



Faculty of Health and Medical Sciences



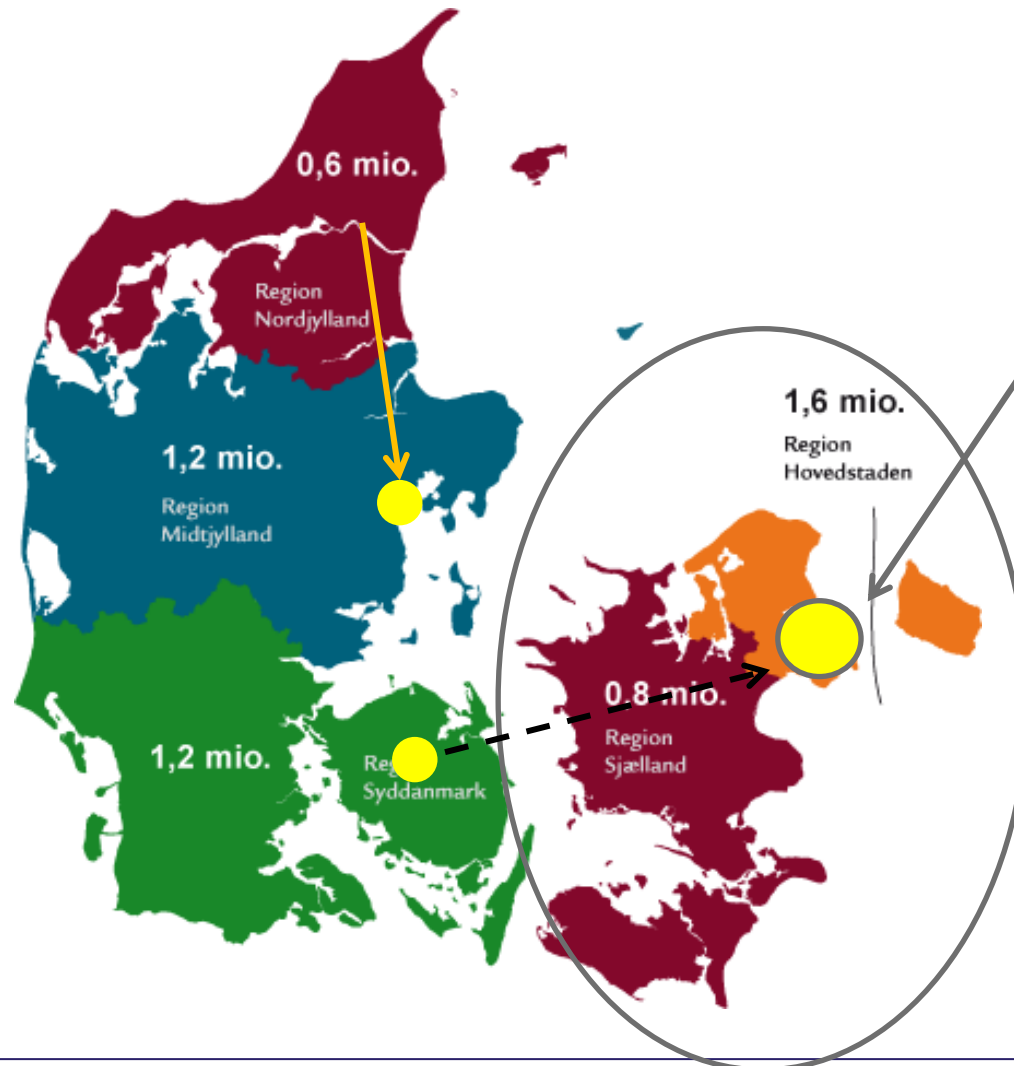
Gastro-Entero-Pancreatiske Neuroendocrine neoplasmer

Ulrich Knigge

Neuroendocrine Tumor Centre of Excellence
Rigshospitalet
University of Copenhagen
Denmark



NET Centre i Danmark



Faroe Islands
Greenland

PRRT

Region Syd
Norway
Sweden
Ireland
Canada
USA

Neuroendocrine neoplasmer

Udvikles fra det

Diffuse Neuroendocrine Celle System

Definition

Enkelt celler eller øer af celler med ensartet morfologi og danner bestemte

- generelle neuroendocrine markører
chromogranin og synaptophysin
- celle type-specifikke peptid hormoner og neurotransmittorer
f.eks. gastrin, insulin, serotonin

