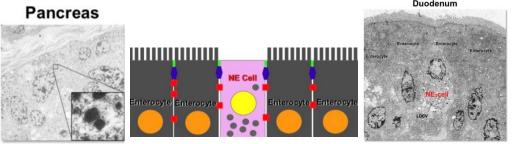


Neuroendocrine Tumors



Practical Approach for the Endocrinologist

8th SPED/AACE Endocrine Clinical Update
Caribe Hilton, San Juan PR
Dec 14 2019

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Disclosures

Speaker for the following companies : Janssen, Sanofi, Lilly, Merck

No conflict of interest in the presentation of present topic

Objectives



Epidemiology, classification



Clinical presentation sporadic and Genetic



Diagnostic tests histopathologic, serum, urine and radiologic



Treatment

Neuro: identification of dense core granules than do not contain synapsis, unlike neurons Endocrine: synthesis and secretion of monoamines

NETs are capable of storing and secreting different peptides and amides

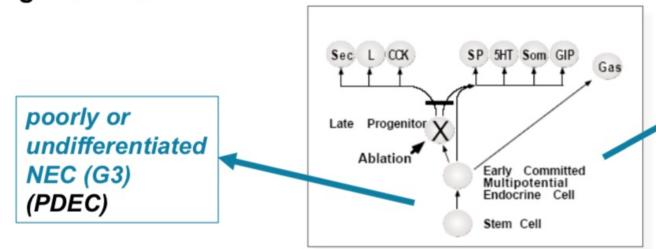
Net patients may be consulted in endocrinology clinics due to symptoms related to hormone

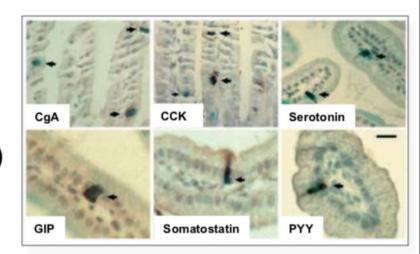
production, or referred by GI or Surgery units

NEN Originate From ...

Either ...

- → An early multipotent endocrine precursor cell (NET)
- → And produce one (or more) hormones (functionality) or...
- → A pluripotent stem cell with less endocrine phenotype (NEC) and can be found...
- All along the endoderm



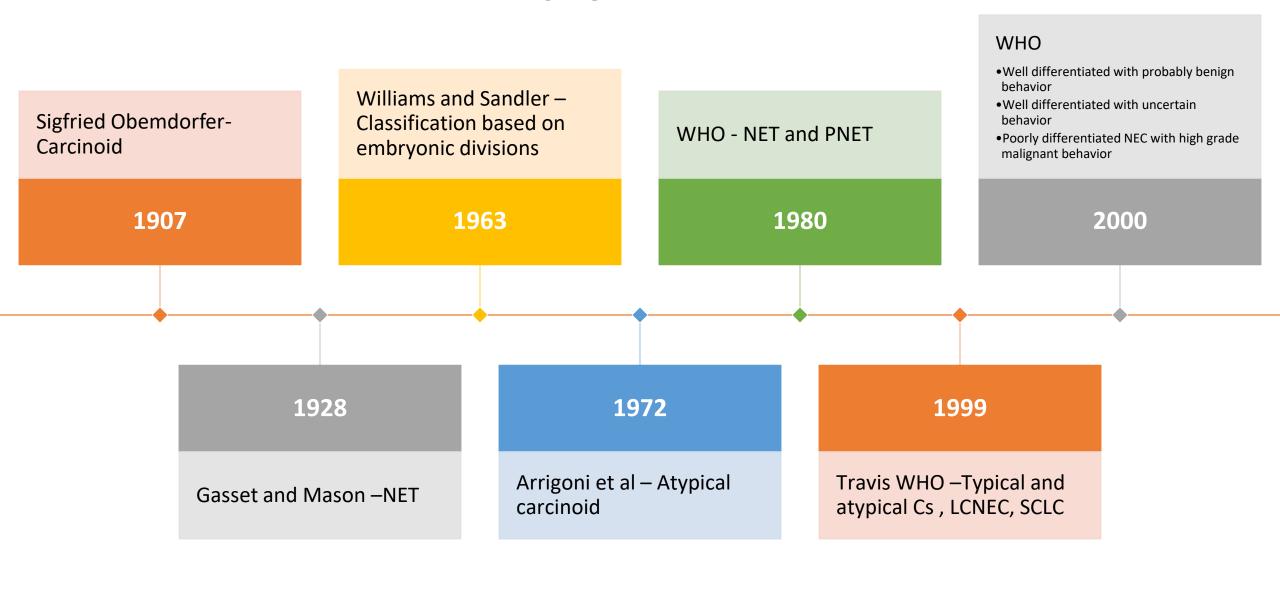


well or moderately differentiated NET (G1/2/3) (WDET/C)

G, grade; PDEC, pancreatic duct epithelial cell; WDET/C, well-differentiated tumors/carcinomas

Rindi G, et al. Development. 1999;126(18):4149-4156. Wang Y, et al. Proc Natl Acad Sci. 2007;104(27):11328-11333. Mey CL, et al. Mol Cell Endocrinol. 2010;323(1):70-75.

HISTORY





0.5 % of all newly diagnosed malignancies



Prevalence of NETs 2014 in USA 171,321 cases, more than all 2013 GI combined malignancies





Women 2.5:1 males



2/3 Nets GEP-NET mostly from distal ileum in small intestine, followed lung



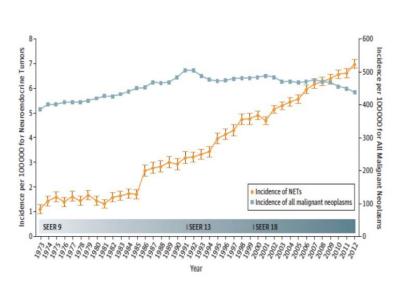
22% metastatic

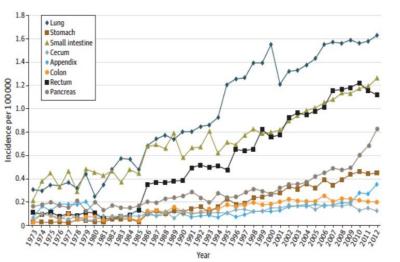


Usual diagnosis is delayed 52 months, seeing 6 healthcare providers a priori

6.4 fold increase rate between 1973 and 2012

NEN: On the Rise!





Dasari A, et al. JAMA Oncol. 2017;3(10):1335-1342.

Epidemiology of Neuroendocrine Tumors

Location	Within NETs (%)	Within GEP-NETs	Incidence SEER (/100,000)	Incidence (% of primary site)	5-year OS (%)
GEP-NETs	67		5.25	< 2	75-82
Gastric		9-20	0.3	1	45-64
Small intestine		39-42	1.1	37-52	62-71
Appendix		6	0.15	30	90
Colon		9-20	0.35	<1	67
Rectum		26	1.1	<1	90
Pancreas		7-12	0.5-1.0	1-2	27-38
Bronchopulmonary	27		0.46	< 2	44-87
Other sites ^a	6		0.38		

NETs = neuroendocrine tumors, GEP-NETs = gastroenteropancreatic neuroendocrine tumors, SEER = Surveillance, Epidemiology and End Results Program, OS = overall survival aEsophageal, endometrium, ovary, breast, etc

Other Curiously sites:

Sphenoid sinus

Middle ear

Renal pelvis

Mediastinum

Retroperitoneum

Cavernous sinus

Lymph node

Fallopian tube

Parotid gland



Size matters

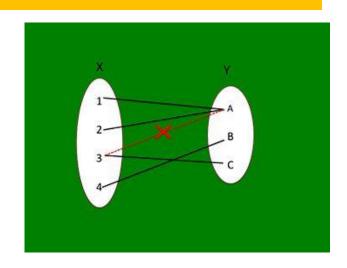


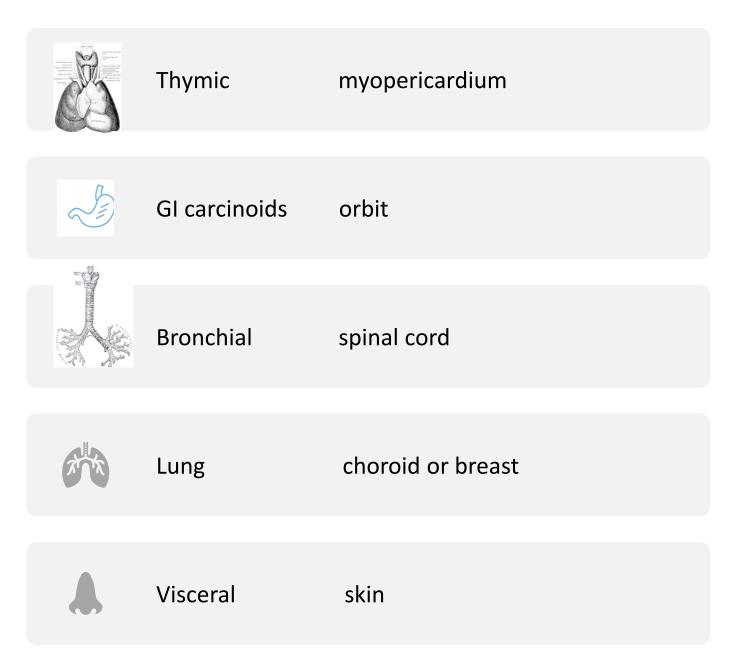


Over 2 cm Malignant

Less than 1 cm
Benign

Metastasis behavior unpredictable

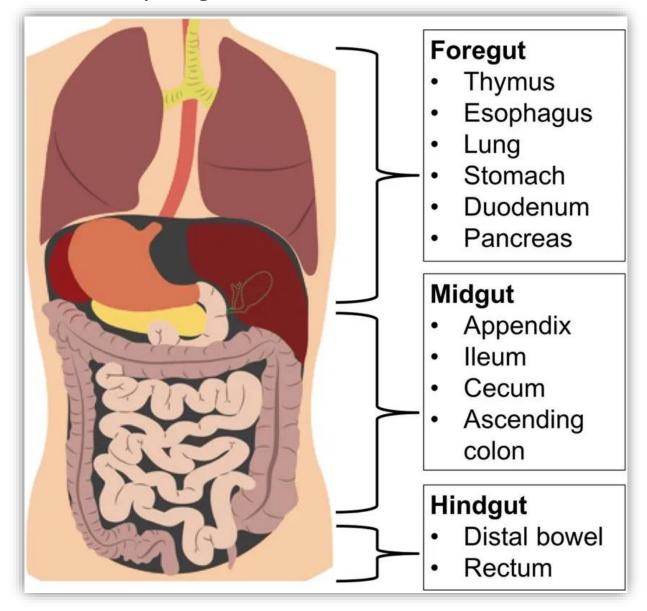




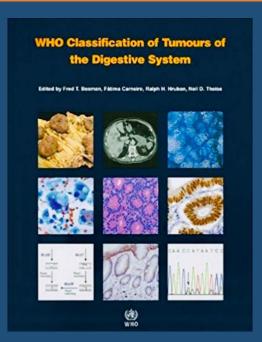
However ...

It does seem that NETs have a general predisposition to Myocardium metastasis to non classic sites, such as: Eye Breast

Embryological site classification



WHO Classification



- 2010
- Low proliferative
 NETs
- Poorly differentiatedNEC

- 2015
- G1 ki 67 less than 2 %
- G2 Ki 67 2-20 %
- G3 NEC Ki 67 over 20%

Ki 67 index: measure the % cancer cells that stain for this marker of cell proliferation

WHO CLASSIFICATION For NENs of the GI Tract

Grade	Mitotic Count (per 10 HPFs)	Ki-67 Index, %
G1	<2	<2
G2	2-20	>2-20
G3	>20	>20

WHO Classification of Pancreatic Neuroendocrine Neoplasms: From 2010-2017

G3 tumors with Ki-67 20-55% are referred to G3 NETs, those with Ki-67 I 55-100% are to be referred as G3 NECs

- The 2017 WHO classification applies only to pancreatic neuroendocrine tumors
- The classification of gastrointestinal (along with pancreatic) neuroendocrine tumors is currently in revision (scheduled 2019/2020)

Important Message: «Internal Coherence»

"Well differentiated" NET with 'high' Ki-67 index:

DANGER!

"Poorly differentiated" NET with 'low' Ki-67 index: DANGER!

