ESMO ADVANCED COURSE ON NENS

How “functionality” makes a difference to patient care

Simona Glasberg, MD
Neuroendocrine Tumor Unit, ENETS CoE,
Endocrinology & Metabolism Department,
Hadassah-Hebrew University Medical Center, Jerusalem, Israel

14 June 2019

DISCLOSURES

Grants/research supports from Novartis, Ipsen, Lexicon

Receipt of honoraria/consultation fees from Novartis, Pfizer, Ipsen, Lexicon

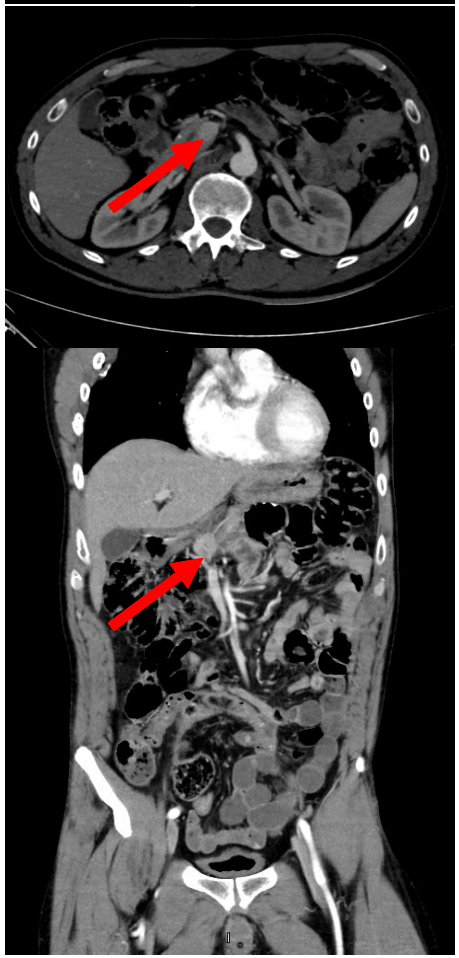
Participation in company sponsored events by Novartis, Ipsen, Lexicon

Case study, 1 Insulinoma

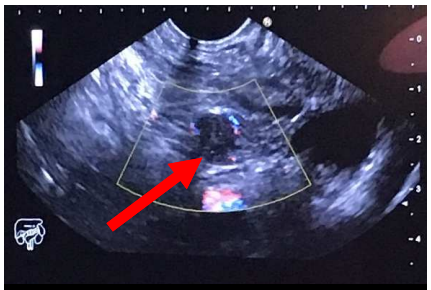
- A.Y, a 64 yo patient, teacher
- Episodic confusion/speech difficulties/blurred vision/weakness
- Evaluation:
  - glucose 55mg% (70-100)
  - brain CT normal
  - 26h/72h fast: glucose=38mg%, insulin=130pmol/l (17.8-173), C-Peptide=860pmol/l (298-2350).
- HRCT/EUS & FNA: a 12mm WD NET G1 (Ki67=2%) (+) CG, SYN, insulin
- On retrospect:
  - low glucose levels since 2015 (40-67mg%)
  - used small meals every 2-3 hours including in the nights
  - a same size lesion already seen in 2014 on a CT (car accident)

- Tx (MDT): Patient offered Whipple or RFA
- F/U: glucose 100-120mg%, lost 5 kg under diet

