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ENETS Centers of Excellence
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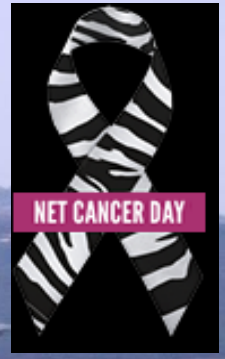
World NEN Lives 2020 Congress

23-24 September 2020



THE COMPLEX JOURNEY OF THE NEN PATIENT
Carcinoid Syndrome and Carcinoid Heart Disease

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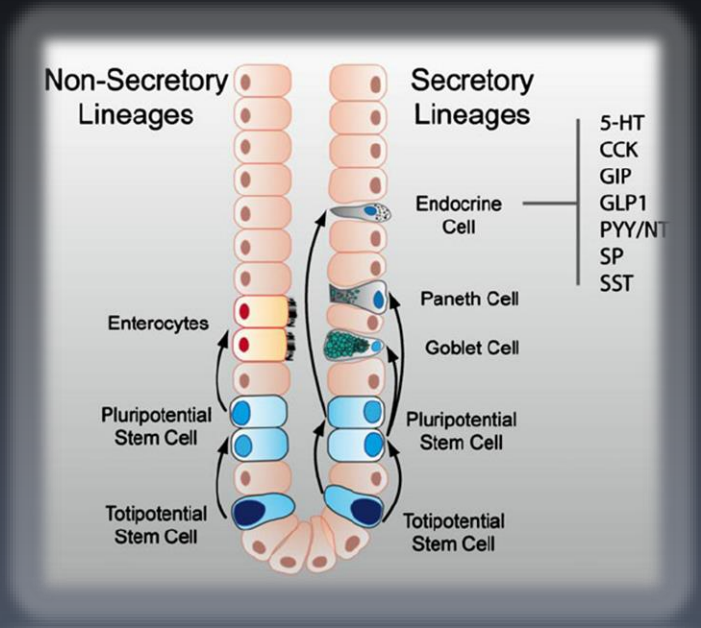
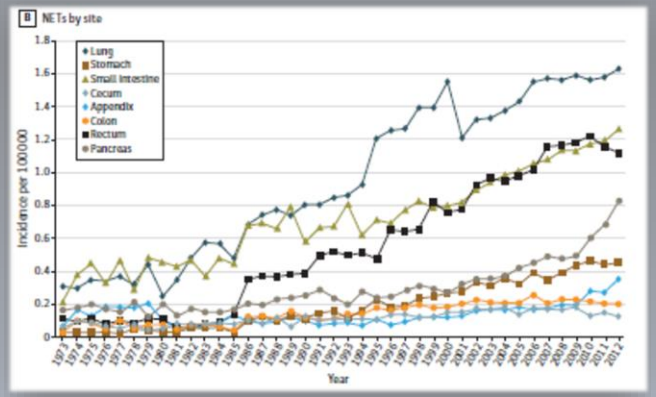
Introduction: Many Challenges in NENs

- Heterogeneous
- Arise from cells throughout the body:
  - NE/EC/ECL cells, migrated from the neural crest (from multipotent stem cells) to the gut endoderm & throughout the body
- Increasing incidence
- Sporadic/ Hereditary (MEN/VHL/NF1/TSC)
- Majority Well Differentiated ENETS G1 & G2
- Frequently (65%) metastatic at diagnosis
- Variety of therapeutic options (need for dedicated NET-MDT)





Dasari A. et al., JAMA Oncol, April 2017
Pavel M. et al, ENETS Guidelines, Neuroendocrinology, 2016