Hereditary Tumor Syndromes Associated with Neuroendocrine Tumors

Name	Neuroendocrine tumor (NET) (frequency)	
MEN-1 syndrome (MEN-1) (MIM 131100)	Pituitary adenoma (5-65%)	
(Werner's syndrome)	Pancreatic NET (80-100%)	
	Thymic NET (mostly \$) (<10%)	
	Lung NET (20-25%)	
	Gastric, type 2, NET (ZES related) (5-35 %)	
MEN-2a syndrome (MEN-2a) (MIM 171400)	Medullary thyroid carcinoma	
(Sipple syndrome)	Pheochromocytoma	
MEN-2b syndrome (MEN-2b) (MIM 162300)	Medullary thyroid carcinoma	
	Pheochromocytoma	
Familiarly medullary thyroid carcinoma (FMTC) (MIM 155240)	Medullary thyroid carcinoma	
von Hippel-Lindau (VHL) syndrome (MIM	Pancreatic NET (5-10 %)	
193300)	Pheochromocytomas (10-20 %)	
Neurofibromatosis I (NF 1, MIM 162200)	Periampullary NET	
	(Somatostatinoma)	
	Pheochromocytoma	
Tuberous sclerosis (TSC, MIM 191100)	Pituitary adenoma??	
	Pancreatic NET?	
Carney complex I (CNC1, MIM 160980)	Pituitary adenoma	
Carney-Stratakis syndrome (MIM 606864)	Paraganglioma	
MEN-4 (MEN-X) syndrome (MIM 610755)	Pituitary adenoma	
Familial paraganglioma syndromes	Paraganglioma	
(MIM 115310, MIM 168000, MIM 601650, MIM 605373, MIM 614165)	Pheochromocytoma	
MIM: OMIM-online catalog of Merdelian inheritance in man catalo	g number	

Lesson from Hereditary Syndromes

Genetic syndromes

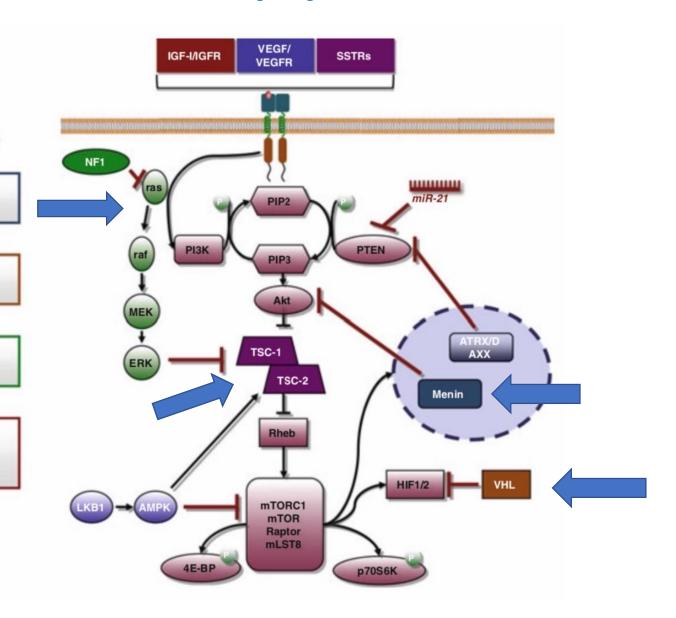
MEN type I - Menin (11q13)

Von Hippel-Lindau disease - *VHL* (3p25-26)

Von Recklinghausen's disease - NF1 (17q11.2)

Tuberous sclerosis complex

- TSC1 (9q34)
- TSC2 (16p13.3)



Diagnostic Pathology



Well differentiated NETs : CgA and Synaptophysin



Figure 3 Immunohistochemical staining showing strong and diffuse staining for NSE, Syn, and CgA. Note: Magnifications ×100.

Abbreviations: CgA, chromogranin A; NSE, neuron-specific enolase; Syn, synaptophysin.



NEC: solid proliferation of tumor cells with irregular nuclei, high mitotic features and less cytoplasmic secretory granules



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Up to 40% of NECs contain elements of non endocrine histology, yet the endocrine component has to exceed30% to be called NEC; otherwise it is called mixed adenoneuroendocrine carcinoma



Circulating Biomarkers in Neuroendocrine Tumors



Chromogranin A (CgA)

Chromogranin B (CgB)

Secretogranin II (CgC)

Secretogranin III (1B1075)

Secretogranin IV (HISL-19)

Secretogranin V (7B2)

Secretogranin VI (NESP55)

CgA

- The precise function of CgA is unknown
- Thought to be involved in packaging and processing of neuropeptide precursor and peptide hormones
- May play a role in organization of matrix

Physiologic : parathyroid inhibitor

pancreas inhibitor of insulin, increases glucagon

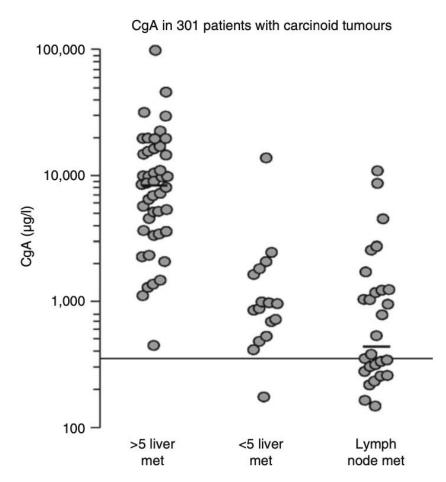
adrenal inhibitor of catecholamines

fat inhibits leptin

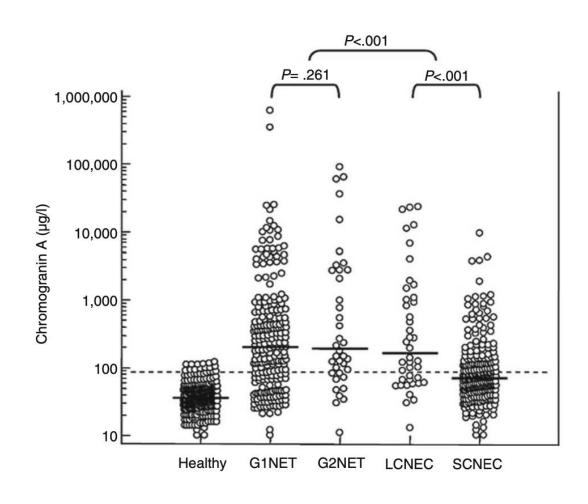
Also has a role in reproductive and cardiovascular functions

CgA is also elevated in inflammatory conditions: RA, SLE, COPD, IBD

Circulating Biomarkers in Neuroendocrine Tumors

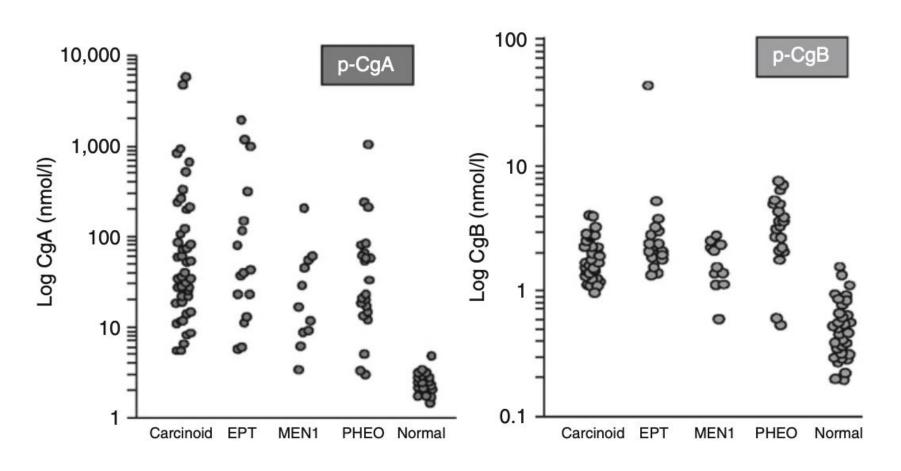


Chromogranin A levels in patients with malignant carcinoid tumors in relation to tumor mass



Chromogranin A levels in patients with tumors with different histological grading

Circulating Biomarkers in Neuroendocrine Tumors



Comparison between circulating levels of chromogranin A and chromogranin B in patients with various NETs. *EPT* endocrine pancreatic tumors, *MEN1* multiple endocrine neoplasia type 1, *PHEO* pheochromocytomas

Causes of false elevation of CgA

Sensitivity 71-83%
MEASURED AT FASTING

Exercise

Stress

Colon, lung, breast, liver and prostate cancer

CKD

Parkinson

Untreated HTN

Steroids

Chronic atrophic gastritis type A

PPI (NEED TO DISCONTINUE X MORE THAN 2 W)

IBS

Liver disease

HPT

General Biomarkers

- Biomarkers
- Cga, CgB. Pancreastatin

• PP, NSE. Neurokinin, neurotensin

- HCG alpha, Betta
- Pro-gastrin releasing peptide (GRP)
- Cytokeratine fragments (CKfr)

- Specificity
- High for prognosis of small intestinal nets(CgA), MEN I, duodenal, rectal and pheo (CgB)
- I yet elevated CgA and PP s95% for functional pNETs

NSE small cell lung CA MTC pNET and PHEOs

- L increased in malignant pNETS
- Small cell lung CA
- Malignancies of epithelial origin

Site-SPECIFIC Markers

Site	Biomarkers	Specificity	
Thymus	ACTH	I	
Luna	ACTH, ADH, serotonin, 5-HIAA	I	
Lung	Histamine, GRP, GHRH, VIP, PTHrp	L	
Ctomoob	Histamine, gastrin	I	
Stomach	Ghrelin	L	
Pancreas	Gastrin, insulin, proinsulin, glucagon, somatostatin	.H	
	C-peptide, neurotensin, VIP, PTHrp, calcitonin	L	
Duodenum	Somatostatin, gastrin	H	
lleum	Serotonin, 5-HIAA	Н	
	NKA, neuropeptide K, SP	I	
Colorectum	Peptide YY, somatostatin	I	
H: high, I: intermediate, L: low			



It is recommended to use CgA and CKfr in well differentiated NETs (G1, G2) whilst in NEC G3, pro – GRP, CKfr, and NSE

Circulating biomarkers in Neuroendocrine tumors, Kjell Oberg, Neuroendocrine tumors page 127

Types and clinical features



• Gastroenteropancreatic NET 50-60 y

Incidental at surgery

Vague abdominal

symptoms

- **a.** Appendiceal :usual post op diagnosis , less than 1 % Cs
- **b. Gastric NEN**: type I Chronic atrophic gastritis with or without pernicious anemia

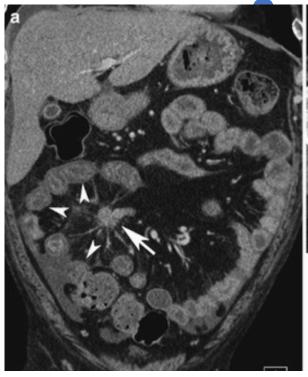
type II Zollinger Ellison at MEN

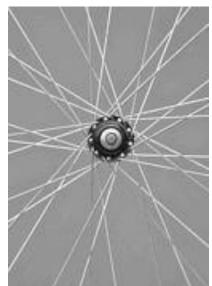
type III sporadic, large solitary, invasive, occasionally producing atypical Cs mediated by histamine and serotonine

c. Colorectal NEN Aggressive, associated with poor prognosis

Criteria for the CLASSIFICATION of Pulmonary NETs

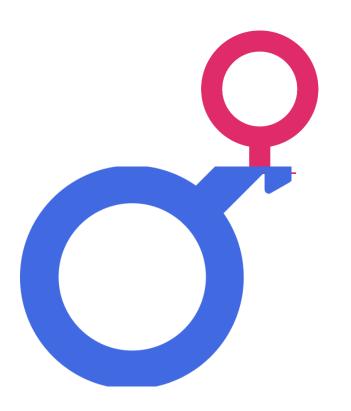
	Typical Carcinoid	Atypical Carcinoid	LCNEC	Small-Cell Lung Cancer
Differentiation grade	Low	Intermediate	High	High
Mitotic count per 10 HPF fields (diameter with a ×40 objective)	<2	2-10	>10	>10
Necrosis	Absent	Focal	Extensive	Extensive
Lymph node metastases at diagnosis	10-15%	50%	60-80%	60-80%
Distant metastases at diagnosis	3-5%	20-25%	40%	60-70%
Association with smoking	No	Yes	Yes	Yes
Paraneoplastic syndromes	+	++	+	++++
Common anatomical location in the lung	Central	Peripheral	Peripheral	Hilar/perihilar





