Penn NET Center – Overview of Clinical and Basic Science Research

March 6th, 2020

Bryson W. Katona, MD, PhD
Division of Gastroenterology

Heather Wachtel, MD
Division of Endocrine and Oncologic Surgery

Perelman School of Medicine
University of Pennsylvania

Disclosures

- Bryson Katona
  - Consulting: Exact Sciences
  - Paid travel: Janssen
  - Clinical trial/study funding: Janssen, Immunovia, Epigenomics

- Heather Wachtel
  - None

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

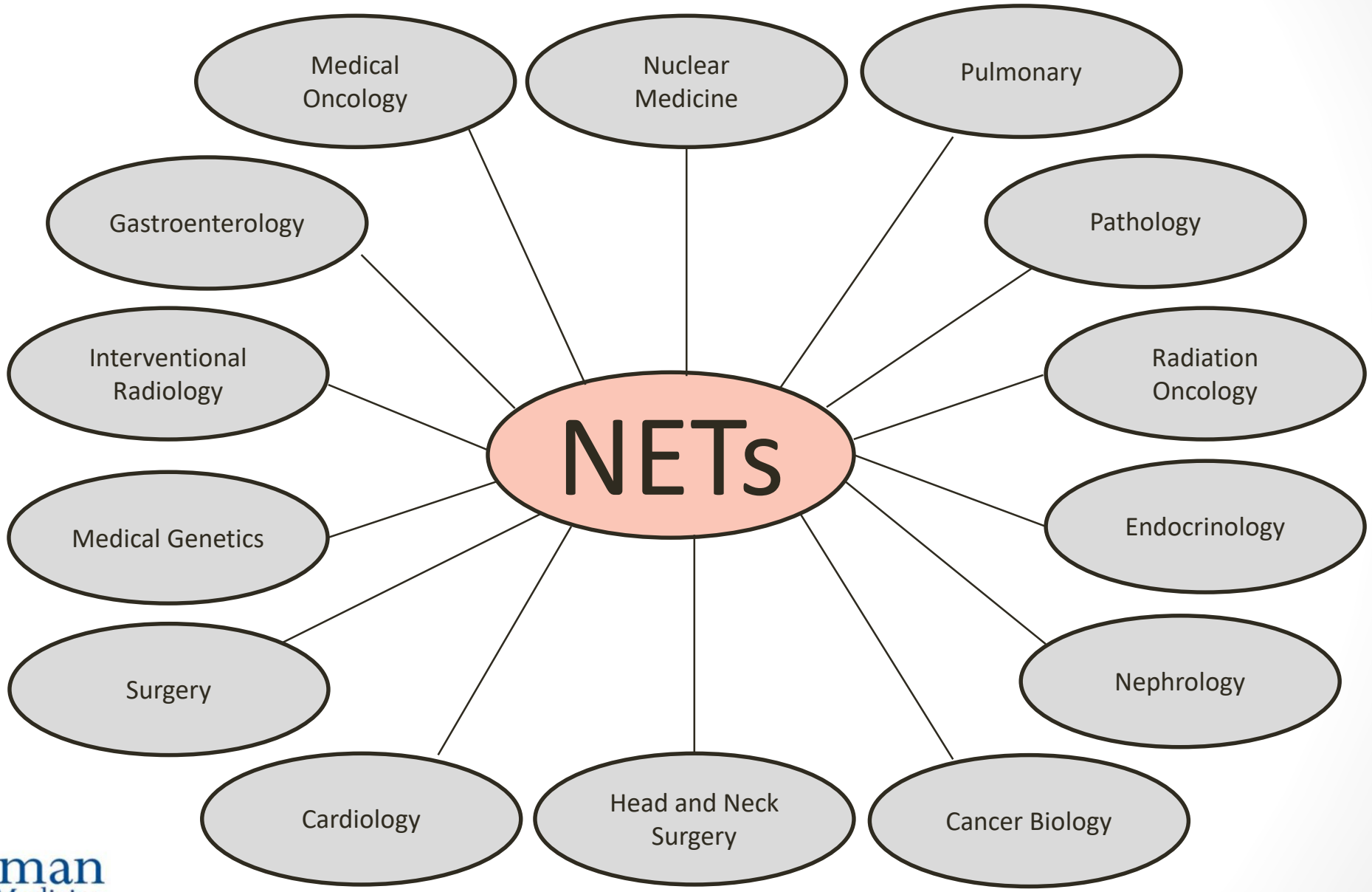
Perelman School of Medicine
University of Pennsylvania

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Perelman School of Medicine
University of Pennsylvania

PENN NET Center Overview



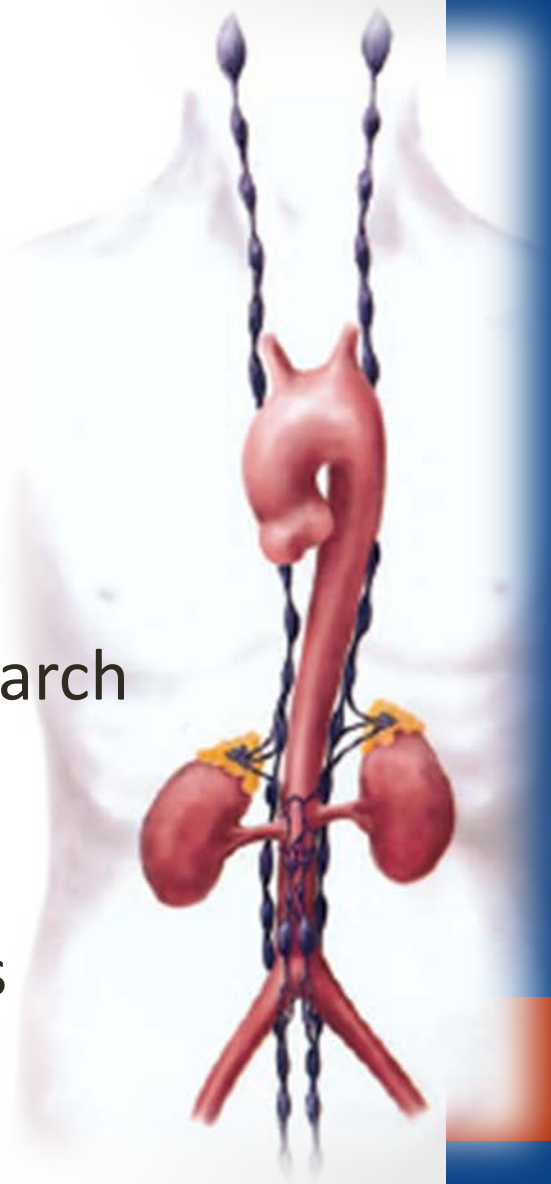
Perelman School of Medicine
University of Pennsylvania