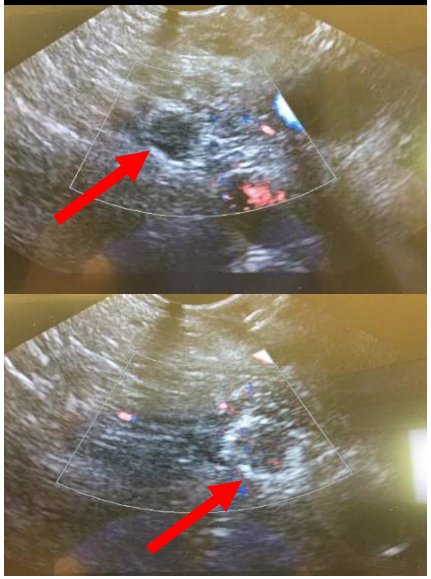
Retrospect, 22/08/2014



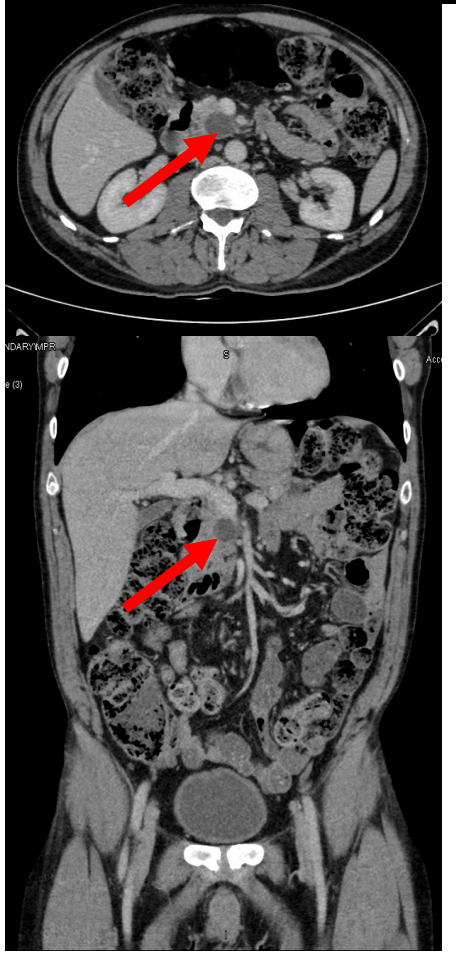
Pre-ablation, 22/10/2017



Post-ablation, 22/10/2017

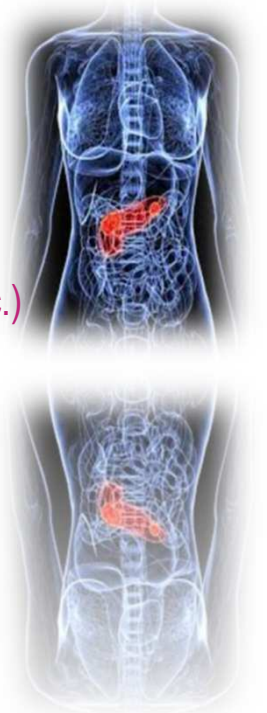


Follow-up, 22/04/2018



Insulinoma

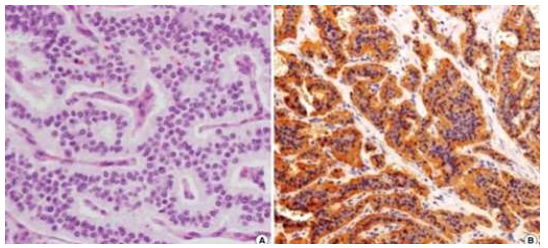
- The most common F-PNETs (~3/1.000.000/y); most WD.
- "Rule of 10" (multiple, malignant, MEN1, ectopic).
- Clinically *Whipple's triad*
  - Symptoms of hypoglycemia
    - neuroglycopenia (headache, blurred vision, confusion, etc.)
    - autonomic (sweating, weakness, hunger, tremor, anxiety, etc.)
    - occasionally, non specific symptoms
  - Low glucose ≤2.2mmol/l (≤40mg/dl)
  - Relief of symptoms with glucose administration
- Diagnosis - high index of suspicion
  - glucose ≤ 2.2mmol/l (≤40 mg/dl)
  - insulin ≥6µU/l (≥36pmol/l) & C-peptide ≥200 pmol/l;
  - the 72-hour fast is the gold standard
  - HRCT/MRI; EUS/IOUS; ^{68}Ga-DOTATATE, ^{68}Ga-exendin-4, etc. PET/CTs



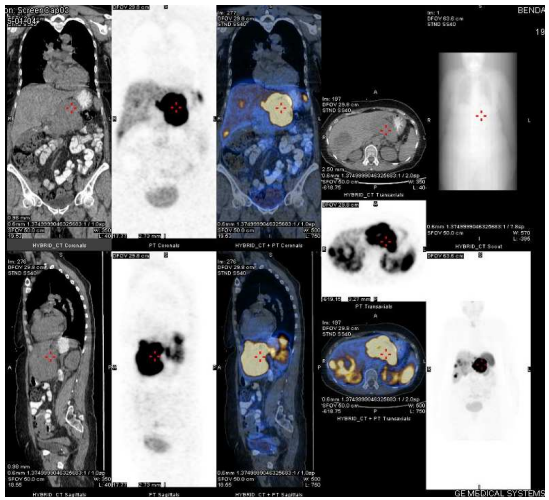
Grozinsky-Glasberg S. et al. (2015) Insulinoma. In: Yalcin S., Öberg K. (eds) Neuroendocrine Tumours. Springer, Berlin, Heidelberg

Case study, 2 Gastrinoma

- B.D., a 66 yo patient
- Last year: increasing upper abdominal pain, heartburn, diarrhea, nausea & vomiting - sudden deterioration
  - urgently operated d/t acute abdomen (perforated duodenal ulcer)
  - HRCT & liver biopsy: a 7.6 cm WD pNET G2 (KI67=8%) & liver lesions; (+) CG, SYN, Gastrin
  - gastroscopy: severe esophagitis & gastritis
- After the operation:
  - gastrin=449, CgA=322ng/mL (20-98) (on PPI)
  - SRI: increased uptake
- Tx (MDT): SSA, everolimus (4y SD), PRRT

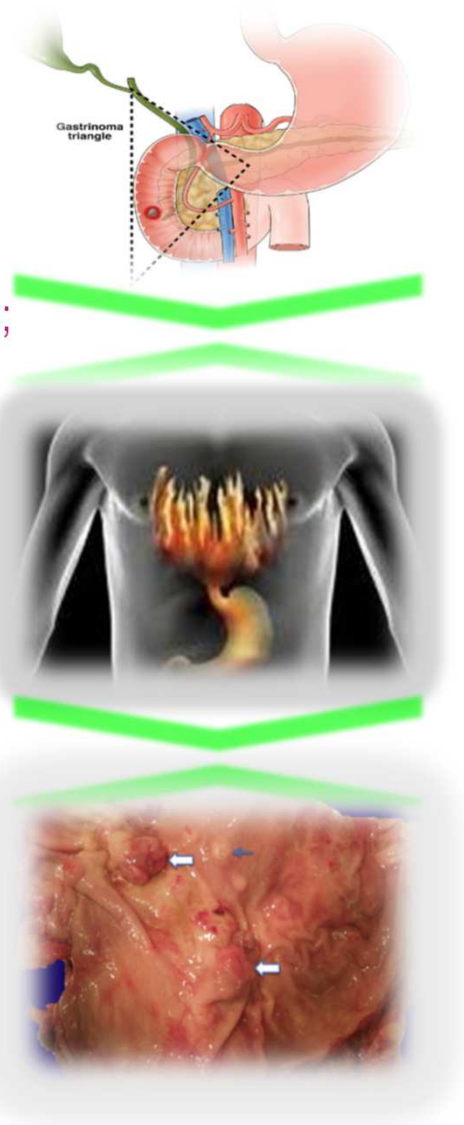


Hematoxylin/eosin sections show a WD NET
IHC stain positive for gastrin



Gastrinomas & Zollinger-Ellison Syndrome (ZES)