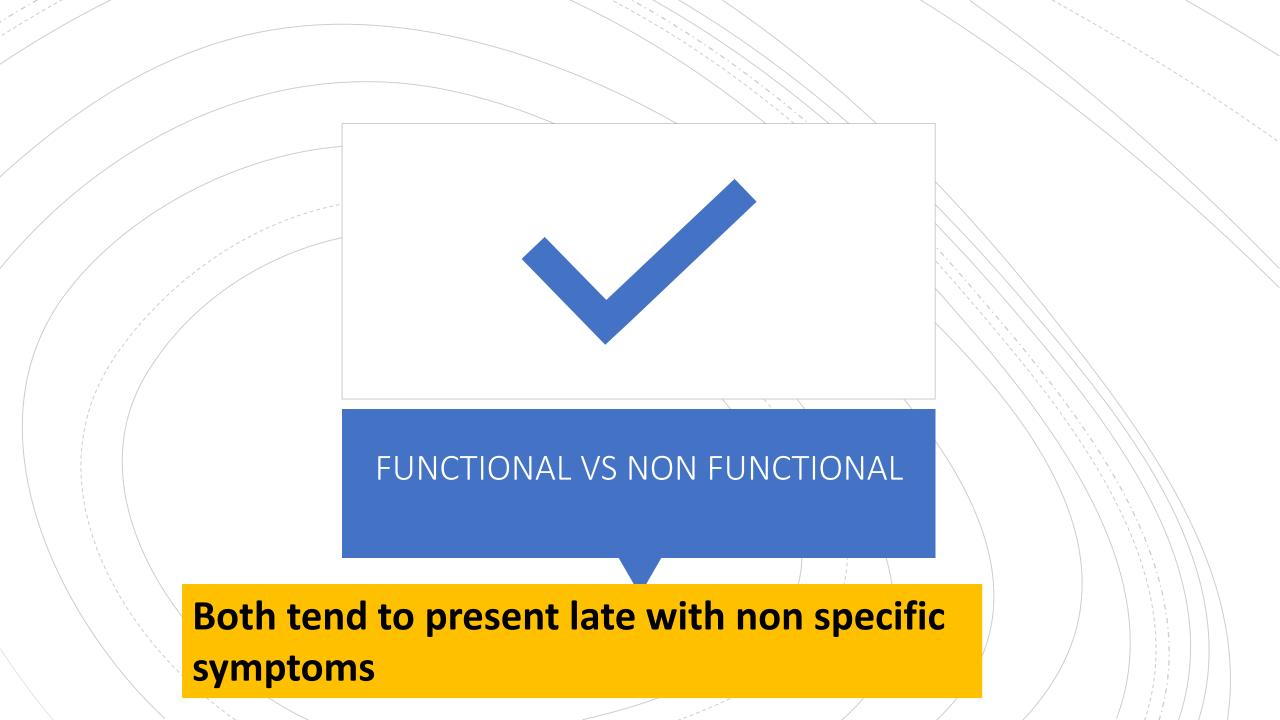
Mesenteric fibrosis

- 50% pathognomonic of Midgut NET
- Spoke wheel appearance
- Ischemia of vessels and intestinal obstruction
- Decreased absorption of nutrients
- Ascites
- Rare, uretheral obstruction
- Elevated 5 HIAA TGFs



NEN of GU tract

- Rare, primarily in the kidney and urinary bladder
- Presentation: abdominal pain, abdominal mass, weight loss, hematuria
- cervix and ovaries, endometrial, vulva, vagina
- prostate, testicles, scrotum, penis, urethral
- Less than 10% with symptoms of hormone production or carcinoid



Presenting Symptoms for Neuroendocrine Tumor				
Symptom	Percentage of cases			
Gastroenteropancreatic				
Abdominal pain	28–79			
Bowel obstruction	18–24			
Diarrhea	10–32			
Carcinoid heart disease	8–19			
Flushing	4–25			
Gastrointestinal bleed	4–10			
Incidental	9–18			
Bronchopulmonary				
Cough	5–27			
Hemoptysis	23–32			
Recurrent infection	41–49			
Incidental	17–39			

Functional Neuroendocrine Tumor Syndromes				
Tumor	Tumor location	Hormone	Symptoms and signs	Syndrome
Atypical carcinoid	Foregut	5-HTP, histamine	Pruritus, cutaneous wheals, bronchospasm	Atypical carcinoid
Carcinoid	Small intestine, lung (< 5%),* pancreas (< 1%)*	Serotonin, tachykinin, prostaglandins	Flushing, diarrhea, valvular disease, bronchospasm	Carcinoid
Insulinoma	Pancreatic β cells	Insulin, proinsulin	Hypoglycemic symptoms	Whipple triad
Gastrinoma	Gastrinoma triangle†	Gastrin	Diarrhea, peptic ulcer disease	Zollinger–Ellison
Glucagonoma	Pancreatic α cells	Glucagon	Diabetes, deep vein thrombosis, depression, dermatitis (necrolytic migratory erythema)	4D syndrome
Somatostatinoma	Pancreatic δ cells	Somatostatin	Diabetes, cholelithiasis, steatorrhea, weight loss, achlorhydria	Somatostatinoma
VIPoma	Non-β islet cells	Vasoactive intestinal peptide	Watery diarrhea (profuse), hypokalemia, achlorhydria	Verner–Morrison (WDHA syndrome)
ACTHoma	Lung (4%)*	ACTH	Fat redistribution/obesity, facial plethora, skin atrophy/easy bruising/ striae, proximal myopathy, hyperglycemia	Cushing syndrome

Note: ACTH = adrenocorticotropic hormone, 5-HTP = 5-hydroxytryptophan, VIP = vasoactive intestinal peptide.

^{*}Percentage of NETs at that site resulting in the specific syndrome.

[†]Gastrinoma triangle boundaries include the confluence of the cystic and common bile duct (superiorly), junction of the 2nd and 3rd portions of duodenum (inferiorly) and the junction of the neck and body of the pancreas (medially).

Insulinomas

- Most common functional pNETS
- Absorptive Hypoglycemia classically, however 5 % might be postprandial
- ENETS consensus guidelines recommend concomitant BG less or equal 40mg/dL and an insulin level over6 pU/L
- Endocrine Society 2009 glucose less than 55mg/dL, insulin of at least 3pu/mL, c peptide of at least 0.6ng/mL and proinsulin of at least 5pmol/L documents endogenous hyperinsulinism

Gastrinomas

- Second most common functional
- 80% arise in 2-nd and 3rd portion of duodenum

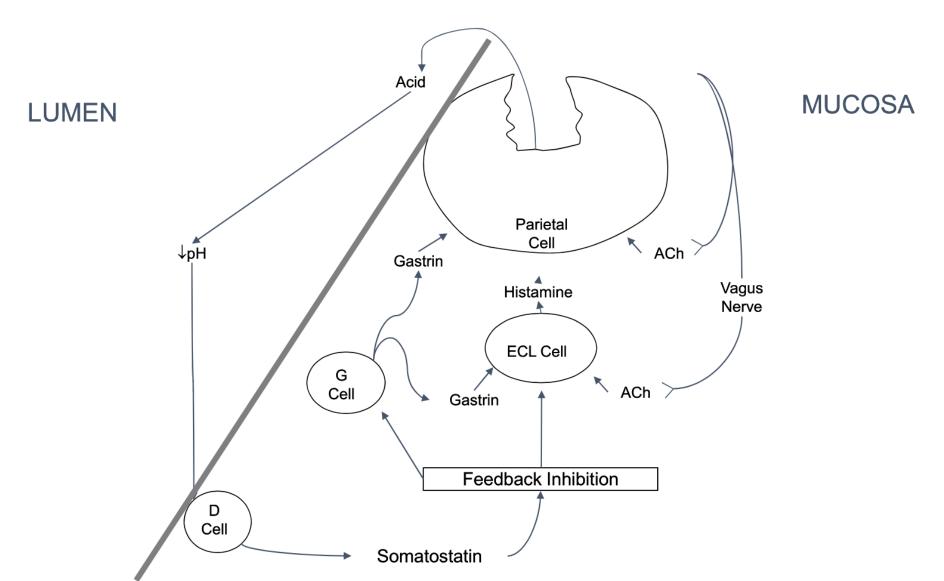
Increased gastrin over 1000 pg/mL or negative gastric PH in the absence of atrophic gastritis

Guidelines recommend secretin test for FSG 200-1000pg/mL

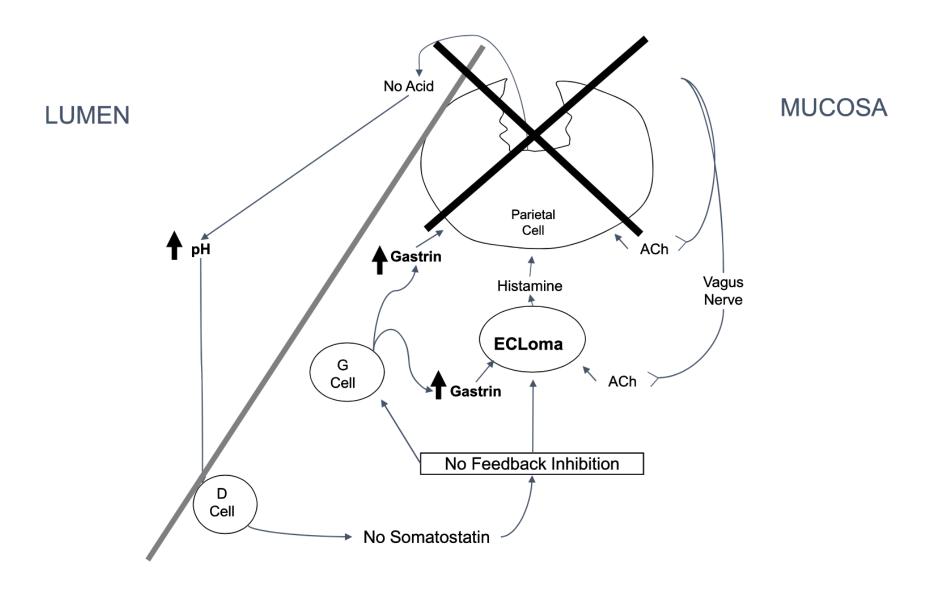
Characteristics of Gastric NETs

	Type I	Type II	Type III
Prevalence (%)	70-80	5-10	15-20
Background	Chronic atrophic gastritis	Gastrin om as (Zollinger-Ellison syndrome)	Normal mucosa
Other Syndromes	Autoimmune polyglandular syndrome	MEN-1 syndrome	
Number of lesions	Multiple	Multiple	Single
Site of tumor	Fundus/body	Fundus/body	Fundus/body
Cell of origin	ECL	ECL	ECL, EC, or X cell
Serum gastrin levels (Elevated	Elevated	Normal
Gastric pH	High	Low	Normal
Underlying mucosa	Atrophic	Hypertrophic	Normal
Size of tumors (usual)	1–2 cm	1 cm	>2 cm
Invasion	Rare	More common	Common
Metastases Lymph nodes Liver	5-10% 2-5%	,	50-100% 22-75%
Prognosis	Excellent	Very good	Similar to gastric adenocarcinoma

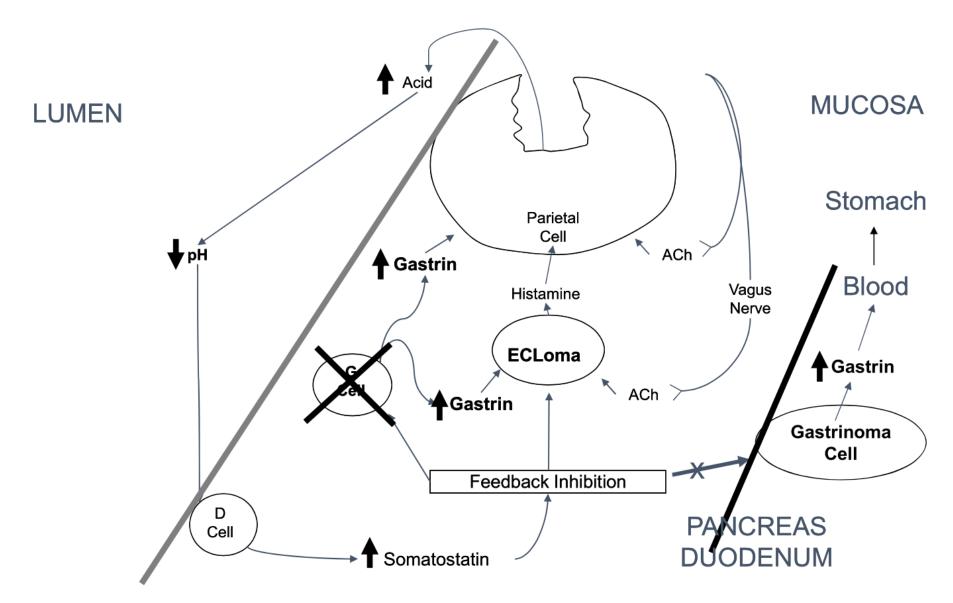
Physiological Acid Secretion from Parietal Cells