Challenges associated with research in NETs

- Rarity and heterogeneity of NETs
- Few researchers compared to other fields
- Limited funding
- Limited/poor models for studying NETs in the lab

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
  - Database and tumor collection
  - Basic science and translational laboratory research
  - Clinical studies and trials
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)



Perelman School of Medicine
University of Pennsylvania

IT STARTS WITH YOU



Pheochromocytoma/Paraganglioma

Patient samples | Research | Novel Therapies

- Patients consented:

  402

- Banked DNA samples:

  335

- Tumor samples:

  91



Perelman School of Medicine
University of Pennsylvania

Pheochromocytoma/Paraganglioma

Patient samples → Research → Novel Therapies

- **Genomic profiles and targeted therapy for malignant PCC/PGL**
  Heather Wachtel, Kate Nathanson
- **Examining modifiers for sporadic and SDHx-related PGL/PCC**
  Lauren Fishbein (UC Colorado), Kate Nathanson
- **DNA methylation in pheochromocytomas and paragangliomas**
  Prodromos Chatzikyriakou, Rebecca Oakey (Kings College, London)
- **Comparison of PASS/GAPP histopathologic scoring of PCC/PGL**
  Heather Wachtel, Lauren Fishbein (UC Colorado)

Pheochromocytoma/Paraganglioma

Patient samples → Research → Novel Therapies

- **Weight changes after PCC/PGL surgery**
  - Heather Wachtel
- **Oncologic associations and penetrance in succinate dehydrogenase pathogenic variants**
  - Heather Wachtel, Kate Nathanson
- **Multi-center study of PCC/PGL identified during pregnancy**
  - Debbie Cohen, Irina Bancos (Mayo Clinic)
- **Multi-institutional study to examine current screening in SDHx pathogenic variant carriers**
  - Kate Nathanson, Lauren Fishbein (UC Colorado)
- Enrollment in American-Australian-Asian-Adrenal Alliance (A5)

Pheochromocytoma/Paraganglioma

Patient samples

Research

Novel Therapies



Perelman School of Medicine
University of Pennsylvania

Efficacy and Safety of High-Specific-Activity I-131 MIBG Therapy in Patients with Advanced Pheochromocytoma or Paraganglioma

Daniel A. Pryma[1], Bennett B. Chin[2], Richard B. Noto[3], Joseph S. Dillon[4], Stephanie Perkins[5], Lilja Solnes[6], Lale Kostakoglu[7], Aldo N. Serafini[8], Miguel H. Pampaloni[9], Jessica Jensen[10], Thomas Armor[10], Tess Lin[10], Theresa White[10], Nancy Stambler[10], Stuart Apfel[10], Vincent DiPippo[11], Syed Mahmood[10], Vivien Wong[10] and Camilo Jimenez[12]

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
  - Database and tumor collection
  - Basic science and translational laboratory research
  - Clinical studies and trials

Perelman School of Medicine
University of Pennsylvania

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
  - Database and tumor collection
  - Basic science and translational laboratory research
  - Clinical studies and trials

Perelman School of Medicine
University of Pennsylvania

Database and tumor collection

- GEP-NETs as of 2020
  - Patients consented in the database

    428
  - Banked blood samples

    269
  - Tumor samples

    121

Perelman School of Medicine
University of Pennsylvania

Use of database information



ORIGINAL ARTICLE

Predictors of Recurrence and Survival in Patients With Surgically Resected Pancreatic Neuroendocrine Tumors

Rachel E. Rosenblum, MD, Cynthia K. Harris, MD,* Kiwoon Joshua Baeg, BS,* Julie A. Starr, BS,†*
Lauren K. Brais, MPH,‡ Kristen M. Stashek, MD,§ Stephen C. Ward, MD, PhD,|| Bryson W. Katona, MD, PhD,†
Thomas E. Clancy, MD,¶ Juan P. Wisnivesky, MD, DrPh, Matthew H. Kulke, MD,‡ David C. Metz, MBBCh,†*
Michelle Kang Kim, MD, PhD,# and Jennifer A. Chan, MD, MPH‡

Pancreas • Volume 49, Number 2, February 2020

Collaboration between Penn, Dana Farber, and Mount Sinai

Examined 501 patients with surgically resected pancreatic NETs

Use of tissue samples are critical for research

- Tissue sharing collaborations outside of Penn:
  - Dr. Juanita Merchant (University of Arizona)
  - Dr. Scott Oakes (UCSF → University of Chicago)
  - Tron corporation (Europe)

- Tissue use within Penn:
  - Dr. Xianxin Hua (Department of Cancer Biology)
  - Dr. Xiaolu Yang (Department of Cancer Biology)

