Patient Care Conference

March 6, 2020

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Neuroendocrine Tumors

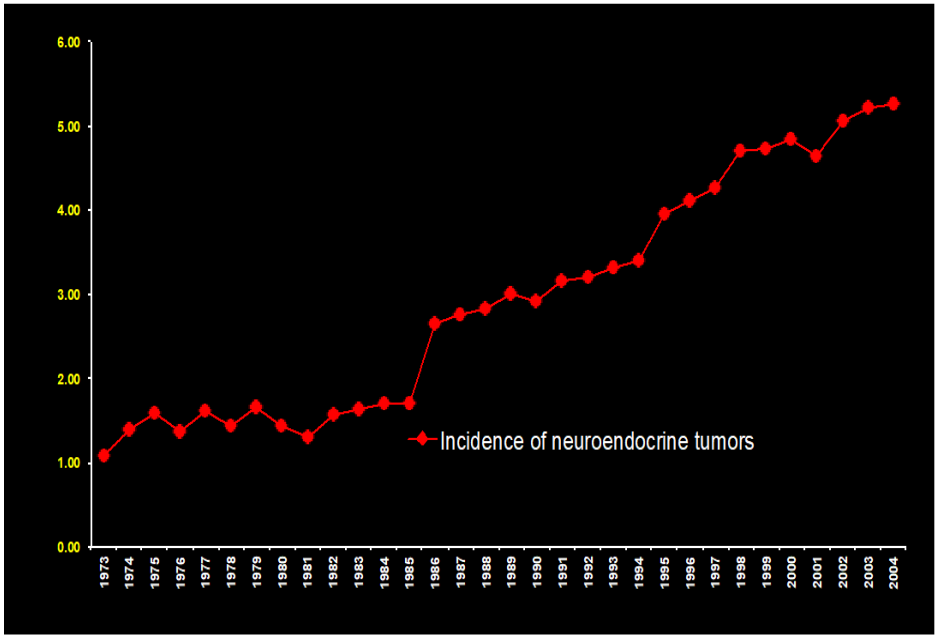
- Second most prevalent cancer of the GI tract behind colorectal cancer[1]
- Over 170,000 patients are living with NETs in the United States
- 6-fold increase in incidence over 4 decades
- Principles of care are different/unique compared to other solid tumors

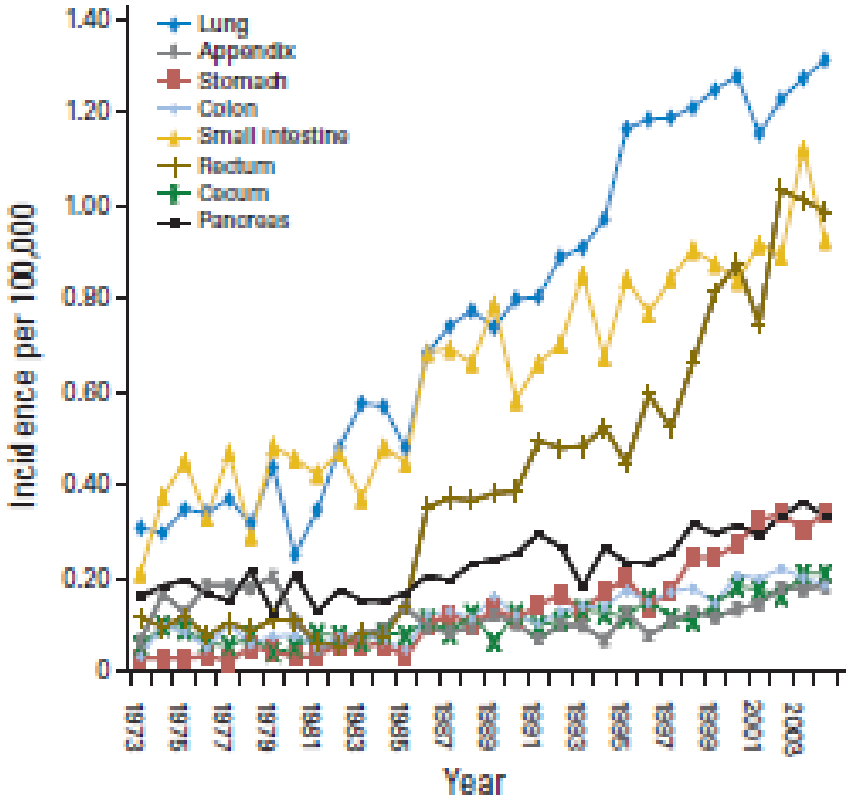
Yao JC et al. One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:18:3063–72.

Dasari A et al. Trends in the incidence, prevalence and survival outcome in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335-42

Incidence of Neuroendocrine Tumors Over Time is Increasing

Analysis of SEER database (1973–2004)

