MAYO CLINIC
Cancer Center

Neuroendocrine Tumors

Overview of Diagnosis and Therapy and the Role of Team Approach

Thor R. Halfdanarson, MD.
Professor of Oncology
Consultant, Medical Oncology
Mayo Clinic
Rochester, Minnesota

Disclosures

- Research Support
  - Esanex
  - Ipsen
  - Thermo Fisher
- Consultancy
  - Ipsen
  - Novartis
  - Lexicon
  - Laser Analytica
  - Wren Laboratories
- Other
  - Panel member, NCCN guidelines on management of NETs
  - Member of the NANETS NET guidelines group

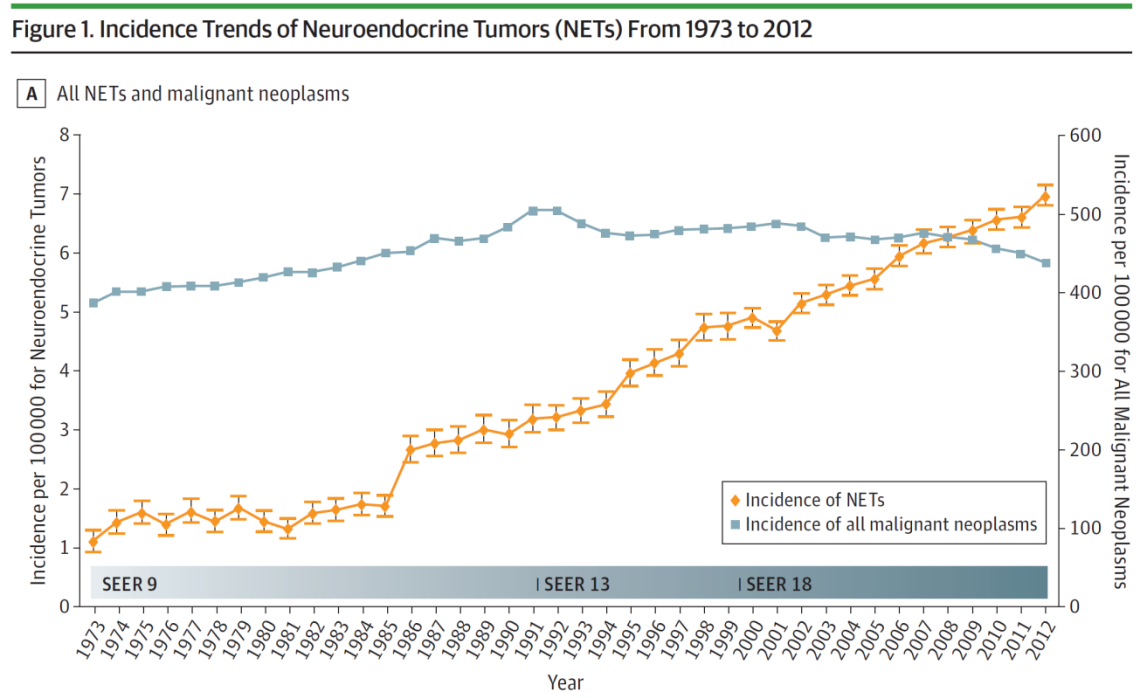
Objectives

- How common are NETs?
- Why do we need better medical therapy?
  - Why do we need medical oncologists to manage NETs?
- What are the current options for drug therapy
  - And how do we best sequence therapy
- Where does PRRT fit in?
- What's on the horizon for drug therapy?
- What about genomic testing?

Epidemiology

The Number of New NET Cases is Rising

- The incidence is rising
  - All sites: 7/100,000
  - GI NETs: 3.65/100,000
- Median age at diagnosis: 63 years
- 400 cases/year in the state of Minnesota??
- The most common sites of NETs
  - Lung
  - Small bowel
  - Pancreas
  - Rectum
  - Appendix

