Gastroenteropancreatic neuroendocrine neoplasms

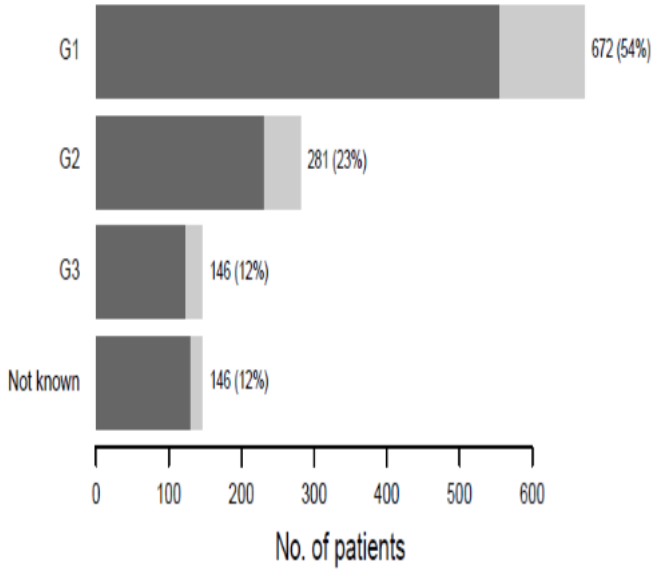
Benjamin Misselwitz, Marion Bionda 16.06.2021

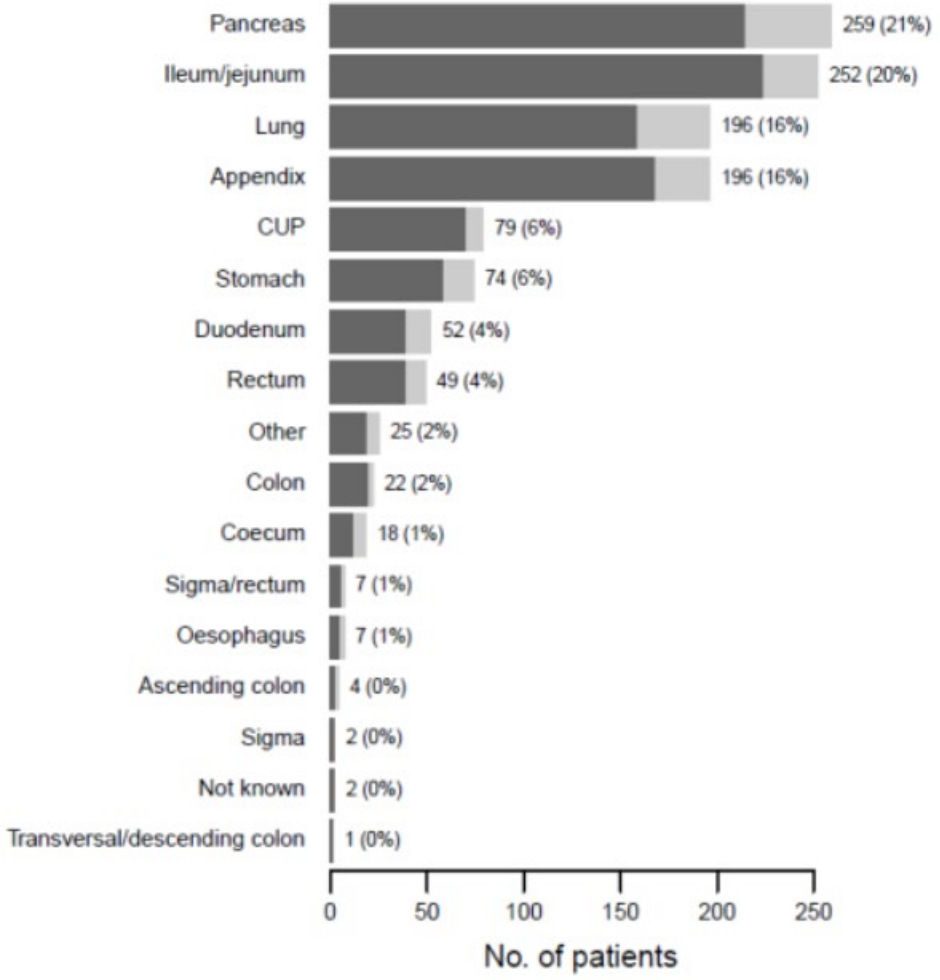
History

- Siegfried Oberndorfer first described and depicted carcinoid ("carcinoma-like") tumors in 1907
- He initially thought carcinoids were benign, but later recognized that «*karzinoide*» might exhibit malignant features and metastasize
- These tumors are "*certainly not so rare. . .I am convinced that if more attention is paid to them in the future, then its number will rapidly increase*".

Modlin et al., Human pathology 2005; 35:1440

NET in Switzerland – SwissNET data base





- 180 cases per year in CH
- Male/ female: 53%/ 47%
- Mean age at diagnosis: 59-60 years
- Rare tumors, 2/3 affect GI tract

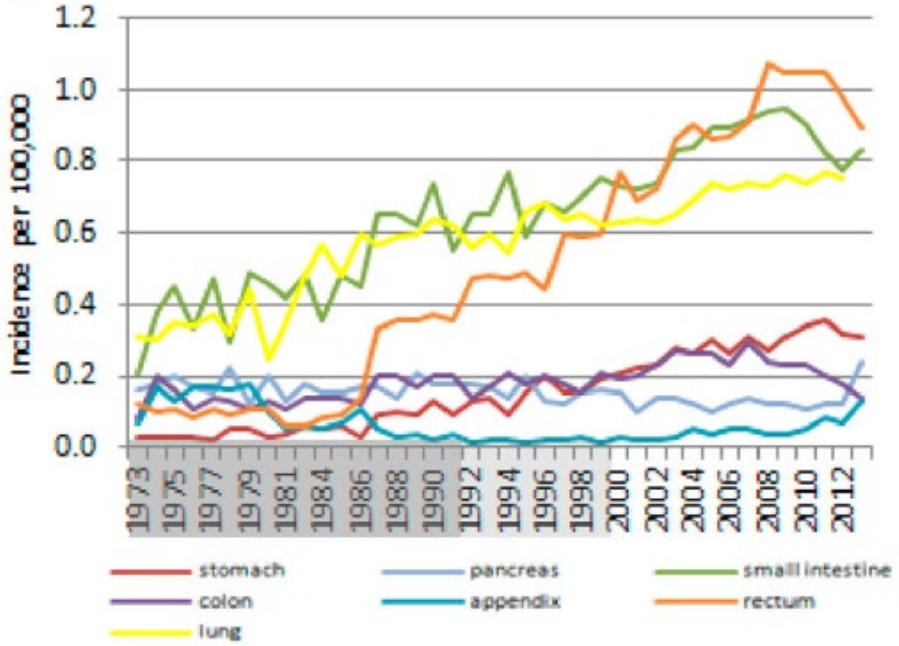
https://www.swissnet.net/images/files/SwissNETReport2016.pdf

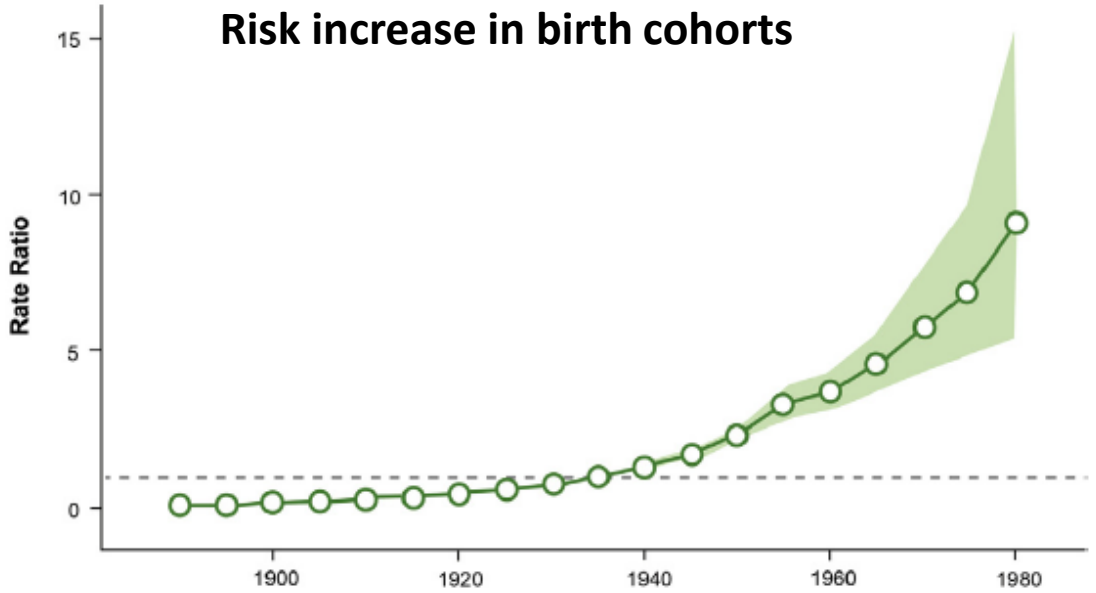
What is the incidence of NETs?

- 7/ 100’000 per year
- Ontario: 1994: incidence 2.5/ 100’000, 29% metastasis
  2009: incidence 5.9/100’000, 13% metastasis
- USA (SEER data base)
  1973: incidence 1.1/ 100’000
  2012: incidence 7/ 100’000

Hallet et al., Cancer 2015; 121:589; Dasari et al., JAMA Oncology 2017; 3:1335

Increase in the incidence of NET





Reasons: increase in diagnostics?

- 54% increase in upper endoscopy 2000-2009
- Participation in screening doubled 2000-2010

→ Why did small intestine NET also increase

→ Why is colon NET stable?

Leoncini et al., Endocrine 2017; 58:368; Lee et al., Clin Gastroenerol Hepatol 2019; 17:2212

Genetics

NETs are mainly sporadic, but may occur as part of a complex **familial endocrine cancer syndrome**.

