Update in the Diagnosis & Management of Neuroendocrine Cancer

By
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University of Iowa

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Edison, New Jersey
October 3, 2015

UNIVERSITY OF IOWA HEALTH CARE
Secretin 1902

Evolution of Neuroendocrine Medical Therapy
Secretin
1902

Gastrin
1905

“Karzinoide”
1907

Siegfried Oberndorfer

Evolution of Neuroendocrine Medical Therapy

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Evolution of Neuroendocrine Medical Therapy

Secretin 1902
Insulin 1921
Gastrin 1905
“Karzinoide” 1907
Endocrine Cell (Helle Zellen) 1938
CCK 1925
Zollinger-Ellison Syndrome 1955
I-131 Therapy 1930
Gastrinoma

R.M. Zollinger
E.H. Ellison

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Evolution of Neuroendocrine Medical Therapy

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NET Incidence Increasing Faster Than Other Neoplasms

Incidence of all malignant neoplasms
Incidence of neuroendocrine tumors

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
BY STAGE

BY GRADE

BY KI-67

Neuroendocrine Cells
(Specific Characteristics)

- Take up hormone precursors (Tryptophan)
- Synthesize, store, release amines and neuropeptides (serotonin, insulin)
- Express specific receptors and transporters (sst2A receptors, norepinephrine transporter)
- Express specific genes – neuropeptides that can predict tumor activity and behavior (pancreastatin, Neurokinin A)

• CAN BE TUMOROGENIC

Modified from Karel Pacak, with permission
$Y = \text{Somatostatin receptor subtype 2}$

In memory of Stephen Qualman, Pathology
The Ohio State University Children’s Hospital
2008
NET cell-specific characteristics currently used for their localization

Adapted from co-author, Karel Pacak, with permission
Diffuse (Neuro)Endocrine System (DES)

- Thyroid
- Lung
- Pancreas (non-carcinoid)
- Adrenal
- Small Intestine
- Rectum/Colon

Other
- Thyroid / MTC
- Adrenal / Pheo / Parag
- Cervix / Ovary
Diffuse (Neuro)Endocrine System (DES)

- Lung – Bronchus (20-25%)
- Pancreas (17-20%) (non-carcinoid)
- Small Intestine (55%)
- Rectum/Colon (<5%)
- Other (<3%)
  - Thyroid / MTC
  - Adrenal / Pheo / Parag
  - Cervix / Ovary

- Metastasis: Liver > Lung > Bone

Concept: Thomas M. O'Dorisio, A.T. Vinik
Design: Teresa Ruggie
© University of Iowa
TTP = Time to Progression
Detection of the Ki67 Antigen in Fixed and Wax-Embedded Sections with the Monoclonal Antibody MIBI

Histopathology 1993; 22:355-360

Demonstrated that MIBI (anti-Ki67 antibody) is an excellent “robust” marker of cell proliferation easily applicable to archival material.
Ki67

• An antibody that recognizes an antigen Mr, 345 and 395 kDa
  Encoded by single gene (chromosome 10)
  Expression tightly associated with cell cycle
  Excellent indicator of tumor proliferation

• MIBI is a monoclonal antibody raised against a ki67 c DNA fragment and perpetuated in E. Coli

• Although, another antibody, it recognizes a different epitope of the ki-67 fragment than MIBI

MIB1 (Ki-67) – a marker of increased proliferation
Enrico Solcia

Professor of Pathology
University of Pavia, Pavia, Italy
2008
General WHO Neuroendocrine Tumor Categories

*1. Well-differentiated endocrine tumor (+) chromogranin A, synatophysin, earlier term, “carcinoid” (ki67 < 2%)

*2. Well-differentiated endocrine carcinoma earlier term “atypical carcinoid” (ki67 2-20%)

*3. Poorly-differentiated endocrine (small cell) carcinoma scant CgA high mitotic index (ki67 > 20%)

4. Mixed exocrine – endocrine tumor

5. Tumor-like lesions

E. Solcia, 2000, WHO Classification
Normal liver tissue

membrane
cytoplasm

sst2 receptor stain of tumor

Courtesy of B. DeYoung, M.D., MS O’Dorisio, MD, TM O’Dorisio, MD
Somatostatin Receptor Subtype 2A Immunohistochemistry Using a New Monoclonal Antibody Selects Tumors Suitable for In Vivo Somatostatin Receptor Targeting

M. Korner, B. Waser, A. Schonbrunn, A. Perren

J – C Reubi

(doi:10. 1097/PAS. 060 13 e 31823 do 7f3)
Methods

• A highly specific monoclonal antibody, UMB-1 was developed per an immunohistochemistry (IHC) Protocol for 89 neuroendocrine tumors

• All tumors’ somatostatin receptor binding site levels were quantified with in vitro

