An Update in the Diagnosis and Management of Carcinoid (NET)
Learning Objectives

- Recognize the clinical syndromes and different types of Neuroendocrine tumors responsible for the constellation of these features
- Provide aids to differentiate NETS from masquerading diseases
- Understand the choices of management and the use of an algorithm for clinical, biochemical and radiological diagnosis
- Understand and make informed choices based upon a "decision tree" for management of NETS
How's heaven Steve?
Perfect, Bill. It's just that it doesn't have any wall or fence...
We don't need windows and gates
10 years ago the USA had Steve Jobs, Bob Hope and Johnny Cash ....
Now they have no Jobs, no Hope and no Cash.
NETS The Neglected Side of Cancer
NET Incidence Increasing Faster Than Other Neoplasms

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
NETs: More Prevalent Than Stomach and Pancreatic Cancer *Combined*³,⁶

- Colon & Rectum: 1,141,407 Cases
- Neuroendocrine: 103,312 Cases
- Stomach: 65,836 Cases
- Pancreas: 32,353 Cases
- Esophagus: 28,664 Cases
- Hepatobiliary: 21,427 Cases
Neuroendocrine Tumor Distribution

- **Foregut**
  - Lung – Bronchus (20-25%)
  - Pancreas (17-20%) (non-carcinoid)

- **Midgut**
  - Small Intestine (55%)
  - Rectum/Colon (<5%)

- **Hindgut**
  - Other (<3%)
    - Thyroid / MTC
    - Adrenal / Pheo / Parag
    - Cervix / Ovary

- **Metastasis**
  - Liver > Lung > Bone

Concept: Thomas M. O'Dorisio
Design: Teresa Ruggle
Evolution of Neuroendocrinology
It Ain’t What you Don’t Know

- It ain’t what you don’t know that gets you into trouble
- It’s what you know for sure that just ain’t so!

Mark Twain
Functioning versus Non-functioning NET

Morbidity and mortality resulting from:
• Hormonal or hormone-related symptoms/syndromes

Functioning

Non-functioning

Morbidity and mortality resulting from:
• Tumor expansion

Secretory but non-functioning

Morbidity and mortality resulting from Tumor expansion

Marianne Pavel, Vinik et al 2017
The Ubiquitous Neuroendocrine Cell

5-HT into gut lumen

Prosecretory granules (processing of prohormones and CgA)

Golgi

Packaging of prohormones and CgA

5-HIAA

MAO

5-HT into portal circulation

VMAT

Formation of prohormones and CgA

Tryptophan

Secretory granules (e.g. pancreastatin, chromostatin and CgA)

Into portal circulation

5-HTP

RER

Tryptophan

5-HT
The Multipotency of the EC Cell

Protodifferentiated Adult Stem Cell

Alpha
Glucagonoma

Beta
Insulinoma

Delta
Somatostatinoma

EC
Gastrinoma/CCKoma

PP
PPoma

- EC Cell
- Gastrin
- ACTH
- GHRH
- Calcitonin
- VIP
- CGRP
- Substance P
- HHM
- IGF 11
- GLP-1
- INGAP
- Ghrelin

- Carcinoid
- Gastrinoma
- Cushing’s
- Acromegaly
- Diarrhea/Flushing
- Diarrhea/Flushing
- Diarrhea/Flushing
- Hypercalcemia
- Hypoglycemia
- Nesidioblastosis


Vinik and Perry Degroot 2017
Pathology of NETs

A.

B.

C.

D.

E. CgA

F. Ki67

G. Ki67
Genetics of NETS

MEN-1 gene in $\gg 44\%$

- DAXX 25%
- ATRX 17.6%
- MTOR pathway $\gg 14\%$
- Mutations survive 10y
- No mutations $\gg 60\%$ died in 5y
- WREN 51 mRNA markers

Jiao et al. Science 331, 1199-1203, 2011
Biomarkers in Neuroendocrine Tumors

- Vague abdominal symptoms
- Diarrhea
- Flushing
- Metastases
- Death

Primary Tumor Growth

Diagnosis
- Irritable Bowel

Correct Diagnosis
- Chromogranin
- Pancreastatin
- Neurokinin A

Years

0 2 4 6 8 10 12 14 16 18 20

Improvement of NET Grading System using Mitoses and Ki-67

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)</th>
<th>Ki-67 index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

