Neuroendocrine Tumors- Changing Data, and a New Hope

Sam Lubner, MD FACP
Fellowship Director
UW Carbone Cancer Center

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosures

- None

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Objectives

- Review the variable symptomatic presentations of neuroendocrine tumors.
- Understand possible causes of elevated chromogranin A.
- Identify the critical pathologic components required for neuroendocrine tumors.
- Describe the evidence and consensus recommendations for treatment of low grade pancreatic neuroendocrine tumors.
- Describe the evidence and consensus recommendations for treatment low grade non-pancreatic neuroendocrine tumors.
- Introduce novel concepts in diagnosis and treatment of neuroendocrine tumors.

Neuroendocrine Tumors defined

- Neuroendocrine tumor (NET) is a catch all term describing a spectrum of malignancies arising from cells with neuroendocrine differentiation
  - Pancreatic islet cells
  - Bronchial neuroendocrine tumors
  - Enterochromaffin cells of the GI tract
  - Pheochromocytoma
  - Medullary thyroid cancer
  - Parathyroid carcinoma

Neuroendocrine Tumors defined

- Tumors range from very slow growing to incredibly fast growing
  - GI carcinoid cells typically slower
  - High grade NET behave like small cell lung cancer

Neuroendocrine Tumors defined

- The “endocrine” part of the nomenclature stems from the secretory capability of these tumors
- What the tumors secrete, if anything, predicts the symptoms, presentation, and even the behavior/metastatic potential of these tumors

Incidence

- Very difficult to actually determine incidence/prevalence, as this tumor type has not always been categorized as a malignancy
- Appears to be on the rise in USA
  - Nearly 50-50 male-female
    - Women with more lung primaries
  - Racial incidence reflects population
    - Whites with more lung primaries, Asians with few
  - Median age 63

Incidence on the rise?

- 1.09/100k in 1973 (SEER)
- Now 6.98/100k as of most recent SEER update (2012)

- Detection?

Risk Factors?

- Genetic syndromes
  - MEN-1
  - von Hippel-Lindau
  - Neurofibromatosis
  - Family history with 3.6x risk
- No known exposure histories
- No known other PMH risk factors

Histopathology

- Heavily vascularized
- “Salt and pepper” chromatin
- Immunohistochemistry for chromogranin and/or synaptophysin
- Other markers include neuron-specific enolase
- Electron microscopy with proliferation of secretory granules

Cells of origin

- Carcinoid tumors
  - Kulchitsky cell
- Insulinomas
  - Beta cell of pancreas
- Glucagonomas
  - Alpha cell of pancreas
- Somatostatinomas
- VIPoma

Presentation

- Often asymptomatic
  - Seen on CT scans performed for other reasons
  - Increase in CT scans thought to at least partially explain increase in incidence
- Vague abdominal pain
- Poor appetite

Endocrine syndromes

- Insulinoma
  - Hypoglycemia, inappropriately high insulin
- Glucagonoma
  - Hyperglycemia, specific skin rash
- Somatostatinoma
- Gastrinoma
  - Lots and lots of gastric ulcers, gi bleeding

Carcinoid syndrome

- Flushing
  - Brought on by stress, amine-rich foods, alcohol
- Watery diarrhea
- Wheezing/bronchospasm
- Palpitations/Right-sided heart disease
  - Tricuspid regurgitation

Symptoms

- Mass effect may also be evident
  - Obstruction
  - Intestinal angina
    - May have metastatic deposits within the mesentery causing arterial obstruction

Diagnosis

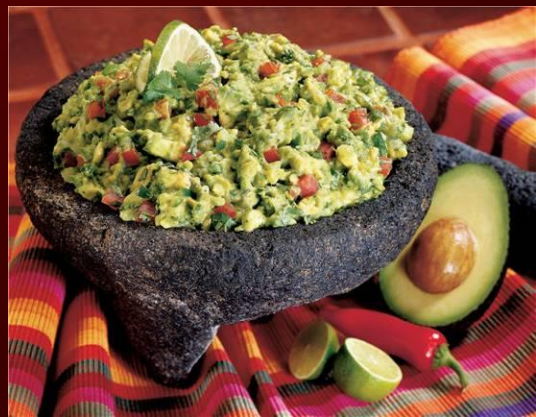
- Suspicion based on clinical history
- Exam may reveal tricuspid regurgitant murmur
  - LE edema
- Rash (maybe)

Biochemical Manifestations

- Glucose intolerance
- Low-grade anemia
- Electrolyte imbalances indicative of chronic diarrhea

5-HIAA

- Many NET, carcinoid especially produce serotonin
- Serotonin is broken down into a water soluble form for urinary excretion
- 24-hour collection of 5-HIAA
  - Specific (99% for carcinoid), not sensitive (73%)
  - Affected by intake of certain foods
    - Avocados, walnuts should be avoided during collection



Chromogranin confusion

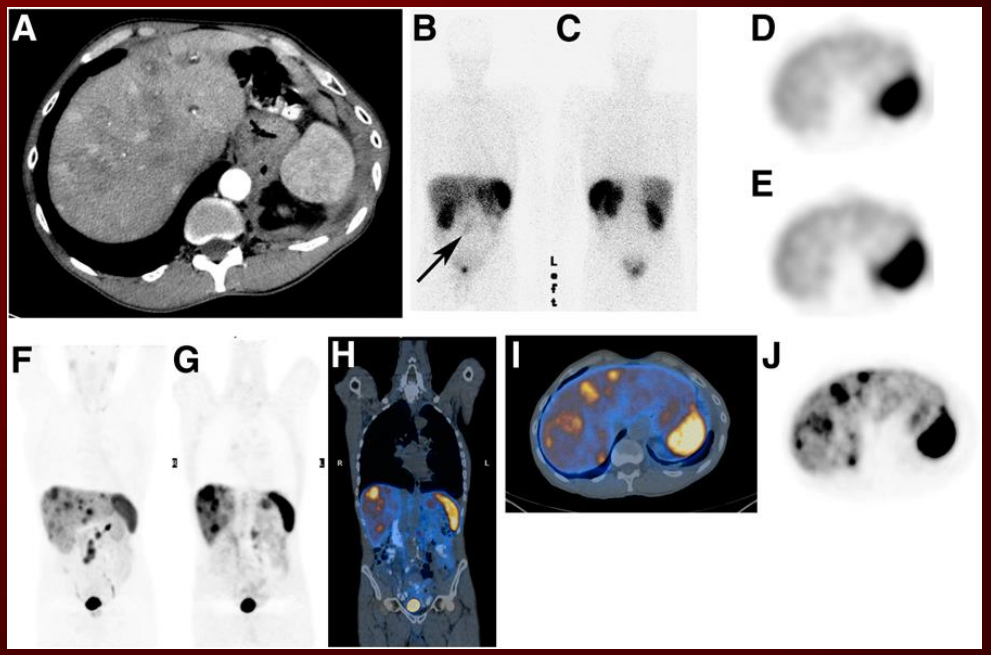
- Chromogranin is a protein commonly made in neuroendocrine cells
- While sensitivity and specificity are ok (80-90%), rarity of the tumors makes positive predictive value less than one would think
- Commonly elevated in PPI or H2B use
- Commonly elevated in hepatic or renal insufficiency
- HAVING AN ELEVATED CgA IS NOT A DISEASE

Imaging

- Variety of scans available for diagnosis/staging
  - CT scan with contrast
    - Pancreatic protocol if pancreatic lesion
    - Timing of contrast bolus is critical
  - MRI with contrast
  - Octreotide nuclear medicine scan (OctreoScan)
    - Octreotide scans may not be as definitive as once thought
- New technology emerging…

