Gastro-Entero-Pancreatic Neuroendocrine neoplasms

Ulrich Knigge

Neuroendocrine Tumor Centre of Excellence
Rigshospitalet
University of Copenhagen
Denmark

Diffuse Neuroendocrine Cell System

Central group

- Hypothalamus
- Pituitary gland
- Pineal gland

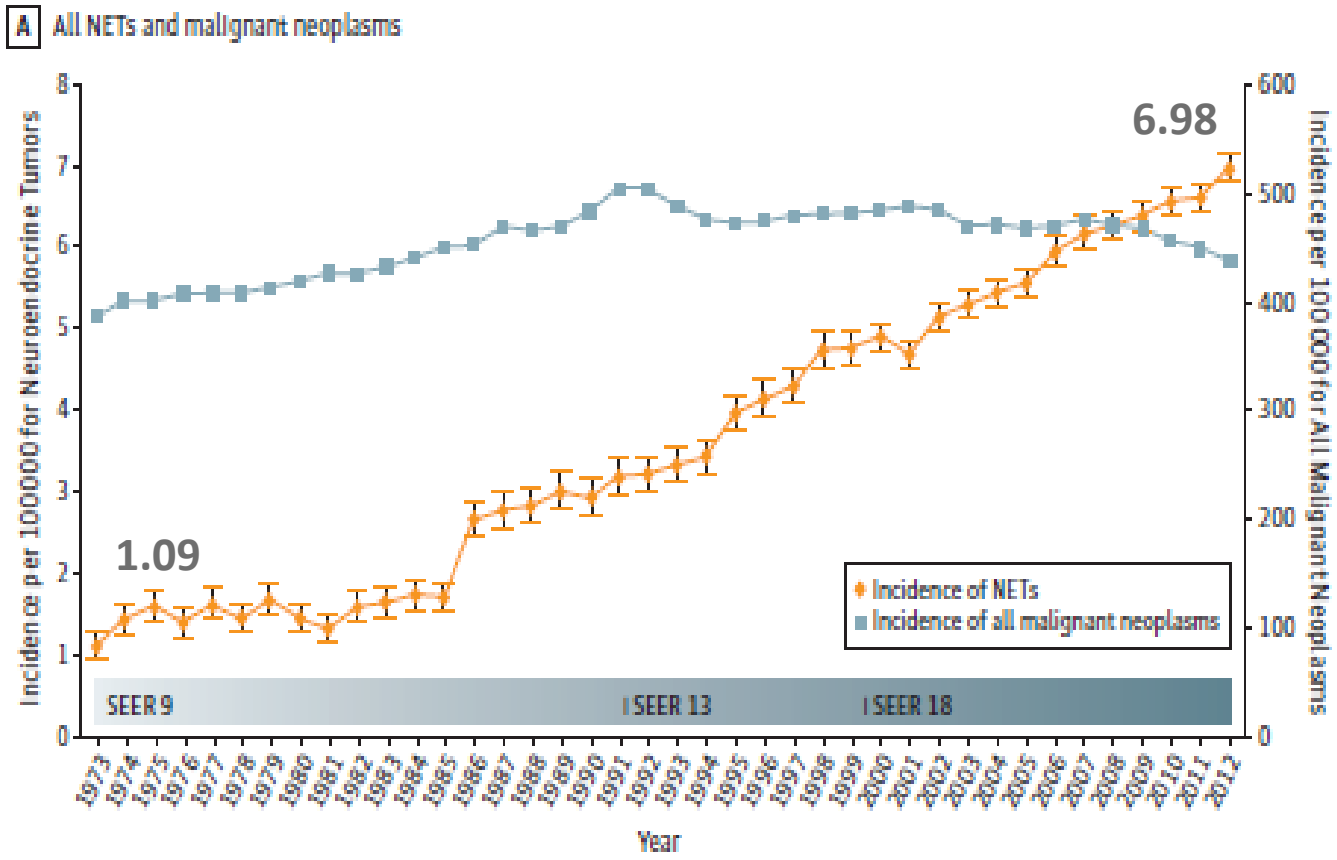
Peripheral group

- Parathyroid gland
- C-cells of the thyroid gland
- Sympathetic nervous system
- Adrenal medulla
- Islet cells of the Pancreas
- NE cells of the
  - Gastrointestinal tract
  - Broncho-pulmonary system
  - Urogenital tract
  - Thymus
- Merckel cells of the skin