Univariate analysis:

- G1 vs. G2: p = 0.040
- G1 vs. G3: p < 0.0001
- G2 vs. G3: p < 0.0001


Tumor cells display a neuroendocrine phenotype

Balanced amounts of neuroendocrine and exocrine tumor cells

1. NET G1
2. NET G2
3. NET G3
4. NEC (small cell & large cell carcinoma)
5. Mixed neuroendocrine-non neuroendocrine neoplasm

Lloyd RV, Osamura RY, Klöppel G, Rosai J WHO Classification of Tumours of Endocrine Organs, 2017
Diagnosis of GEP NETS

Pepper . . . and Salt
THE WALL STREET JOURNAL

“With the Internet, my patients come self-diagnosed, have second opinions and already belong to a support group.”
Clinical Presentation of Neuroendocrine Tumors

Major Clinical Manifestations

- Flushing 84%
- Diarrhea 79%
- Heart Disease 37%
- Bronchoconstriction 17%

Seldom Discussed

- Diabetes, Metabolic Syndrome, NASH 37%
- Hypertension 50%
- NeuroMyopathy 7%
- Pigmentation, arthropathy 5%
- Hyper-hypoglycemia, (NIHHPS) <1%
- Ulcer disease, Skin rashes <1%
- Psychological Disturbances <1%

Tumor production of cytokines (TNF a. IL6, NFκb)
- Fever, fatigue, weight loss, cachexia

Tumor stimulation of antibody formation (Ca Channels) P,Q) Ach receptor, CANCA, PANCA, Hu
- Neurological syndromes, Peripheral Neuropathy, Autonomic Neuropathy, Cerebellar Ataxia, Eaton Lambert, Myaesthenia, CIDP
Flushing

- Dry Neurendocrine Tumor
- Wet Other
## Features Associated with Flushing

<table>
<thead>
<tr>
<th>FLUSHING SYNDROME</th>
<th>ASSOCIATED FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Diarrhea, wheezing</td>
</tr>
<tr>
<td>Medullary Carcinoma Thyroid</td>
<td>Mass in neck, Family history</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal hypertension, pallor, tachycardia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Autonomic neuropathy/Chlorpropamide</td>
</tr>
<tr>
<td>Menopause</td>
<td>Cessation of Menses</td>
</tr>
<tr>
<td>Autonomic Epilepsy</td>
<td>Diencephalic seizures</td>
</tr>
<tr>
<td>Panic Syndrome</td>
<td>Phobias, anxiety</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Dyspepsia, peptic ulcer, dermatographia</td>
</tr>
<tr>
<td>Polycythemia, renal cell Ca</td>
<td>Plethora</td>
</tr>
<tr>
<td>Food</td>
<td>Alcohol, MSG, Nitrites, Cheese, Tyramine containing foods</td>
</tr>
<tr>
<td>Drugs</td>
<td>Niacin, Phosphodiesterase 5 Inhibitors</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Destitute</td>
</tr>
<tr>
<td>CLINICAL CONDITION</td>
<td>TESTS</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>5HIAA, 5 HTP, SP, CGA, Pancreastatin, NKA, Pro BNP</td>
</tr>
<tr>
<td>Medullary Carcinoma Thyroid/ C cell hyperplasia</td>
<td>Calcitonin, Calcium Infusion, CEA, Ret Proto-oncogene</td>
</tr>
<tr>
<td>Pheochromocytoma, paraganglioma</td>
<td>Fractionated Metanephrines in plasma, Methoxytyramine, SHDB(C)</td>
</tr>
<tr>
<td>Diabetic AN</td>
<td>HRV, 2h PP glucose</td>
</tr>
<tr>
<td>Menopause</td>
<td>FSH</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>EEG</td>
</tr>
<tr>
<td>Panic</td>
<td>Pentagastrin/ACTH</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Plasma histamine, urine tryptase</td>
</tr>
<tr>
<td>Hypomastia, Mitral prolapse,</td>
<td>Cardiac Echo</td>
</tr>
</tbody>
</table>
Diarrhea

Secretory
persists with fasting
Endocrine

Non-secretory
Improves with fasting
Gastroenterological
Character of Secretory and Osmotic Diarrhea

