THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

# “34 Year Old Man With A Pancreatic Neuroendocrine Tumor”

Dr. Darji does not have any relevant financial relationships with any commercial interests.

# ENDORAMA:
# 34 Year Old Man With A Pancreatic Neuroendocrine Tumor

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# Objectives

- Discuss the classification and diagnostic evaluation of pancreatic neuroendocrine tumors
- Review the systemic therapy options for metastatic pancreatic neuroendocrine tumors

# Chief Complaint

34 year old Indian male presents with weight loss and muscle weakness

# HPI

- Patient reports the following symptoms over the last 2-3 months:
  - 20 lb weight loss
  - Muscle weakness, loss of muscle mass
  - Lower extremity swelling
  - Increased waist circumference
  - Early satiety
  - Irritability

# Review of Systems

- Constitutional: **+weight loss**; Negative for fevers, chills, night sweats
- HEENT: **+headaches**; Negative for blurry vision, sore throat
- Respiratory: **+shortness of breath**; no cough
- Cardiovascular: Negative for chest pain, palpitations
- Gastrointestinal: **+early satiety, bloating, increased waist circumference**; denies nausea, vomiting, diarrhea, constipation
- Genitourinary: Negative for urinary frequency, hematuria
- Skin: Negative for diaphoresis, new rash
- Extremities: **+LE edema and muscle weakness**
- Neurological: Negative for numbness, tingling
- Psychiatric/Behavioral: **+irritability**; Negative for anxiety, depression

# Additional history

- Past Medical History: metastatic pancreatic neuroendocrine tumor with liver mets, diagnosed in 2015
- Past Surgical History: none
- Family History: maternal grandmother had gastric cancer, details unknown
- Social History: internal medicine physician, married with one child, Denies tobacco, alcohol, and illicit drugs

# Oncology History

- Patient was diagnosed with metastatic pancreatic neuroendocrine tumor in 5/2015
  - Initially presented with abdominal pain and diarrhea
  - EGD in 6/2015 showed erythematous mucosa in stomach and duodenum
  - CT triphasic of the liver on 7/9/15 showed innumerable arterial enhancing liver lesions and 2 cm mass in the pancreaticoduodenal groove concerning for metastatic pancreatic cancer
  - Liver biopsy on 7/10/15 with pathology confirmed metastatic neuroendocrine carcinoma
    - Two specimens: one had Ki67 5% and other had Ki67 15%
  - Octreotide scan on 7/20/15 showed uptake in pancreas and multiple liver mets
  - He was started on octreotide LAR 7/28/15

# Oncology History

- CT triphasic of the liver 4/2016 showed increase in size and number of liver mets
- Began treatment with a Phase I/II Study of the Combination of Temozolomide and Pazopanib in 5/2016
  - Underwent two cycles of treatment
  - Continued to have disease progression
- Underwent hepatic arterial embolization in 9/2016 and 10/2016.
  - Subsequent MRI in 11/2016 showed mixed response in the liver
- He went to Basel, Switzerland for PRRT (peptide receptor radionuclide therapy, usually targeted to somatostatin receptors) in 3/2017

# Oncology History

- Pt developed hypercalcemia in 4/2017, PTHrP level elevated -> was treated with denosumab
- Gastrin level elevated -> started on pantoprazole
- Pt underwent 4 rounds of hepatic arterial embolization and PRRT
- Most recent MRI in 7/2018 shows progression of two hepatic lesions
  - Oncology planning another round of hepatic arterial embolization and PRRT
- Genetic testing negative for MEN syndrome