Diffuse Neuroendocrine Celle System

Central gruppe

- Hypothalamus
- Pituitary gland
- Pineal gland

Perifer gruppe

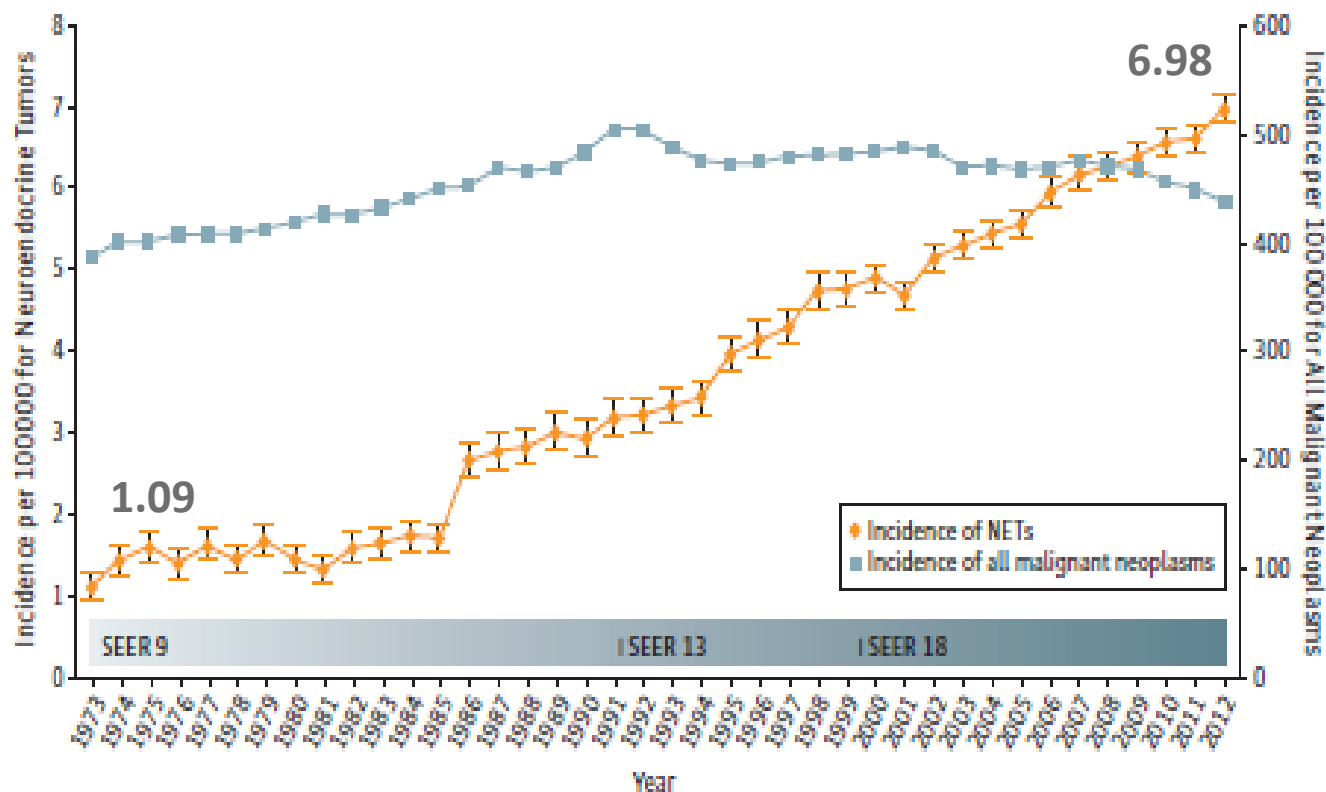
- Parathyroidea (biskjoldbrusk kirtlen)
- C-celler i skjoldbruskkirtlen
- Sympatiske nervesystem
- Binyre marven
- NE celler i bugspytkirtlen (pancreas)
- NE celler i
 - Mave-tarm kanalen
 - Lungerne
 - Urinvejene
 - Bristlen
- Merckel celler i huden

Epidemiologi: Incidens

SEER data-base – ca. 65.000 NEN patienter

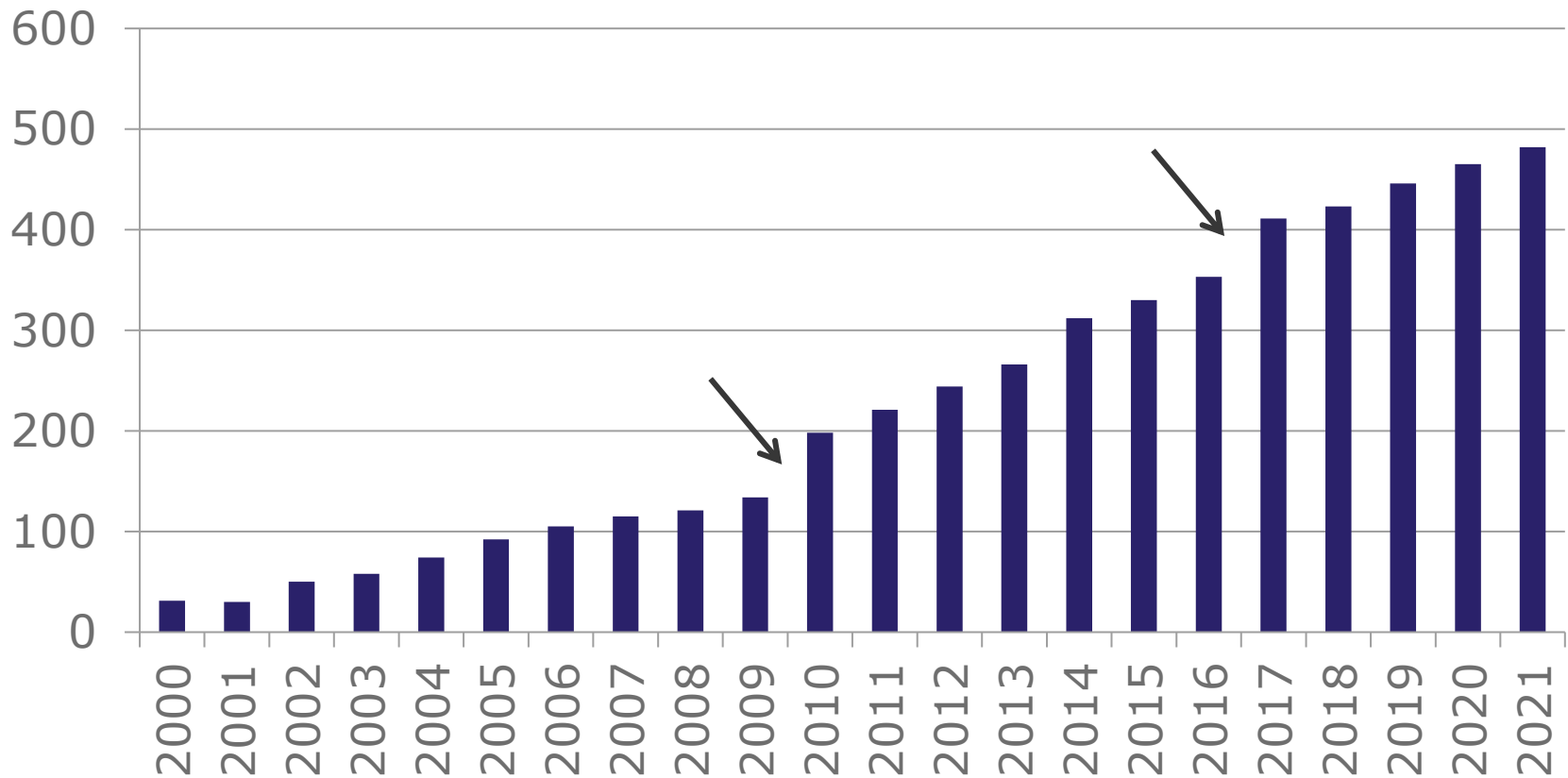
Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012

