (PI)
- Tumour grade
- Patient age
- Performance status

<table>
<thead>
<tr>
<th>WHO 2000</th>
<th>WHO 2010</th>
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<tbody>
<tr>
<td>Well-differentiated endocrine tumour (WDET)</td>
<td>Neuroendocrine tumours</td>
</tr>
<tr>
<td>Well-differentiated endocrine carcinoma (WDEC)</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Poorly differentiated endocrine carcinoma/small-cell carcinoma (PDEC)</td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine carcinoma</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Mixed exocrine-endocrine carcinoma (MEEC)</td>
<td>Mixed adenoneuroendocrine carcinoma (MANEC)</td>
</tr>
<tr>
<td>Tumour-like lesions (TLL)</td>
<td>Hyperplastic and preneoplastic lesions</td>
</tr>
</tbody>
</table>
ENETS/AJCC Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)*</th>
<th>Ki-67 index (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

*10 HPF (high power field) = 2 mm², at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.
**MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labeling.

3American Joint Committee On Cancer. AJCC Cancer Staging System. 7th ed.
## ENETS/AJCC TNM Staging Systems

### ENET/AJCC Classification Criteria – GI NET

Stage includes tumour location, size, lymph node involvement/distant metastasis

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

ENETS = European Neuroendocrine Tumour Society  
AJCC = American Joint Committee on Cancer  

3 American Joint Committee On Cancer. *AJCC Cancer Staging System. 7th ed.*
Correlation of Tumour Grade and Cumulative Survival (ENETS Grading Proposal)

1ENETS grading system.
210 HPF = 2 mm² at least 40 fields (40 × magnification) evaluated in areas of highest mitotic density.
3Percentage of 2,000 tumour cells in areas of highest nuclear labeling with MIB1 antibody.

Biomarkers in NET

• CgA is the best available biomarker for diagnosis of NET
  – Elevated CgA may correlate with tumour progression
  – CgA is elevated 80% to 100% of the time
• NSE is also expressed in NET
  – Not as commonly used as CgA
  – Also elevated in pNET and poorly differentiated NEC
• 5-HIAA reflects serotonin levels
  – Elevated serotonin levels over time lead to comorbidities such as cardiac disease
• Specific markers for different syndromes
• New biomarkers in NET are needed to provide better diagnostic and prognostic information

CgA = Chromogranin A; 5-HIAA = 5-hydroxy-3-indoleacetic acid, 5-HT = serotonin, NSE = neuron-specific enolase, VIP = vasoactive intestinal peptide; SSTR = somatostatin receptor

CgA raised for a median of 30 mo before recurrence was confirmed by imaging

Welin, et al, 2009: P-CgA first marker to indicate recurrence
Radiological Techniques

CT/MRI/US – diagnosis and follow-up
Endoscopic ultrasonography
Intraoperative ultrasonography
Rarely angiography

\[
\begin{align*}
&\text{60-95\% of metastases} \\
&\text{50-70\% of primary tumours} \\
&\text{75-90\%} \\
&\text{>90\%}
\end{align*}
\]
Functional techniques

- OctreoScan® (somatostatin receptor scintigraphy [SRS])
- Metaiodobenzylguanidine (MIBG)-scintigraphy
- Positron emission tomography (PET) ($^{11}$C-5-HTP, $^{18}$F-DOPA, $^{68}$Ga-DOTA-octreotide, $^{68}$Ga-exendin 4)
- For staging and localization
PET/CT with $^{11}$C-5-HP improves morphological accuracy.

Örlefors et al. JCEM 2005
Hofmann et al, Eur J Nucl Med 2001: Biokinetics and imaging with somatostatin PET radioligand $^{68}$Ga-DOTATOC: preliminary data

**PET/CT with $^{68}$Ga-DOTA-octreotide**
Methods for identification of primary and metastatic GEP NET

PET ([¹¹C], [¹⁸F], [⁶⁸Ga], or [⁶⁴Cu])

SRS

SRS/CT

CT

MRI

PET ([¹⁸F]FDG)

Identification of primary and metastatic tumours (%)

S = calculated sensitivity.