- **Secretory**
  - Large volume stools
  - Persists during fasting
  - $2X [Na^+ + K^+] = \text{stool osmolality}$

- **Osmotic**
  - Small volume <1L/d
  - Disappears with fasting
  - $2X [Na^+ + K^+] < \text{stool osmolality i.e. osmotic gap, search for idiogenic osmoles}$
Causes of Secretory Diarrhea

- Watery diarrhea, hypokalemia, hyperchlorhydria, acidosis syndrome
- Zollinger Ellison syndrome
- Carcinoid
- Medullary carcinoma of thyroid
- Secreting villous adenoma of rectum
- Surreptitious laxative abuse
- Idiopathic
Pathogenesis of Endocrine Diarrhea

Gastrin/CCK
- Increased Acid secretion
- Decreased absorption
- And impaired digestion
- Exceeds absorptive capacity

VIP, PP, SP, CGRP, TCT
- Increased net secretion of fluid and ions
- Exceeds absorptive capacity

Stomach

Small Intestine

Colon

Increased Fecal Volume
Metastatic Neuroendocrine Tumors: What are the Systemic Treatment Options?

- Somatostatin analogs
- Cytotoxic Chemotherapy
- “Targeted” Therapies
- PRRT
Diagnosis of NETS

- Localization Procedures
  - Ultrasound
  - CAT
  - MRI
  - PET
  - Octreoscan
  - Gallium DOTA TOC(NOC)
  - MIBG
  - Angiography
  - Venous sampling
# Sensitivity, Specificity, Positive and Negative Predictive Values for Diagnosis of NETS

<table>
<thead>
<tr>
<th>TEST</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>83%</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>93%</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>50-85%</td>
<td>76-97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OctreoScan</td>
<td>52-78%</td>
<td>93%</td>
<td>98%</td>
<td>47%</td>
</tr>
<tr>
<td>PET/CT ¹⁸⁸Ga-DOTATOC</td>
<td>97%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT ¹⁸⁸Ga-DOTANOC</td>
<td>78%</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT ¹⁸F-FDG-PET (NETs with proliferation index &gt;15%)</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PET with $^{68}$Ga-DOTA-Octreotide Facts and Fallacies

- **Advantages:**
  - no cyclotron required
  - more sensitive than Octreoscan 40-100 fold
  - possible to use for radioactive or tumor-targeted treatment
  - may be possible to quantify somatostatin receptors - tumor-targeted therapy

- If you find Mets Gallium Scanning finds more
- If you cannot find the tumor Gallium scanning may not find it for you
68Ga-DOTA-Octreotide Scanning

Current Targeting Paradigm
One Receptor – One Ligand

- High receptor expression
- Native peptide sequence known
- High affinity/specificity/avidity for target
Octreoscan vs.
PET/CT with $^{68}\text{Ga}}$-DOTA-Octreotide
Solid Tumor Metastases
What Makes Bone a Favorable Site?

**Osteolytic**
- Breast & lung
- Bone destruction mediated by OCL

**Osteoblastic**
- Prostate & breast
- Bone formation mediated by OB

**NETS:** Osteoblastic, osteolytic

Bone Alk Phos and NTX
Evaluation of Neuroendocrine Tumors

Clinical Syndrome

Flushing, Diarrhea, hypertension
Hypoglycemia, ulcer, rash

Exclude other causes
Flushimg wet or dry
Secretory vs. non secretory
Carcinoma, thyrotox, Cushing’s
MCT, Pheo, factitious

Biochemical and Tissue Diagnosis

Pancreastatin, CGA, NKA, NSE, insulin, gastrin, glucagon IGF2, PThrp, Tryptase, histamine, Alk Phos, NTx, fractionated Metanephrines, Calcitonin PNET

Tissue: CGA/Ki-67, Synaptophysin, Specific hormone

Negative

Symptomatic Treatment
Management of Neuroendocrine Tumors

- Localization and Resection
  - Ultrasound
  - CAT
  - MRI
  - PET
  - Octreoscan/Gallium 68 scan
  - Angiography

Localized Surgery
Management of Neuroendocrine Tumors

Localization and Resection
- Ultrasound
- CAT
- MRI
- PET
- Octreoscan
- Angiography

