Recent update on diagnosis, clinical features and management of Multiple Endocrine Neoplasia (MENs)

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Agenda

- MENs - Introduction
  - definition, incidence, classification, etc.
- The approach of MEN-NENs: *what clinicians should know?*
  - clinical features
  - markers
  - histo-pathology
  - molecular imaging & theranostic
  - treatment
  - case study
- Take Home Messages

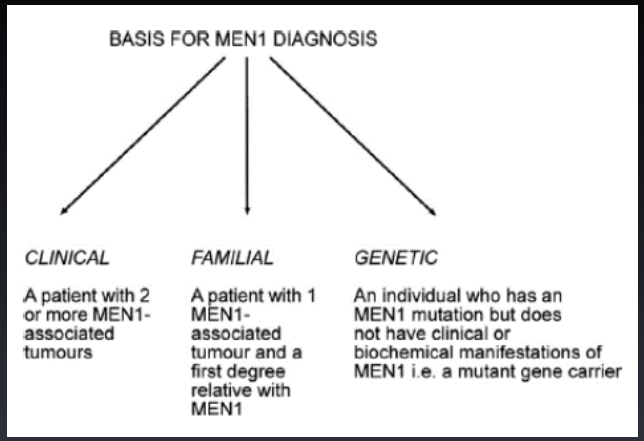
Introduction: MENs

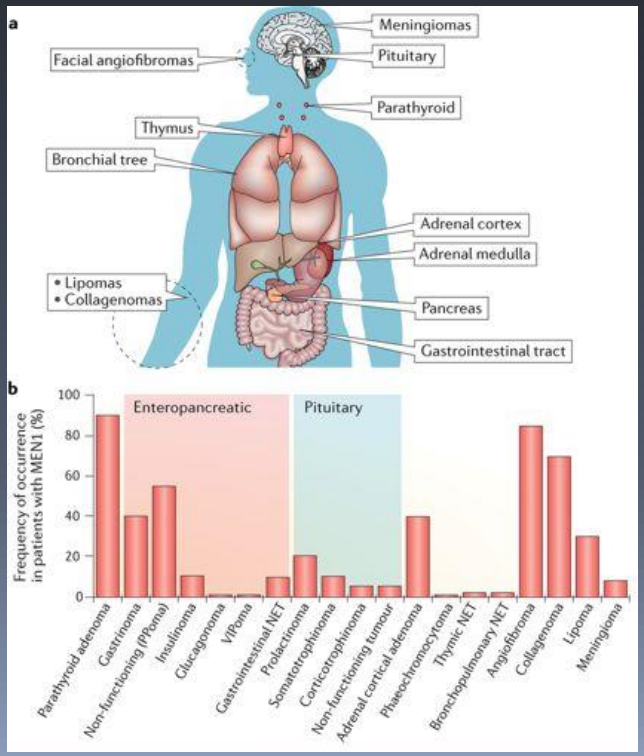
- The occurrence of tumors ≥2 endocrine glands in a single patient.
- 4 major forms (AD disorders) associated with specific tumors
  - MEN1 (Wermer's syndrome, menin mutations)
    - Hyperparathyroidism (parathyroid hyperplasia)
    - Anterior pituitary tumors
    - Pancreatic NENs, multiple
  - MEN2 (previously MEN2A, mutations of a TK receptor encoded by RET)
    - Medullary thyroid carcinoma (MTC)
    - Pheochromocytomas
    - Hyperparathyroidism (parathyroid hyperplasia)
    - *(MTC-only)*
  - MEN3 (previously MEN2B, RET mutations)
    - MTC
    - Pheochromocytomas
    - marfanoid habitus, mucosal neuromas, medullated corneal fibers, intestinal autonomic ganglion dysfunction, leading to megacolon
  - MEN4 (MEN X, cyclin-dependent kinase inhibitor (CDNK1B) mutations)
    - parathyroid, anterior pituitary (and pancreatic tumors)
    - tumors of the adrenals, kidneys, and reproductive organs.

Thakker RV., Mol Cell Endocrinol. 2014 Apr 5; 386(1-2): 2–15.

MEN1 (Wermer Syndrome)

- Prevalence: 2/10000
- Definition (consensus):
  - ≥ 2 main tumor types
  - at least one MEN1 tumor + 1st degree relative with MEN1
- The gene: 1997, on chr 11q13
  - encodes a 610 aac protein (menin)
  - involved in cell division, genome stability and transcription regulation.
  - may increase/decrease gene expression by epigenetic regulation via histone methylation.
- The degree of penetrance at 20yo is ~ 43%, at 35yo ~ 85%, and at 50yo ~ 94%.