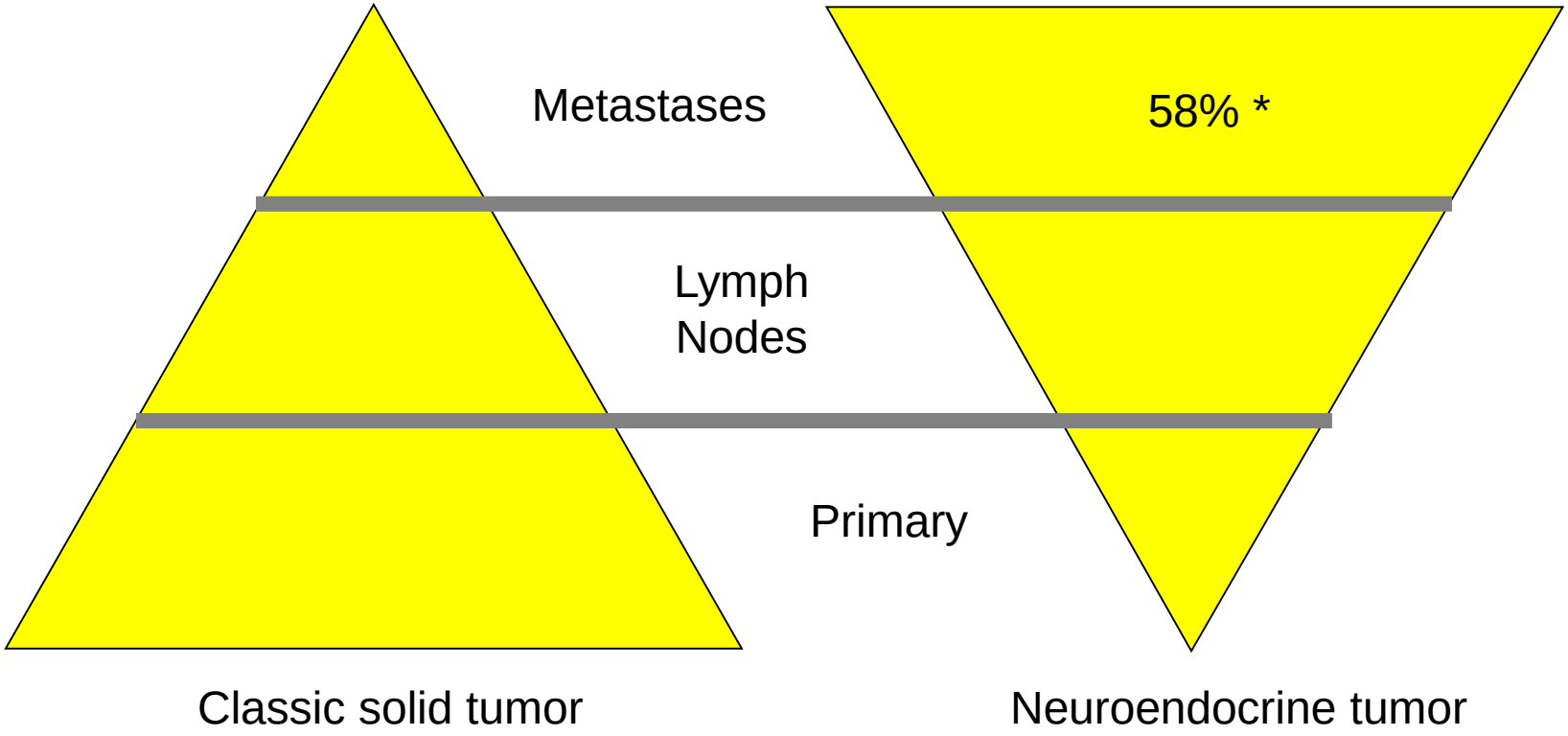




Yao JC et al. One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26(18):3063–72.

Pommier's Classic vs NET Paradigm

(excludes pheo/paras, some pNETs)



** Singh S et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2016;2:43-53*

NETs: Three Patterns of Presentation

1. Hormonal syndrome
   Need to put 2 and 2 together (requires expertise)
2. Tumor symptoms (from growth)
   Usually present late (with mets)
3. Asymptomatic (incidental finding)
   Locoregional (resectable) vs. Widespread

Early diagnosis has prognostic implications as surgery is the **ONLY** curative treatment modality

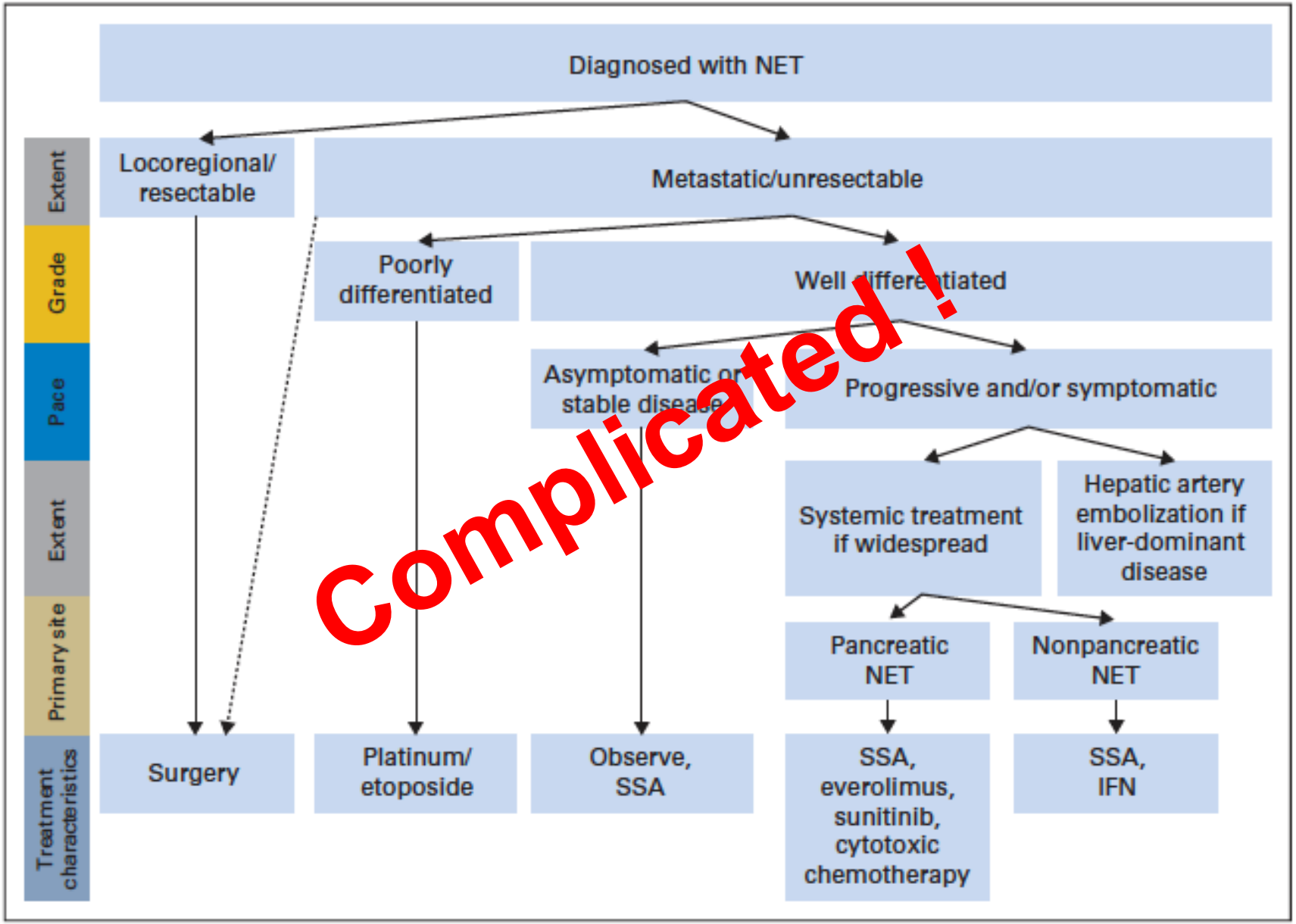
Requires astute physician with a high index of suspicion (mean delay 5-7 yrs)

Functional NET Syndromes

- Carcinoid syndrome
  - Flushing, diarrhea, wheezing, pellagra, cardiac disease
- Zollinger-Ellison syndrome (Gastrinoma)
  - Gastric acid hypersecretion (pain, ulcers, diarrhea)
- Insulinoma Syndrome
  - Neuroglycopenia, sympathetic overdrive, obesity
- Glucagonoma
  - hyperglycemia, rash (MNE), anemia, hypoaminoacidemia, weight loss, thromoboembolism, glossitis
- VIPoma
  - watery diarrhea, hypokalemia, achlorhydria and others (hyperglycemia, hypercalcemia, flushing)
- Others:
  - ACTHoma – Cushing's syndrome
  - GRFoma - acromegaly
  - Somatostatinoma – hyperglycemia, steatorrhea, gallstones
  - Rare syndromes (calcium, erythropoeitin, etc)