• $^{125}$[-Tyr$^3$]-octreotide autoradiograph
# Results

<table>
<thead>
<tr>
<th>SST2A 1HC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>(+) Pred Val</th>
<th>(-) Pred Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10% tumor cell</td>
<td>86%</td>
<td>95%</td>
<td>95%</td>
<td>84%</td>
</tr>
<tr>
<td>Stain Intensity 2⁺ or 3⁺</td>
<td>96%</td>
<td>80%</td>
<td>86%</td>
<td>94%</td>
</tr>
<tr>
<td>Any Tumor Cell</td>
<td>98%</td>
<td>67%</td>
<td>79%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Am J Pathol 2012; 36(2):242
Results

• The presence of more than 10% positive tumor cells (stained positive for sst2A Receptor Antibody) correctly predicted high sst2A receptor levels in 95% of the tumors studied.

• “For the first time, a reliable recommendation concerning eligibility of an individual patient for in vivo somatostatin receptor targeting based on sst2A receptor immunohistochemistry.”

Definition of Symptom

- Latin – Symptoma
- Greek - συμπίπτω – “I FALL”

“Subjective evidence of disease or physical disturbance observed by the PATIENT”

(Webster’s Third New International Dictionary, 1993 Wikipedia)
Problems with Neuroendocrine Tumor Therapeutic Intervention(s)

- Decisions made primarily based on the “Gold Standard” CT, MR, Ultrasound demonstration of disease progression.
- Both “symptomatic” and “asymptomatic” changes are subjective and clinical signs, like art, are often in the eye of the beholder.
- Tumor-secreting amines and neuropeptides may be episodic initially & sustained later with tumor progression.
- In U.S., calibrations between neuropeptide plasma markers are sorely lacking between commercial labs.
Functioning Neuroendocrine Tumors

Basic Principles:

• Syndromes and symptoms (e.g., hypoglycemia) are due to sudden or sustained elevations of circulating amines (e.g. serotonin, catecholamine, or neuropeptides (e.g., insulin, VIP).

• Documentation of elevated amines and neuropeptides should be done whenever possible.
# Neuroendocrine Tumors Symptoms and Biomarkers

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid, small intestine (Mid-Gut)</td>
<td>Diarrhea, flushing, sweats, fatigue, pain, obstruction, nocturnal perspiration</td>
<td>[Serotonin] 5-HIAA (urine or plasma) CgA, pancreastatin, NK A</td>
</tr>
<tr>
<td>Carcinoid, Lung (Fore Gut)</td>
<td>Cough, pneumonia</td>
<td>Serotonin (?) Substance P (?) CgA</td>
</tr>
<tr>
<td>N/E Pancreas Non-functional (70%)</td>
<td>Pain, nausea, Weight loss, jaundice</td>
<td>CgA and PP</td>
</tr>
<tr>
<td>Functional (30%)</td>
<td>Low sugar, ulcers, etc.</td>
<td>Insulin, Gastrin, etc.</td>
</tr>
</tbody>
</table>
Carcinoid Tumors
Small Bowel (mid gut)

- **Serotonin** EDTA (Plasma + ascorbic acid)
  - most sensitive, episodic
  - Collection critical for preservation
- **Commercially available**
- **5-HIAA** (5-hydroxy-indoleacetic acid, urine) formed by metabolism of serotonin by monoamine oxidase
  - Almost NEVER elevated without liver METS
    (usually 15-20\% burden)
  - Plasma 5-HIAA correlates \((R=0.8)\) with urine 5-HIAA

Pancreas 2013;42(6):937-4
Serotonin and Carcinoids

• Mid-gut carcinoids are rich in serotonin containing granules and are frequently associated with carcinoid syndrome

• Foregut carcinoids (Stomach, Lungs) have few serotonin granule

• Hind-gut carcinoids have very few serotonin granules

• Pancreatic NETs?

Chromogranin A (CgA)

- Acidic, water soluble, secretory glycoprotein (ng/ml)
- Stored in matrix of secretory granules of nervous & neuroendocrine cells / tumors
- Cleared by prohormone convertase I (PC-1) to pancreastatin (pg/ml)
- An accurate “marker” of neurocrine tumor burden and metastasis
“Pearls” on Chromogranin A (CgA)

- Try and stay with the same lab (five in US)
- Is very helpful when you know you have a N/E tumor.
- May be elevated when there is no actual N/E tumor
  - Severe hypertension
  - Gastric acid suppression (PPI’s)
  - Check gastrin
  - Renal insufficiency
Purpose

- To develop a pancreastatin radioimmuno assay (RIA) that is highly sensitive (pg/ml) and specific with negligible cross reactivity with CgA.

- To compare with split-sample analysis, The Ohio State University Reference Lab pancreastatin values with our assay.