- Incidence 1.5/100,000/y
- Gastrinoma triangle (~70% duodenum; ~20% pancreas; ~10% LN)
- Sporadic (~80%), hereditary (~20%, MEN1)
- Malignant ~60-90% of cases.
- *Clinically, symptoms d/t gastrin-related high gastric acid output (ZES) ± tumor mass*
  - abdominal pain, diarrhea, severe peptic disease, etc.
- Diagnosis - high index of suspicion
  - elevated fasting gastrin (~90-98% patients, after stopping anti-acid drugs, *if possible*)
  - localization: HRCT/MRI, EUS, SRI

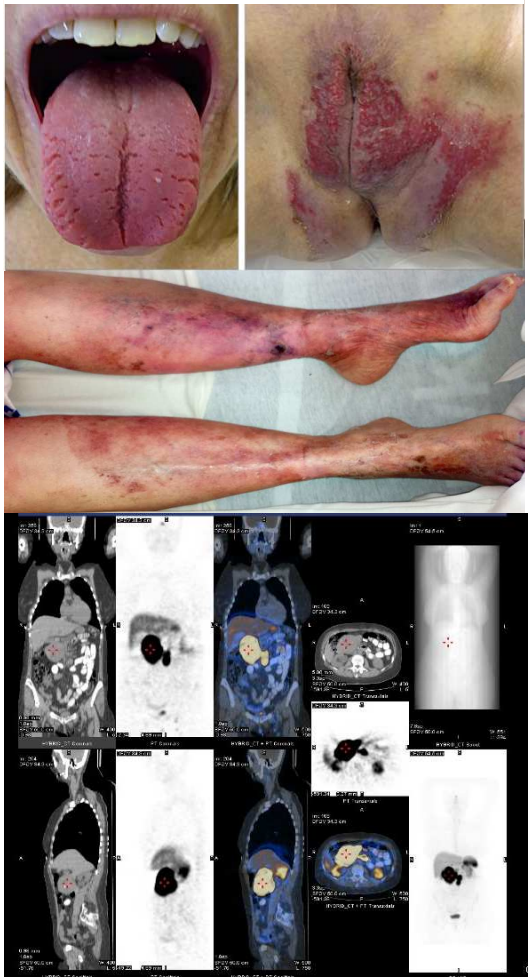


Norton JA. et al. Endocrinol Metab Clin North Am. 2018; 3:577-601.
Grozinsky-Glasberg S. et al. J Hepatobiliary Pancreat Sci. 2015; 22:578–585.
Jensen RT. et al. Neuroendocrinology 2006; 84:173–182.

Case study, 3 Glucagonoma

- K.H, a 50 yo patient:
  - 2y angular cheilitis & glossitis
  - 3m perianal, genital & legs pruritic eruption
  - weakness, anorexia, weight loss (~ 20 kg/y)
  - numbness & tingling in the extremities
- Evaluation:
  - fasting glucose 143mg% (70-100), HGBA1C 7.8%(4.0-5.7).
  - HRCT & EUS/FNB: a 5cm WD pNET G1 (Ki67=3%)
  - glucagon>500pmol/L (<50-150), CgA=980ng/mL (20-98)
  - SRI: high uptake
- Tx (MDT):
  - aac solution - marked improvement in the eruption
  - neo-adjuvant PRRT; tumor resection; SSA

Fissured and erythematous tongue. Erythematous migratory plaques with irregular, erosive, scaly borders and hypopigmented centers on the genital and legs skin (NME).



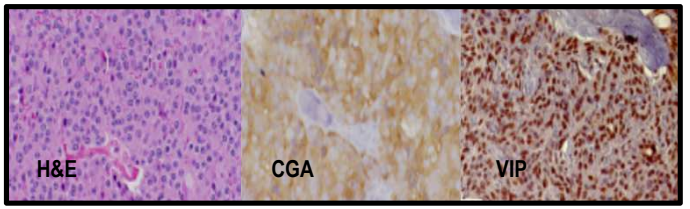
Glucagonoma

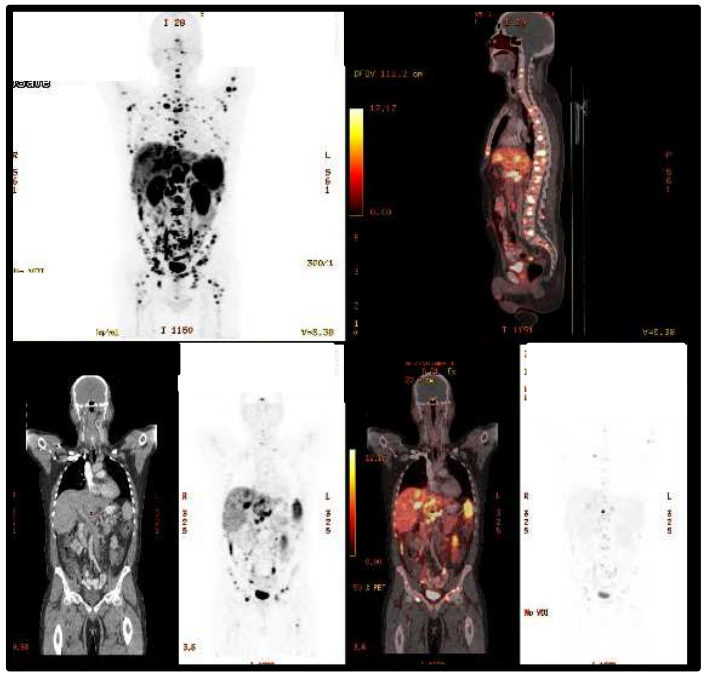
- ~7% of F-pNETs
  - large (>5 cm) and metastatic (~80% liver) at Dx.
- Clinically, *Glucagonoma Syndrome*:
  - necrolytic migratory erythema (NME): erythematous papules/plaques (face, perineum, extremities); nail dystrophy, conjunctivitis, cheilitis, glossitis, stomatitis.
  - new/uncontrolled DM (75-95%)
  - abdominal pain, anorexia, diarrhea
  - thromboembolism (~30%)
  - neurologic: ataxia, dementia, optic atrophy.
- Diagnosis - high index of suspicion
  - fasting glucagon >500pg/ml (50-150)
  - localization: HRCT/MI; EUS; SRI