A All NETs and malignant neoplasms



RH NET Center of Excellence

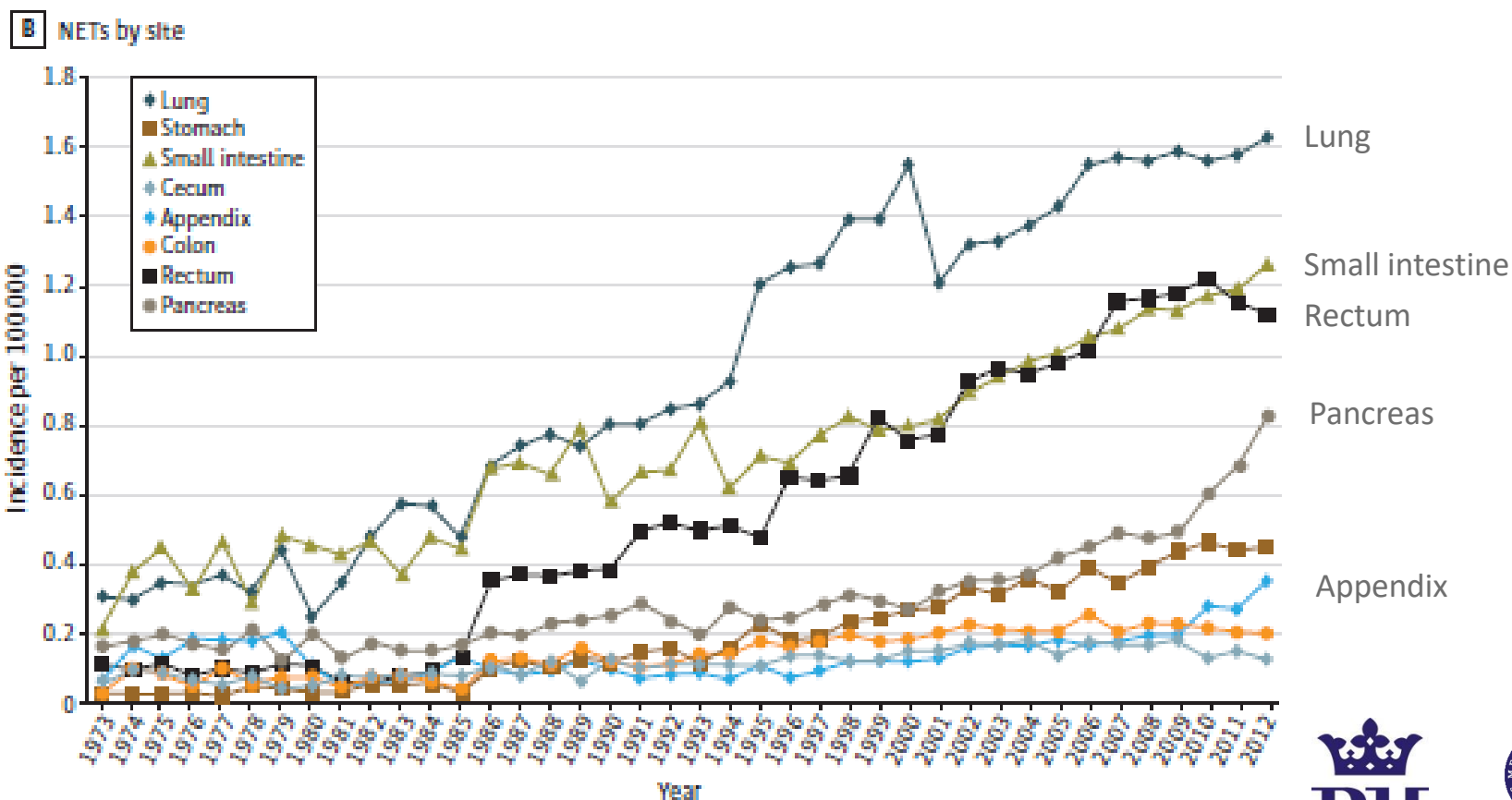
Nye NEN patienter henvist pr år (GEP + BP + andre)