Epidemiology: Incidence

SEER data-base – app. 65.000 NEN patients

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012

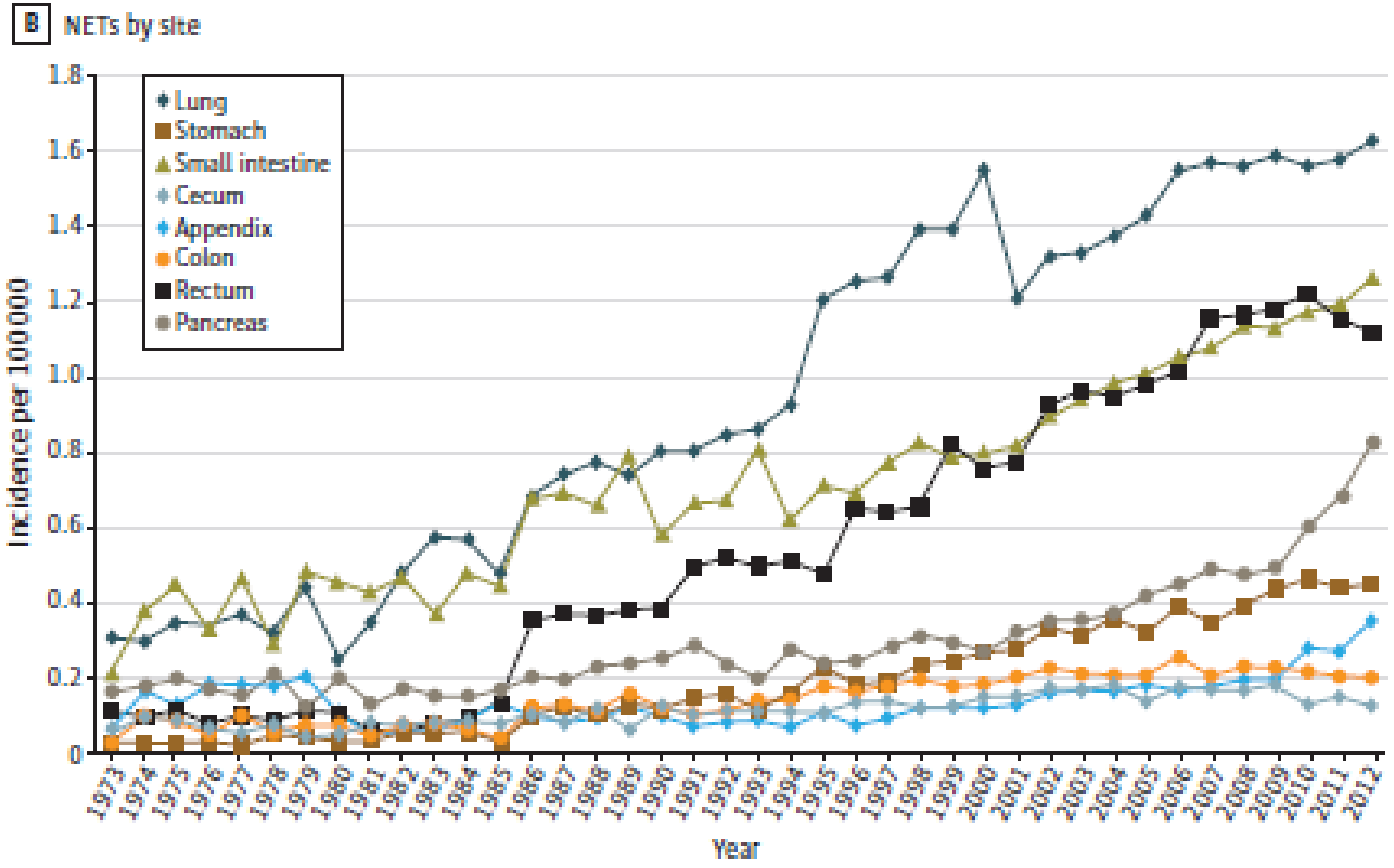


Dasari, JAMA Oncology 2017

Epidemiology: Incidence

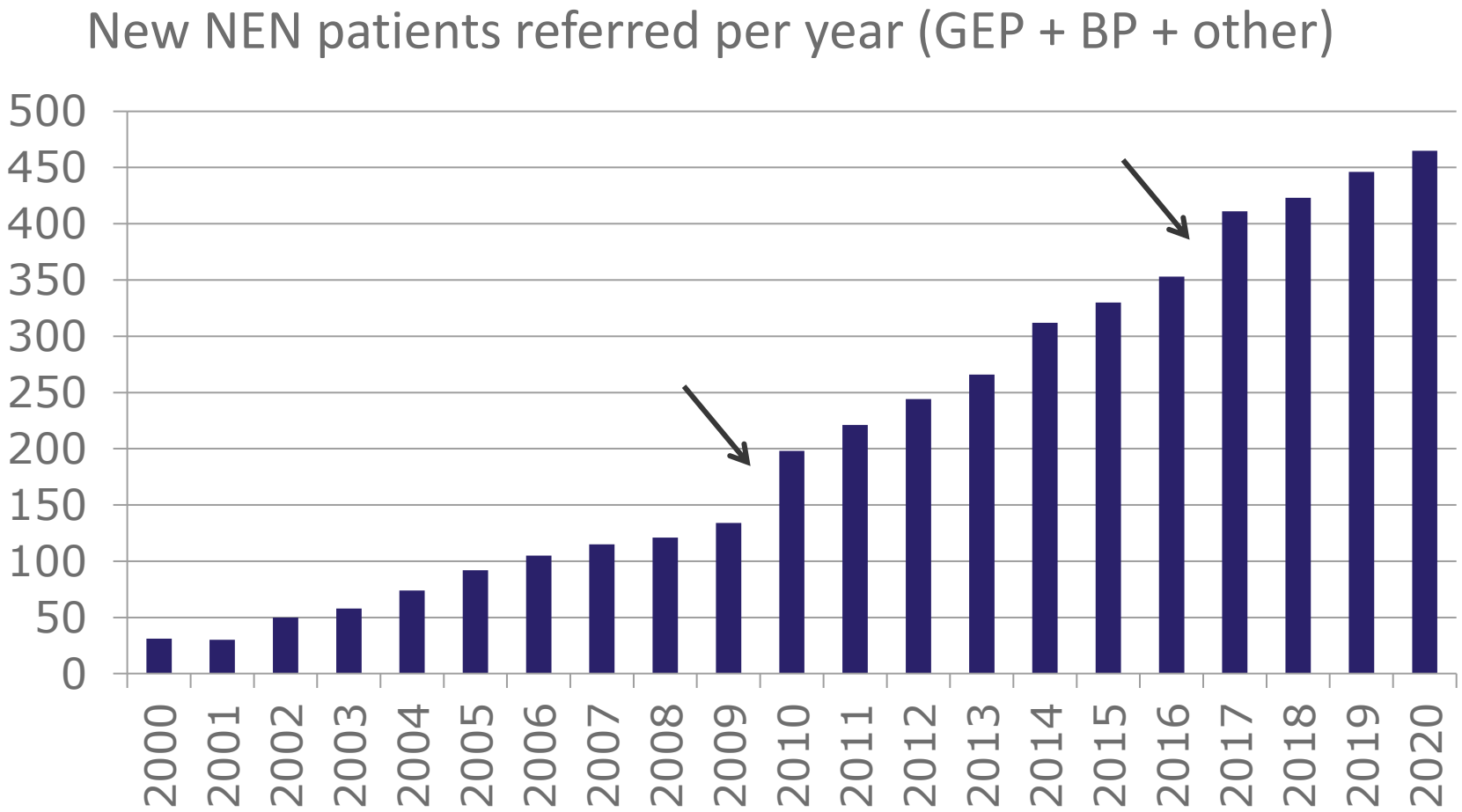
SEER data-base – app. 65.000 NEN patients

Incidence related to GEP and BP NEN



Dasari, JAMA Oncology 2017

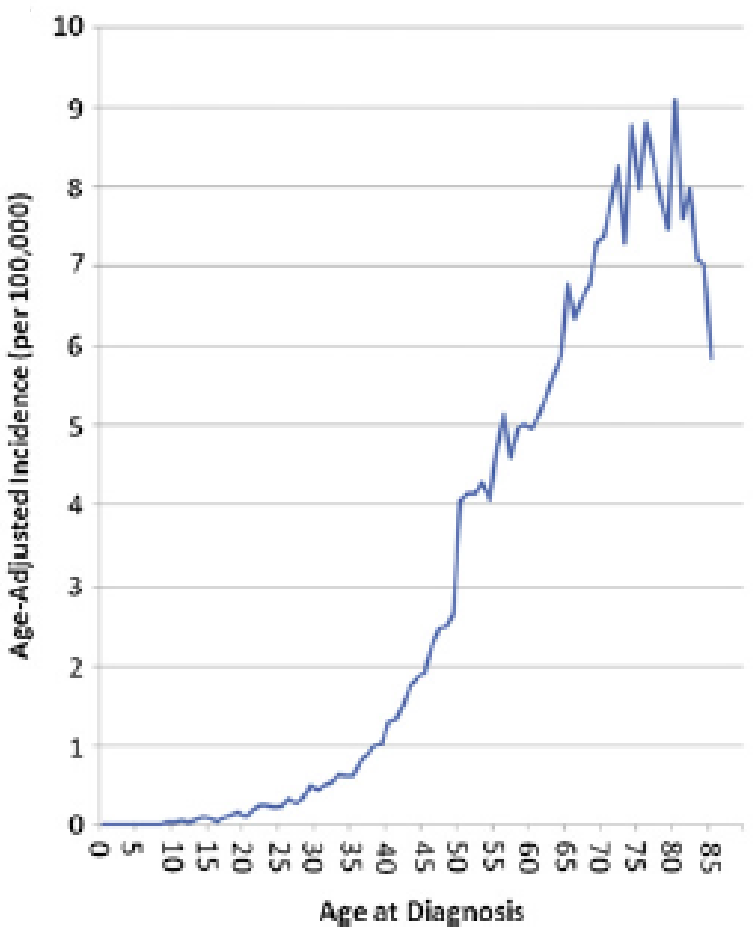
RH NET Centre



Incidence and prevalence of Neuroendocrine neoplasms

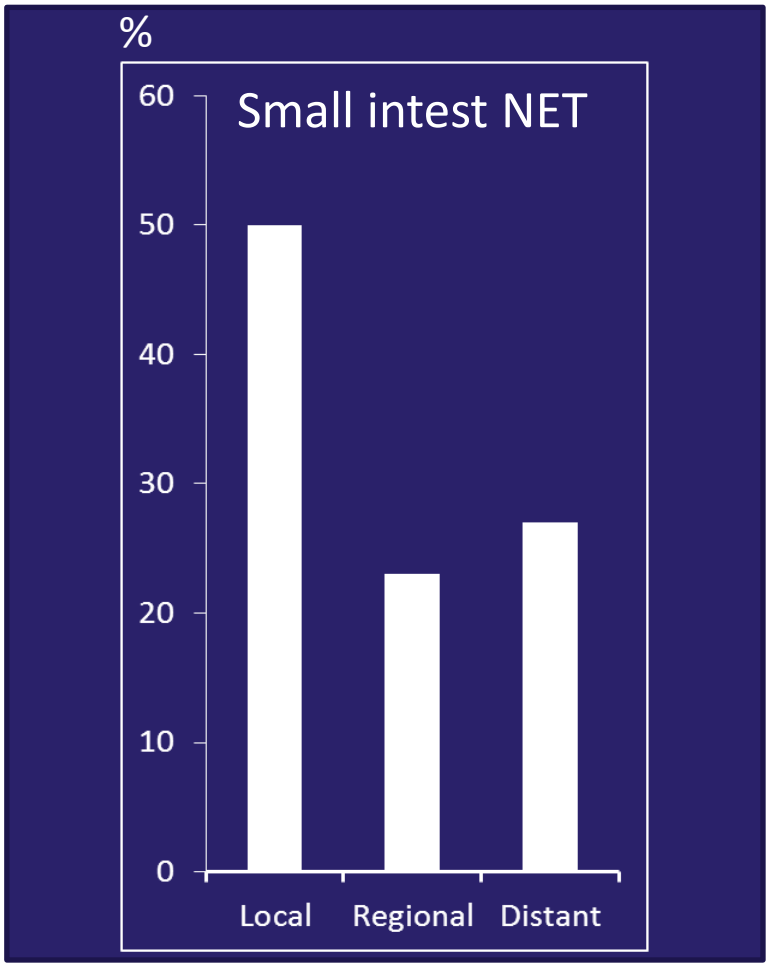
- Incidence: increasing
  - Increased awareness of physicians, surgeons and pathologists
  - Improved registration (by referral to specialized NET Centers)
  - New and improved diagnostic tools
    - p Chromogranin A (CgA)
    - Immunohistochemistry (CgA, synaptophysin and tumor specific hormones)
    - Somatostatin receptor imaging (^{64}Cu- or ^{68}Ga-DOTATATE-PET/CT)
  - A true increase in incidence
  - Incidence: app. 14/100.000 / year (RH 2018)
  - Prevalence: app. 70/100.000 /year (RH 2018)

