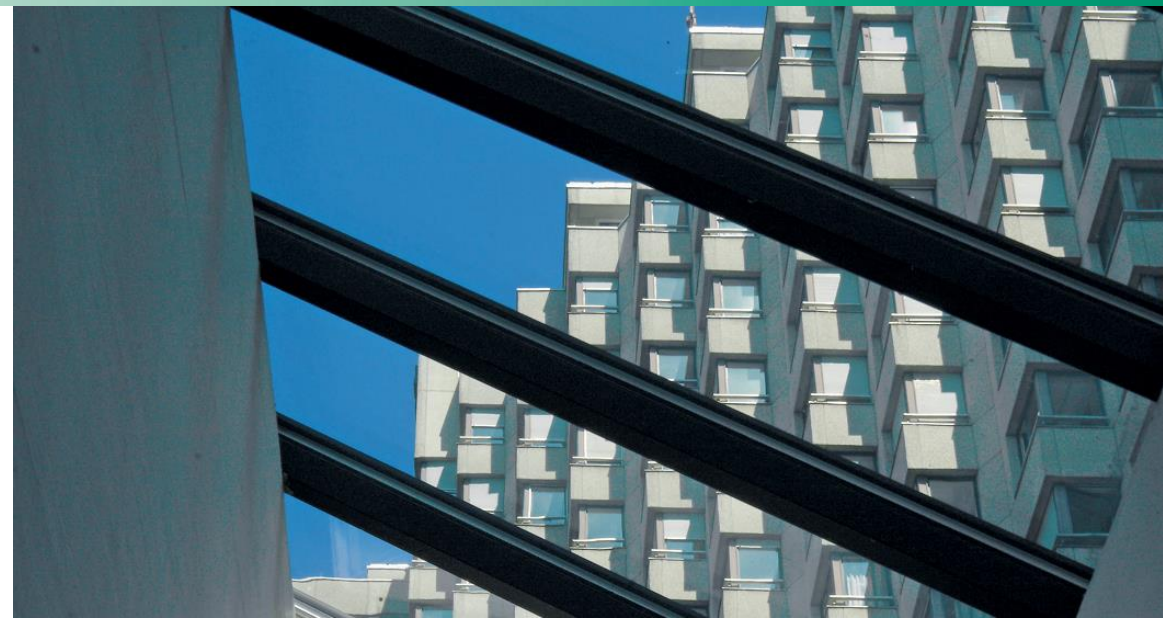
Gastroenteropancreatic neuroendocrine neoplasms

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL



- Epidemiology
- Genetics
- Classification
- Diagnostics
- Treatment

Oberndorfer first described and depicted carcinoid tumors in 1907

Rare, all organs

Similarities with neurons

Ability to produce hormones

Epidemiology

Incidence NETs?

7/100.000

Hallet J, 2015
Dasari A, 2017

→ Rare tumors, 2/3 GI tract

SwissNET 2018

Measurement	2014	2015	2016	2017
Number of patients	835	1050	1245	1428

~180 patients per year

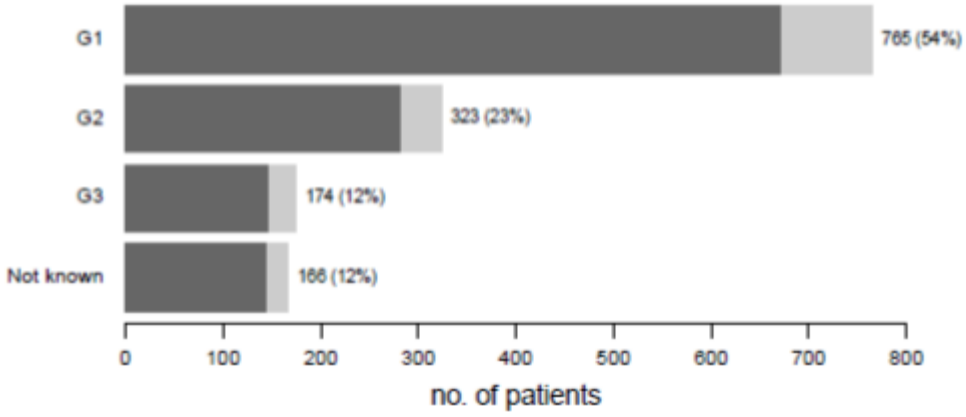
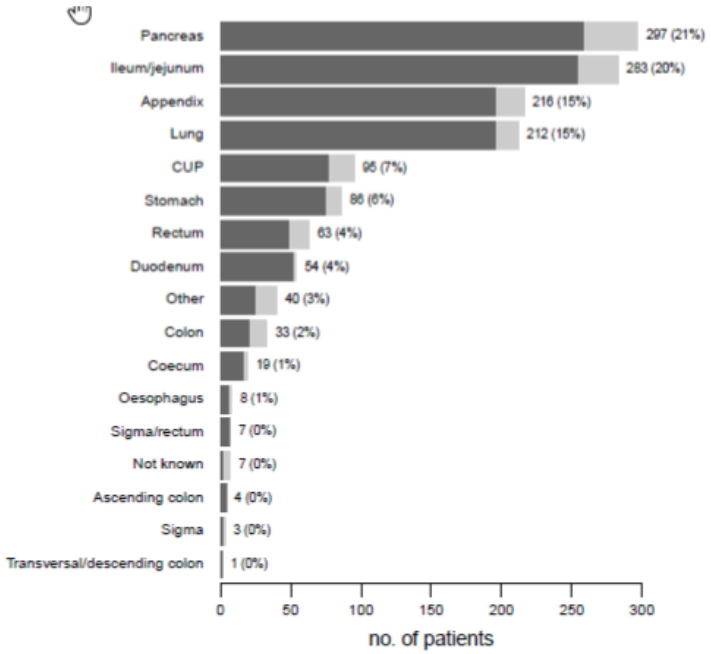
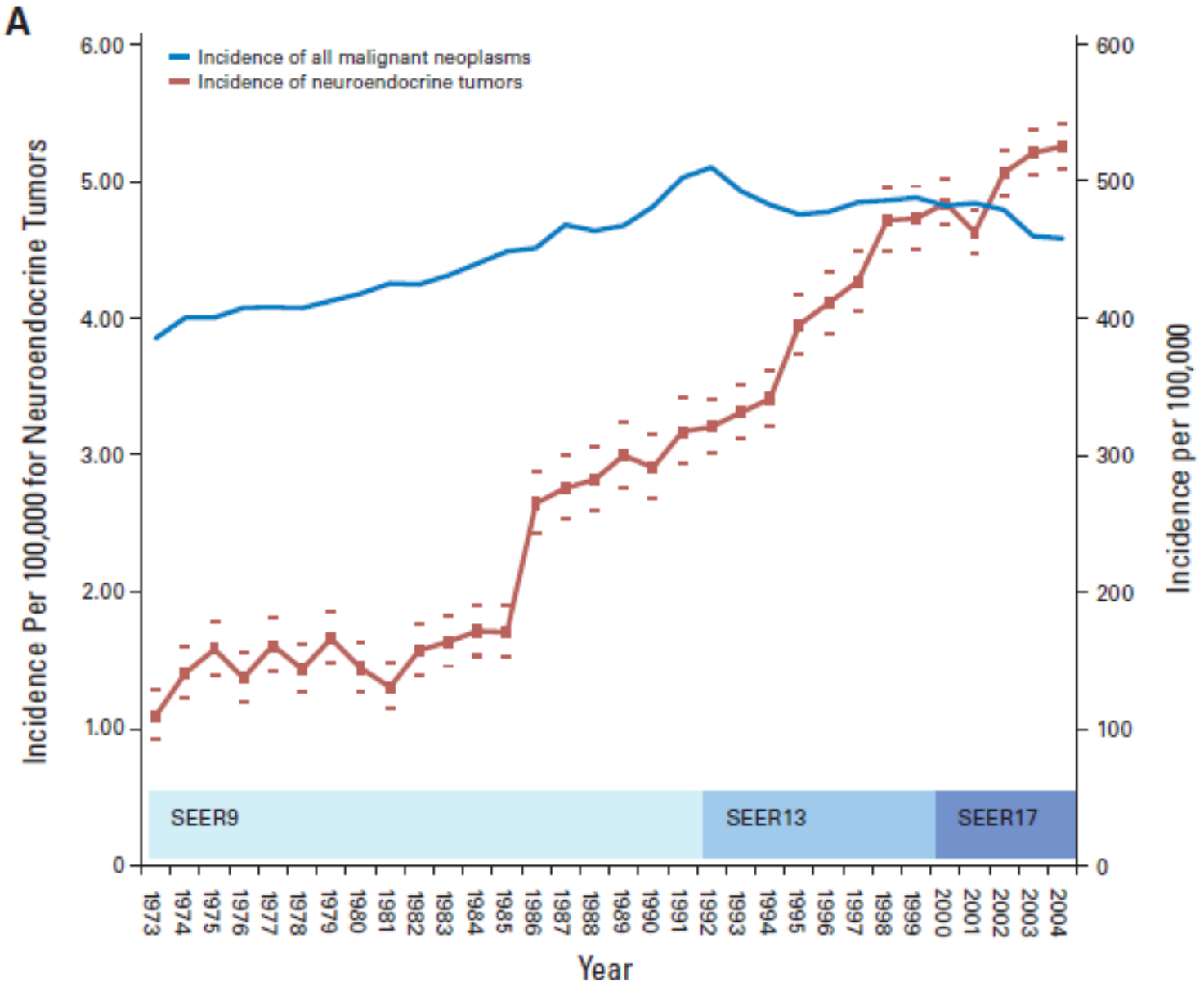