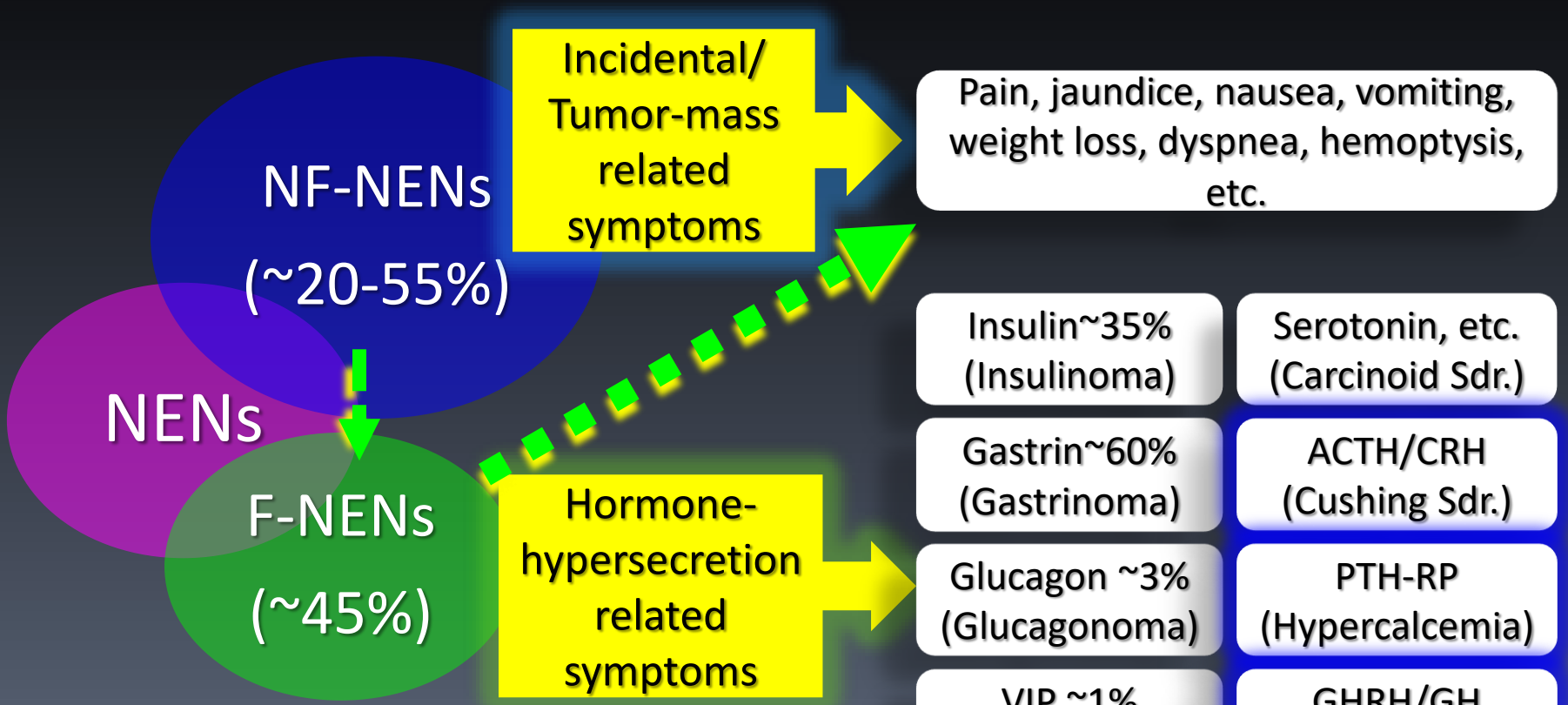
Thakker RV., Mol Cell Endocrinol. 2014; 386(1-2): 2–15.
Frost M, Lines KE and Thakker RV, Nature Rev Endocrinol 2018; 14, 216–227.