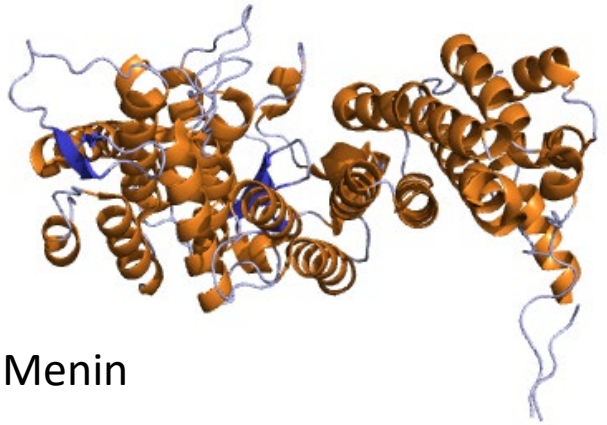
Which syndromes are these?

MEN1, MEN2
Neurofibromatosis type 1
Von Hippel Lindau
Tuberous sclerosis complex

→ **detailed family history**, clinical examination
→ Genetic counseling

MEN 1

- Autosomal dominant
- > 2 typical tumours, positive familiy history, relatives with known MEN-mutation



Menin

- Mutation in tu nin)
- Which tumours
  - Parathyroid h
  - Islet cell tumours of the **pancreas (often multifocal)**
  - Pituitary adenomas and
  - Rarer lung and thymus carcinoids
  - Frequently type 2 gastric carcinoid in case of **gastrinoma (often multifocal)**

Pancreatic NET/ Gastrinoma
→ be aware of MEN1 associated tumors and ask for familiy history and other symptoms!!!!

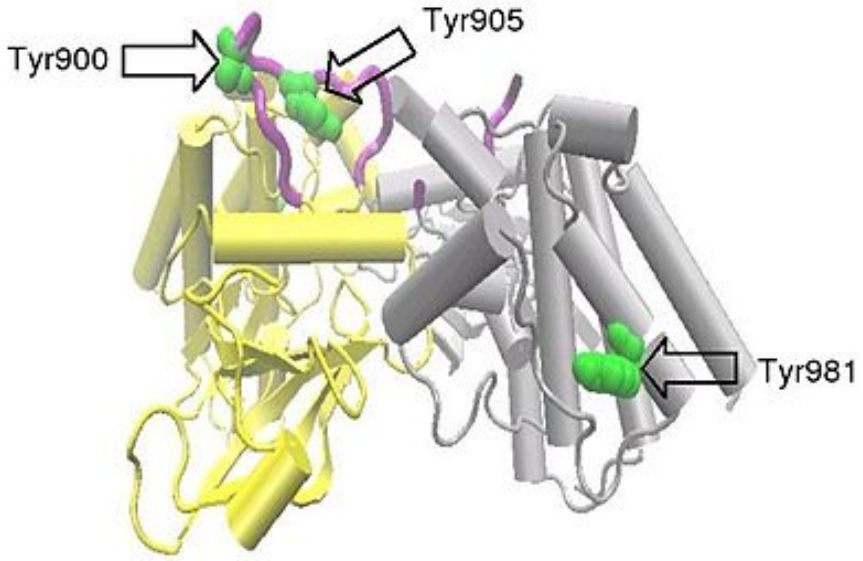
MEN 2

- Mutation in RET protooncogene
- 98 % of MEN 2 patients have?

  → Medullary thyroid cancer
- Which tumours/associations?

  MEN 2A
  - Medullary thyroid cancer
  - Pheochromocytoma
  - Parathyroidadenoma/hyperplasia
  - Hirschsprungs disease

  MEN2B
  - Medullary thyroid cancer
  - Mucosal neuromas or intestinal ganglioneuromas
  - Pheochromocytoma
  - „Marfanoid“ body habitus, ectopic lenses



Receptor tyrosine kinase
glial cell line-derived neutrotrophic factor family

Which subclassifications with prognostic value can be made?

- Localisation/ Stage
  - Embryological origin → unexact (WHO 2000)
  - Side of origin
  - TMN Stage: localized, regional or distant metastases
- Histopathological features
  - Grading and differentiation
- Clinical presentation
  - Symptoms of hormonal hypersecretion

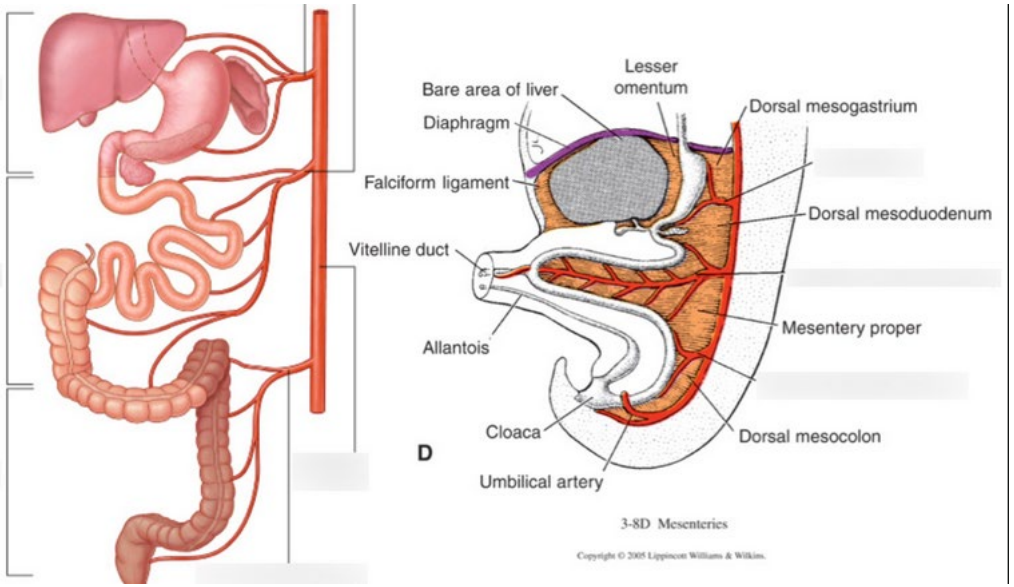
    → Nonfunctional vs functional

Williams 1963

Unexact classification

Embryological origin

- **foregut** (bronchi,stoma… as, gallbladder, duodenum… till liga… reitz)
- **midgut** (jejunum… endix, right colon) and
- **hindgut** (distal of… cture, left colon, rectum)



Oronsky Neoplasia 2017; 19:991

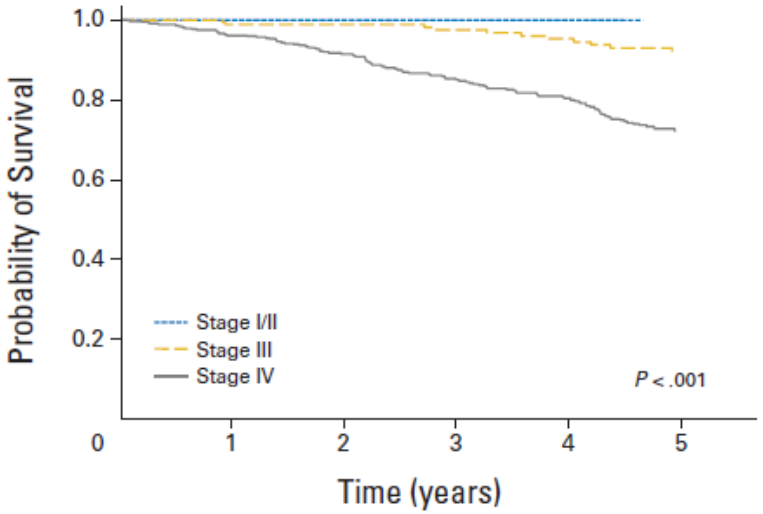
Staging – small intestinal NEN

Primary Tumor (T)	
T1	Tumor invades lamina propria or submucosa and is size 1 cm or less
T2	Tumor invades muscularis propria or is size > 1 cm
T3	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized tissue
T4	Tumor invades the visceral peritoneum (serosa) or any other organs or structures
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

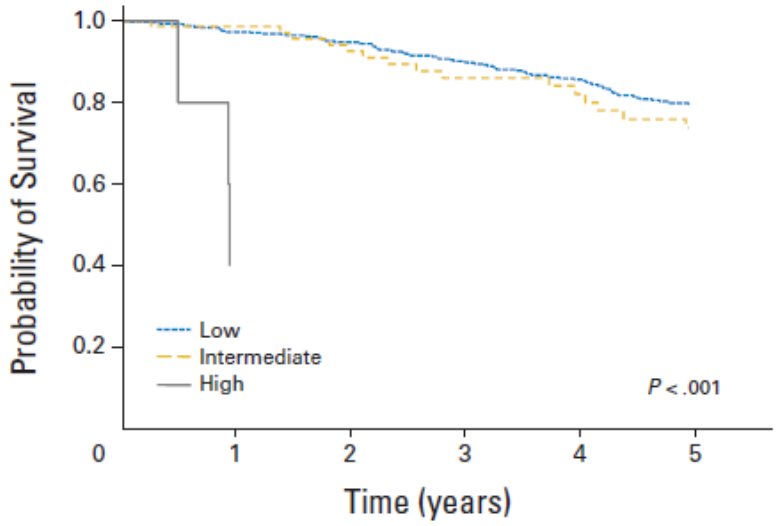
Stage			
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

Differentiation/Grade	Mitotic Count (10 HPF)	Ki-67 Index (%)
Well differentiated		
Low grade	< 2	≤ 2
Intermediate grade	2-20	3-20
Poorly differentiated	> 20	> 20

TNM Stage



Grading low – intermediate – high



G2: Hazard ratio 1.9
G3: Hazard ratio 38.4

TMN→ Stage: localized (N0), regional (N1) or distant metastases (M1)
→ *Si NET stage I-IV 5-y OS 100%,100%, 91%, 72 %*