Eldor R, et al. Clin Endocrinol (Oxf) (2011) 74(5):593-598.
Grozinsky-Glasberg S., et al. J Hepatobiliary Pancreat Sci (2015) 22:578–585

Case study, 4 VIPoma

- S.J., a 57 yo patient
- Admitted (2013) d/t:
  - weight loss, abdominal pain
  - severe watery diarrhea X10-14/d
  - hK^+ 2.5mEq/l (3.5-5.0), acidosis
  - HRCT & liver biopsy: a 2.5 cm metastatic WD pNET G2 (KI67=15%), IHC + CG, SYN, VIP
  - VIP=1050 pg/ml (<70), CGA=202ng/ml (<98);
  - SRI: High uptake pancreatic, liver & skeleton.
- Disease course: PR alternating PD
  - Tx (MDT) multiple: SSA (HD), PRRT, TACE, CAPTEM, denosumab





VIPoma

- Very rare (< 5%) (< 1/ 10 million/y), large & sporadic (5% MEN1)
  - predominantly pancreatic tail (colon, lung, esophagus, jejunum, liver)
  - elevated VIP - rarely in other tumours originating from the sympathetic chain (ganglioneuroblastomas, neurofibromas, pheochromocytomas)
  - ~80% metastatic by the time of diagnosis
- Clinically, *Verner-Morrison (WDHA; Pancreatic cholera) Syndrome*:
  - debilitating watery diarrhea (> 3 L/d), persisting with fasting
  - severe dehydration, hypokalemia, achlorhydria, acidosis
  - abdominal pain, lethargy, nausea, vomiting, muscle weakness & cramps
  - vasodilation, flushing & hypotension, hypercalcemia and hyperglycemia
- Diagnosis - high suspicion index
  - hypokalemia, achlorhydria, acidosis, etc. in the clinical context
  - VIP usually 2-10 times the normal range (20-30 pmol/L).
  - HRCT/MRI, EUS, SSRI, etc.

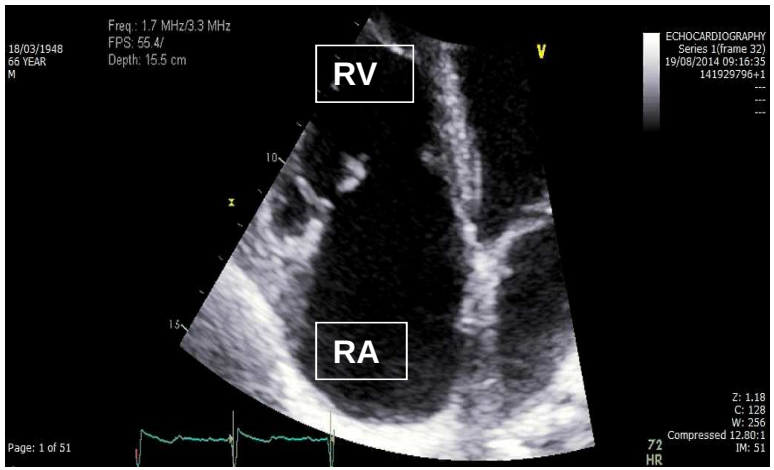
Smith SL, et al. Surgery. (1998) 124(6): 1050-5.
de Mestier L, et al. Eur J Endocrinol. (2015) 172(1):1-3.

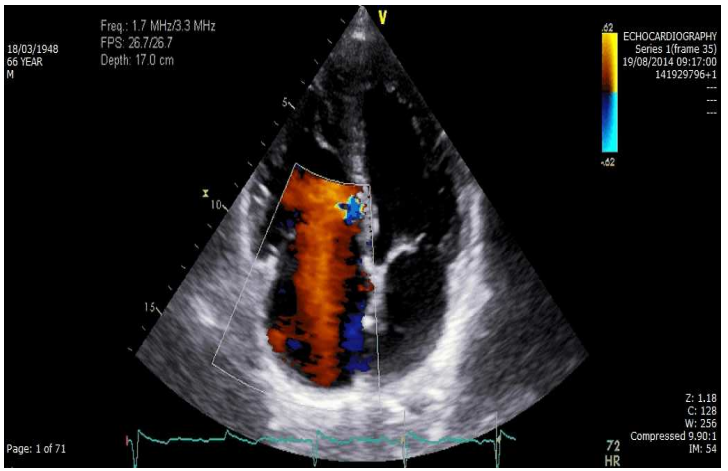
Case study, 5

- H.B., a 67 yo, geoarchaeological desert scientist
- Referred to our NET MDT cardiologist for labile HTN
- Personal History
  - In his mid-50's, mild physical problems (swollen legs, elevated blood pressure).
  - GP prescribed medication, which helped but didn't solve the problem.
  - In addition, chronic diarrhea & frequently turned red, as if flushing.
  - He was still able, though, to go on with his teaching, research & rich family life.