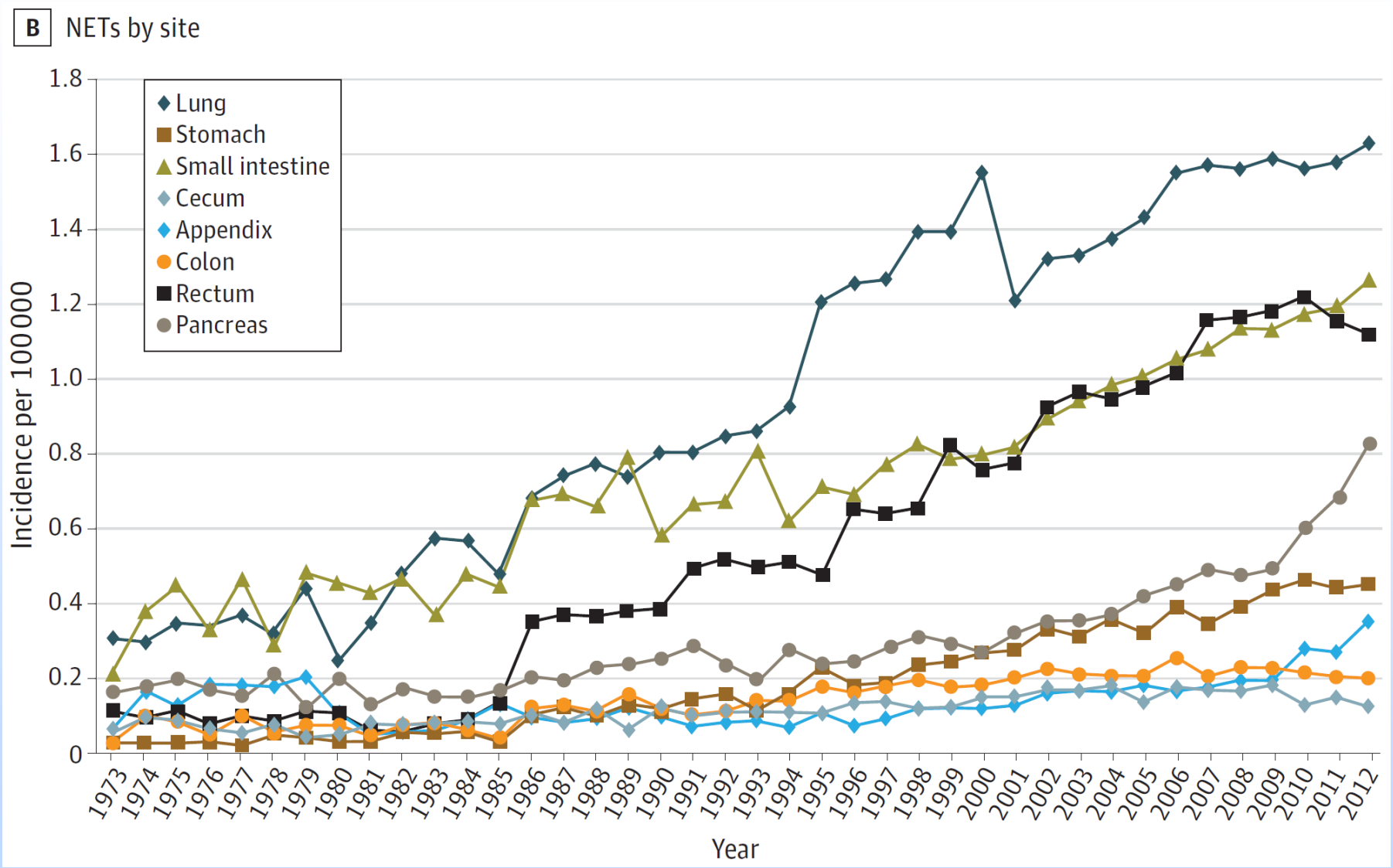


- Long survival
- High prevalence

MAYO CLINIC
Cancer Center

Dasari A et al. JAMA Oncol 2017
Lawrence B et al. Endocrinol Metab Clin North Am. 2011;40:1-18

The Increase Is Seen Across All Types of NETs



MAYO CLINIC
Cancer Center

Dasari A et al. JAMA Oncol 2017

Diagnostic Considerations

Diagnosis – It is a Team Effort…

- An experienced pathologist is crucial
  - The pathologic diagnosis is tricky
  - An accurate diagnosis is essential for selecting the right therapy
- Diagnostic Radiology and Nuclear Medicine
  - Experience matters
  - Selecting the right studies for the right occasion…
- Other specialties
  - Gastroenterology
  - Clinical Chemistry
  - Pulmonary Medicine

Markers (chromogranin A, 5-HIAA etc)

- A useful additional tool
  - Sometimes useful to determine the frequency of scans
- Markers are never sufficient to make a diagnosis
  - They are just one piece of the puzzle
- No perfect marker exists
  - All suffer severe limitations
- Markers should almost never be used as a reason to change therapy
- Markers are probably overused

What Do We Want in a Tumor Marker…?

- The ideal tumor marker
  - A reliable test for screening and diagnosis (high sensitivity and specificity)
  - Robust determination of prognosis
  - Accurate prediction of therapeutic efficacy
  - Sensitive marker of recurrence in surveillance
  - Inexpensive (priced in accordance to its clinical value)
  - Highly reproducible results (standardized testing)
  - Short turnaround time
- In other words, clinically useful…

The Ideal Marker Does Not Exist Yet…

Adapted in part from Duffy MJ. Eur J Int Med 2007;18:175-184.

Why Do We Need Better Treatment Options?

Why Do We Need Medical Oncologists…?

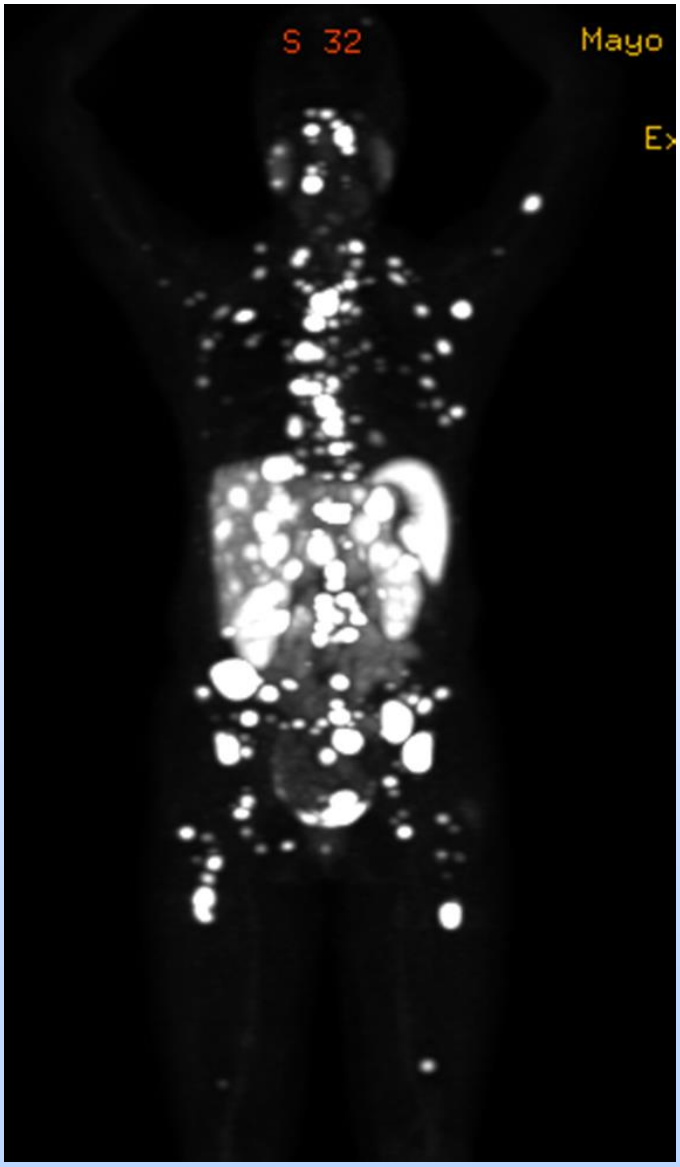
Why Do We Need Better Drug Therapy?