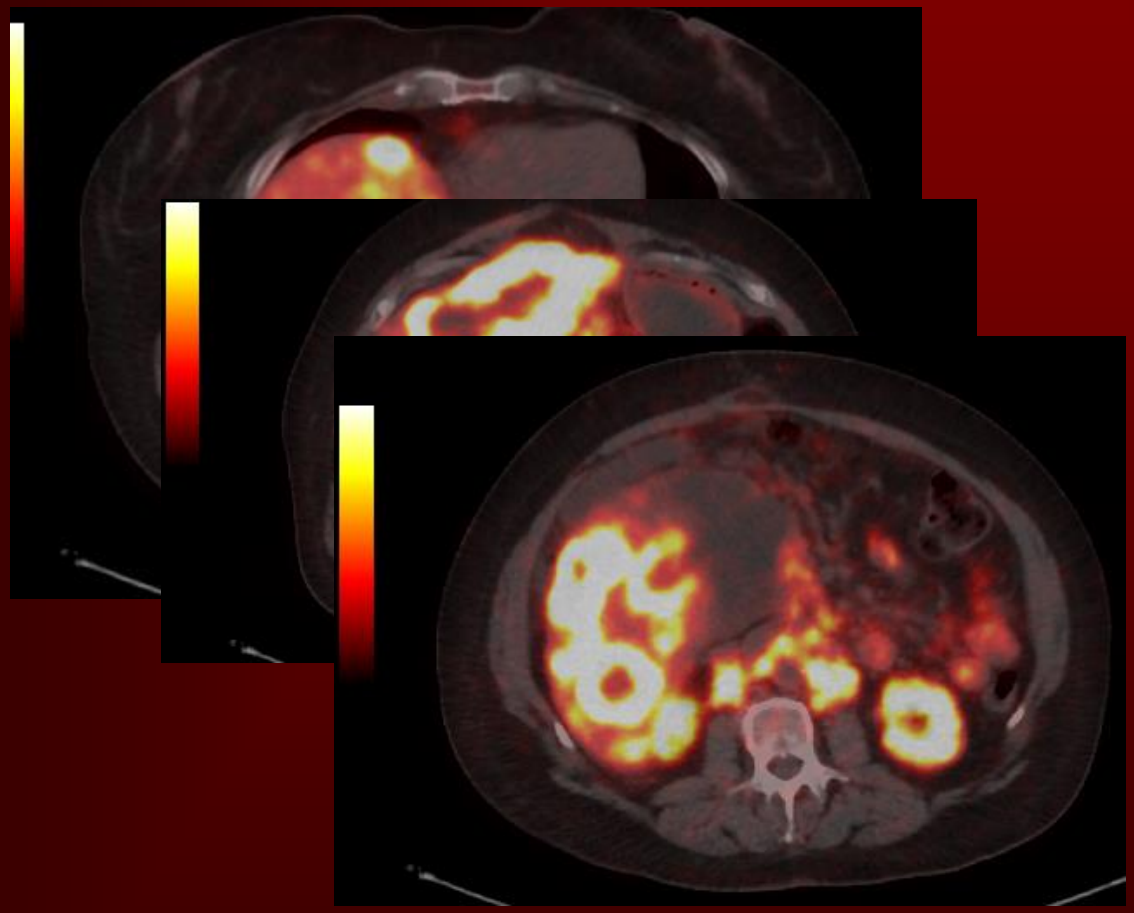
Next Big Thing

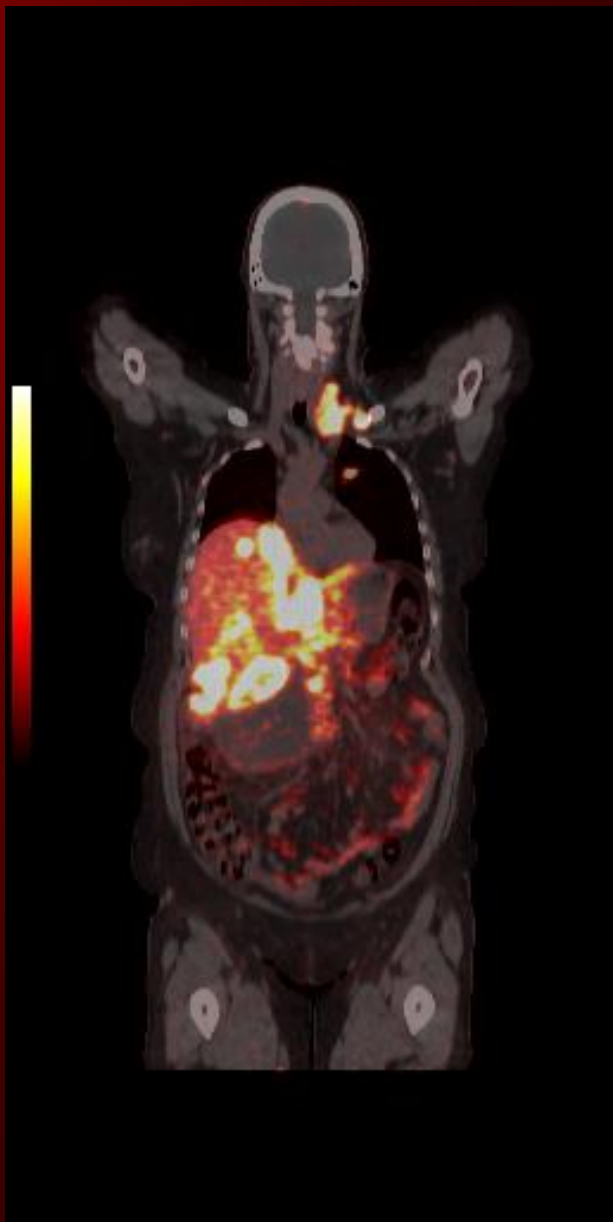
- Improvements in detection and anatomic localization will yield better understanding of treatment options
- ^{68}Ga-DOTATATE PET can improve tumor localization
  - Improved sensitivity
  - Improved specificity
  - Better anatomic localization



Srirajaskanathan et al J Nucl Med 2010; 51 875-882
Deppen et al J Nucl Med 2016; 57 708-14

Next Big Thing





Pathology

- Key components
  - Size
  - Primary site
  - Grade
  - Immunohistochemistry
- Grade 1 tumors rarely metastatic at diagnosis, grade 3 (poorly differentiated) nearly 50% with metastatic disease

Histologic Classification of NETs

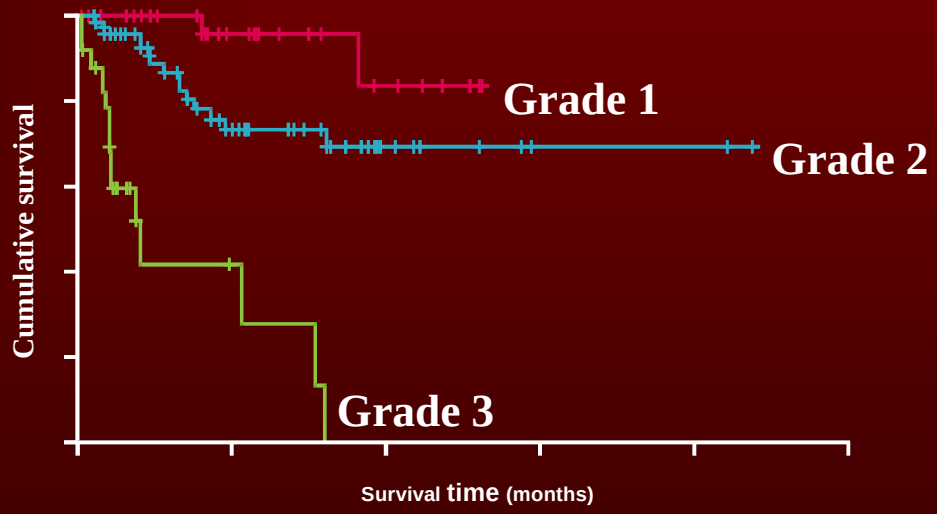
Differentiation and grade	Mitotic count*	Ki-67 index† (%)	Traditional classification	ENETS/WHO classification[2]	Moran et al[3]
Well differentiated					
Low grade (grade 1)	<2	≤2	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	NET, grade 1	NEC, grade 1
Intermediate grade (grade 2)	2–20	3–20	Carcinoid, atypical carcinoid,‡ islet cell, pancreatic (neuro) endocrine tumor	NET, grade 2	NEC, grade 2
Poorly differentiated					
High grade (grade 3)	>20	>20	Small-cell carcinoma	NEC, grade 3, small cell	NEC, grade 3, small cell
			Large-cell NEC	NEC, grade 3, large cell	NEC, grade 3, large cell

NEC = neuroendocrine carcinoma
*Per 10 high-power fields
†Cellular proliferation marker
‡Applies only to intermediate-grade NET of the lung

1. Kulke MH, et al. *J Clin Oncol* 2011;29:934–943
2. WHO Classification of Tumours of the Digestive System, 4th ed., 2010
3. Moran CA, et al. *Am J Clin Pathol* 2009;131:206–221

Why is that so important?