Strosberg J Clin Oncol 2013; 31:420

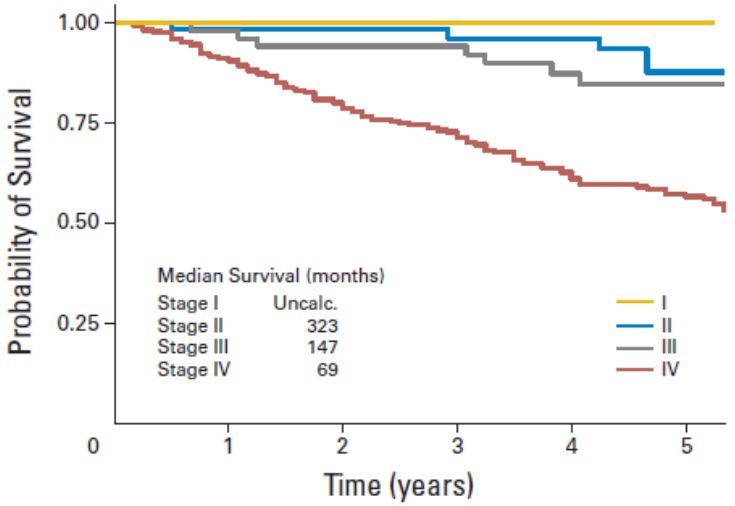
Staging – pancreatic NEN

ENETS Staging Classification

T1	Tumor limited to the pancreas, < 2 cm
T2	Tumor limited to the pancreas, 2-4 cm
T3	Tumor limited to the pancreas, > 4 cm, or invading duodenum or CBD
T4	Tumor invades adjacent structures
N0	No regional LN metastasis
N1	Regional LN metastasis
M0	No distant metastasis
M1	Distant metastasis

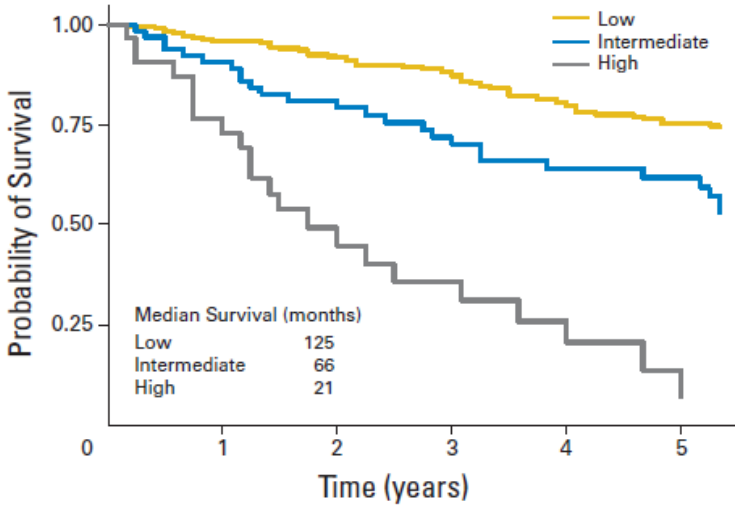
Stage	T	N	M
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

TNM Stage



Stage II: HR 1.2
Stage III: HR 1.7
Stage IV: HR 5.8

Grading low – intermediate – high



G2: HR 2.0
G3: HR 5.4

TMN→ Stage: localized (N0), regional (N1) or distant metastases (M1)
→ *pancreatic NEN stage I-IV 5-y OS 92%, 84%, 81%, 57%*

Strosberg J Clin Oncol 2011; 29:3044

Covariate	HR (95% CI) Total SEER 18 NET Cohort (n = 14 757)	Distant GI NET (n = 2681)	Distant Pancreatic NET (n = 850)
Year			
2000-2004	1 [Reference]	1 [Reference]	1 [Reference]
2005-2008	0.83 (0.78-0.89)	0.76 (0.67-0.86)	0.76 (0.61-0.96)
2009-2012	0.79 (0.73-0.85)	0.71 (0.62-0.81)	0.56 (0.44-0.70)
Grade			
1: Well differentiated	1 [Reference]	1 [Reference]	1 [Reference]
2: Moderately differentiated	1.76 (1.59-1.94)	1.81 (1.52-2.14)	1.36 (1.04-1.77)
3 and 4: Poorly differentiated and undifferentiated; anaplastic	5.26 (4.85-5.71)	6.72 (5.89-7.67)	4.81 (3.85-6.02)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
American Indian/Alaska Native	1.45 (1.00-2.11)	1.73 (0.86-3.47)	2.07 (0.66-6.50)
Asian or Pacific Islander	1.03 (0.91-1.17)	1.40 (1.11-1.76)	1.00 (0.69-1.46)
Black	1.23 (1.13-1.34)	1.31 (1.12-1.52)	1.28 (0.98-1.68)
Age, y			
≤30	0.23 (0.17-0.33)	0.46 (0.28-0.76)	0.44 (0.23-0.86)
31-60	0.54 (0.51-0.57)	0.62 (0.56-0.69)	0.58 (0.48-0.70)
≥61	1 [Reference]	1 [Reference]	1 [Reference]
Stage		NA	NA
Localized	1 [Reference]		
Regional	1.73 (1.57-1.90)		
Distant	5.05 (4.64-5.50)		
Site		NA	NA
Lung	[Reference]		
Appendix	0.53 (0.43-0.65)		
Cecum	0.81 (0.72-0.91)		
Colon	0.99 (0.88-1.12)		
Liver	1.85 (1.46-2.36)		
Pancreas	0.86 (0.78-0.94)		
Rectum	0.71 (0.62-0.82)		
Small intestine	0.53 (0.48-0.59)		
Stomach	1.20 (1.07-1.34)		

Unfavorable prognostic factors

- High Grading
- Advanced Stage
- Older age
- Site (Lung, Colon, Liver, Stomach)

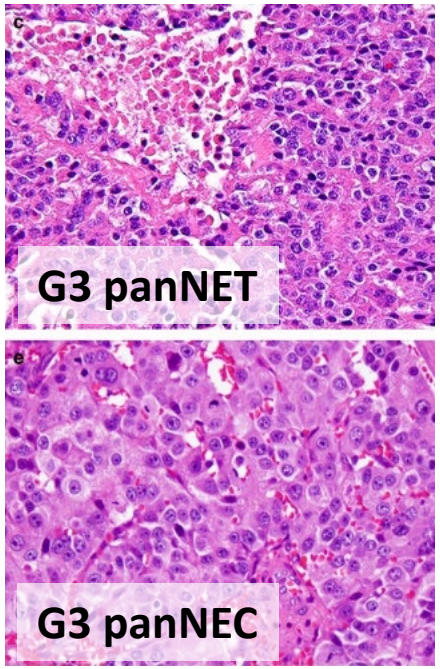
Slow improvement of survival over time…
→ more frequently diagnosed?

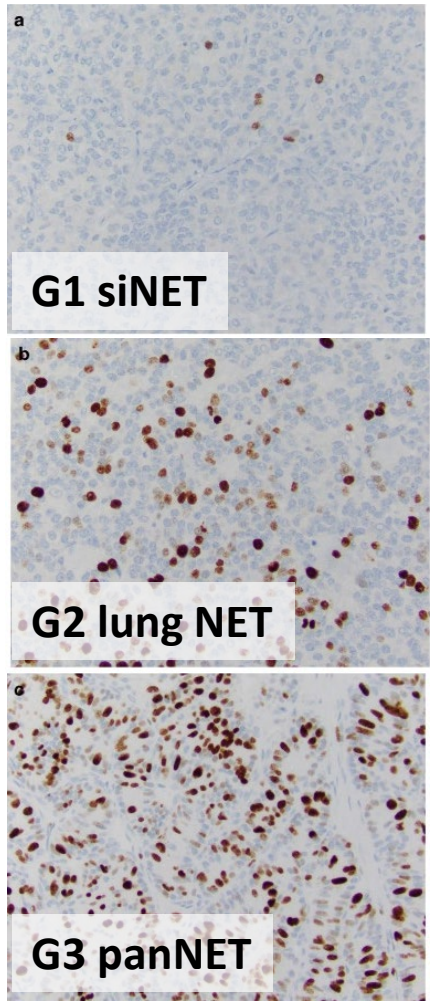
Dasari JAMA Oncology 2017; 3:1335

WHO classification 2017

- To which major groups are GI neuroendocrine tumours classified according to WHO 2017 according to grading and differentiation?
- Which two pathomorphologic parameters of the tumours are used for grading?

Differenzierung	Grading	Mitotic rate: Mitosen/10 HPF (better: per area!)	Ki-67 Index %
Well-differentiated NET	**G1**	< 2	< 3
Well-differentiated NET	**G2**	2-20	3-20
Well-differentiated **Pancreatic-NET** … also supported for other gastroenteric NETs	**G3**	> 20	> 20
Poorly-differentiated **NEC** (small or large cell type)	**G3**	> 20	> 20





Rindi Mod Pathol 2018; 31:1770

1907 Oberndorfer „carcinoid“

- WHO 1980 carcinoids all
- WHO 2000 → GEP-NET, carcinoids well-differentiated GI/lung
- WHO 2010 → … cell type) and mixed (MANE…

G3 panNET ≠ panNEC
→Different genetics
→Better prognosis (panNET)
→Different therapy (like G1/G2 NET)

- **WHO 2017**

NEW: **poorly d…**
G3 NETs

NET G1/G2, **NET G3**, NEC G3, mixed
MANEC (mixed adenoneuroendocrine Carcinoma
→ MiNEN (mixed neuroendocrine-nonneuroendocrine tumors)