Case study 5, *cont.*

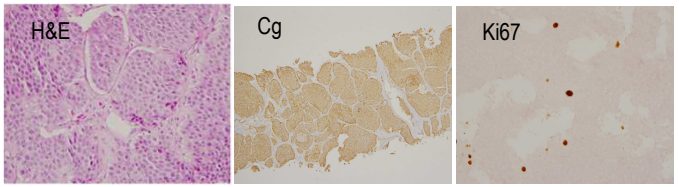
- Physical Exam:
  - Flushing on and off
  - A palpable mass, left supra-clavicular area
  - Leg edema
  - Pansystolic murmur (left lower sternal border)
  - Increased JVP
- Echocardiography: Severe/free TR, cusps fibrosis & retraction

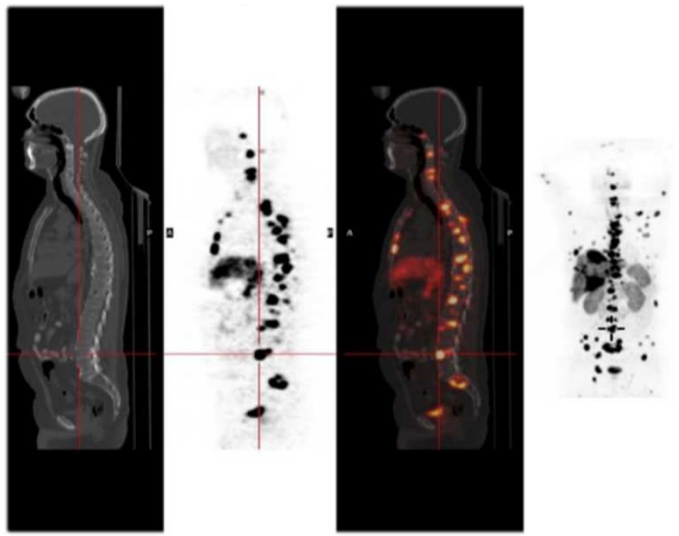




Case study 5, *cont.*
Carcinoid & Carcinoid Syndrome (CS)

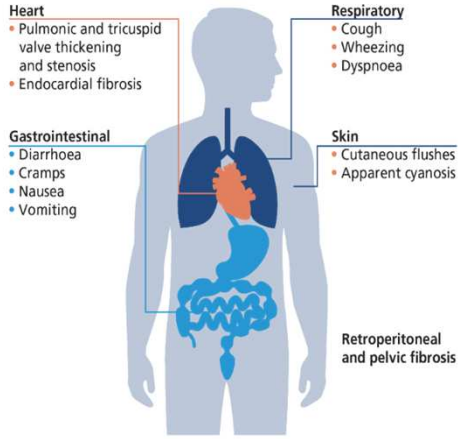
- Diagnostic procedures (Aug 2014):
  - LN biopsy: WD NET G2, Ki67=3%
  - CGA=492ng/ml (19.4-98.1)
  - u5HIAA=235mg/24h (2-8)
  - ^{68}Ga-DOTATATE PET/CT: increased uptake

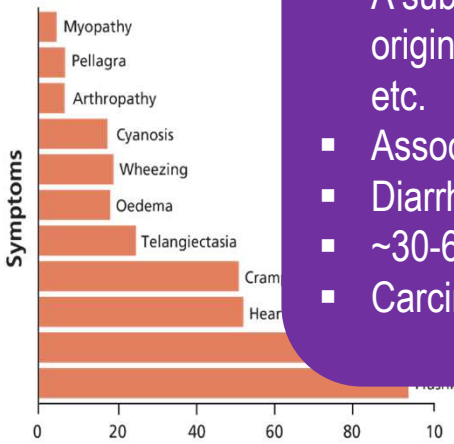




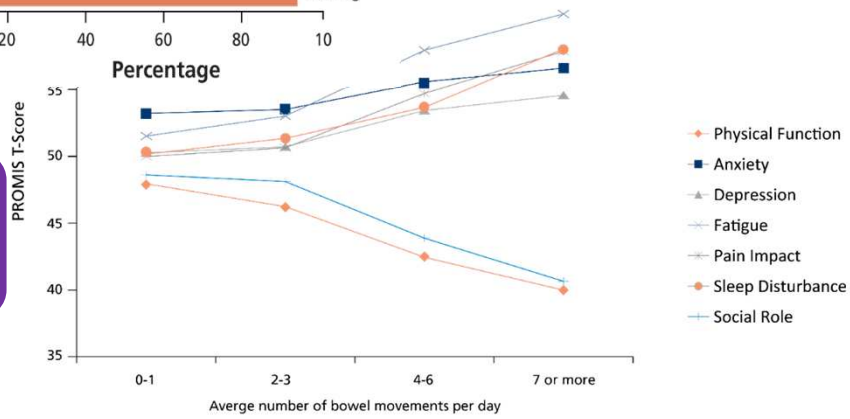
- Dg: <u>WD SI NET G2, CS & CHD</u>
- Initial treatment (MDT):
  - SSA & zolendronic acid
  - diuretics, low salt diet
- F/U: CGA=276ng/ml; u5HIAA=49mg/24h
- Nov 2014 (MDT): TVR (mechanical prosthesis)
- On HD SSA + Telotristat ethyl

Carcinoid Syndrome & CHD





- A subgroup of F-NETs (~ 19%) originating in SI, lung, pancreas, ovary, etc.
- Associated with high serotonin (5HIAA)
- Diarrhoea, flushing, bronchospasm
- ~30-60% CHD - increased mortality
- Carcinoid crisis - life-threatening



- Is associated with reduced QOL & shorter survival

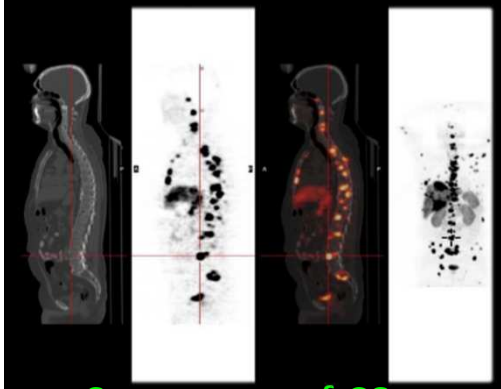
Grozinsky-Glasberg S et al. Neuroendocrinology (2015) 101(4):263-73. ;
Davar J et al., J Am Coll Cardiol. (2017) 69(10):1288-1304.
Halperin DM, et al. Lancet Oncol. (2017) 18(4):525-534.