- To demonstrate the utility of pancreastatin measurements as a sensitive marker of liver tumor activity.
Results

Cross-reaction of Anti P-Pan ISI-56 with human Pan 1-52 and CgA 260-454

<table>
<thead>
<tr>
<th>pg/ml</th>
<th>PanP  1-49</th>
<th>H  1-52</th>
<th>CgA260-454</th>
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<tr>
<td>10</td>
<td>89.1</td>
<td>95.9</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>82.9</td>
<td>96.5</td>
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</tr>
<tr>
<td>40</td>
<td>73.2</td>
<td>96.6</td>
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</tr>
<tr>
<td>80</td>
<td>57.3</td>
<td>98.2</td>
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</tr>
<tr>
<td>160</td>
<td>37.5</td>
<td>96.3</td>
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<td>320</td>
<td>21.1</td>
<td>96.2</td>
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<tr>
<td>640</td>
<td>11.9</td>
<td>97.5</td>
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<tr>
<td>1280</td>
<td>6.7</td>
<td>96.6</td>
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</tr>
<tr>
<td>7800</td>
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<td>97.5</td>
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<td>15600</td>
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<td>31200</td>
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<td>93.5</td>
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<td>250000</td>
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<td>94.6</td>
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</tr>
<tr>
<td>1000000</td>
<td></td>
<td>93.1</td>
<td></td>
</tr>
</tbody>
</table>
Results

Sequential Marker Measurement

Marker in Appropriate Units

- 5-HIAA
- CGA
- Pancreastatin

PANCREAS 39(5):611-616, 2010
Neurokinin (NK) A Levels Predict Survival in Patients with Stage IV Well Differentiated Small Bowel Neuroendocrine Neoplasia


Surgery 2012; 152(6):1172-76
Patients and Methods
(Surgery 2012; 152(6):1172)

- 180 patients: retrospective – prospective
- Group 1: NK A persistently < 50 pg/ml
- Group 2: NK A elevated at least once – now < 50 pg/ml
- Group 3: NK A always > 50 pg/ml
- Median follow-up time: Kaplan-Meier Method
Results

(NKA > 50 pg/mL vs. NKA < 50 pg/mL)
Pancreastatin Predicts Survival in Neuroendocrine Tumors

Sherman SK, Maxwell JE, O’Dorisio MS, O’Dorisio TM, Howe JR

Ann Surg Oncol 2014; 21:29
Patients and Methods
(Ann Surg Oncol 2014; 21:2971-2980)

- 98 small bowel NETS: 78 pancreatic NETS
- Event times were estimated by the Kaplan-Meier Method
- Pre and postoperative labs for correlation with outcomes
- A multivariate Cox model adjusted for confounders
Results (1)
(Ann Surg Oncol 2014; 21:2921)

• Preoperative serotonin levels significantly associated with progression free survival (PFS) \( (p=0.02) \)
• Postoperative reduction of serotonin by 88 ng/ml or more was significantly associated with PFS \( (p=0.01) \)
• Preoperative CgA and preoperative pancreastatin showed significant correlation with PFS and OS \( (p<0.05) \)
Elevated preoperative PAN associated with shorter median PFS and OS vs normal PAN

- PFS 1.7 yrs vs 6.5 yrs vs median not reached
- 5 yr PFS 14.9% (high prePAN: 59% (normal PAN)
- Normalization of post-op pancreastatin significantly improved PFS and OS (3.9 yrs and 100%)
- Elevated post-op pancreastatin, 5 yr PFS dropped to 8.6% and OS decreased to 6.5 yrs
Conclusion
(Ann Surg Oncol 2014; 21:2921)

- Higher pancreastatin levels are significantly associated with worse PFS and OS in SBNETS and PNETS
- Independent of age, primary tumor site, and nodal or metastatic disease
“Pancreastatin provides valuable prognostic information and identifies surgical patients at high risk of recurrence who could benefit most from novel therapies”
Thoughts Regarding Whole Blood Serotonin

- Several commercial, CLIA-approved and College of American Pathology (CAP) approved assays in US
Biomarkers

• CgA levels can reflect total tumor burden (when metastatic) for both pancreatic and mid-gut (ileal) N/E tumors

• Neurokinin A is predictor for aggressive mid-gut (ileal) tumors

• Pancreastatin may be a very early marker for liver tumor activity and predicts both PFS and OS
Somatostatin and its Congeners