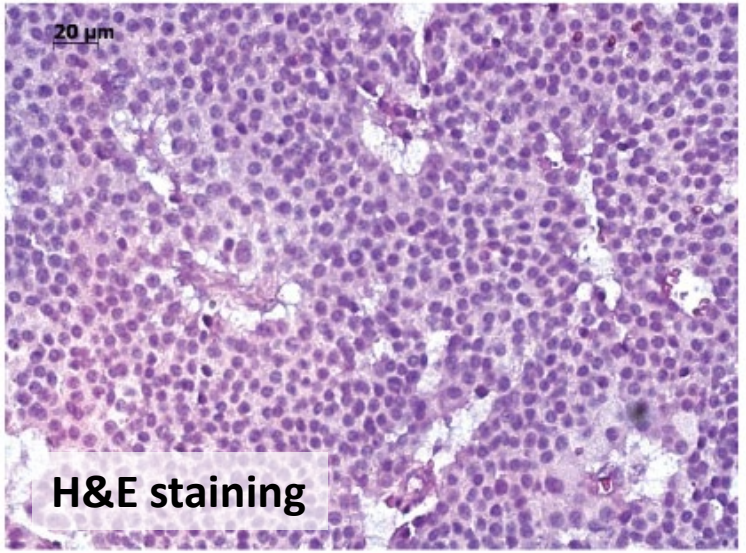
Rindi Mod Pathol 2018; 31:1770

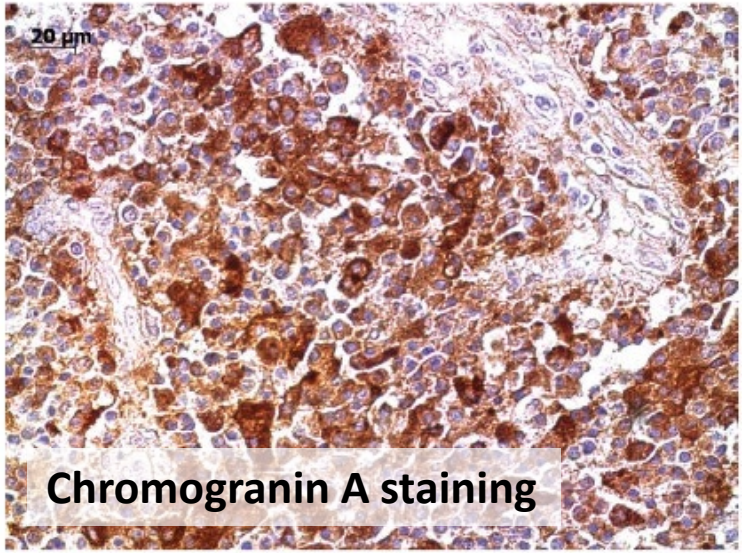
Immunhistochemistry

Specific markers are
- Chromogranin A
- Synaptophysin

→ can help to establish the neuroendocrine differentiation

In case of unkown origin:
- Midgut → CDX2 Homeobox protein CDX2, nuclei of intestinal cells
- Lung → TTF1 ThyroidalTranscription factor 1
- Pancreas → Isl-1/PAX8 ISL LIM hombebox 1





Neuroendocrine tumor of Papilla Vateri
- → **Whipple procedure**
- → **No abnormalities after 9 years**

Kyriakopolous Ann Transl Med 2018; 6:252, Waisberg J Pancreas 2016; 17:538

Clinical features: Non-functioning GI neuroendocrine tumors

Which are the typical symptoms of non-functioning NETs?

No symptoms at all or:

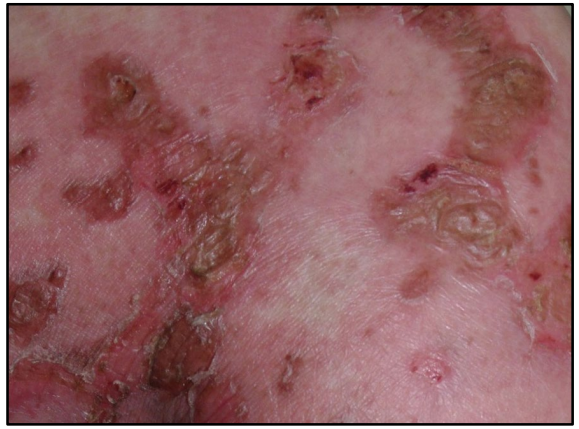
- Symptoms from pancreatic mass and/ or liver metastases
- Abdominal pain, nausea and vomiting
- Weight loss
- Gastrointestinal bleeding
- Obstruction

Functioning GI neuroendocrine tumors

Which are the typical symptoms of functioning NETs (of the Pancreas)?

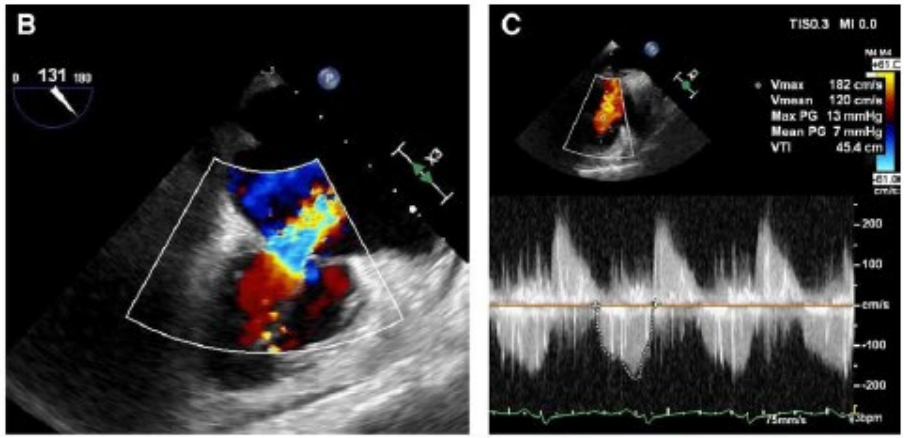
Functioning NETs	Clinical features
Insulinoma	Whipple Trias (1938) • Hypoglycaemia (<2.5 mmol/l) • Hypoglycamic symptoms: confusion, sweating, dizziness… • Relief with eating or i.v. glucose
Gastrinoma	Zollinger-Ellison-Syndrome (1955) • Severe peptic Ulceration, reflux, diarrhoea
VIPoma	Verner-Morrison Syndrom; WDHA (1958) • Profuse watery diarrhea, hypokalemia, achlorhydria
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, thrombosis, depression, diarrhoea
Somatostatinoma	Cholelithiasis, Steatorrhoe

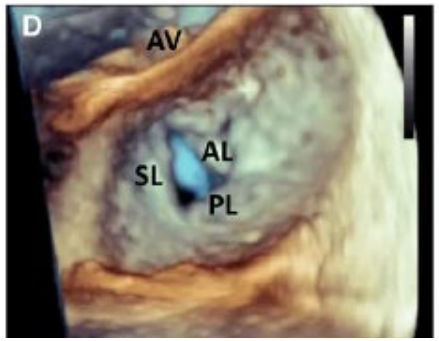
Delay of diagnosis after symptom onset 7 years

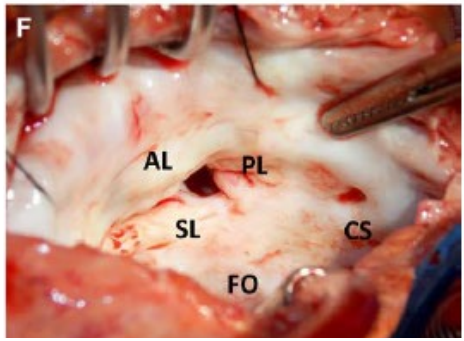


Necrolytic migratory erythema

Carcinoid syndrome (Thorson, 1954)

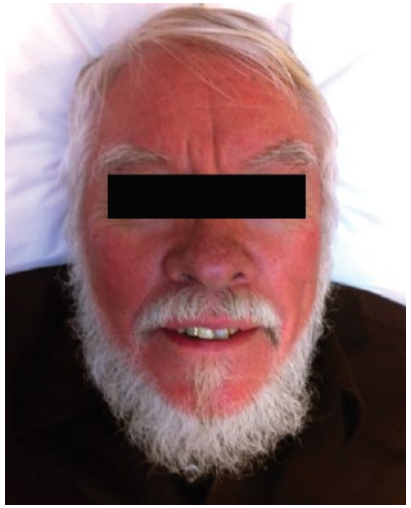






Release of Serotonine
<u>also</u>: Histamine, kallikrein, hydroxytryptophan, prostaglandines, Substance P, neuropeptide Y

Typical symptoms?
- Dry flushing +/- palpitations 80 %
  - Only with liver metastasis/ liver dysfunction/ high tumor burden
  - Bright red face, neck, torso
  - Minutes OR 2-4 hours OR long standing with teleangicetasias
  - Precipitated by sxercise, stress, alcohol, some food.
- Secretory diarrhoea 80 %
- Intermittend abdominal pain 40 %
- Wheezing < 10%
- Possible carcinoid heart disease 20-50 %



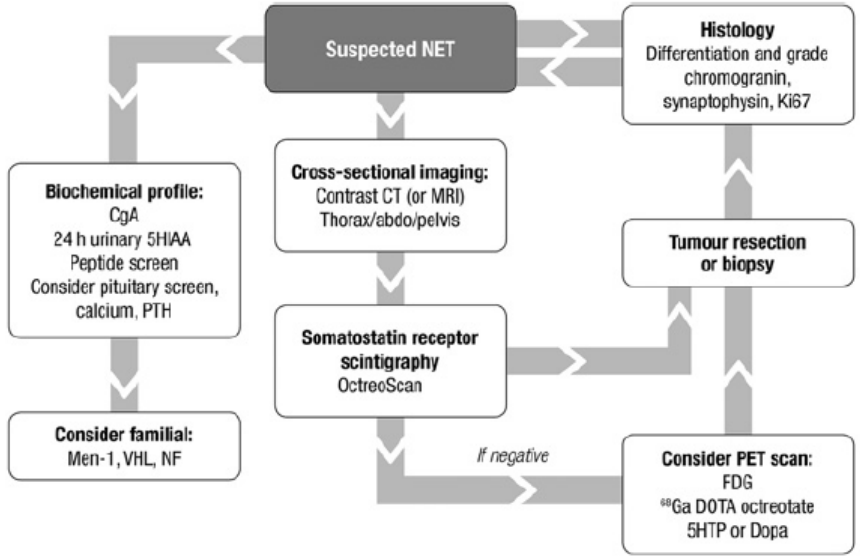
Carcinoid crisis: Profound flushing, bronchospasm, cardiac arrythmias and fluctuating blood pressure