- **Survival in an institutional series of pancreatic (n=131), duodenal (n=23), and gastric (n=48) NETs**
- **Proportion alive at 5 years:**
  - **Grade 1: 96%**
  - **Grade 2: 73%**
  - **Grade 3: 28%**



Pape UF, et al. *Cancer* 2008;113:256–265

Staging

- Some controversy
  - T stage based on size
  - T1 <2 cm
  - T2 2-4 cm
  - T3 >4cm
  - T4 invading adjacent structures
- Any nodal deposit is N1, any metastasis is M1

Local Treatments

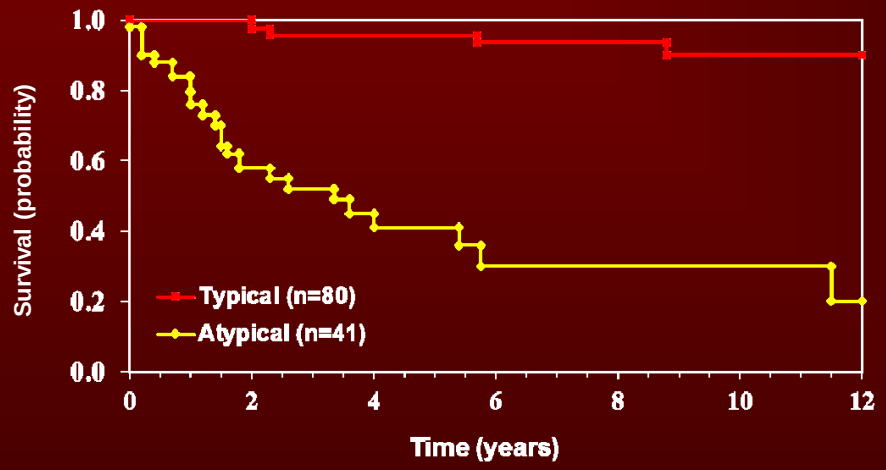
- Surgical resection is the gold standard
  - Type of surgery depends on primary location
    - Foregut: 33%
    - Midgut: 34%
    - Hindgut 14%

Different types of surgical options

- Appendectomy with R hemicolectomy
  - Appendiceal tumors >2cm
    - For tumors <1cm, appendectomy alone is OK
- Pancreaticoduodenectomy (Whipple)
  - Pancreatic NET
  - Enucleation
- Lobectomy or VATS lobectomy
  - Bronchial carcinoid

Bronchial Carcinoid Tumors

- Present with hemoptysis, cough, wheezing
- Common cause of Cushing's syndrome due to ectopic ACTH (carcinoid syndrome rare)
- Prognosis correlates with Ki67: typical vs "atypical"



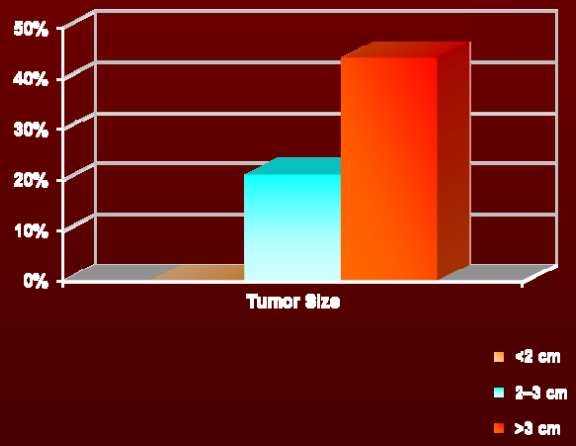
Harpole DH et al. *Ann Thorac Surg 1992; 54: 50-55*

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Challenge of Appendiceal Primaries

Most commonly present as incidental finding with acute appendicitis; usually in younger pts (30's)

Prevalence of Metastases According to Tumor Size



Treatment Recommendations

Size	Treatment
<2 cm	Simple appendectomy
>2 cm	Octreotide scan, right colectomy

Moertel CG et al. *N Engl J Med*. 1987; 317: 1699-701

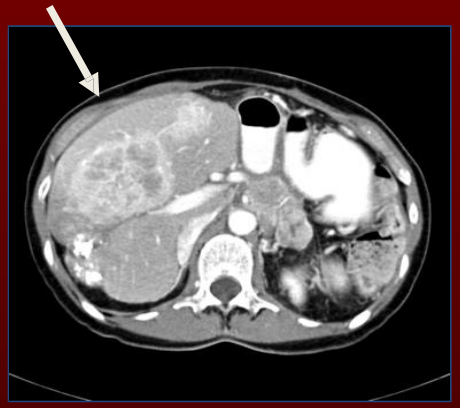
Any role for transanal excision?

Rectal Carcinoids:
Treatment Recommendations

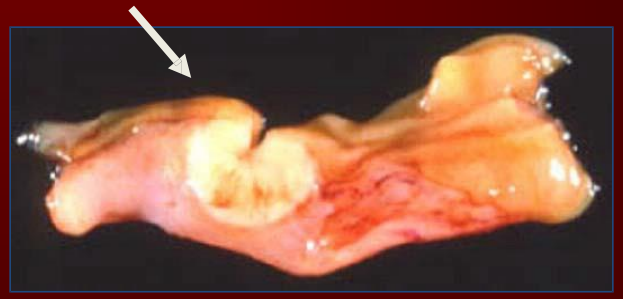
Size	Treatment	% Metastatic
<2 cm	Transanal or endoscopic excision, if possible	<5%
>2 cm	Octreotide scan, CT, then LAR or APR	>50%

Small Bowel Carcinoid

- Present at advanced stage due to difficulty in diagnosis
- Associated with intermittent obstruction/bowel ischemia.
- Resection recommended for symptoms even with metastatic disease



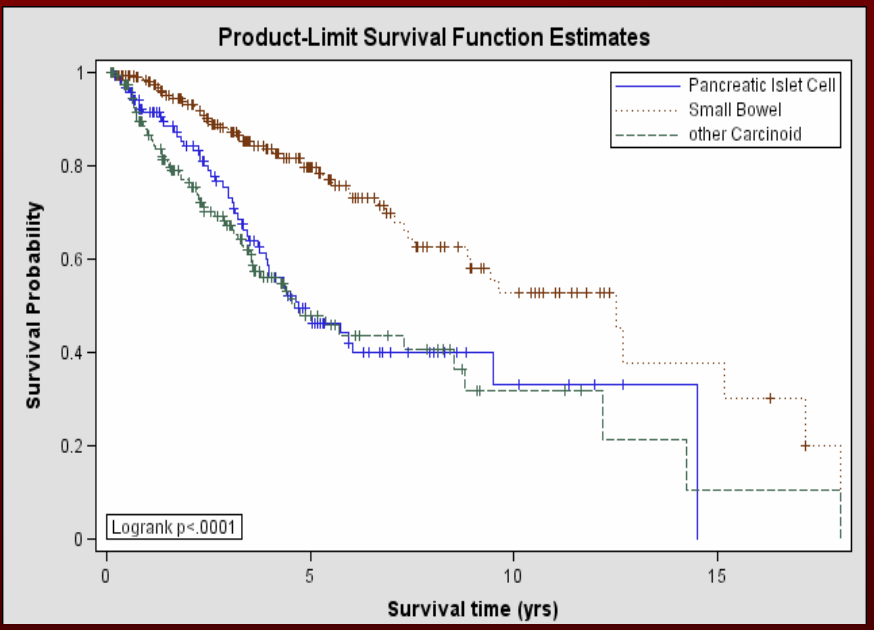
Hepatic metastases from carcinoid tumor



Primary Small Bowel Carcinoid

Metastatic Neuroendocrine Tumors: Survival by Tumor Subtype

Single Institution Database (N=677)