MEN 1

Organ involved		Specific tumor (prevalence by 40 y)	Clinical Presentation
Parathyroid disease (95%)		Diffuse Hyperplasia	Symptoms related to hypercalcemia or hypercalciuria
		Adenoma, Multiple	
NETs	**PNETs (30%-80%)**	Gastrinomas (>50%)	ZES, diarrhea, abdominal pain
		Insulinomas (10%-30%)	Whipple triad
		Glucagonomas (~3%)	necrolytic migratory erythema, weight loss, anemia, stomatitis
		VIPomas (extremely rare)	Verner-Morrison syndrome
		NF PNETs (20%-100%)	Asymptomatic, but with malignant potential
		Somatostatinomas (extremely rare)	Somatostatinomas syndrome, rare
		Other (e.g., GHRH-secreting)	Rare, increased GH & IGF1 levels
	Foregut NETs (2%-10%)	Thymic, gastric, bronchial NETs	Organ specific
Pituitary Tumors		Prolactinomas (20%)	oligomenorrhea, galactorrhea, infertility in woman; impotence and infertility in men
		Other: ACTH, TSH, GH+PRL, GH, NF (each 2-9%)	Hormone-dependent
Other Endocrine Manifestations		Benign adrenocortical tumors (73%)	Most non-functioning
		Adrenocortical carcinoma (13%)	Hormone-dependent
		Pheochromocytomas (<1%)	Rarely described, mainly asymptomatic
		Thyroid adenomas, goiter and carcinoma (25%)	Usually incidental finding
CNS-tumors		Ependymomas, schwannomas, meningiomas (1%)	Mainly asymptomatic
Cutaneous manifestations		Multiple subcutaneous lipomas (33%); visceral, pleural, or retroperitoneal lipomas (rare) Facial angiofibromas and collagenomas (up to 88%)	

Grozinsky-Glasberg S & Gross DJ, In © Springer-Verlag Berlin Heidelberg 2015 S. Yalcin, K. Öberg (eds.), Neuroendocrine Tumours; DOI: 10.1007/978-3-662-45215-8_20

MEN1-related NENs: a Clinical Challenge



- Multicentric
- May be malignant
- Average life expectancy with NF pNENs is decreased.

Thakker RV., Mol Cell Endocrinol. 2014; 386(1-2): 2–15.
Frost M, Lines KE and Thakker RV, Nature Rev Endocrinol 2018; 14, 216–227.

MEN1-related NENs: Biomarkers

- ❑ General Tumor markers
  - Chromogranin A
  - α-, ß-subunit-hCG
  - Pancreatic Polypeptide
- ❑ Specific NET markers
  - Gastrin
  - Insulin
  - Glucagon, VIP, SST
  - Serotonin, 5-HIAA
  - Calcitonin
  - PTHrP, ACTH, GHRH…..
- ❑ NSE
- ❑ ProGRP - lung NENs
- ❑ Alk. Phos., Platelets & LDH
- ❑ Novel biomarkers
  - VEGF expression & plasma levels (angiogenesis, spread, progression and decreased PFS)
  - SSTR subtype expression - prognostic factor of survival
  - Downregulation of mTORi expression (TSC, PTEN) - shorter PFS & OS
  - CTC - prognostic markers (need validation)
  - NETest - expression of 51 NET genes in peripheral blood (needs validation)

MEN1-related NENs: Histo-pathology
WHO 2017-2018 Grading System for NENs

- To distinct between WD NETs & PD NECs
- Changes:
  - Alteration in set point of Ki67 cut offs
  - Subdivision of NENs with Ki67>20% into WDG3 NETs & PDG3 NECs
  - Recommendations on interpreting Ki67 (if mitotic count and Ki67 are discordant, the higher figure (almost always Ki67) is used

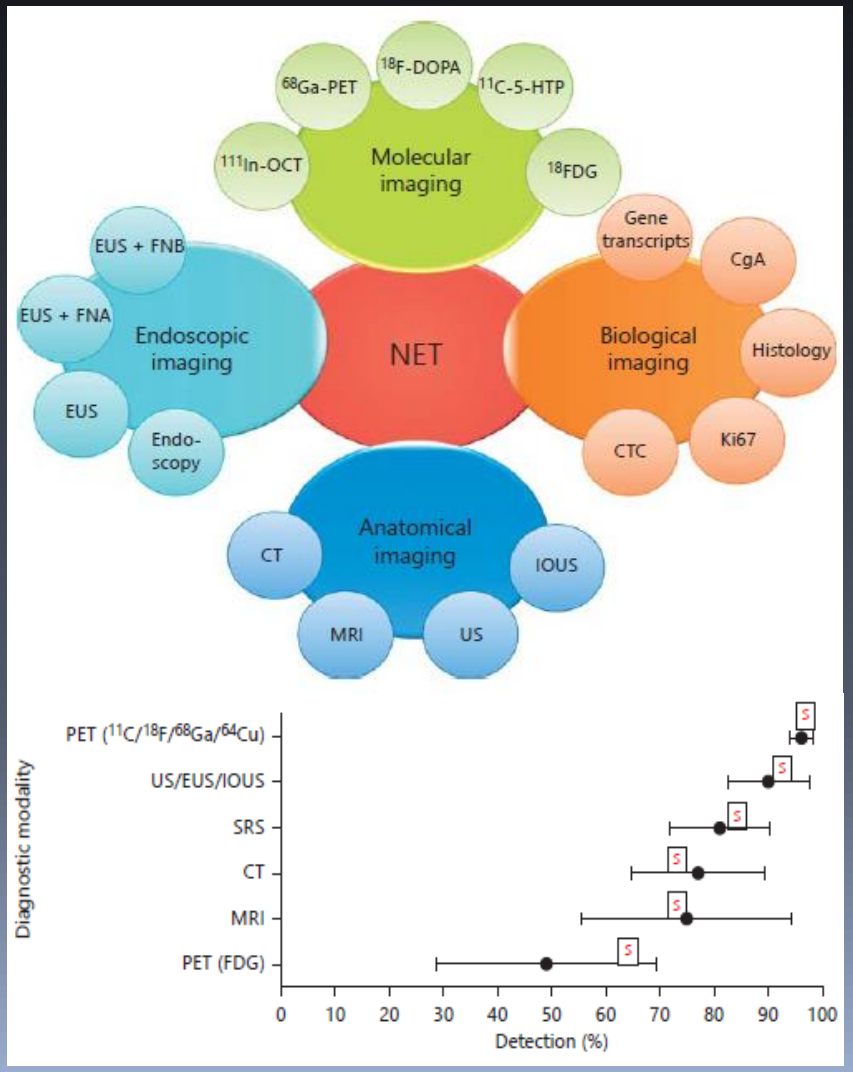
World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