Real Life Approach to a Patient with CHD
- Principles of Therapy, 1

- Be Aware of the Diagnosis
- Understand its Pathophysiology
- It's a Complex Patient **!**
  (the need for a multidisciplinary specialized team in a specialized center)

CHD - A Double-Edged Sword

- A Metastatic Tumor



- Symptoms of CS

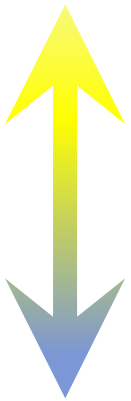
- CHD
  - TVR ± PVR
  - Rt. Heart Failure
  - Easily decompensate

Real Life Approach to a Patient with CS & CHD - Principles of Therapy, 2

- 1st - Decrease Hormonal Levels, *crucial*:
  - control the symptoms (±tumor growth)
  - control the negative haemodynamic impact of serotonin
  - PREVENT CHD appearance/progression/recurrence
- 2nd - Identify & Treat RHF
- 3rd - Decide on Valve Replacement (NET MDT)

1st - Decrease Hormonal Levels in CHD

- Somatostatin Analogues (SSA, also high dose)
- Serotonin synthesis (TH) inhibitor - Telotristat Ethyl
- (PRRT), OR
- (mTOR inhibitor - Everolimus), OR
- (INF-α) (rarely used), OR
- (Locoregional (TACE/SIRT), surgical debulking), OR

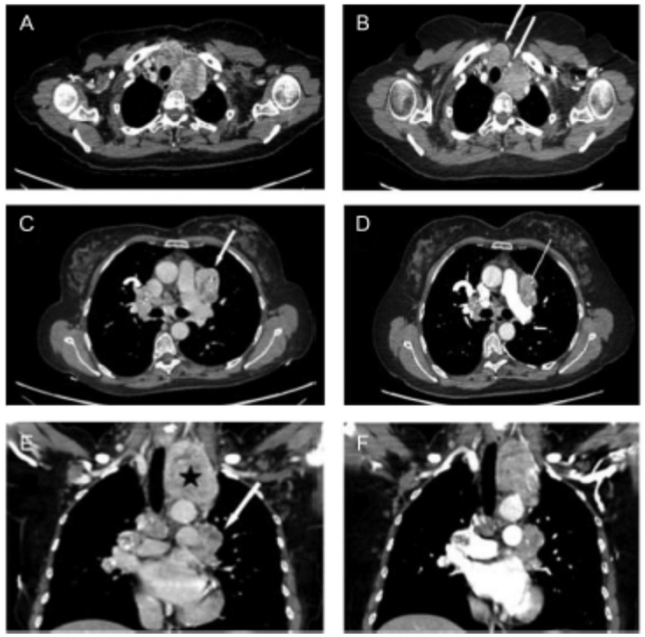


- ❑ SSAs ALWAYS (± Telotristat)
- ❑ All Other Options Sequence (before/after cardiac surgery) should be Considered Individually, Depending on CHD Severity
- ❑ Most patients receive a combination of treatment modalities.

Pavel M. et al., Neuroendocrinology; ENETS Consensus Guidelines 2016

Case study, 6 Ectopic ACTH secretion & Cushing Sdr.

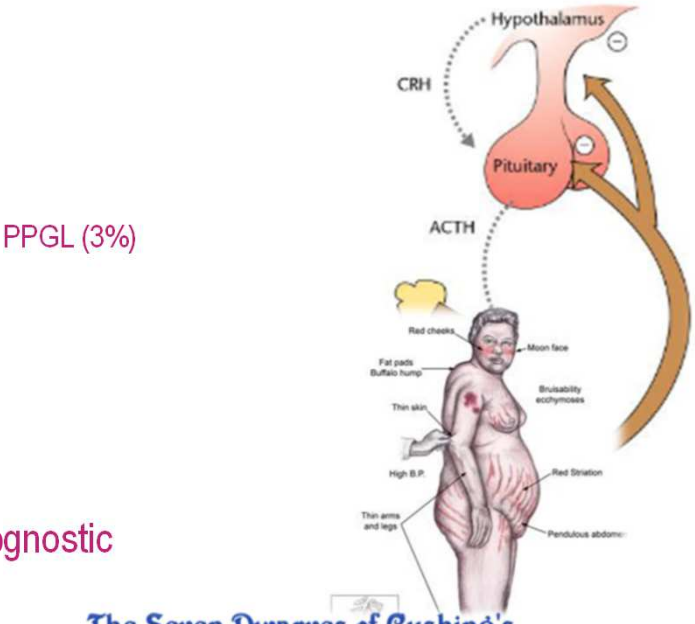
- M.N, a 55 yo patient:
  - s/p thymic atypical carcinoid excision (MI=8/10HPF, Ki67=5%) 10y ago
  - s/p rec.neck dissection (persistent LN)
  - Tx: SSAs
  - slow PD (neck, mediastinum, ileac bone).
- F/U visit:
  - moon face, central obesity, edema, HTN
- Evaluation:
  - no cortisol suppression on 1 & 8mg DST
  - 24h UFC 501µg/24h (9-90).
  - Plasma ACTH 79pg/mL (<46)
  - pituitary MRI (-); IPSS: EAS; CT/SRI: PD
- Tx (MDT): PRRTX4 (PR)

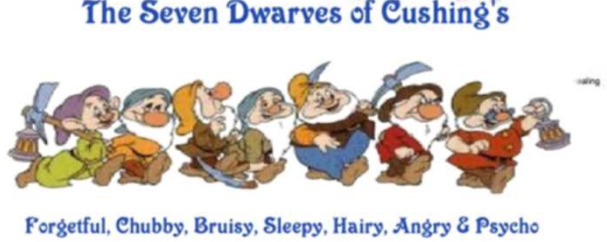


CT of the neck and chest (axial and coronal) showing a decrease in tumor size observed in our patient under the treatment with PRRT.

