Neuroendocrine Tumors: Advances in Options for Systemic Therapy

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Neuroendocrine Tumor Symposium
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I have no financial conflicts to disclose.
A Tribute to

Dr. Charles Moertel:

Father of chemotherapy for GI cancers (NCCTG)

Mayo Clinic 1954-1994
Cancer center director 1975-86

Pioneer in cancer clinical trials (NCCTG) and outspoken patient advocate

Honored with Karnofsky Award 1986 by American Society of Clinical Oncology

What did he choose to talk about?

NET’s:
“Odyssey in the Land of Small Tumors”

Lecture presented at Karnofsky Award presentation
ASCO June, 1987
Published in Journal of Clinical Oncology Oct. 1987

Definition of “Odyssey”:
from the epic poem by Homer about the mythological hero Odysseus’ 10 year journey to return home

Long wandering journey, usually marked by many changes in fortune.

Underscores the slow-growing often unpredictable nature of NET
The alternate title of this talk:

*Systemic Therapy Advances made on our Odyssey in the Land of Small Tumors*

OR

*Small but Mighty Tumors*
Neuroendocrine Tumors

• Definition: NET’s are tumors arising from cells throughout the nervous and endocrine systems which produce and secrete regulatory hormones.

• Incidence seems to be increasing:
  — Classically: 1/100,000 (Godwin 1975)
  Moertel: So rare that one oncologist will see one NET patient in his practice lifetime
  — NCCN: 5.4/100,000 (2010)

There have been major changes in the field in past 7 years.
Why are they so confusing?

• Variety of organs/systems involved
  — GI tract, Lung, Endocrine, Skin (Merkel)

• Sporadic (Carcinoid) vs Inherited (MEN 1 and 2)

• Unpredictable Course over Time
  — Non-Functional (non-secretory) becomes Functional
  — Changing pattern of hormonal secretion

• Variety of Presentations
  — Small tumor burden with severe carcinoid Sx’s
  — Large tumor burden with no Sx’s
Multiple Classifications are used

- Cell type
- Site of Origin (foregut, midgut, hindgut): still used unfortunately
- Differentiation (WD, MD, PD)
- Typical vs Atypical carcinoid
- Many terms and specifics re NET have been used "incoherently": hard to compare

AJCC did not have TNM Staging system till 2010!

Multiple disciplines involved: Endocrinologists, Pathologists, Medical Oncologists, Radiation Oncologists, Interventional Radiologists, Oncologic Surgeons, ENT Surgeons, Transplant Surgeons.
Where do they come from?
Embryologic Derivation

- 19 days: Ectoderm thickens into Neural Plate
- 3 Weeks: Neural Plate indents into Neural Fold
- 4 Weeks: Convergence: Arms of Neural Fold join to be Neural Tube $\rightarrow$ CNS

- Cells at border of Neural tube abutting the Ectoderm $\rightarrow$ Neural Crest

- Neural Crest is the Anlage for NET’s
Neural Crest

- Some cells stay in situ: cranial and spinal ganglia
- Some cell migrate and are pluripotential
  - Autonomic ganglia throughout body
  - Diffuse Endocrine System: glandular cells throughout the body
  - Merkel cells (touch receptors in skin)
  - These all have the ability to produce biologically active amines or peptides (neurotransmitters or hormones): “APUDomas”
Neural Crest Cells (APUDomas)

- Amine Precursor Uptake and Decarboxylation
- Produce Serotonin, Dopamine, Histamine
- Malignant Transformation
  - CNS neuroblasts → Medulloblastoma
  - Skin melanocytes → Melanoma
  - GI tract (largest endocrine organ) → GI NET’s
  - Adrenal Medulla cells → Pheochromocytoma
  - Thyroid C cells → Medullary CA of Thyroid
  - Lung Kulitschitsky cells → Carcinoid/Small Cell CA
  - Endocrine Pancreas cells → Islet Cell Tumors
  - Skin Touch Receptors → Merkel Cell Tumors
CLINICAL PRESENTATIONS AND DIAGNOSIS

Neuroendocrine tumors of the gastrointestinal tract, lung and thymus (carcinoid tumors)\(^b\)
Clinical presentations:
• Jejunal, ileal, colon (See CARC-1)
• Duodenal (See CARC-1)
• Appendix (See CARC-2)
• Rectal (See CARC-3)
• Gastric (See CARC-4)
• Bronchopulmonary, thymus (See CARC-5)
• Atypical lung carcinoid
• Locoregional unresectable disease and/or distant metastases (See CARC-6)