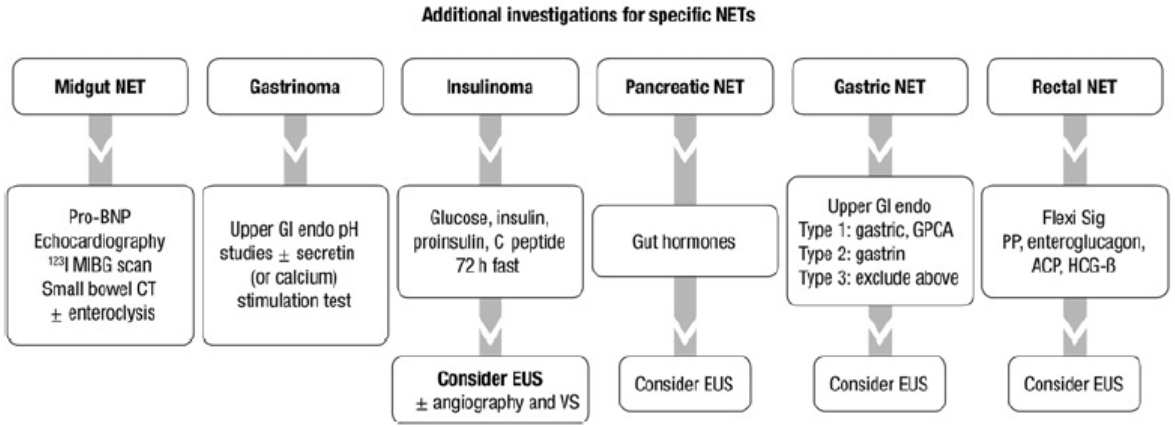
Pasieka, Int J Endo Oncol 2014; 1:87, Miyasaka Circ Cardiovasc Imaging 2019; 12:e009555

Diagnosis

Diagnosis of NETs is based on the followings:

- Pathology as the gold standard
- Clinical manifestations
- Peptide and amine secretion (biochemical)
- Radiological and nuclear imaging
  - Contrast CT or MRI
  - Ga-DOTATATE PET-CT
    → If negative consider FDG-PET
  - Primary tumour? Extension?
- Endoscopy, EUS, ±Enteroklyses, capsule endoscopy





Ramage, Gut 2012; 6:61; Andreasi, Dig Liver Dis 2021; 53:171

Biochemistry

- To assist with initial diagnosis
- To assess the efficacy of treatment
- To assess changing prognosis
- Absence of a marker does not equate to the absence of a tumour
- Screening for hormones in asymptomatic patients is not required
- In case of metastatic lung or GI NEN, evaluation for Serotonin and baseline Chromogranin A as tumormarkers is recommended

- Chromogranin A
- 5-hydroxyindolacetic acid
- Gastrin
- Insulin, C peptide, glucose
- HCG-β glucose
- PTH
- Somatostatin, vasoactive intestinal peptide, pancreatic polypeptide,

Chromogranin A

Chromogranin A: nonspecific general marker

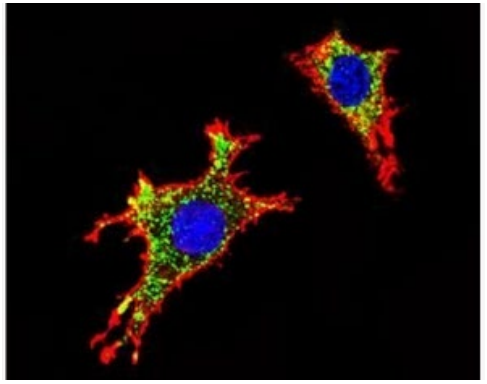
→ most guidelines recommended against screening marker, but for surveillance/follow-up as tumor marker

but

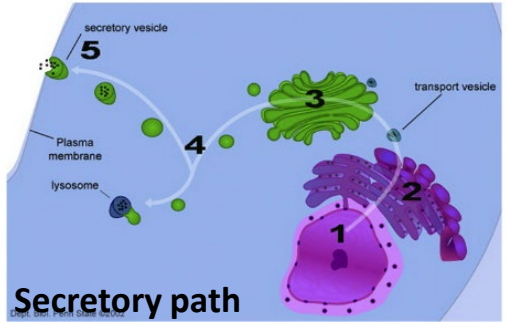
Sensitivity 73%, specifity 95%, diagnostic OR 56.3
non-functioning and functioning, well differentiated NETs

What are confounding conditions for the detection of chromogranin A?

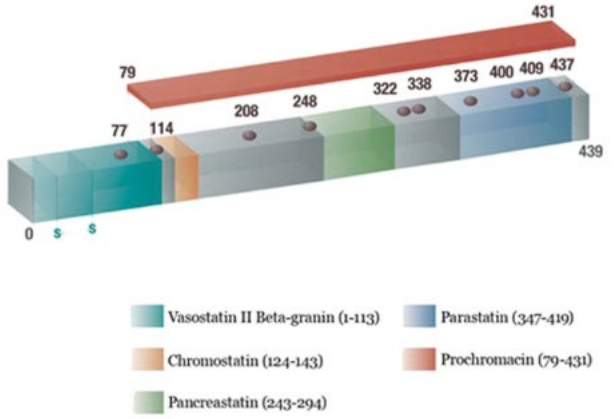
- PPI (stop 1-2 weeks bevor measurement)
- Chronic atrophic gastritis
- Impaired liver and kidney function, congestive heart failure
- HCC, medullary thyroid cancer



460 amino acid protein
→ Staining of secretory granula in pheochromocytoma cells



Secretory path



Precursor for functional peptides

Yang, PLoS One 2015; 10:e0124884, Kanakis Best Practice Clin Gastroenterol 2012; 26:791

Biochemistry: Peptide markers according to tumor site

Peptide markers specific to the tumour site

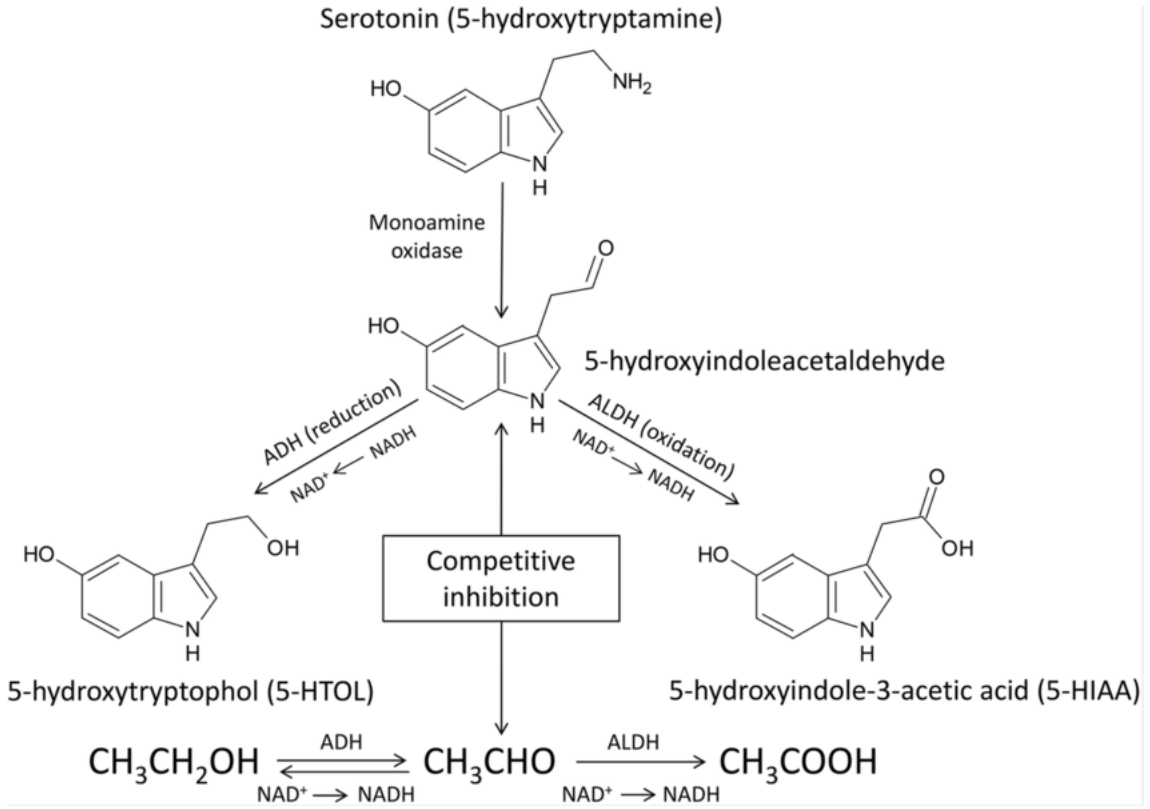
Site	Type	Laboratory tests required	Results expected
Gastric	I and II	CgA, gastrin	Raised
	III	CgA, gastrin	Raised CgA, gastrin not raised
Duodenal		CgA, gastrin, PP, urinary 5-HIAA, SOM	Raised CgA in 90%
			Consider MEN1
Jejunal, ileal and proximal colon		CgA, urinary 5-HIAA, NKA	Raised CgA (>80%), U-5-HIAA (70%) and/or NKA (>80%); see text
Proximal colon		CgA, urinary 5-HIAA, NKA, (PP)	Raised CgA (>80%), U-5-HIAA (70%) and/or NKA (>80%); see text
Appendiceal		CgA, urinary 5-HIAA, NKA, (PP)	None raised unless metastatic
			Metastatic: markers as ileal
Goblet cell		CgA, urinary 5-HIAA, NKA, (PP)	None raised
Rectal		CgA, CgB, PP, glucagon, HCG-β	Raised CgA (rarely); see text
			Raised CgB, PP, glucagon and/or HCG-β in some
Pancreatic		CgA	Raised CgA in metastatic tumours only
	Insulinoma	CgA, insulin, blood glucose,	Insulin inappropriate to glucose; see text
		C peptide or pro-insulin	Raised C peptide and pro-insulin
	Gastrinoma	Gastrin	Raised gastrin; see text
	Glucagonoma	Glucagon, enteroglucagon	Raised glucagon
	VIPoma	VIP	Raised VIP
	Somatostatinoma	SOM	Raised SOM
	PPoma	PP	Raised PP
	MEN1	CgA, gastrin, (calcium, PTH), insulin, glucagon, PP	

Items in parentheses may be helpful for diagnosis and monitoring in individual patients.
CgA, chromogranin A; CgB, chromogranin B; HGC-β, human chorionic gonadotrophin β; 5-HIAA, 5 hydroxyindoleacetic acid; NKA, neurokinin A; PP, pancreatic polypeptide; PTH, parathyroid hormone; SOM, somatostatin; VIPoma, vasoactive intestinal peptide-secreting tumour.