Perelman School of Medicine
University of Pennsylvania

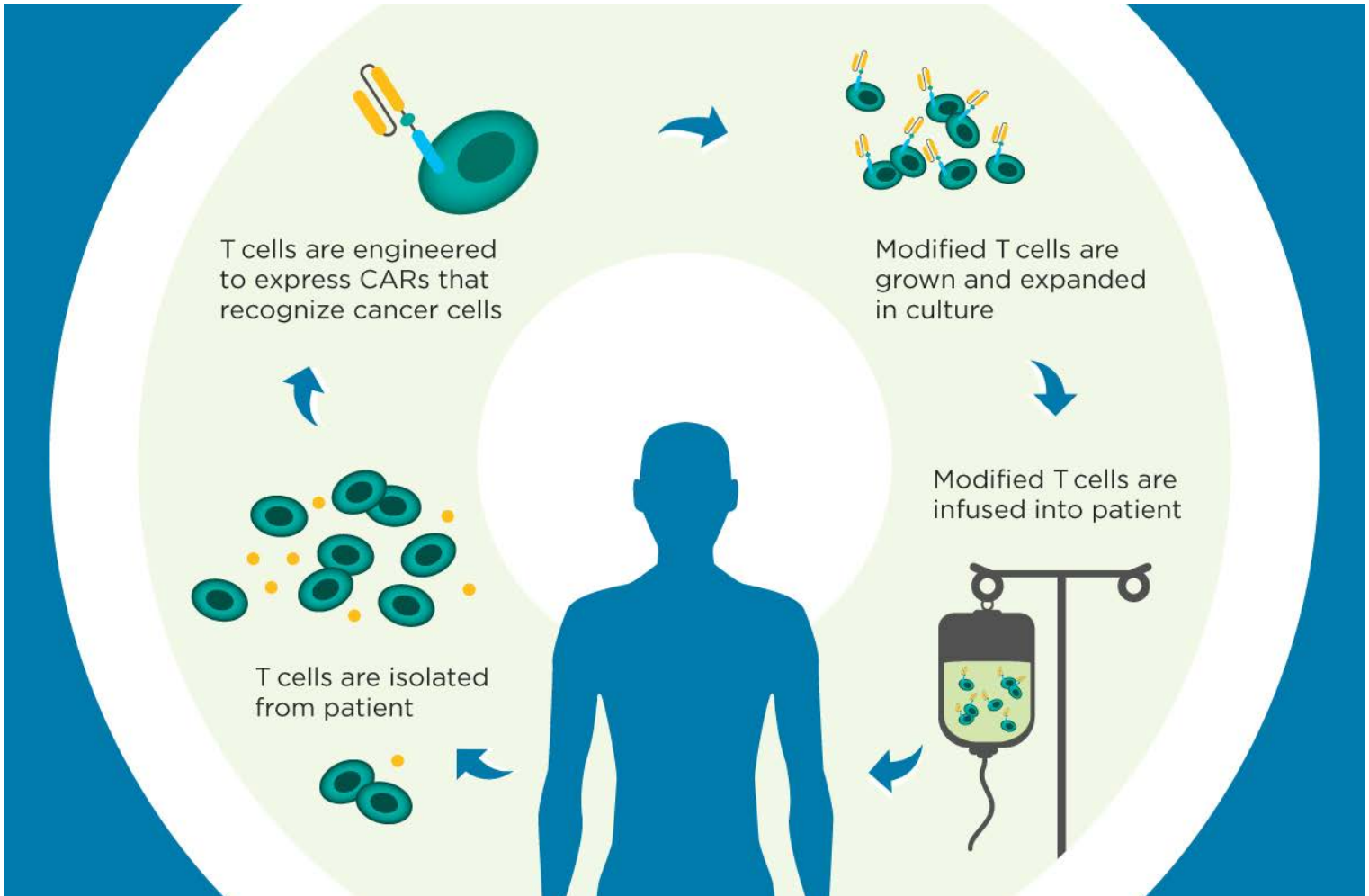
Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
  - Database and tumor collection
  - Basic science and translational laboratory research
  - Clinical studies and trials