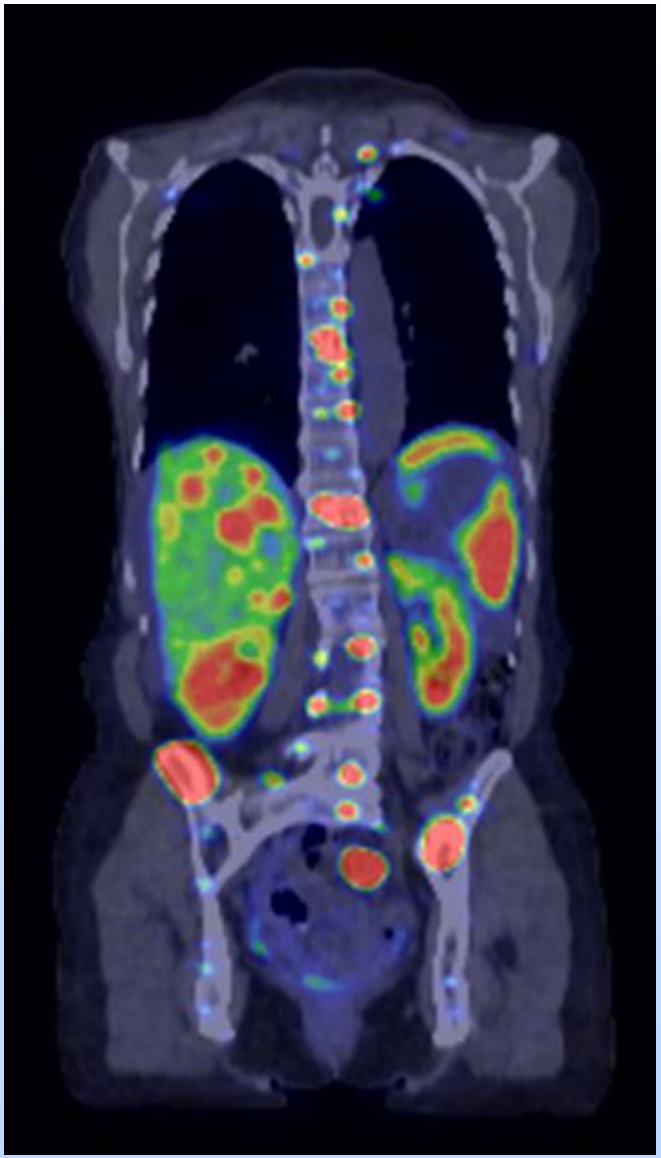
58 year-old man

NET of an unknown primary

Minimal symptoms

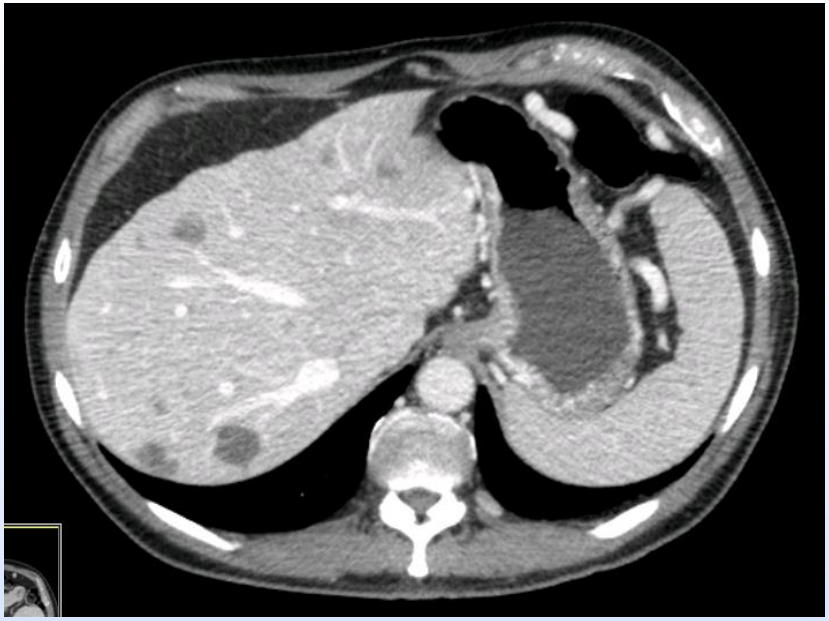
Ga68 PET/CT





Does Everyone Need to be Treated?

- **No!**
- Patients with no symptoms, low tumor burden and low-grade tumors can be observed
- Such patients need close monitoring
- Many go for months or even years without needing therapy



Asymptomatic, low tumor burden, and stable disease	• Observe with markers and abdominal/pelvic multiphasic[a] CT or MRI every 3–12 mo and chest CT (± contrast) as clinically indicated • Consider octreotide[k,y] or lanreotide[k,y]

Observation is an option per the NCCN 2017 Guidelines

Treatment Considerations

Why Do We Treat NETs?