Management Principles

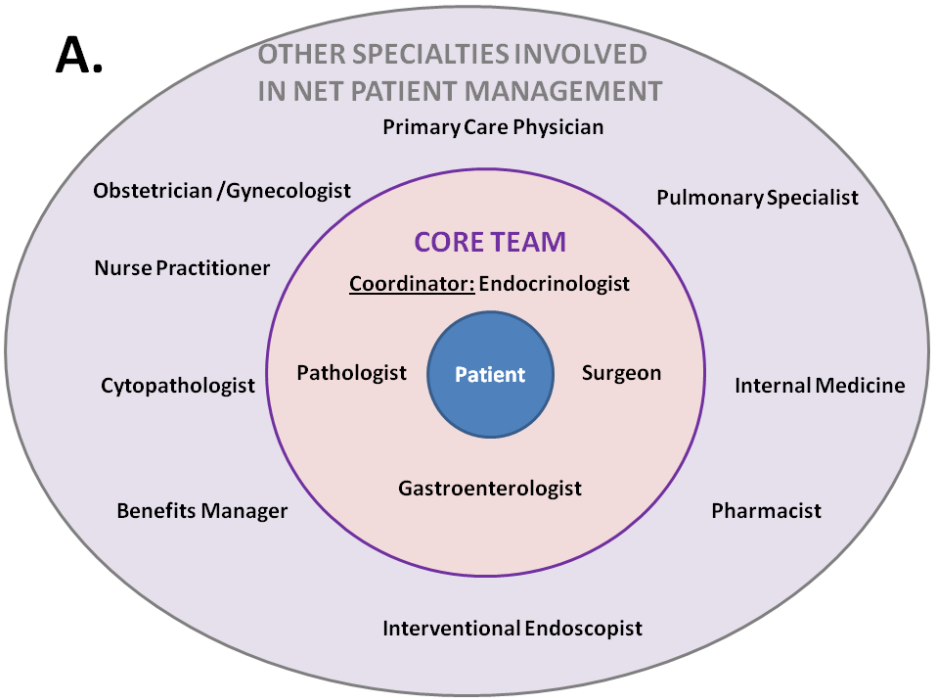
- Confirm the diagnosis
- Control the hormonal syndrome (if present)
- Determine MEN-1 status
- Determine extent of disease
- Consider surgery
  - For cure (if possible)
  - For debulking (if not)
- Long term management
  - Hormonal syndrome (if present)
  - Growth

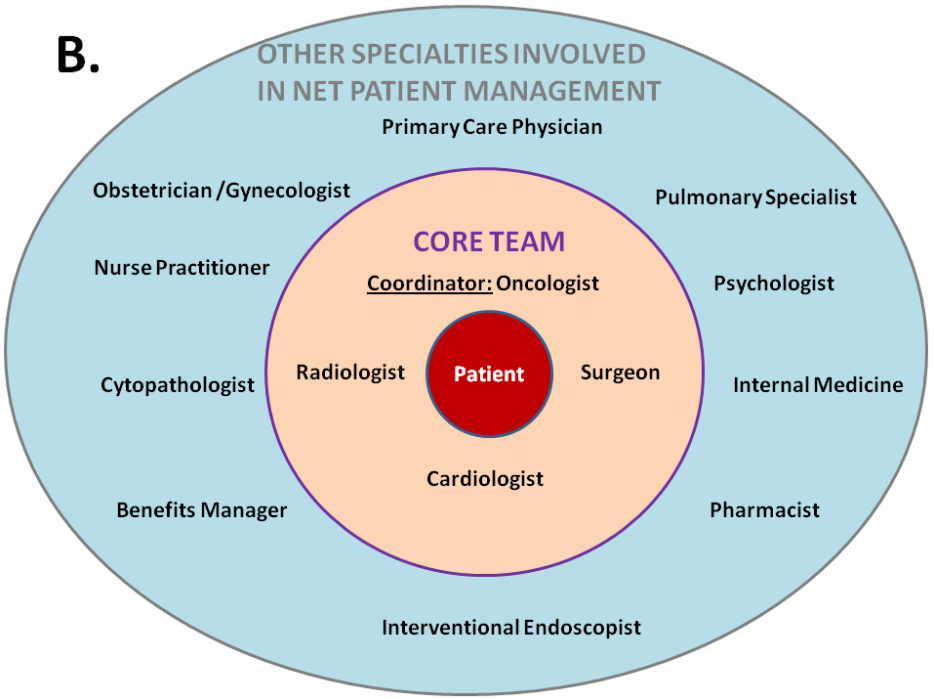


Kunz P, J Clin Oncol 33:1855-1863

Multidisciplinary Care is Ideal

- Many options and no standard algorithm exists (therapy should be individualized)
- Tumor Board is **ESSENTIAL** component
- Flexibility is **KEY**





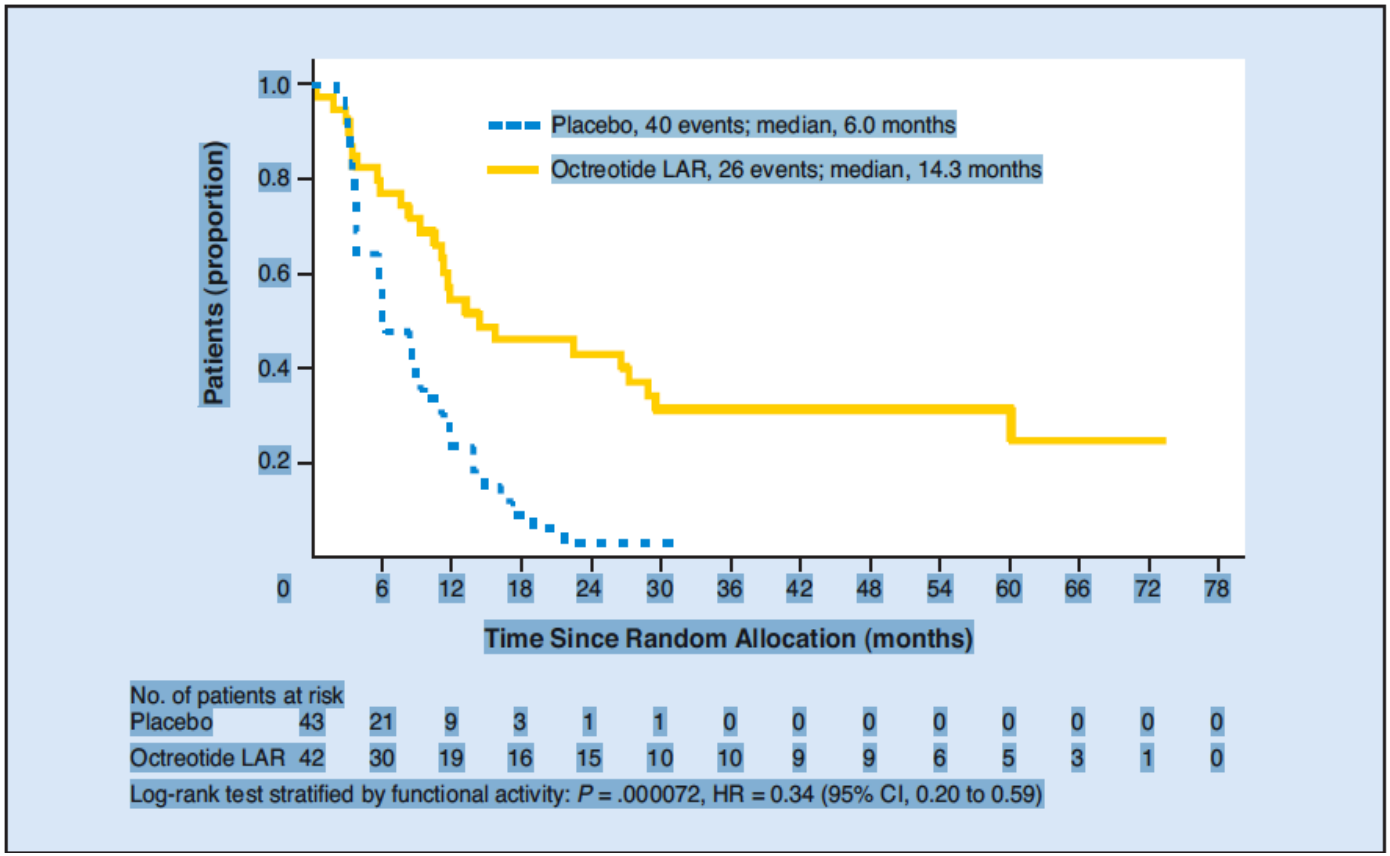
WHAT ABOUT PRRT???

