Carcinoid/NETs
A Brief Review & Comments on Recent Developments

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## GEP-NETs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Peptide</th>
<th>Symptoms/Syndrome</th>
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</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Serotonin</td>
<td>Carcinoid syndrome</td>
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<tr>
<td></td>
<td>Tachy and bradykinins</td>
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<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Hypoglycemia</td>
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<tr>
<td>VIPoma</td>
<td>VIP</td>
<td>Verner-Morrison</td>
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<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>DM, NME*, cachexia</td>
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<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>Bile stones, steatorrhea, DM</td>
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<tr>
<td>GRFoma</td>
<td>GH releasing factor</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>Zollinger-Ellison Syndrome: Abdominal pain, diarrhea, GERD, ulcers</td>
</tr>
</tbody>
</table>

* Necrolytic migratory erythema
Distribution of Carcinoid Tumors by Site

- *Bronchopulmonary System: 28%*
  - Colon and Rectum: 28.6%
  - Other: 2.3%
- *Small Intestine: 28.5%
  - Duodenum: 3%
  - Jejunum: 2%
  - Ileum: 15%
  - NOS: 8%
- *Stomach: 4.6%
- *Other: 0.5%

NOS, not otherwise specified.

Prevalence of GI NETs is more than three times greater than pancreatic adenocarcinoma.1

Although the incidence of all NETs is increasing, the largest increase has been seen in the diagnosis of lung and small intestinal NETs\(^1\)
Diagnosis is often delayed 5 to 7 years on average, and the probability of metastatic disease at diagnosis is increased\(^2\)

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Natural History of NET

Diagnosis:
Irritable Bowel Syndrome

Vague abdominal symptoms

Primary tumor present

Correct Diagnosis

Death

Diarrhea

Flushing

Metastases

Increasing Severity of Disease

Disease Duration (Years)

0  2  4  6  8  10  12  14  16  18  20

Midgut Carcinoid Tumors
Commonest Presenting Features

- Abdominal pain
- Obstruction
- Incidental
- Bleeding
- Mass
- CS
Carcinoid of the Lung Presenting Features

- Incidental finding
- Recurrent infection (pneumonia)
- Hemoptysis
- Chronic Cough
- Distant metastases
- Endocrine syndrome (Carcinoid, Cushing’s, etc.)
Diagnosis of Carcinoid

- Suspicion
- Markers
- Imaging
- Biopsy
Carcinoid Tumor Markers (1)

- Urine 5-HIAA
- Serotonin (5-HT)
- Chromogranin A (CgA)
Serotonin Metabolic Pathway

- Tryptophan Protein, Nicotinic Acid
- 5-Hydroxytryptophan (5-HTP)
- 5-Hydroxytryptamine (5-HT, serotonin)
- 5-Hydroxyindole-3-acetaldehyde
- 5-Hydroxyindoleacetic acid (5-HIAA)
Carcinoid Tumor Markers (2)

- Neuron specific enolase (NSE)
- Substance P
- Pancreatic poly peptide (PP)
- Pancreastatin
- Neurokinin A
- $\alpha/\beta$ subunits of HCG
Specific NET Markers

- Gastrin
- Insulin and related substances
- VIP
- Glucagon
- Calcitonin
- ACTH
- VMA, Catachole amines, Metanephhrines
CgA – Elevated in

- ↓ renal function, ↓ liver function
- PPI
- Eating
- Retained antrum
- Hypergastrinemia (ZES and atrophic gastritis)
- IBD
- Physical stress and trauma
Newly Emerged Diagnostic Techniques
Based on molecular gene and DNA analysis to aid choice of treatment drug

1. Molecular profiling tumors (tissue) using:
   • IHC
   • FISH
   • MA
   • Q PCR
   
2. Molecular diagnosis (to find origin of metastases, Cancer Type ID) by profiling 92 genes from RNA extracted from fixed paraffin embedded tumor biopsy via QRT-PCR Technique. Commercially Available.
Newly Emerged Diagnostic Techniques
(continued)

3. Early diagnosis of GEP NETS by blood PCR of the signature of 51 genes in 3 micro array data sets. Far more sensitive and specific than chromogranin A.

Commercially Available.
Standard Imaging Techniques

- X-Ray
- CT-scan
- MRI-scan
- Ultrasound scan (sonography) (EUS)
- Isotope bone scan
- *OctreoScan® (SRS) NET specific
- FDG PET scan
- OctreoScan® (PET) / CT Fusion scan
- MIBG scan
Diagnosis: CT/MRI

Contrast-enhanced CT scan (top) and MRI (bottom) of patient with metastatic small bowel carcinoid
Rectal carcinoid
Bulges

- Stretched mucosa
  - White appearance of stretched and thinned mucosa attests to submucosal process
- Lobulated mucosa
  - Not a single, smooth bulge of an adjacent bowel loop
Minimum Pathology Data Set

- Depends on tissue source

- Common requirements:
  - Site of tumor/metastasis
  - Grade
  - Mitotic index
  - Proliferation index (Ki-67 or MIB-1)
  - Diagnosis

- Immunohistochemical staining
  - Chromogranin
  - Synaptophysin

- TNM staging

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TMN, tumor, lymph node, metastasis.

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<tr>
<th>Grade</th>
<th>KI-67%</th>
<th>5 Yr. Survival</th>
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<tr>
<td>G1</td>
<td>≤ 2/5</td>
<td>80-90%</td>
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<td>G2</td>
<td>&gt; 2/5 ≤ 20</td>
<td>40-80%</td>
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<td>≤ 2</td>
<td>79-95%</td>
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<tr>
<td>G2</td>
<td>&gt; 2 ≤ 10</td>
<td>65-85%</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>0-50%</td>
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KI-67

A good predictor of tumor recurrence after radical surgery.
Treatment of Carcinoid Tumors and Syndrome

- Supportive
- Surgery
- Antiproliferative
“Wait and See” For NETS is Out!

• Surgery is more cost-effective than periodic surveillance

• Exceptions are small PNETS (Lee-Mayo Clinic)
Boudreaux’s Data – PNETS With Liver METS

5 & 10 year survival 19.5% and 7.1%.

With aggressive surgery, and multi-disciplinary care, 69% and 49%.
Radiomicrospheres
- Advantages -

• Outpatient application
• Minimum post embolization syndrome
• Gentler onset of effect and less hepatotoxicity than TACE
• Minimal hematologic toxicity
• Approximately equal beneficial response as TACE and longer duration
Advances in SIRT  
(Liver Therapy via hepatic artery)

- Embolus injection: blood, chemo, Y90 particles (effectiveness varies – Y90 better in study by Y.U. Wu)
  - Sure Fire Catheter
  - Conjunction with systemic chemotherapy
  - SP Y90 clinical trial
Significant New Clinical Trials in Progress

• Teletristat (Telestar) – Testing experimental tryptophan hydroxylase inhibitor, which inhibits serotonin synthesis

• 5HT3 Blockade with Ondonsetron improves carcinoid syndrome diarrhea unresponsive to Octreotide (1998, 2013)

• PRRT with LU-177 vs. Octreotide in treatment of carcinoid
Oncolytic Viruses

• 11 clinical trials

• For carcinoid-Seneca Valley virus (Picorno Virus)

• A genetically engineered adenovirus, selectively killing NET cells (intra-hepatic injection), reduced BON carcinoids in rats
Conclusion

Many diagnostic and treatment procedures are available for NETS to guide, supplement and often precede surgery.
Carcinoid/ NETS expert debate - ? Conclusion