Rindi G. et al., Modern Pathology volume 31, pages1770–1786 (2018)

MEN1-related NENs: Imaging (Molecular)

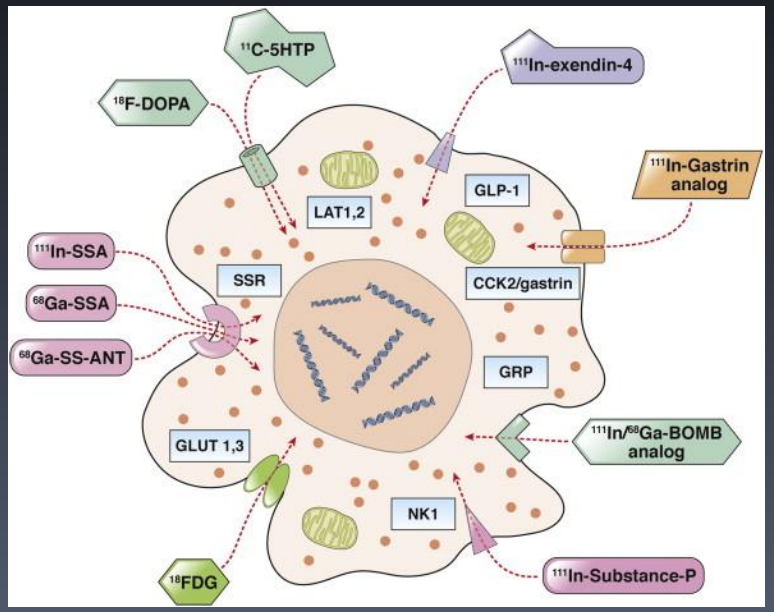
- A combination of anatomic & functional techniques is mandatory to optimize sensitivity & specificity
- Imaging phenotype of the tumor is mandatory - THERANOSTICS:
  - using tracers that specifically target a molecular pathogenesis pathway
  - translate it into a precision approach to patient management.

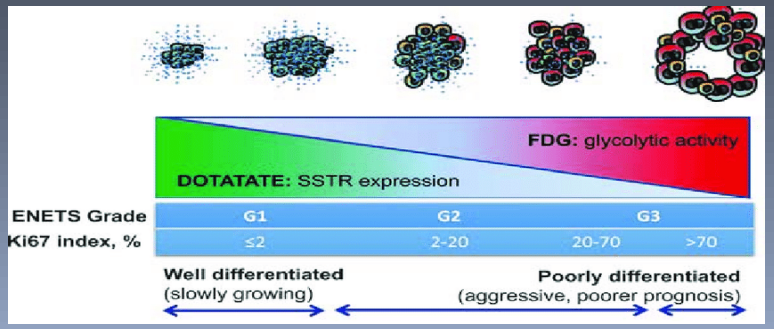


Bodei L et al. Neuroendocrinology 2015;101:1–17.

MEN1-related NENs: Functional imaging of MEN-NENs using radiolabeled ligands.