Pathophysiology of Type I Gastric NETs



Pathophysiology of Type II Gastric NETs

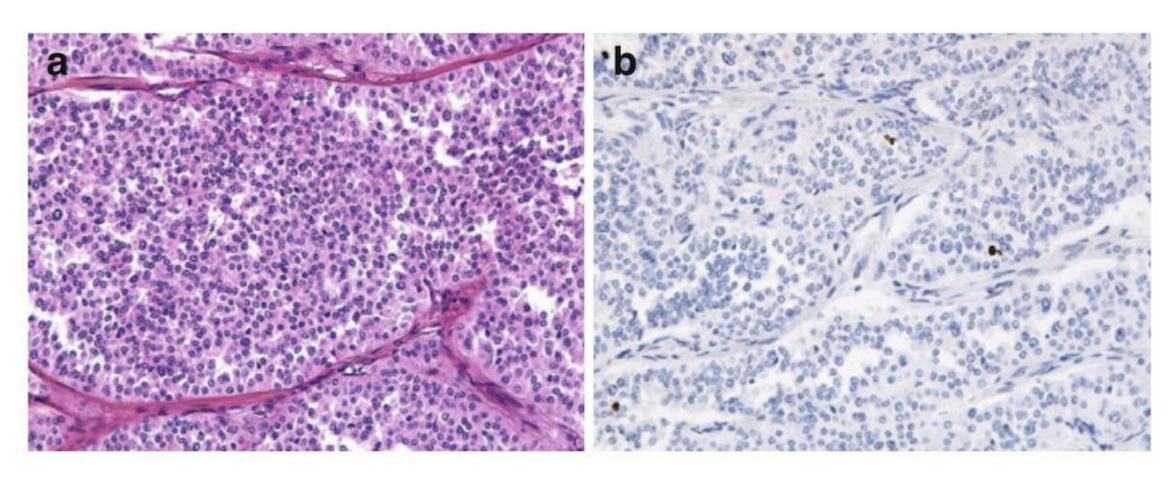


CLASSIFICATION and Characteristics of Gastric NETs

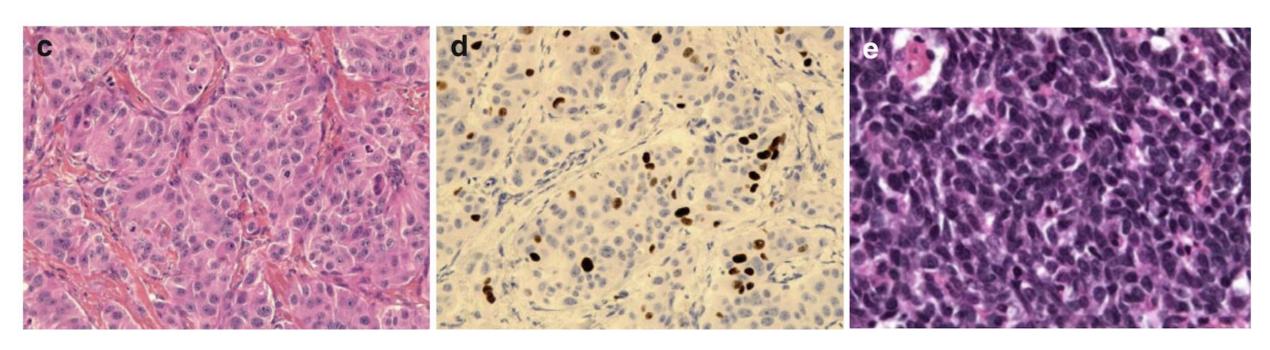
	Type 1	Type 2	Type 3	Type 4
Incidence (among gastric NETs)	70-80%	5-6%	14-25%	Rare
	Multiple, small, intramucosal lesions	Multiple, small, intramucosal lesions	Single, large lesion, more extensive stage lesions	Single, large
Pathological Features	<1 % MI		>2 % MI	Severe, grade 3 histology
	CgA and NSE	CgA and NSE	CgA positive	> 30 % MI
	positive	positive		CgA negative
				NSE positive
	Very good	Good	Less good	Poor
Prognosis	Metastatic potential very low	10 - 30% metastatic potential	50 - 100% metastatic potential	100% metastatic potential
Treatment strategy	Endoscopic resection	Endoscopic resection or limited surgery	Radical surgery	Radical surgery if amenable
		NN	Usually NN	Combination chemotherapy:
				Cisplatin - etoposide
Chemotherapy	NN			Carboplatin - octreotide/ pasireotide
				Somatostatin analogues
Radiotherapy	NN	NN	Usually NN	Targeted radiotherapy with 177Lu-octreotate (177Lu) and 90Y- labelled somatostatin analogue
Biological treatment				Interferon
and targeted treatment	NN	NN	Usually NN	Sunitinib
treatment				Everolimus

S. Yalcin, K. Öberg (eds.), Neuroendocrine Tumours: Diagnosis and Management, DOI 10.1007/978-3-662-45215-8

Pathological Evaluation and CLASSIFICATION of Digestive NETs

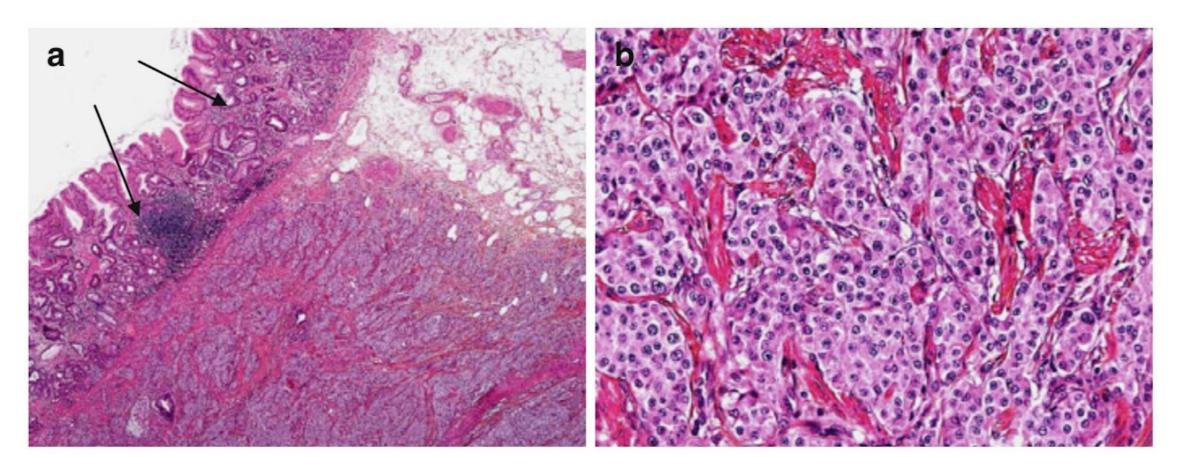


A well-differentiated neuroendocrine tumor (NET) of grade G1 (Ki-67 < 1 %)



A well-differentiated neuroendocrine tumor (NET) of grade G2 (Ki-67=12 %)

A gastric small-cell poorly differentiated neuroendocrine carcinoma (NEC)



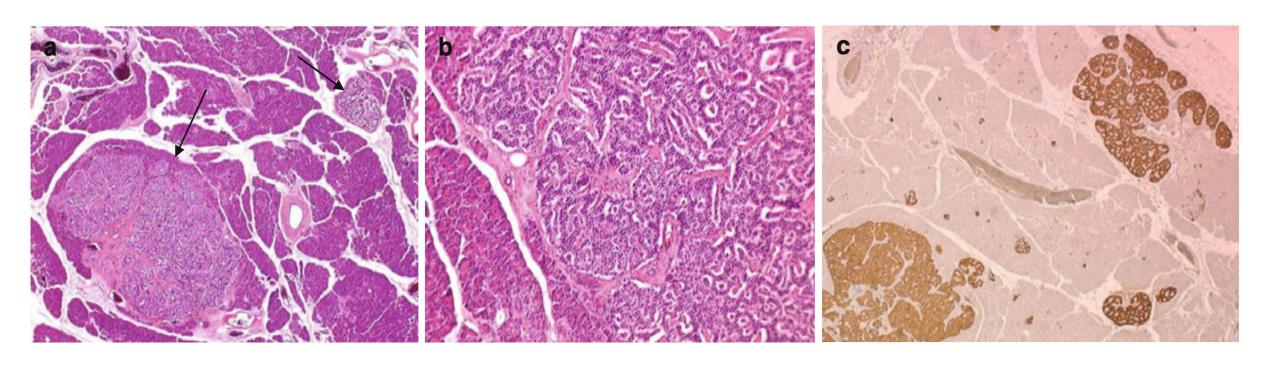
A type 1 gastric NET (**a**, see the overlying inflammatory fundic mucosa, *arrows*), measuring 1.5 cm and infiltrating the submucosa (pT2, according to UICC TNM), well-differentiated (**b**) of grade G1

Clinical Manifestations in MEN1

	Organ involved		Specific tumor (prevalence by 40 years)	Clinical presentation
MEN1		(2=24)	Diffuse hyperplasia	Symptoms related to
	Parathyroid di	isease (95%)	Adenoma, multiple	hypercalcemia or hypercalciuria
	NETs	PNETs (30-80 %)	Gastrinomas (>50%)	ZES, diarrhea, abdominal pain
			Insulinomas (10-30%)	Whipple trad
		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 and IGF1 levels
		Foregut NETs (2-10%)	Thymic, gastric, bronchial NETs	Organ specific

Clinical Manifestations in MEN1

	Organ involved	Specific tumor (prevalence by 40 years)	Clinical presentation	
MEN1	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	Bening adrenocortical tumors (73%)	Most nonfunctioning	
		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%)		



Two pancreatic microadenomas (**a**, *arrows*) in a patient with multiple endocrine neoplasia type 1, well delimited and composed by regular cells (**b**) expressing chromogranin A (**c**).

Clinical Presentation of Zollinger-Ellison Syndrome

Symptom	Percentage of patients (%)
Abdominal pain	78-94
Peptic ulcer disease	74-96
Duodenal ulcer	60-96
Gastric ulcer	24
Jejunal ulceration	29
Bleeding	27-42
Diarrhea	72
Gastroesophageal reflux	42
Esophageal ulceration or stricture	4-6
Weight loss	7-18

Clinical Manifestations in MEN2

		Organ involved	Specific tumor (prevalence by 40 years)	Clinical presentation							
MEN2	MEN2A (<75%)	Thyroid	MTC (90%)	Neck mass or neck pain, diarrhea, flushing							
		Adrenal	Pheochromocytomas (50%)	Subtle symptoms, usually bilateral							
		Parathyroid	Multigland adenoma/ hyperplasia (20-30%)	Usually asymptomatic							
									Skin	CLA	Pruritic, lichenoid skin lesion in the upper portion of the back
		MEN2A genetically related	HSCR	Bowel enlargement and constipation/ obstipation							
			PTC	Concomitant PTC and MTC							
	FMTC (10-20%)	Thyroid	MTC (100%)	≥ 4 individuals with MTC in the same family in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia							

Medullary thyroid Ca

- Typical feature is increased calcitonin, also VIP, serotonin
- Majority sporadic
- 5th 6th decade
- Women more than men
- Survival 15-20 y
- Mets to bone, lung, liver and brain
- Diagnosis, FNA 50%, also CEA, CgA stain for calcitonin, washout fluid calcitonin; serum calcitonin correlates with tumor load and multifocality, useful for f/u

Clinical Manifestations in MEN2

		Organ involved	Specific tumor (prevalence by 40 years)	Clinical presentation
MEN2	MEN2B (5%)	Thyroid	MTC (90%)	Very aggressive, usually metastatic
		Adrenal	Pheochromocytomas (50%)	Usually multiple/ bilateral (50%)
		Other	Mucosal neuromas, frequent	Tongue, palate, or pharynx; eyelid
			Ocular signs, frequent	Inability to cry tears, thickened corneal nerves, ptosis, eyelid eversion
			Diffuse ganglioneuromatosis of the GIT (40%)	Abdominal distension, megacolon, constipation, or diarrhea
			Marfanoid habitus (75%)	Associated with kyphoscoliosis or lordosis, joint laxity, decreased subcutaneous fat, proximal muscle wasting, weakness

Clinical Manifestations in MEN2



MEN2B-associated oral mucosal neuromas

Symptoms, associated syndromes, secretory products and tumor locations of NETs with special emphasis on GEP-NETs

Substrates Causing Carcinoid Tumors

Amines	Polypeptides
Serotonin	Gastrin
5-Hydroxytryptophan	Corticotropin (ACTH)
Norepineprine	Bradykinin
Dopamine	Pancreatic polypeptide (PP)
Histamine	Somatostatin
	Vasoactive intestinal peptide (VIP)
	Substance P
	Peptide YY
	Neurokinin A and B
	Motilin
	Kallikrein
	Growth hormone
	Neuropeptide K
	Glucagon
	Beta-endorphin
	Neurotensin
	Chromogranin A