# Additional history

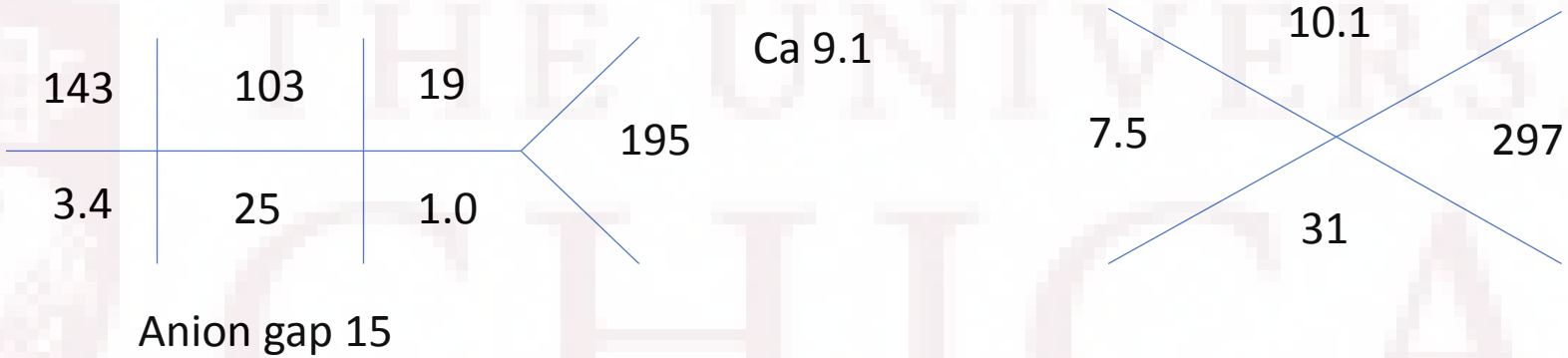
- Meds: pantoprazole 40mg daily, sandostatin LAR every month, potassium chloride 60mEq daily

- Allergies: amoxicillin (hives)

# Physical Exam

- Vitals: 59 kg, BMI 19, Temp 97.2, HR 83, RR 19, **BP 154/105**, SpO2 100%
- Constitutional: no acute distress
- HEENT: EOMI, oropharynx clear
- Neck: **buffalo hump**; supple, no thyromegaly
- Cardiovascular: regular rate and rhythm
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: **central adiposity, mildly tender to palpation**, no guarding
- Extremities: **2+ bilateral lower extremity edema**
- Neurological: alert, oriented, **4/5 muscle strength in all four extremities**
- Skin: warm, dry, **purple striae on abdomen**
- Psychiatric: not agitated

# Admission Labs




| | | | |
|---|---|---|---|
| Total protein | 6.4 | Alkaline phosphatase | 115 |
| Albumin | 3.5 | ALT | 20 |
| Total bilirubin | 0.3 | AST | 24 |

# Previous labs

- In 4/2017:
  - Gastrin 9840 pg/mL
  - Calcium  11.1, normal albumin, PTHrP 63
  - Potassium 2.4
  - Cortisol 94 μg/dL
  - ACTH 882 pg/mL
  - 24 hour urine cortisol 1017 mcg/24 hr

# Cushing's Syndrome

- Pt presented with symptoms and physical exam findings c/w Cushing's
  - Also p/w hypertension, hyperglycemia, hypokalemia
  - 24 hour urine cortisol elevated
  - ACTH elevated
- Cushing's syndrome thought to be 2/2 ectopic ACTH secretion
- Pt was treated with potassium chloride supplementation, eplerenone, and mifepristone
- Given severe and persistent symptoms, pt was referred for bilateral adrenalectomy

# Pancreatic Neuroendocrine Tumor (PNET)

- Defined as a rare neoplasm in the endocrine tissue of the pancreas
- Estimated 50-75% are nonfunctioning
- PNETs are classified according to their histologic features
  - Measures of proliferative index, Ki-67 and mitotic index, are used to assign histologic grade
- Pancreatic neuroendocrine carcinoma (NEC) describes cases with poorly differentiated histology and a high proliferative rate

# PNET classification

**2017 World Health Organization (WHO) classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)**

| Classification/grade | Ki-67 proliferation index* (percent) | Mitotic index* |
|---|---|---|
| **Well-differentiated PanNENs: Pancreatic neuroendocrine tumours (PanNETs)** | | |
| PanNET G1 | <3 | <2 |
| PanNET G2 | 3 to 20 | 2 to 20 |
| PanNET G3 | >20 | >20 |
| **Poorly differentiated PanNENs: Pancreatic neuroendocrine carcinomas (PanNECs)** | | |
| PanNEC (G3) | >20 | >20 |
| Small cell type | | |
| Large cell type | | |
| **Mixed neuroendocrine-non-neuroendocrine neoplasm** | | |

# Functional PNETs

- Classified according to the predominant hormone secreted
  - Insulinoma
  - Gastrinoma
  - Glucagonoma
  - Somatostatinoma
  - VIPoma
- Most functioning PNETs have well-differentiated histology