Liver Involvement
- <50% RFA, Resection
- >50% Consider Partial RFA, Resection

Surgery
- Therapeutic Trial
Management of Neuroendocrine Tumors

- Localization and Resection
  - Ultrasound
  - CAT
  - MRI
  - PET
  - Octreoscan/$^{68}$Ga-DOTA-Octreotide
  - Angiography

Surgery Debulking

Extrahepatic Mets
Management of Neuroendocrine Tumors

- Metastatic
  - OctreoScan®
  - Gallium DOTATOC

- Angiography

- Positive
  - Sandostatin LAR Lanreotide

- Negative
  - H.A.C.E.
    - Hep Art Chemo Embo
    - SIR Spheres Therapy
    - Conventional Chemo
Management of Metastatic Tumors

LAR for 3 months + Octreotide for arrest or reversal

Continuing LAR + Octreotide

Progression

Interferon α

Indium Pentreotide (<2 cm), Lutecium 177 DOTATOC (2-4 cm), Ytrium 90 DOTATOC (>4 cm)

LAR (mg/month)

Pamidronate for bone metastases

Octreotide: Plasma

0 pg/ml

N = LAR (mg/month)

60 30 20 10

Management of Metastatic Tumors

LAR/Somatuline for 3 months + Octreotide for escape

Arrest or Reversal
Continue LAR+ Octreotide

Check Octreotide/Lanreotide Level
< 10,000 pg/ml
Increase LAR+ Octreotide

Progression
>10,000 pg/ml
Chemotherapy/Interferon α
Radiation
Infarction
Pamidronate for Bone metastases
Somatostatin Analogs

Human somatostatin

- ala
- gly
- cys
- lys
- asn
- phe
- phe
- trp

Amino acids essential for receptor binding

- inhibit multitude of hormones
- $T^{1/2}$ 3 minutes
- binds all 5 receptor sub-types

Octreotide

- more specific
- $T^{1/2}$ 100 min

Lanreotide

- D phe
- cys
- phe
- D trp
- lys
- Thr
- ol
- cys
- thr
- D bnal
- cys
- tyr
- D trp
- lys
- Thr
- ol
- cys
- val
## Comparison of Approved Somatostatin Analogs

<table>
<thead>
<tr>
<th>Octreotide LAR</th>
<th>Lanreotide Depot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires reconstitution</td>
<td>Ready to use, prefilled syringe</td>
</tr>
<tr>
<td>10, 20, 30 mg</td>
<td>60, 90, 120 mg</td>
</tr>
<tr>
<td>IM q 4 wks (~1.5 inch needle)</td>
<td>Deep SC q 4 wks (~3/4 inch needle)</td>
</tr>
<tr>
<td>Volume; 2-2.5 mL</td>
<td>Volume; 0.3-0.5 mL</td>
</tr>
<tr>
<td>Healthcare professional administration</td>
<td>Self or partner administration possible</td>
</tr>
</tbody>
</table>

**Notes:**
- Octreotide LAR is a long-acting somatostatin analog that requires reconstitution.
- Lanreotide Depot is ready to use, prefilled in a syringe.
- Octreotide LAR is available in 10, 20, 30 mg strengths for IM injection (q 4 wks, ~1.5 inch needle).
- Lanreotide Depot is available in 60, 90, 120 mg strengths for deep SC injection (q 4 wks, ~3/4 inch needle).
- Octreotide LAR and Lanreotide Depot differ in terms of reconstitution, administration site, and volume.

**References:**

**Image:**
- Long-acting Lanreotide octreotide depot syringes.
Octreotide and Lanreotide for the Treatment of Advanced NET


ELECT: Exploratory Endpoint (Supportive Analyses)

Treatment Response (Number of Days of Octreotide SC Use) In the 4 Weeks Following Final Injection

- Greater Chance of Complete/Partial Success With Lanreotide
  $P=0.04 \ OR \ 2.4 \ [95\% \ CI: \ 1.1, \ 5.3]$

<table>
<thead>
<tr>
<th></th>
<th>Complete Success</th>
<th>Partial Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide 120 mg</td>
<td>40.7%</td>
<td>6.8%</td>
<td>52.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>23.2%</td>
<td>5.4%</td>
<td>71.4</td>
</tr>
</tbody>
</table>