Clinical presentation	Syndrome	Tumor type	Tumor location	Mediator peptides and hormones	Diagnostic markers
Flushing	Carcinoid syndrome	NET	Foregut, midgut, rarely hindgut, pancreas, testes, presacral, pituitary	Serotonin, prostaglandins, kinins, progastrin-releasing peptide VIP, calcitonin gene-related peptide, histamine, 5-HTP, substance P, neurotensin, motilin, neurokinin A, kallikrein, neuropeptide K, somatostatin, dopamine	CgA, 24-hour urinary 5- HIAA
	MTC, C-cell hyperplasia	C-cell	Thyroid	Calcitonin	Calcitonin
	Phaeochromocytoma/ paraganglioma	Chromaffin cell	Adrenal medulla, sympathetic nervous system	Adrenalin, noradrenalin, rarely dopamine	Plasma or 24-hour urinary, metanephrines, normetanehrines, dopamine
Diarrhea/abdominal pain, dyspepsia	Cardinoid syndrome	NET	Foregut, midgut, appendix, rarely hindgut, pancreas, testes, presacral	As above	CgA, 24-hour urinary 5- HIAA
	Zollinger-Ellison syndrome (ZE)	Gastrinoma	Duodenum (70%), pancreas (25%), other sites (5%)	Gastrin	CgA, gastrin, PP
	Pancreatic polypeptide	PPoma	Pancreas	PP	CgA, PP
	MTC NET	C-Cell NET	Thyroid Lung, pancreas, stomach, appendix	Calcitonin	Calcitonin
	WDHHA (Verner- Morrison syndrome)	VIPoma	Pancreas (90%, adult), other (10%, neural, phaeochromocytoma, periganglionic)	VIP, neurotensin	CgA, VIP
		Secretinoma	Pancreas	Secretin	Secretin (tissue immunohistochemistry)
Wheezing, dermatitis, heart disease	Cardinoid syndrome	NET	Foregut, midgut, appendix, rarely hindgut, pancreas	Substance P, histamine, 5-HT	CgA, 24-hour urinary 5- HIAA
Ulcer, dyspepsia, epigastric pain	ZE	Gastrinoma	Duodenum (70%), pancreas (25%), other sites (5%)	Gastrin	CgA, gastrin, PP
Hypoglycemia	Whipple's triad	Insulinoma/ nesidioblastosis	Pancreas (~98%) Ectopic insulinoma (~2%)	Insulin	Glucose, insulin, C-peptide
		Ectopic insulin secreting NET	Ovary, kidney, paraganglioma, liver, cervix NET (SCC), bronchial carcinoid, appendix	Insulin	Insulin
		Proinsulinoma	Pancreas	Proinsulin	Proinsulin

Clinical presentation	Syndrome	Tumor type	Tumor location	Mediator peptides and hormones	Diagnostic markers
Hypoglycemia (cont) Non-islet cell tumour hypoglycemia (NICTH)	IGF2-oma	Gastric NET, bronchial carcinoid, pheochromocytoma, pancreas	Big IGF2	IGF2 isoforms (thin-layer chromatography) (accompanying low insulin, GH and IGF-1)	
		IGF1-oma	Large cell Ca of lung	IGF-1	IGF-1
		GLP-1 secreting NET	Pancreas, ovary	GLP-1	GLP-1
Silent pancreatic mass or diarrhea, liver metastases	Silent	PPoma	Pancreas	PP	CgA, PP
Diabetes, diarrhea, steatorrhoea, cholelithiasis, deep vein thrombosis	Somatostatin	Somatostatinoma	Pancreas (55%), duodenum/ small intestine (44%), kidney, ovary	Somatostatin	CgA, somatostatin
deep vein thombosis		Pheochromocytoma	Adrenal medulla	Somatostatin, adrenalin, noradrenalin	Somatostatin, 24-hour urinary or plasma metanephrine, normetanephrine
		C-cell	Thyroid	Somatostatin, calcitonin	Somatostatin, calcitonin
Diabetes, diarrhea, necrolytic migratory erythema, pellagra (somatitis, glossitis, angular cheilitis)	Glucagonoma	Glucagonoma	Pancreas Foregut, midgut, rarely hindgut, pancreas	Glucagon As above	CgA, glucagon CgA, 24-hour urinary 5- HIAA
Fever	With weight loss	All (especially pheochromocytoma)	All	Cytokines (IL-1, IL-6, TNF-α, IFN-γ)	
Acromegaly	Acromegaly	GHRH-secreting NET Pheochromocytoma/ paraganglioma	Lung (54%), pancreas (30%), jejunum (7%), other (e.g.thymus) (13%) Mediastinal paraganglioma, adrenal medulla	GHRH	GHRH, GH, IGF-1 (pituitary hyperplastic/normal on imaging)
		GH-secreting NET	Pancreas, bronchial carcinoid	GH	GH, IGF-1
		GH and IGF-1 secreting NET	Pulmonary carcinoid	GH, IGF-1	

Clinical presentation	Syndrome	Tumor type	Tumor location	Mediator peptides and hormones	Diagnostic markers
Cushing's syndrome Cushing's syndrome	ACTH-secreting NET (50% of ectopic Cushing syndrome are due to lung)	Foregut, midgut, appendix, rectum, pancreas, bladder, prostate SCC, ovary	ACTH	ACTH, midnight salivary cortisol, 24-hour urinary free cortisol, dynamic tests	
	Pheochromocytoma	Adrenal medulla			
		C-cell	Thyroid		
		ACTH and/or CRH secreting NET C-cell	Thymus, pancreas Thyroid	ACTH, CRH	
Anorexia, nausea, vomiting,	Hypercalcemia	PTHrP-oma	Pancreas, thymus, liver	PTHrP	PTHrP
abdominal pain		Pheochromocytoma	Pheochromocytoma		
		PTH-oma	Lung, MTC,ovary, pancreas, neck NET, paraganglioma, gastric NET	РТН	РТН
		1,25-dihydroxyvitamin D secreting NET	Pancreas	1,25-dihydroxyvitamin D	1,25-dihydroxyvitamin D
Weakness, lethargy, apathy	y Hyponatremia, SIADH	ADH-secreting NET	Larynx, lung, rectum, cervix, pancreas, prostate	ADH	ADH
		ADH/ANP-secreting NET	Lung, thymus	ADH and ANP	ADH and ANP
Hypertension	Severe hypertension	Pheochromocytoma/ paraglangioma	Adrenal medulla Sympathetic nervous system	Adrenaline, noradrenaline, dopamine	Plasma or 24-hour urinary metanephrines, normetanehrines, dopamine
		NET Adrenal	Pancreas, bronchial carcinoid Pheochromocytoma	Renin	Plasma renin activity, prorenin
Hyperandrogenism, virilization	LHoma	pNET	Pancreas	LH	LH
Constipation		NET	Ovary	Peptide YY	
			Unknown origin, intraabdominal mass	GLP-1, GLP-2, peptide YY	
Ovarian hyperstimulation	FSHoma	NET	Mediastinal, pancreas	FSH	FSH
Gastroparesis	Ghrelinoma	NET Pancreas	Stomach, presacral region Pancreas	Ghrelin	Ghrelin
Diarrhea, peptic ulcer, bile stone attacks	CCKoma	pNET	Pancreas	ССК	ССК
Polycythemia		pNET	Pancreas	Erythropoietin	Erythropoietin

Clinical presentation	Syndrome	Tumor type	Tumor location	Mediator peptides and hormones	Diagnostic markers
paraneoplastic syndrome polyradic autonomi	Painful axonal polyradiculoneuropathy, autonomic neuropathy	Mostly SCLC	Lung	CRMP5 (collapsin response- mediator protein-5)	
	Myopathy	NET	Lung		
	Myasthenia gravis	NET	Lung, small intestine, ileum, thymus	AChR Ab (anti-acetylcholine receptor Ab)	
	Paraneoplastic cerebellar degeneration	Mostly SCLC, also NET	Oropharynx, stomach, pancreas, lung, thymus, midgut NET	Anti-Yo Ab (Purkinje cell cytoplasmic Ab type 1-PCA1), Anti-Ri Ab (anti-neuronal nuclear Ab type 2-ANNA-2), anti-GAD Ab (glutamic acid decarboxylase Ab)	
	Limbic encephalitis	Mostly SCLC, NET	Pancreas, midgut, bronchus, thymus, lung, tonsil	Anti-Ma2 Ab, anti-Hu Ab, anti-Ri Ab	
	Lambert-Eaton syndrome	Mostly SCLC, NET	Lung, oropharynx, larynx	P/Q type voltage-gated calcium channel Ab	
	Autoimmune retinopathy	Mostly SCLC, NET	Lung, small bowel	Antirecoverin Ab	
	Neuromyelitis optica spectrum disorder	NET	Stomach, small bowel		
	Axonal Guillian-Barre-like syndrome	Mostly SCLC	Lung		
	Sensory neuropathy	Mostly SCLC, NET	Lung, bronchus, duodenum	Anti-Hu Ab	
gastrointestinal pseudoobstruction) Neuromyotonia, amyolateral sclerosis, mult hypertrophic monone	1 0	Mostly SCLC, NET	Lung, bronchial NET	Anti-Hu Ab, Anti-CV2 Ab	
	Neuromyotonia, amyotrophic lateral sclerosis, multifocal hypertrophic mononeuropathy	SCLC	Lung		
	Brainstem encephalitis	NET	Rectum	Anti-Ri Ab	
		NET	Lung		
	Paraneoplastic neuropathy	NET	Cecum		
Miscellaneous				HCG, CGRP, motilin, dopamine, neuropeptide K, neurotensin, neurokinin A	

NETs whimsical behavior: Expecting the unexpected



SILENT



SECRETOR
Y:
HORMON
ES



AMINES DIFFERENT PRODUCTS



CLINICAL
SYMPTOMS
MAY
CHANGE
OVER TIME
DUE TO
SECRETED
PEPTIDES



1/3 PATIENTS
MAY PRESENT
WITH HISTORY
OF
INTERMITTENT
ABDOMINAL
PAIN
MISDIAGNOSED
AS IBS

Misdiagnosis of NETs

Symptoms

Abdominal pain

Nausea

Diarrhea

Indigestion

Weight Loss

Flushing

Persistent

Cough

Vomiting

Wheezing

1 in 2

NET patients who report having originally been misdiagnosed

Incorrect Diagnoses

Stomach ulcers
Irritable Bowel Syndrome
Obstructed Bowel
Pneumonia
Gastritis
Asthma
Anxiety or Depression
Menopause

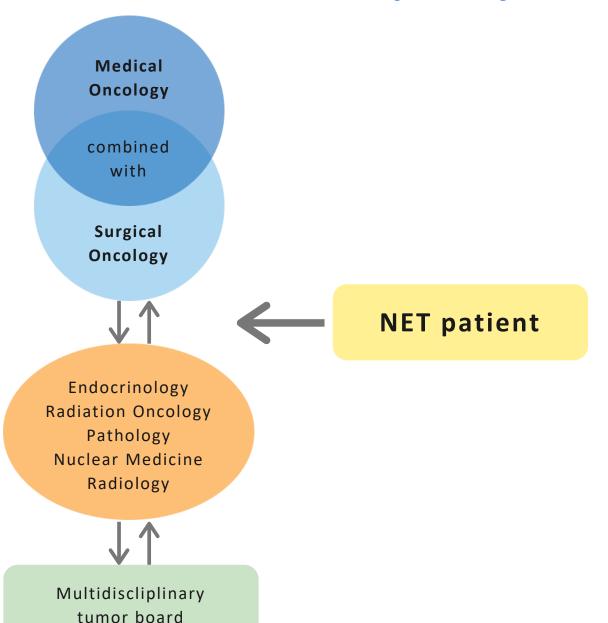
4.3 years

Median time from first symptoms to correct diagnosis of NETs Correct

Diagnosis

NETs

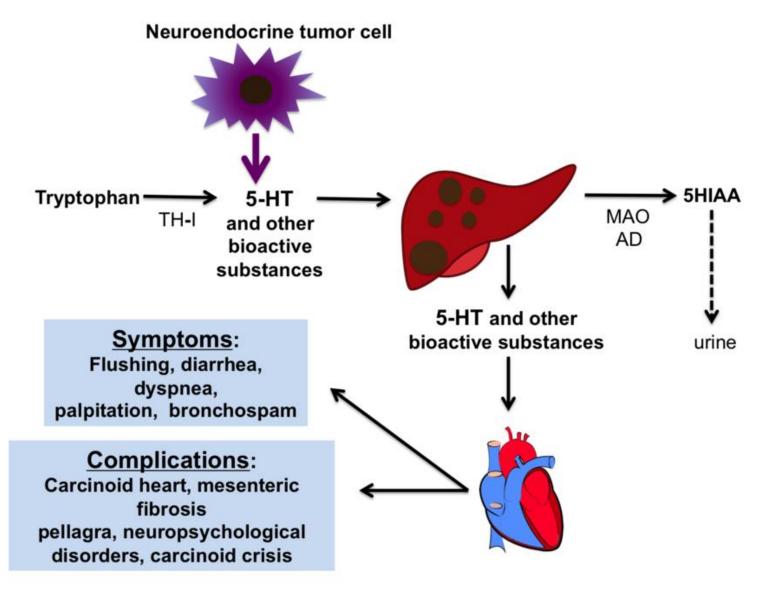
Neuroendocrine Multidisciplinary Team



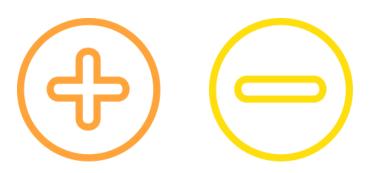
Carcinoid Syndrome

Primary tumor location, peptides secreted from the tumor cells, and frequency of carcinoid syndrome				
Location	Secretory products	Carcinoid syndrome		
Foregut	5-Hydroxytryptophan histamine, multiple polypeptides	Rare		
Midgut	Serotonin prostaglandins, polypeptides	Often		
Hindgut	Variable	Rare		