Pancreatic NET: 5.9 yrs
Small Bowel Carcinoid: 10.1 years

SEER Database

Median Survival (months)

Site	Localized	Regional	Distant
Appendix	>360	>360	27
Cecum	135	107	41
Colon	261	36	5
Duodenum	107	101	57
Gastric	154	71	13
Liver	50	14	12
Lung	227	154	16
Pancreas	136	77	24
Rectum	290	90	22
Small bowel	111	105	56
Thymus	110	68	40

Pancreatic NET: 2 years
Small Bowel Carcinoid: 4.6 years

Ter-Minassian et al, Endocrine Related Cancer, 2013; *20: 187-96*
Yao JC et al. J Clin Oncol. 2008;26:3063-3072

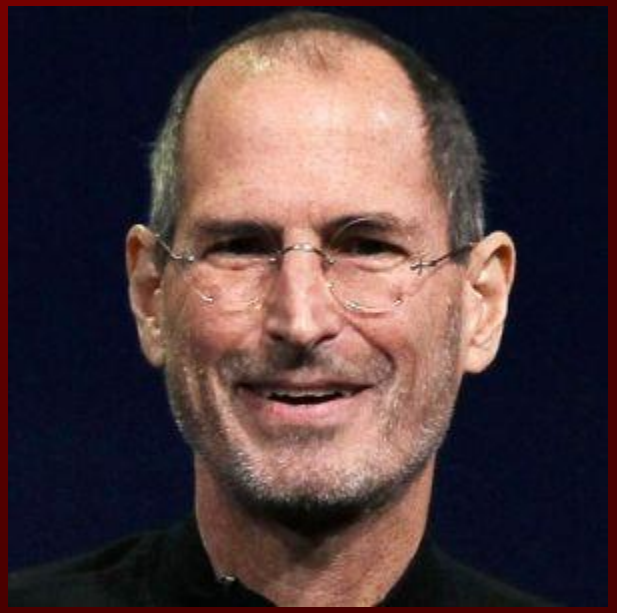
Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Role for debulking?

- Many patients with symptomatic disease already have metastases to the liver
- Curative surgery not possible
- Suggested survival benefit for tumor debulking or resection of primary tumor
- Not commonly performed at UW

Role for Transplantation?

- Mostly retrospective data
- 5-year DFS ranges from 9-48%
- No consensus criteria on who/how selection for transplant looks



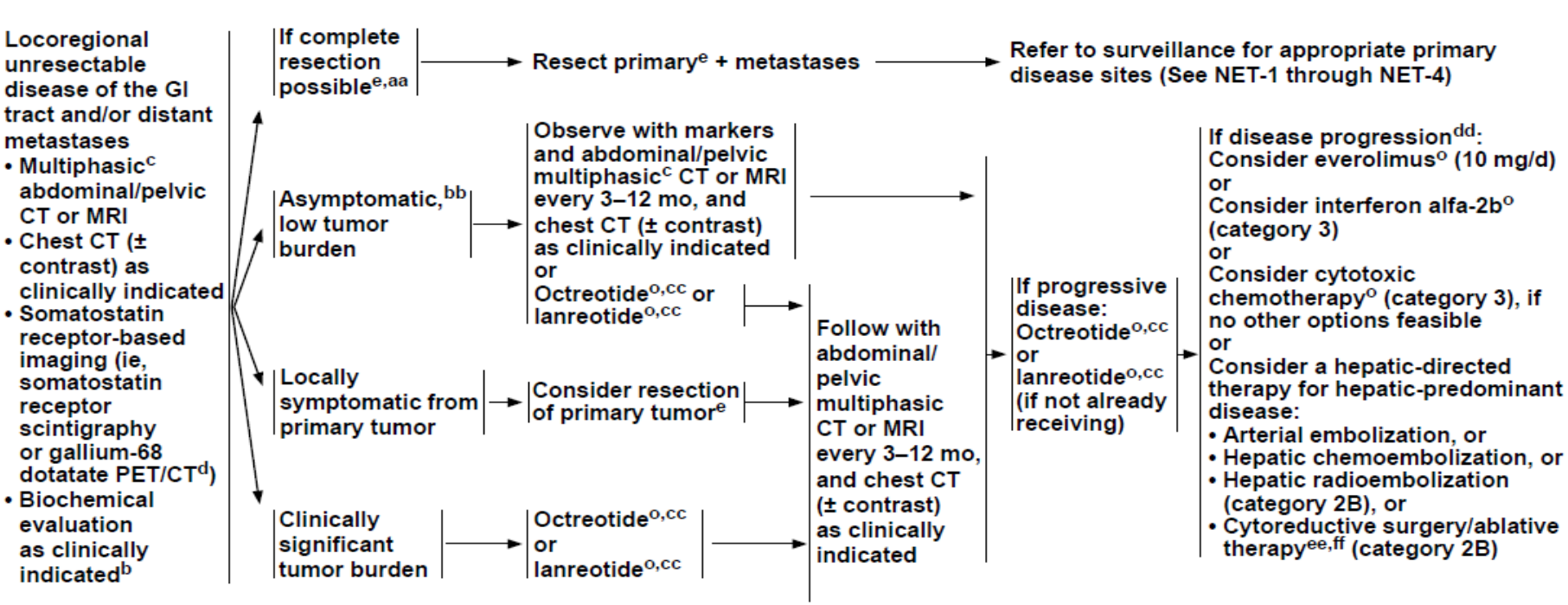
Ablation

- Tumor targeted with ultrasound or CT, performed by body radiology
- Radiofrequency energy applied to tumor producing thermal cell kill
- Used primarily for symptomatic tumors akin to debulking

Liver Directed Therapy

- Consider TACE, ^{90}Y embolization
- Be cautious in patients with significant liver burden
- Late radiation hepatitis

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT



[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] Noncurative debulking surgery might be considered in select cases.
[bb] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[ee] 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.
[ff] 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.