Figure 3: Distribution of primary sites of NET



increase in reported annual age-adjusted incidence from



Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

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 + 2

- Autosomal dominant
- > 2 typical tumours, positive fa ry, relatives with known MEN-mutation

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

MEN 1

- Mutation tumou MEN1 (menin)
- Which tum
  - Parat (98%)
  - Islet cel **pancreas (often multifocal)**
  - Pituitary ad mas and
  - Rarer lung and thymus carcinoids
  - Frequently type 2 gastric carcinoid in case of **gastrinoma (often multifocal)**

MEN 2

- Mutation RET protooncogen
- 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

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

Staging

Staging according to site-specific TNM of ENETs or AJCC TNM 8th edition

- GEP-NENs: Stomac, duodenum, pancreatic, small bowel, colorectal, appenix, unknown origin
- TMN→ Stage: localized (N0), regional (N+) or distant metastases (M+)

    - *Si NET stage I-IV 5-y OS 100%,100%, 91%, 72 %*

      Strossberg 2013
    - *Pan NET stage I-IV 5-y OS 92%, 84%, 81%, 57% (SEER database only 19.5% for IV)*

      Strossberg 2011

Williams 1963

Embryological origin

- **foregut** (bronchi,stomach, pa…eas, gallbladder, duodenum… till ligamentu… treitz)
- **midgut** (jejunum, ileum, …ppendix, right colon) and
- **hindgut** (distal of ri… flecture, left colon, rectum)

WHO 2000: unexact

- Rare tumors but very heterogeneous

Table 3. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Univariate and Multivariate Cox Proportional Hazards Analysis of G1/G2 NETs Diagnosed From 1973 to 2004

Parameter	Median Survival (months)	Univariate		Multivariate		Multivariate *P*
		Hazard Ratio	95% CI	Hazard Ratio	95% CI	
Disease stage						
Localized	223	1*	—	1*	—	< .001
Regional	111	1.89	1.79 to 2.01	1.60	1.50 to 1.71	
Distant	33	4.93	4.68 to 5.21	3.85	3.60 to 4.11	
Primary tumor site						
Jejunum/ileum	88	1*	—	1*	—	< .001
Lung	193	0.53	0.50 to 0.57	1.01	0.93 to 1.08	
Thymus	77	1.12	0.82 to 1.53	1.47	1.06 to 2.03	
Stomach	124	0.83	0.75 to 0.91	1.54	1.38 to 1.73	
Duodenum	99	0.89	0.78 to 0.99	1.42	1.24 to 1.62	
Cecum	83	1.16	1.05 to 1.29	1.06	0.96 to 1.18	
Appendix	NR	0.33	0.29 to 0.37	0.66	0.57 to 0.76	
Colon	121	0.93	0.84 to 1.03	1.54	1.38 to 1.71	
Rectum	240	0.32	0.29 to 0.34	0.74	0.67 to 0.82	
Pancreas	42	1.65	1.53 to 1.78	1.65	1.53 to 1.79	
Liver	23	2.20	1.76 to 2.75	2.92	2.25 to 3.79	
Histology						
Well-differentiated	134	1*	—	1*	—	< .001
Moderately differentiated	64	1.67	1.53 to 1.82	1.26	1.15 to 1.40	
Mixed	135	1.02	0.92 to 1.14	1.65	1.45 to 1.88	
Sex						
Female	145	1*	—	1*	—	< .001
Male	114	1.21	1.16 to 1.26	1.20	1.14 to 1.25	
Race						
White	126	1*	—	1*	—	< .001
AI/AN	NR	0.56	0.36 to 0.87	0.79	0.50 to 1.26	
Asian/P Islander	204	0.65	0.58 to 0.72	0.94 (0.83 to 1.07)		
African American	117	1.04	0.98 to 1.10	1.28	1.19 to 1.37	
Age, years						
≤ 30	NR	1*	—	1*	—	< .001
31-60	247	3.31	2.74 to 4.00	3.03	2.41 to 3.81	
≥ 61	71	10.08	8.36 to 12.15	9.23	7.34 to 11.61	
Year of diagnosis						
1973-1987	95	1*	—	1*	—	< .001
1988-2004	138	0.75	0.72 to 0.79	0.73	0.69 to 0.77	