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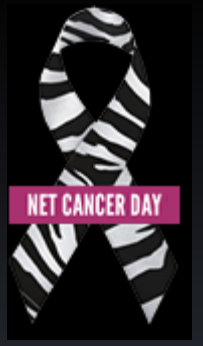
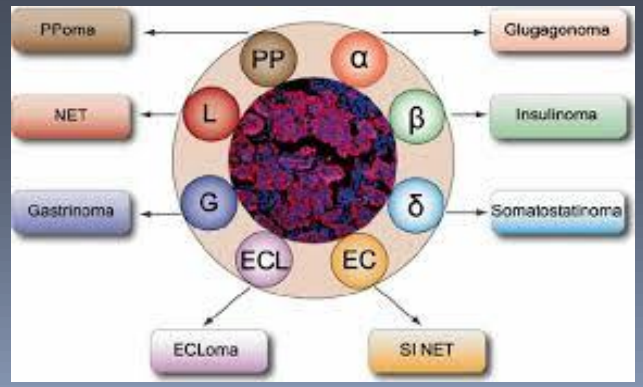
Introduction: Synthesis of amines & peptides



- A special feature of NE cells
- Usually, more than 20 single „hormonal markers“ described in NET
- Rarely, multiple & secondary hormone secretion develops (ACTH, PTH-RP, Calcitonin, GHRH etc.)



Cell	Amine/ Peptide hormone
α	Glucagon
β	Insulin
CCK	Cholecystokinin
δ	Somatostatin (SS)
EC	Serotonin, Substance P
ECL	Histamine
G	Gastrin
GIP	Gastric inhibitory peptide
L	Glucagon like Peptide (GLP)
PP	Pancreatic Polypeptide
S	Secretin, etc.

Vinik A et al., De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet], [Updated 2018 Jun 12]

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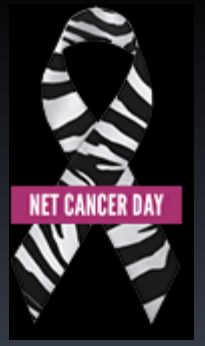
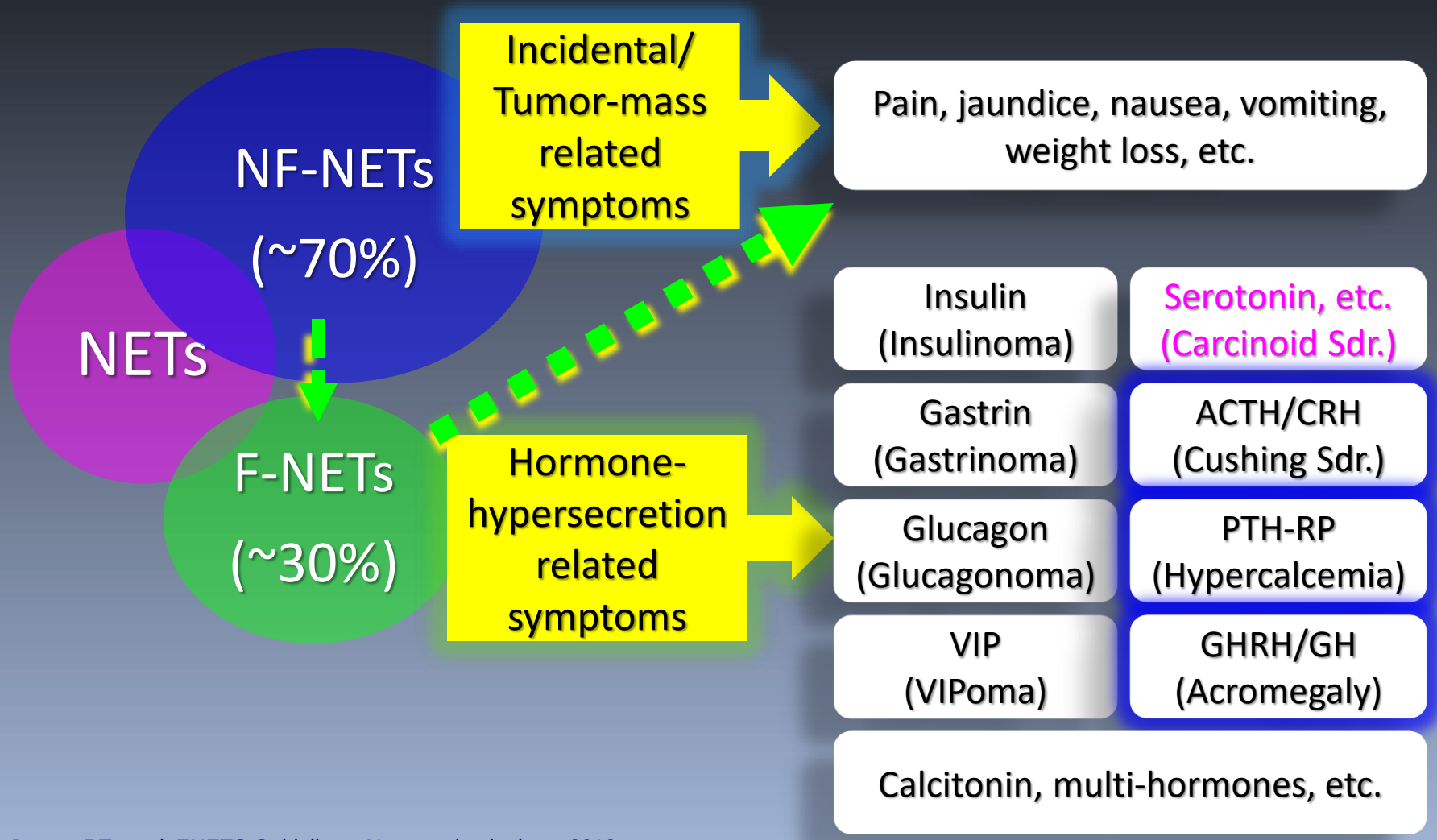
Introduction: NETs, a Clinical Challenge