Perelman School of Medicine
University of Pennsylvania

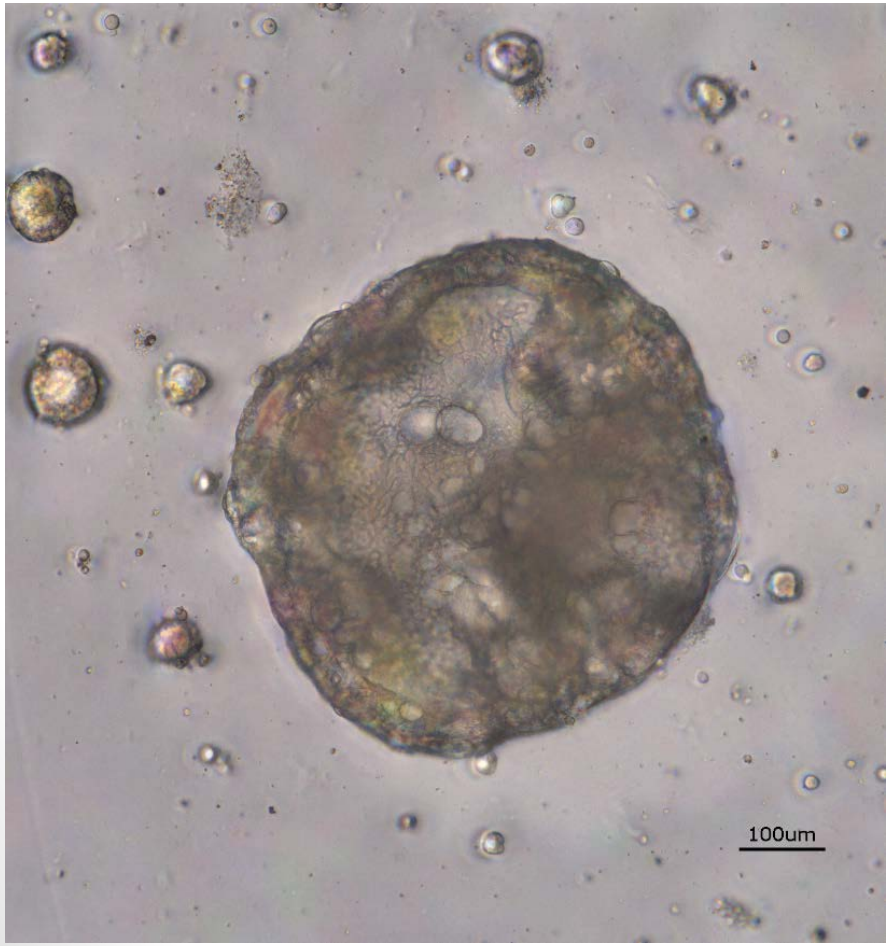
Advances in NET CAR-T therapy

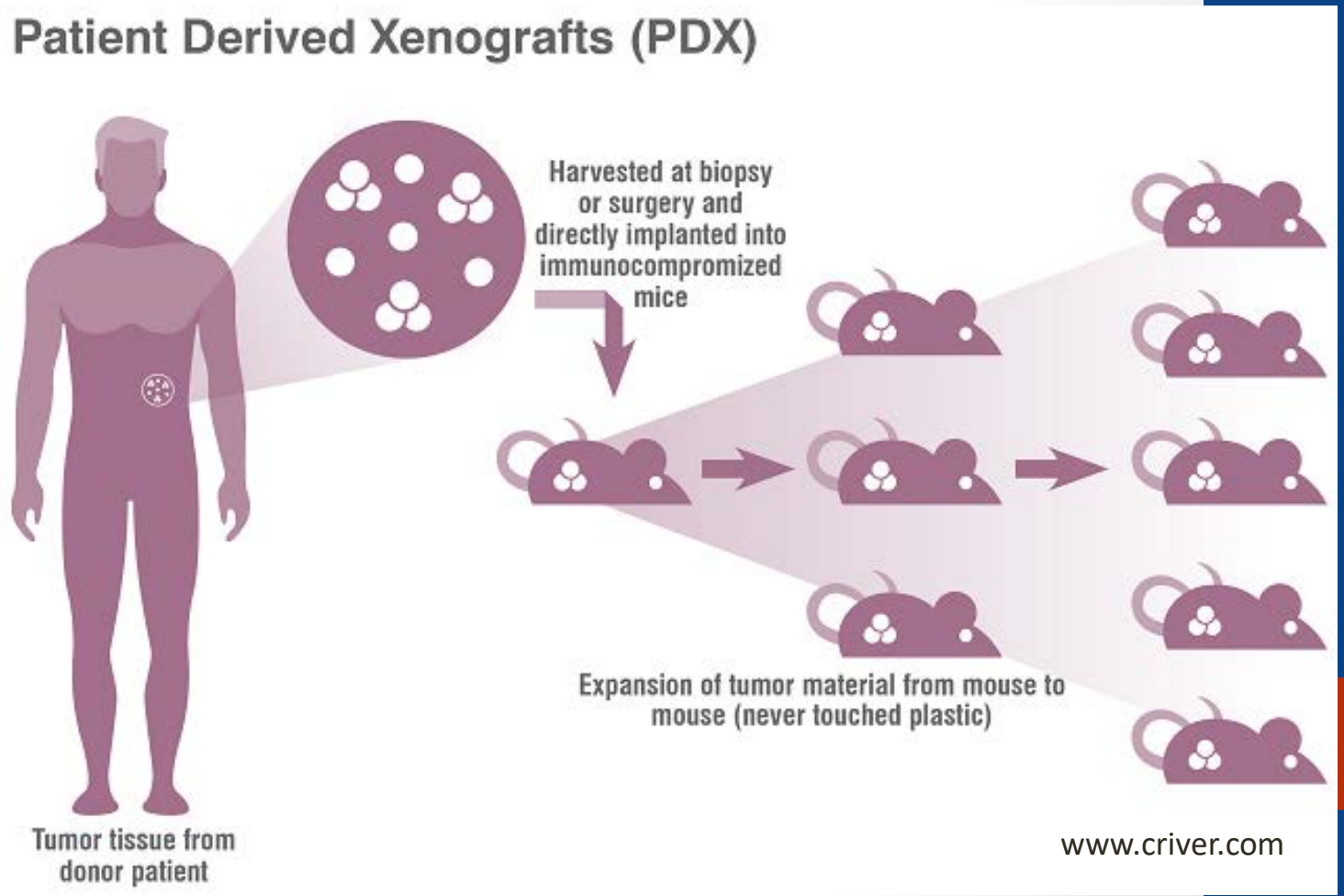
- Dr. Xianxin Hua's talk will go into this in detail!



Study of NET liver metastases

- Dr. Terence Gade's talk will go into this in more detail





Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
  - Database and tumor collection
  - Basic science and translational laboratory research
  - Clinical studies and trials

Perelman School of Medicine
University of Pennsylvania

CapTem+Y90

ORIGINAL ARTICLE

Safety and Feasibility of Integrating Yttrium-90 Radioembolization With Capecitabine-Temozolomide for Grade 2 Liver-Dominant Metastatic Neuroendocrine Tumors

Michael C. Soulen, MD, Diana van Houten, CRNP,* Ursina R. Teitelbaum, MD,† Nevena Damjanov, MD,† Keith A. Cengel, MD,‡ and David C. Metz, MD§*

Pancreas • Volume 47, Number 8, September 2018

CapTem+Y90

- The Phase 2 trial of CapTem plus Y90 TARE for liver-dominant G2 NETS is funded and will be opening this year
- Recruitment goal is 50 patients
- 3 centers participating:
  - University of Pennsylvania
  - Roswell Park
  - Emory