Age at diagnosis – GEP NENS



Lawrence, Endocrinol Metab Clin N Am 2011

Distribution of localized, regional and distant NEN – SEER data-base



Dependent on tumor type

Yao, J Clin Oncol 2008
(SEER database)

Staging of GEP NEN

ENETS and UICC: Tumor (T); Nodes (N); Metastases (M) – (resected specimens)

WHO 2019 Classification

Neuroendocrine Neoplasms (NEN)

Terminology	Differentiation	Grade	Mitotic rate	Ki-67 index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2	Well differentiated	Intermediate	2-20	3-20%
NET, G3	Well differentiated	High	>20	>20%
NEC, small cell	Poorly differentiated	High	>20	>20%
NEC, large cell	Poorly differentiated	High	>20	>20%
MiNEN	Well or Poorly diff. (mostly poor)	Variable (mostly high)	Variable (mostly >20)	Variable (mostly >20%)

Pathology

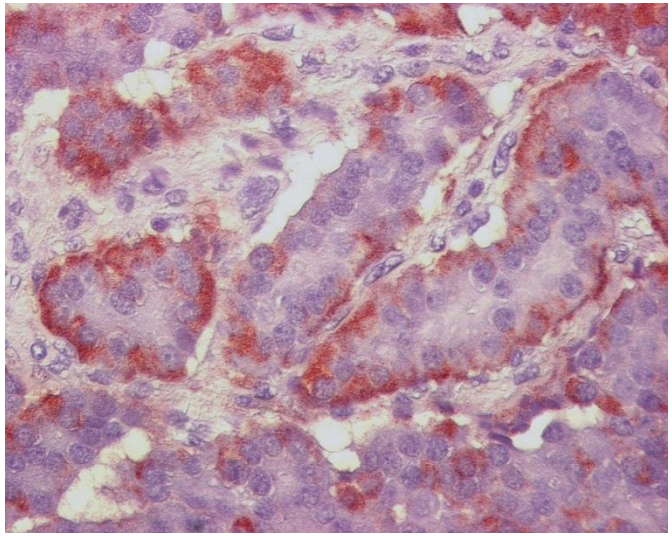
Immunohistochemistry

- general tumor cell markers
  - synaptophysin
  - chromogranin-A
- tumor cell specific hormones, e.g.
  - gastrin
  - serotonin
- Ki-67 proliferation index (or mitotic count)
  - ”hot spot areas” (highest labeling)
- UMB-1 (somatostatin receptor 2)
- p53 and Rb-1 NEN G3)

Next generation sequencing (NGS)
Whole genomic sequencing

- Mutations, e.g. TP53 og RB-1

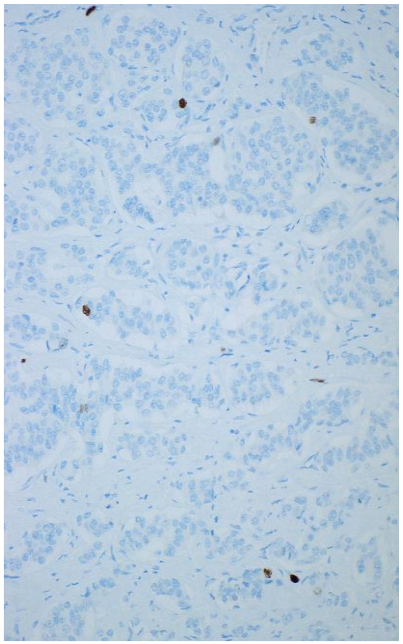
Chromogranin-ir
large secretory granulae