- Radiolabeled SSAs the most exploited (^{68}Ga-SSA PET/CT high sensitivity in MEN1).
  - confirms suitability for PRRT
- Alternative PET (^{18}F-DOPA & ^{11}C-5HTP) - sensitive.
- Experimental: SSR antagonists, GLP-1, etc.
- 18F-FDG PET/CT - to identify increased malignant potential
- The " flip-flop " phenomenon: high DOTATATE & low FDG uptake in WD NENs/sites vs the opposite in PDNENs/sites





Kidd M et al. DOI: 10.1016/j.jcmgh.2014.12.008
Morgat C, et al. Eur J Nucl Med Mol Imaging. 2016 Jul;43(7):1258-66.
Wild D, et al., J Nucl Med 2014; 24;55:1248

MEN1-related NENs: Treatment Principles

- Treatments for MEN1-pNETs have not been formally assessed
  - used on the basis of their effects on sporadic pNETs
- The treatment outcomes less successful
  - concomitant occurrence of multiple tumours in different glands
  - multifocality
  - occult metastases prevalent
  - may be larger, more aggressive, resistant to treatment

Therapeutic approach - NET MDT

Thakker RV., Mol Cell Endocrinol. 2014; 386(1-2): 2–15.
Frost M, Lines KE and Thakker RV, Nature Rev Endocrinol 2018; 14, 216–227.

MEN1-related NENs: Molecular profiling

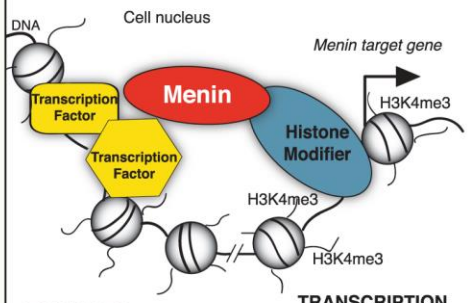
"Twenty years of menin: emerging opportunities for new therapies in MEN1"

- The molecular function of menin - a challenge.
  - gene expression regulation (biochemical, proteomics, genetics, genomics)
  - connects transcription factors to histone-modifying protein complexes.

- Therapeutic implications: to restore the epigenetic changes caused by loss of menin function (by inhibition of histone demethylases).

Transcription Factors

- AP-1 (JunD)
- SMAD
- Forkhead (FOXA2)
- MYC
- Nuclear receptors
- Beta-CATENIN



Histone Modifiers

- MLL1/MLL2 (H3K4me3)
- HDAC/SIRT
- PRMT5 (H4R3me2s)
- SUV39H1 (H3K9me3)

Dreijerink KMA et al. Endocrine-Related Cancer (2017) 24, T135–T145

MEN1-related NENs: Treatment Principles

Medical

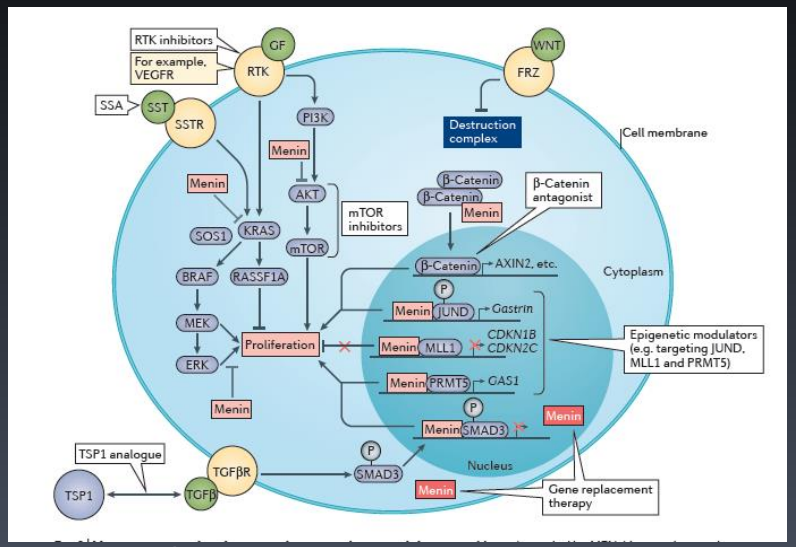
- Biotherapy
  - Somatostatin analogues (SSAs), such as octreotide, lanreotide and pasireotide
  - IFNα
  - Mechanistic target of rapamycin (mTOR) inhibitors, such as everolimus
  - Receptor tyrosine kinase (RTK) inhibitors, including platelet-derived growth factor receptor (PDGFR)[a] and vascular endothelial growth factor receptor (VEGFR)[a] inhibitors, such as sunitinib, sorafenib, imatinib and vandetanib
  - Vascular endothelial growth factor A (VEGFA) antibodies, such as bevacizumab
- Chemotherapy
  - Alkylating agents[b], such as streptozocin, temozolomide and cisplatin
  - Anti-microtubule agents[b], such as etoposide and docetaxel
  - Topoisomerase inhibitors[b], such as doxorubicin and irinotecan
  - Antimetabolites[c], such as 5-fluorouracil (capecitabine[d]) and gemcitabine
  - Cytotoxic antibiotics[c], such as actinomycin D, mitomycin C, doxorubicin and mitoxantrone
  - Nonclassic compounds