Systemic Treatment Options

- Somatostatin analogue
  - Octreotide
  - Lanreotide
- Targeted therapy
  - Everolimus
  - Sunitinib
- Cytotoxic chemotherapy

Octreotide

- Used for symptomatic relief
  - Decrease in diarrhea
  - Decrease in flushing?
- Slowed progression
  - 14.3 vs 6 mo progression in PROMID
- Short acting and long acting formulations

Rinke et al, JCO 2009; 27: 4656-63

Lanreotide

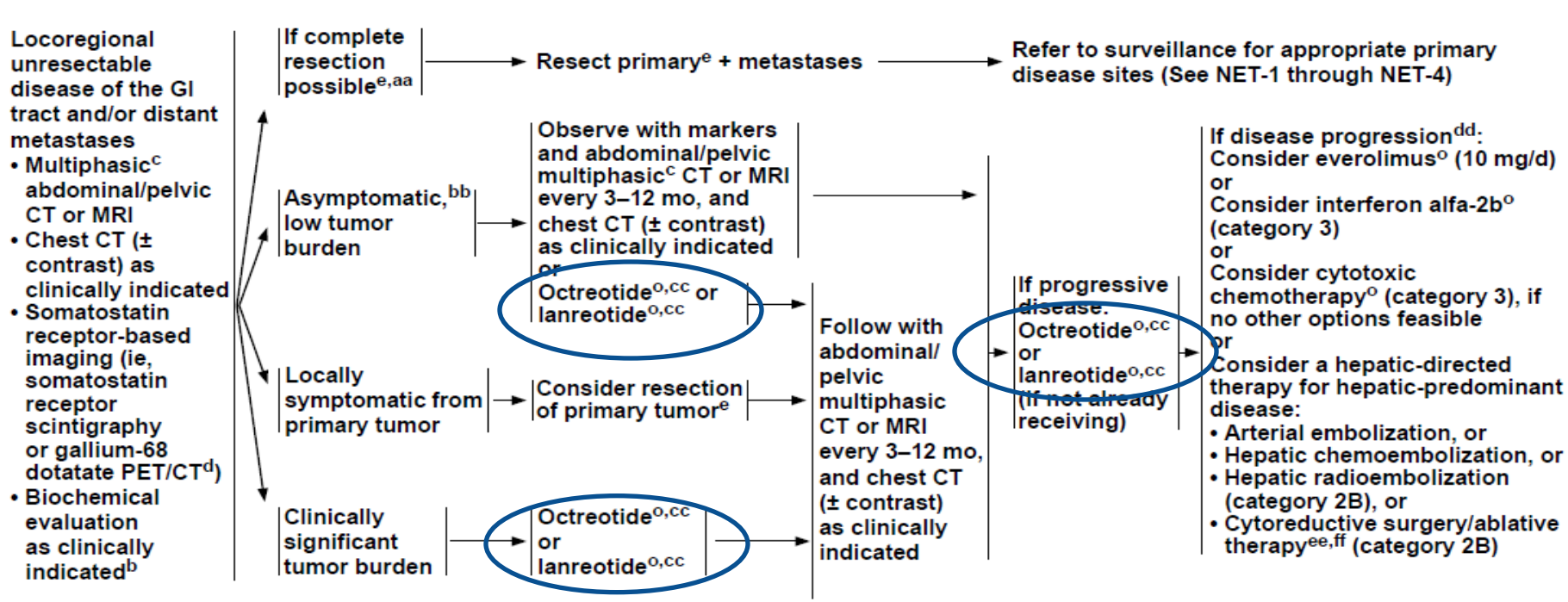
- Subcutaneous rather than intramuscular injection
- No test dose required
- Similar symptom relief
- Median OS not reached vs. 18 mo placebo in CLARINET study

Caplin ME NEJM 2014; 371: 224-233

First-line approach

- Symptomatic relief
- Benefit in PFS demonstrated
- Very favorable toxicity profile

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT



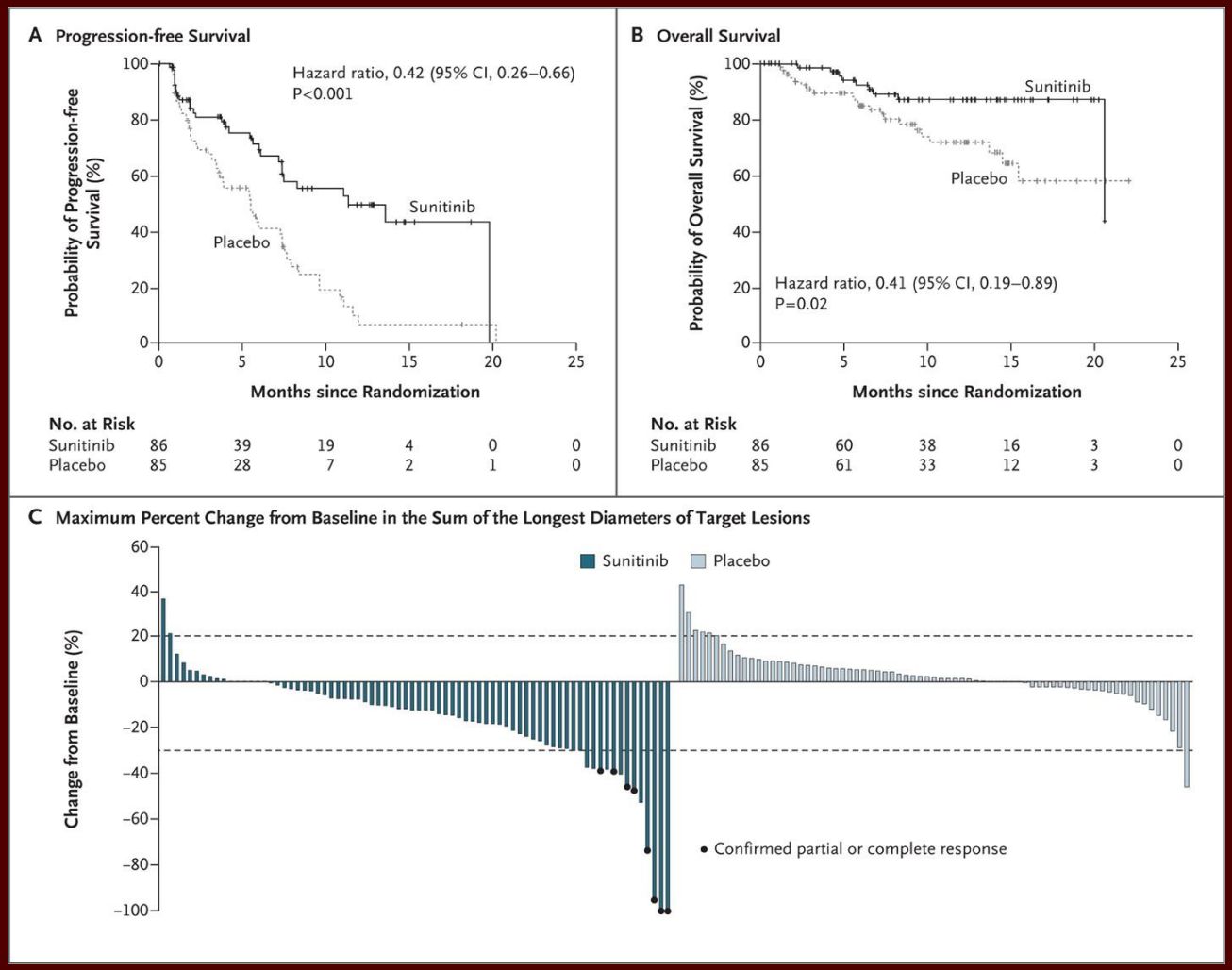
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] Noncurative debulking surgery might be considered in select cases.
[bb] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[ee] 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.
[ff] 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.

Targeted Therapies

- In vitro tumors heavily vascularized, thought to overexpress VEGF
- Sunitinib vs. placebo
- Only 9% response rate
  - Prolonged disease stabilization (PFS 11.4 mo vs. 5.5 mo)
    - Potentially even more effective in low grade NET
    - Relatively ineffective in carcinoid subset

Kaplan-Meier Analysis of Progression-free Survival and Overall Survival in the Intention-to-Treat Population and the Maximum Percent Change from Baseline in the Sum of the Longest Diameters of Target Lesions, According to Patient.



