NeuroEndocrine Tumors
Diagnostic and therapeutic challenges: introduction

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Diagnostic & therapeutic challenges in NET

- Heterogeneous group of tumors with variety of histologic appearance and organ of origin
- 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
  - Gastroenteropancrtic 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>5.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>1983-1998</td>
<td>2.5</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1989-1996</td>
<td>2.0</td>
</tr>
<tr>
<td>Norway</td>
<td>1993-2004</td>
<td>3.0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1974-1997</td>
<td>3.5</td>
</tr>
<tr>
<td>Italy</td>
<td>1985-1991</td>
<td>1.0</td>
</tr>
</tbody>
</table>

NETs Are Second Most Prevalent Gastrointestinal Tumor

NET Prevalence in the US, 2004

- Colon
- Neuroendocrine
- Stomach
- Pancreas
- Esophagus
- Hepatobiliary

103,312 cases (35/100,000)

- Localized: 203 months
- Regional: 114 months
- Distant: 39 months

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)

- Lung: 27%
- Digestive system: 58%
- Other/Unknown: 15%

Percent distribution (%):
- Rectum: 17.2%
- Jejunum/ileum: 13.4%
- Pancreas: 6.4%
- Stomach: 6.0%
- Colon: 4.0%
- Duodenum: 3.8%
- Cecum: 3.2%
- Appendix: 3.0%
- Liver: 0.8%

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%
- Stomach: 6%
- Bile duct and gallbladder: 3%
- Omentum/abdominal lining: 1%
- Rectum: 1%
- Ovary: 1%
- Lung: 1%
- Not reported: 10%

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

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\(^2\)

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Carcinoid Syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases.\(^1\)

- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation.\(^2,3\)

- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease.\(^2,3\)

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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
## WHO Classifications of Neuroendocrine Neoplasms of the GEP System

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

Neuroendocrine tumour/ NET (Carcinoid)

Neuroendocrine carcinoma / NEC
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
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 jejunum, pancreas\(^1\)
  – Lower jejunum and ileum, appendix, and colon and rectum\(^2\)

### ENETS/AJCC TNM Staging Systems

#### ENET/AJCC Classification Criteria – GI NET

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</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>

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

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

3American Joint Committee On Cancer. AJCC Cancer Staging System. 7th ed.
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)
**Systematic Approach to Diagnosing NETs**

**History and physical exam**
- Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)
  - Present in 8% to 35% of metastastic 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
Nomenclature – Summary

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

Clinical research team

Basic research team

Expertise/network

Patient

ENETS Centers of Excellence

University hospitals Leuven
17th World Congress on Gastrointestinal Cancer
1–4 July 2015
Barcelona, Spain
CCIB (International Convention Center of Barcelona)

Chair:
Mario Dicato, MD
Luxembourg Medical Center
Luxembourg, Luxembourg

Eric Van Cutsem, MD, PhD
University Hospital Gasthuisberg
Leuven, Belgium

Vice Chair:
Josep Tabernero, MD, PhD
Vall d’Hebron University Hospital
Barcelona, Spain

Save the Date

www.worldgicancer.com