Surgery

- Curative
- Cytoreduction

Radiological treatment

- Radiotherapy
  - External beam
  - Tumour-targeted (for example, peptide receptor radionuclide therapy (PRRT) using ^{90}Y-DOTATOC or ^{177}Lu-DOTATE)
- Interventional radiology
  - Radiofrequency ablation (RFA)
  - Transarterial embolization (TAE)
  - Transarterial chemoembolization (TACE)
  - Selective internal radiation therapy (SIRT)



Specific therapies targeting NENs are required - preclinical studies promising

- gene therapy
- epigenetic modifiers
- WNT pathway antagonists
- VEGF-signalling antagonists

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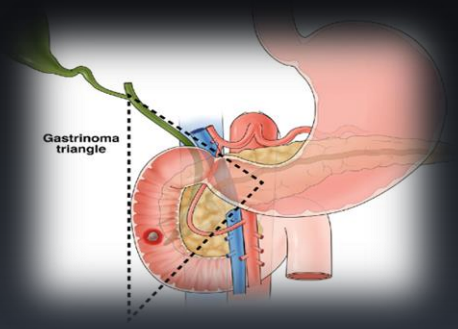
MEN1 - NF PNETs

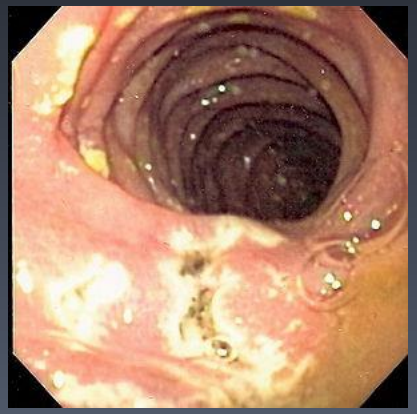
- Most common
  - identification is major
  - iIn patients less than 15 yr of age.
  - no clinical syndrome
  - have malignant potential
  - associated with a worse prognosis
- The diagnosis - delayed
  - radiological screening mandatory (10 yo)
  - optimal screening - still controversial
    - EUS, most sensitive
    - SRI, for metastatic disease.
- Treatment
  - based on tumor size
  - surgery for tumors of more than 2 cm, if excisable
  - medical treatment: as for non-MEN1

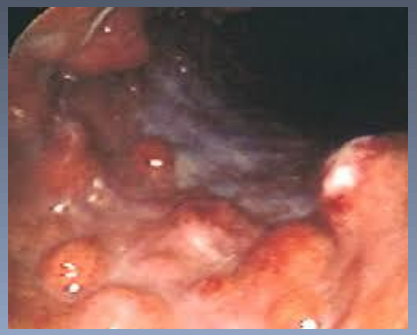
Thakker RV., et al. J Clin Endocrinol Metab. 2012 Sep;97(9):2990-3011.
Chiloro S, et al. Endocrine. 2018 May;60(2):362-367.

MEN 1 - Gastrinomas, ~60%

- Most common MEN1-FNENs
  - duodenal, small, multiple, 50% metastatic at Dx
  - poor prognosis: pancreatic, metastases, high gastrin levels
- Clinically, symptoms d/t gastrin-related high gastric acid output (ZES) ± tumor mass:
  - abdominal pain, diarrhea, severe peptic disease, nausea, heartburn, vomiting.
- Diagnosis - high index of suspicion
  - elevated fasting gastrin (stopping anti-acid drugs, *if possible*; pH<2).
  - localization: HRCT/MRI, EUS, SRI
- Treatment
  - Surgery, controversial (multiple tumors; metastases; exploration for>2 cm; duodenotomy and direct palpation)
  - Medical, SSAs (HD); PRRT; targeted (everolimus; sunitinib); chemotherapy; hepatic loco-regional (RFA, TACE/TAE, SIRT)