WHO classification 2010

Differenzierung	Grading	Mitotic rate: HPF	Ki-67 Index %
Well-differentiated NET	G1		< 3
Well-differentiated NET	G2		3-20
Poorly-differentiated = small or large cell type)			> 20
MANEC			

5-year survival rates for grades 1, 2 and 3 tumours are 96%, 73% and 28%

G1/G2 largest part of NENs

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**	**Ki-67 Index %**
Well-differentiated NET	**G1**	< 2	< 3
Well-differentiated NET	**G2**	2-20	3-20
Well-differentiated **Pan-NET** …probably also true for the other gastroenteric NETs	**G3**	> 20	> 20
Poorly-differentiated **NEC** (small or large cell type)	**G3**	> 20	> 20
MiNEN Mixed neuroendocrine-nonneuroendocrine tumors			

Rindi et al

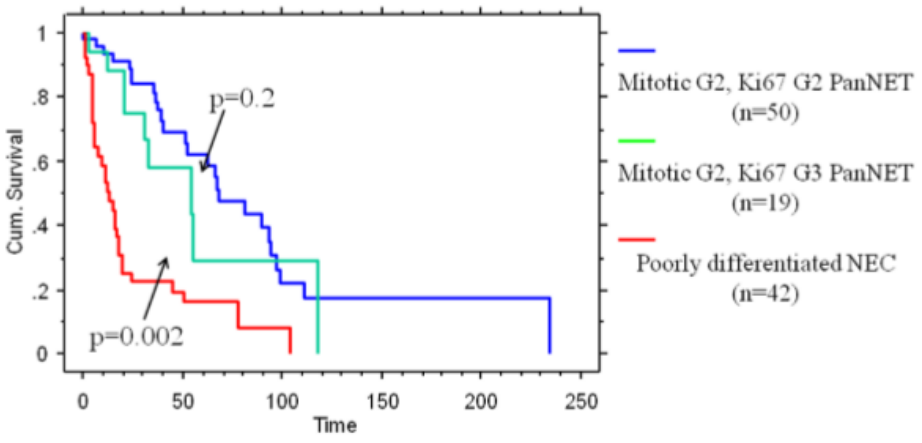
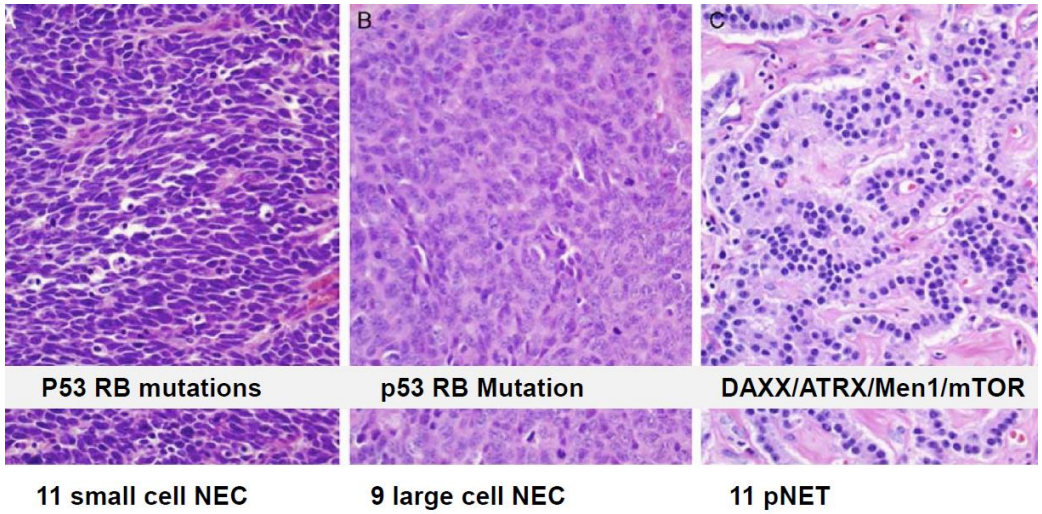


Figure 4.
The Kaplan-Meier analysis comparing the overall disease-specific survivals of all grade-concordant pancreatic neuroendocrine tumors, grade-discordant pancreatic neuroendocrine tumors, and poorly differentiated neuroendocrine carcinomas (All cases)

Some PanNETs show discordance between the mitotic rate and Ki67 index.

Overall, patients with grade-discordant PanNETs had significantly longer survival time compared to patients with poorly differentiated NEC (median survival of 54.1 months vs 11 months and 5-year survival of 29.1% vs 16.1%; *p=0.002*).

Basturk 2015



Neuroendocrine Carcinomas of the Pancreas Are Genetically Similar and Distinct from Welldifferentiated Pancreatic Neuroendocrine Tumor

Yachida 2012

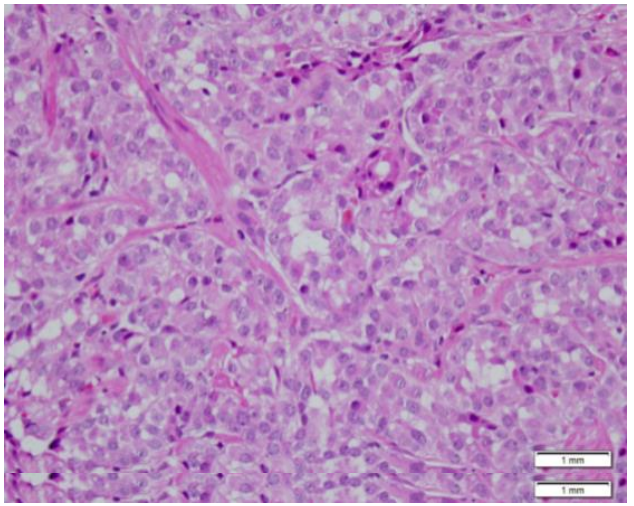
From carcinoid to neuroendocrine neoplasms