Summary of the Pathophysiology of Carcinoid Syndrome



Reasons of Falsepositive and Falsenegative 5-HIAA Urinary Excretion



False positive	False negative	
Drugs	Drugs	
Phenobarbital	Corticotrophin	
Phentolamine	Levodopa	
Nicotine	MAO inhibitors	
Acetaminophen	Phenothiazines	
Fluorouracil	Aspirin	
Melphalan	Isoniazid	
Guaifenesin	Ethanol	
Ephedrine	Streptozotocin	
Phenacetin	Methyldopa	
Methamphetamine	Heparin	
Foods and drinks		
Pineapples		
Bananas		
Walnuts		
Avocados		
Tomatoes		
Pecans		
Hickory nuts		
Kiwi fruit		
Caffeine		

Carcinoid Symptoms and Frequencies

Symptom	Frequency (%)	
Flushing	85	
Telangiectasia	25	
Cyanosis	18	
Pellagra	2-25	
Diarrhea	75-80	
Abdominal cramp	75	
Bronchospasm	20	
Valvular lesions	50	
Right heart	40	
Left heart	13	
Asthenia	<5	
Neuropsychiatric symptoms	<5	
Musculoskeletal	<5	



Differential Diagnosis of Flushing		
Carcinoid syndrome		
Phaeochromocytoma, paraganglioma		
Medullary thyroid cancer		
Renal cell carcinoma (due to secretion of gonadotrophin-like hormones)		
Systemic mastocytosis		
Pancreatic NETs		
Cushing's syndrome		
Autonomic neuropathy		
Post-menopausal hot flashes (80% of post-menopausal women)		
Medical or surgical castration for prostatic cancer (more than 65% of men)		
Malignant histiocytoma, neuroblastoma, ganglioneuroma (due to VIP secretion)		
Anxiety, panic attacks		
Simultaneous ingestion of alcohol and chlorpropamide		
Drugs (nitroglycerine, nitro-derivatives, phosphodiesterase-5 inhibitors, calcium channel blockers-mainly dihydropyridine, cholinergic drugs, prostaglandin D2 and E, non-steroidal antiinflammatory drugs, nicotinic acid, vancomycine, rifampicin, cyclosporine, cisplatin, dacarbazine, TRH, bromocriptine, morphine, opioids, triamcinolone, metoclopramide, isoflurane, fentanyl, serotonin reuptake		

inhibitors-can cause night sweats, radiologic contrast agents)

Symptoms and Signs of Carcinoid Syndrome

Symptom	Frequency %	Characteristics	Involved mediators
Flushing	90	Foregut: long-lasting, purple	Catecholamines, 5-HT, histamine, substance P
		Midgut: short-lasting, pink to red color, face and trunk, can occur several times a day for a few minutes	Catecholamines, histamine, substance P, prostaglandins
Diarrhea	60-80	Secretory: intermittent accompanied by abdominal cramping	Gastrin, 5-HT, histamine, prostaglandins, VIP
Abdominal pain	35	Progressive	Small bowel obstruction, hepatomegaly, ischemia
Bronchospasm	15	Wheezing	Histamine, 5-HT
Pellagra	5	Dermatitis, diarrhea, dementia	Niacin deficiency
CHD	19-60	Dyspnea, holosystolic murmur radiating to the right side of the chest	5-HT, bradykinins, tachykinins, activin A, tissue growth factor
Mesenteric Fibrosis	50	Ischemia of vessels: decreased absorption of nutrients, ascites, intestinal obstruction, ureteral obstruction	5-HT, TGF-beta

Patient with Pellagra





Carcinoid Syndrome

- Neuropsychological symptoms: extreme tryptophan deprivation can lead to 87-97% decreased levels of 5HT in the brain; cognitive dysfunction
- Skin : pellagra 5%



to the triad of **Dermatitis**

Diarrhea

Dementia



Carcinoid Heart disease

- Present in 19-60 %
- Mechanism is unclear
- Symptoms of right heart failure:
 peripheral edema, abdominal discomfort,
 indigestion, early satiety and
 cachexia.....as the condition worsens,,
 dyspnea, jugular swelling, ascites death
 heart failure
- Fibrous tissue valves, right heart chambers particularly tricuspid

Role of 5HT in fibrogenesis



A. 5HIAA in CHD more than those without



B. 5HT2b receptor in cardiovascular system is involved in fibrogenesis



C. In animal models overexpression of 5HT2b in the heart lead to cardiac hypertrophy by increased deposition and remodeling of extracellular matrix; whereas deletion of 5HT2b leads to ventricular dilation and incomplete development of the heart





Symptoms caused by increased amines in circulation



Hypotension





Arrythmias



Tachycardia



Flushing



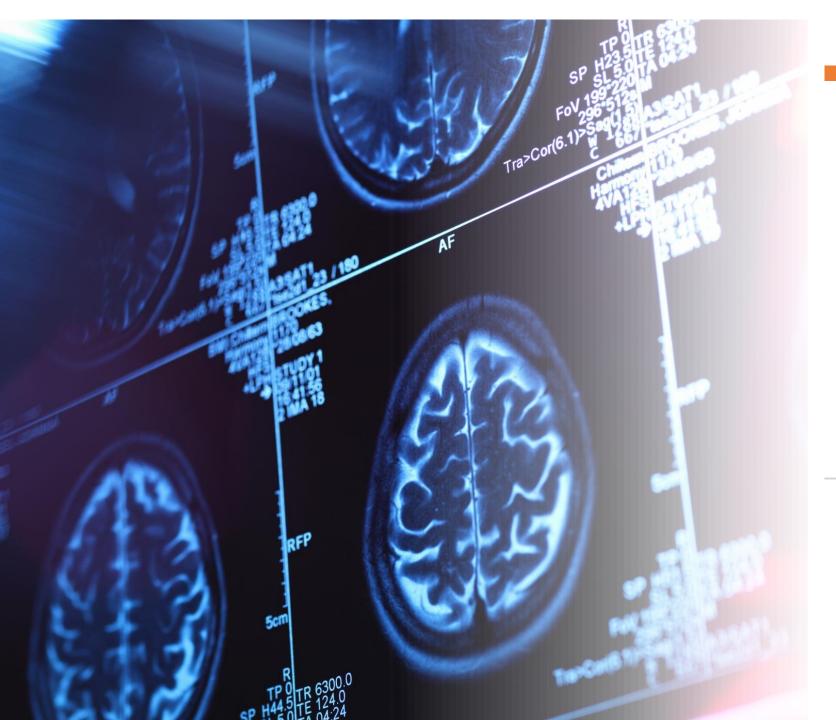
Bronchospasm



Post anesthesia surgery or radiologic interventions



octreotide in intraoperative, hepatic embolization ,liver biopsies and surgical procedures



Cross sectional imaging of NET

Sensitivities of imaging techniques used for NET detection

Technique	Primary carcinoid tumor (%)	Carcinoid liver metastases (%)	Primary gastrinoma (%)	Gastrinoma liver metastases (%)	Primary insulinoma (%)†
Ultrasound	46	83	23	50	27
СТ	64	88	38-75	54-88	30
MRI	56	85	22-90	63-90	10
SRS	80	90	72	97	25
EUS	80 (gastric)		90-100		88
Angio+Ca Stim			93		95

[†]Metastatic insulinoma is rare.

Angio+Car Stim: Angiography with calcium stimulation; CT: Computed tomography; EUS: Endoscopic ultrasound; SRS: Somatostatin-receptor scintigraphy (Octreoscan®).

Sensitivities of imaging techniques used for NET detection

Indium labeled Pentreotide

sensitivity

46-100 % for abdominal NET

46-83% for pancreatic NET

71% for bronchial NET

. Gallium Dotatate Pet CT

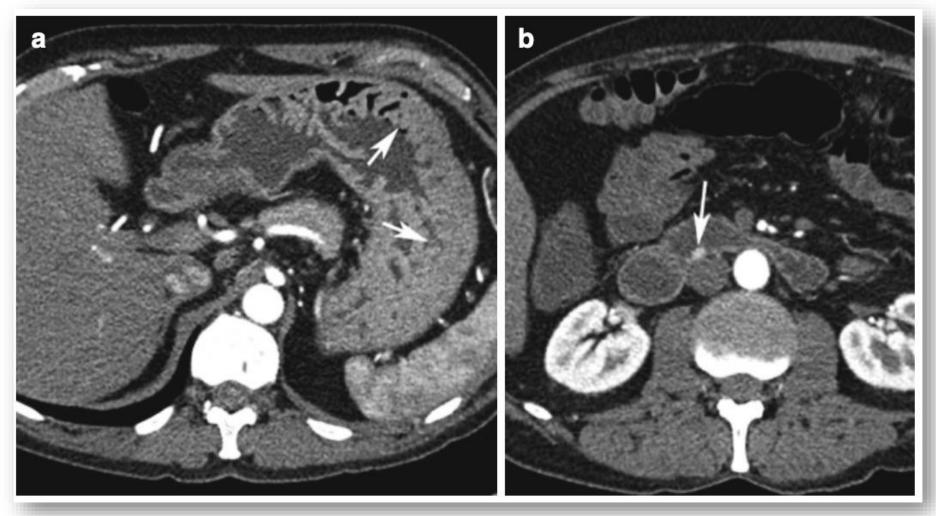
96% sensitivity vs 72% for Indium Pentreotide Scan

Poorly differentiated: FDG-PET CT

IMAGING

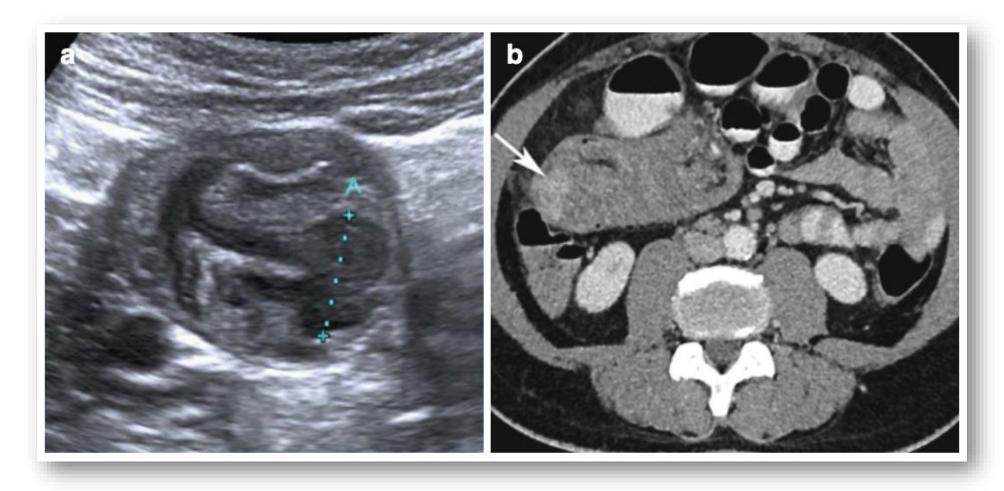
- Somatostatin receptor Imaging targeting st2r is a key in diagnostic workup and staging in NE
- Pet based tracers, Ga-DOTATATE, Ga-DOTATOC and Ga-DOTANOC were introduced for clinical use
- FDG-PET may be used in somatostatin receptor imaging negative cases
- Endoscopic US is the most sensitive method to diagnose pancreatic
 NETs

Duodenal Gastrinoma



A 49-year-old gentleman presented with Zollinger-Ellison syndrome. (**a**) Arterial-phase CT shows generalized gastric rugal hypertrophy consistent with hypergastrinaemia. (**b**) A small hypervascular lesion on the posterior wall of the third part of the duodenum was identified consistent with a gastrinoma, shown here on axial CT (*white arrow*).

Intussusception due to small bowel NET



(a) Ultrasound demonstrates an intussusception, and the lead point is a small bowel NET, shown here between the calipers. (b) CT demonstrates the enhancement of the primary lesion.