Diagnosis: 5-HIAA

If the 24 h urine collection of 5'-hydroxyindolaecetic acid (5'-HIAA) is positive, the most probable and second most probable site site of tumour is?

- Midgut (jejunum, ileum, proximal colon and appendix (>70%))
  * carcinoid syndrom only with extensive liver metastastes (> 95%)
- Respiratory system (10-35%)



Helander, Handbook of Analytical Separations 2008

Diagnosis: 5-HIAA

Patient instructions for the 5-HIAA 24 h urin collection?

- 48 h – 72 h before dietary and drug restrictions:
- 48 h before no avokados, bananas, eggplant, cantaloupe, pineapple, plums, tomatoes, kiwi, hickory nuts, dates, grapefruit, walnuts
  → contain serotonine
- Avoid coffee (catecholamines), nicotine and alcohol
- False high values with paracetamol, cumarine, phenobarbital, diazepam;
- False low values with ASS, chlorpromazin, isoniazid, levodopa, Streptozotocin

https://www.carcinoid.org/for-patients/diagnosis/diagnosis-and-follow-up-tests/preparing-for-the-24-hour-urine-5hiaa-test/

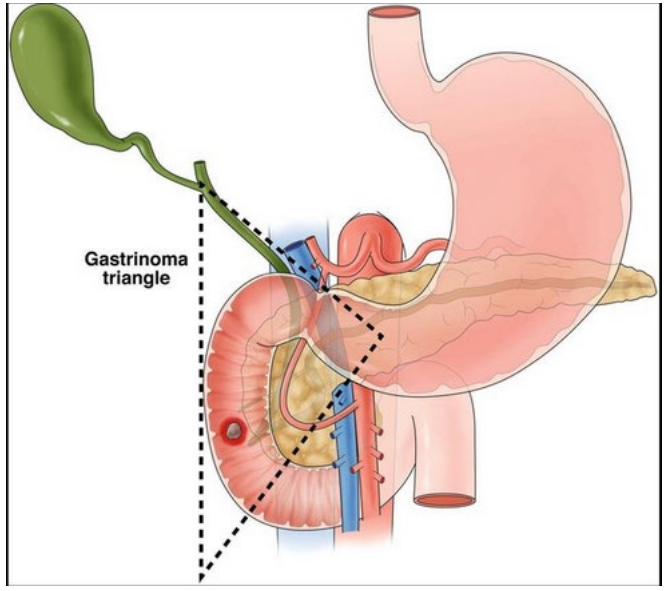
Diagnosis Gastrinoma (Zollinger-Ellison Syndrom)

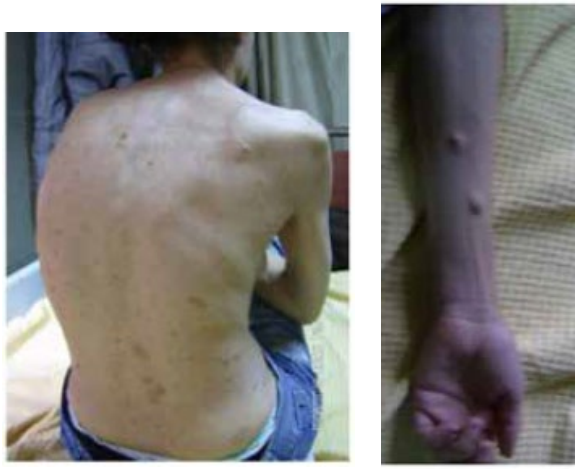
Gastrinoma (Zollinger-Ellison Syndrom)

- Acid hypersecretion in the presence of hypergastrinemia
- 25% of the patients have MEN I
- Mostly located in the duodenum (>50%) and pancreas

Diagnostic?

- Gastroscopy (> 50 % duodenal) and histology
- Basal gastrin level (Norm 13 -115 pg/ml)





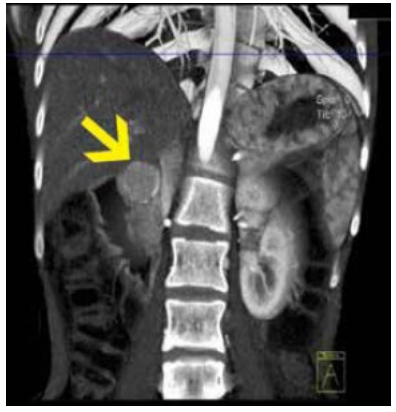
Freckling and multiple café-au-lait spots, neurofibromas
→ Neurofibromatosis 1

↓

Epigastric soreness, heartburn, nausea, vomiting, diarrhea, and a significant weight loss

↓

EGD: multiple ulcers in the duodenum + upper jejunum.
Fasting gastrin >10x upper limit of normal



Alshikho, Am J Case Rep 2016; 17:398

Diagnosis: Gastrinoma (Zollinger-Ellison Syndrom)

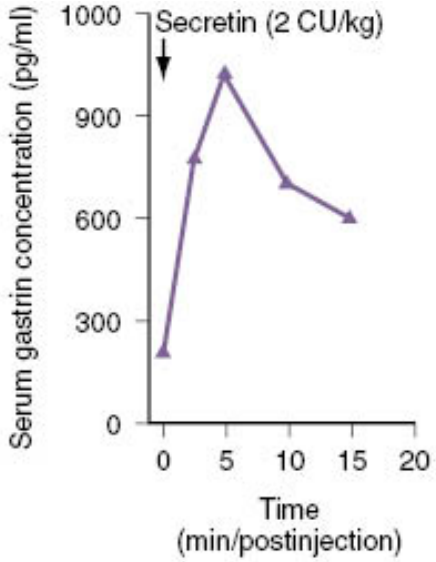
What are confounding conditions for the detection of gastrin?
= Differential diagnosis of hypergastrinaemia?

- Not fasting
- PPI
- Atrophic gastritis, achlorhydria, *H. pylori*, gastric outlet obstruction, short-bowel syndrom, liver or kidney failure

→ Patient has to be fasting > 8 h, PPI stopp for minimal 1 week

With high suspicion of gastrinoma but you cannot stopp PPI…what do you do?

- Stopp PPI, H2-antagonists are possible + recommended
- Or EUS/ endoscopy first most tumors are located in pancreas or duodenum



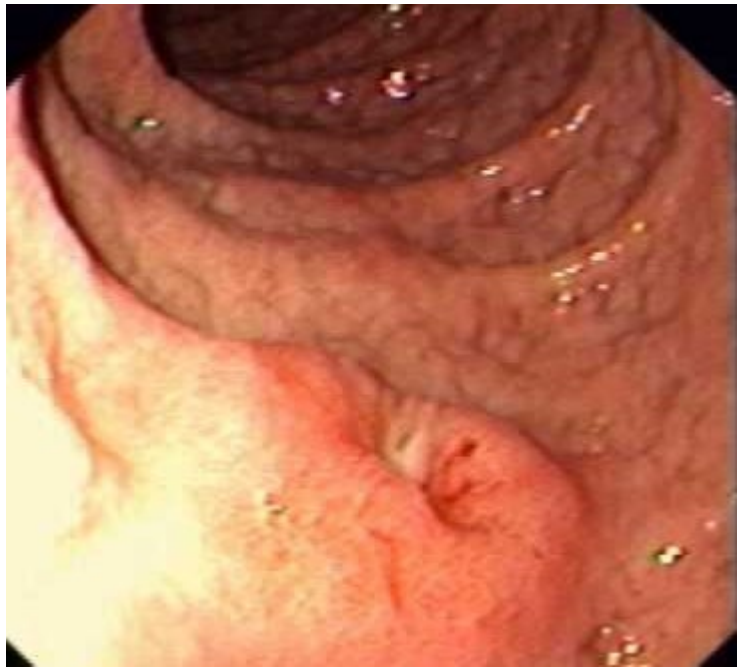
What other test is available?

Secretin test: paradox gastrin increase >120 pg/ml
after i.v. secretin (2 IE/ kg within 30 min

Diagnosis: Gastrinoma (Zollinger-Ellison Syndrom)

In reality most cases remain unclear (… PPI, liver or kidney failure…)
→ additional diagnostics during endoscopy?