Thera(g)nostics

A treatment strategy that combines therapeutics with diagnostics.

It associates both a diagnostic test that identifies patients most likely to be helped or harmed by a new medication, and targeted drug therapy based on the test results

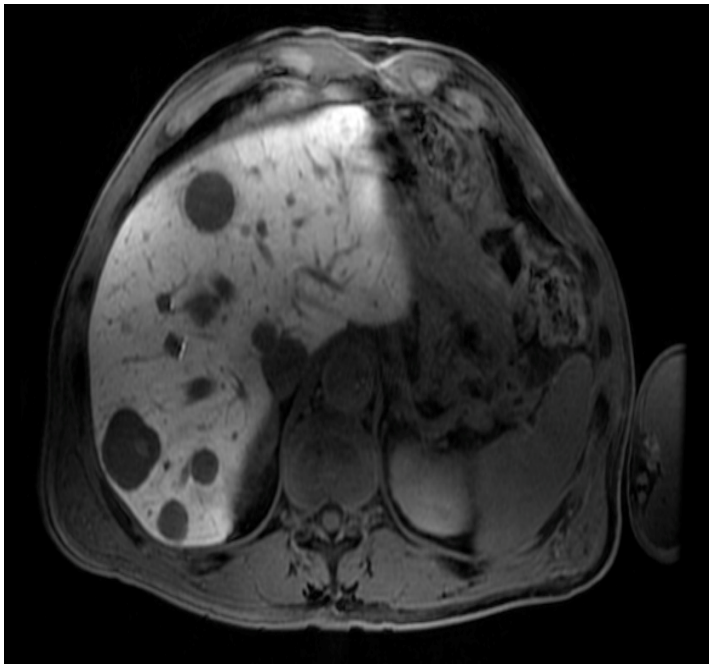
PROMID: Time to Progression

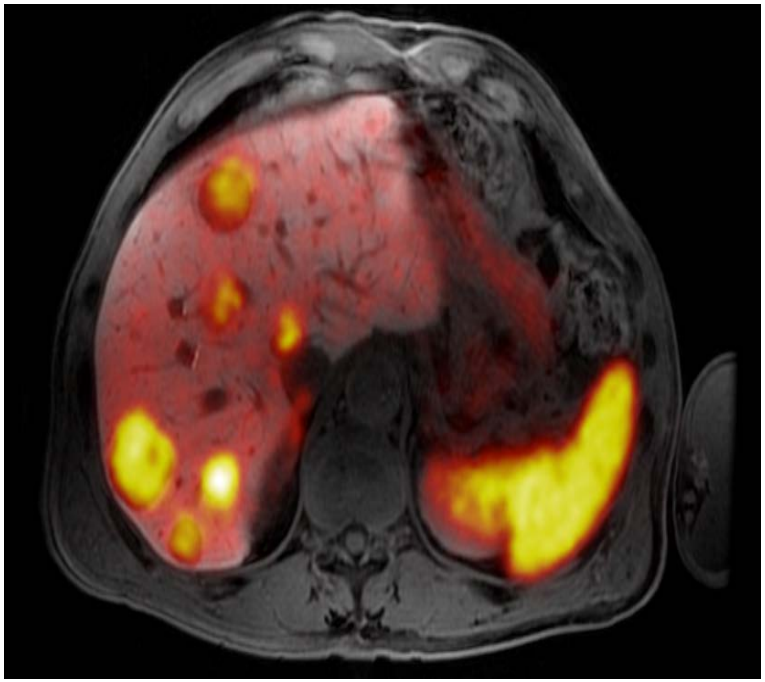


CLARINET (Lanreotide) trial with similar outcome

Rinke A, et al. J Clin Oncol 2009;27:4656-63
Caplin M et al. Clarinet NEJM

Gallium Dotatate PET CT



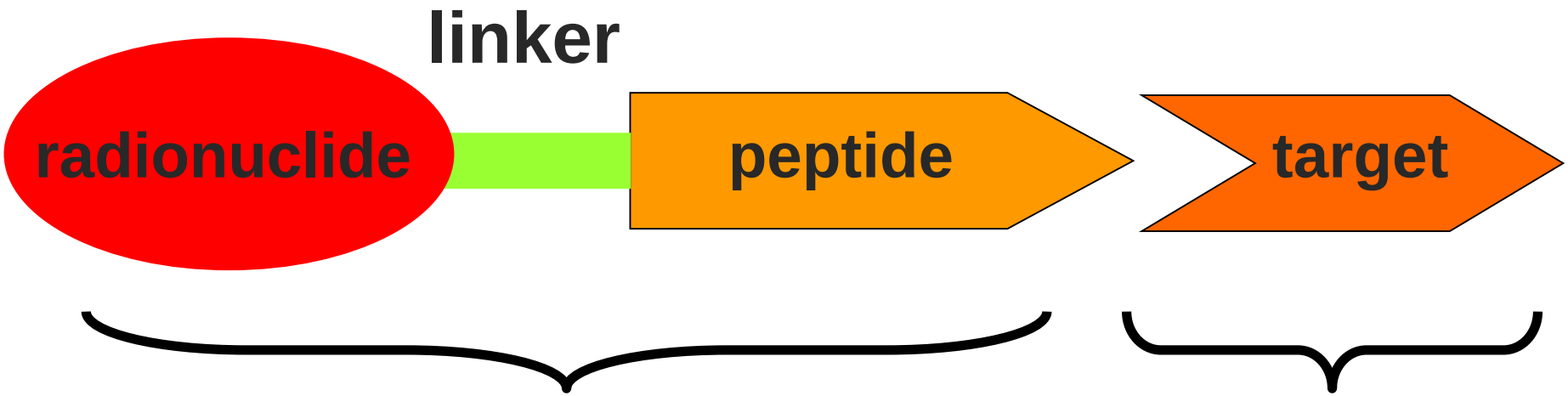


Courtesy Thomas Hope, MD

Peptide Receptor Radiation Therapy (PRRT)