Neuroendocrine tumors of the pancreas\(^b\)
Clinical presentations:
• Nonfunctioning pancreatic tumors (See PanNET-1)
• Gastrinoma (See PanNET-2)
• Insulinoma (See PanNET-3)
• Glucagonoma (See PanNET-4)
• VIPoma (See PanNET-5)
• Recurrent disease (See PanNET-6)
• Locoregional unresectable disease and/or distant metastases (See PanNET-7)

Neuroendocrine tumors of unknown primary (See NUP-1)\(^b\)

Adrenal gland tumors (See AGT-1)\(^c\)

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated (high-grade) neuroendocrine tumors/Large or small cell carcinoma other than lung (See HGNET-1)

Multiple endocrine neoplasia, type 1 (See MEN1-1)
• Parathyroid
• Pancreatic neuroendocrine tumors (PanNET)
• Pituitary tumor

Multiple endocrine neoplasia, type 2 (See MEN2-1)
• Medullary thyroid carcinoma (Also see NCCN Guidelines for Thyroid Carcinoma)
• Parathyroid
• Pheochromocytoma

Merkel cell carcinoma (See NCCN Guidelines for Merkel Cell Carcinoma)

\(^a\)See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
\(^b\)Guidelines pertain to well-differentiated tumors. For poorly differentiated/high-grade/large or small cell carcinomas, see HGNET-1.
\(^c\)Includes adrenal cortical tumors and incidentalomas.
**PRINCIPLES OF BIOCHEMICAL TESTING (1 OF 3)**

- Some neuroendocrine tumors can secrete specific neuroendocrine hormones. Hormonal workup should be guided by the presence of symptoms of the excess hormone.
- For most of the blood studies, an 8-hour fast is generally recommended in addition to certain dietary adjustments depending on the test.
- Also be aware that many medications can affect the results of specific tests.
- Proton pump inhibitors are known to cause false elevations in serum gastrin and chromogranin A.
- If Multiple Endocrine Neoplasia Type 2 (MEN2) is suspected, then all patients should be evaluated for pheochromocytoma/paraganglioma in addition to pituitary or pancreatic tumors prior to any procedures. Recommended annual screening for pancreatic NET is gastrin, glucagon, VIP, pancreatic polypeptide, chromogranin A, and insulin.

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Testing</th>
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</table>
| Carcinoid Tumor  | Primary tumors in GI tract (ileum, appendix, rectum, pancreas) are usually non secreting unless extensive liver metastasis. More common to have carcinoid syndrome with extra-GI primary such as lung or bronchi | May be non-secreting or may be associated with flushing, diarrhea, cardiac valvular fibrosis, bronchoconstriction | • Chromogranin A (category 3)  
- 24-hour urine 5-HIAA  
  - Foods to avoid for 48 hours prior to testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts.  
  - Additionally, patients should avoid coffee, alcohol, and smoking. |
| Pancreatic NET   | Pancreas                                                                  | Depends on hormone secreted, can be clinically silent                    | • Serum pancreatic polypeptide (category 3)  
- Chromogranin A (category 3)  
- Calcitonin  
- PTH-rp  
- GHRH |
| Insulinoma       | Pancreas                                                                  | Hypoglycemia                                                            | • Serum insulin, pro-insulin, c-peptide  
- Consider 72-hour observed fast if diagnosis is in question |
| VIPoma           | Most common in pancreas, can be extra pancreatic                         | Diarrhea, hypokalemia                                                   | Serum VIP |
| Glucagonoma      | Pancreas                                                                  | Flushing, diarrhea, hyperglycemia                                        | Serum glucagon |
| Gastrinoma       | Pancreas                                                                  | Gastric ulcers                                                          | Serum gastrin* |

*Basal, stimulated as indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page
See References on NE-B (3 of 3)
Carcinoid Syndrome: Some Secrets on Secretions

- Classic carcinoid syndrome Sx’s:
  - Flushing, Diarrhea, Wheezing
  - Olden days: pulmonary and retroperitoneal fibrosis
  - Pulsatile or episodic

- Cellular phenotype does not predict secretory product

- Gut NETs can secrete wide variety of hormones and even change secretions

- Non-secretory NETs → Secretory over time

- Mets can change secretory properties of Primary
Carcinoids – a subset of NETs

- First described 1867
- 1907 Oberndorfer: “karzinoide”
- Hormonal features identified 1914
- Initially felt benign but unpredictable
- Slow-growing but protean
Primary Sites of Carcinoid Tumors