Gastrinoma

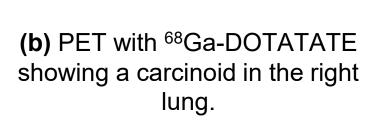


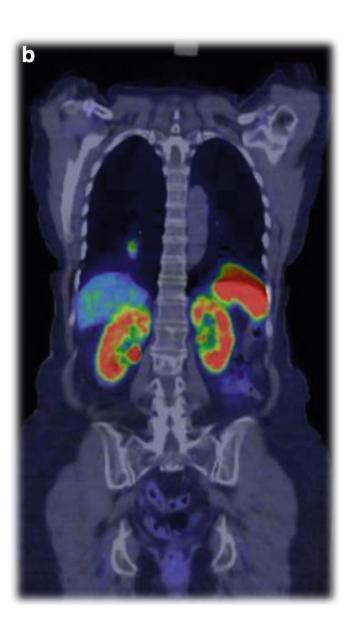
Octreotide scan demonstrating positive uptake in a patient with metastatic Zollinger-Ellison syndrome

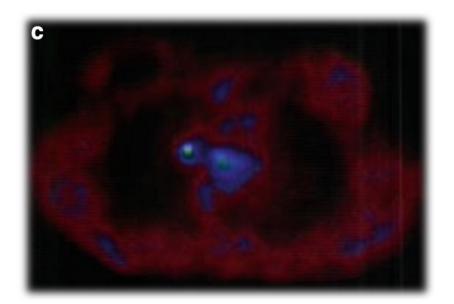
Neuroendocrine Tumors of the Lung



(a) CT Scan showing a carcinoid in the right lung.

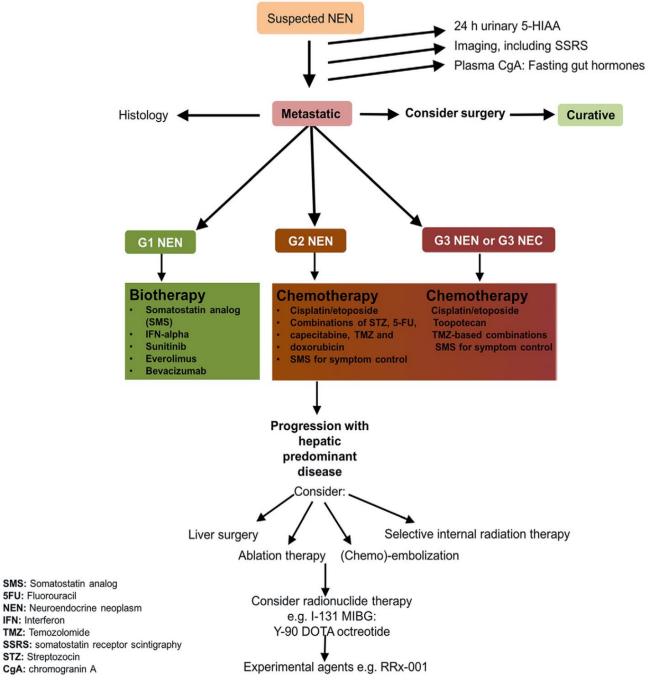






(c) PET with ¹¹C-5-HTP showing a right hilar lymph node metastasis from a typical carcinoid in the right lung, 9 years after primary surgery.

Algorithm Overview for the Investigation and Treatment of **NENs**



5FU: Fluorouracil

TMZ: Temozolomide

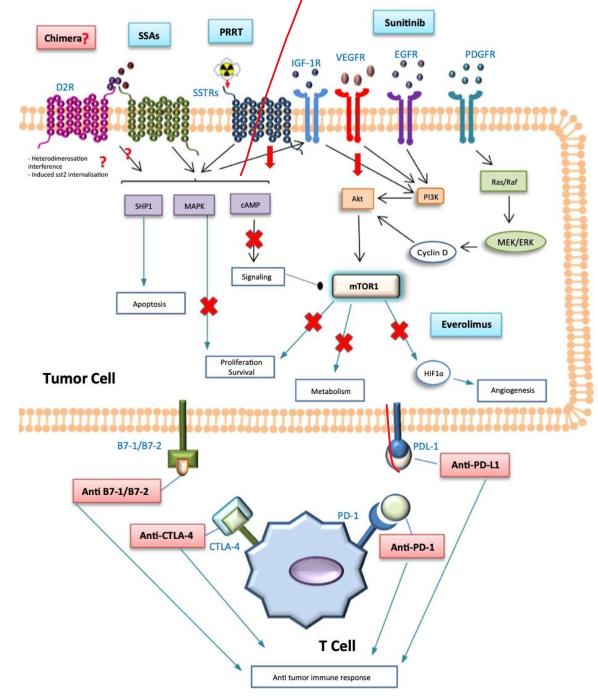
STZ: Streptozocin

IFN: Interferon

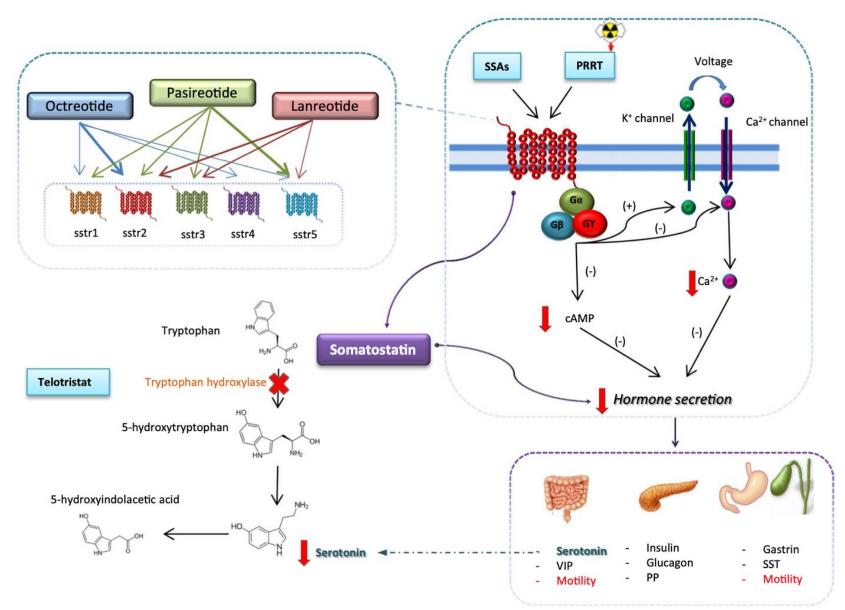
Surgery is the only potentially curative treatment modality

- Early stage disease
- Locoregional and ressectable mets
- Selected symptomatic patients
- However, many patients are diagnosed at an advance stage, hence medical therapy is necessary for both symptom and tumor control

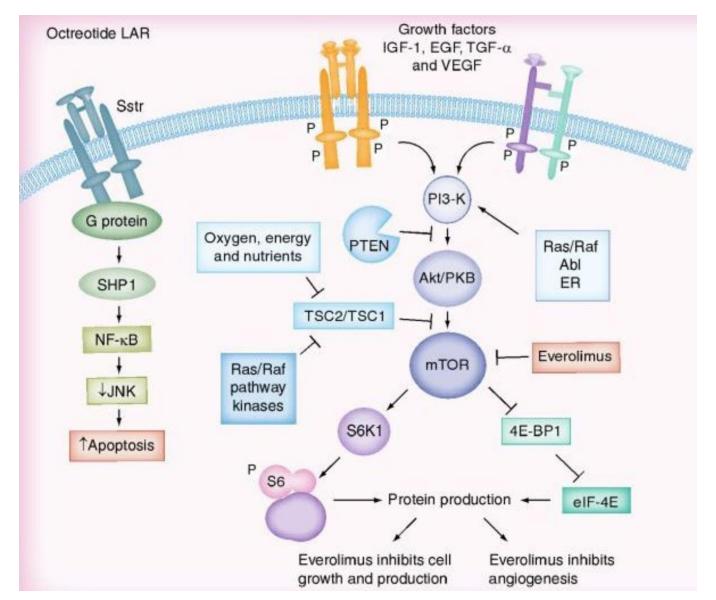
Current and Future Medical Options Tumor in NETs



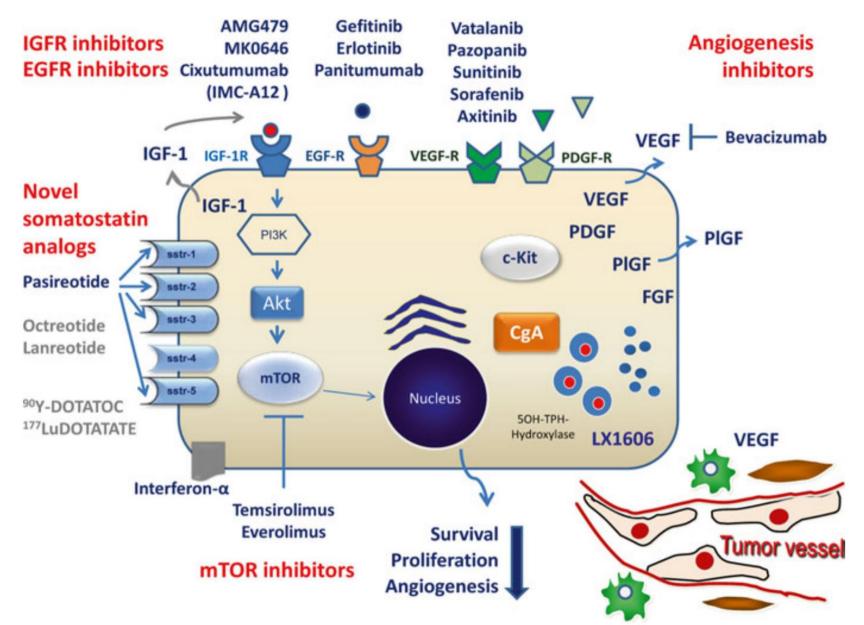
Current Medical Treatment for Symptoms Control in NETs



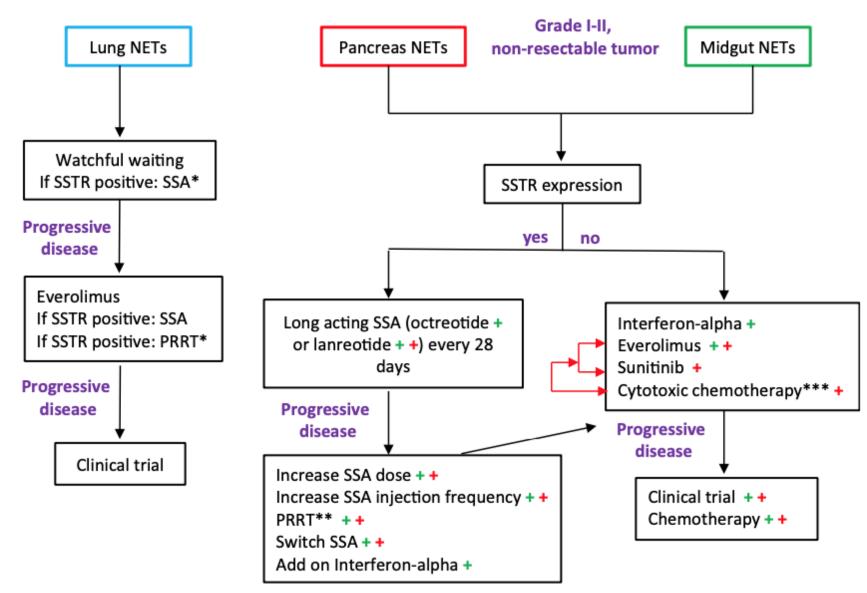
mTOR Signaling and Mechanisms of Action of mTOR Inhibitors