- What are the goals of systemic (drug) therapy?
- **A: To relieve symptoms**
  - Carcinoid syndrome
  - Symptoms from functional pancreatic NETs
  - Symptoms from bulky tumors/metastases
- **B: To prolong the survival of patients**
  - Not all systemic treatments have been shown to prolong survival
  - Be mindful of treatment toxicities
    - It is easy to harm with therapy…
    - Harm can occur in terms of side effects and “financial toxicity”

Do Not Forget!

Each patient is an unique individual and the NETs differ greatly among patients

One size does **NOT** fit all!

Things to Consider Before Starting Therapy

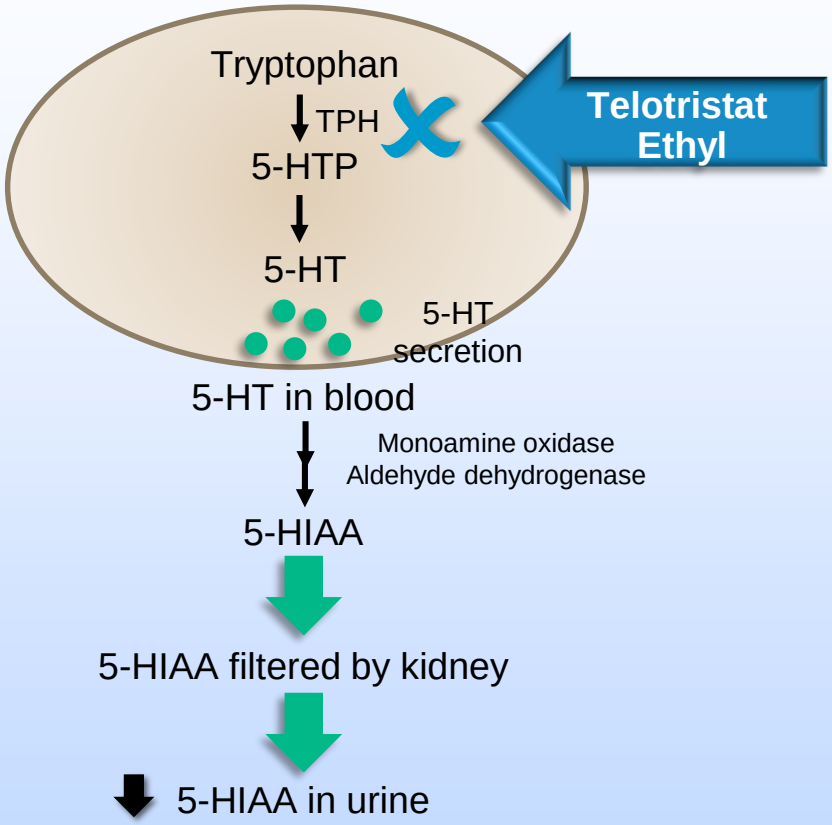
- Is therapy really needed now?
  - Are there troublesome symptoms?
  - Is the tumor growing rapidly?
- Where did this NET start?
  - The origin of the primary is critical
- What is the stage of the tumor?
- What is the grade and differentiation of the tumor (how aggressive is it)?
  - We absolutely need the grade in ALL cases
  - Higher grade tumors are treated very differently

Treatment of Symptoms

- Somatostatin analogs (octreotide and lanreotide)
  - Very effective controlling the symptoms of the carcinoid syndrome
  - Useful to control symptoms of some pancreatic NETs
  - Pancreatic enzyme supplementation needed by some
- Other drugs for symptoms
  - Telotristat (for diarrhea)
  - Everolimus (for hypoglycemia)
  - Ondansetron (for diarrhea)
  - Chemotherapy (for bulky and painful tumors)
  - PRRT…?

New Treatment For Carcinoid Diarrhea

- Serotonin is the main cause of diarrhea in carcinoid syndrome
- Greatly affects quality of life of patients
- A novel oral inhibitor of tryptophan hydroxylase (TPH)
- Telotristat – first in class drug for diarrhea



Systemic Therapy for Small Bowel NETs

Small Bowel NETs – Anti-Tumor Therapy

- Somatostatin analogs (SSAs)
  - Octreotide and lanreotide
  - Objective tumor responses are unusual (<10%) but stability is observed in up to 80%
  - Biochemical responses seen in up to 80%
  - Very well tolerated treatment
- Interferon alpha (IFN)
  - Effective but side effects are troublesome
  - Pegylated IFN may be better tolerated
  - Uncertain role of IFN nowadays

Chemotherapy

- Classic chemotherapy has a very small role **small bowel** NETs
  - Works best in higher grade tumors
  - Very limited activity in lower grade tumors
- Chemotherapy works much better in **pancreatic** NETs
  - CAPTEM (capecitabine and temozolomide)
  - Can be very useful to shrink large tumors causing severe symptoms
  - Can even be used to prepare patients for surgery

Systemic Therapy for Pancreatic NETs (pNETs)