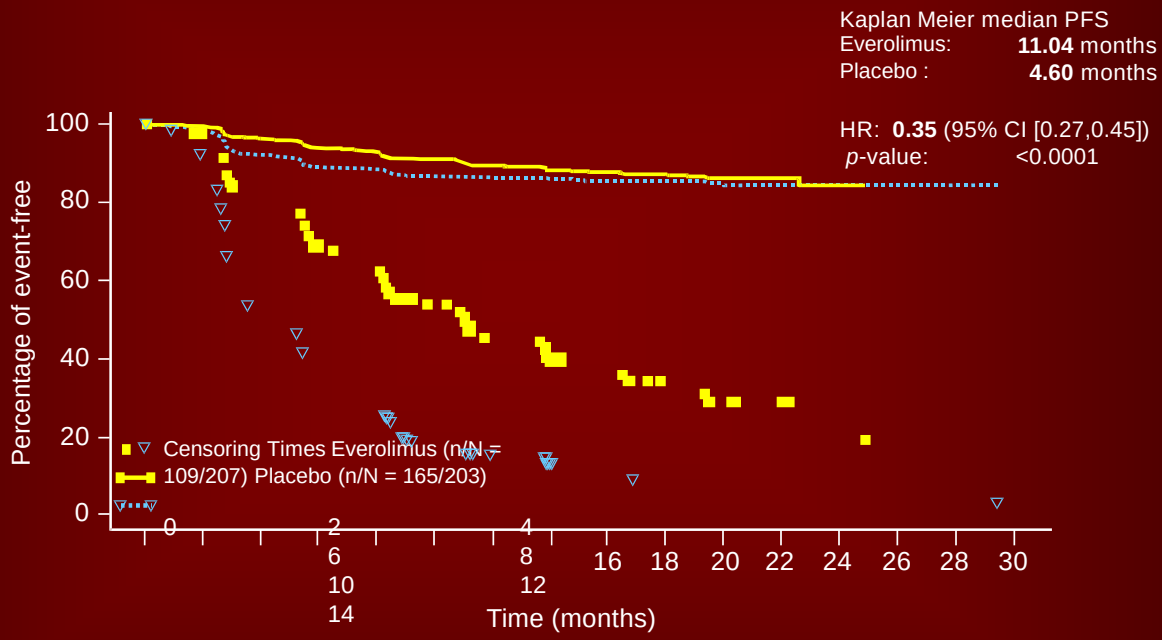
Raymond E et al. N Engl J Med 2011;364:501-513.

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

mTOR Inhibitors

- Autocrine activation of mTOR mediated by IGF-1 thought to increase NET proliferation in vitro.
- Early phase studies showed response rates of 4-8% in pNET, stable disease in luminal GI NET.
- RADIANT studies launched to test efficacy
  - RADIANT-2, all comers
  - RADIANT-3, pNET
  - RADIANT-4, non-pancreatic NET

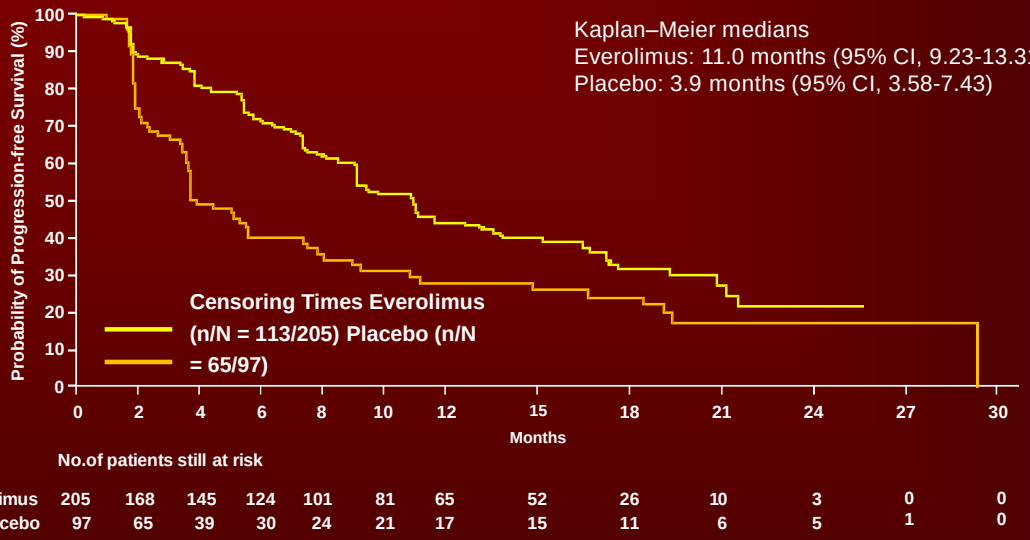
Everolimus in Pancreatic NET (RADIANT 3): Investigator-Assessed Progression-Free Survival



Yao et al, N Engl J Med 2011; 364: 514-23

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

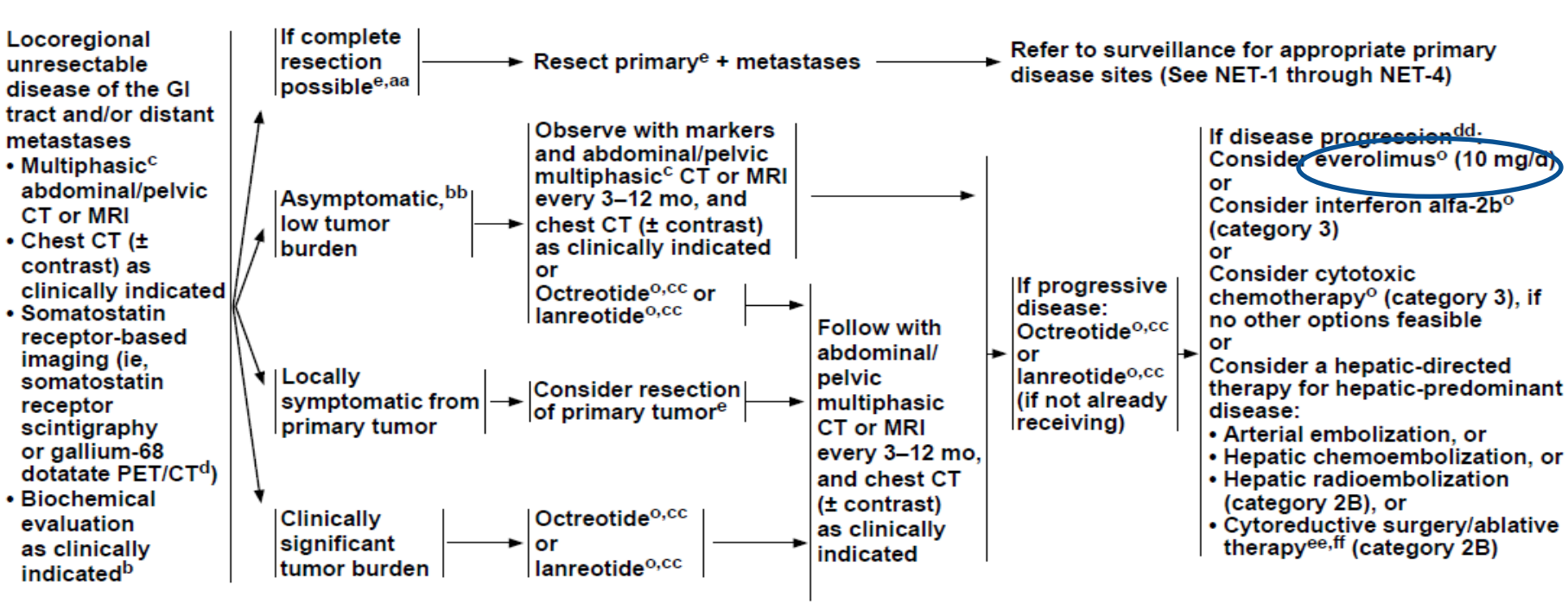
RADIANT-4; all NET



Kaplan–Meier medians
Everolimus: 11.0 months (95% CI, 9.23-13.31)
Placebo: 3.9 months (95% CI, 3.58-7.43)

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model. CI, confidence interval; HR, hazard ratio.

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT



[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] Noncurative debulking surgery might be considered in select cases.
[bb] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[ee] 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.
[ff] 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.