Jensen RT. et al, ENETS Guidelines, Neuroendocrinology, 2012
Falconi M. et al, ENETS Guidelines, Neuroendocrinology, 2016

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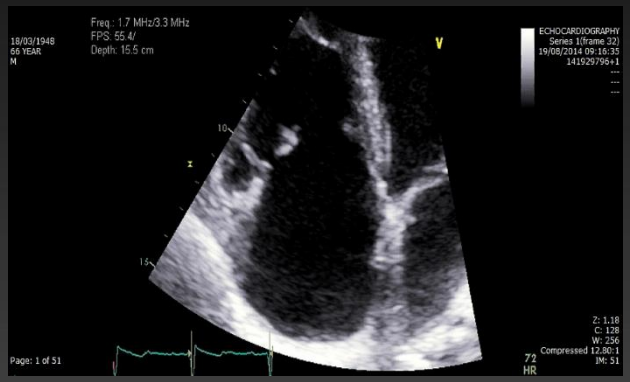
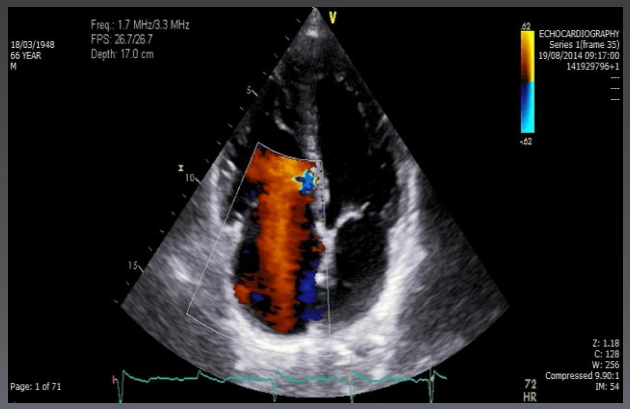
A “Case”

- H.B., a 67 yo, geoarchaeological scientist
- Personal History
  - in his mid-50’s: swollen legs, elevated blood pressure.
  - GP prescribed medication, which helped but didn’t solve.
  - chronic diarrhea & frequently turned red (flushing).
  - still able to go on with his teaching, research & family life.
- Physical Exam:
  - flushing (redness) on and off
  - a palpable mass, left supra-clavicular area
  - legs edema
  - increased JVP
  - pansystolic murmur (left lower sternal border)
- Echocardiography: Severe/free TR, cusps fibrosis & retraction