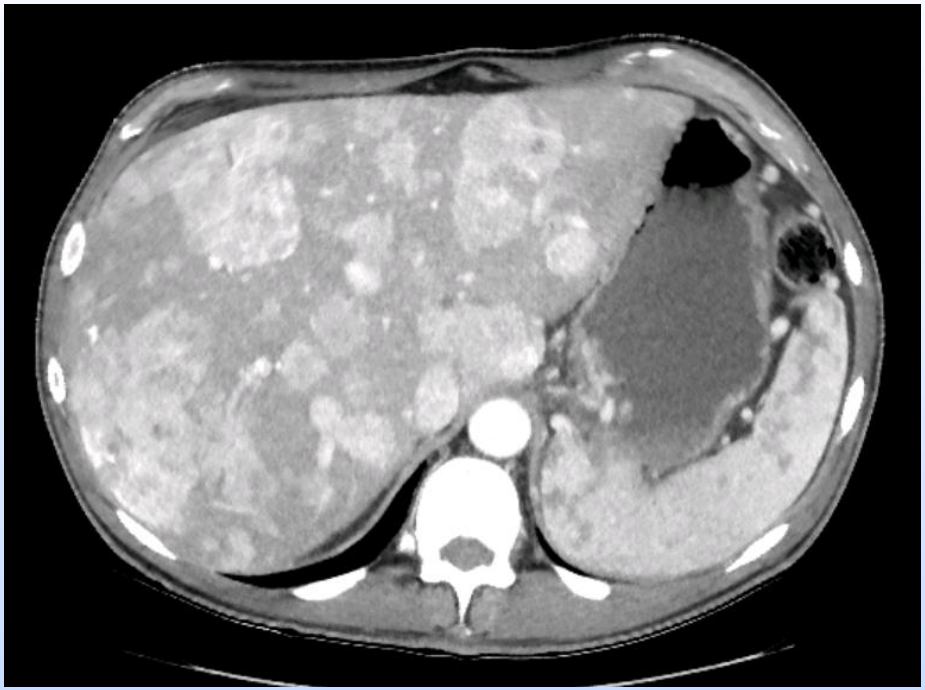
Systemic Therapy for pNETs

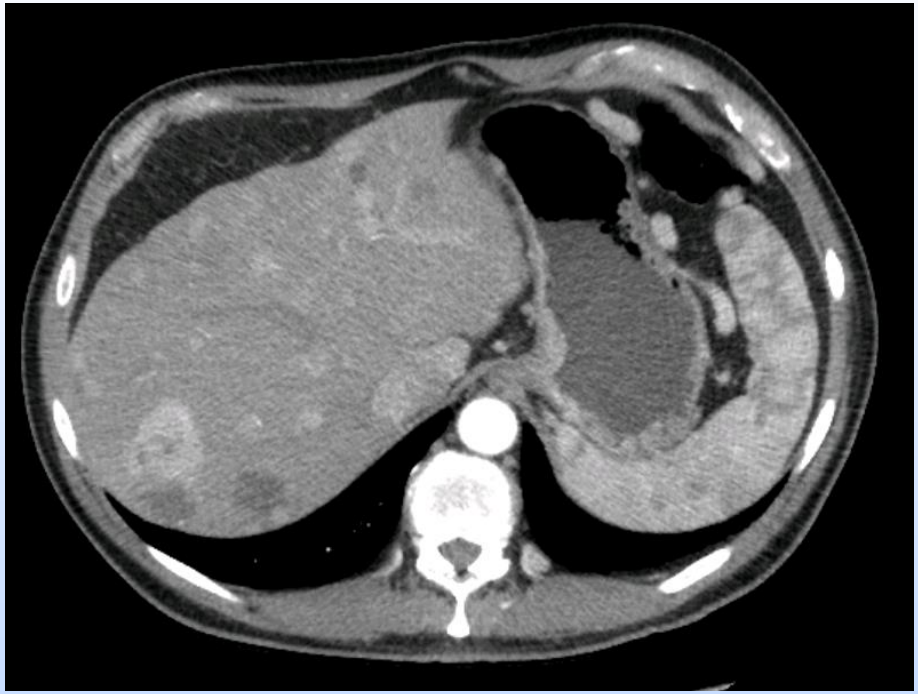
- pNETs are a heterogeneous group of tumors
  - Very variable presentation and prognosis
  - Pay attention to both the grade and differentiation
- Overall, patients with pNETs seem to do worse than small bowel NETs
  - Survival is shorter in patients with pNETs
- pNETs are generally **more sensitive** to systemic therapy than small bowel NETs
- Patients treated at large specialized centers seem to do much better
  - Why is that…?

Systemic Therapy for pNETs

- Octreotide or lanreotide is a reasonable initial therapy
  - Especially if symptoms of hormone overproduction
- Chemotherapy is indicated for symptomatic patients with bulky disease
  - CAPTEM (capecitabine and temozolomide)
- Targeted therapy with either everolimus or sunitinib is also reasonable as initial therapy
- PRRT

CAPTEM is Very Effective for PNETs

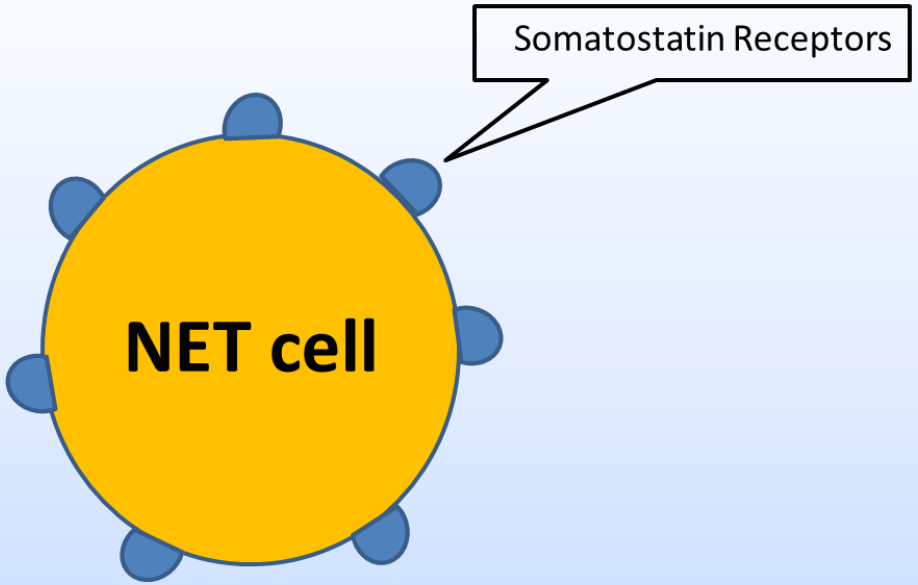




Peptide Radionuclide Therapy (PRRT)

