Neuroendocrine Tumors: The GI Perspective

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Neuroendocrine Tumors

• Second most prevalent cancer of the GI tract behind colorectal cancer

• Over 100,000 patients are living with NETs in the United States

• Principles of care are different/unique compared to other solid tumors

Neuroendocrine Terminology

- Neuroendocrine tumors include carcinoid tumors and pancreatic neuroendocrine tumors (PNETs).
- Carcinoid tumors are in the alimentary tract or elsewhere (lung, thymus, testis, ovary, etc); PNETs are in the pancreas.
- Carcinoid tumors may be functional (carcinoid syndrome) or non-functional.
- PNETs may be functional (various types) or non-functional.
- Functional syndromes require production of biologically active amines.

Incidence of Neuroendocrine Tumors Over Time is Increasing

Classic vs NET Tumor Size Paradigm

Grade and Differentiation

- **GRADE** refers to pathologic features of growth rate
  - Mitoses or Ki 67 staining (biologic aggressiveness)
- **DIFFERENTIATION** refers to pathologic features of malignancy
  - Histologic appearance (degree of resemblance to normal)

- Grade and differentiation are related but not equal
- Biological behavior of low or Intermediate grade well differentiated tumors can only be determined clinically during follow up
Pathologic Classification of NETs

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well</td>
<td>Low</td>
<td>Common</td>
<td>&lt;2 mitoses/10hpf</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low Ki 67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variable prognosis</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Less common</td>
<td></td>
<td>Intermediate prognosis</td>
</tr>
<tr>
<td>Poor</td>
<td>High</td>
<td>Rare</td>
<td>Poor prognosis</td>
</tr>
</tbody>
</table>

Klimstra, DS. Pancreas 2010;39:707-12

Hereditary vs. Sporadic

• **Multiple Endocrine Neoplasia syndrome type 1**

• Three of the five phacomatoses
  – Von Hippel-Lindau (VHL)
    • PETs (non-functional >> insulinoma/vipoma) in 12-17%
  – Von Recklinghausen's disease (NF-1)
    • Occasional duodenal somatostatinomas (often non-functional) >> insulinoma/gastrinomas
  – Tuberous sclerosis
    • Rare PETs (non-functional, insulinomas/gastrinomas)
MEN-1 Syndrome

- Multiple Endocrine Neoplasia syndrome type 1
- Autosomal dominant (Knudsen’s two hit hypothesis; retinoblastoma)
- Gene cloned (11q13), product Menin
- 3 P’s: Parathyroid hyperplasia (early)
  - Pituitary adenomas (Prolactinoma, Cushings)
  - Entero-Pancreatic tumors
  - Others: Lipomas, adrenal hyperplasia, etc

Biochemical Products

- Functional products
  - Carcinoid syndrome
    - Serotonin, 5HIAA, 5HTP, substance P, kallikrein, etc
  - Pancreatic endocrine tumors
    - Gastrin
    - Insulin
    - VIP
    - Others (glucagon, somatostatin, etc)
  - Utility
    - Syndrome diagnosis and to monitor hormonal therapy
- Neuroendocrine markers
  - Chromogranin A
  - Others (pancreatic polypeptide, bHCG, etc)
  - Utility
    - Tumor diagnosis and to monitor growth or anti-tumor therapy
Functional NET Syndromes

- Carcinoid syndrome
  - Flushing, diarrhea, wheezing, pellagra, cardiac disease
- Zollinger-Ellison syndrome (Gastrinoma)
  - Gastric acid hypersecretion (pain, ulcers, diarrhea)
- Insulinoma Syndrome
  - Neuroglycopenia, sympathetic overdrive, obesity
- Glucagonoma
  - Hyperglycemia, rash (MNE), anemia, hypoaminoacidemia, weight loss, thromboembolism, glossitis
- VIPoma
  - Watery diarrhea, hypokalemia, achlorhydria and others (hyperglycemia, hypercalcemia, flushing)
- Others:
  - ACTHoma – Cushing’s syndrome
  - GRFoma - acromegaly
  - Somatostatinoma – hyperglycemia, steatorrhea, gallstones
  - Rare syndromes (calcium, erythropoeitin, etc)

Octreotide for Functional NETs

- Drug of choice for syndrome management (FDA-approved for carcinoid, VIPoma and acromegaly)
- Role in tumor stabilization established for alimentary tract tumors (Promid)
- Correlate with hormonal measurements in nadir
  - Functional (24 hr urine)
  - Structural (CgA)
- Correlate with functional and structural imaging
Anatomic Classification of NETs\textsuperscript{1,2}

Pancreatic NETs

- Gastrinoma
- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma
- Pancreatic polypeptidoma

Other NETs (also referred to as carcinoid tumors)

- Foregut
  - Lungs
  - Stomach
  - First part of duodenum

- Midgut
  - Second part of duodenum
  - Jejunum
  - Ileum
  - Right colon

- Hindgut
  - Transverse, left, sigmoid colon
  - Rectum

Like other NETs, pancreatic NETs can also be non-functional tumors.