1907 Obernorder „carcinoid“
→ WHO 1980 carcinoids all
→ WHO 2000 → GEP-NET, carcinoids well-differentiated GI/lung
→ WHO 2010 → NEN = NET (G1/G2), NEC (G3/small cell and large cell type) and mixed (MANEC)

→ **WHO 2017**
→ NEW: **poorly differentiated NECs (small, large cell) G3 vs well-differentiated G3 NETs (well-differentiated but high proliferation index)**
→ NET G1/G2, **NET G3**, NEC G3, mixed (MANEC → mixed neuroendocrine-nonneuroendocrine tumors MiNEN)

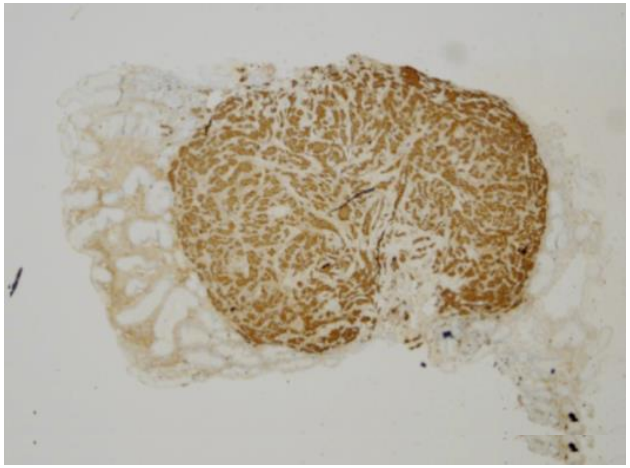
Immunhistochemistry

•Specific markers as Chromogranin A und Synaptophysin can help to establish the neuroendocrine differentiation



• In case of unkown origin:

CDX2	→ midgut
TTF1	→ lung
Isl-1/PAX8	→ pancreas



Clinical features

- Functioning vs. non-functioning

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
- GI-bleeding
- Obstruction

Functioning GI neuroendocrine tumors

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

Functioning NETs	**Clinical features**
Insulinoma	Whipple Trias (hypoglycamic symptoms: confusion, sweating, dizziness, relief with eating, Hypoglycaemia)
Gastrinoma	Zollinger-Ellison-Syn[illegible] [illegible]otic Ulceration)
VIPoma	Verner-Morrison Syn[illegible] [illegible]oea, hypokaliaemia, Acho[illegible]
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, thrombosis, depression, diarrhoea
Somatostatinoma	Cholelithiasis, Steatorrhoe

Delay of diagnosis after symptom onset 7 years

Carcinoid syndrome

Typical symptoms?

- Dry flushing +/- palpitations 80 %
- 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

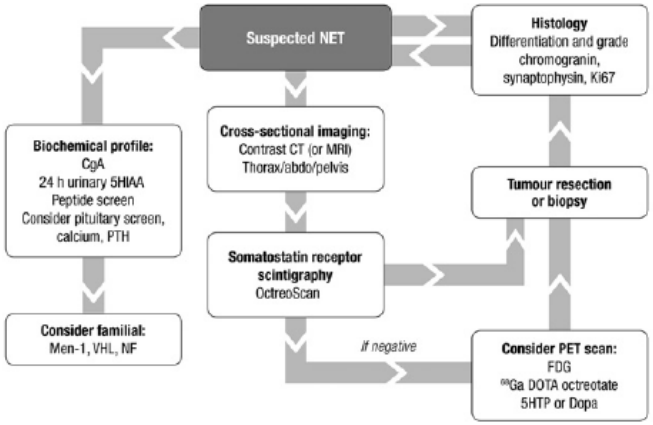
Diagnosis

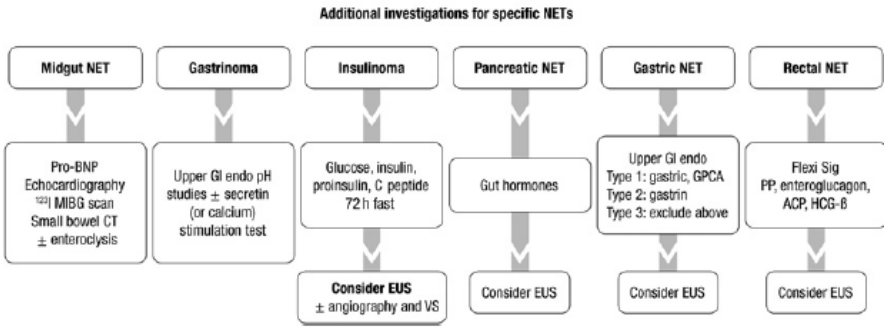
Diagnosis of NETs is based on the followings:

- Pathology gold standard
- Clinical manifestations
- Peptide and amine sectretion (biochemical)
- Radiological and nuclear imaging

(Primary tumour, extension)

- Endoscopy, EUS, +/- Enteroklyses, capsule endoscopy





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 tumormarker is recommended**

Biochemistry

Which marker can be used in non-functioning NETs?

- Chromogranin A (nonspecific general marker)

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

but

Sensitivity 73 % specifity 95 % non-functioning and functioning, esp well differentiated NETs

Yang PLoSone 2015

What are confounding conditions for the detection of chromogranin A?

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

Biochemistry

Peptide markers specific to the tumour site

Table 5 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

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%)

Diagnosis

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
- Avoid coffee, nicotine and alcohol
- False high values with Paracetamol, Cumarine, Phenobarbital, diazepam; false low values with Aspirin, Chlorpromazin, Isoniazid, Levodopa, Streptozotocin

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)

Diagnosis Gastrinoma (Zollinger-Ellison Syndrom)

What are confounding conditions for the detection of Gastrin/ differentialdiagnosis 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

In case of high suspescion of gastrinoma you should not stopp PPI…what do you do?