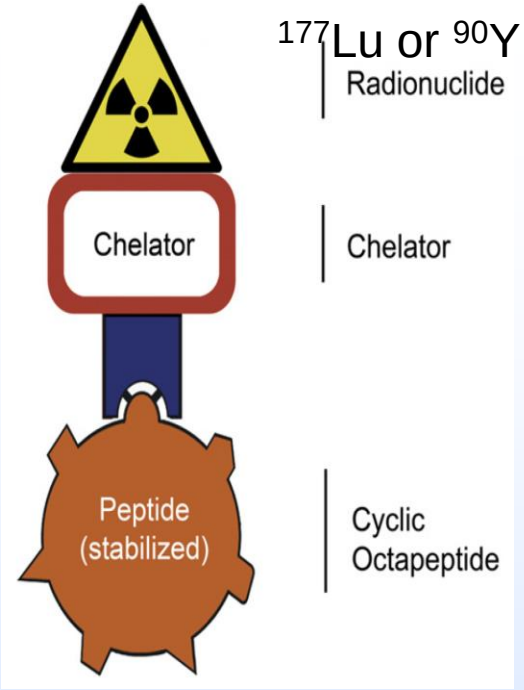
The Rationale for PRRT and Receptor Imaging

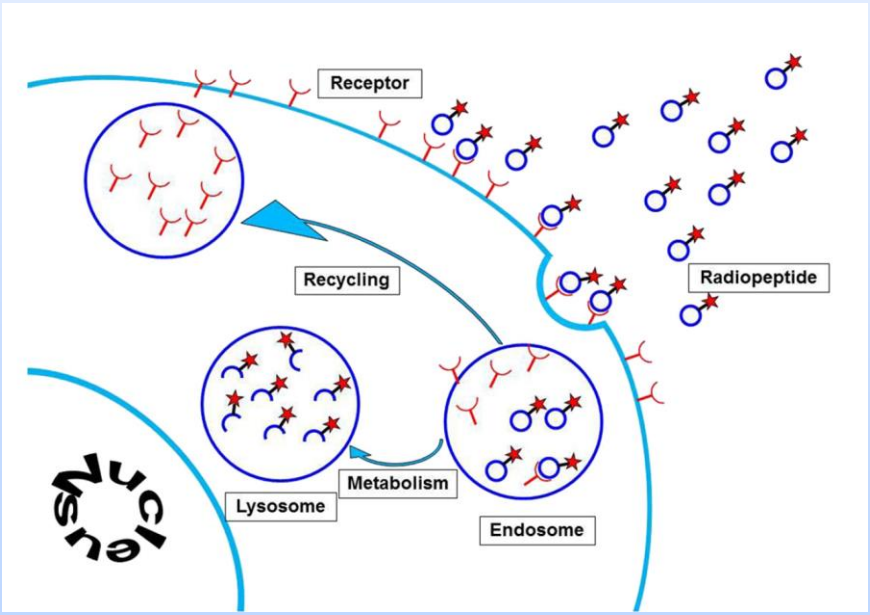
- NET cells have somatostatin receptors
- These receptors can be used to:
  - Take pictures of the tumor
    - OctreoScan
    - Gallium 68 PET/CT
  - Treat it with drugs
    - Octreotide/Lanreotide
  - Treat it with radioactive chemicals
    - PRRT



Peptide Radionuclide Therapy (PRRT)

- Radiolabeled SSA (^{177}**Lu,** ^{90}**Y**,)
  - Radiates tumor cells directly
- The NETs need to express SST receptors
- Objective responses in up to 30% of patients (usually partial responses)
- Well tolerated





MAYO CLINIC
Cancer Center

Kwekkeboom DL, Krenning EP, Hematol Oncol Clin N Am 2016;30;179–191.
Van Vliet et al. Neuroendocrinology. 2013;97:74-85.

What's Going To Happen With PRRT…?

- Not yet approved
- Available but very expensive
- Expecting FDA approval this month
- What will the FDA approval look like?
  - Just small bowel NETs…?
  - All NETs with activity on Ga68 PETor Octreoscan?
  - Something else...?
- Lots of interest within pharma companies

High-Grade (Aggressive) NETs

Poorly Differentiated NETs

- Heterogeneous group of tumors
  - Can be exceptionally aggressive
  - Survival without therapy measured in weeks (in some cases – others much more slow growing)
  - Respond well to chemotherapy but quickly come back once therapy is stopped
  - Sometimes surprisingly slow growing
- Access to an experienced pathologist is crucial
  - We need to know the tumor grade (as defined by Ki67) and the differentiation (how does it look in the microscope?)

Sorbye H et al. Ann Oncol. 2013;24:152-160.
Sorbye H et al. Cancer. 2014 15;120:2814-23.

What's on the Horizon…?