RETNET Trial

Chen *et al. Trials* (2018) 19:390
https://doi.org/10.1186/s13063-018-2782-5

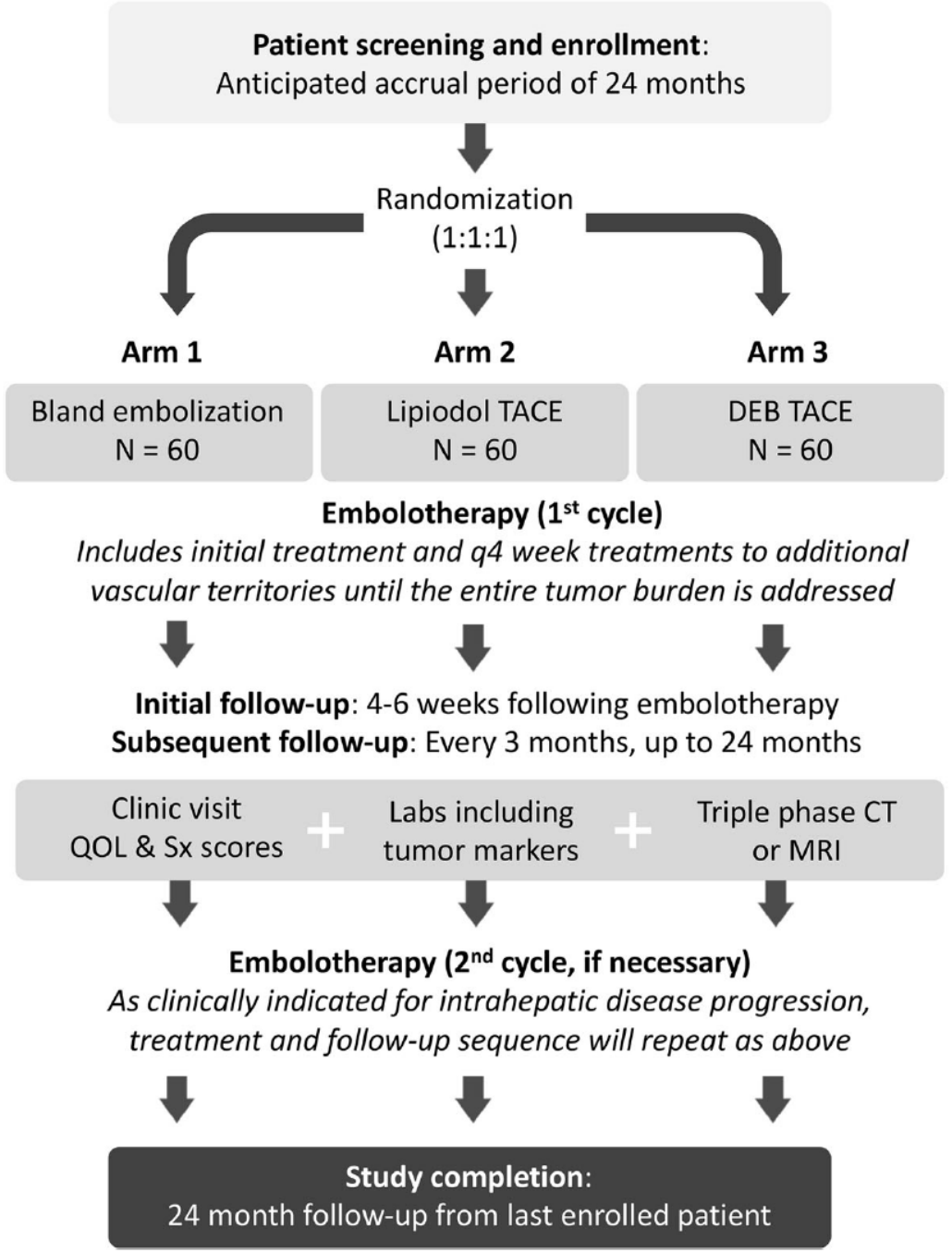
Trials

STUDY PROTOCOL Open Access

Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial

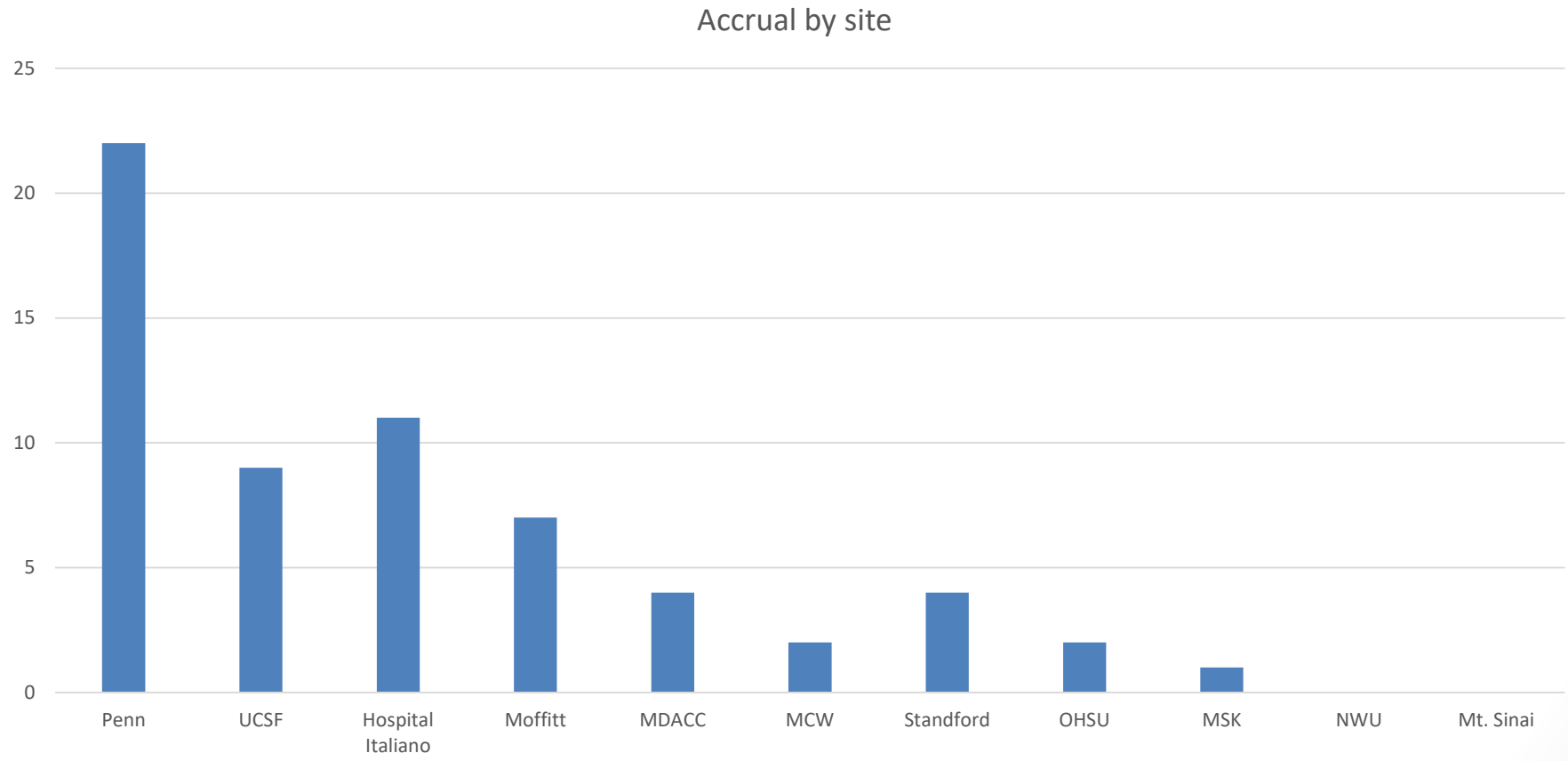
James X. Chen[1], E. Paul Wileyto[2,3] and Michael C. Soulen[1,3,4*]

The RETNET trial is a prospective, multicenter randomized controlled trial designed to determine the optimal embolotherapy technique for NET liver metastases.



RETNET Trial

- 12 active sites
- 62 out of 130-170 patients recruited



The Oncologist®

Gastrointestinal Cancer

Abnormal Pretreatment Liver Function Tests Are Associated with Discontinuation of Peptide Receptor Radionuclide Therapy in a U.S.-Based Neuroendocrine Tumor Cohort

Jason M. Heckert,[a] Sarit T. Kipnis,[a] Shria Kumar,[b] Samuel Botterbusch,[b] Alice Alderson,[b] Bonita Bennett,[b] Caroline Creamer,[b] Jennifer R. Eads,[c] Michael C. Soulen,[d] Daniel A. Pryma,[d] David A. Mankoff,[d] David C. Metz,[b] Bryson W. Katona[b]

[a]Division of Internal Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [b]Division of Gastroenterology, [c]Division of Hematology and Oncology, and [d]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

- PRRT can be administered to a diverse NET population
- Baseline liver function test abnormality increases the likelihood of PRRT discontinuation