• 60% Gut (largest endocrine organ)
  — Small bowel
    >> Appendix > Rectum > Anus > Gallbladder > Esophagus

• 25% Tracheo-bronchopulmonary

• 4% Undetectable Primary: worst prognosis

• Other sites (rare)
  — Prostate
  — Testis
  — Ovary
Be Aware of Synchronous Neoplasia in Carcinoid Patients

• 2\textsuperscript{nd} malignancies are present 25% of the time
  – Adenocarcinomas of colon (25%) > rectum (14%) > small bowel (7%) > stomach (7%)
  – Lung CA (7%)
  – Prostate CA (7%)
  – Cervix CA (7%)

• Multiple Carcinoids can be present (15-30%).

• Growth Factors secreted by Carcinoids responsible for increasing cell growth?
Presenting Sx’s in NETs


- 87% have Clinical Sx’s
  - Non-specific (Non-functional) Sx’s (70%)
  - Functional/Secretory Sx’s (30%)

- 13% No Sx’s- incidental finding: better prognosis
### Non-Specific Sx’s of GEP NETs

- Abdominal Pain, 79%
- Weight loss, 36
- Bowel obstruction, 18
- Fatigue, 17
- GI bleed, 11
- Sweats (night), 3
- Fevers, 3
- Abdominal mass, 3

- Could precede Dx by decades
Specific (Functional) Sx’s (30% of all pts)

- Carcinoid Syndrome 71%
  - Flushing (83%)
  - Diarrhea (secretory, hypermotility, fibrosis) (73)
  - Bronchospasm (6)
  - Carcinoid Heart Disease (19)

- Zollinger-Ellison Syndrome (gastrinoma) 17%
- Whipple Triad (Insulinoma) 9
- Verner Morrison (MEN I, diarrhea) 2
- Glucagonoma Syndrome 1
Natural History of Carcinoid

• Assume Span of 20 years
• Nonspecific Sx’s Phase (“Irritable Bowel”): Yrs 1-15
• Metastases occur: Year 8
• Functional secretions
  — Flushing: Year 14
  — Diarrhea: Year 16
• Correct Diagnosis is made: Year 17
• Treatments: Yrs 17-20
• Death: Year 20

Site of Metastases of GEP NETs

- Liver 85%
- Peritoneum 21%
- Bone 16%
- Lung 13%
- Brain 3%

Causes of death: Tumor cachexia, liver failure, peritoneal carcinomatosis, respiratory failure from lung mets
Carcinoid Heart Disease (CaHD) - 19%

- Serotonin induces fibrosis of heart valves - Tricuspid and Pulmonic, also of lungs and peritoneum
- 5-HIAA may be marker for CaHD
- Baseline Echo for all pts with Carcinoid Syndrome
- OS correlates with valve replacement in cohort of pts followed between 1981 and 2000
- Up to 64% of pts with CaHD had valve replacement
MEN1-Endocrine Manifestations (From C. Rybak)

Pituitary
- Prolactinoma (20%)
- GH and GH plus prolactin (10%)
- NF (5%)
- ACTH (2%)
- TSH and other (rare)

Parathyroid
- Adenoma (90%)

Foregut carcinoid
- NF gastric enterochromaffin-like cell tumor (10%)
- Bronchial carcinoid (2%)
- Thymic carcinoid (2%)

Entero-pancreatic
- Gastrinoma (40%)
- Insulinoma (10%)
- NF, including PP (20%)
- Other – glucagonoma, VIPoma and somatostatinoma (2%)

Tumors with substantial malignant potential

Schussheim et al. Trends Endocrinol Metab. 12:173-8, 2001
Multiple Endocrine Neoplasia Type 2 (From C. Rybak)

MEN2

Three subsets – all due to mutations in the RET gene

MEN2A

- MTC in early adulthood
- 5% cases due to de novo mutations
- >90% chance MTC
- 50% chance pheochromocytoma
- 20% chance parathyroid hyperplasia

MEN2B

- MTC in early childhood
- 50% of cases due to de novo mutations
- >98% chance MTC
- 50% chance pheo
- Intestinal ganglioneuromatosis
- Mucosal neuromas (>98%)
- Marfanoid habitus