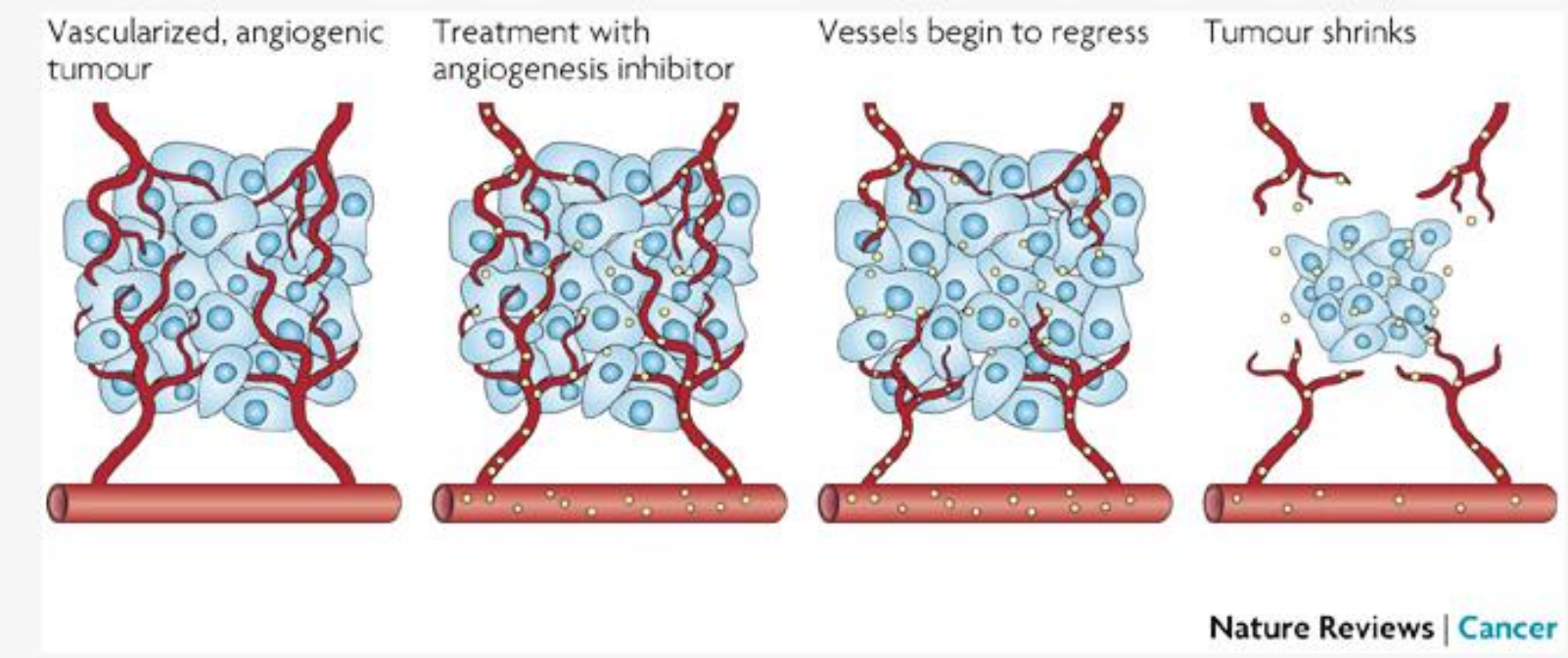
Targeted Therapy is Here to Stay…

- We have reached the limit with old-fashioned chemotherapy
- Advances in drug therapy will likely be in the form of targeted therapy (including immune therapy)
- There are several attractive targets
  - Formation of new blood vessels
  - Specific targets in the growth machinery of the tumor cells
  - Your own immune system

Targeting Blood Vessels

- Tumors need to make their own blood vessels to be able to grow

- Angiogenesis
- NETs are very rich in blood vessels



Immune Therapy

- A broad term that applies to many different treatments
  - Stimulation of the immune system
  - Vaccine therapy
- Immune therapy is currently used for several different cancers
  - Melanoma and lung, kidney, bladder cancer
- The most promising approach is stimulation of the immune system with drugs
  - Taking the brakes off the immune system
  - The immune system can be “trained” to recognize cancer cells

Immune Therapy

- Considerable interest in immune therapy for NETs
- No large studies completed yet
- Anecdotal evidence suggest there may be some effect
- Once clinical trial recently completed accrual and multiple others are either ongoing or soon to be opened
- We need solid evidence of efficacy prior to using immunotherapy for NET patients

Personalized Therapy

- We can now do extensive evaluation of mutated genes that are important for cancer growth
  - Whole genome sequencing (scanning all genes in the tumor) is still very expensive
  - Commercially available platforms allow for sequencing of dozens to several-hundred genes
    - Less expensive and faster
    - Focuses on commonly mutated genes
  - If a mutated gene is found, we may be able to pick effective therapy
    - Treatment tailored to a particular tumor
  - Some mutations predict prognosis

Problems With Personalized Therapy

- There is no guarantee that we will find a mutation that we can act on
  - Not all mutations have a known role
  - Mutations of unknown significance
  - We often come up empty handed
- What if we find a mutation?
  - Is there a treatment (drug) available?
    - This may be a drug used for another kind of tumor
  - If there is, can we get even the drug?
    - Who will pay for it (many of the drugs are very expensive)

Personalized Therapy of NETs

- Not a reality yet for most NET patients
- There are no frequent mutations in small bowel NETs
  - Most individual mutations are uncommon
  - No recurrent theme
- Pancreatic NETs are more likely to have mutated genes
  - But there are still no available drugs for most of those mutations
- There is a great need for better clinical trials
  - We need new trial designs (for example basket studies)
  - Good review of such studies in the NY Times recently
    - http://www.nytimes.com/2015/02/26/health/fast-track-attacks-on-cancer-accelerate-hopes.html

Personalized Therapy of NETs

- It is the future (or at least a part of it)
- With better understanding of the biology of individual tumors, the better we will be able to target tumors with personalized therapy
- There is a knowledge explosion in tumor biology
  - Advances in understanding cancer behavior and therapy are advancing rapidly
  - We may eventually have drugs for most mutations
  - We are still a bit behind when it comes to available drugs that are effective

What About Alternative Therapy?