# PNET

- Incidence is ≤1 case per 100,000 individuals per year
  - 1 to 2 percent of all pancreatic tumors
- Can occur at any age, most often manifests during the fourth to sixth decades of life
- Sporadic vs hereditary
  - Most cases are sporadic
  - Can be associated with multiple endocrine neoplasia type I (MEN1), von Hippel Lindau (VHL) syndrome, neurofibromatosis type I (NF1), and tuberous sclerosis

# Clinical Presentation

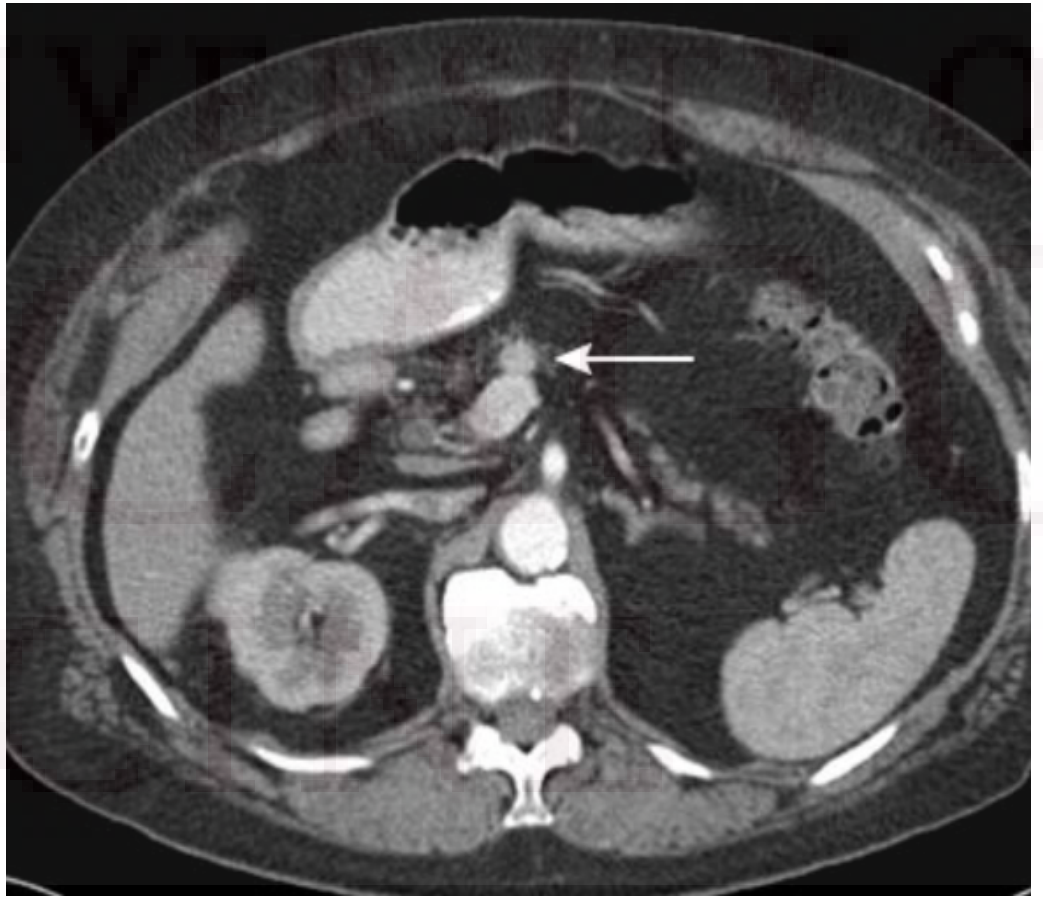
| Name | Biologically active peptide(s) | Most common symptoms/signs |
|---|---|---|
| **Most common syndromes** | | |
| Insulinoma | Insulin | Hypoglycemic syndromes (Whipple's triad) |
| Zollinger-Ellison syndrome | Gastrin | Abdominal pain, gastroesophageal reflux, diarrhea, duodenal ulcers, PUD/GERD |
| **Less common syndromes (additional, rarer syndromes also exist)** | | |
| VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA syndrome) | Vasoactive intestinal peptide | Diarrhea, hypokalemia, dehydration |
| Glucagonoma | Glucagon | Rash, glucose intolerance, necrolytic migratory erythema, weight loss |
| Somatostatinoma | Somatostatin | Diabetes mellitus, cholelithiasis, diarrhea |
| ACTHoma/Cushing's syndrome | ACTH | Cushing's syndrome |
| Pancreatic NET causing carcinoid syndrome | Serotonin | Flushing, diarrhea |
| PTHrp-oma (hypercalcemia) | PTHrp, others unknown | Symptoms due to hypercalcemia (mimics primary hyperparathyroidism) |