Ectopic ACTH Secretion (Cushing's Syndrome)

- ACTH/CRH production tumors:
  - SCLC 50%
  - NETs:
    - lung (typical & atypical) ~ 15%
    - pancreas (10%), thymus (5%), MTC (5%), PPGL (3%)
    - rarely ovary, gallbladder, etc.
- Features suggestive of Cushing's:
  - indolent (lung)
  - cyclic (thymic)
  - rapid (MTC, thymic, pNETs) - poor prognostic
- Diagnosis - high index of suspicion
  - diabetes, hK^+
  - ACTH dependent hypercortisolemia
  - normal pituitary MRI; IPSS, SRI

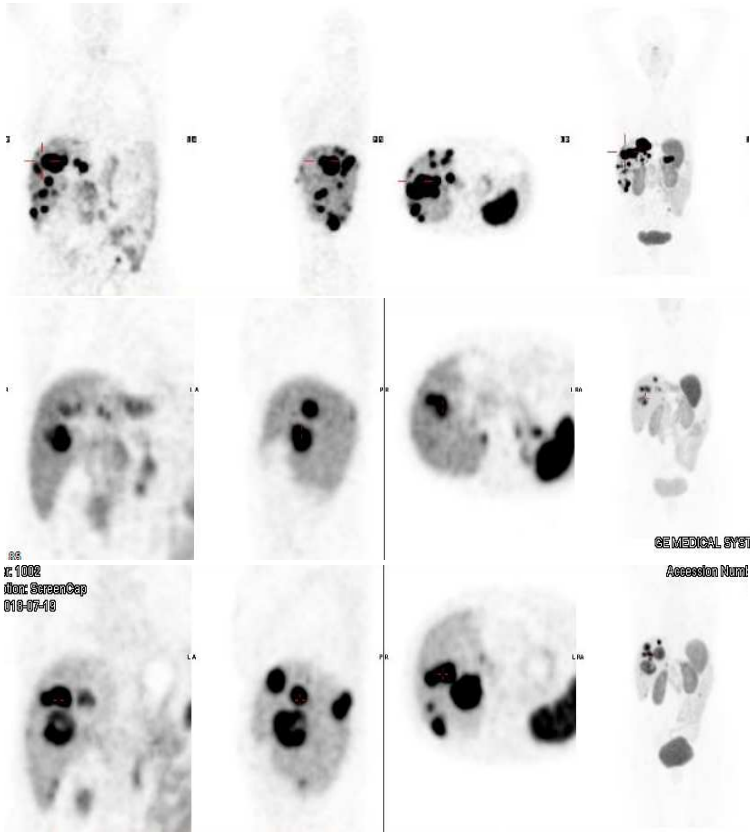




Kaltsas G et al., Endocrine-Related Cancer (2010) 17 R173–R193.

Case study, 7 Hypercalcemia of Malignancy

- R.M, a 58 yo patient, in 2015:
  - weight loss, abdominal pain, diarrhea X4-6 BM/d
  - WD pNET G2 (Ki67=8%), liver mets.
  - CgA=680ng/mL (20-98), 5HIAA=34mg/24h (<8)
  - SRI: high uptake
  - Tx (MDT): SSA (HD), everolimus, sunitinib, PRRTX4 - PR
- Last visit (12m since last PRRT)
  - CgA=1400ng/ml, 5HIAA=2.4mg/24h
  - Ca=12.8mg% (<10.5), P=2.4mg% (>2.5), PTH<4.6pg/ml (4.6-38)
  - SRI: PD



Humoral Hypercalcemia of Malignancy (HHM) & NETs

- ~5 % of patients with cancer
  - rare in NETs: pNETs, PPGL, MTC
  - increased morbidity & mortality
- PTHrP secretion - most common cause
  - structural homology with PTH-N terminus
  - activates PTH receptor (bone, kidney, etc.)
  - hypomethylation of the promoter - a mechanism of its aberrant gene expression
- hypo-Phosphatemia & low PTH.
- Treatment
  - the underlying neoplasm
  - medical treatment of hypercalcemia (the calcimimetic cinacalcet - effective)

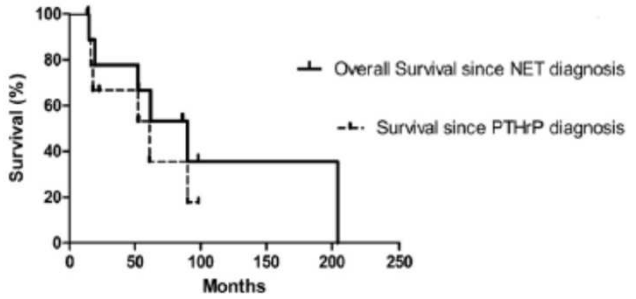
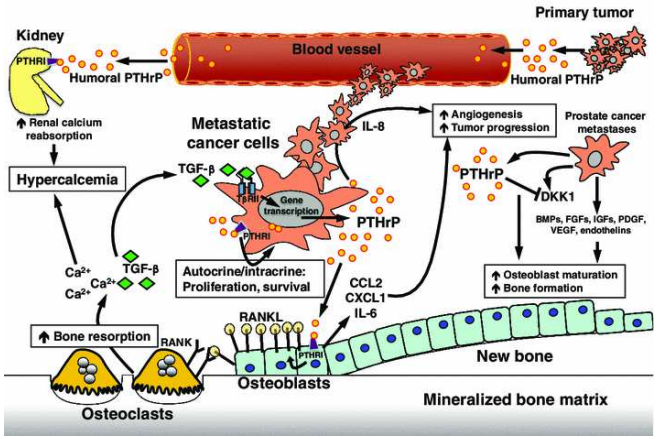