Somatostatin

Ala-Gly-Cys-Lys-Asn-Phe

Phe

Trp

Lys

Cys-Ser-Thr-Phe

Thr

Phe

Cys

Phe

Thr

Thr

Thr

OL

Lys

Thr

Asn

Phe

Phe

Thr

Nal-Cys

Tyr

dTrp

Lys

Thr

NH2

Cys

Val

Octreotide
*(J. Pless, et al.)*

Lanreotide
*(D.H. Coy, et al.)*

Dawn A. Wray & M. Pedersen
Placebo-Controlled, Double-blind, Prospective, Randomized study on the effect of Octreotide – LAR in the control in patients with metastatic neuroendocrine mid-gut tumors: A Report from the PROMID Study Group

Anja Rinkie, Hans-Helge Mueller….Rudolf Arnold

- 85 patients (well-differentiated midguts); ki-67 < 2%
- Placebo versus Sandostatin-LAR 30 mg monthly
- Median time to tumor progression (TTP)
  6 months = placebo
  14.3 mo Octreotide-LAR (29.4 mo; Liver < 10%)(Non-Crossover)
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors (CLARINET Study Group)

M. E. Caplin, M. Pavel, J.B. Cwikta.... P. Rusznieswski

- 107 Patients (well-differentiated midgut & hindgut) ki-67<10%
- Placebo versus Lanreotide Depot 120mg monthly
- Median time to progressive (TTP)
  18 months = Placebo
  LAN-DEP median not reached
  (Cross-over Study)
DOTA-DPhe\textsubscript{1}-Tyr\textsubscript{3}-Octreotide (DOTA-TOC)

**Theranostic Application**

\[
\text{Isotope}^D\text{-DOTA-Phe-Cys-} \quad \text{Ty}r \\
\text{DTrp} \\
\text{Lys} \\
\text{Thr}_{\text{OL}} \quad \text{Cys-} \\
\text{Thr} \\
\text{(SMS 204-090)}
\]

**Isotope (Radiometal):**

- \text{Ga}^{68}\text{-DOTA-TOC-PET}: sensitive; quantifiable
- \text{Y}^{90}\text{-DOTA-TOC}: hard beta; 7-9 mm range “kill”
- \text{Lu}^{177}\text{-DOTA-TOC}: soft beta; 3-5 mm range “kill”
Current Targeting Paradigm

One Receptor – One Ligand

- High receptor expression
- Native peptide sequence known
- High affinity/specificity/avidity for target
- Synthetically feasible (<50 residues)

Original: Helmut Maecke
Concept & design by M Schultz
Outcome of Peptide Receptor Radionuclide Therapy (PRRT) in Patients with Metastatic Low Grade Neuroendocrine Tumors


PANCREAS 2012; 41(2):347 (Abs)
Methods

- 150 Metastatic Neuroendocrine tumors:
  - Small Bowel (Mid Gut, 44%)
  - Pancreas (PNET 28%)
  - Lung (Foregut 5%)

- Peptide Receptor Radio-Nuclide Therapy (PRRNT), 72% Basel, 26% Iowa

- 86% $^{90}$-DOTA-TOC and 13% $^{177}$ Lu DOTATOC

- ALL followed up for 10 years in NETC
- ALL maintained on Octreotide

B.G. Nareav, PANCREAS 2012
<table>
<thead>
<tr>
<th>Site</th>
<th>OS from Diagnosis (years)</th>
<th>OS from PRRT #1 (months)</th>
<th>TTP from PRRT #1 (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>9.9</td>
<td>40.6</td>
<td>39.6</td>
</tr>
<tr>
<td>SNETs</td>
<td>13.7</td>
<td>96.7</td>
<td>60.3</td>
</tr>
<tr>
<td>PNETs</td>
<td>5.7</td>
<td>39.4</td>
<td>63.1</td>
</tr>
<tr>
<td>Lung</td>
<td>2.7</td>
<td>22.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Unknown Primary</td>
<td>4.1</td>
<td>20.7</td>
<td>24.1</td>
</tr>
<tr>
<td>Other</td>
<td>7.2</td>
<td>52.0</td>
<td>26.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>P&lt;0.0001</td>
<td>P=0.1</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

OS: Median overall survival  
TP: Median Time to Progression
“PRRNT appears to be a valuable treatment option for mNETs, especially SBNETs, and its role earlier in the disease course warrants investigation”

B.G. Nareav, PANCREAS 2012
Reference Laboratories in the United States

- ARUP, Quest, MAYO, LabCorp, Viracor, Inter Science Institute (ISI), Cambridge Lab, OSU-URL

**ALL** CLIA (Clinical Laboratory Improvement Act) accredited

**ALL** CAP (College of American Pathologists) accredited

**Serotonin**: ARUP, Quest, LabCorp

**CgA**: ARUP, Quest, MAYO, LabCorp, ISI, Cambridge (?)

**Pancreastatin**: ISI (published), URL (published), Cambridge (?)

**NkA**: ISI (published), Cambridge (?)
Neuroendocrine Tumor Faculty

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