- Stopp PPI, H2 antagonists are possible/recommended
- Servere cases/highly suspicious EUS/Endoscopy first since they are located in pancreas or duodenum

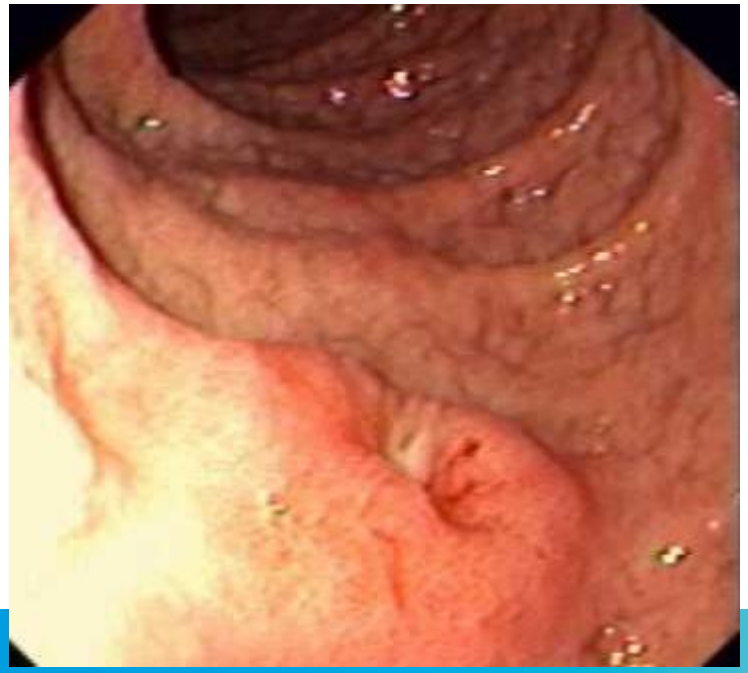
Diagnosis Gastrinoma (Zollinger-Ellison Syndrom)

In reality most cases remain unclear (… PPI, liver or kidney failure…) what do you do during endoscopy as additional test if gastrinoma is suspected? which findings make the diagnosis of a gastrinoma likely?

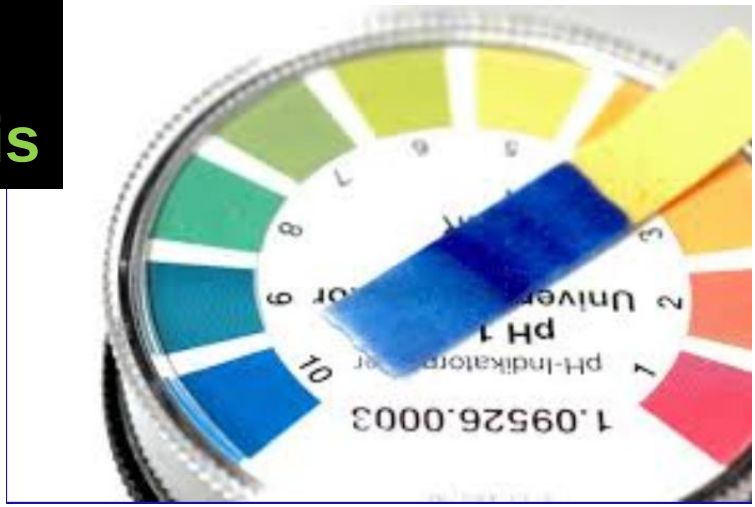
Gastrin > 1.000 pg/ml + gastric pH > 2 exclusion gastrinoma

Gastrin > 1.000 pg/ml + gastric pH < 2 gastrinoma → tumourlocalisation

Gastrin 110 – 1.000 pg/ml (if gastric pH < 2) secretin test

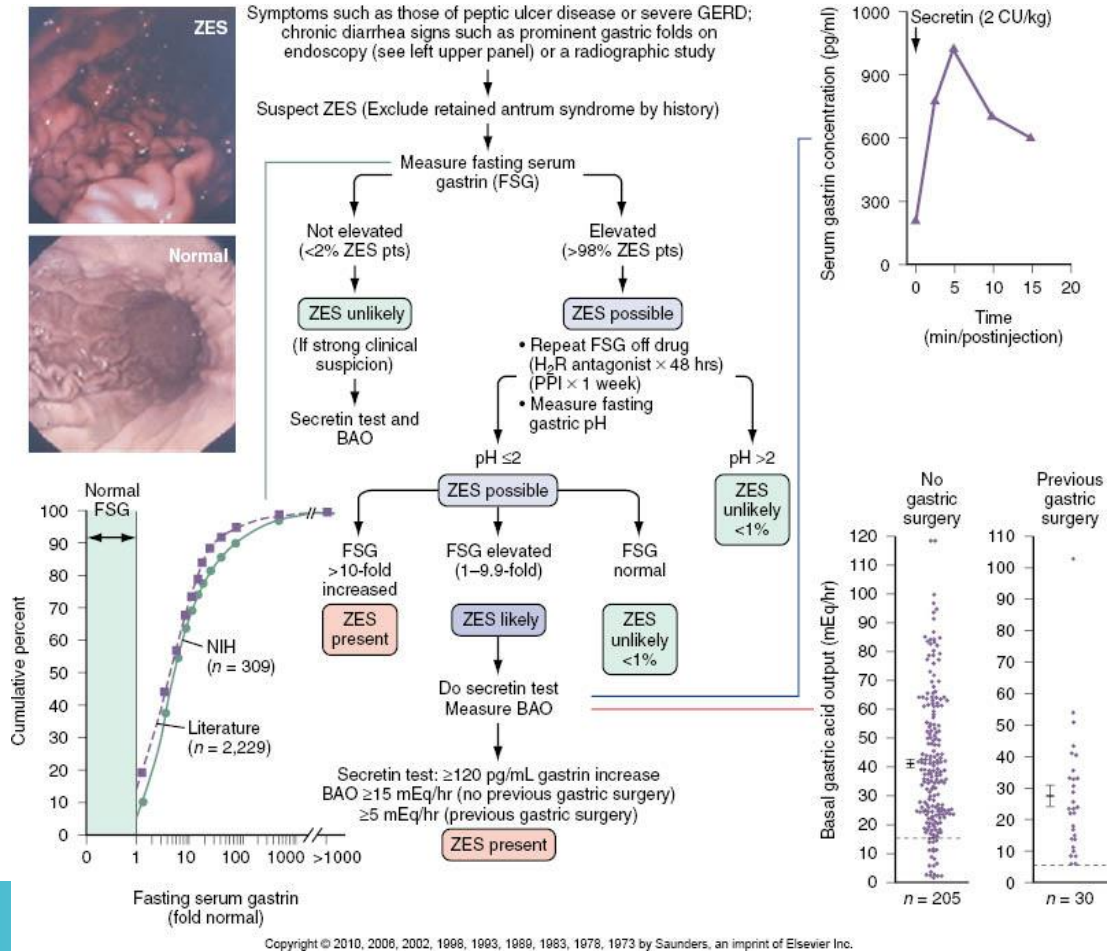


+
Bx →
HP
A-gastritis



Secretin test:

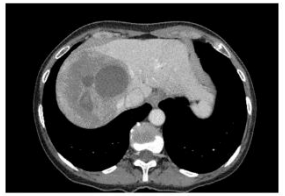
- Paradox gastin increase of 120pg/ml after i.v. secretin (2IE/kg) after 30 minutes.
- Sensitivitity/specificity > 90 %



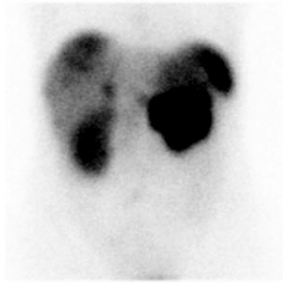
Imaging studies

Which imaging studies would you use for the primary tumour detection/ assessing extend of disease for gastroentero-pancreatic NET?