Gastrin > 1.000 pg/ml + gastric pH > 2	exclusion gastrinoma
Gastrin > 1.000 pg/ml + gastric pH < 2	**gastrinoma → tumor localisation**
Gastrin 110 – 1.000 pg/ml + gastric pH < 2	secretin test

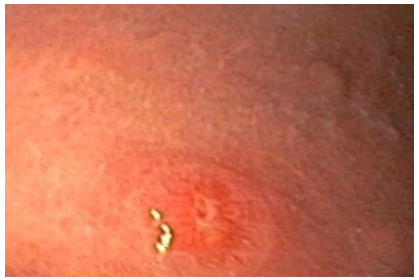


+
Bx →
HP
A-gastritis

Berna, Medicine 2006; 85:295

Diagnosis gastric neuroendocrine tumors

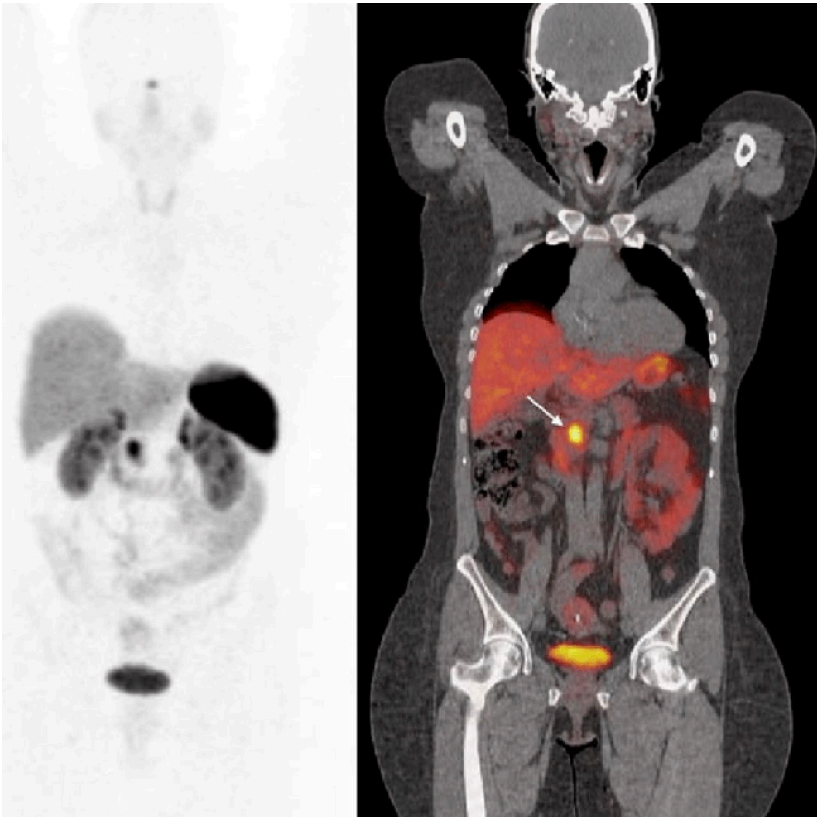
How would you distinguish between different types of NET in the stomach?



Gastric NET	**Typ I**	**Typ II**	**Typ III**
Number of tumours	Solitary or multiple	Solitary or multiple	Solitary
Tumour size	small	small	Often large, > 2 cm
ECL -hyperplasia	yes	yes	absent
Gastrin	**Hypergastrinaemia**	**Hypergastrinämie,** MEN I,	no
Association	**Autoimmune gastritis**	**Zollinger-Ellison-Syndrom**	Sporadic tumours
Metastasis	rare	rare	often
Therapy	< 1cm **endoscopic** removal, > 2 cm surgical removal	< 1cm **endoscopic** removal, > 2 cm surgical removal	Surgical removal with lymphnodes
Prognosis	Very well	Very well	**Variabel**

Somatostatin Receptor PET Imaging in NET

Chelator	**Octreotide analogon**
DOTA	TOC = d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr(OH)
DOTA	TATE = d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr. ← 9x higher affinity to somastotatin receptors
68-Gallium:	fast renal elimination



Neuroendocrine tumor of pancreatic head

SSTR-PET: ^{68}Ga-DOTATATE

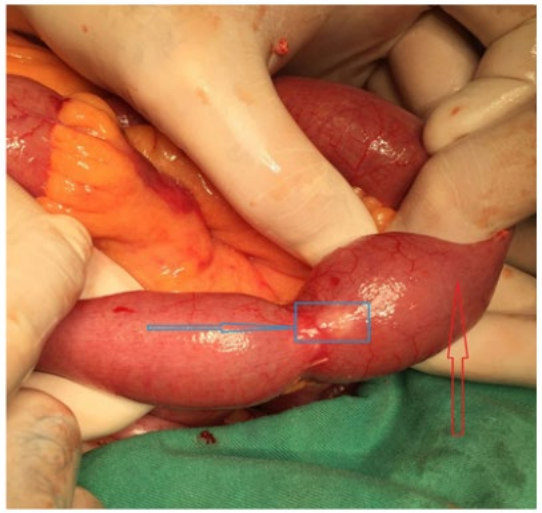
- Better sensitivity than scintigraphy scans
- Clinical use
  - ➢ Localisation of unknown primaries/at initial diagnosis
  - ➢ Selecting patients for PRRT
  - ➢ Response to therapy/ surveillance
- Best studied in G1/G2
- Variable sensitivity in NEC
  - ➢ poorly differentiated NECs often have low SSTR expression
  - ➢ may be better imaged on fluorodeoxyglucose (18F-FDG) PET/CT

Rodrigues, PET Clin 2021; 16:365

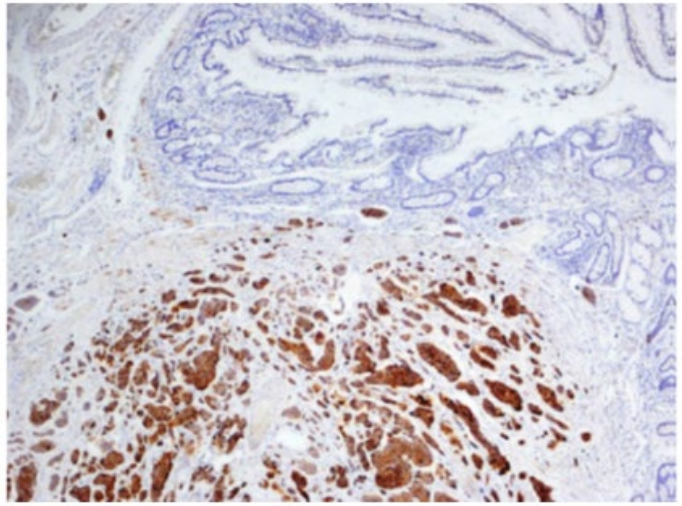
Treatment

What is the primary treatment approach for most localized neuroendocrine tumors?

- Resection



Small intestinal obstruction



Synaptophysin staining

Alexander, M J Surg 2017; 1:008

Which NETs can be treated endoscopically?

Table 5 Therapy of gastric NENs

	No risk factors (for metastatic disease)		risk factors[a]
Size	⩽ 1 cm	1-2 cm	
Type 1	Surveillance[b] optionally EMR	EMR followed by surveillance	Surgery[c]
Type 2	Surveillance[b]	EMR followed by surveillance	S-
Type 3	EMR	Surgery[c]	
Type 4	-	-	

Table 6 Therapy of duodenal NENs

Type	⩽ 1 cm[a]	1-2 cm[a]	Any size but risk factors[b]
Sporadic NET		Surgery (in case of surgical risk: EMR followed by surveillance)	Surgery
		Surgery[c]	Surgery[c]
		(particularly strinoma g) or PPI mbined llance	Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk)
		-	Surgery or cytoreductive chemotherapy

Table 7 Therapy of rectal NENs

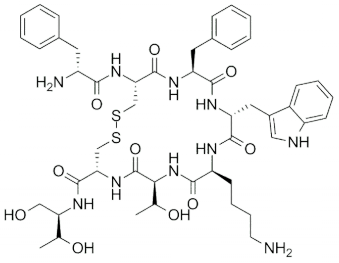
	No risk factors (for metastatic disease		
Grade/Size	⩽ 1.0 cm	1.1 - 2 cm	
G1	EMR or polypectomy or ESD	Surgery[b] (EMR or ES in case of surgical risk or for carcinoids of 11-14 mm in diameter)	
G2	EMR, ESD, surgery[b]	Surgery[b]	
G3	-	-	Surgery[b]

Gastric, duodenal, rectal

Early:
≤ 1 cm, G1
No infiltratration of muscularis propria
No angio-invasion

EMR, ESD, FTRD

Treatment



First-line Management in symptomatic patients with tumor-related symptoms or carcinoid syndrom and unresectable or progressive NENs

- Somatostatin analogues are the first-line long-term medical treatment of NETs.

Which effect do they have on NETs/ indications?

- Control of symptoms
  → Biochemical response = inhibition of hormone production (carcinoid syndrome)

- Antiproliferative effects → indication for progressive disease
  → delay progression, cannot prolongate survival

» Octreotide?

PROMID study: 85 patients, 30 mg octreotide-LAR vs. placebo.

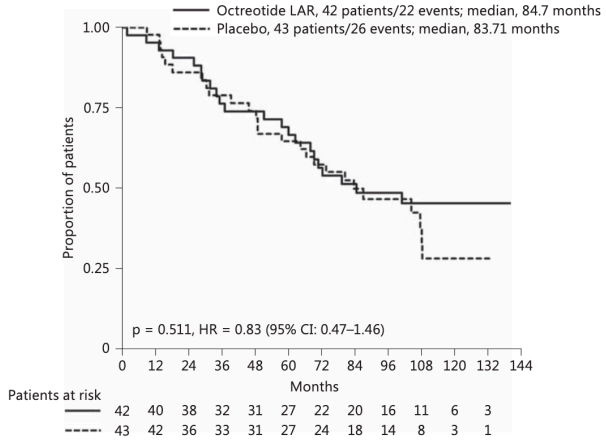
→ HR for progression 0.34; 67% stable disease at 6months

→ Longterm survival (>10 years): 43%; no advantage for Octerotide

» Lanreotide?