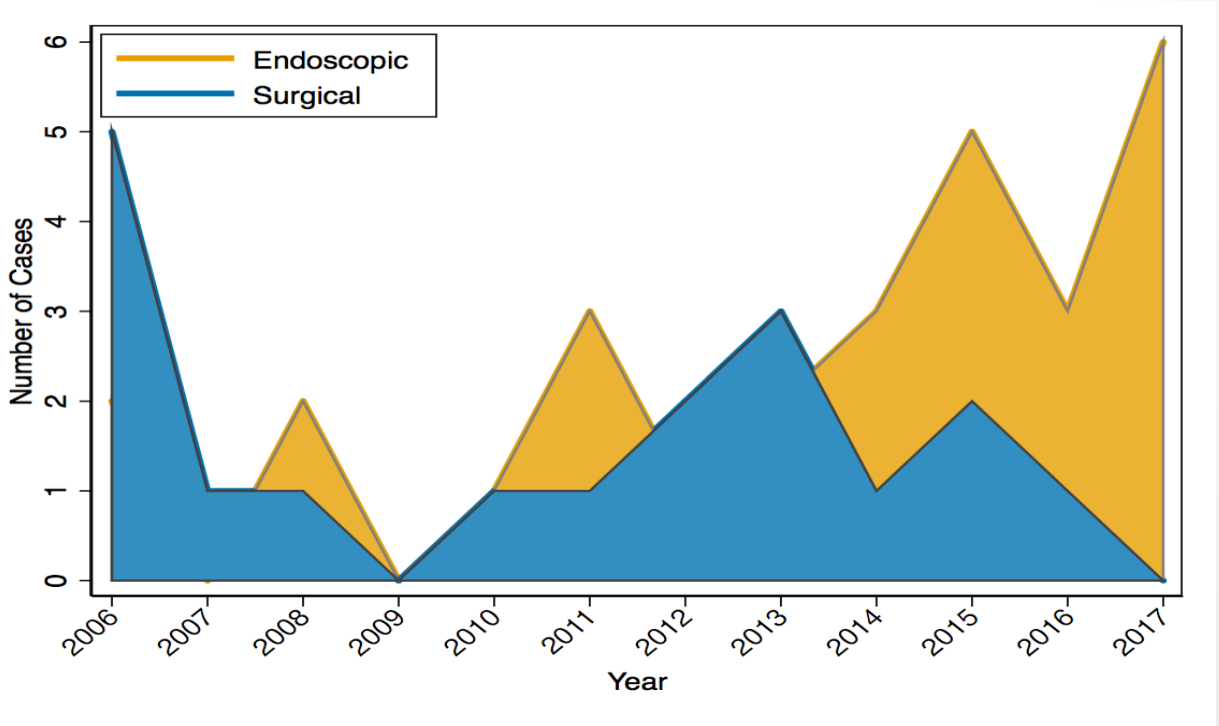
Recently Published in *Pancreas*, January 2020

Resection Trends for Duodenal Carcinoid Tumors: A Single Center Experience

S. Kumar, N. Mahmud, R. Roses, B.W. Katona, G. G. Ginsberg, D.C. Metz

- Results support considering endoscopic resection of duodenal carcinoids less than 10 to 15 mm

- Operative resection reserved for those lesions with higher-grade, high mitotic rate, and positive resection margins after endoscopic resection



Ann Surg Oncol
https://doi.org/10.1245/s10434-019-07848-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

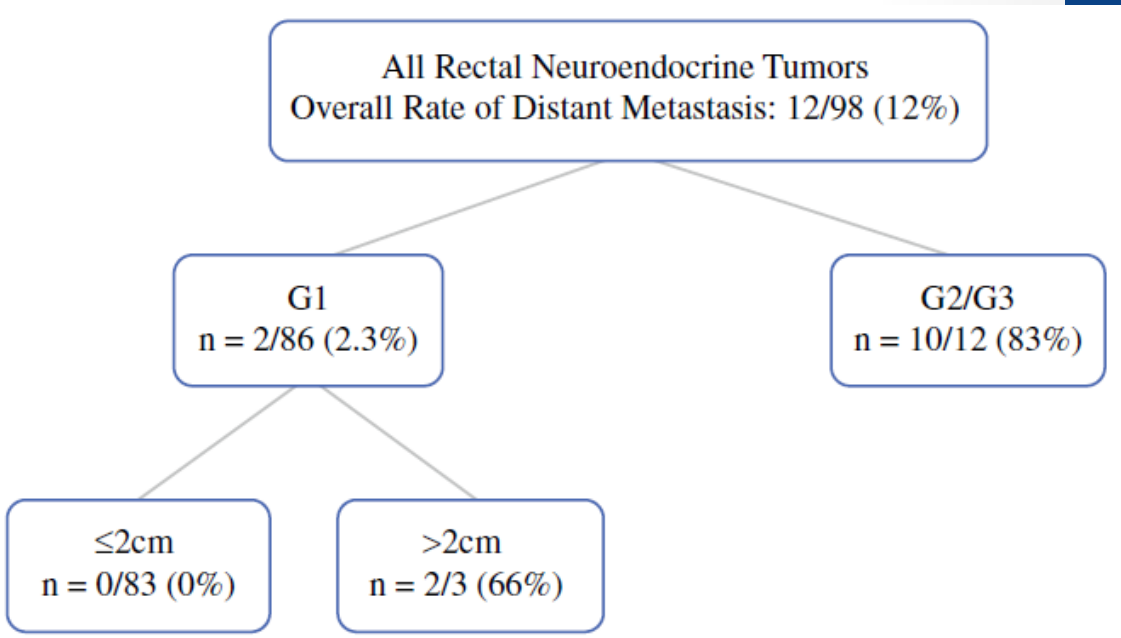
ORIGINAL ARTICLE – ENDOCRINE TUMORS

Grade is a Dominant Risk Factor for Metastasis in Patients with Rectal Neuroendocrine Tumors

Ian W. Folkert, MD[1], Andrew J. Sinnamon, MD[1], Seth J. Concors, MD[1], Bonita J. Bennett, BSN RN[2], Douglas L. Fraker, MD[3], Najjia N. Mahmoud, MD[4], David C. Metz, MD[2], Kristen M. Stashek, MD[5], and Robert E. Roses, MD[3]

- Patients with diminutive and small rectal NETs (< 2cm) are at risk of metastatic disease, especially if grade 2 or grade 3

- Tumor grade is a dominant predictor of dissemination



ORIGINAL ARTICLE

The impact of surgery for metastatic pancreatic neuroendocrine tumor: a contemporary evaluation matching for chromogranin a level