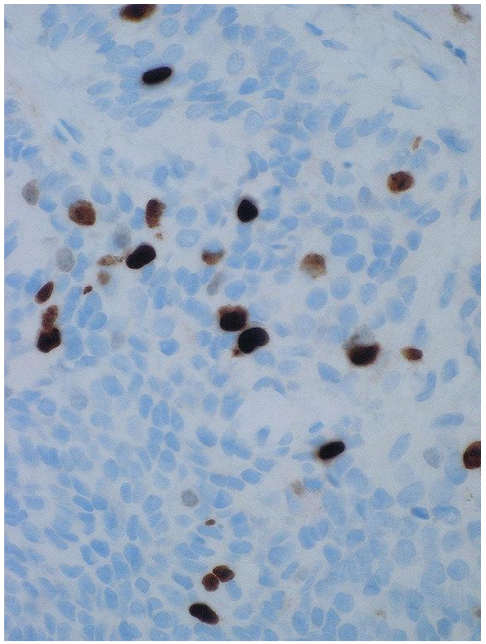
Ki-67 proliferation index

Important for
- Grading (WHO)
  - Referral
  - Treatment
  - Prognosis

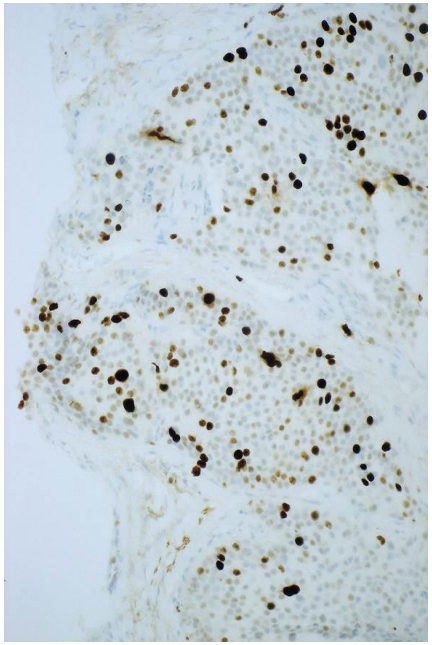
NET G1: <3 %

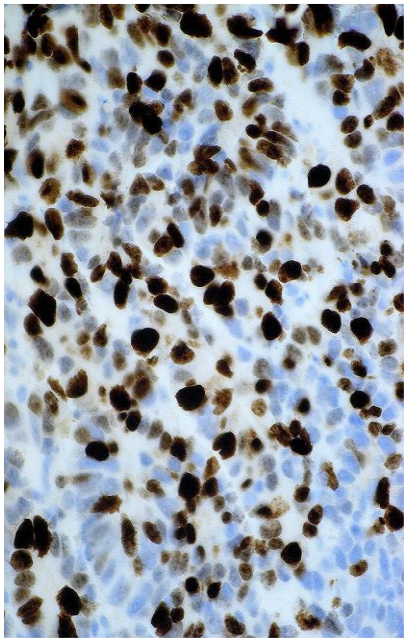


NET G2: 3-20%



NET G3 or NEC: >20%





Referral to NET Center

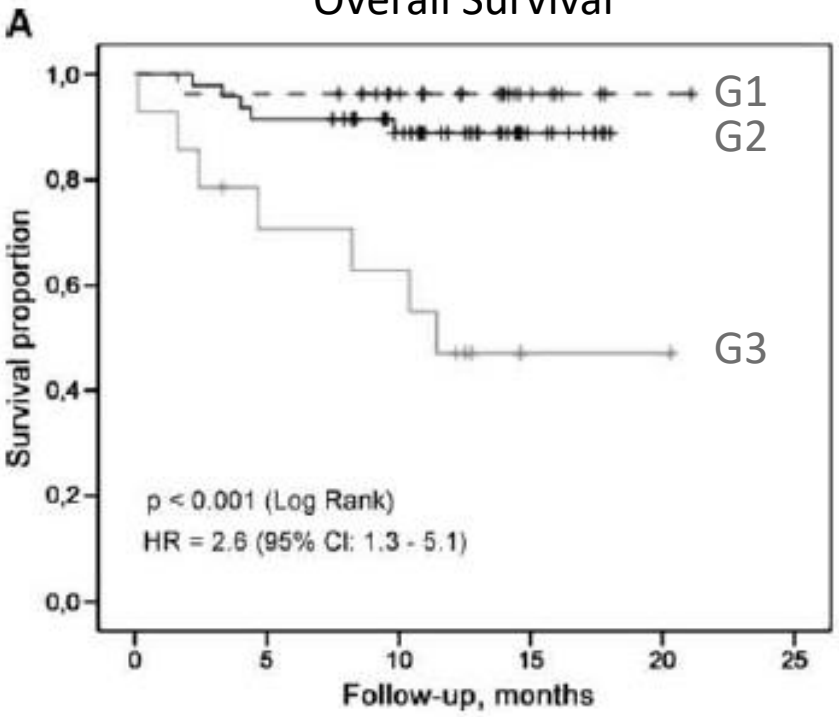
Endocrinology/Gastroenterology

Oncology

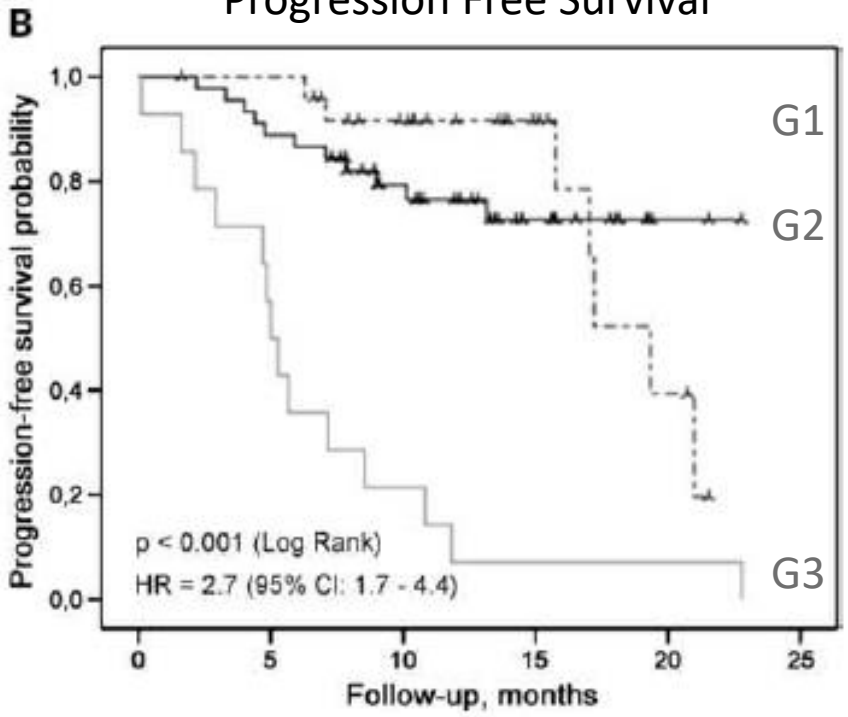
Ki-67 proliferation index

Prognostic factor

Overall Survival



Progression Free Survival



App. 100 NEN

Binderup, Clin Canc Res 2010;16:978-995

Diarrhoea in patients with neuroendocrine neoplasms (NEN)

- Gastrinomas
- Glucagonomas
- VIPomas
- Other rare pancreatic NEN

- Small intestinal NEN
  - Partly small bowel obstruction
  - Vascular encasement
  - Carcinoid syndrome

Diarrhoea in patients with neuroendocrine neoplasms (NEN)

- ~~Gastrinomas~~
- ~~Glucagonomas~~
- ~~VIPomas~~
- ~~Other rare pancreatic NEN~~

- Small intestinal NEN
  - Partly small bowel obstruction
  - Vascular encasement
  - Carcinoid syndrome

↓

Multiple liver metastases from small intestinal NEN

Neuroendocrine neoplasms of the small intestine

Clinical manifestations

Related to metastatic and advanced disease

Carcinoid syndrome

- Caused by serotonin and peptides released from liver metastases to the major circulation
- Hormones released from the primary tumor to the portal venous circulation are metabolized by the liver and rarely cause carcinoid syndrome

Neuroendocrine neoplasms of the small intestine

Carcinoid syndrome

Clinical manifestations

Vasomotor symptoms (90%)

- Flushing (facial and breast)
- Teleangiectasias
- Chronic facial cyanosis
- Rhinitis

Increased intest. motility (80%)

- Diarrhoea
- Borborygmia
- Abdominal pain

Right-sided heart failure (<15%)

- Endocardial fibrosis
- Pulmonary stenosis
- Tricuspid insufficiency
- Tricuspid stenosis

- Mostly both valves are affected

Bronchial constriction (<10%)

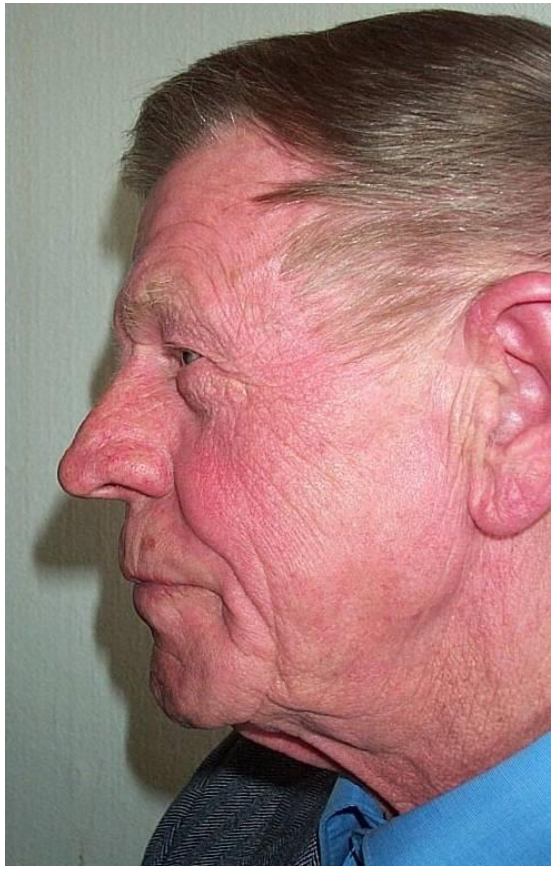
- Astma

Øget svedtendens er ikke en del af carcinoid syndrom

Neuroendocrine neoplasms of the small intestine

Carcinoid syndrome

Facial flushing



Diarrhoea in neuroendocrine neoplasms (NEN)