- Multiphase CT/MRI +/- Chest



- SSRS (somatostatin receptor) imaging: SSRS scintigraphy or PET/CT



- Additional: site-specific
  - EUS (+/- KM), endoscopy, enteroclysis, capsule endoscopy

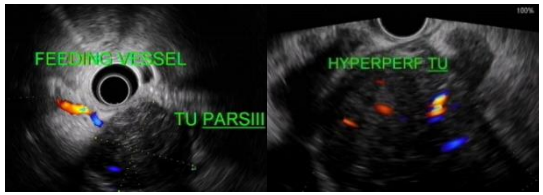


Table 6 Sensitivities of the various imaging modalities for locating specific NETs[80 84–92]

Pancreatic NETs	Tumour and Frequency
Dual-phase multi-detector CT	57–94%
MRI	74–94%
EUS	82–93%
SSRS insulinomas	50–60%
SSRS gastrin/VIP/somatostatin	75%
^{68}Ga DOTATOC PET	87–96%
Primary gastrointestinal NETs	
CT enteroclysis	85%
MR enteroclysis	86%
SSRS for detection of lesions in non-pancreatic GI NETs	86–95%
Neuroendocrine liver metastases	
CT	44–82%
MRI	82–95%

CT for detection primary of tumor of unknown primary: 22-45 %

For liver-metastases 79 % MR 95%

Dromain 2005

EUS gastrinoma duodenal 45-60 %,
EUS pan NEN 90-100 %

Anderson 2000

Appropriate Use criteria for Somatostatin Receptor PET Imaging in NET *Hope et al*

SSTR-PET should replace Somatostatinreceptor scintigraphy

- Gallium-68-dotatate PET/CT sensitivity >>> somatostatin receptor scintigraphy Indium-111-DPTA (Octreoscan)
  - Localisation of unknown primaries/at initial diagnosis
  - Determining receptor status
  - Selecting patients for PRRT
  - Improved patient convenience: shorter study

  Time + decreased radiation exposure

  - Gallium-68 – DOTATATE (FDA 2016) +- DOTATOC

- Best studied in G1/G2
- Unclear sensitivity in NEC - poorly differentiated NECs often low SSTR expression → may be better imaged on fluorodeoxyglucose (18F-FDG) PET/CT

Appropriate Use criteria for Somatostatin Receptor PET Imaging in NET *Hope et al*

- AUC:
  - Initial staging after the histologic diagnosis of NET,
  - Evaluation of an unknown primary
  - Evaluation of a mass suggestive of NET and not amenable to endoscopic or percutaneous biopsy
  - Staging of NET prior to planned surgery
  - Monitoring of NET seen predominantly on SSTR-PET
  - Selection of patients for PRRT
  - Evaluation of patients with biochemical evidence of a NET without evidence on CI or a prior histologic diagnosis
  - Restaging at time of clinical or laboratory progression without progression on CI
  - New indeterminate lesion on CI with unclear progression

Treatment

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

- Resection

Which NETs can be treated endoscopically?

Table 5 Therapy of gastric NENs

	No risk factors (for metastatic disease)	ri
Size	⩽ 1 cm	1-2 cm
Type 1	Surveillance[b] optionally EMR	EMR follo
Type 2	Surveillance[b]	E
Type 3	EMR	Sur
Type 4	-	-

Table 7 Therapy of rectal NE

Grade/Size	No risk factors (for n ⩽ 1.0 cm		
G1	EMR or polypectomy or ESD	Surge in case or for olds of 11-14 mm in diameter)	
G2	EMR, ESD, surgery[b]	Surgery[b]	Surgery[b]
G3	-	-	Surgery[b]

Table duodenal NENs

	cm[a]	1-2 cm[a]	Any size but risk factors[b]
		Surgery (in case of surgical risk: EMR followed by surveillance)	Surgery
		Surgery[c]	Surgery[c]
		Surgery (particularly if the gastrinoma s growing) or PPI erapy combined h surveillance	Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk)
(G3)	-	-	Surgery or cytoreductive chemotherapy

Gastric, duodenal, rectal

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

EMR, ESD, FTRD

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	Surgery[c]
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 (no gastrin…	EMR	Surgery (in case of surgical risk: EMR followed by surveillance)	Surgery
		Surgery[c]	Surgery[c]
	…rapy and surveillance (or surgery)	Surgery (particularly if the gastrinoma is growing) or PPI therapy combined with surveillance	Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk)
NEC (G3)	-	-	Surgery or cytoreductive chemotherapy

Table 7 Therapy of rectal NE…

	No risk factors (for n… …ease)		Risk factors[a]
Grade/Size	⩽ 1.0 cm	1.1 - 2 cm	Any size
G1	EMR or polypectomy or ESD	Surgery[b] (EMR or ESD in case of surgical risk or for carcinoids of 11-14 mm in diameter)	Surgery[b]
G2	EMR, ESD, surgery[b]	Surgery[b]	Surgery[b]
G3	-	-	Surgery[b]

G2?
1-2 cm?
EUS

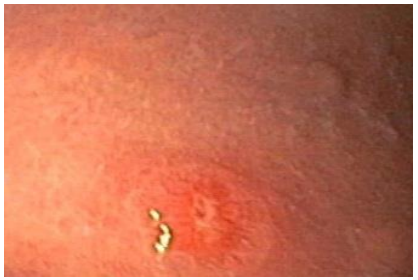
Early rectal NETs

- Rectum < 1 cm no follow-up
- Rectum intermediate margin → endoscopy after 6-12 months→ if recurrent MR/EUS → ESD vs surgery
- Rectum 11-19 mm: 66-87 % G1/2 N+

Gleeson 2014

Diagnosis gastric neuroendocrine tumors

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



Typ IV gastric NEC: treated according to castric carcinoma guidelines

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**	no
Association	**autoimmune atrophic gastritis**	MEN I, **Zollinger-Ellison-Syndrom**	Sporadic tumours
Metastasis	rare		often
Therapy	< 1cm **endoscopic** removal, > 2 cm operative removal	< 1cm **endoscopic** removal, > 2 cm operative removal	Surgical removal with lymphnodes
Prognosis	Very well	Very well	**Variabel**

- All the other intestinal localized NENs optimal treatment generally needs **surgery** and/or medical therapy depending on type, biology and stage of the tumor, as well as the individual situation of the patient (curative, also resectable liver metastasis or palliation with debulking)

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, esp carcinoid syndrome
  - » Octreotide?