Seth J. Concors[1], Andrew J. Sinnamon[1], Brett L. Ecker[1], David C. Metz[2], Charles M. Vollmer[1], Douglas L. Fraker[1] & Robert E. Roses[1]

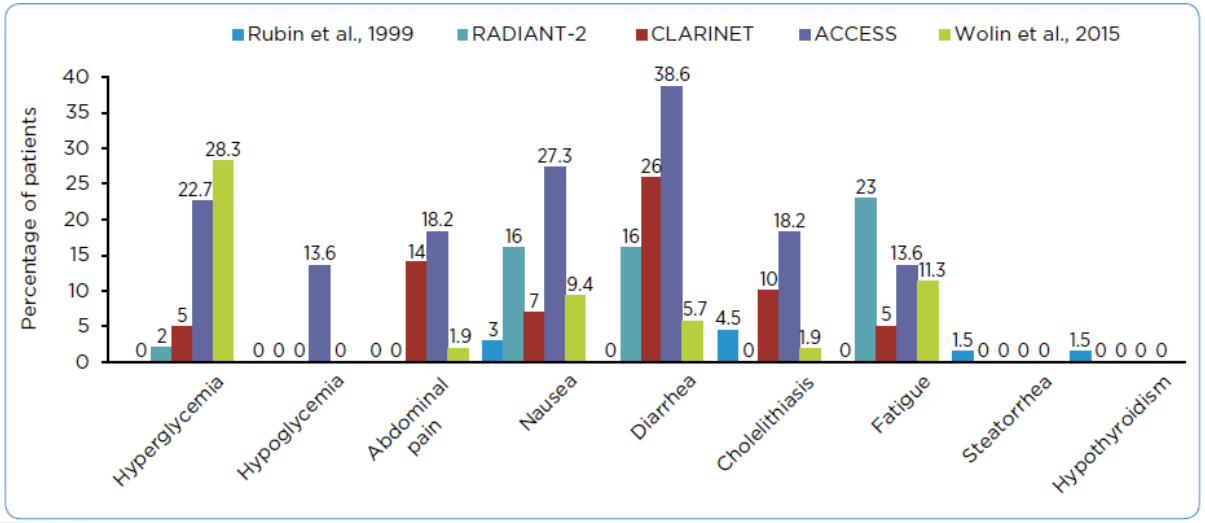
HPB
THE OFFICIAL JOURNAL OF THE
International Hepato-Pancreato-Biliary Association
Americas Hepato-Pancreato-Biliary Association
Asian-Pacific Hepato-Pancreato-Biliary Association
European-African Hepato-Pancreato-Biliary Association
IHPBA

- 1478 patients with PNET from the National Cancer Database (2004-2014)
- Chromogranin A levels were predictive of metastatic disease and how well patients did
- When matching chromogranin A levels, metastatic PNET patients undergoing surgery did better

Long-Acting Somatostatin Analogue Safety Monitoring Protocol for Outpatients With Neuroendocrine Tumors

J Adv Pract Oncol 2019;10(7):646–659

JORDAN GABRIELSEN,[1] PharmD, GIANNA GIRONE,[1] PharmD, BONITA BENNETT,[2] BSN, RN, and ANNA JUNG,[2] PharmD, BCPS



Baseline (prior to initiation)
- Gallbladder US (if no prior imaging)
- CBC, complete metabolic panel, TSH, HbA1c, vitamin B_{12}, zinc
- Stool studies for osmolality and electrolytes, Sudan stain, pancreatic elastase
- Vital signs
- Physical exam

6 months post-initiation
- Gallbladder US
- CBC, complete metabolic panel, TSH, HbA1c
- Vital signs
- Physical exam
- Evaluation of TRAEs

Annual
- Gallbladder US
- CBC, complete metabolic panel, TSH, HbA1c
- Vital signs
- Physical exam
- Evaluation of TRAEs

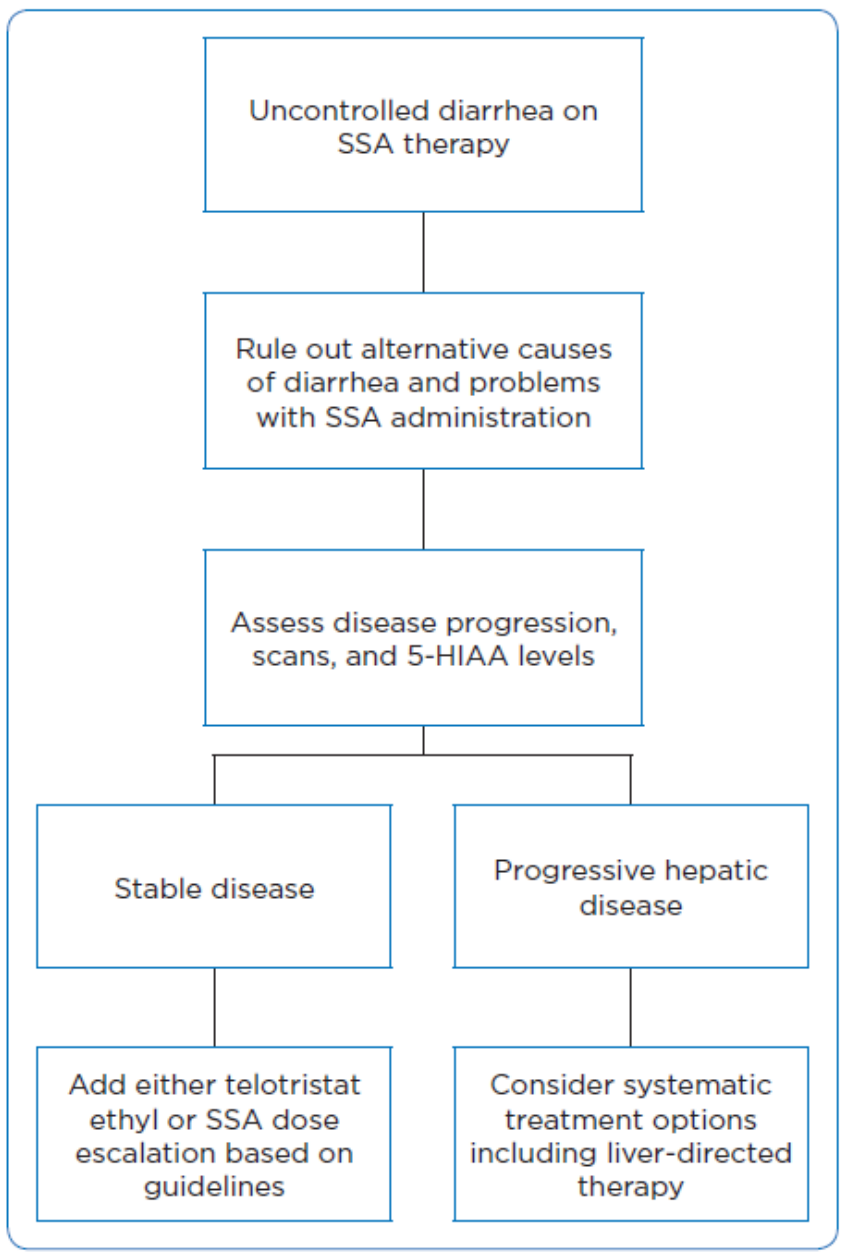
Other considerations
- Cardiovascular disease
  - » Can consider a baseline and annual ECG and echocardiogram
- Vitamin B_{12}[a]
  - » If normal at baseline, test every 12 months
  - » If low, test every 6 months
- Zinc
  - » Measure every 3 months for patients with excessive fluid losses maintained on TPN
- HbA1c[b]/glucose[c]
  - » If normal at baseline, test annually
  - » If elevated in the prediabetic range, test every 6 months
  - » If diabetic, test every 3 months
- Diarrhea
  - » If patient reports diarrhea, consider further testing (i.e., stool studies, hydrogen breath test)