>3/4 of all NEN are diagnosed before referral by histology or endocrine symptoms

If not

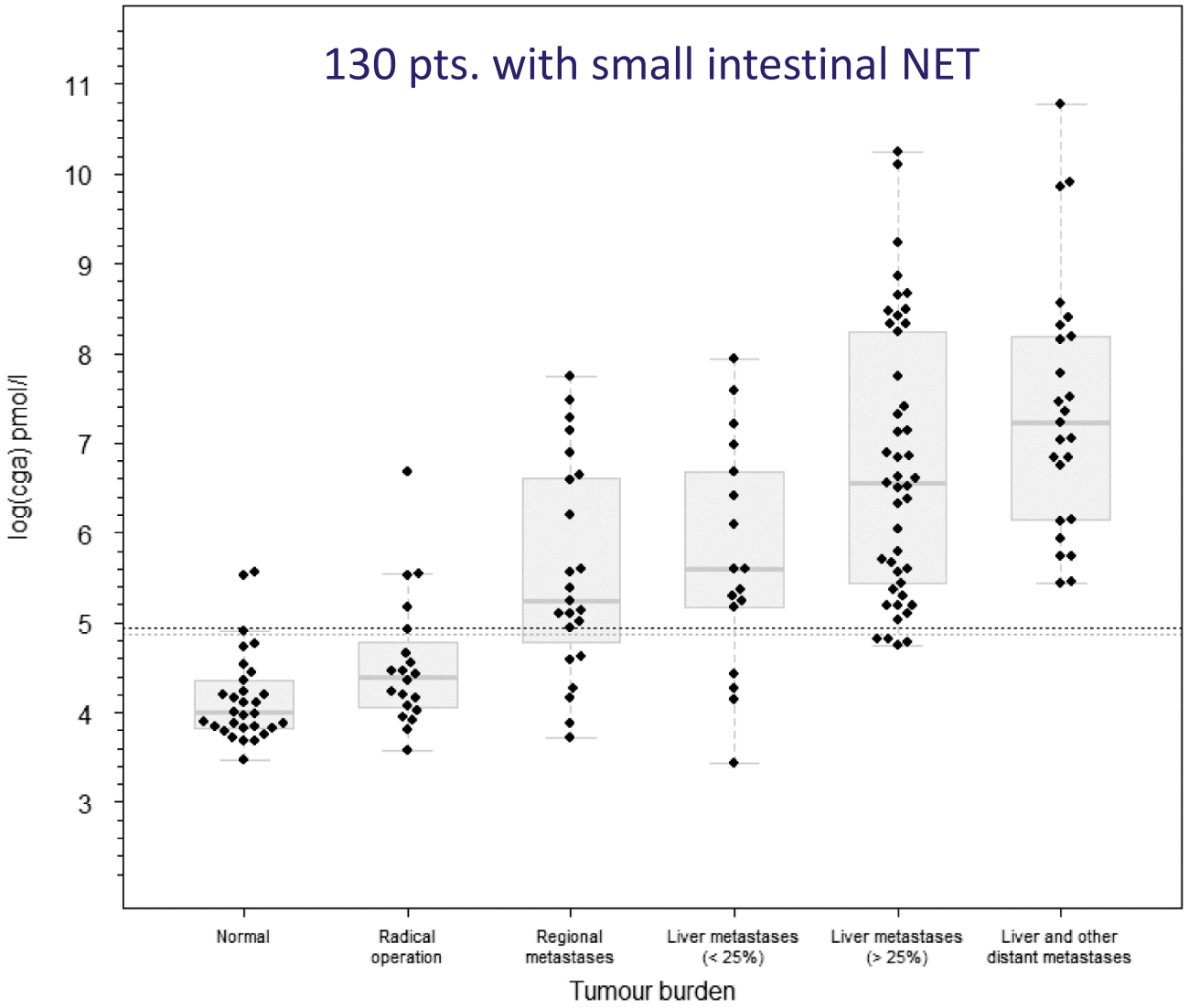
Diagnostic workup

considering

small intestinal NEN

- p Chromogranin A (eventually repeat if elevated)
- p Chromogranin A (trypsin clevage – only at RH)
- s 5-hydroxy-indolyl-acetic-acid (5-HIAA) (serotonin metabolite)
- Thoraco-abdominal-pelvic CT (primsry tumor and liver metastases)

p Chromogranin A (RH assay)



Rehfeld et al. Scand J Gastroenterol 2020;55:565-73.

p Chromogranin A

p Chromogranin-A: normal or only slightly elevated

- insulinomas
- very small NET, e.g. in the stomach, appendix and rectum
- poorly differentiated NEC with no secretory capacity

p Chromogranin-A: day-to-day variation of 25%

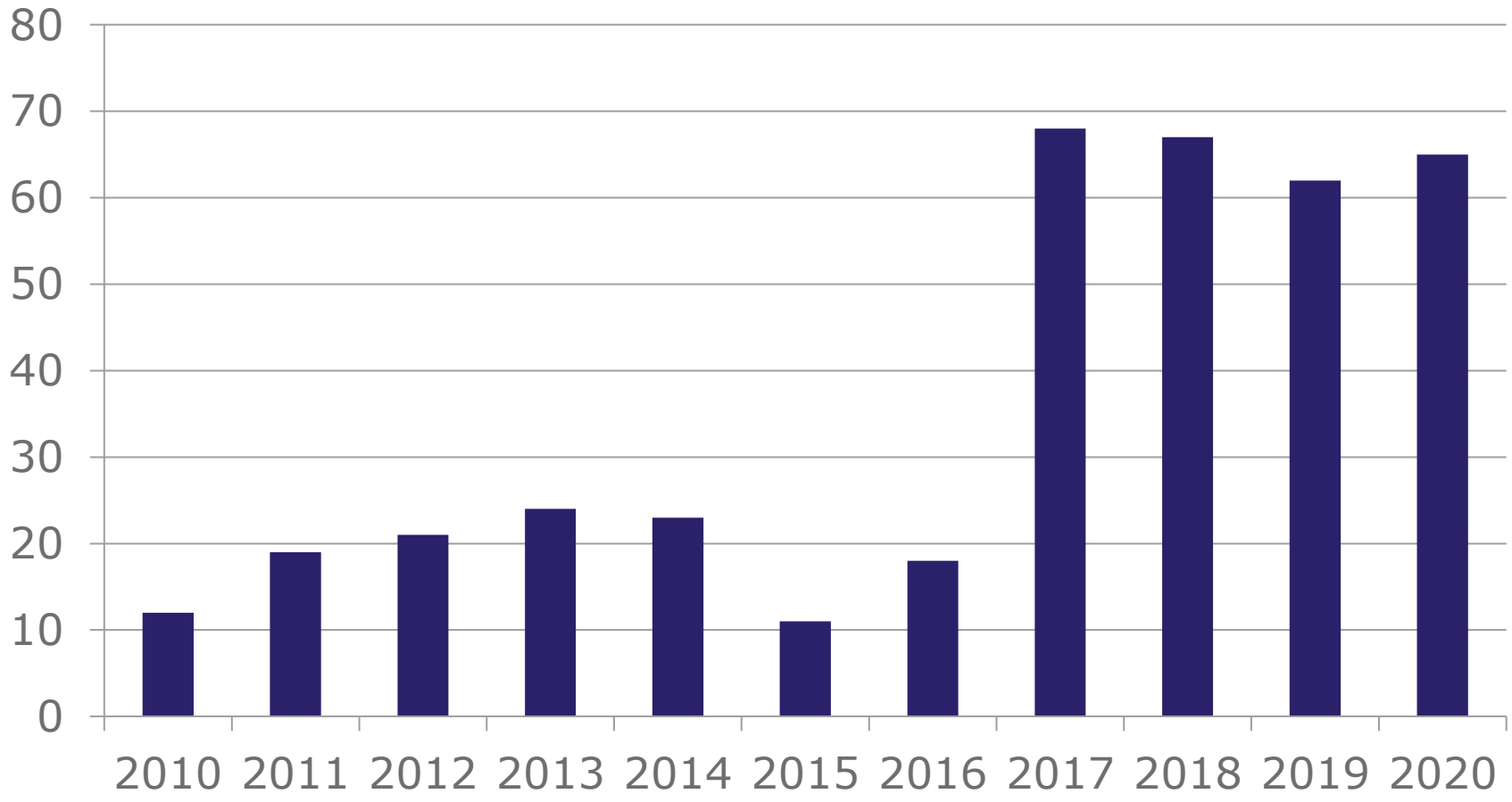
- if elevated more than one determination is required

p Chromogranin-A: elevated without presence of NET

- impaired renal or liver function
- chronic atrophic gastritis (autoimmun disease with parietalcell AB)
- prostatic carcinoma
- inflammatory bowel disease
- cardiac diseases, hypertension
- inflammation
- stress
- pharmaceuticals: PPI and other?
- unknown factors

1-2 weeks treatment stop – if possible

No. of pts. referred suspected for NET (elevated CgA) NET "not found"



p Chromogranin A

diagnostics Published: 29 October 2020 MDPI

Article

Limited Diagnostic Utility of Chromogranin A Measurements in Workup of Neuroendocrine Tumors