# Clinical Presentation

- Nonfunctioning PNETs
  - Tends to present later in disease with symptoms of local compression or metastatic disease
  - Symptoms may include abdominal pain, weight loss, anorexia, nausea, obstructive jaundice
  - Can develop into functional PNET later in disease course
  - Can secrete substances like chromogranins, pancreatic polypeptide, and ghrelin
- Metastatic PNETs
  - Estimated between 32 and 73 percent of cases are metastatic at diagnosis
  - Most common site of metastases is the liver

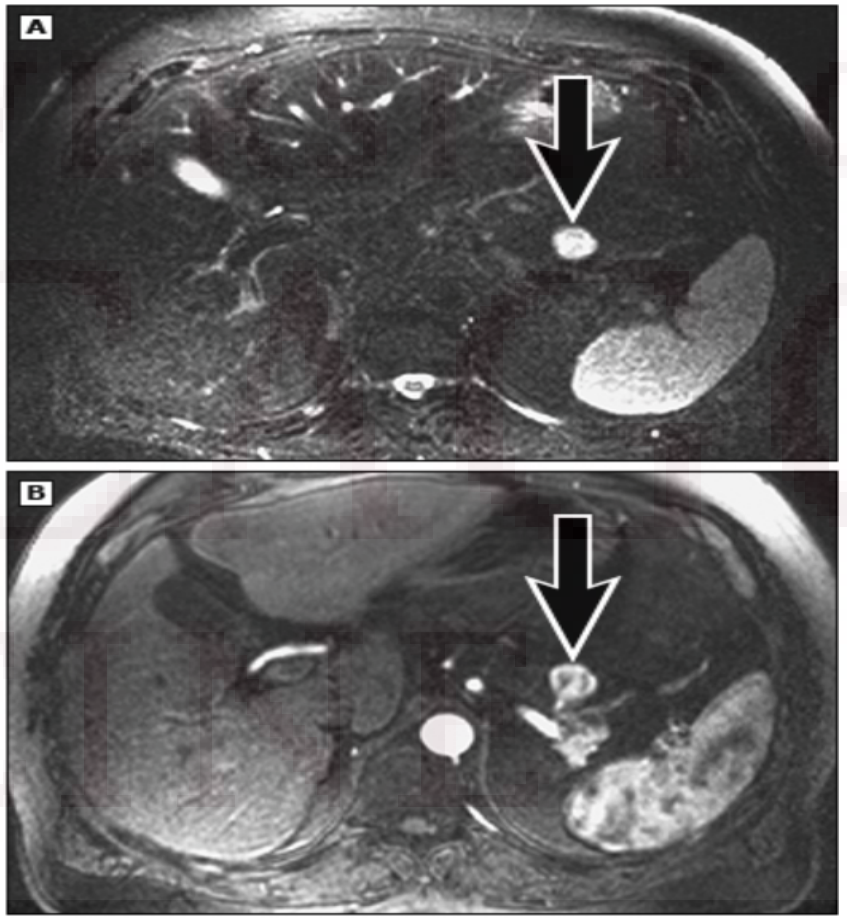
# Diagnostic evaluation

- Helical (spiral) multiphasic contrast-enhanced CT
  - Sensitivity >80% for detecting primary pancreatic NETs
  - Tumors as small as 4 mm can be visualized with CT scan



# Diagnostic evaluation

- MRI
  - Low signal intensity on T1-weighted images
  - High signal intensity on T2-weighted images
- Dromain et al.
  - Prospective study
  - The number of detected hepatic metastases was significantly higher with MRI than with CT