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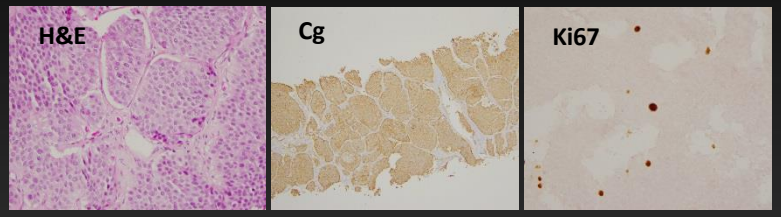
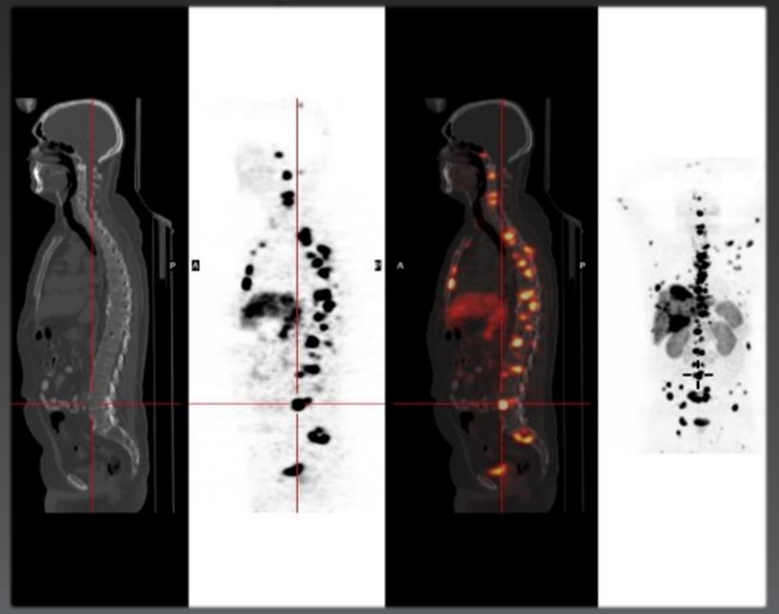
A “Case”, cont.

- Diagnostic procedures
  - 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>
- MDT - Initial treatment:
  - SSA & zolendronic acid
  - diuretics, low salt diet
- F/U: CGA=276ng/ml; u5HIAA=49mg/24h
- MDT: TVR (mechanical prosthesis)
- To date: continued on HD SSA, Xermelo