Chemotherapy options

- For higher-grade tumors, chemotherapy with platinum doublet akin to small cell lung cancer treatment
- Consider multimodality therapy
  - Chemo+radiation
- High-grade NET from outside of the lung do not have the same propensity for CNS mets.
  - PCI not routinely recommended

Chemotherapy options

- Low grade tumors are typically chemotherapy resistant
- Single-agent activity
- Combinations associated with increased toxicity, increased response rate

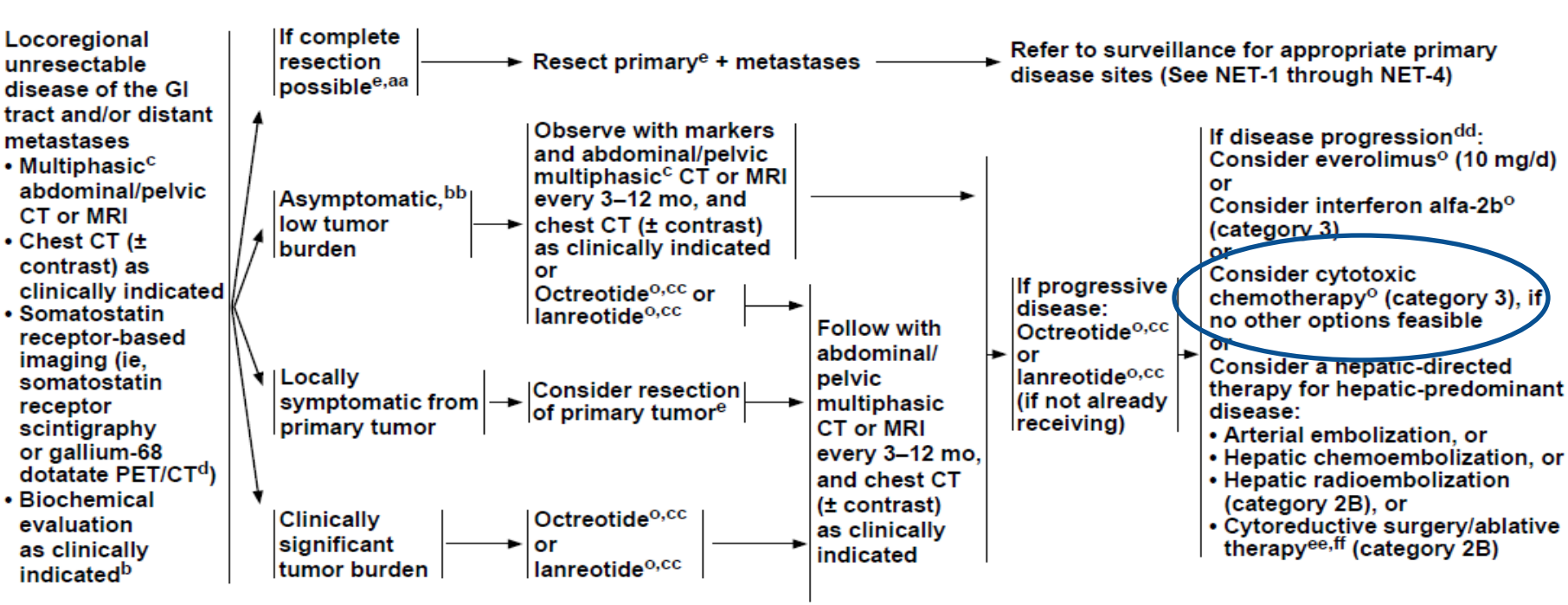
Chemotherapy options

- Streptozocin approved for NET in 1982
- Improvements in OS (1.5 vs 2.2 years), response rates around 30% in retrospective series.
- Response rates well predate RECIST

Chemotherapy options

- Temozolomide-based therapy
  - Tem/Cape with a 70% ORR in 30 pt study
  - Current UW study Tem/TAS 102 (PI-Uboha)
- Role for high-grade?
  - Also have a trial-tem/cape versus cis/etoposide
  - Have had a hard time accruing due to perceived clinical urgency

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT



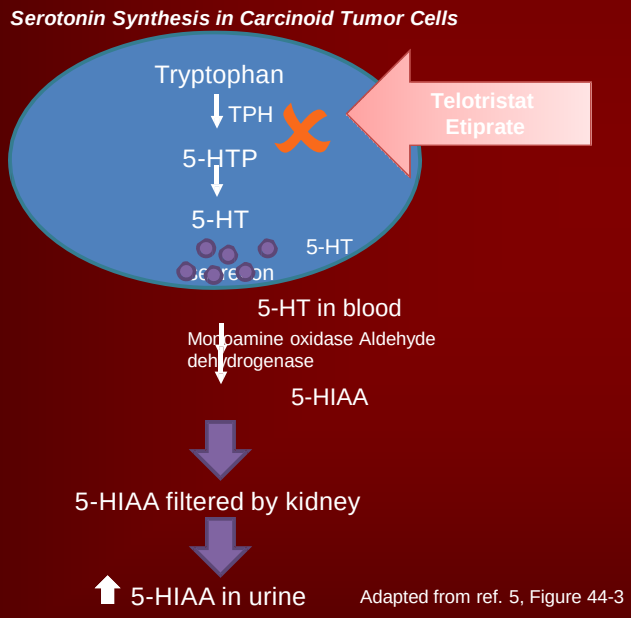
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] Noncurative debulking surgery might be considered in select cases.
[bb] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[ee] 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.
[ff] 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.

Clinical trials

- It is reasonable to have a patient with carcinoid (non-pancreatic NET) enroll on a clinical trial as front-line therapy
  - Looking for better therapies/combinations

A Tryptophan Hydroxylase (TPH) Inhibitor



Adapted from ref. 5, Figure 44-3

Telotristat Etiprate:

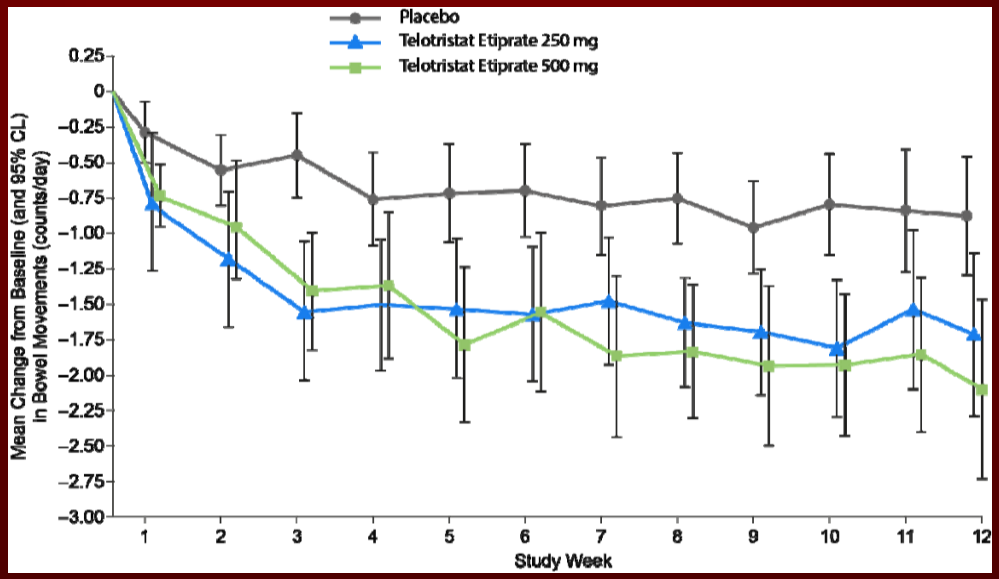
- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis[1]
- Two early-stage clinical studies demonstrated the safety and evidence of clinical activity in carcinoid syndrome[2,3]
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity[1-3]

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

1.Liu Q, Yang Q, Sun W, *et al. J Pharmacol Exp Ther* 2008; 325:47–55. 2. Kulke MH, O'Dorisio T, Phan A, *et al. Endocr Relat Cancer* 2014;21:705–714. 3. Pavel M, Horsch D, Caplin M, *et al. J Clin Endocrinol Metab* 2015;100:1511–1519. 4. FDA Orphan Drug Designations. Available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index. Accessed September 2015. 5. Kronenberg HM, Melmed S, Polonsky KS, *et al. Williams Textbook of Endocrinology*, 11th edn. 2008:1823–1824.