FMTC

- Familial Medullary Thyroid Cancer: 4 cases of MTC in the family
- MTC=only feature
- MTC in middle age
- >90% chance of MTC

When to Consider Genetic Risk Assessment?
(From C. Rybak)

**Single indicators:**

- PPGL
  - Pheochromocytoma = Paraganglioma
- Thymic carcinoid
- Zollinger Ellison Syndrome
- Adrenal Cortical Ca
- MTC

**In general:**

- Cancer occurring at an earlier age than expected
- Multiple generations affected
- Clustering of rare cancers in a family
- Multiple primary cancers in an individual
- Bilateral disease

Brandi ML et al J Clin Endocrinol Metab 2001;86:5658-71
Therapy for NETs

• Somatostatin analogues (1986)

• Loco-regional Therapies for liver mets
  — Hepatic artery chemo-embolization
  — Hepatic Artery radio-embolization (SIRTEX, Theraspheres)
  — Come to Monthly NET Tumor Board Conferences to hear

• Newer Paradigms in past 7 years
  — Promise of PROMID
  — Targeted agents
    -- Chemotherapy
    -- PRRT
  -- Aggressive Surgical Approaches
Somatostatin

(Growth Hormone Inhibitory Hormone = Somatotropin Release Inhibitory Factor)

• Inhibitory peptide hormone of 14 AA’s

• Secreted by hypothalamus and GI tract (stomach, intestine, pancreas)

• Regulates endocrine system

• Affects neurotransmission and cell proliferation
  — Inhibits growth factors: prolactin, IGF, PDGF, VEGF
  — Inhibits GH and TSH in pituitary
  — There are 5 Somatostatin receptors – found in majority of NETs
Somatostatin Actions

In GI Tract

— Inhibits secretion of GI hormones (gastrin, secretin, glucagon)

— Slows gastric and gut motility (Used for chemotherapy-induced diarrhea)

— Decreases splanchnic blood flow (Used for variceal bleeding)

— Suppresses exocrine function of pancreas
Somatostatin analogues

- Octreotide (8 AA’s): first targeted therapy
  - More powerful than Somatostatin at Somatostatin Receptors SSR 2 and 5
  - Longer T1/2 (90 min vs 2-3 min)
  - Subcut 200 microgm Q 8-12 hrs for 2 weeks
  - Then Sandostatin LAR 20 mg IM Q 4 weeks
  - OctreoScan for Dx: Caveats
  -- Radiolabelled octreotide trials

1986: Larry Kvols at Mayo Clinic described first successful use of SMS 210-995 in GEP NETs: First major improvement for these pts.
  (Personal communication 2012)
Other Somatostatin Analogues

- Lanreotide (Somatuline)
  - Also an octapeptide
  - Used in Europe more
    -- CLARINET trial: FDA approval December 2014.
    -- Deep subcut needle, not IM.

- Ongoing development of others that bind to:
  - SSTR 2 and 5 in GEP NETs
  - SSTR 1 in Prolactinomas
Placebo-controlled double blind prospective Randomized study on the effect of Octreotide LAR in the control of tumor growth in patients with metastatic Neuroendocrine Midgut Tumors

First randomized trial for NETs to assess anti-tumor effects

Presented at ASCO GI 2008
Published *Journal of Clinical Oncology* Oct. 2009: Rinke at al
NCCN Guidelines changed 2009
PROMID Study

- 162 pts at 18 German academic medical centers
- NETs of midgut
- Well Differentiated histology and low Ki-67 index
- Functional and non-functional tumors

Patients were randomized to:
Placebo versus Octreotide LAR 30 mg IM q mo
Results

- TTP = 16 months vs 6 months

- Best group: Pts with low hepatic tumor burden (10% liver volume) and resected primaries

- Only group with objective response was those same pts.

No difference in OS due to crossover
This study changed the NCCN Guidelines.

Previously for ASxotic, unresectable carcinoid patients a wait-and-watch attitude had been taken, to allow assessment of pace of progression of disease.

Now Octreotide was added as an option.