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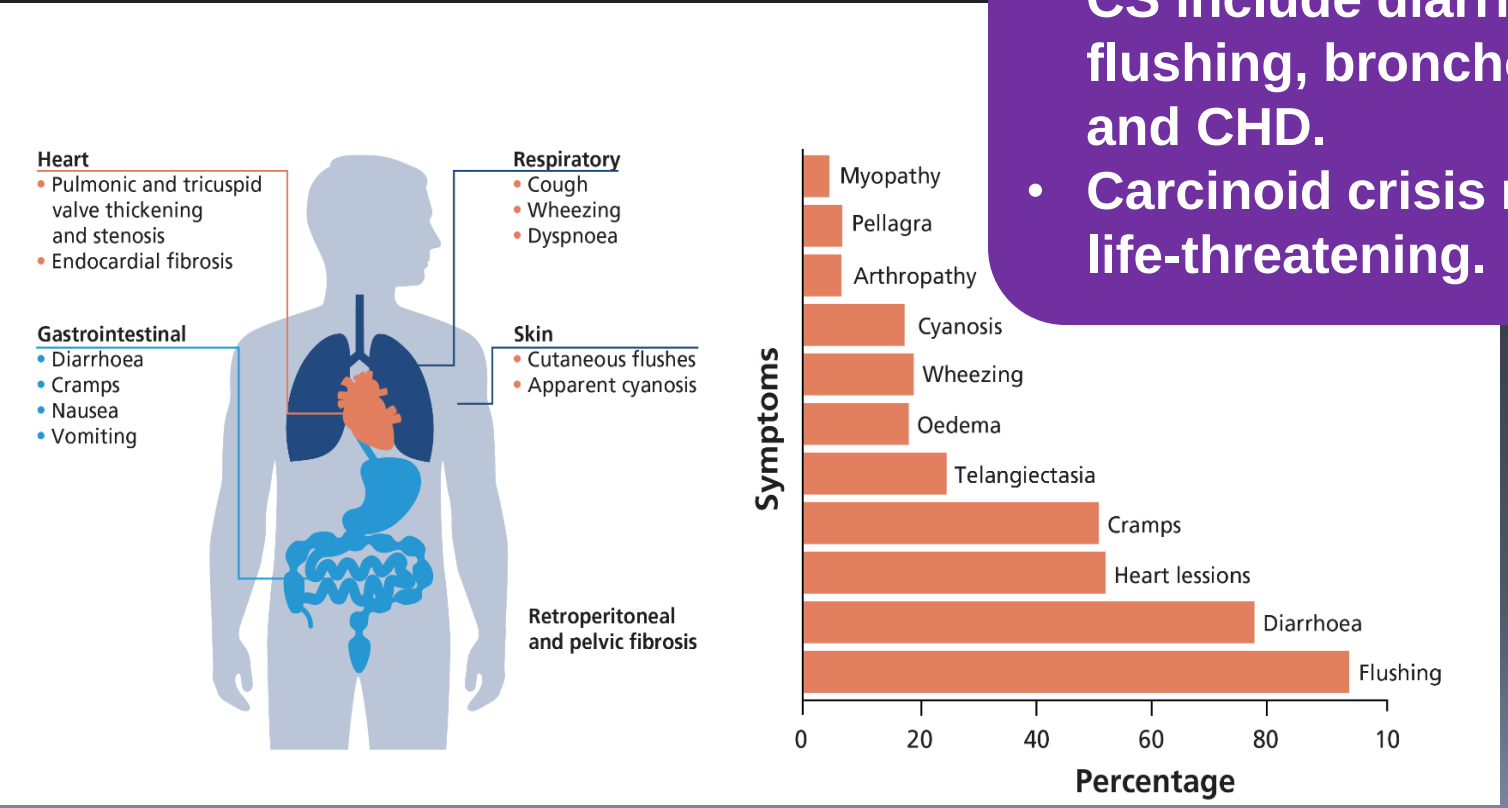
Carcinoid & Carcinoid Syndrome (CS)

- Carcinoid tumors - a subgroup of F-NENs oversecreting:
  - 5-hydroxytryptamine (5-HT, serotonin; the most prominent)
  - Tachykinins
  - Kallikrein
  - Prostaglandins, etc.
- These tumour products are usually inactivated by the liver.
  - When the hormonally active tumour products exceed the hepatic capacity for degradation, the CS ensues.
  - In ~ 5% of patients, mainly with ovarian or pulmonary NETs, or with retroperitoneal metastases, CS may present in the absence of liver metastases.

Grozinsky-Glasberg S, et al. Neuroendocrinology 2015; Davar J et al., J Am Coll Cardiol. 2017.