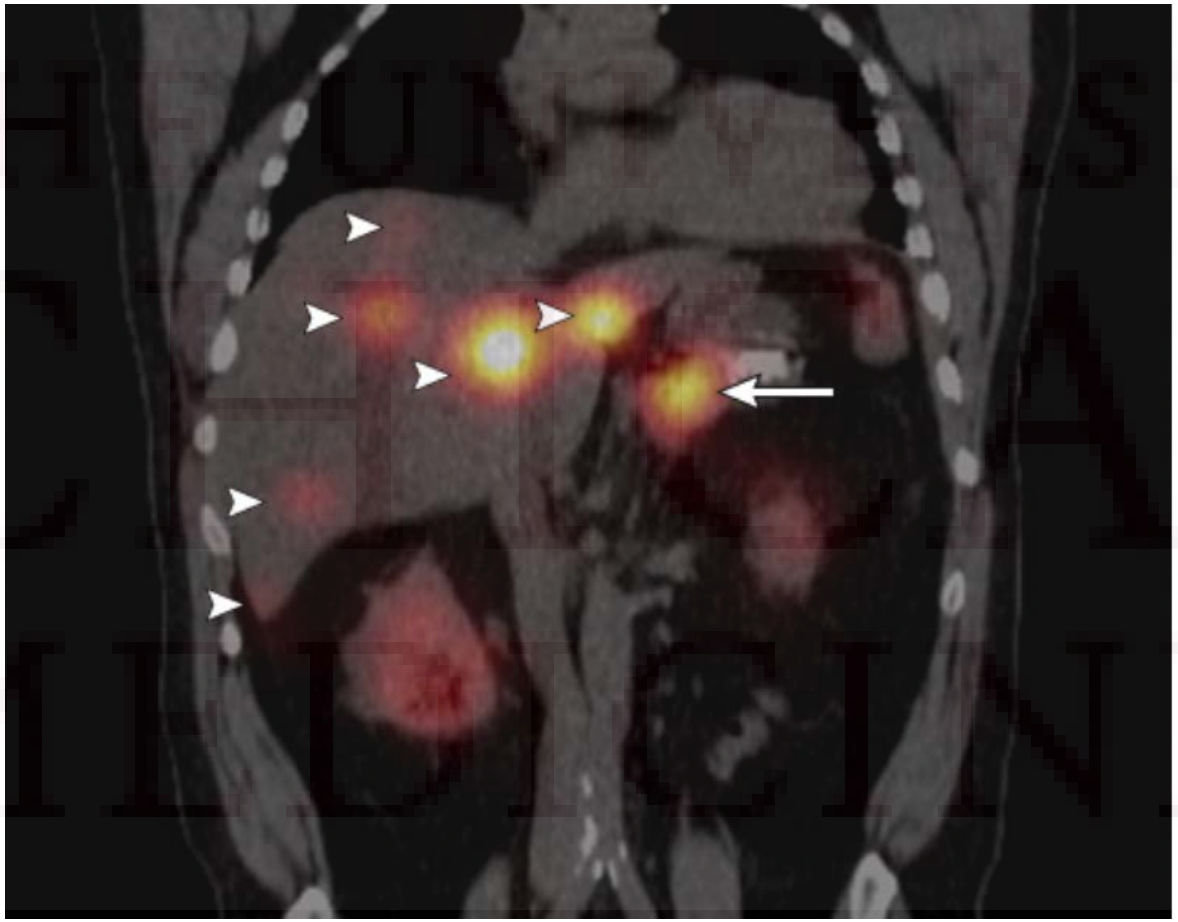
# Diagnostic evaluation

- In cases with suspected PNET but lack of evidence on CT scan or MRI, endoscopic ultrasonography or arterial stimulation with venous sampling can be used
- Endoscopic ultrasonography (EUS)
  - High-resolution imaging of the pancreas
  - Can detect lesions as small as 2 to 3 mm in diameter
  - EUS-guided fine-needle aspiration biopsy is an option
- Arterial stimulation with hepatic venous sampling
  - Involves injection of a stimulating secretagogue (secretin for gastrinomas and calcium gluconate for insulinomas) into arteries supplying the pancreas and subsequent sampling of the hepatic venous effluent
- Transhepatic portal venous sampling - small peripancreatic veins are accessed and tested for levels of hormones

# Indium-111 pentetreotide (OctreoScan)

- Many PNETs express high levels of somatostatin receptors
  - Can be imaged with a radiolabeled form of the octreotide (111-In pentetreotide)
  - Uptake of radiolabeled octreotide can help predict response to treatment with somatostatin analogs and peptide receptor radionuclide therapy; it can also help identify primary tumor site
- 111-In pentetreotide
  - Effective for detecting gastrinomas, glucagonomas, and nonfunctioning pancreatic tumors
  - Not as effective in detecting insulinomas or poorly differentiated NETs as they express low somatostatin receptor levels

# OctreoScan



# Functional PET imaging

- PET tracers such as 68-Ga DOTATATE with high-resolution PET scan for functional imaging
  - Provide higher spatial resolution than 111-In pentetreotide
  - Associated with improved sensitivity for detection of small lesions
- Sadowski et al.
  - Prospective study, 131 patients
  - 68-Ga DOTATATE PET detected lesions in 65.2% of patients, 40% of which were detected neither by anatomic imaging nor by (111)In-pentetreotide SPECT/CT.