Current Challenges in Treating Patients with Advanced NET

- More than half of NET patients are diagnosed with advanced disease
- Advanced NET are incurable and most patients will succumb to the disease
- There is a need for new therapeutic options for patients with advanced NET

Therapeutic Options for Patients with Advanced NET

Surgery
  – curative or ablative

Debulking
  – radiofrequency ablation (RFA)
  – embolisation/chemo-/radio

Medical therapy
  – chemotherapy
  – biological treatment:
    • somatostatin analogs
    • alpha interferon
    • m-TOR inhibitors
    • VEGF-R inhibitors
    • other TKI’s

Irradiation
  – external (bone, brain metastases)
  – tumour targeted, radioactive treatment ($^{90}$Y-DOTATOC, $^{177}$Lu-DOTATE)
Chemotherapy for NET

- Streptozotocin, a chemotherapeutic agent, approved in some countries (US, France) for pancreatic NET (pNET), however, it is not effective in the treatment of GI-NET

- Most recent reports of outcome with STZ/Dox or STZ/5-FU describe PR (WHO, RECIST) of 36-39% with median duration of 9.3, PFS 18 months, SD 50%; first-line in G2

- Toxicity; gastro-intestinal (grade 1-2), renal (mainly grades 1-2, grade 3: 8%, grade 4: 0%) with appropriate monitoring and dose adjustments

Kouvaraki, J Clin Oncol, 2004
Chemotherapy: Temozolomide

Ekeblad; Clin Cancer Res 2007
- 36 patients (35 foregut: 12 EPT, 12 bronchial 7 thymus)
- median 2.4 prior antitumour medical therapies
- RR 14% (40% in low MGMT)
- TTP 7 months

Kulke; ASCO 2006 abstract 4044
- + bevacizumab
- 34 patients (18 EPT, 16 carcinoids)
- 12 prior chemo
- EPT 24% PR, carcinoids 0%
- PFS 8.6 months

Kulke; Clin Cancer Res 2009
- correlation MGMT-deficiency and response

Strosberg; Cancer 2011
- + capecitabine
- 30 patients with EPT
- first line
- PR 21/30 (70%)
Biotherapy in NET: Interferon Studies

- 27 studies, 679 patients
- 3 randomised trials
- Biochemical responses 50%, symptomatic 60%, tumour response 10%
- Side-effects constitute a problem; mainly given in combination with somatostatin analogs in low-proliferative tumours
Octreotide LAR Provides Effective Symptom Relief

42% REDUCTION in Diarrhea Frequency\textsuperscript{1,2}

Median Number of Stools/Day

Baseline: 4.3
Week 24: 2.5

N = 47

84% REDUCTION in Flushing Frequency\textsuperscript{1,2}

Median Number of Flushings/Day

Baseline: 4.5
Week 24: 0.7

N = 33

PROMID: Phase III Randomised, Double-Blind, Placebo-Controlled Study

Patients:
- Well-differentiated midgut NETs
- Treatment naïve
- Locally inoperable or metastasised
  \( N = 85 \)

Primary endpoint:
- Median time to tumour progression

Secondary endpoints:
- Objective tumour response rate
- Symptom control
- Overall survival

Treatment until CT/MRI-documented tumour progression or death

Octreotide LAR
30 mg im / 28 days

Placebo
im / 28 days

im = intramuscular; CT = computed tomography; MRI = magnetic resonance imaging

## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Octreotide LAR n = 42</th>
<th>Placebo n = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>63.5 (38-79)</td>
<td>61.0 (39-82)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (%)</td>
<td>47.6</td>
<td>53.5</td>
</tr>
<tr>
<td>female (%)</td>
<td>52.4</td>
<td>46.5</td>
</tr>
<tr>
<td><strong>Time since diagnosis, months (range)</strong></td>
<td>7.5 (0.8-271.2)</td>
<td>3.3 (0.8-109.4)</td>
</tr>
<tr>
<td><strong>Karnofsky score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 (%)</td>
<td>16.7</td>
<td>11.6</td>
</tr>
<tr>
<td>&gt;80 (%)</td>
<td>83.3</td>
<td>88.4</td>
</tr>
<tr>
<td><em><em>Carcinoid syndrome</em> (%)</em>*</td>
<td>40.5</td>
<td>37.2</td>
</tr>
<tr>
<td><strong>Resection of primary (%)</strong></td>
<td>69.1</td>
<td>62.8</td>
</tr>
<tr>
<td><strong>Hepatic tumour load</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>16.7</td>
<td>11.6</td>
</tr>
<tr>
<td>0% - 10%</td>
<td>59.5</td>
<td>62.8</td>
</tr>
<tr>
<td>10% - 25%</td>
<td>7.1</td>
<td>4.7</td>
</tr>
<tr>
<td>25% - 50%</td>
<td>11.9</td>
<td>9.3</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>4.8</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Octreoscan positive (%)</strong></td>
<td>76.2</td>
<td>72.1</td>
</tr>
<tr>
<td><strong>Ki-67 up to 2% (%)</strong></td>
<td>97.6</td>
<td>93.0</td>
</tr>
<tr>
<td><strong>CgA elevated (%)</strong></td>
<td>61.9</td>
<td>69.8</td>
</tr>
</tbody>
</table>

* Not requiring octreotide for symptom control

Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression

66% reduction in the risk of tumour progression
HR = 0.34; 95% CI: 0.20-0.59; P = .000072

[177Lu-DOTA0, Tyr3] Octreotide

310 patients
Dose 600-800 m Ci (22.2 to 29.6 GBq)

PR  30%  • higher remission rates –
MR  16%  higher uptake on Octreoscan grade 3-4
SD  35%  • Performance status KPS >70
PD  20%

Median time to progression: 40 mo
Serious adverse events:
MDS (3 patients), acute leukemia, liver toxicity (2 patients)

• higher response rates but shorter duration in EPT

Kwekkeboom et al, JCO, 2008
Rationale for the Use of Angiogenesis Inhibitors in NET

- NET are highly vascularised and express VEGF and VEGF-R\textsuperscript{1}

- Angiogenesis inhibitors that target VEGF have been shown to have clinical activity in NET\textsuperscript{3}

New Antiangiogenic Agents

- VEGF antibodies
  - Bevacizumab
- Inhibition of PDGF + VEGF receptors
  - Sunitinib, sorafenib, vandetanib
- Inhibition of mTOR which regulates HIF-1 impacting the transcription of VEGF-A
  - Everolimus
- ("Old": IFN-α, somatostatin analogs)

PDGF = platelet-derived growth factor; HIF = hypoxia inducible factor
Sunitinib vs Placebo in Advanced pNET

- Phase III randomised, placebo-controlled, double-blind trial
- Trial terminated after unplanned early analysis

Well differentiated advanced pNET patients (N = 171 enrolled / 340 planned)
- Disease progression in past 12 mo
- Not amenable to curative treatment

Primary Endpoint:
- PFS
  Statistical significance required nominal critical z value ≥3.8809

Secondary Endpoints:
- OS
- ORR
- TTR
- Duration of response
- Safety
- Patient-reported outcomes

* With best supportive care
Somatostatin analogues were permitted
Progression-Free Survival*

Kaplan-Meier median PFS
Sunitinib: 11.4 months
Placebo: 5.5 months

HR = 0.42; 95% CI [0.26-0.66]

\[P \text{ value } < .001; \text{ nominal critical } z \text{ value } = 3.8506\]

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>0</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>2</td>
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<td>15</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Local review

Adverse Events: Sunitinib

- Most frequently reported all-grade AEs with sunitinib were diarrhea (59%), nausea (45%), asthenia (34%), vomiting (34%), and fatigue (33%)
- Grade 3/4 AEs (≥ 5%) in the sunitinib arm included neutropenia (12%), hypertension (10%), leukopenia (6%), PPE* (6%), asthenia (5%), diarrhea (5%), fatigue (5%), and abdominal pain (5%)

* Palmar-plantar erythro-dysesthesia

Rationale for mTOR Inhibition in NET

- mTOR is a central regulator of growth, proliferation, cellular metabolism, and angiogenesis\textsuperscript{1-3}
  
- mTOR pathway activation is observed with genetic cancer syndromes associated with pNET\textsuperscript{4}
  - TSC2, NF1, VHL
  
- Everolimus has demonstrated antitumour activity in pNET in phase II and phase III studies\textsuperscript{5-7}

TSC2 = tuberous sclerosis 2; NF1 = neurofibromatosis type I; VHL = von Hippel-Lindau disease

RADIANT-3 Study Design: Phase III
Double-Blind, Placebo-Controlled Trial

Patients with progressive advanced pNET, N=410
- Advanced low- or intermediate-grade pNET
- Radiologic progression ≤12 months
- Prior antitumor therapy allowed
- WHO PS ≤2

Stratified by:
- WHO PS
- Prior chemotherapy

Randomisation: August 2007-May 2009
* Concurrent somatostatin analogues allowed

Primary Endpoint:
- PFS
  Statistical boundary ≤.025

Secondary Endpoints:
- OS
- ORR
- Biomarkers
- Safety
- PK

Progression-Free Survival

Kaplan-Meier median PFS
Everolimus: 11.0 months
Placebo: 4.6 months
Hazard ratio = 0.35; 95% CI 0.27-0.45
P value: <.0001

148 placebo patients crossed over to everolimus at the time of progression

P value obtained from stratified 1-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model

Adverse Events: Everolimus

- Most frequently reported all-grade treatment-related AEs with everolimus were stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), and infections (23%)
- Grade 3/4 AEs (≥ 5%) in the everolimus arm included stomatitis (7%), anemia (6%), and hyperglycemia (5%)

RADIANT-2 Study Design: Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of secretory symptoms (N = 429)
- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhea)
- Prior antitumour therapy allowed
- WHO PS ≤2

Primary Endpoint:
- PFS
  Statistical boundary = .0246

Secondary Endpoints:
- OS
- ORR
- Biomarkers
- Safety
- PK

Enrollment January 2007-March 2008
PD = progressive disease; ORR = overall response rate; PK = pharmacokinetics

Requirements for improved therapeutic outcome in NET

• Applied classification and grading, possibly refined (Rindi et al. 2012; Ki-67 >5%)
• Elucidation of molecular genetics and cell biology
• Identification of serum markers for early diagnosis and follow-up; age at diagnosis
• Improved molecular imaging (PET) for therapy evaluation
• Markers that serve as predictors of response (SST, MGMT, PTEN? hLMHI?)
• Individualize treatment
• Establishment of Centres of Excellence with multidisciplinary specialized clinical teams for NET

PET = positron emission tomography.
NET Treatment Algorithm

**Metastatic NET**

**Surgery (resection, debulking, RF, embolisation)**

- **Low proliferation, Ki-67 ≤ 2%**
  - **Biotherapy**
    - Somatostatin analogue (SSA)
    - α-IFN
    - Everolimus
    - Sunitinib
    - SSA + IFN
    - SSA + everolimus
    - SSA + sunitinib
    - SSA + bevacizumab

- **Intermediate, Ki-67 3-20%**
  - **Chemo-/Biotherapy**
    - STZ+5-FU/DOX
    - Everolimus+SSA
    - Temozolomide + capecitabine
    - Sunitinib + SSA
    - SSA for symptom control

- **High proliferation, Ki-67 >20%**
  - **Chemotherapy**
    - Cisplatin + etoposide
    - Carboplatin + etoposide
    - Temozolomide + capecitabine + bevacizumab
    - SSA for symptom control

**Targeted Radiotherapy**
177Lu-DOTATATE, 90Y-DOTATOC

**Experimental protocols**