Somatostatin-analog linked Radiopeptide

Somatostatin Receptor



Netter 1: Progression-Free Survival

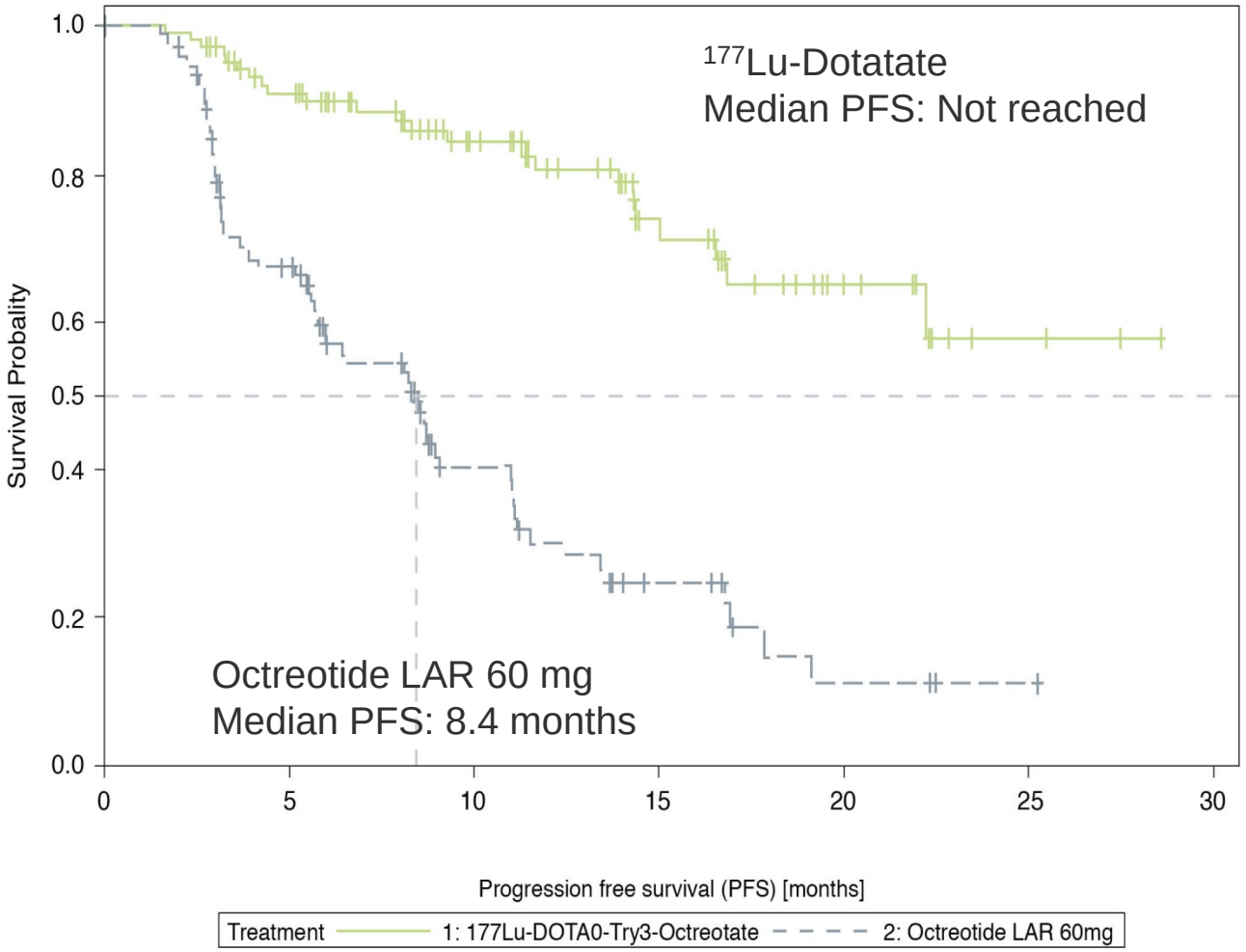
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm
≈ 40 months



Managing the Effects of Therapy

- Pancreatic surgery (Distal or Whipple's)
  - Pancreatic insufficiency
  - Dumping syndrome
  - Diabetes
  - Immunity (spleen)
- Terminal ileal resection
  - B12 deficiency
  - Bile Salt Diarrhea
  - Overgrowth
- Somatostatin Analogs (SSAs)
  - Gallstones
  - Steatorrhea
  - Dysmotility
  - Diabetes
- Others
  - Adhesions
  - Anemia
  - Hepatorenal fn.

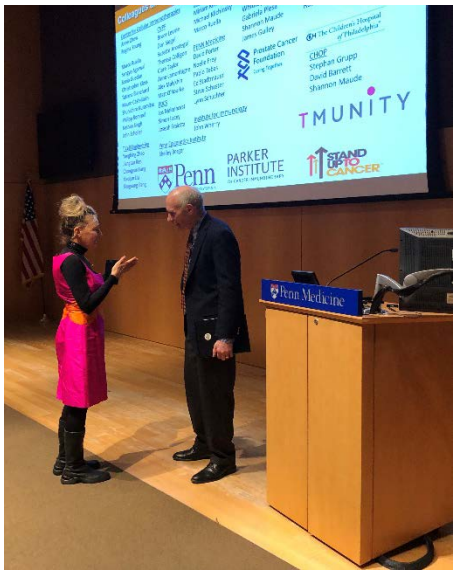
The Extended NET Community

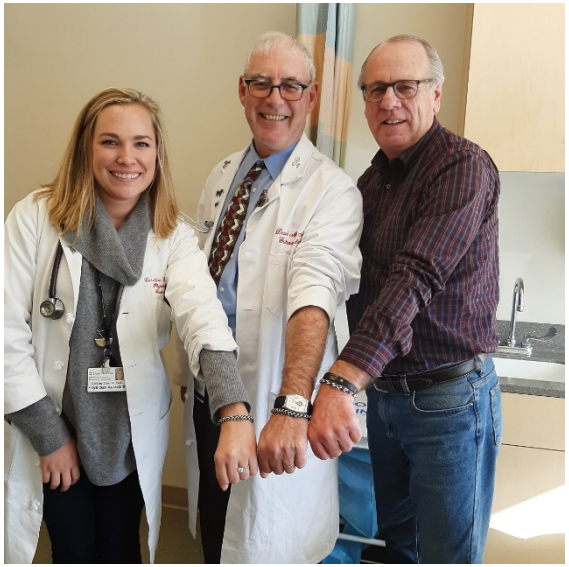
- Even widely metastatic NETs should be considered a chronic disease state (i.e., aim to live **with** the disease)
- Increasing focus on the non-medical aspects of care (i.e., support services, financial toxicity, support groups, educational activities, etc)
  - Run for the Stripes (Andy Steinfeld, Lori & Dave Canzanese)
  - Patient support meetings (Diann Boyd)
  - Navigator expansion (Bonnie Bennett and Diann Boyd)
  - Yearly patient care meeting (live streamed)
  - Professional provider organizations (NANETS, ENETS)
  - Other support organizations
    - Carcinoid Cancer Foundation –Grace Goldstein
    - NETRF, NCAN, HNF, INCA

NET Awareness Day 11/10

Run for the Stripes

CAR T, Azedra, etc.





Conclusions

- NETS present in varied ways but have many features in common and differ significantly from other solid malignancies
- Clinical management is complicated and requires attention to tumor growth, pattern of presentation, syndromic symptoms and side effects of therapy
- Surgery is the only curative therapeutic modality (also effective for debulking, as is liver directed therapy)
- SSAs are drugs of choice for syndromic management (except ZES/insulinoma) and initial tumor growth
- No clear algorithm yet for regional (debulking/LDT) or systemic therapies (chemo, small molecules, PRRT)
- Multidisciplinary care is essential
- NETs are **CHRONIC** conditions that need a holistic approach

Management of Pheochromocytoma & Paraganglioma

March 6, 2020

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Perelman School of Medicine at the University of Pennsylvania

Pheochromocytoma/Paragangliomas

- Pheochromocytoma/Paragangliomas (PCC/PGL) are rare neuroendocrine tumors
- Approximately 1000 new cases annually in the US
- We are seeing an increasing number of patients due to identifying more family members with inherited asymptomatic disease
- Inherited mutations are autosomal dominant
  - A 50% chance of inheritance for every pregnancy
- Each patient is unique and treatment needs to be individualized

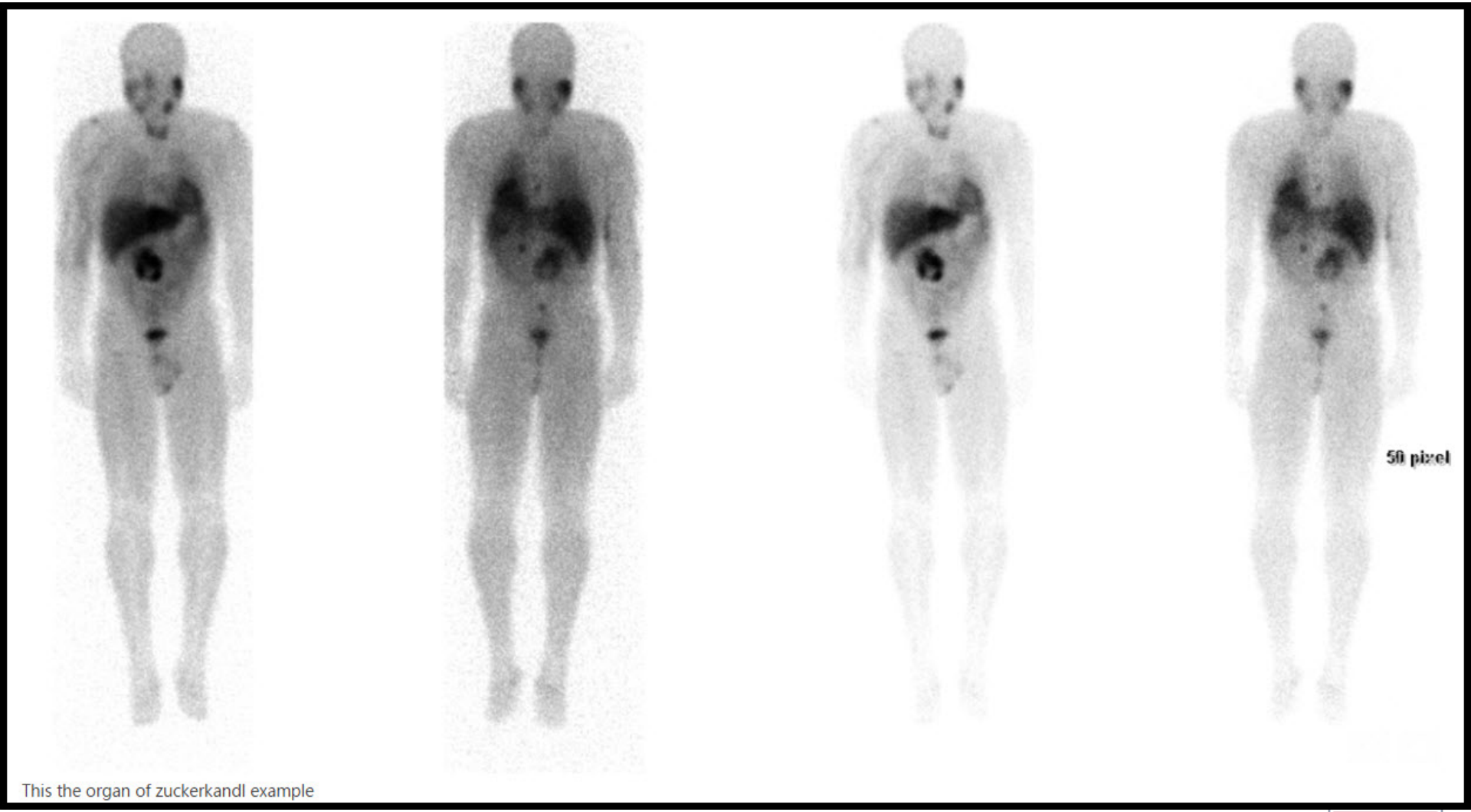
PCC/PGL Clinical presentation

- Classic – labile hypertension, palpitations, headaches and sweating
- Patients can have minimal symptoms and BP is not always elevated
- Tumor size does not correlate with symptoms
- Early diagnosis has prognostic implications because surgery is the **ONLY** curative treatment modality

Management Principles

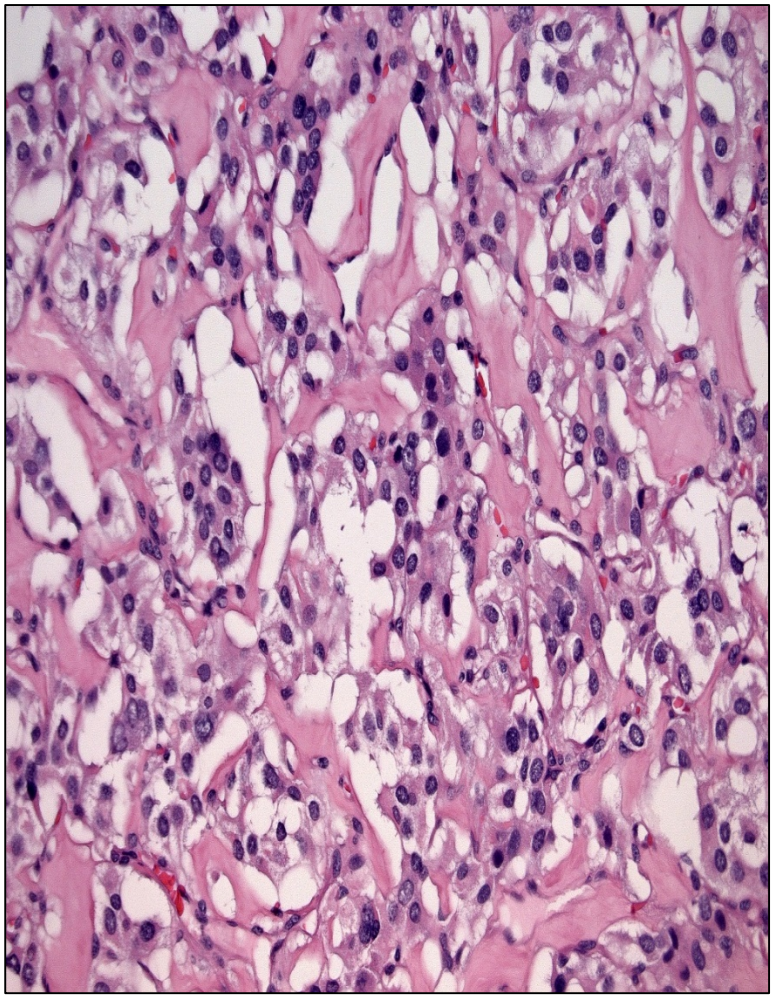
- Confirm the diagnosis
- Control the BP before and during surgery
- Surgery is the definitive treatment
- Can use adjunctive treatment with MIBG, chemotherapy and newer experimental therapies

MIBG scan of paraganglioma in organ of Zuckerkandl

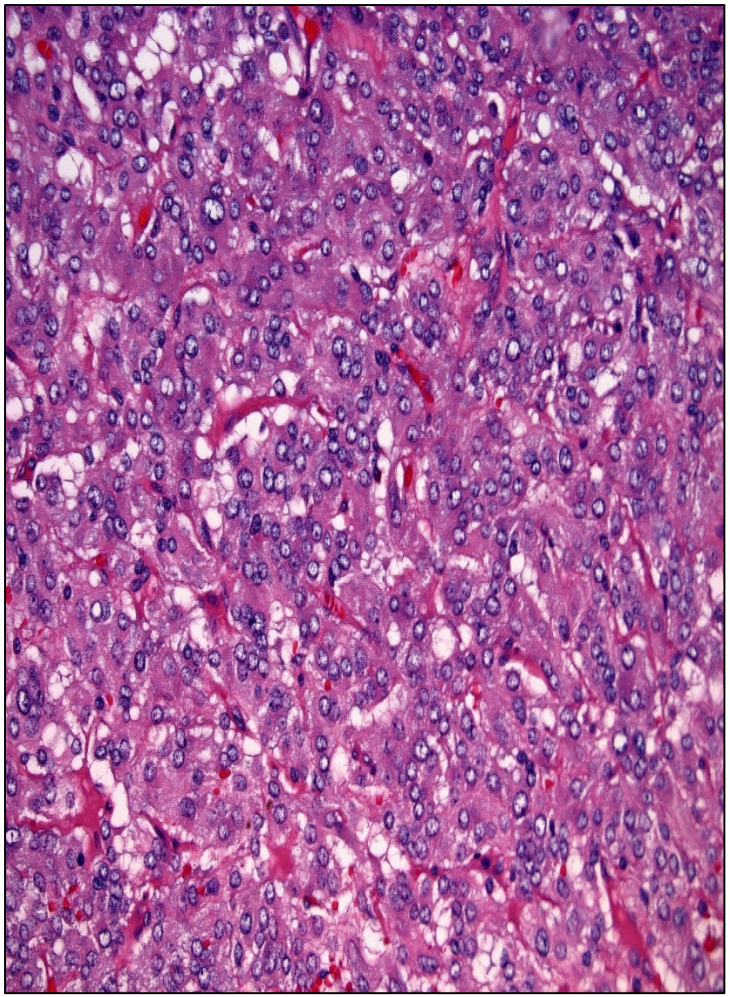


New therapies with Azedra, PRRT

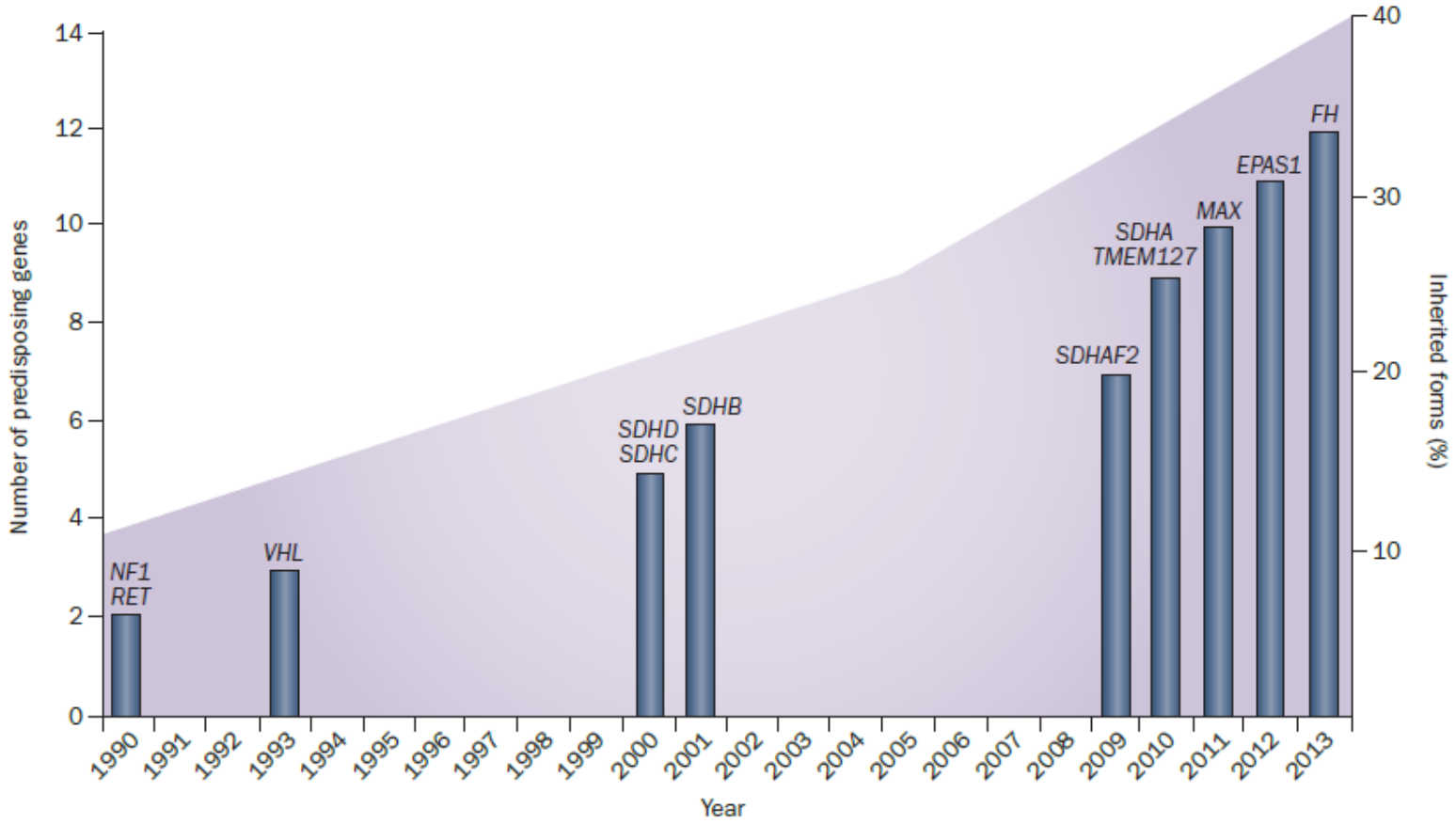
Paraganglioma



Pheochromocytoma



Genetics of PCC/PGL

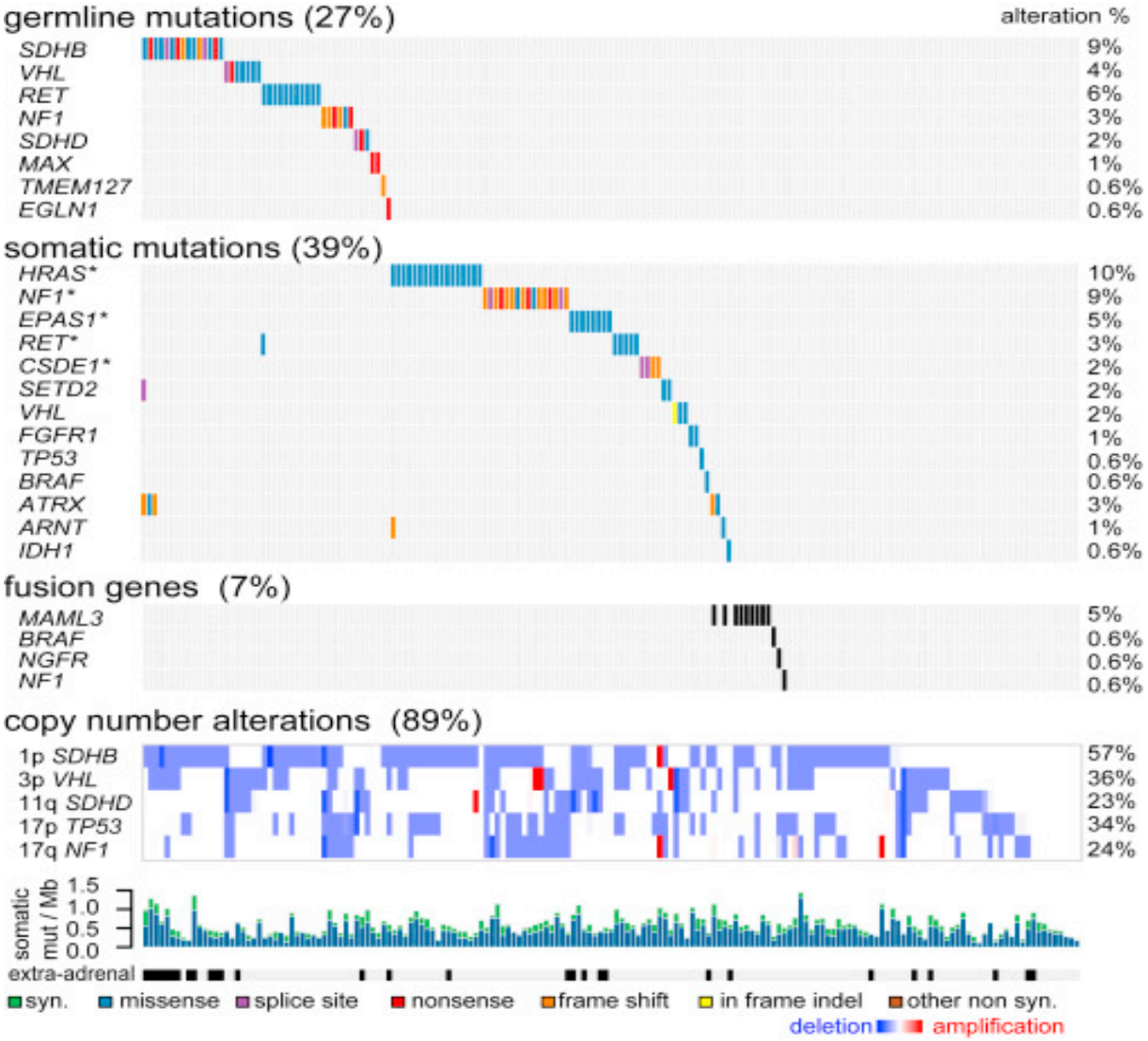


Favier et al. *Nat Rev Endocrinol.* 2015.

Genetics of PCC/PGL

- Now over 13 genetic mutations identified to be associated with PCC/PGL
- Screening family members -> identifying more asymptomatic patients
- Leads to early disease detection and better clinical outcomes
- About 30-40% of patients have a genetic mutation without a positive family history
- Very important that ALL patients get genetic testing

The Cancer Genome Atlas (TCGA): Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma



.**Fishbein L**, et al. Cancer Cell. 2017 Feb 13;31(2):181-193.

Future Directions

- Currently few options for treating metastatic disease
- Azedra – FDA approved in 2018
- Diversity of single drivers among PCCs/PGLs makes these tumors a model for future targeted therapy
- Potential for multi-modality treatment with immunotherapy or targeted therapies

Conclusions

- Important to have a multidisciplinary approach and be treated at a specialized center dedicated to care of PCC/PGL patients
- Individualize treatment
- Genetic testing for all patients
- Surgery is only curative treatment
- Annual lifetime screening is essential after surgery
- New promising therapies for recurrent/metastatic disease