Pancreatic Neuroendocrine Tumors: Work-up and Treatment
UCSF Postgraduate Course in General Surgery
Stanford Court Hotel
San Francisco, CA
April 30, 2010
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Neuroendocrine Tumors: What’s New?
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Neuroendocrine Tumors: What’s New?
Overview
•Terminology
•Epidemiology
•Outcome (What’s not new: Lack of progress)
•Case Presentation
•Neuroendocrine liver metastases with unknown primary
•UCSF experience

Total pancreatectomy and lymphadenectomy for non-functioning NE carcinoma of the pancreas: 12 cm, LNs: 0/17
GI Neuroendocrine Tumors (NETs)
Epidemiology

Increasing incidence of GI NETs in the US population, 1973-2005

Pancreatic Neuroendocrine Tumors
Epidemiology and Outcome

• SEER database
  • 1973-2003
  • N = 1310 patients

• Incidence:
  • 1.3% of pancreas cancers

• Prevalence:
  • 10% of pancreas cancers

Neuroendocrine tumors (NETs)
Outcome

SEER (n=17,312) and NRC (n=2030) databases for NETs, 1993-2004

Neuroendocrine tumors (NETs)
Outcome

No significant increase in survival (P = 0.968)
Neuroendocrine tumors (NETs)

Summary

- Gastrointestinal and bronchopulmonary origins most common
- Overall, < 50% have localized disease
  - ~10% pancreatic NETs
  - ~30% small intestinal NETs
- Curative surgery not possible for most due to extensive disease
- Careful assessment of patients with advanced disease:
  - Is complete resection feasible?

Hauso et al. Cancer 2008

NETs Unknown Primary Site

Case Presentation

- 60-year-old man
- Fall 2008: abdominal pain
- Evaluated at a local hospital

Case Presentation

- Bilobar liver masses
- Core-needle biopsy: CgA, Syn positive; CK20 negative
- Well-differentiated NE carcinoma
- Unknown primary site

NETs Unknown Primary Site

Case Presentation

- Does finding the primary site matter?
- What should be done to find the primary site?
- Where is the most likely primary site?
- Should the NET liver metastases be resected?
- How do you determine whether the liver metastases are resectable?
- Any new markers to suggest primary site?
Neuroendocrine tumors (NETs) Neuroendocrine tumors (NETs)

Unknown primary site

- ~11-14% patients with NETs have metastatic disease with unknown primary site.
- Identification of primary site—even in patients with unresectable liver metastases—may impact management.
- Distinguishing site of origin is not possible by morphology.
- Immunohistochemical analysis using current markers has yielded conflicting results.
- No accepted guidelines on how to find the primary site.

Wang et al. Arch Surg 2010

NETs Unknown Primary Site Case Presentation

- Does finding the primary site matter?

Neuroendocrine tumors (NETs) of the GI tract

Unresectable liver metastases

- Symptomatic
- Asymptomatic
  - Prevent bowel obstruction (32-46%)
  - Prevent ischemia
  - Improve survival
- Perioperative octreotide drip to prevent carcinoid crisis
- Cholecystectomy

Diffuse, bilobar liver metastases

Hellman et al. World J Surg 2002
Givi et al. Surgery 2006
GI Neuroendocrine Tumors
Intestinal ischemia

Unresectable NET Liver Metastases
Resection of primary

5-year actuarial survival rates:
- Primary resected 81%
- Primary not resected 21%

Givi et al. Surgery 2006

NETs Unknown Primary Site
Case Presentation

- What should be done to find the primary site?

Neuroendocrine tumors (NETs)
UCSF: Patients with NET liver metastases

- **Study design**: Retrospective analysis of pathology database from 1993-2008.
- **Setting**: UCSF
- **Patients**: 123 patients with NET liver metastases.
- **Main outcome measures**:
  1) Preoperative detection of primary tumor.
  2) Laparoscopic or open exploration to identify and resect an unknown primary tumor.

Wang et al. Arch Surg 2010
Neuroendocrine tumors (NETs)
UCSF: Locating NETs in the GI tract

Despite extensive evaluation, 13.8% had occult primary tumors.

<table>
<thead>
<tr>
<th>Neuroendocrine Tumors</th>
<th>GI Neuroendocrine Tumors</th>
<th>Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1907 Siegfried Oberndorfer (Pathological Institute of Geneva)</td>
<td>1929 Oberndorfer recognized potential to metastasize</td>
<td></td>
</tr>
<tr>
<td>1) multiple tumors in submucosa of ileum</td>
<td>karzinoide: “carcinoma-like”</td>
<td>Carcinoid site (no islet cell)</td>
</tr>
<tr>
<td>3) borders sharply circumscribed</td>
<td></td>
<td>n = 2425</td>
</tr>
<tr>
<td>4) (do not metastasize)</td>
<td></td>
<td>%</td>
</tr>
</tbody>
</table>

**NETs Unknown Primary Site**

Case Presentation

• Where is the most likely primary site?