# Diagnostic evaluation

- Nonfunctioning
  - Chromogranin A is the most commonly secreted tumor marker associated with all types of PNETs
    - Levels are elevated in an estimated 50 to 70 percent of patients with nonfunctioning PNETs
    - Levels are thought to correlate with tumor burden
- Functioning
  - Levels of the secreted hormone are monitored

# Surgery

- Indicated in patients with PNETs to alleviate symptoms due to hormone overproduction or compression due to local mass effect
- Surgical resection is indicated in patients with malignant, sporadic PNET
  - With no evidence of distant metastatic spread of disease for curative intent
  - With potentially resectable metastatic disease
- In patients with low-volume metastatic well-differentiated low-grade tumors, resection of metastatic sites in conjunction with adjuvant therapies
- In patients with well-differentiated tumors with high-volume metastatic disease and a rapid growth rate, medical therapy is recommended
  - Palliative debulking may be indicated for relief of local symptoms or systemic symptoms related to hormone production

# Initial treatment

- For patients with symptoms of hormone hypersecretion from a well-differentiated PNET, management includes somatostatin analogs and other agents based on the specific syndrome
  - Initial treatment of insulinomas include carbohydrates and diazoxide to directly inhibit the release of insulin from insulinoma cells
    - Everolimus can also be effective in improving glycemic control in patients with insulinoma
  - Gastrinoma – treatment is high doses of oral PPIs
    - Somatostatin analogs may be effective for refractory cases

# Systemic therapy options for metastatic well-differentiated PNET

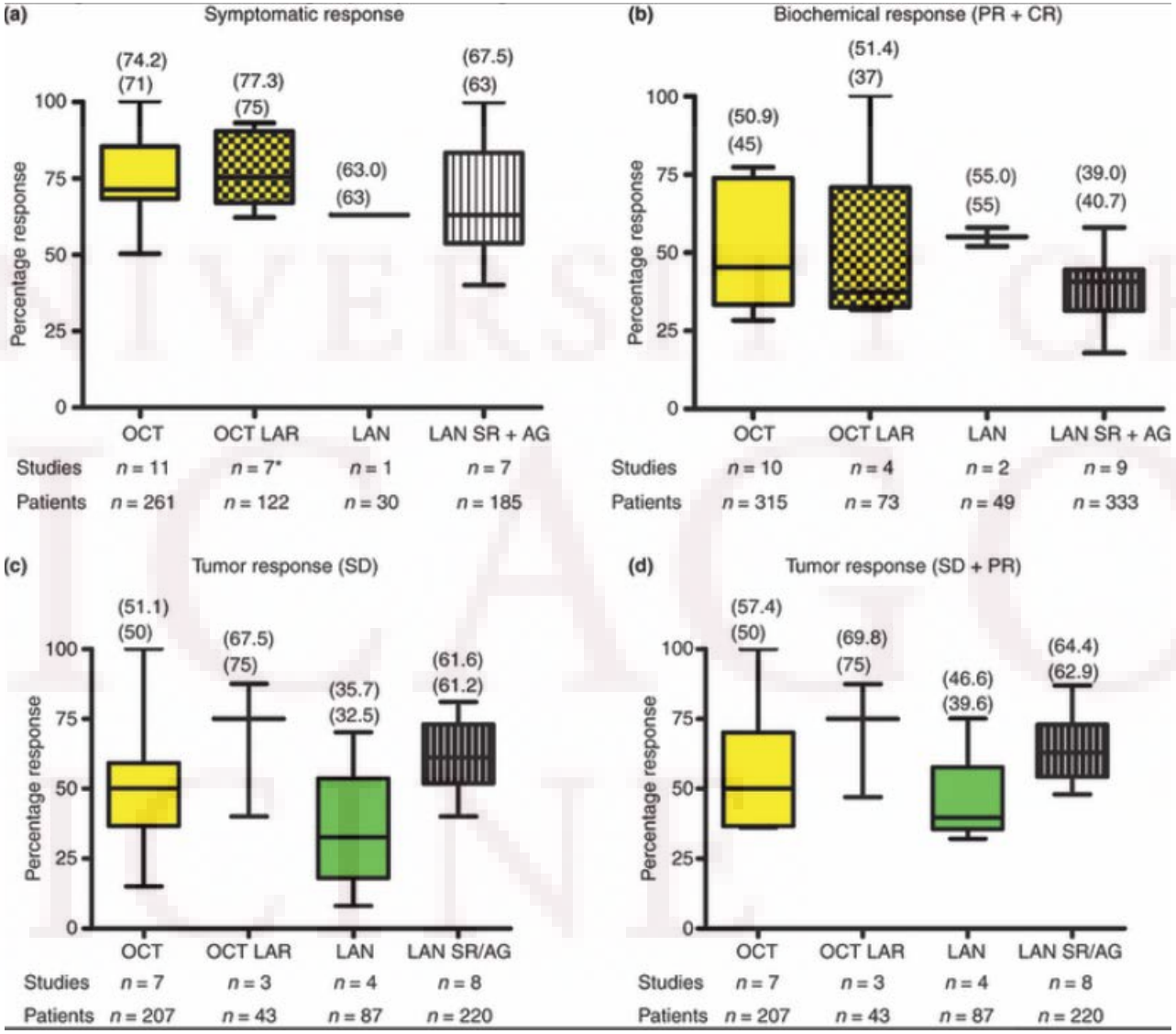
- For patients with unresectable disease:
  - Somatostatin analogs
  - Cytotoxic therapies
  - TK inhibitors or mTOR inhibitors
  - Peptide receptor radioligand therapy