- This is a very common question
- There are no good trials to guide us
- Most alternative/complementary therapies have not been studied at all in a scientific way
  - Many products make very dubious claims
  - There is little or no regulation of these compounds
  - Some may have significant interactions with other medications
  - Some are clearly harmful
  - Most are probably harmless

The Team Approach at Mayo

The Whole is Greater Than the Sum of its Parts

- Patients with NETs are ideally managed by a team approach
- While there is usually a key care provider most involved, there is a whole team behind the scene
- Team members are “pulled in” as needed
  - Never more appropriate than when planning surgery, embolization therapy or PRRT

The NET Team Approach

- What happens before the first visit?
  - A team member reviews outside documents before the consultation is set up
    - What has already been done?
    - What needs to be set up at the consultation
  - The tumor specimen is requested and reviewed by specialist pathologist
  - All available outside scans are electronically uploaded
    - If more scans are needed, especially “NET-specific” scans, we will order those
    - Basic laboratories

The NET Team Approach

- What happens at the first visit?
  - You will meet with a NET team member
    - Usually a member of the Medical Oncology group
    - Sometimes NET patients are first seen by other specialties, especially Surgery and Cardiology
  - The medical history, past and present treatments and current problems are reviewed
    - Are there particular reasons for this visit (recent diagnosis, second-opinion, refractory symptoms, interest in trials etc…)?
  - Additional tests are discussed if needed
  - Treatment plans discussed
    - The goal is to have a plan that is effective and convenient
    - Co-operation with primary/community oncologists is crucial
    - Tumor Board discussion as needed

The Mayo Medical Oncology NET Team

Providers/Clinicians in the NET Clinic

Timothy Hobday, M.D.

Thor Halfdanarson, M.D.

Rachel Eiring, P.A.-C.

Diane Briggs Fabin, R.N.

The Mayo NET Team is actually much larger than this!

The Mayo Medical Oncology NET Team

MDs

Axel Grothey
Harry Yoon
Frank Sinicrope
Aminah Jatoi
Wen Ma
Sakti Chakrabarti






Steven Alberts
Henry Pitot
Amit Mahipal
Robert McWilliams
Joleen Hubbard

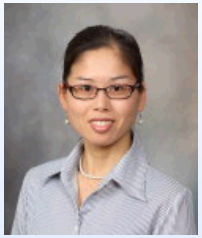


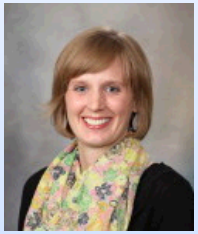


NPs/APRNs

Mindy Hartgers
Jessica Mitchell
Akiko Okano
Erin Deering
Anna Schwecke

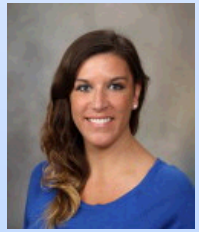
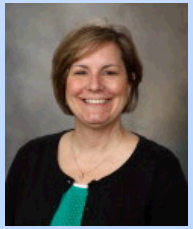






RNs

Ashley Neve
Jackie Reitz
Alison Jacobson

MAYO CLINIC
Cancer Center

The Mayo Surgical Oncology NET Team

David Nagorney, M.D.

Michael Kendrick, M.D.

Mark Truty, M.D.

Rory Smoot, M.D.

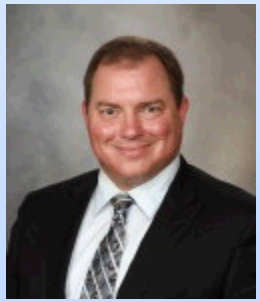
Sean Cleary, M.D.

Travis Grotz, M.D.

Interventional Radiology

James Andrews, M.D.

Chad Fleming, M.D.



David Woodrum, M.D.

MAYO CLINIC
Cancer Center

The Mayo Carcinoid Heart Disease Team

Cardiology

Heidi Connolly, M.D.

Patricia Pellikka, M.D.

Allen Luis, M.D.

Cardiac Surgery

Hartzell Schaff, M.D.

The Mayo Endocrine Oncology Team

Keith Bible, M.D., Ph.D.

Ashish Chintakuntlawar, M.D., Ph.D.

Mabel Ryder, M.D.

John Morris III, M.D.

MAYO CLINIC
Cancer Center

The Mayo Lung NET Team

Medical Oncology

Julian Molina, M.D., Ph.D.

Alex Adjei, M.D., Ph.D.

Kostas Leventakos, M.D.

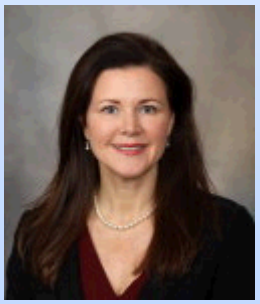
Aaron Mansfield, M.D.

Randolph Marks, M.D.

Thor Halfdanarson, M.D.

Thoracic Surgery

Dennis Wigle, M.D., Ph.D.



Shanda Blackmon, M.D.

Stephen Cassivi, M.D.

Francis Nichols, M.D.

Robert Shen, M.D.

MAYO CLINIC Cancer Center

Other NET Team Members

- Gastroenterology
  - Advanced Endoscopy
- Diagnostic Radiology
- Pulmonary Medicine
- Radiation Oncology
- Scheduling Office
- Pathology
- Physical Medicine and Rehabilitation
- Endocrinology and Nutrition
- Clinic Assistants (CAs)

And, of course, all the other members not mentioned…

New Appointments

MAYO CLINIC
Cancer Center

Appointment Office: 507-538-3270