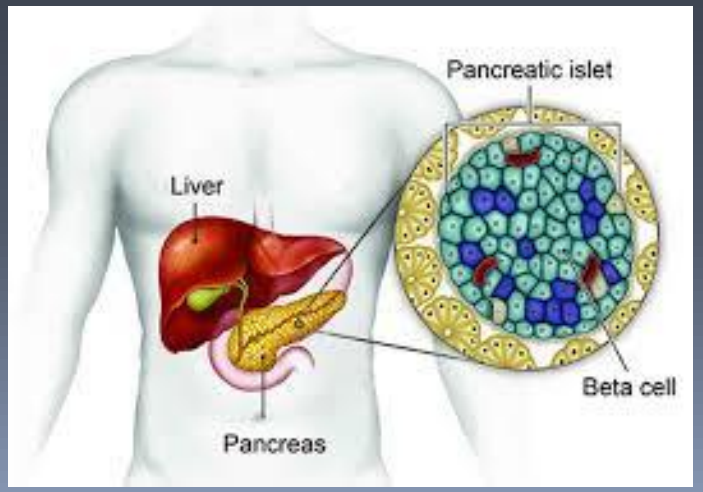




Norton JA. et al. Endocrinol Metab Clin North Am. 2018; 3:577-601.
Grozinsky-Glasberg S. et al. J Hepatobiliary Pancreat Sci. 2015; 22:578–585.
Jensen RT. et al. Neuroendocrinology 2006; 84:173–182.

MEN 1 - Insulinomas, ~35%

- Multicentric, 25% metastatic
- DIAGNOSIS
  - Fasting hypoglycemia & high insulin and C-peptide
  - selective intra-arterial Ca stimulation + portal/hepatic vein sampling for insulin
- SURGERY = treatment of choice
  - Whipple's/subtotal pancreatectomy-splenectomy, excision of liver metastases
- RFA ?
- MEDICAL Therapy
  - diazoxide, SSAs
  - everolimus
  - chemotherapy
  - hepatic loco-regional



Thakker RV., et al. J Clin Endocrinol Metab. 2012 Sep;97(9):2990-3011.

MEN 1 - Glucagonomas, ~3%

- 50-80% metastatic
- Commonly in pancreatic tail
- Silent or *Glucagonoma Syndrome*
  - necrolytic migratory erythema (NME); nail dystrophy, 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 plasma glucagon >500pg/ml (50-150)
  - localization: HRCT/MI; EUS; SRI
- Therapy
  - Surgical removal if possible
  - TPN, SSAs, PRRT, targeted therapies, etc.

Thakker RV., et al. J Clin Endocrinol Metab. 2012 Sep;97(9):2990-3011.

MEN1: Other NENs, ~3%

- NENs (carcinoids) of bronchi/lung or thymus:
  - women predominance for lung NETs
  - male predominance for thymic NETs
  - mostly asymptomatic (ectopic ACTH/CRH, etc.)
  - MEN1- thymic NENs are aggressive (a median survival ~ 9.5y)

- The current guidelines recommend CT/ MRI every 1-2 y.

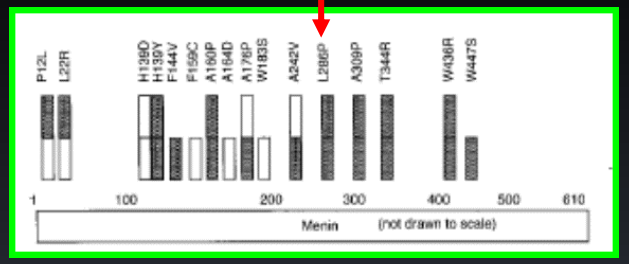
- Treatment:
  - surgical excision - treatment of choice
  - for unresectable/metastatic disease: SSAs, everolimus, PRRT, chemotherapy or radiotherapy

Thakker RV., et al. J Clin Endocrinol Metab. 2012 Sep;97(9):2990-3011.

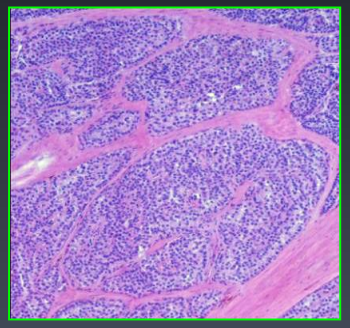
Case study: LD

- 58yo male patient, m+3, MD
- Family history
  - Father, MEN1 (PHPT, ESRF)
  - Brother, MEN1 (prolactinoma, insulinoma)
- 1986, 34yo PHPT, serum calcium ~ 11.5mg%
  - total parathyroidectomy - hyperplasia
  - 1 parathyroid implantation left forearm
  - Since then, normal calcium
- 1990 ZES & Gastrinoma/s
  - diarrheic stools, nausea, vomiting
  - **gastrin** = 35.000 U/L (n < 105) & **CgA** ~ 30.000 ng/ml (19.4-98)
  - Gastric Carcinoids
  - Multiple NENs in & around pancreatic head
    - PPI; SSA→ gastrin 2405 U/L