# Somatostatin analogs

- Somatostatin and analogs of somatostatin like octreotide act by binding to somatostatin receptors (SSTR) to inhibit the secretion of a broad range of hormones
  - SSTRs are expressed on the majority of PNETs
  - Mediated mainly through SSTR-2 and SSTR-5
  - The presence of SSTR can be determined by diagnostic imaging like the OctreoScan
- Modlin et al. showed over 70% of symptom control with treatment of gastroenteropancreatic neuroendocrine tumors with somatostatin analogues

# Modlin et al.

- Systematic review of 15 studies including 481 patients
  - Sandostatin LAR achieved symptomatic relief in 77.3% (61.9-92.8%) and biochemical response in 51.4% (31.5-100%)



# Somatostatin analogs

- Symptomatic benefit is dose dependent and differs based on the type of functioning PNET
  - Effective in treating symptoms of VIPomas and glucagonomas
  - Symptom control in insulinomas and gastrinomas is less clear
- Sandostatin LAR depot preparation
- Side effects – usually mild
  - Nausea, bloating, loose stools
  - Mild glucose intolerance
  - Gallstones

# Cytotoxic therapies

- Consider in patients with advanced PNET and symptoms related to tumor bulk
- Dacarbazine (DTIC) and temozolomide-based regimens
  - Dacarbazine is an alkylating agent
  - Temozolomide is a less toxic analog of dacarbazine
- Streptozocin-based combination therapy
  - Streptozocin is an alkylating agent
  - Combined with fluorouracil and/or doxorubicin
- Oxaliplatin-containing regimens

# Cytotoxic therapies

| Regimen | Number of patients* | Tumor response rate (%) | Median progression-free survival (months) | Median overall survival (months) | Author; year |
|---|---|---|---|---|---|
| **Prospective studies** | | | | | |
| Chlorozotocin | 33 | 30¶ | 17 | 18.0 | Moertel C; 1992 |
| Fluorouracil + streptozocin | 33 | 45¶ | 14 | 16.8 | |
| Doxorubicin + streptozocin | 36 | 69¶ | 18 | 26.4 | |
| Dacarbazine (DTIC) | 50 | 34 | NR | 19.3 | Ramanathan R; 2001 |
| Temozolomide + thalidomide | 11 | 45 | NR | NR | Kulke M; 2006 |
| Temozolomide + bevacizumab | 15 | 33 | 14.3 | 41.7 | Chan JA; 2012 |
| Temozolomide + everolimus | 40 | 40 | 15.4 | NR | Chan JA; 2013 |
| Temozolomide + capecitabine | 72 | 33 | 22.7 | not reached | Kunz PL; 2018 |
| Temozolomide | 72 | 28 | 14.4 | 38 | |