\textsuperscript{2} NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors.

Gastric Carcinoids and Hypergastrinemia

<table>
<thead>
<tr>
<th>Carcinoid</th>
<th>% total</th>
<th>Assoc.</th>
<th>Gastrin</th>
<th>Acid Sec.</th>
<th>Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>75</td>
<td>PA/atrophy</td>
<td>Inc.</td>
<td>Low</td>
<td>V. rare</td>
</tr>
<tr>
<td>Type II</td>
<td>5-10</td>
<td>ZES/MEN-1</td>
<td>Inc.</td>
<td>High</td>
<td>Rare</td>
</tr>
<tr>
<td>Type III</td>
<td>15-25</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
<td>Common</td>
</tr>
</tbody>
</table>

Midgut Carcinoids

<table>
<thead>
<tr>
<th>Location</th>
<th>Multiplicity</th>
<th>Functional</th>
<th>Surgically curable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal</td>
<td>Yes</td>
<td>Yes (mets)</td>
<td>Rarely (mets)</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>No</td>
<td>Rarely</td>
<td>Yes (esp &lt;1-2 cm)</td>
</tr>
</tbody>
</table>


Extent of Disease at Diagnosis

- Diagnosis is often delayed 5–7 years on average, and the probability of metastatic disease at diagnosis is increased

- The median age of diagnosis for NETs of the rectum is 56 years, for NETs of the lung is 64 years, and for NETs of the jejunum/ileum is 66 years

Staging of Disease

• Imaging
  – Cross sectional studies (CT/MRI)
  – Functional Imaging (Octeoscan/MIBG scan)

• Endoscopy
  – Optical (EGD/Colonoscopy)
  – Capsule Endoscopy
  – Deep Enteroscopy (Spiral/Single-/double Balloon)
  – Endosonography (EUS-PNETs)
Two endoscopic images that may show the location of the patient’s primary tumor in the submucosa

Fluoroscopic Results

Anterograde route

Retrograde route

Images courtesy David Jaffe, MD

Primary Tumor Identification

MRI

EUS

Octreoscan

Metz DC. Gastroenterology 2008;135:1469-1492
Kwekkeboom DJ. Neuroendocrinology 2009;90:184-189
Liver Metastases

<table>
<thead>
<tr>
<th>CT</th>
<th>MRI</th>
<th>Octreoscan</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-90%</td>
<td>80-95%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

Sundin A. Neuroendocrinology 2009;90:167-183

68 Ga Octreotide PET Imaging with CT fusion: Imaging of the future

Photographs Courtesy Kjell Oberg, MD
Management Principles

- Confirm the diagnosis
- Control the hormonal syndrome (if present)
- Determine extent of disease
- Consider surgery
  - For cure (if possible)
  - For debulking (if not)
- Long term management
  - Hormonal syndrome (if present)
  - Growth
Management Principles (Cont.)

- Management is multidisciplinary
  - Medicine (GI, endocrine, oncology)
  - Surgery
  - Radiology (XRT, IR)
- Non-surgical therapy should not be squandered
  - Wait for symptoms or evidence of rapid growth

Therapy for Metastatic Disease: Limited Options

- Watch (especially if asymptomatic)
- Octreotide (? retards growth)
- Chemotherapy (temporizing, PNETs>> GI NETs)
  - Streptozotocin, capecitabine/temozolomide
- Small molecules
  - Everolimus, sunitinib
- PRRT (experimental)
  - Yttrium or lutetium octreotide/tate
- Regional therapy (XRT to bone, chemoembo cryotherapy, yttrium beads, etc)
- Transplantation (difficult to qualify)
PROMID: Time to Progression

Other Methods of Debulking

Interventional Radiology
- Chemo/bland embolization
- Radioactive beads
- Radiofrequency ablation

Surgery
- Transplantation (controversial)
Systemic Therapies

- Radioactive
  - MIBG
  - PRRT
- Chemotherapy
- Small molecules (PNETs)
  - Sunitinib
  - Everolimus
  - Many more to come

Managing the Effects of Therapy

- Pancreatic resections (Distal or Whipple’s)
  - Pancreatic insufficiency
  - Dumping syndrome
  - Diabetes
  - Immunity (spleen)
- Octreotide
  - Gallstones
  - Steatorrhea
- Others
  - Adhesions
- Terminal ileal resection
  - B12 deficiency
  - Bile Salt Diarrhea
  - Overgrowth
Multidisciplinary Care is Ideal

- Many options and no standard algorithm exists (therapy should be individualized)
- Tumor Board is **ESSENTIAL** component
- Flexibility is **KEY**

Conclusions

- NETS come in many different flavors but have lots of features in common
- They differ in many important ways from other more typical solid malignancies
- Management requires consideration of both functionality and tumor growth
- Multidisciplinary care is the norm