Jonas Baekdal [1,2,*], Jesper Krogh [1,2], Marianne Klose [1,2], Pernille Holmager [1,2], Seppo W. Langer [1,3], Peter Oturai [1,4,5], Andreas Kjaer [1,4,5], Birgitte Federspiel [1,6], Linda Hilsted [1,7], Jens F. Rehfeld [1,7], Ulrich Knigge [1,2,8] and Mikkel Andreassen [1,2]

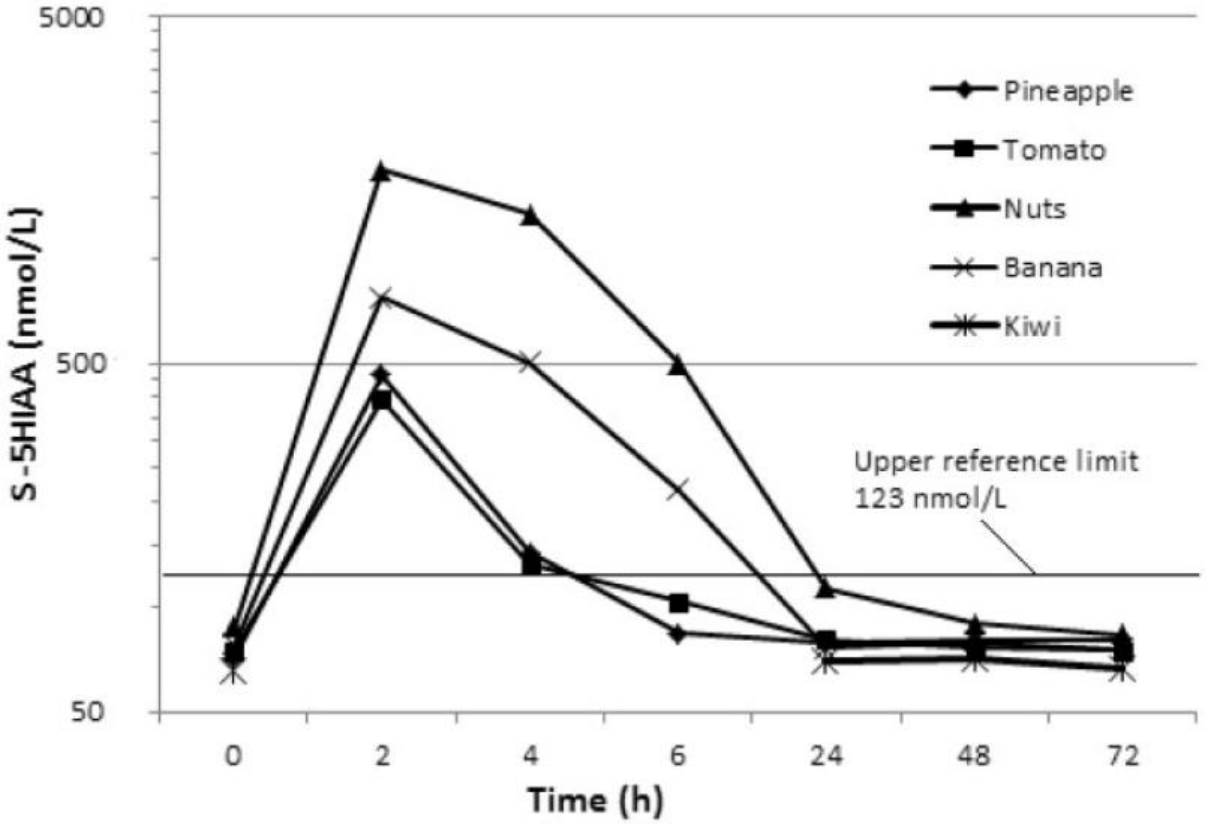
2020, RH database:

Of 65 referred patients suspected for NET based on elevated Chromogranin A only one patients had a NET (benign ECLoma)

s 5-HIAA

At least 24 h break in digestion of the following serotonin containing food items – **including red wine**

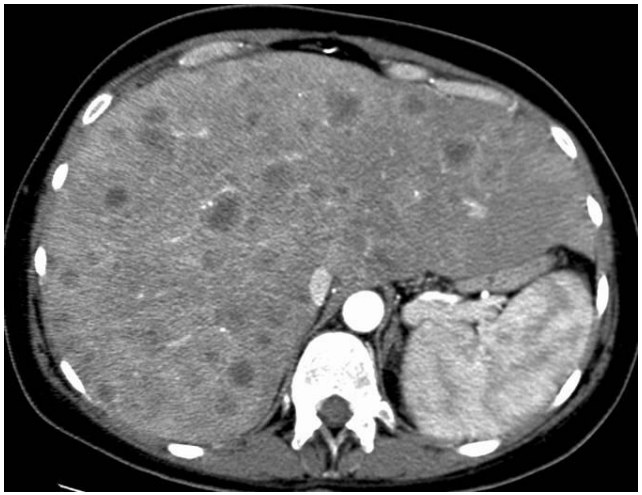
→ false positive elevation of the serotonin metabolite

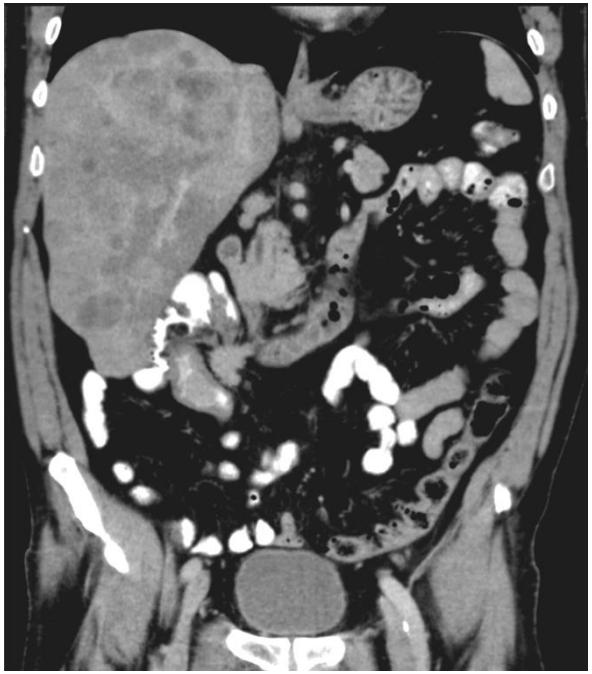


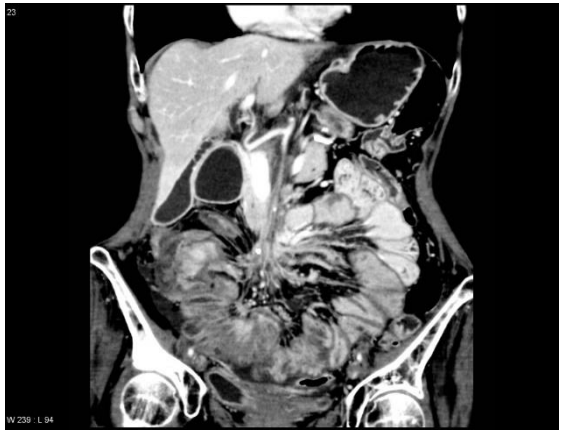
Tohmola et al. Ann Clin Biochem. 2014, Dec 27