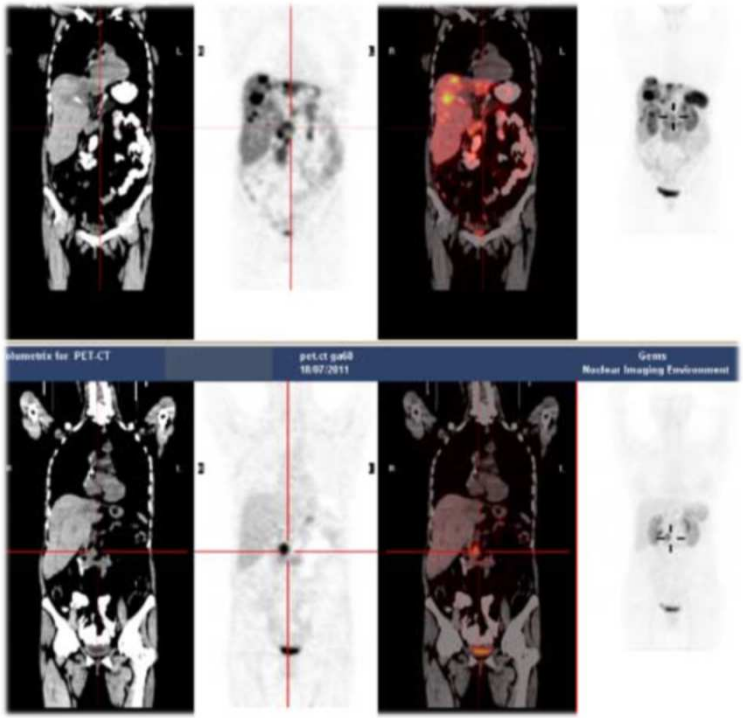
Figure 1. Survival Kaplan-Meier curve of 10 patients with plasma PTHrP-hypersecreting NETs: overall survival and survival since the diagnosis of PTHrP hypersecretion. Median overall survival was 86.0 months. Median survival since PTHrP diagnosis was 52.2 months.



Kamp K et al., J Clin Endocrinol Metab (2014) 99: 3060 –3069.
Wright LE & Guise TA, Clin Rev Bone Miner Metab (2014) 12: 119.
Kanakis G, Kaltsas G et al., J Clin Endocrinol Metab (2012) 97 (4) E627–E631.

Case study, 8
pNET with transformation to Insulinoma

- A.M., a 45 yo patient:
  - abdominal pain, weight loss
  - HRCT & liver biopsy: WD pNET G2 (KI67=7%)
  - SRI: high uptake
  - Tx: SSA; PRRTX4
- 10m later - severe hypoglycemia
  - glucose 1.6mmol/l (4–6)
  - insulin 2021pmol/l (<180), C-peptide 2876pmol/l (<1274)
  - SRI: PD
  - Liver re-biopsy: Ki67=20%
- Tx (MDT): everolimus, STZ & 5-FU
- Died 18m later (PD)



Nahmias A, Grozinsky-Glasberg S et al., Endocrinol Diabetes Metab Case Rep. (2015) 150032.

Secondary Hormone Secretion in Patients With Metastatic NETs

- Most NET, non-functioning (~75%)
- When functioning (~25%) - typically one hormone & distinct syndrome
- A minority (9.3%) - multiple hormones (at diagnosis/later)
  - unclear mechanism (a pluripotent progenitor cell, simultaneous expansion of different tumor cell clones, cell plasticity, etc.)
  - exclusively in patients with advanced/progressive disease - poor prognosis

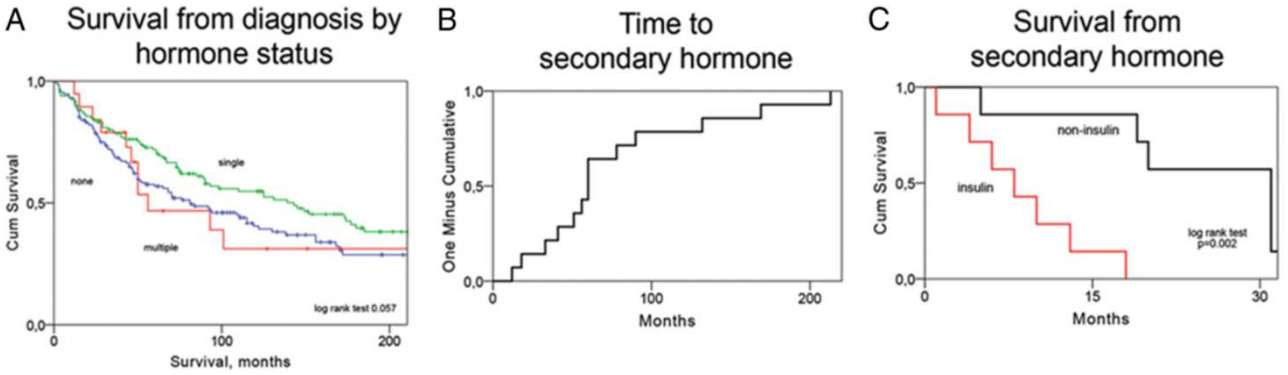


Figure 1. A–C, Kaplan-Meier curves showing survival from diagnosis stratified by hormone secretion pattern (A), time elapsed until secondary hormone secretion (B), and survival from secondary hormone secretion stratified into patients with insulinoma and noninsulinoma (C).

Crona J. et al., J Clin Endocrinol Metab 2016 101(2):445-52. Patel P. & Galoian K. Oncol Letters (2018) 15: 2715-2725. Nahmias A et al., Endocrinol Diabetes Metab Case Rep. (2015):150032; Vinik AI. Endocrine Practice (2014) 20:1222–1230.

How “functionality” makes a difference to patient care, Take Home Messages

- NETs present a pronounced interpatient heterogeneity (diverse tumor biology, clinical presentations, treatment response & related-outcomes).
- A high index of suspicion is needed as increased secretion of neuropeptides & amines that cause distinct clinical syndromes is a major determinant of the clinical course.
- A NET MDT approach is mandatory for a timely diagnosis, appropriate treatment & follow-up, and for improving disease-related outcomes.

Thank you for your attention!