Epidemiologi: Incidens

SEER data-base – ca. 65.000 NEN patienter

Incidens relateret til GEP and BP NEN

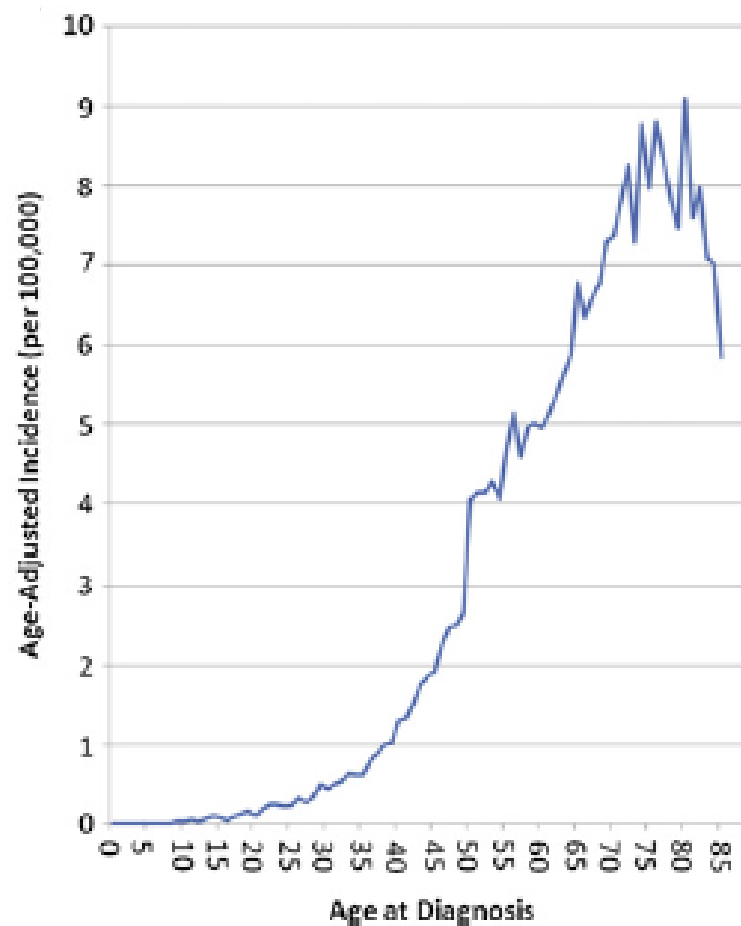


Dasari, JAMA Oncology 2017

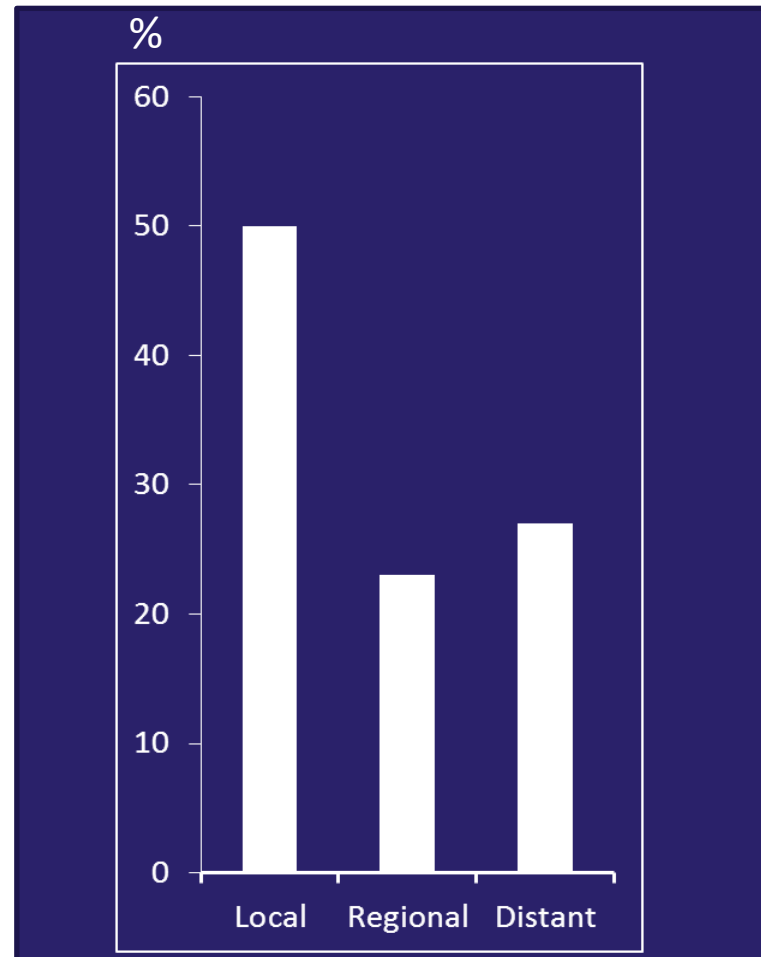
Incidens og prevalens af Neuroendocrine neoplasmer

- Incidens: stigende
 - Øget opmærksomhed blandt læger, kirurger og især patologer
 - Forbedret registrering (ved henvisning til specialiseret NET Center)
 - Nye og forbedrede diagnostiske redskaber
 - p Chromogranin A (CgA)
 - Immunohistokemi (CgA, synaptophysin og tumor specifikke hormoner)
 - Somatostatin receptor billeddiagnostik (^{64}Cu - or ^{68}Ga -DOTATATE-PET/CT)
 - En reel stigning i incidensen
 - Incidens RH 2018: ca. 14/100.000/år
- Prevalens: 35/100.000 /år (SEER data-base 2008)
- Prevalens: ca. 70/100.000 /år (RH 2018)

Alder på diagnosetidspunkt – GEP NENS



Fordeling af GEP-NEN: Localiseret, regional spredning og fjern metastaser – SEER data-base



Afhængig af tumor type
og lokalisation

NEN i tyndtarm

Yao, J Clin Oncol 2008
(SEER database)

Stadieinddeling af GEP-NEN

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

WHO 2019 Classification

Neuroendocrine Neoplasms (NEN)

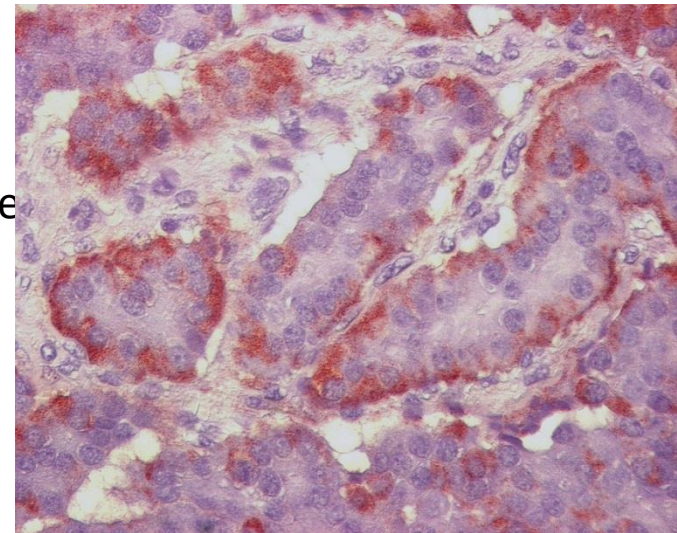
Terminology	Differentiation	Ki-67 index
NET, G1	Well differentiated	<3%
NET, G2	Well differentiated	3-20%
NET, G3	Well differentiated	>20%
NEC, small cell	Poorly differentiated	>20%
NEC, large cell	Poorly differentiated	>20%
MiNEN	Well or Poorly diff. (mostly poor)	Variable (mostly >20%)