PROMID

- Antiproliferative → Indication progressive disease
  - » Lanreotide?

CLARINET

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%)

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 1302,- CHF
- Octreotide LAR 30 mg i.m. 1200, - CHF

Management of locoregional advanced or distant metastatic disease

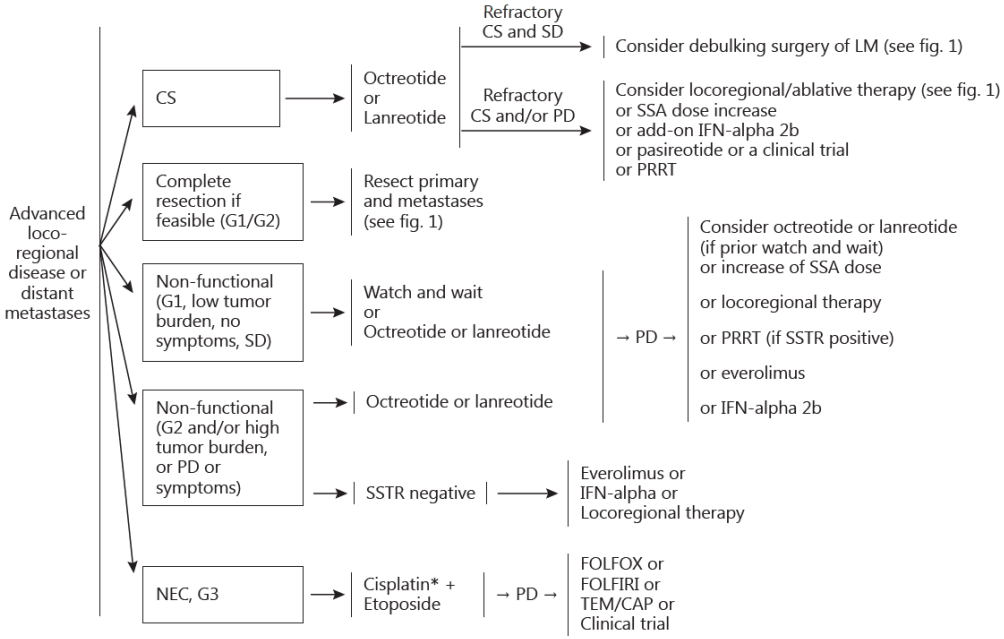
Other therapeutic modalities in GI NETs/second/third line treatment?

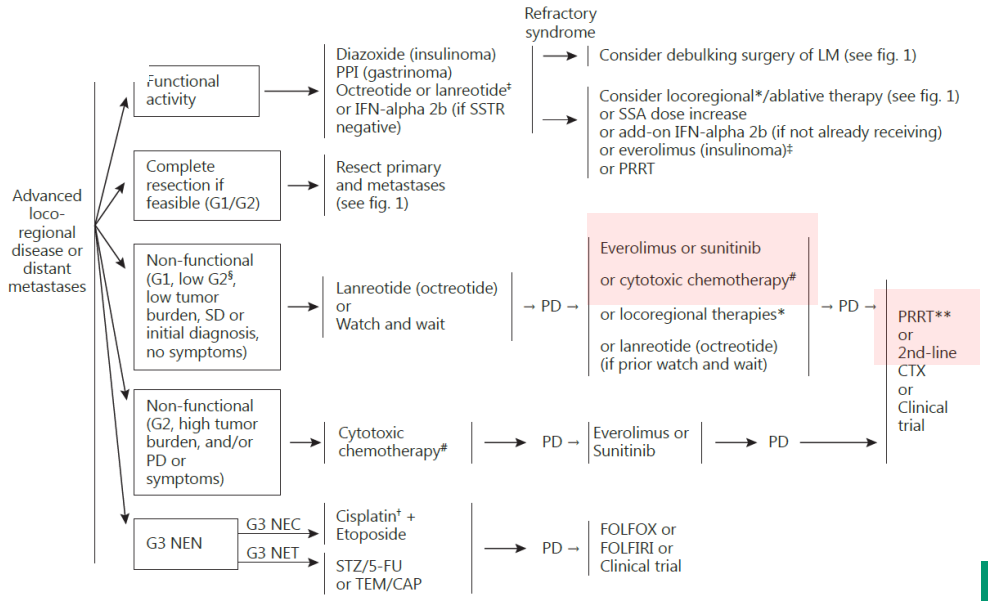
- Lack of data for sequencing specific therapies → multidisclipinary discussions
- Observation as option
- PRRT Peptide receptor radionulcide therapy
- Hepatic directed therapies (embolisation), debulking surgery in case of clinically significant tumor burden or progressive disease
  - » RETNET ongoing
- Molecularly targeted therapies: Everolimus → esp PanNET, nonmidgut NETs, Sunitinib – PanNET

RADIANT -4/-2

- Cytotoxic chemotherapy: moderate benefits in intestinal NETs, PanNET or G3-NECs option → side-specific
- IF-a option, no data, adverse events, one randomized trial without PFS