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>No. of Patients</th>
<th>Primary Identified (Sensitivity), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography</td>
<td>76</td>
<td>27 (35.6)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Somatostatin receptor scintigraphy</td>
<td>42</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>PET scan</td>
<td>8</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>21</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Lower endoscopy</td>
<td>42</td>
<td>20 (47.6)</td>
</tr>
<tr>
<td>All colorectal NET</td>
<td>33</td>
<td>20 (60.6)</td>
</tr>
<tr>
<td>Carcinoid NET</td>
<td>15</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Ileum NET</td>
<td>16</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Capsule endoscopy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>1</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>Ultrasoundography</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: NET, neuroendocrine tumor; PET, positron emission tomography.
Neuroendocrine tumors (NETs)
UCSF: Unknown primary site

- Primary site successfully identified in 13/15 patients (86.7%) by surgical exploration.
- All primary tumors were in the small intestine.
- Primary tumors were small (1.4 cm) and often multifocal (54%).
- Careful palpation of small intestine is essential.
- A multidisciplinary team assessment and evaluation consisting of CT, somatostatin receptor scintigraphy, upper and lower endoscopy should be done prior to surgery.

Wang et al. Arch Surg 2010

NETs Unknown Primary Site
Case Presentation

- Should the NET liver metastases be resected?

GI Neuroendocrine Tumors (NETs)
Resection of NET liver metastases

5-year actuarial survival rates:
- resected 73%
- unresected 29%

How Do We Define Resectable?

Before

By what comes out
- How many metastases? < 4 lesions, unilobar
- How large? < 5 cm resectable
- Extrahepatic disease? If none, resectable

Now

By what stays in
- Can R0 resection (negative margins) be achieved?
- Can two contiguous liver segments be preserved?
- Can adequate future liver remnant (> 20%) be preserved?

Determining Resectability

- Preoperative cross-sectional imaging
  - Multidetector contrast enhanced CT or MRI
  - Selected 3-D rendering and liver volumetrics

- Intraoperative assessment
  - Visual inspection
  - IOUS

How Can We Increase the Number of Patients Eligible for Liver Resection?

- Reduce tumor size
  - Chemotherapy

- Increase hepatic reserve
  - Portal vein embolization
  - Staged liver resection

CT = computed tomography; MRI = magnetic resonance imaging; IOUS = intraoperative ultrasonography.
**Case Presentation**

- Any new markers to suggest primary site?

**Neuroendocrine tumors (NETs)**

- Distinguishing site of origin is not possible by morphology.
- Bronchopulmonary tree and GI tract most common NET sites.
- Immunohistochemical analysis using current markers has yielded conflicting results.
  - CK7, CK20, TTF-1, CDX2
- Better markers are needed.

**NETs Unknown Primary Site**

- Nkx2.2 in GI-NET Marker


**NETs with Unknown Primary**

- Nkx2.2 is a sensitive & specific GI NET marker

Wang et al. Endocr Relat Cancer 2009
NETs Unknown Primary Site
Case Presentation

• 60-year-old man
• Fall 2008: abdominal pain
• Evaluated at a local hospital

NETs Unknown Primary Site
Case Presentation

Bilobar liver masses
Core-needle biopsy: CgA, Syn positive; CK20 negative
Well-differentiated NE carcinoma
Unknown primary site

NETs Unknown Primary Site
Case Presentation

No flushing, diarrhea, or wheezing
urine 24h 5-HIAA = 157 (normal < 6 mg/24h)
CgA = 15.8 (normal < 36.4 ng/ml)
OctreoScan: uptake in liver only
ECHO = no valvular heart disease
Local oncologist: somatostatin analog therapy started
Patient informed his disease was inoperable
UCSF for second opinion by multidisciplinary GI oncology group

NETs Unknown Primary Site
Case Presentation

Winter 2008:
Laparoscopic identification and resection of ileum primary tumor
Wang et al. Arch Surg 2010
**Netes Unknown Primary Site**

**Case Presentation**

- **Fall 2009:** diarrhea, flushing (carcinoid syndrome)
- Liver metastases stable on somatostatin analog therapy

**Winter 2009:**
- Right hepatectomy and microwave ablation of two left lobe tumors
- No diarrhea and flushing

**Spring 2010:**
- Feels well. No flushing or diarrhea.
- urine 24h 5-HIAA = 3.3; previously 157 (normal < 6 mg/24h)
- CgA = < 5.0; previously 15.8 (normal < 36.4 ng/ml)
- No evidence of disease on imaging.