But: Not recommended in the adjuvant setting.
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

Locoregional unresectable disease and/or distant metastases
- Imaging:
  - Multiphasic CT or MRI
  - Consider Somatostatin scintigraphy
- Consider 24-hour urine 5-HIAA, if not already done
- Consider chromogranin A (category 3)

If complete resection possible

Locally symptomatic from primary tumor

Asymptomatic, low tumor burden

Resect primary + metastases

Clinically significant tumor burden

Octreotide or lanreotide, if not already receiving

Observe with markers and scans every 3–12 mo or Octreotide or lanreotide

Clinically significant progressive disease

Octreotide or lanreotide, if not already receiving

Consider hepatic regional therapy (arterial embolization, chemoembolization, radioembolization [category 2B]) or Consider cytoreductive surgery/ablative therapy (category 2B)

Consider everolimus (10 mg/d) (category 3) or Consider interferon alfa-2b (category 3) or Consider cytotoxic chemotherapy (category 3), if no other options feasible

Carcinoid Syndrome

- Octreotide or lanreotide
- Echocardiogram

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See Principles of Biochemical Testing (NE-B).
See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
See Principles of Systemic Anti-Tumor Therapy (NE-D).
Noncurative debulking surgery might be considered in select cases.
Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

If signs and symptoms of heart disease or planning major surgery.
Includes ablative techniques such as radiofrequency, microwave, and cryotherapy.
There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.
Only if near complete resection can be achieved.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
• NETs over-express Growth Factors
  — VEGF, PDGF, IGF-1
  — Receptors found on NET cells:
    • PDGFR-alpha and -beta
    • KIT
    • mTOR
    • EGFR
# Trials of Novel Targeted Therapies in Neuroendocrine Tumors


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<tr>
<th>Agent</th>
<th>Molecular target (s)</th>
<th>Patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Tumor type</th>
<th>Tumor response rate (%)</th>
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<td>Bevacizumab</td>
<td>VEGF</td>
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<td>Carcinoid</td>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Sunitinib</td>
<td>VEGFR-1, -2, -3; PDGFR-α, -β; KIT; RET; CSF-1R; FLT3</td>
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<td>RAD001 (Everolimus)</td>
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<td>PDGFR-α, -β; KIT; Bcr-Abl</td>
<td>27</td>
<td>Carcinoid</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Everolimus in NET therapy

- Novartis initiated a series of trials to target mTOR pathway in NET cells by using mTOR inhibitor everolimus.

- RADIANT 1, 2, 3, 4:
  
  RAD 001 in Advanced Neuroendocrine Tumors
  
  RADIANT 1 and 3: Pancreatic NET
**Radiant 3 Trial**

- Randomized Phase III trial for Pancreatic NET tumors
- Statistically significant improvement in PFS (11.0 vs 4.6 mo)
- NCCN level 2A recommendation
• Radiant 4 Trial (2015)
  – Randomized Phase III trial versus Placebo for Non-functional NET of GI or lung origin
  – Statistically significant improvement in PFS (11.0 vs 3.9 mo)
  – Level 2A recommendation from NCCN
    • Patients included were both treated and untreated with SS analogue therapy

Note: Radiant 2 trial showed lack of efficacy in functional carcinoids
Sunitinib for Pancreatic NET

- Phase III trial
- Exploiting the anti-angiogenic properties of sunitinib
  - Closed early due to early stopping rule
  - **PFS benefit found** (11.4 vs 5.5 mo)
  - Objective response of 9%
  - Level 2A for Pancreatic NET
  - Fatigue and Cardiac toxicities
Oral Tyrosine Kinases for Medullary Thyroid Cancer

- **Cabozantinib** and **Vandetanib**
- FDA approved in last 2-3 yrs.
- Produce significant improvement in PFS but do not produce cures
- Not indicated for simply elevation of tumor markers
- Need to balance QOL vs toxicities
  - GI side-effects
  - Hypertension
  - Dermatologic
  - Expect many dose adjustments
Chemotherapy for Pancreatic NET

- Pancreatic NET is more aggressive (level 2A)
- Older drugs
  - Streptozocin
  - 5FU
  - DTIC
  - Doxorubicin
- Recent enthusiasm for Capecitabine and Temozolimide
  - Capecitabine (1500 mg/m2/d) D1-14 and Temozolomide D10-14 q 28 days
    - Nausea and vomiting
    - 70% OR and 92% OS at 2 yr
    - Small series of 30 pts (Strosberg, Cancer, 2/2011)
    - Ongoing Phase II trial nationally
**Somatostatin Receptor-targeting Radiopeptides = Peptide Receptor Radionuclide Therapy (PRRT)**

- **SSR is target for Radionuclide Treatment**
- **European experience primarily until recently**
  