Pathologi

Immunohistokemi

- generelle tumor celle markører
 - synaptophysin
 - chromogranin-A
- tumor celle specifikke hormoner, f.eks.
 - gastrin
 - serotonin
- Ki-67 proliferations index (eller mitose tal)
 - "hot spot areas" (højeste antal farvede tumorcelle)
- UMB-1 (somatostatin receptor 2)
- p53 (normal or abnormal i NEN G3)
- Andre prognostiske markører i NEN G3, e.g. RB-1)

Chromogranin-ir
store sekretoriske granulae



Next generation sequencing (NGS)

Whole genomic sequencing

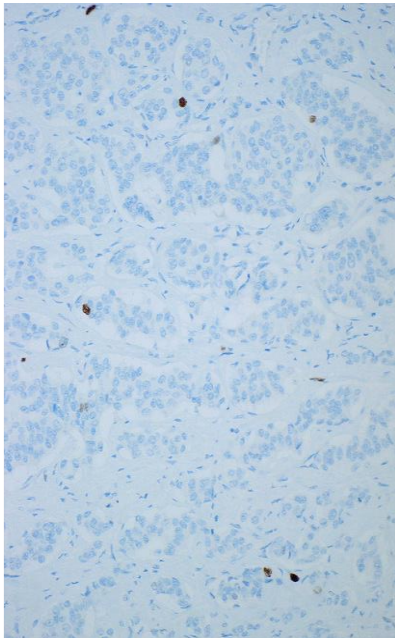
- Mutations, f.eks. TP53 og RB-1

Ki-67 proliferations index

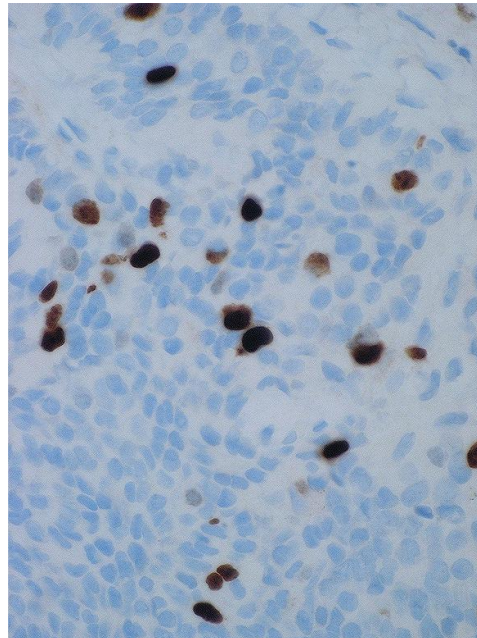
Har betydning for • Gradering (WHO classification)

- Henvisning til hvilken afd.
- Behandlings valg
- Prognose

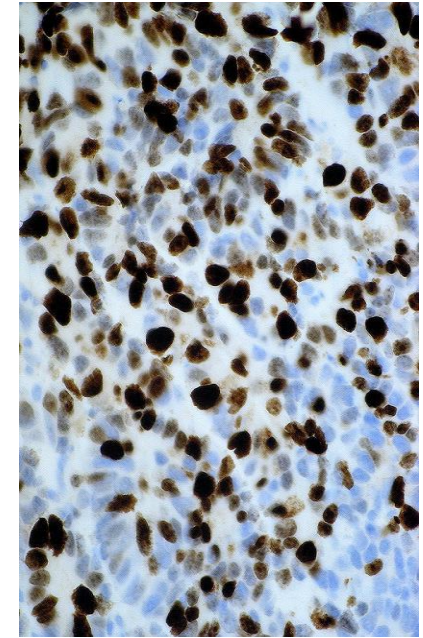
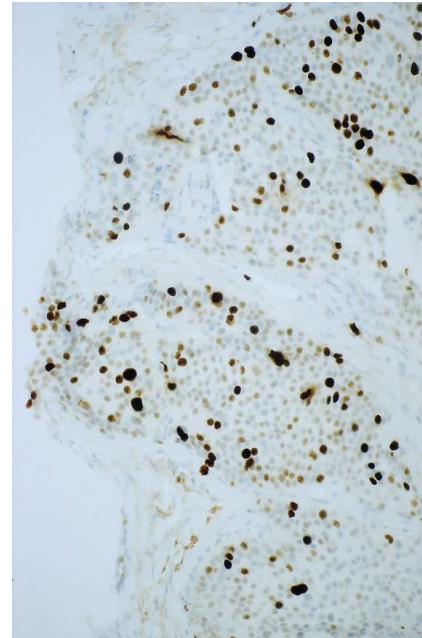
NET G1: <3 %