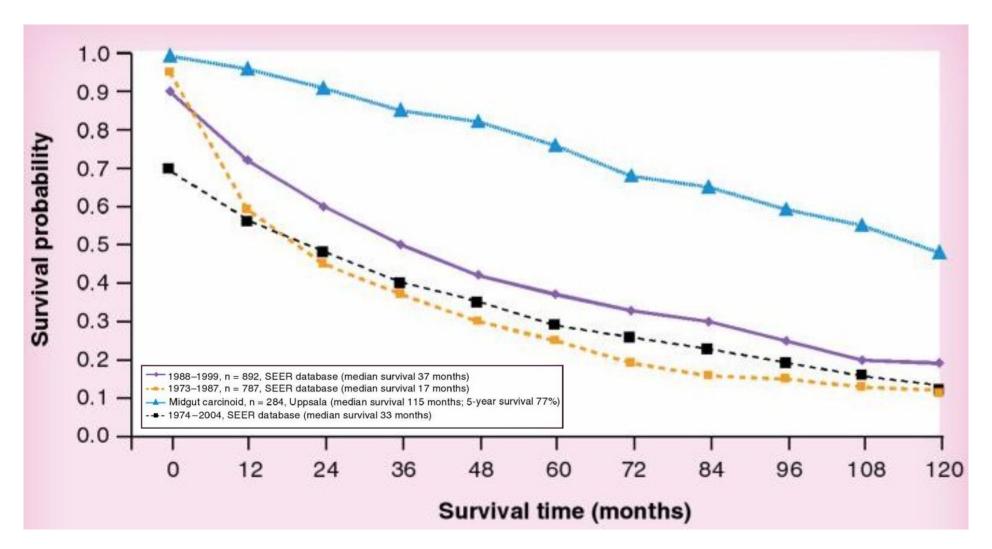
Targeted Therapies



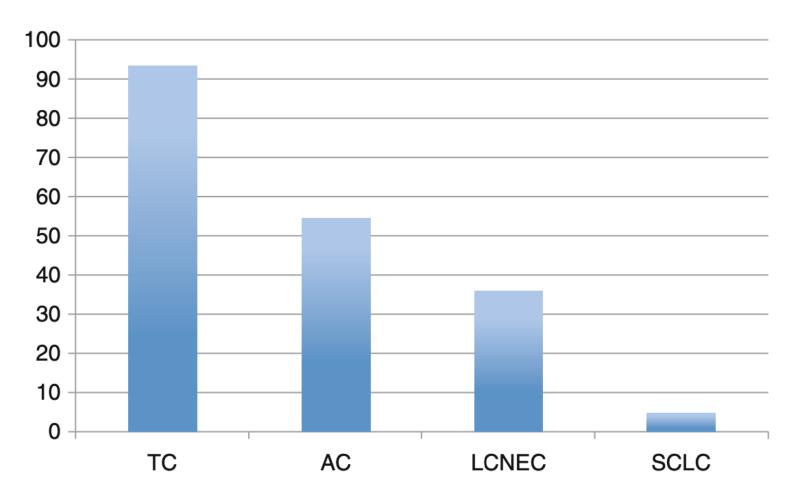
Treatment Algorithm for Tumor Control in NETs



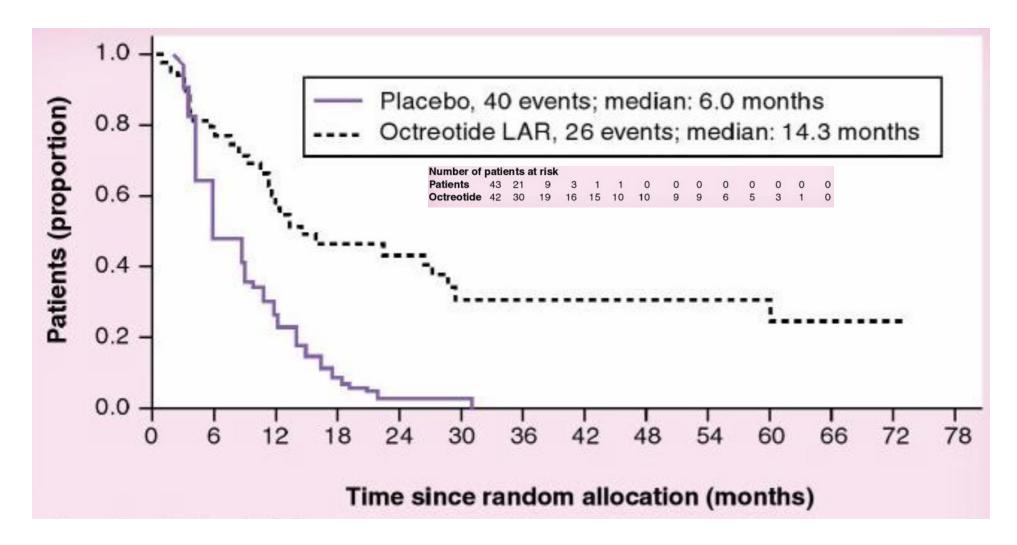
Survival duration in patients with NETs during the last four decades: a clinician's view



Neuroendocrine Tumors of the Lung

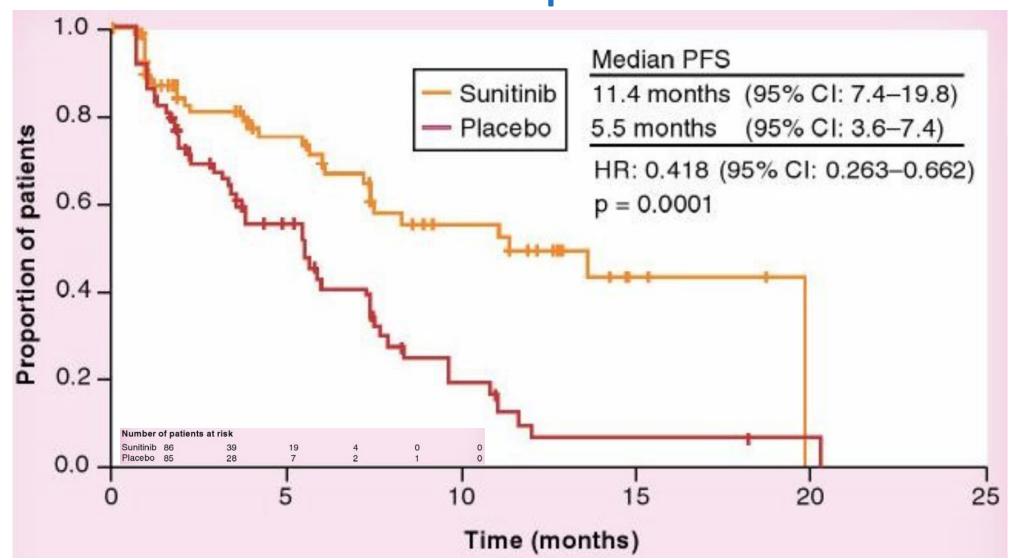


Median 5-year survival in patients with typical carcinoids (*TC*), atypical carcinoids (*AC*), large-cell neuroendocrine carcinomas (*LCNEC*), and small-cell lung carcinomas (*SCLC*)



Time to progression or tumor-related death in patients with well-differentiated, metastatic, functioning or nonfunctioning, midgut neuroendocrine tumors treated with octreotide long-acting repeatable or placebo

Kaplan-Meier Analysis Progression-Free Survival in patients treated with sunitinib vs placebo







1. A generic label of convenience of NE may do more harm than good, for these "biologically benign "tumors are not reliably indolent.



NET's are increasing in incidence and prevalence in various areas of the world

Conclusion



Word of caution: few patients present with the classical carcinoid syndrome



Clinicians should have a high index of suspicion to ensure timely diagnosis and referral to multidisciplinary subspecialty centers

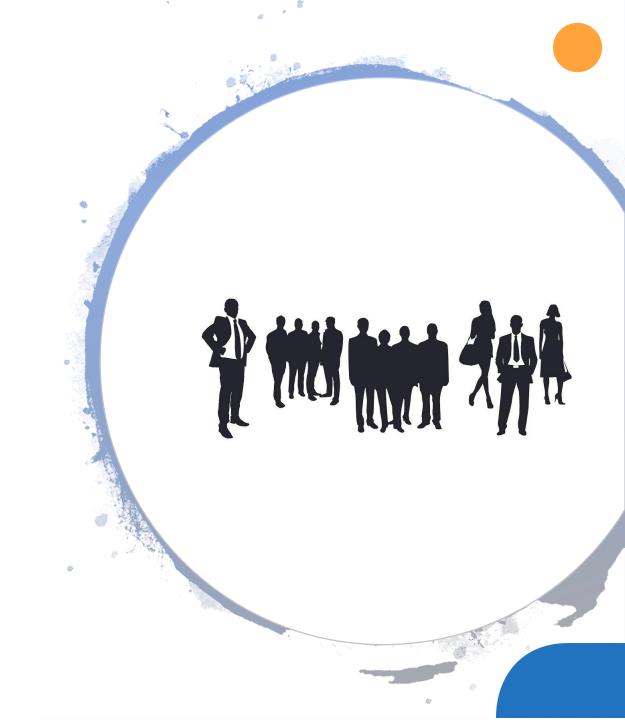


Treatment options are rapidly expanding

Conclusion

- Several questions remain :
- Best predictive and prognostic markers
- Optimal follow up strategy
- QOL

There is a real need of collaborative efforts among researchers to investigate the mechanisms underlying Cs, to study prognostic and predictive factors of current treatments and to generate epidemiological data to evaluate the real impact of Cs



2019 Boston Neuroendocrine Tumor Patient and Caregiver Education Conference

August 23, 2019

The Neuroendocrine Tumor Research Foundation (NETRF) and the North American Neuroendocrine Tumor Society (NANETS) have joined together to bring NET patient and caregiver education to New England.

Top expert speakers from around the world will present...

OncLive Summit on Neuroendocrine Tumors at Markey Cancer Center, Kentucky

March 19, 2019

The UK Markey Cancer Center in Lexington, Kentucky, will host OncLive's State of the Science Summit on Neureoendocrine Tumors (NETs) on Saturday, April 20, 2019. The Summit is "designed to educate healthcare professionals on the clinical benefits...

Let's Talk About NET Survivorship: An Evening for Neuroendocrine Cancer Patients and Caregivers

June 13, 2019

"Let's Talk About NET Survivorship!" is a special evening presentation for neuroendocrine cancer patients and caregivers and their health care providers. Attend in person at the Grand Hotel Minneapolis in Minneapolis, Minnesota...

Florida Neuroendocrine Cancer Patient Conference, West Palm Beach

April 30, 2019

The Neuroendocrine Cancer Awareness Network, NCAN, will present a daylong NET Patient Conference in West Palm Beach, Florida, on Saturday, December 7.

NET Cancer Day Symposium, California

September 17, 2019

LACNETS, the Los Angeles Carcinoid and Neuroendocrine Tumor Society, will present a special **NET Cancer Day Symposium** at City of Hope in Duarte, California. Symposium details and registration coming soon!

2019 Chicago Neuroendocrine Tumor Conference

June 11, 2019

The 2019 Chicago Neuroendocrine Tumor (NET) Patient and Caregiver Education Conference will offer educational and networking opportunities for people living with NETs, their caregivers, family members, and friends.

Neuroendocrine Cancer Patient Conference, Tulsa,

Oklahoma

March 20, 2019

The Neuroendocrine Cancer Awareness Network is presenting a day-long conference for neuroendocrine cancer patients and their loved ones on Saturday, April 13 at the Stoney Creek Conference Center in Broken Arrow,

Virginia Neuroendocrine Cancer Patient Conference

April 15, 2019

Sponsored by the Neuroendocrine Cancer Awareness Network, NCAN, the Virginia Neuroendocrine Cancer Patient Conference will be held on Saturday, May 4 at the Crown Plaza Old Town Alexandria. Among the topics to be presented are:

An Overview of NETs

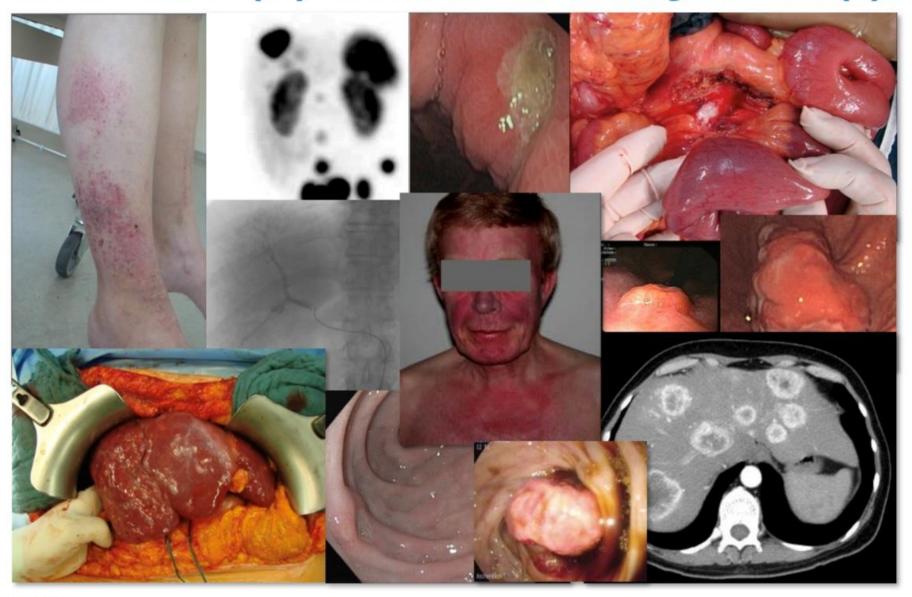


Tennessee NET Patient Conference, Nashville

April 15, 2019

The Neuroendocrine Cancer Awareness Network, NCAN, will present a daylong NET Patient Conference in Nashville, Tennessee, on Saturday, September 14.

NEN: One (?) Disease, Many Face(t)s!



Acknowledge



- Cynthia Alvarez, Consultant, Medical Scie. Liaison Diabetes Lilly
- Vilmarie Colon ,MPH PharmD Class 2020