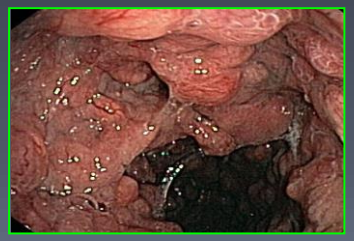
L286P germline mutation, C-terminal end of Menin on exon 6



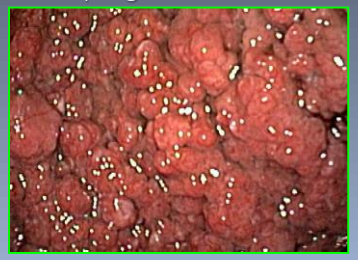
hyperplastic parathyroid



multiple duodenal gastrinomas

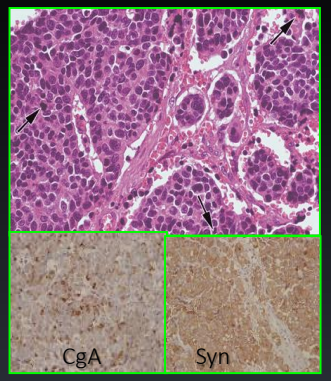


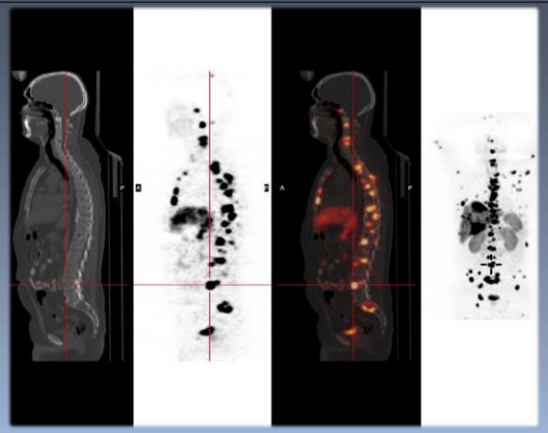
multiple gastric carcinoids



Case study: LD, cont.

- 2003 a 10 cm mass, lung Carcinoid on biopsy
  - right pneumonectomy + Left Atrial Reconstruction
    - Atypical Carcinoid, 7X5X7 cm
    - MI= 8/10HPF; KI67 10%
- 2012
  - laboratory: elevation in CgA, stable gastrin
  - imaging (CT, MRI, SRI) PD (LN, liver, spine)
  - PRRTX4 - PR + SD, continued SSAs
- 2015 - PD - everolimus
- 2016
  - adrenal mass increasing in size
  - new Cushing's, started nizoral, anticoagulation
  - refused surgery
  - 2017 - surgery for ACC (died of massive PE)





MEN1-related NENs: Genetic testing and screening in MEN1

- Helpful in clinical practice for:
  - confirmation of the clinical diagnosis
  - identification of family members who harbor the MEN1 mutation and require screening
  - identification of the 50% of family members who do not harbor the MEN1 mutation (reassure and alleviate the burden of anxiety of developing tumors).
- The mutational analysis for MEN1 difficult, d/t
  - absence of genotype/phenotype correlations
  - a wide diversity of mutations (1336)

Summary of biochemical and radiological screening guidelines in individuals at high risk of developing MEN1.

Tumor	Age to begin (yr)	Biochemical test (annually)	Imaging test (every 3 years)
Parathyroid	8	Calcium, PTH	None
Pancreatic neuroendocrine			
Gastrinoma	20	Gastrin (±gastric acid output)	None
Insulinoma	5	Fasting glucose, insulin	None
Other enteropancreatic	<10	Chromogranin-A; pancreatic polypeptide, glucagon; VIP	MRI, CT or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-1	MRI (every 3 years)
Adrenal	<10	None, unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified	MRI or CT annually with pancreatic imaging
Foregut carcinoid	20	None	CT or MRI (every 1–2 years)

Thakker RV., et al. J Clin Endocrinol Metab.97(2012) (9):2990-3011.
Thakker RV. Molecular and Cellular Endocrinology 386 (2014) 2–15

Where we are now in the understanding of MEN-NENs: Take Home Messages

- Recognizing MEN specific features improves patient management and facilitates a screening protocol on time.
- There are advances in treatment
  - surgery (always to be considered)
  - systemic therapies - most induce SD (except PRRT, CAPTEM, loco-regional)
  - new therapies are promising (gene therapy; epigenetic modifiers; WNT pathway antagonists; VEGF-signalling antagonists)
- A NET MDT is mandatory for improving disease-related outcomes.
- Unmet Needs:
  - MEN-NENs dedicated studies
  - selection for treatment & optimal timing & sequence
  - which imaging examination
  - which response evaluation criteria

Thank you for your attention!