NET G2: 3-20%



NET G3 eller NEC: >20%



Henvisning til NET Center

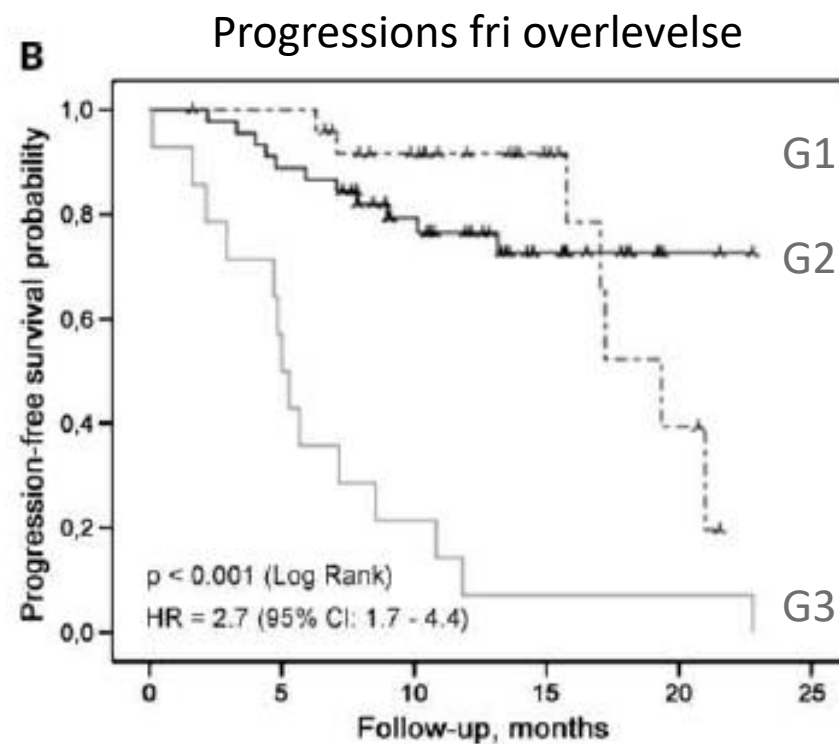
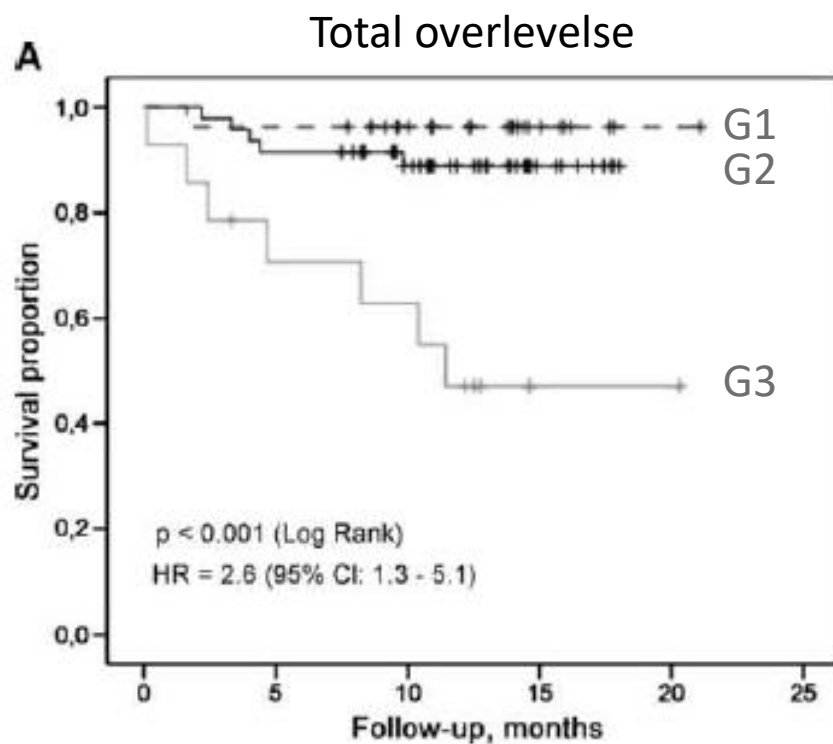
Endokrinologi/Gastroenterologi

Onkologi



Ki-67 proliferations index

Prognostisk faktor



App. 100 NEN

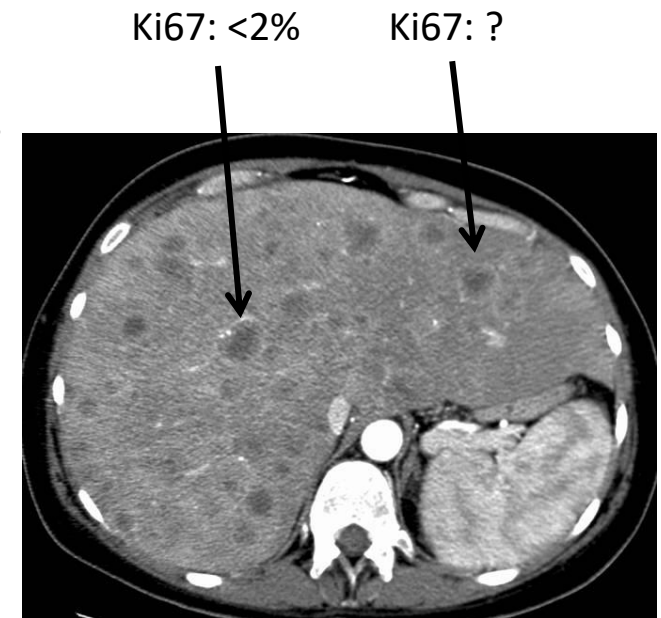
Ki-67 proliferations index

Ki-67 proliferations index kan være forskellig

- mellem primær tumor og metastaser
 - generalt højere i mets. end i primær tumor
- blandt metastaserne
 - kan skyldes forskellige tumor celle populationer

Ki-67 proliferations index kan stige med tiden (transformation – nye cloner udvikles i tumor/mets.)