CS has many distinct symptoms

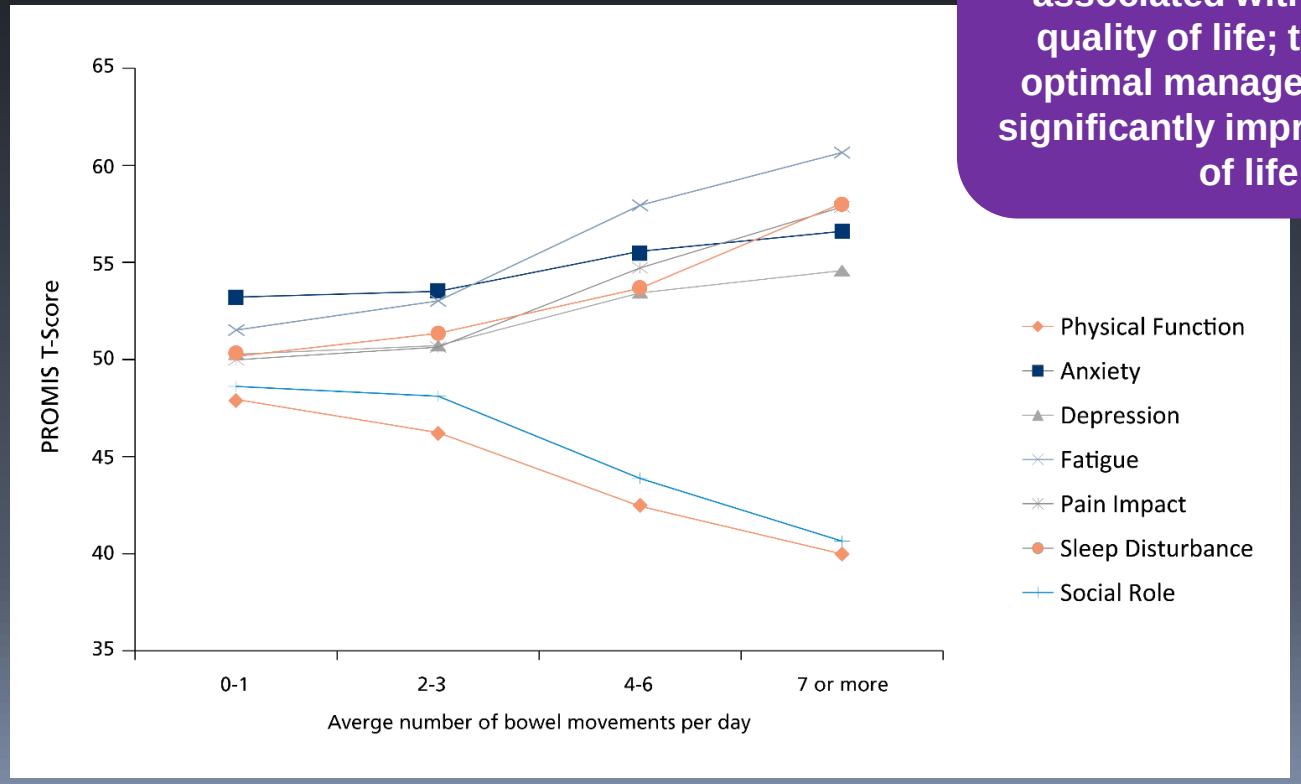
- **The main manifestations of CS include diarrhoea, flushing, bronchospasm, and CHD.**
- **Carcinoid crisis may be life-threatening.**



Mamikunian G, et al. (eds). Neuroendocrine Tumours: A Comprehensive Guide to Diagnosis and Management. 4th ed. Inglewood, CA: Inter Science Institute; 2009; Pasieka J, et al. Can J Surg 2001.

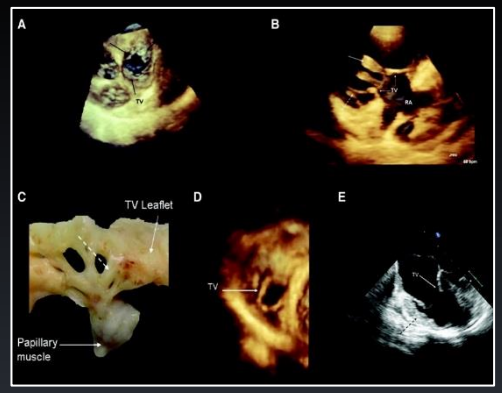
Symptoms of CS reduce patients' QOL

Symptoms such as diarrhoea and flushing are associated with reduced quality of life; therefore, optimal management may significantly improve quality of life



Pearman TP, et al. *Supp Care Cancer* 2016.