Optimizing the Management of Carcinoid Syndrome to Reduce the Impact of Diarrhea

RORY RANDALL,[1] CNP, AOCNP®, BONITA BENNETT,[2] RN, BSN, TIFFANY VALONE,[3] PA-C, MS, OT, and KIRSTEN BLUE,[3] PA-C, MS

J Adv Pract Oncol 2019;10(8):

- Overview of functional NETs and treatment paradigms
- Overview of carcinoid syndrome-specific therapies
- Differential diagnosis of diarrhea in the setting of a NET
- Assessment of the impact of diarrhea on patient's daily lives



NET Clinical Trials at Penn

- Update provided by Dr. Jennifer Eads later today

Overview

- Overview of the Penn NET Center
- Pheochromocytoma/Paraganglioma (PCC/PGL)
- Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Perelman School of Medicine
University of Pennsylvania

Thank you!

- **Our patients**
- **Co-Directors of Penn NET Center**
  - **Debbie Cohen**
  - **David Metz**
- **NET Center Support**
  - Bonnie Bennett
- **Medical Genetics**
  - Katherine Nathanson
  - Staci Kallish
  - Maria Bonanni
  - Anna Raper
  - Stephanie Asher
  - Zoe Bogus
  - Megan Lawrence
- **Surgery**
  - Douglas Fraker
  - Robert Roses
  - John Kucharczuk
  - Douglas Bigelow
  - Bert O'Malley
  - M. Sean Grady
  - Heather Wachtel
  - Major Kenneth Lee
  - Charles Vollmer
  - Thomas Guzzo
  - Frank Venuto
  - Caitlin Perch
  - Pamela Sellers
  - Ben Jackson
  - Paul Foley
  - Ara Chalian
  - Ian Folkert
  - Kelley Culley
- **Medical Oncology**
  - Ursina Teitelbaum
  - Jennifer Eads
  - Nevena Damjanov
  - Mark O'Hara
  - Kim Reiss-Binder
  - Vivek Narayan
  - Charles Schneider
  - Thomas Karasic
  - Aditi Singh
  - Kathryn Green
  - Dana Weyrick
  - Adam Freda
  - Abigail Smith
  - Suzanne McGettigan
  - Bethany Mooney
  - Melissa Fritz
  - Stephen Keefe
  - Elizabeth Prechtel Dunphy
  - Gamil Hanna
  - Courtney Gabriel
  - Elizabeth Fox
  - Paul Wissel
  - Marcia Brose
  - Ryan Massa
- **Cancer Patient Family Services**
  - Heather Sheaffer
  - Doris Piccinin
  - ACC Staff and Dieticians
- **Infusion Services**
  - Rob Tobin
- **Radiation Oncology**
  - Keith Cengel
  - Michelle Alonso-Basanta
- **Cancer Biology/Immunotherapy**
  - Xianxin Hua
  - Carl June
  - Terence Gade
- **Gastroenterology**
  - Bryson Katona
  - Caroline Creamer
  - Samboun Bo-Khao
  - Trish Gambino
  - Diann Boyd
- **Pathology**
  - Virginia LiVolsi
  - Kathleen Montone
  - Beth Furth
  - Stuti Shroff
  - Rashmi Tondon
  - Danielle Fortuna
  - Zhaohai Yang
- **Nuclear Medicine**
  - Daniel Pryma
  - David Mankoff
  - Hwan Lee
  - Ayana Smith
  - Glafirah Dumas
  - Mehran Makvandi
- **Radiology**
  - Jennifer Gillman
  - Thomas Anderson
  - Stamatoula Pilati
  - Jennifer Schroeder
- **Renal**
  - Jordana Cohen
  - Yonghong Huan
  - Matthew Denker
  - Maria Bonanni
- **Endocrinology**
  - Julia Kharlip
  - Anastassia Amaro
  - Caitlin White
- **Research**
  - Julie Starr
  - Alice Alderson
  - Benita Weathers
  - CHTN Staff
- **Pharmacy**
  - Anna Jung
- **Cardiology**
  - Victor Ferrari
  - Joseph Carver
- **Interventional Radiology**
  - Michael Soulen
  - Mandeep Dagli
  - Jeffrey Mondschein
  - William Stravropoulos
  - Diana Van Houten
  - Laura Herron
  - Amanda Davis
  - Ginna Deitrick
  - Scott Trerotola
  - Deepak Sudheendra
- **Social Work**
  - Megan Melick
- **Palliative Care/Pain**
  - Alyssa Wold
  - Pain management team
- **Giving**
  - Andrew Bellet
- **Funding**
  - NIH
  - NET Research Foundation
  - PheoPara Alliance
  - NANETS
  - Run for the Stripes

Perelman School of Medicine
University of Pennsylvania

NET
Neuroendocrine Tumor Research Foundation
Dedicated to curing neuroendocrine cancer
www.netrf.org

National Institutes of Health

NANETS
North American Neuroendocrine Tumor Society

Run for the Stripes

PheoPara Alliance
Pheochromocytoma & Paraganglioma