Imaging

Abdomial CT

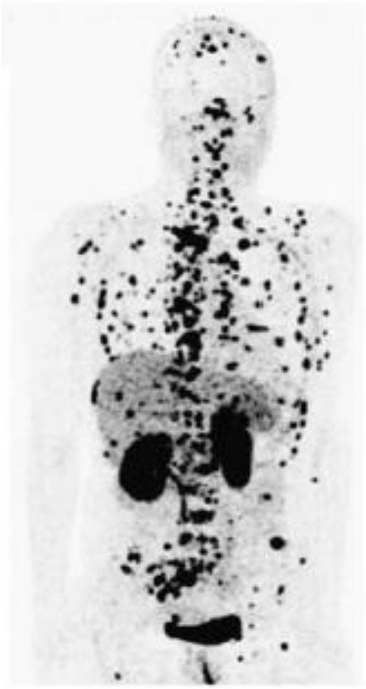






Imaging

^{64}Cu-DOTATATE PET/CT



^{64}Cu-DOTATATE

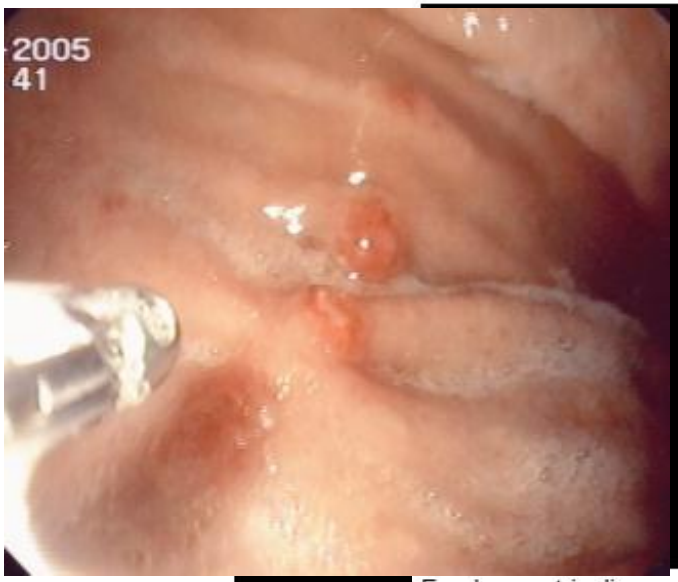
Neuroendocrine neoplasms of the stomach

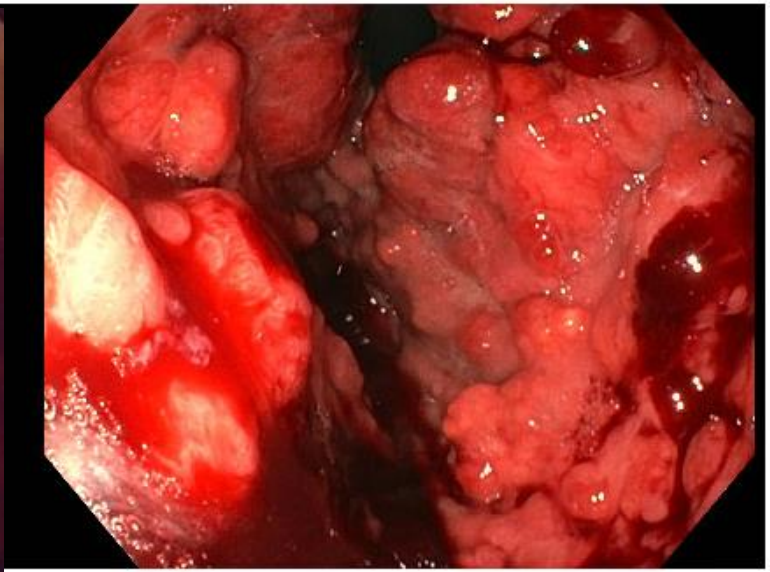
	Type 1 ECLomas	Type 2 ECLomas	Type 3
Proportion	70-80 %	5 %	20 %
Characteristics	1-2 cm, multiple	1-2 cm, multiple	>2 cm, sporadic
Associated with	CAG, autoimmune	Gastrinoma, MEN-1	None
Pathology	NET G 1-2	NET G 1-2	NET G 2-3, NEC
S Gastrin	Sec. elevated	Prim. elevated	Normal
Gastric pH	Elevated	Low	Normal
Metastases	<5 %	5-10 %	50-100 %
Tumor related death	0	<10 %	30 %
Treatment	Obs.; rarely resection	Resection; obs.	Resection, chemo

Type 1 ECLomas

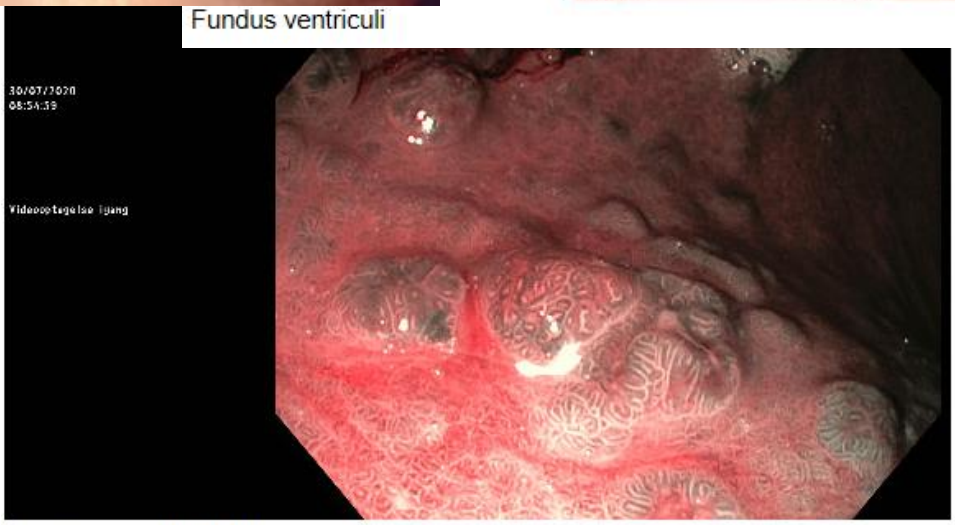
- NET → referral to NET Center
- Micronodular neuroendocrine hyperplasia → referral to NET Center
- Linear neuroendocrine hyperplasia → no referral

Gastric ECLomas





Fundus ventriculi



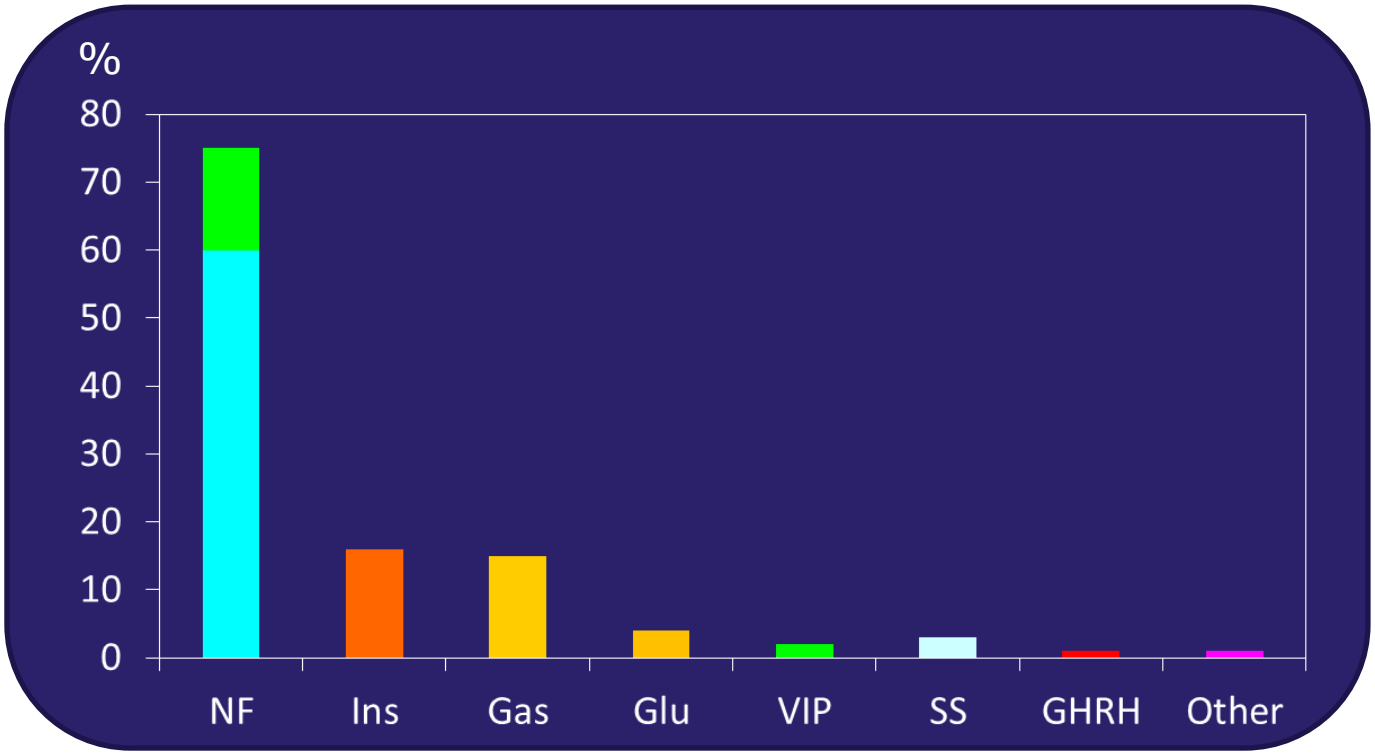
Corpus ventriculi, NBI-lys

Neuroendocrine neoplasms of the pancreas

Incidence: 0.4 – 1.2 / 100.000 / year

2-10% of all pancreatic neoplasms

Distribution of non-functioning (NF) and functioning pancreatic NENs (indicated by hormone)