# Cytotoxic therapies

| Regimen | Number of patients* | Tumor response rate (%) | Median progression-free survival (months) | Median overall survival (months) | Author; year |
|---|---|---|---|---|---|
| **Retrospective series** | | | | | |
| Steptozocin + doxorubicin + fluorouracil | 84[Δ] | 39 | 18 | 37 | Kouvaraki M; 2004 |
| Temozolomide (diverse regimens) | 53 | 34 | 13.6 | 35.3 | Kulke M; 2009 |
| Streptozocin + fluorouracil | 96 | 43 | 19.4 | 54.8 | Dilz LM; 2015 |
| Temozolomide (single agent) | 12 | 8 | NR | NR | Ekeblad S; 2007 |
| Temozolomide + capecitabine | 30 | 70 | 18 | NR | Strosberg J; 2011 |

# TK inhibitors and mTOR inhibitors

- Recommended in patients with progressive disease and potentially in patients with newly diagnosed metastatic PNET with high volume disease
- Tyrosine kinase inhibitors
  - Sunitinib
  - Sorafenib and pazopanib
  - Cabozantinib
- Mammalian Target of Rapamycin (mTOR)
  - Everolimus
  - Temsirolimus

# TK inhibitors and mTOR inhibitors

**Randomized trials of molecularly targeted agents in advanced pancreatic neuroendocrine tumors (NETs)**

| Agent | Number of patients | Tumor response rate (percent) | Median TTP or PFS (months) | Reference |
|---|---|---|---|---|
| Sunitinib | 86 | 9 | 11.4 | Raymond et al, 2011 |
| versus | | | | |
| Placebo | 85 | 0 | 5.5 | |
| Everolimus | 207 | 5 | 11 | Yao et al, 2011 (RADIANT-3) |
| versus | | | | |
| Placebo | 203 | 2 | 4.6 | |
| Everolimus | 75 | 12 | 14 | Kulke et al, 2015 (Alliance) |
| versus | | | | |
| Everolimus + Bevacizumab | 75 | 31 | 16.7 | |

PFS: progression-free survival; TTP: time to progression.

# Peptide receptor radioligand therapy (PRRT)

- Treatment option for patients with disease that expresses somatostatin receptors and has progressed on therapy including at least a somatostatin analog
- Uses radiolabeled somatostatin analogs
  - Most frequently used radionuclides yttrium (90Y) and lutetium (177Lu)
  - Differ in terms of emitted particles, particle energy, and tissue penetration
- Clinical trials are being planned - no data yet comparing PRRT with other therapeutic agents
- Use of PRRT should be based on the availability of PRRT and patient preference

# Hepatic arterial embolization (HAE)

- Serves as alternative to medical therapy alone for symptomatic patients with hepatic-predominant unresectable, metastatic PNET
- Bland embolization, chemoembolization, or radioembolization
- Based on the principle that hepatic tumors receive most of their blood supply from the hepatic artery, while normal hepatocytes receive most of their blood supply from the portal vein
- Kennedy et al., 2015 systematic review
  - Reviewed the safety and clinical efficacy and safety of HAE for patients with neuroendocrine liver metastases
  - Patients with bland embolization or chemoembolization, objective radiological response rates ranged from 11 to 100%. Median survival duration ranged between 18 to 80 months

# Back to our patient

- CT triphasic of the liver 4/2016 showed increase in size and number of liver mets
- Began treatment with a Phase I/II Study of the Combination of Temozolomide and Pazopanib in 5/2016
  - Underwent two cycles of treatment
  - Continued to have disease progression
- Underwent hepatic arterial embolization in 9/2016 and 10/2016.
  - Subsequent MRI in 11/2016 showed mixed response in the liver
- He went to Basel, Switzerland for PRRT (peptide receptor radionuclide therapy, usually targeted to somatostatin receptors) in 3/2017

# Back to our patient

- Given severe and persistent symptoms, pt was referred for bilateral adrenalectomy
- Surgery done via retroperitoneal approach given significant hepatomegaly
- Pt started on steroid replacement
- Pathology showed nodular adrenocortical hyperplasia with no evidence of metastatic neuroendocrine carcinoma

# Objectives

- Discuss the classification and diagnostic evaluation of pancreatic neuroendocrine tumors
- Review the systemic therapy options for metastatic pancreatic neuroendocrine tumors

# References


- Uptodate, Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms
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