Somatostatin in NETS

- Somatostatin analogs are safe and effective
- Long-term administration of somatostatin analog is safe and effective
- In NETs, these analogs control symptoms and some tumor markers, and are effective in controlling tumor growth; symptomatic escape may require short-acting analogs
- Radioactive analogs “Lutathera” are promising but not available for all
- New and better drugs are still needed
Inherited syndromes associated with NET

Growth Factors:

Growth Factor Receptors:

PI3-K

AKT

mTOR

Cell Growth & Survival

Therapeutic Agents in NET

VEGF Bevacizumab

PDGFR Sunitinib, Sorafenib, Pazopanib

VEGFR

RET

Pi3-K

AKT

mTOR

The RTK/PI3-K/AKT/mTOR Pathway in Neuroendocrine Tumors
SUN 1111 and RADIANT-3 Trials Show Similar Efficacy Results on Primary Endpoint (PFS)*

**SUN 1111: Median PFS**
- Sunitinib: 11.4 months (95% CI: 7.4–19.8)
- Placebo: 5.5 months (95% CI: 3.6–7.4)

HR=0.42 (95% CI: 0.26–0.66)  
*P<.001*

**RADIANT-3: Median PFS (Investigator review)**
- Everolimus: 11.4 months
- Placebo: 5.4 months
- Censoring times

HR=0.35 (95% CI: 0.27–0.45)  
*P<.0001 by one-sided log-rank test*

*Data from separate trials. This is not a head-to-head comparison.*

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Telotristat Etiprate
A Tryptophan Hydroxylase (TPH) Inhibitor

Serotonin Synthesis in Carcinoid Tumor Cells

- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis
- Two early-stage clinical studies demonstrated the safety and evidence of clinical activity in carcinoid syndrome
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity
- Granted Fast Track Status and Orphan Drug Designation

Adapted from ref. 5, Figure 44-3

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 5-HP, hydroxytryptophan; CNS, central nervous system; TPH, tryptophan hydroxylase.

• Hodges–Lehmann estimator of treatment differences showed a median reduction versus placebo of
  – −0.81 BMs daily for telotristat etiprate 250 mg dose \((P<0.001)\)
  – −0.69 for telotristat etiprate 500 mg dose \((P<0.001)\)

BM, bowel movement.
Peptide Receptor Radionuclide Therapy (PRRT)

Endocrine Tumours - Molecular Radiation on Target
Peptide Receptor Radionuclide Therapy with Lutetium-octreotate

From: Oberg, Theranostics 2012; 2: 448-58
Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors


N engl j med 376;2 nejm.org January 12, 2017
Progression-free survival and overall survival in LUTATHERA TRIAl

Strosberg J et al. NEJM 2017; 376:125-35
Practical points for LUTATHERA:

• Outpatient administration in U.S.

• Relatively low-risk to family members and general public: avoid sharing bed and limit contact with children x 1 week after each treatment

• Amino acid infusion: commercial formulation vs. compounded arginine/lysine

• Duration of time off long-acting SSA: 4 weeks vs. 6 weeks
Where does PRRT fit in?

- Phase 3 randomized data only in midgut NETs.
- Early phase data suggesting higher response rates in non-midgut NETs (esp. pancreatic).
- Approved both by EMA and FDA for advanced GEP-NETs
- Somatostatin-receptor (SSTR) expression is strong predictive marker.
- Consider as 2nd line therapy in patients with strong SSTR expression.
- Advantages: Limited treatment course (4x), long PFS, relatively low toxicity
“Do not go where the path may lead, go instead where there is no path and leave a trail"

-Ralph Waldo Emerson
Health Related Quality of Life (HQOL) Requires a Multidimensional Assessment of:

- **Quality of Life**
  - **Generic Tools**
    - PROMIS and SF 36
  - **Disease Specific Tools**
    - Norfolk QOL-NET
    - QLQ-GINET-21
    - QLQ-C30

**Quality of Life Features**
- Physical
- Cognitive
- Emotional
- Depression
- Anxiety
- Social
- ADLs

**Symptoms**
- Appetite loss
- Ulcer, rash, Hypoglycemia
- Pain
- Constipation
- Hand Foot Syndrome
- Diarrhea
- Fatigue
- Dyspnea
- Nausea
- Vomiting
- Insomnia
- Injections
- Flushing