Pancreatic neuroendocrine incidentalomas

- With improved imaging more often hypervascular NEN <1-2 cm in size are found by incident by CT or MRI

  Diagnosis
  - $^{64}Cu/^{68}Ga$-PET-CT: pos. imaging
  - EUL+biopsy: pos. histology, Ki67 index

- Non-functioning
- Benign behaviour ?
- Observation or Resection ?
- Considering high rate of complications to pancreatic surgery
- Tendency toward observation even in younger patients
- Resection only if growing or > 2cm

Neuroendocrine neoplasms of the rectum

Mostly small polyps < 10 mm found by incident
e.g.

- Rectal bleeding
- Colo-rectal screening
- Bowel obstruction is rare

Distant metastases at diagnosis are uncommon

EMR or removed by biopsies

- Residual tumor or uncertain resection margins
- → new endoscopy and biopsies as soon as possible

Larger (>20 mm) polyps/tumors require

- more extensive investigations
- more extensive treatment

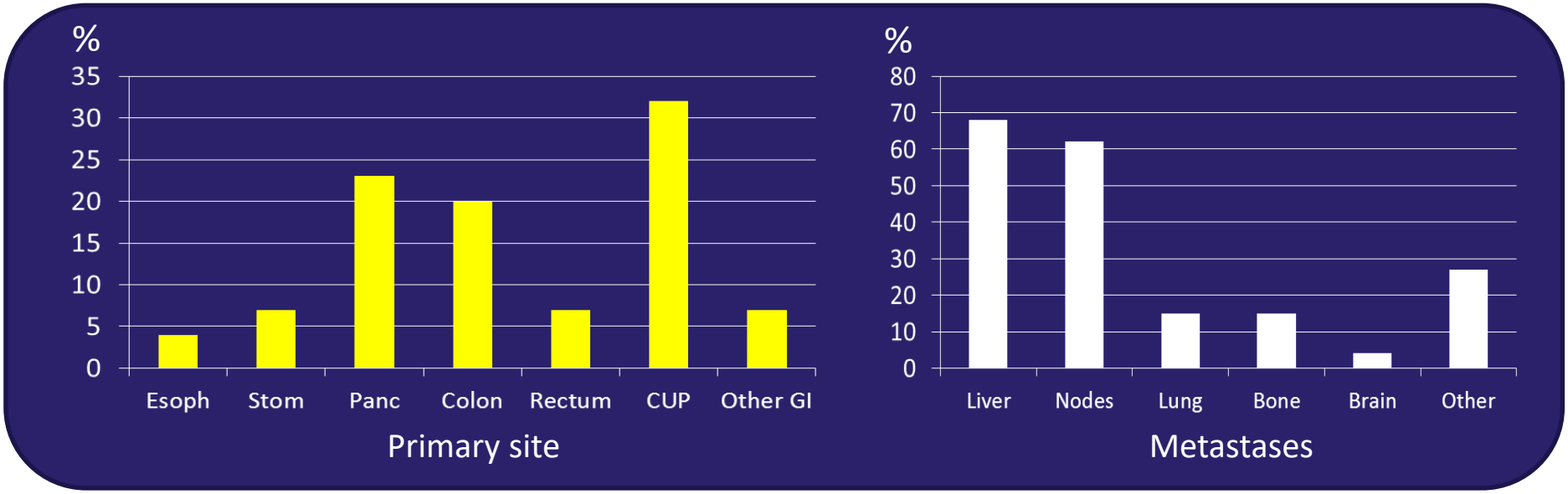
Neuroendocrine Tumors G3 and Neuroendocrine Carcinomas

Annals of Oncology 24: 152–160, 2013
doi:10.1093/annonc/mds276
Published online 11 September 2012

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

H. Sorbye[1*], S. Welin[2,†], S. W. Langer[3,†], L. W. Vestermark[4], N. Holt[5], P. Osterlund[6], S. Dueland[7], E. Hofsli[8], M. G. Guren[9], K. Ohrling[10], E. Birkemeyer[11], E. Thiis-Evensen[12], M. Biagini[13], H. Gronbaek[5], L. M. Soveri[6], I. H. Olsen[14], B. Federspiel[15], J. Assmus[16], E. T. Janson[2,‡] & U. Knigge[14,‡]

Period
2000-2009

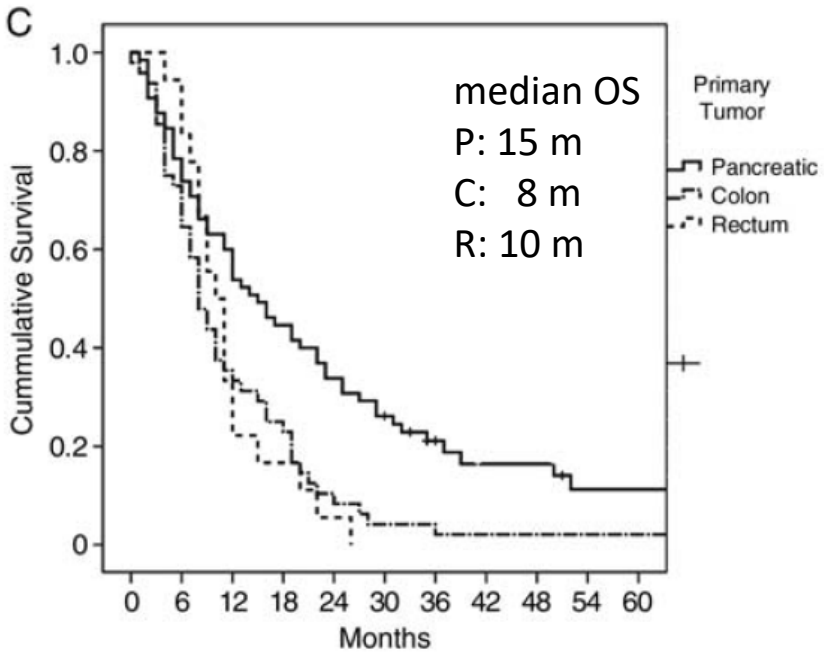


Neuroendocrine Tumors G3 and Neuroendocrine Carcinomas

NEC: Etoposide + Cis-/Carboplatin

NET G3: Temozolomide + Capecitabin

Primary tumor



If untreated – OS: 1 month

Neuroendocrine tumors G3 and Neuroendocrine carcinomas

Surgery of the primary tumour in 201 patients with highgrade gastroenteropancreatic neuroendocrine and mixed neuroendocrine-non-neuroendocrine neoplasms.
H-C. Pommergaard. J Neuroendocrinology 2021; March 26

	Chemo	Surgery
PFS months	4	9
OS months	11	26

"Upfront surgery should be considered in patients with loco-regional high-grade GEP NEN and GEP MiNEN (Stage I-III). Stage IV patients may benefit from surgery if an R0 resection can be obtained."
H-C. Pommergaard. J Neuroendocrinology 2021; March 26

Treatment of Neuroendocrine neoplasms

Observation

Surgery

Somatostatin analogs

Radionuclide therapy (PRRT)

Everolimus

Sunitinib

STZ + 5-FU

Tem-Cab
etoposide + platin

Radiotherapy

RFA

Liver embolisation