CLARINET study: 204 patients with gastroenteropancreatic NET

→ HR for progression at 18 months: 0.43 with Lanreotite

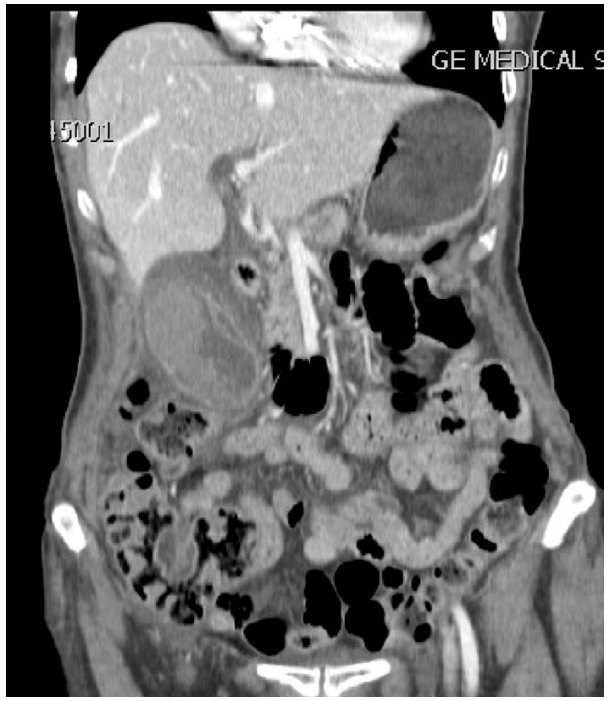


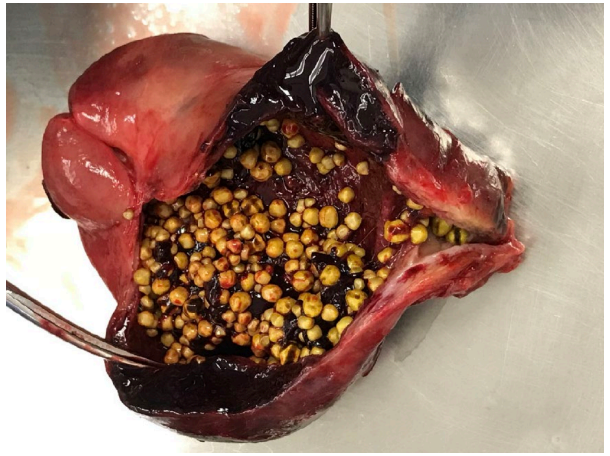
Rinke et al., J Clin Oncol 2009; 27:4656, Rinke et al., Neuroendocrinology, 2017; 104:26, Caplin et al., NEJM 2014; 371:224

Treatment

Why is prophylactic cholecystectomy is recommended ín patients who already receiving, or are due to start long-term treatment with somatostatin analogues?

- Risk of cholelithiasis (10-50%)





7 years octreotide
For metastatic carcinoid

Other side effects of somatostatin treatment?

- Local reactions (pain and erythema) at the injection site
- Abdominal cramps, nausea, flatulence, diarrhoea and steatorrhoea
- Bradycardia

- Lanreotide 120 mg s.c. monthly 2268,- CHF
- Octreotide LAR 30 mg i.m. 1185, - CHF

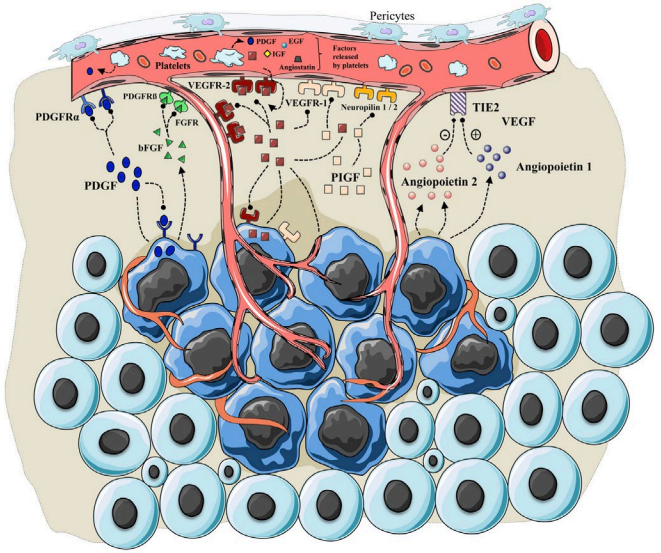
Bergeron Int J Surg Case Rep 2019; 61:107

Molecularly targeted therapies

NETs are highly vascularized, via VEGF, PDGF activity

→ Tyrosine kinase inhibitors block VEGF/ PDGF signaling

→ Everolimus inhibits mTOR and downstream signaling



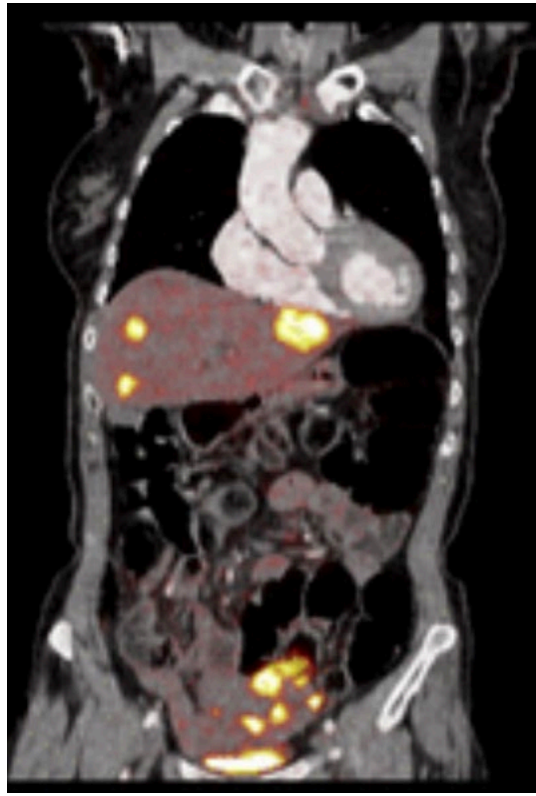
- Everolimus, targeting mTOR
  - RADIANT 2: 429 patients with advanced GI-NET, octreotide +/- 10 mg Everolimus
    → PFS 16 vs. 11 months, significant only after adjustment for confounders
  - RADIANT 4: 302 patients, advanced lung or GINET: everolimjs vs. Placebo
    → HR progression 0.48; disease control 1 year: 81% vs. 64%
    → FDA approved
- Tyrosine kinase inhibitors: sunitinib, sorafenib, pazopanib, lenvatinib, cabozantinib
  - Pazopanib: 171 patients, PFS: 11.6 vs. 8.5 months, HR: 0.53
  - Sunitinib: 171 patients, PFS: 11.4 vs. 5.5 months.
    → FDA approved

Cuny Enocr Rel Cancer 2018; 25:R519, Pozas et al. Int J Mol Sci 2019; 20:4949

Peptide receptor radioligand therapy

Chelator	Octerotide analogon
DOTA	TOC = d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr(OH)
DOTA	TATE = d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr. ← 9x higher affinity to somastotatin receptors

90-Yttrium:	2 mm range
177-Lutetium:	12 mm rante



- ^{17}Lu-DOTATATE in a RCT
  - 230 patients, progressive disease with octreotide 20 or 30 mg
  - Randomized vs. octreotide 60mg
    - Progression free survival at 20 months: 65% vs. 10.8%
    - Median PFS: >30 months vs. 8.4 months
    - Overall survival 14 vs. 26 deaths at 30 months

    → FDA approved
  - Side effects:
    - Myelotoxicity, hematologic malignany 2.6%
    - nephrotoxicity

Strosberg, NEJM 2017; 376:125

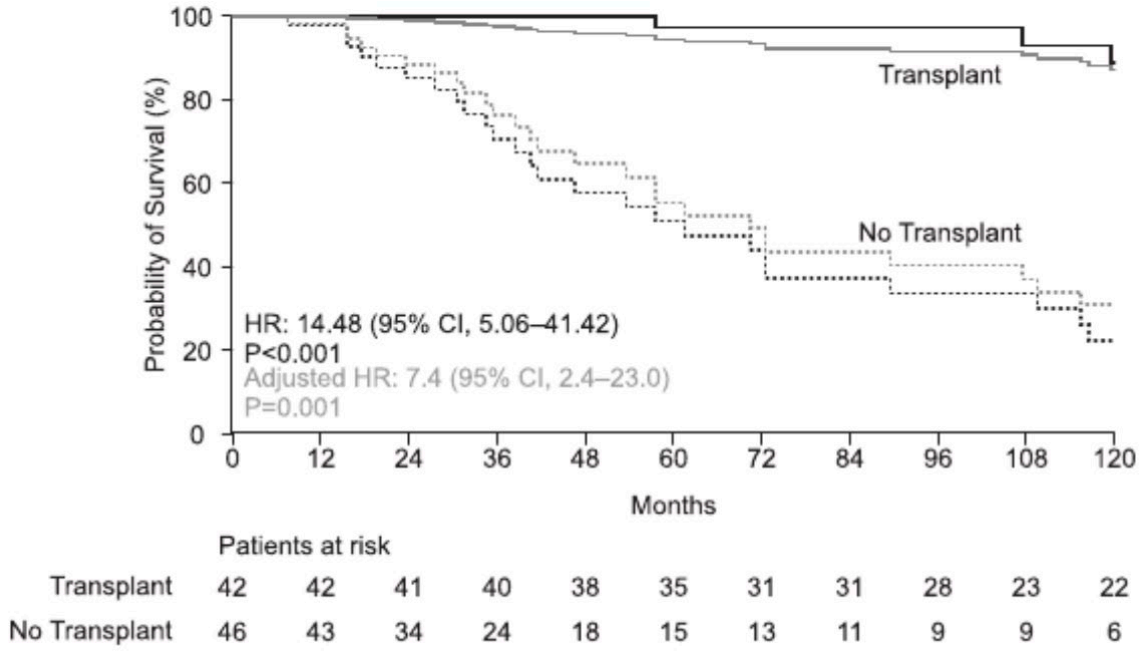
Management of locoregional advanced or distant metastatic disease

Lack of data for sequencing specific therapies → multidisclipinary discussions

- Observation is an option
- PRRT: Peptide receptor radionucleotide therapy
- Liver directed therapies (embolisation), debulking surgery
  - » RETNET ongoing
- Molecularly targeted therapies
- Cytotoxic chemotherapy
  - → no good data, moderate benefits in NETs (streptozotocin)
  - → more useful in G3-NECs
- IFN-α: reserve option
  - → no difference to octreotide in RCT
  - → severe side effects

Is OLT an option?

- Considered investigational of nearly all institutions/guidelines
- “an option with careful patient selection for NET metastatic to the liver”
- UNOS (USA): 150 Tx 1998-2008:
  survival data 1 year: 81%; 3 years: 65%, 5 years: 49%
- Modified Milan criteria «Milan NET» criteria
  - Age < 60 (relative)
  - G1/G2, primary tumor has been removed
  - Metastatic involvement to the liver
  - Hepatic tumor burden not > 50%
  - 6 month no tumor progression with therapy
  - Exclusion: G3 or small-cell carcinoma non-gastrointestinal tumors



Mazzaferro Am J Transplant 2016; 16: 2892