Carcinoid Heart Disease (CHD) - in ~30% of CS patients



- A major cause of morbidity & mortality.
- Fibrous thickening & dysfunction of the valves (mostly TV & PV) with RHF.
- Without appropriate treatment, poor prognosis (3y survival ~ 31%)
- May progress very fast!
- The management of CHD is complex
  - pharmacotherapy for RHF
  - aggressive lowering of 5-HIAA levels
  - cardiac valve replacement (in selected individuals) - after valve replacement, >40% of new valves are destroyed if serotonin remains high (biological valves)

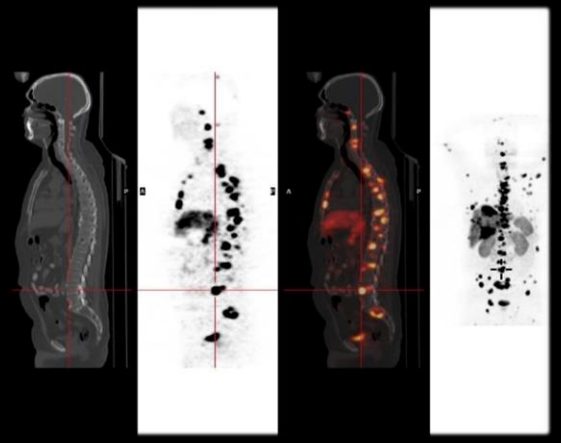
Davar J et al., J Am Coll Cardiol. 2017; Zuetenhorst J, et al. Cancer 2003; Denney W, et al. J Am Coll Cardiol. 1998; Zacks J, et al. Poster ENETS (abstr. 2016).

Real Life Approach to a Patient with CS & 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)

CS & CHD - A Double-Edged Sword

- A Metastatic Tumor



- Symptoms of CS

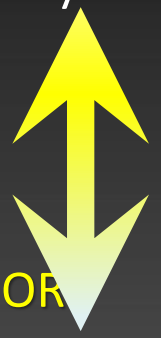
- CHD
  - TVR ± PVR
  - Rt. Heart Failure
  - Easily decompensate

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 (NEN 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

2nd - Identify & Treat CHD-related RHF

- Initially, relieve the symptoms of right heart failure with:
  - loop diuretics
  - fluid & salt restriction
  - compression stockings
- *Cautious* … in advanced right ventricular failure, these measures become deleterious due to the depletion of intravascular volume, further reducing of the cardiac output.

Fox DJ, Khattar RS. Heart 2004; 90: 1224–1228.
Grozinsky-Glasberg S et al, Neuroendocrinology; 2015;101(4):263-73.

3rd - NET MDT - Individualized Approach

"Choosing the Right Valve at the Right Time"

- Evaluation of CHD severity (imaging, markers)
  - life-time expectancy (3y survival 68% without vs 31% with CHD).
- Risk of bleeding
- Decide on time of surgery & type of prosthesis (>40% of new biological valves are destroyed if serotonin remains high)
- Discuss with the patient (RISK/BENEFITS/PREFERENCE/AVAILABILITY)

Davar J et al., J Am Coll Cardiol, 2017;69(10):1288-1304.
Korach A, Grozinsky-Glasberg S, et al. J Heart Valve Dis. 2016;25(3):349-355.
Grozinsky-Glasberg S et al, Neuroendocrinology; 2015;101(4):263-73.

Take Home Messages

- CHD Prevention by CS control - The Best Treatment
- CHD-related Right HF - the cause of death in ≤ 50% pts
  - may progress very fast!
- The Heart (Of the Matter) Needs an MDT Approach
  - aggressive lowering of 5-HIAA levels
  - pharmacotherapy for RHF
  - timely valve replacement (selected individuals)
- The Survival Rates Are Improving
- Unmet needs
  - serotonin inhibition
  - studies on CHD prevention/reversibility?

Eriksson B. et al, ENETS Guidelines, Neuroendocrinology, 2016
Davar J. et al., J Am Coll Cardiol, 2017;69(10):1288-1304.