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

TELESTAR: Reduction in Daily Bowel Movement Frequency Averaged Over Double-Blind Treatment Phase



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)

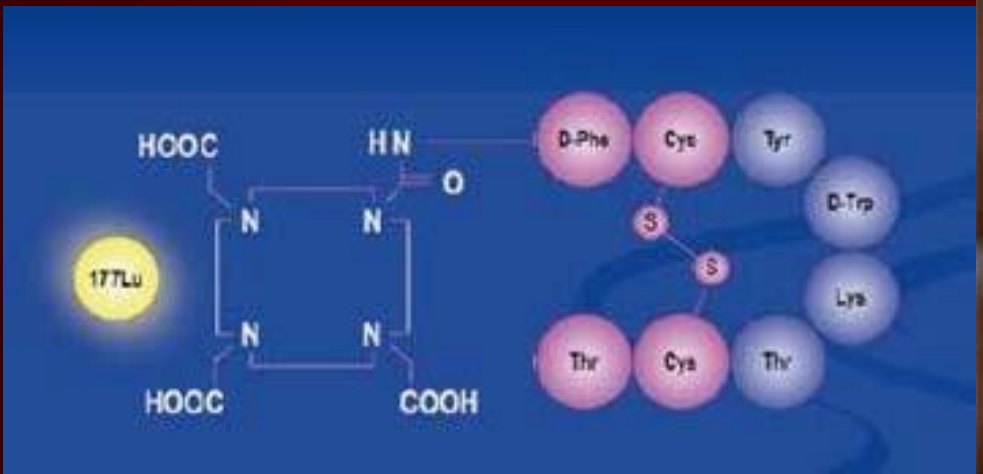
Kulke M et al, J Clin Oncol 2017; 35: 14-23

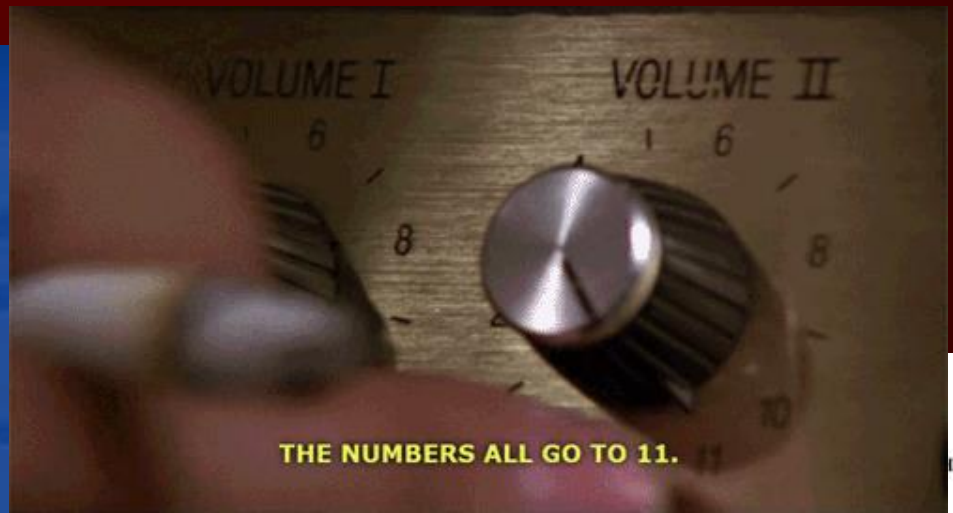
Telotristat Etirpate

- FDA Approved 3/1/2017 for diarrhea associated with carcinoid syndrome
- No clear role as a cytotoxic or cytostatic agent
- Cost burden remains significant
  - $8000

A New Hope…

- Better localization of somatostatin receptors allows for targeted delivery of radiotherapy
- ^{68} Gallium allows for imaging
- What if we just gave more radiation?

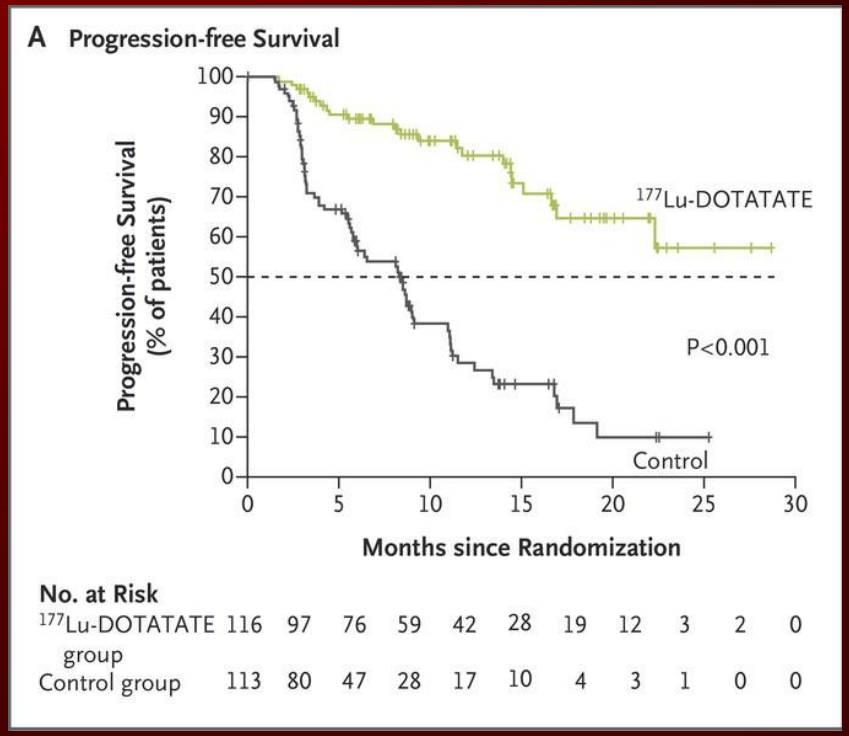




NETTER-1 Study

- Game-changingly positive study
- mPFS not reached in study time
- Not a lot of responses (17%)
- Well-tolerated

Progression Free Survival: 177 Lu Dotatate vs. placebo



Median PFS not reached (177 Lu Dotatate) vs 8.4 mos (placebo)

Strosberg et al, NEJM 2017; 376: 125-135

Peptide-receptor radiotherapy

- Logistically challenging
- Time consuming
- Resource intense

- But, generally, safe and well-tolerated

UW Experience With PRRT

- First patient treated 1/2018

- Few dose holds or dose reductions
  - Primarily for thrombocytopenia
- Reductions in serum biomarkers seen
- Not as much symptomatic relief as we would like

Late toxicity

- Persistent thrombocytopenia
- Theoretical risk of MDS-leukemia
  - 2-10%
- Open questions-can we retreat?
- What happens if we give ^{90}Y after PRRT?
- Before?

What's the best path?

- Confirm the diagnosis with tissue
  - Adequate assessment of grade
- Symptom-directed treatment
- Good anatomic localization
- Where possible, resect for cure

What's the best path?

- Start with SSA
- Next step-PRRT?
- Add targeted agents upon progression
  - I prefer everolimus
- Consider genotyping and tailor therapy based on results
  - MEN1, DAXX, ATRX most common mutations (Scarpa et al, Nature 2017; 543; 65-71)
- Chemotherapy after progression on targeted agents

Working together

- Consider referral anywhere along the way
  - Surgery or local therapy: HPB Tumor Board (Tuesdays 8a-9a)
  - Targeted therapy after NGS results: Molecular Tumor Board (mtb@uwcarbone.wisc.edu)
- Call me anytime 608-335-9379

Thanks and questions…

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH