NeuroEndocrine Tumors
Diagnostic and therapeutic challenges: introduction

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Introduction to Neuroendocrine Tumours

- Neuroendocrine tumours (NET) are relatively rare; this is associated with limited knowledge on disease management.

- The natural history of NET is poorly understood.

- At least 40 different entities are described arising in different organs; different terminologies have also caused confusion.
Diagnostic & therapeutic challenges in NET

- Heterogeneous group of tumors
- Wide variety of clinical presentations
- Late presentation
  - Over 60% of NETs are advanced at the time of diagnosis
  - The median survival for patients with advanced NET is 33 months
- Different terminology and classifications
- Histologic diagnosis may be difficult
- Variety of therapeutic options/approaches
  - Limited phase III evidence for chemotherapy and PRRT
Neuroendocrine Tumors (NETs): A Diverse Group of Malignancies, a Clinical Challenge

- Neuroendocrine cells: migrated from the neural crest to the gut endoderm, from multipotent stem cells
- Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body
- NETs present with functional and nonfunctional symptoms and include a heterogeneous group of neoplasms\(^1,2\)
  - Multiple endocrine neoplasia (MEN)\(de\), type 1 and type 2/medullary thyroid carcinoma
  - Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
  - Islet cell tumors
  - Pheochromocytoma/paraganglioma
  - Poorly differentiated/small cell/atypical lung carcinoid
  - Small cell carcinoma of the lung
  - Merkel cell carcinoma
Overview of Neuroendocrine Tumors (NETs)

- NETs are sometimes called carcinoid tumors
  - Can be both symptomatic and asymptomatic
  - May be undetected for years without obvious signs or symptoms

- NETs are generally characterized by their ability to produce peptides that lead to their syndromes

- NETs are generally classified as foregut, midgut, or hindgut depending on their embryonic origin:
  - Foregut tumors develop in the respiratory tract, thymus, stomach, duodenum, and pancreas
  - Midgut tumors develop in the small bowel, appendix, and ascending colon
  - Hindgut tumors develop in the transverse colon, descending colon, or rectum

Pancreatic NETs
- Insulinoma
- Glucagonoma
- VIPoma
- Pancreatic polypeptidoma

Other NETs
- Foregut
  - Thymus
  - Esophagus
  - Lung
  - Stomach
  - Duodenum

- Midgut
  - Appendix
  - Ileum
  - Cecum
  - Ascending colon

- Hindgut
  - Distal large bowel
  - Rectum
Incidence of NETs Increasing

US and European Incidence of NET

<table>
<thead>
<tr>
<th>Country</th>
<th>Study Period</th>
<th>Incidence rates per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (SEER)</td>
<td>2000-2004</td>
<td>Men: 6.0, Women: 5.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>1983-1998</td>
<td>Men: 2.0, Women: 3.0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1989-1996</td>
<td>Men: 1.5, Women: 2.0</td>
</tr>
<tr>
<td>Norway</td>
<td>1993-2004</td>
<td>Men: 3.0, Women: 2.5</td>
</tr>
<tr>
<td>Switzerland (Vaud)</td>
<td>1974-1997</td>
<td>Men: 4.0, Women: 3.5</td>
</tr>
<tr>
<td>Italy (Tuscany)</td>
<td>1985-1991</td>
<td>Men: 1.0, Women: 1.5</td>
</tr>
</tbody>
</table>

References:
NETs Are Second Most Prevalent Gastrointestinal Tumor

NET Prevalence in the US, 2004

103,312 cases (35/100,000)

29-year limited duration prevalence analysis based on SEER.
SEER: Surveillance, Epidemiology, and End Results.

The GI Tract Is the Most Common Primary Location of NET (US SEER Data)


<table>
<thead>
<tr>
<th>Percent distribution (%)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>17.2</td>
</tr>
<tr>
<td>Jejunum/ileum</td>
<td>13.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.4</td>
</tr>
<tr>
<td>Stomach</td>
<td>6.0</td>
</tr>
<tr>
<td>Colon</td>
<td>4.0</td>
</tr>
<tr>
<td>Duodenum</td>
<td>3.8</td>
</tr>
<tr>
<td>Cecum</td>
<td>3.2</td>
</tr>
<tr>
<td>Appendix</td>
<td>3.0</td>
</tr>
<tr>
<td>Liver</td>
<td>0.8</td>
</tr>
</tbody>
</table>

58% Digestive system
15% Lung
27% Other/Unknown
The Pancreas Is the Most Common Primary Location of NET Breakdown (Middle East & Asia Pacific Region)

- Pancreas 49%
- Small Intestine 11%
- Colon 13%
- Liver 4%
- Not reported 10%
- Bile duct and gallbladder 3%
- Omentum/abdominal lining 1%
- Rectum 1%
- Ovary 1%
- Lung 1%

Neuroendocrine Cells Are Peptide Hormone-Producing Cells that Share a Neural-Endocrine Phenotype

- **Synaptophysin**
  - Small synaptic vesicles

- **Chromogranin A**
  - Membrane protein of neurosecretory granules

- **Peptide hormone**
  - In neurosecretory granule

- Secreted into the serum

Cells of Origin

- Gastrointestinal neuroendocrine lineages arise from a common stem cell precursor in the base of the intestinal crypts or in the neck of the gastric glands.

- Differentiate into diverse types of neuroendocrine cells under the influence of transcription factors Math1 and neurogenin 3 (NGN3).

Image courtesy of IM Modlin.
Role of CgA IHC in the Diagnosis of NET

Benefits:
- Can be detected in the secretory granules of most NET both symptomatic and asymptomatic

Limitations:
- Many NET of the large bowel and some of the appendix primarily secrete CgB
- CgA may be negative in poorly differentiated NET

Role of Synaptophysin IHC in the Diagnosis of NET

Benefits:
- Expressed independently of secretory granules
- Useful in identifying poorly granulated and poorly differentiated NET that may not exhibit CgA staining

Limitations:
- Expression is not limited to neuroendocrine cells

Immunohistochemical NE Markers

Definition of hormonal production

Glucagon
Neuroendocrine Tumours
WHO Classification 2010 of the Digestive System

• Working principles
  – “Neuroendocrine” defines the peptide hormone-producing tumours and share neural-endocrine markers
  – The term “Neuroendocrine neoplasm” includes well- and poorly differentiated tumours

• Premise: All neuroendocrine neoplasms (NEN) have a malignant potential

  *This premise has an influence on the incidence data*

Initially, NET that were regarded as benign were not considered in the incidence data (eg, SEERS data)
NET now have to be included because they are known to have malignant potential
Neuroendocrine Tumours (NET): A Stepwise Diagnostic Approach

1. NET vs nonNET → morphology & NE markers

2. NET vs NEC → structure + grade

3. Grade 1-2-3 → mitoses & Ki67

4. TNM Stage I-II-III-IV → size & invasion
Confusion Caused by the Term “Carcinoid”

• Oberndorfer coined the term “karzinoide” in 1907\(^1\)
  – This term implies that these tumours are benign; this is an unfortunate misnomer for the majority of NET
    • NET have malignant potential and metastasize, generally to the liver
  – Referring to any NET, the term “carcinoid” should only be used in reference to carcinoid syndrome
    • Symptoms of carcinoid syndrome include flushing, abdominal cramps, and diarrhea\(^2\)
    • Most cases are associated with tumours of the intestines, which frequently metastasize to liver\(^2\)

Carcinoid Syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases

- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation

- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease

### WHO Classifications of Neuroendocrine Neoplasms of the GEP System

<table>
<thead>
<tr>
<th>WHO 1980</th>
<th>WHO 2000</th>
<th>WHO 2010</th>
</tr>
</thead>
</table>
| I. Carcinoid | Well-differentiated endocrine tumour (WDET)  
Well-differentiated endocrine carcinoma (WDEC)  
Poorly differentiated endocrine carcinoma/small-cell carcinoma (PDEC) | Neuroendocrine tumours  
Grade 1  
Grade 2 | Neuroendocrine carcinoma  
Grade 3 |
| II. Mucocarcinoid | Mixed exocrine-endocrine carcinoma (MEEC) | Mixed adenoneuroendocrine carcinoma (MANEC) |
| III. Mixed forms carcinoid-adenocarcinoma | Tumour-like lesions (TLL) | Hyperplastic and preneoplastic lesions |
| IV. Pseudotumour lesions | | |

Staging of NET According to Tumour-Node-Metastasis (TNM)

- The European Neuroendocrine Tumour Society (ENETS) and American Joint Committee on Cancer (AJCC) have developed TNM staging systems.

- Staging systems are developed for the following tumour locations:
  - Gastric, duodenum/ampulla/proximal jejenum, pancreas
  - Lower jejenum and ileum, appendix, and colon and rectum

References:
ENETS/AJCC TNM Staging Systems

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour Location</th>
<th>Lymph Node Involvement</th>
<th>Distant Metastasis</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

Correlation of Tumour Stage and Cumulative Survival (ENETS TNM Staging Proposal)

- I vs II \(P = .227\)
- I vs III \(P = .048\)
- I vs IV \(P < .001\)
- II vs III \(P = .171\)
- II vs IV \(P < .001\)
- III vs IV \(P = .004\)

202 cases: gastric (48), duodenal (23), pancreatic (131)
Grading of GEP-NET According to ENETS/WHO/AJCC

<table>
<thead>
<tr>
<th>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</td>
</tr>
<tr>
<td>MI (mitotic count)*</td>
<td>&lt;2</td>
<td>2-20</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.

Metastatic GEP-NET: Correlation Between Mitotic Count and Ki-67 Index

R Sq Linear = 0.813

Correlation of Tumour Grade and Cumulative Survival (ENETS Grading Proposal)

1. ENETS grading system.
2. 10 HPF = 2 mm² at least 40 fields (40 × magnification) evaluated in areas of highest mitotic density.
3. Percentage of 2,000 tumour cells in areas of highest nuclear labeling with MIB1 antibody.

Metastatic Well-Differentiated Neuroendocrine Neoplasms: Prognosis

Prognostic factors (MV analysis):

- Age > 65 years
- Number of liver metastases (>10)
- Tumour progression (100% if Ki67 > 10%)
- Primary not removed

MV = mean variance

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

65% of patients with advanced NET will not be alive in 5 years

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
- Other biomarkers are available, however, few have achieved widespread acceptance
- 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

Correlation of Baseline CgA Levels with Survival


Chromogranin A μg/l

- <100 n = 6
- 100-1000 n = 16
- >1000 n = 16

Cumulative survival vs. Survival time (months)

P = .02
## CgA and NSE: Prognostic Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Nonelevated CgA</th>
<th>Elevated CgA</th>
<th>Nonelevated NSE</th>
<th>Elevated NSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Everolimus, n</strong></td>
<td>121</td>
<td>84</td>
<td>155</td>
<td>48</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>11.2</td>
<td>8.5</td>
<td>13.86</td>
<td>8.11</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.2 (0.82, 1.76)</td>
<td></td>
<td>2.03 (1.33, 3.09)</td>
<td></td>
</tr>
<tr>
<td>P value†</td>
<td>.173</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Placebo, n</strong></td>
<td>97</td>
<td>103</td>
<td>138</td>
<td>56</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>4.9</td>
<td>4.3</td>
<td>5.36</td>
<td>2.83</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.33 (0.98, 1.82)</td>
<td></td>
<td>2.01 (1.43, 2.84)</td>
<td></td>
</tr>
<tr>
<td>P value†</td>
<td>.035</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

- Elevated baseline CgA were associated with shorter PFS in patients who received everolimus or placebo, suggesting that these biomarkers are predictive for outcome
  - Everolimus improved PFS vs placebo regardless of patients’ baseline CgA levels

PFS = progression-free survival

* Obtained from unstratified Cox model.
† Obtained from unstratified 1-sided log-rank test.

CgA and NSE: Predictive Biomarkers*

**CgA**

Median PFS (months)
- Early response (n/N = 16/33) = 13.3
- No early response (n/N = 26/38) = 7.5

HR = 0.25
95% CI: 0.13-0.51
\( P = .00004 \)

**NSE**

Median PFS (months)
- Early response (n/N = 17/28) = 8.6
- No early response (n/N = 10/11) = 2.9

HR = 0.25
95% CI: 0.10-0.58
\( P = .00062 \)

*Data from RADIANT-1 clinical trial.

An early CgA or NSE response was defined as normalization or ≥30% decrease at week 4.
Pathology Report of NET

☑ Define **location** and **tumour type**

☑ Define **differentiation grade** (including Ki-67 proliferative index)

☑ Describe the presence of **additional histologic features**
  (multicentric disease, non-ischemic tumour necrosis, vascular or perineural invasion)

☑ Assess the **TNM stage**

☑ Define the **resection margins**

☑ Define the **hormonal production**, if any

☑ **Upon request**, assess prognostic or **predictive factors** useful for target therapy (e.g. somatostatin receptors, mTor pathway molecules, other target enzymes, ...)

Systematic Approach to Diagnosing NETs

History and physical exam
- Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)
  - Present in 8% to 35% of metastatic NETs

Biochemical markers
- Chromogranin A (CgA)
- Urinary 5-hydroxyindoleacetic acid [(5-HIAA) (with presence of carcinoid syndrome]
- Synaptophysin on biopsies
- Other biomarkers, including glucagon, gastrin

Histologic diagnosis (expertise)

Imaging
- Computerized tomography scan (CT)
- Endoscopic ultrasound (mainly pancreatic-NET and NET in duodenum)
- Magnetic Resonance Imaging (MRI)
- Somatostatin-receptor scintigraphy (Octreoscan™) or DOTA-TOC FDG/PET
Neuroendocrine tumours originate from a wide variety of different cell types that can secrete their own peptide hormone.

**Site** = *Pancreas vs intestine*
- Organ of origin should be determined
- Nomenclature could be simplified by using location of origin

**Classification** = *Give a name to the disease*
- WHO classification is based on morphology and clinical pathological information (and is independent from presence and type of hormone secretion)

**Staging** = *Measure the extent of the disease*
- TNM staging for ENETS and AJCC is same for GI NET but differ for pNET (ENETS has proved preliminary clinical effectiveness while AJCC needs confirmation)

**Grading** = *Measure the pace of NET growth*
- Mitosis count or Ki67 with cut-off at 5% and 20% discern prognosis between diseases
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 tumor stage: TNM
  - AJCC
  - ENETS
- Histologic classification
  - well differentiated - poorly differentiated
  - tumors 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
Collaboration for optimal patient management

Multidisciplinary patient management

Expertise/network

Clinical research team

Basic research team

Patient

ENETS Centers of Excellence

University hospitals Leuven
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