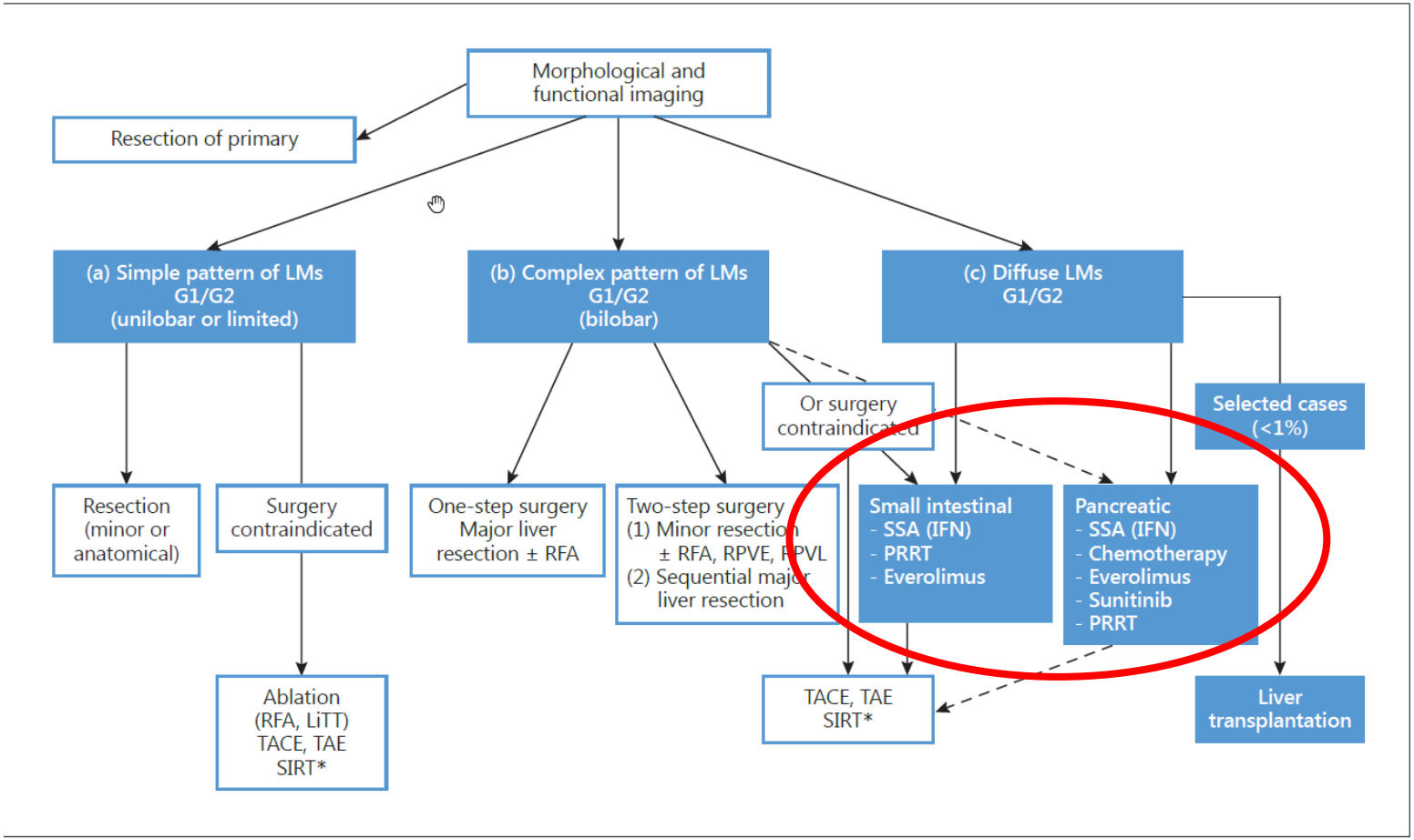
ENETS 2016 therapeutic algorithm midgut vs pancreatic NEN advanced/distant metastases





Pavel et al

ENETS 2016 Management liver metastases G1/G2 NEN

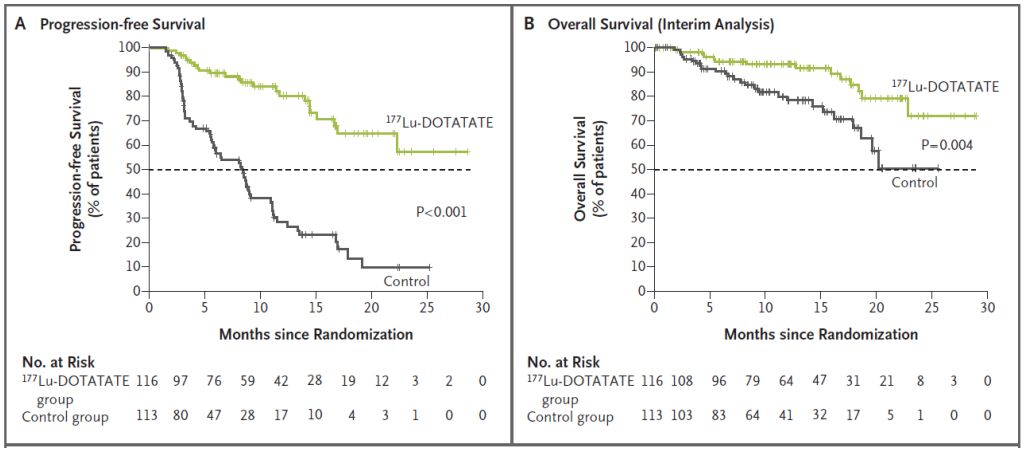


Pavel et al

Radiolabeled Somatostatin Analogs PRRT; 177Lu-Dotatate

- NETTER-1 2017
- Brabander 2017

→



- FDA approved 2018 for somatostatin receptor-positive GEP-NETs
  - SSTR pos in SSTR PET/CT
  - G1/G2, esp. midgut
  - Adequate bone marrow, renal and hepatic function
  - Risk sequence therapy PRRT and local liver directed therapies

  - Long-acting SSAs 4-6 weeks, short-acting 24 h before (no data actually showing interactions

Ayati 2018

Is OLT an option?

- Considered investigational of nearly all institutions/guidelines
- Some surgical papers instead report that it is an option with careful patient selection for NET metastatic to the liver
- Eg modified Milan criteria «Milan NET» criteria
  - Age < 55, G1/G2, primary tumor drained by portal venous system (pan, midgut, Stomach-colon) has been removed, metastatic involvement to the liver, hepatic tumor burden not > 50 %, 6 month of no tumorprogression
  - Exclusion: G3 or small-cell carcinoma, nongastrointestinal tumors

Mazzaferro 2016

Clift EJG 2018

- 5y- OS 63%
- systematic review of Mostly retrospective case series, 64 studies

Moris 2017

Follow-up

Which imaging method and how often would you use for follow-up?

- First year 3 – 6 month intervals, increased to every 12 months up to 10 years
- Multiphasic CT/MRI
- Biochemical markers as indicated (Chromogranin A as tumormarker/ as clinically indicated)

PHASE III trials

Established SSAs as antiproliferative agents, not only for symptom control:

- PROMID – metastatic midgut octreotide LAR siNETs
- CLARINET – lanreotide in nonfunctioning gastroenteropancreatic (esp. Pancreatic) NETs

Everolimus in functioning and nonfunctioning GEP NETs and lung

- RADIANT-4 - nonmidgut NETs, better PFS than 2..
- RADIANT-2 - midgut NETs
- NETTER-1 – LuDOTATATE midgut

Serotonin synthesis inhibitor - Symptom control diarrhoea in carcinoidsyndrom

- Telestar – telotristate - CH Xermelo® 2018

Ongoing: RETNET (embolisation)

No trials comparing PRRT to systemic therapies