**Therapies**

Vinik EJ, Vinik AI 2009
Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [177Lu-DOTA0,Tyr3]Octreotate

- QOL symptoms after [177Lu-DOTA0,Tyr3]octreotate (177Lu-octreotate) therapy in patient with inoperable or metastasized gastroenteropancreatic or bronchial neuroendocrine tumors (NET)
- Two hundred sixty-five Dutch patients completed the QOL questionnaire of
- Significant differences of at least 10 points in global health status (GHS)/QOL scores, symptom scores, and Karnofsky performance

QOL Results

• Regardless of the treatment outcome,
• QOL, insomnia, appetite loss, and diarrhea improved significantly in the total group. And in patients with bone metastases or a decrease of 50% or more in Chromogranin A.

• QOL or symptoms at the start of therapy quality of life improved with therapy in 36%
  – 49%, fatigue;
  – 70%, nausea plus vomiting;
  – 53%, pain;
  – 44%, dyspnea;
  – 59%, insomnia;
  – 63%, appetite loss;
  – 60%, constipation;
  – 67%, diarrhea.
Why Patients with a Carcinoid Tumor are Depressed

In the Presence of a Tumor

Tryptophan

TRP

↓

5HTP

↓

SEROTONIN

5-Hydroxylation (Liver, Platelets Intestinal Cells)

5 - Hydroxytryptophan (5HTP)

Typical Route

Decarboxylase

Decarboxylation

Serotonin5HT

Will enter blood stream, but cannot pass blood brain barrier.

Serotonin Levels

BLOOD

↑

BRAIN

↓

The Changing Face of Management of Neuroendocrine Tumors

- **1900**: Surgery
- **2000**: Chemotherapy
- **2007**: Embolization
- **2015**: Interferon
- **2018**: Octreotide/Lanreotide, GF and Angiogenesis, (MTOR and TKI) Inhibitors, PRRT, immunotherapy, Serotonin synthesis inhibitors, etc.
- **Exenteration**
Norfolk Algorithm for NET Management

Clinical Syndrome
Biochemical and Tissue Diagnosis

Urine: 5HT, 5HTP, Metanephrines, tryptase
Blood: serotonin, CGRP, 5HIAA, NKA Fractionated Meta/Normetanephrines, Calcitonin, Histamine

+ve

Ultrasound
CAT
MRI
PET
Octreoscan or Gallium 68 scan
MIBG
Angiography Scintigraphy

Immunohistochemistry
• Chromogranin A
• Synaptophysin
• Neuron Specific Enolase
• Ki-67, Mitotic Index
• Individual hormones – insulin, glucagon, PP somatostatin, INGAP, etc.

TUMOR

Management

Negative Symptomatic Treatment

Surgery
Chemotherapy
Embolization
PRRT
Octreotide or Lanreotide

GF and Angiogenesis Inhibitors and TKIs, MTOR Inhibitors

CLINICAL TRIALS
Summary and Conclusions

– NETs on the increase, require high level of suspicion
– Monitor
  • Tumor burden
  • Clinical responses
  • Biomarkers,
    – pancreastatin,
    – Neurokinin A
    – Cga

(they may not be parallel)

– Be aggressive. Use tumor debulking procedures judiciously
– Tumor growth can be arrested
  • Carcinoids, Vipomas, Ppomas
  • ACTH, Calcitonin and Gastrin may be resistant
  • May require ancillary measures

– **Octreotide/Lanreotide** controls symptoms and may cause biochemical and tumor burden improvement. Must treat to target plasma

Octreotide/Lanreotide Plasma Levels
– **Gallium Scanning** now a reality and will replace Octreoscan
– New therapies with agents acting on the RTK/PI3-K/AKT/mTOR pathway

PRRT a reality in USA
And the FUTURE
To the world you may be just one person, but to one person you may be the world.
Free on the Web!

Endotext.org is the web-based source of information on endocrine disease directed to physicians around the world caring for patients with these problems. It is comprehensive, authoritative, constantly updated, and available without cost to physicians and trainees. All material may be freely downloaded for personal use. Our site covers the broad area of Clinical Endocrinology, emphasizing clinical endocrine practice, including the most current information on the manifestations of endocrine disease, diagnosis and treatment.

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Your Comprehensive, Authoritative, Updated, Endocrine Web-textbook

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