  (Basel, Rotterdam, Houston)
- **Yttrium (Y-90)**
  - 3.6 mm mean beta range
  - Good for Macrometastases
- **Lutetium (Lu-177)**
  - 0.5 mm mean beta range
  - Micrometastases (Use both? Univ of Basel)

**Others:** Indium 111, Lutetium 171
NETTER 1: first Phase III study of radiolabeled SSA

177 Lutetium-dotatate (octreotate peptide conjugated to Lutetium 177) followed by standard dose octreotide LAR VERSUS Octreotide LAR 60 mg q 4 weeks

- **N = 230 pts**
  - Grade 1-2 midgut NET who had progressed on SSA
  - All tested positive on Octreoscan
- 177 Lu-Dotatate given every 8 weeks x 4 doses

- **PFS** (median F/U of 1.5 yrs):
  - estimated to be 40 mo (not yet reached) *vs* 8 mo (*p* < 0.001)
- **ORR**: 18 *vs* 3% (*p* = 0.0008)
- Suggestion of improved overall survival
  - Adverse events: Lymphopenia (9 *vs* 0%), Emesis (7 *vs* 0%),
  - Elevated gamma GT (18 *vs* 11%)

City of Hope
Case Presentation

• RH is a 63 yo WF

• 2006: St IIIA endometrial cancer treated with RT, brachytherapy and systemic chemotherapy

• 2/2010: 2.5 cm mesenteric mass on CT:
  • Bx low grade NET
  • PET negative except for mesenteric mass
  • Octreotide scan negative

• 3/2010 - Exploratory lap and resection of mesenteric mass. Entire small bowel and cecum evaluated for primary. Liver clear.
Case presentation (continued)

• Patient followed with CT scans and chemistries
• 1/2013: Found to have liver lesions.
• Pre-op octreotide to prevent “carcinoid storm”
• 2/2013: Exploratory laparotomy, wedge resection of 4 liver metastases, cholecystectomy, small bowel resection.
• Primary in terminal ileum found 3 years after met:
  • 12 mm
  • T3 Nx M1
Gastrinoma
Resection of Primary Carcinoids despite Unresectable Liver Mets

• Givi and Pommier, Surgery, 2006
• Retrospective review of 84 pts with abdominal carcinoids and proven liver mets (1995-2006)
• 60 pts had removal of Primary alone
• Median PFS 56 mo in resected VS 26 mo in unresected (p<0.001)
• Median OS not reached in resected VS 47 mo in unresected (p<0.001)
Overall Survival

Fig 3. Survival curves for the primary resected group (N = 60) and the primary nonresected group (N = 24).

MS 159 vs 47 months; 5 year 81% vs 21%

(Surgery 2006;140:891-8.)
Surgical Principles for NET

• Strategies are often counter-intuitive
• Pre-medicate with octreotide to prevent carcinoid storm
• When in the abdomen:
  • Look for synchronous NET primaries
  • Take out the gallbladder
• Even if no primary is found, it may be beneficial to
  • Resect locoregional recurrences/nodes/isolated metastases
• Primary may be resected years after initial metastasectomy (or without metastasectomy)
• Debulking (>90% of tumor) in Sxtic pts may control Sx’s
  • Need surgical JUDGEMENT
SUMMARY

Neuroendocrine Tumors

• Highly variable tumors with low incidence
• Fascinating biology
• Optimal therapy requires multidisciplinary team approach following the patient over years

It's an odyssey.

Understanding of the SSR has advanced the field
• Recent advances in molecular targets and gene mutations and novel PRRT
• Unique (often counter-intuitive) surgical strategies
MULTIDISCIPLINARY NEUROENDOCRINE TUMOR BOARDS

When:

1st Wed of every Month
12 noon - 1.00 pm
Lunch Provided

Where:

Helford Hospital
Radiology Conference Room #1149

To submit cases or more info:

Contact: NET_TumorBoard@coh.org

Surgery
- Resection of the Primary
- Pancreatic Surgery
- Intestinal Surgery
- Resection of Metastatic Disease
- Liver Resections

Interventional Radiology
- Ablative therapies
- Radioembolization
- Chemoembolization
- Sirtex

Medical Oncology
- Octreotide Analogs
- Lanreotide
- Targeted Agents
- Systemic chemotherapies

Genetics
- MEN Syndromes
- VHL Syndrome
- And others

Head & Neck Tumors
- Parathyroid Tumors
- Thyroid Cancers

Moderators
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Thank you for your attention.