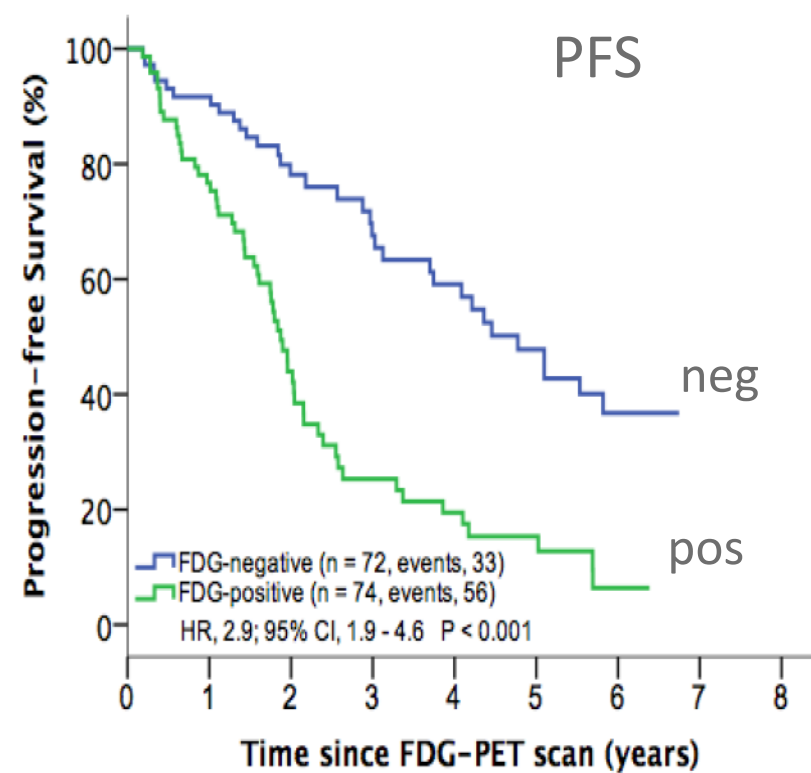
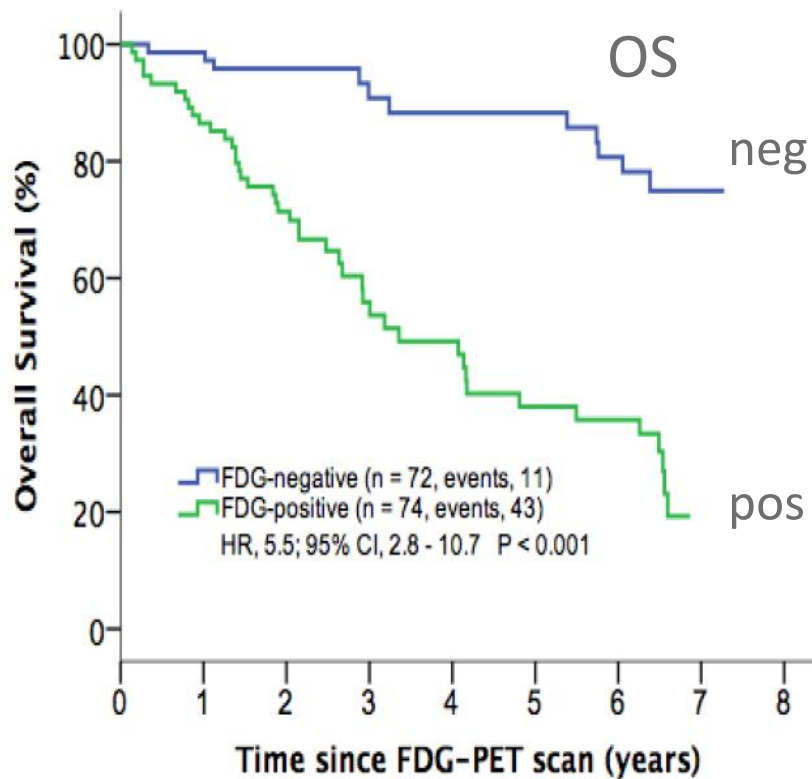
- Nye biopsier er oftest påkrævet hvis
 - Tumor eller metastaser vokser
 - Der opstår nye metastaser



^{18}F -FDG-PET som prognostisk markør

OS og PFS baseret på pos. eller neg. FDG-PET

NET G1 + G2



Neuroendocrine neoplasmer (NEN) Diagnostiske metoder

Typen af diagnostiske metoder der anvendes afhænger af tumor type, lokalisation og spredning

Histopatologiske metoder

- Farvning for NEN specifikke markører
- Farvning for specifikke hormoner
- Ki67 proliferationsindex

Biokemiske metoder

- Pancreas hormoner
- 5-HIAA (metabolit af serotonin)
- Chromogranin A (Mikkel)

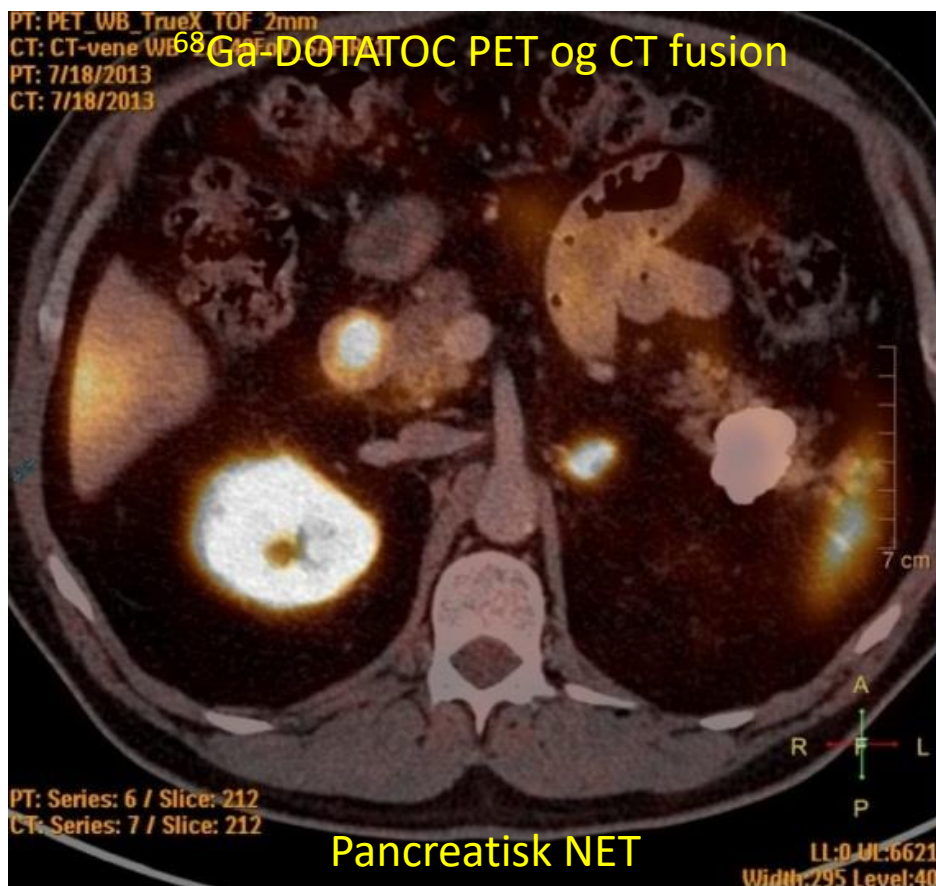
Endoskopiske metoder

Billeddiagnostiske metoder

- CT, MR, UL
- ^{18}F -FDG-PET
- ^{68}Ga -PET eller ^{64}Cu -PET

Somatostatin receptor imaging (SRI)

- > 90% of GEP NET udtrykker somatostatin SSR-2 på celle overfladen
- SS-analoger har høj affinitet til somatostatin SSR-2



Formål

- Detektion af tumor og metastaser
- Tumor stadium (scan af hele kroppen)
- Påvisning af recidiv i kontrolforløb
- Mulighed for PRRT (radionuclid beh.) (SUVmax or Krenning scale)

Sensitivitet

Afhænger af tumor størrelse og SSR-2 tæthed på tumor cellerne

- | | |
|---------------|------|
| • NET | >90% |
| • Insulinomer | <25% |
| • NEC | <50% |

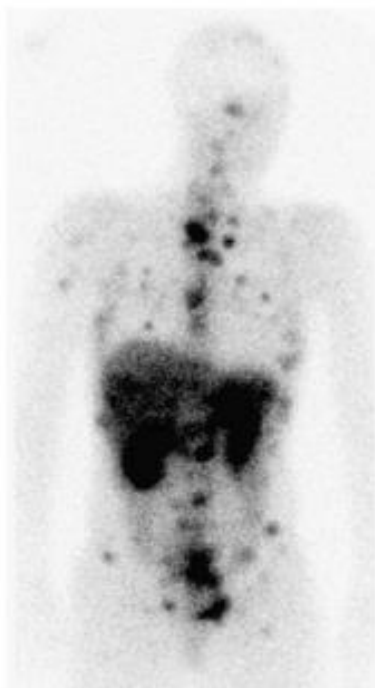
Specificitet

- | | |
|--------|--------|
| • Alle | 80-90% |
|--------|--------|

Somatostatin receptor imaging (SRI)

^{68}Ga -PET og ^{64}Cu -PET er overlegen
 ^{111}In -Octreotide scintigraphy (SPECT)

Prospektiv head-to-head sammenligning af 112 NEN



^{111}In -DTPA-octreotide



^{64}Cu -DOTATATE

^{64}Cu -PET er ^{68}Ga -PET overlegen
i head-to head sammenligning

- afslører flere foci
- længere halveringstid
- mindre stråledosis

Johnbeck, J Nucl Med 2017;58:451-457

Pfeifer, J Nucl Med 2013 & 2015;56:847-854

Kliniske studier (igangværende og planlagte)

Diagnostic/Therapeutic (prospective) trials

- RH PRRT-trial
- Prognostic value of FDG-PET - continued
- QoL studies in NET
- EXPLAIN
- ET-NEC study
- NETest in NEC
- NEC Nordic prospective database
- Carcinoid heart disease
- Prospective PET studies (Esben og Mathias)
- Cu-PET/CT vs. CT alone in Follow-up of GEP NET patients
- Value of Ga/Cu-PET in patients with MEN-1
- NGS in NEC and NET G3
- Ipsen OPS202 (antagonist)
- Pulmonary carcinoids
- 20 years retrospective data-base study on pancreatic NEN
- 20 years retrospective data-base study on small intestinal NEN

Kliniske studier (igangværende og planlagte)

Belzutifan

A Phase 2 Study to Evaluate the Efficacy and Safety of Belzutifan(MK-6482) Monotherapy in Participants with Advanced Pheochromocytoma/Paraganglioma (PPGL) or Pancreatic Neuroendocrine Tumor (pNET)

OXTEND-01

Fase 1b forsøg hos patienter med akromegali eller fungerende gastroenteropankreatiske neuroendokrine tumorer (GEP-NET) til karakterisering af farmakokinetikken, farmakodynamikken, sikkerheden og tolerabiliteten ved Debio 4126, en 12-ugers depotformulering af octreotid.

PDD – study

Phase 3 multicenter clinical trial in patients with carcinoid syndrome

Dropizol – study

Phase 3 multicenter study of the effect of Dropizol on stool frequency in patients with carcinoid syndrome



Diarrhoea in neuroendocrine neoplasms (NEN)

- Gastrinomas
- Glucagonomas
- VIPomas
- Other rare pancreatic NEN

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

Diarrhoea in neuroendocrine neoplasms (NEN)

- ~~• Gastrinomas~~
- ~~• Glucagonomas~~
- ~~• VIPomas~~
- ~~• Other rare pancreatic NEN~~
- Small intestinal NEN
 - Partly small bowel obstruction
 - Carcinoid syndrome



Multiple liver metastases from small intestinal NEN

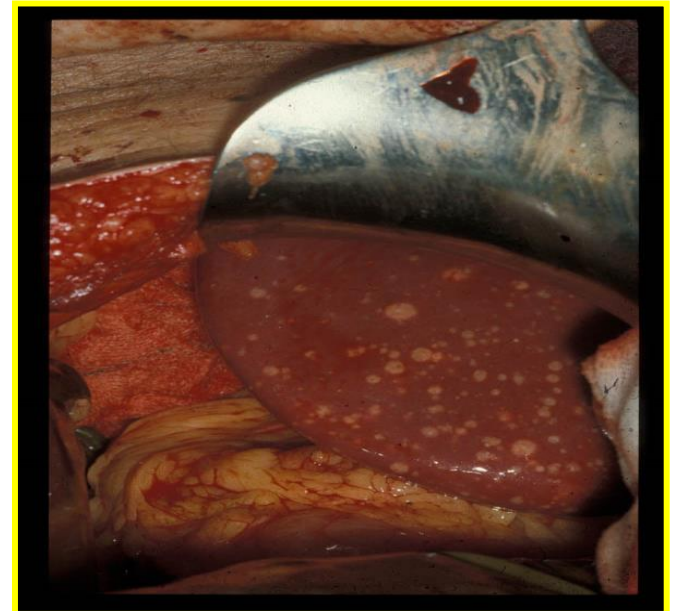
Neuroendocrine neoplasms of the small intestine

Clinical manifestations

Related to metastatic and advanced disease

Carcinoid syndrome

- Incidence: 0.40 - 0.65 / 100.000 / year
- 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

Right-sided heart failure (<15%)

- Endocardial fibrosis
- Pulmonary stenosis
- Tricuspid insufficiency
- Tricuspid stenosis
- Mostly both valves are affected

Increased intest. motility (80%)

- Diarrhoea
- Borborygmia
- Abdominal pain

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)

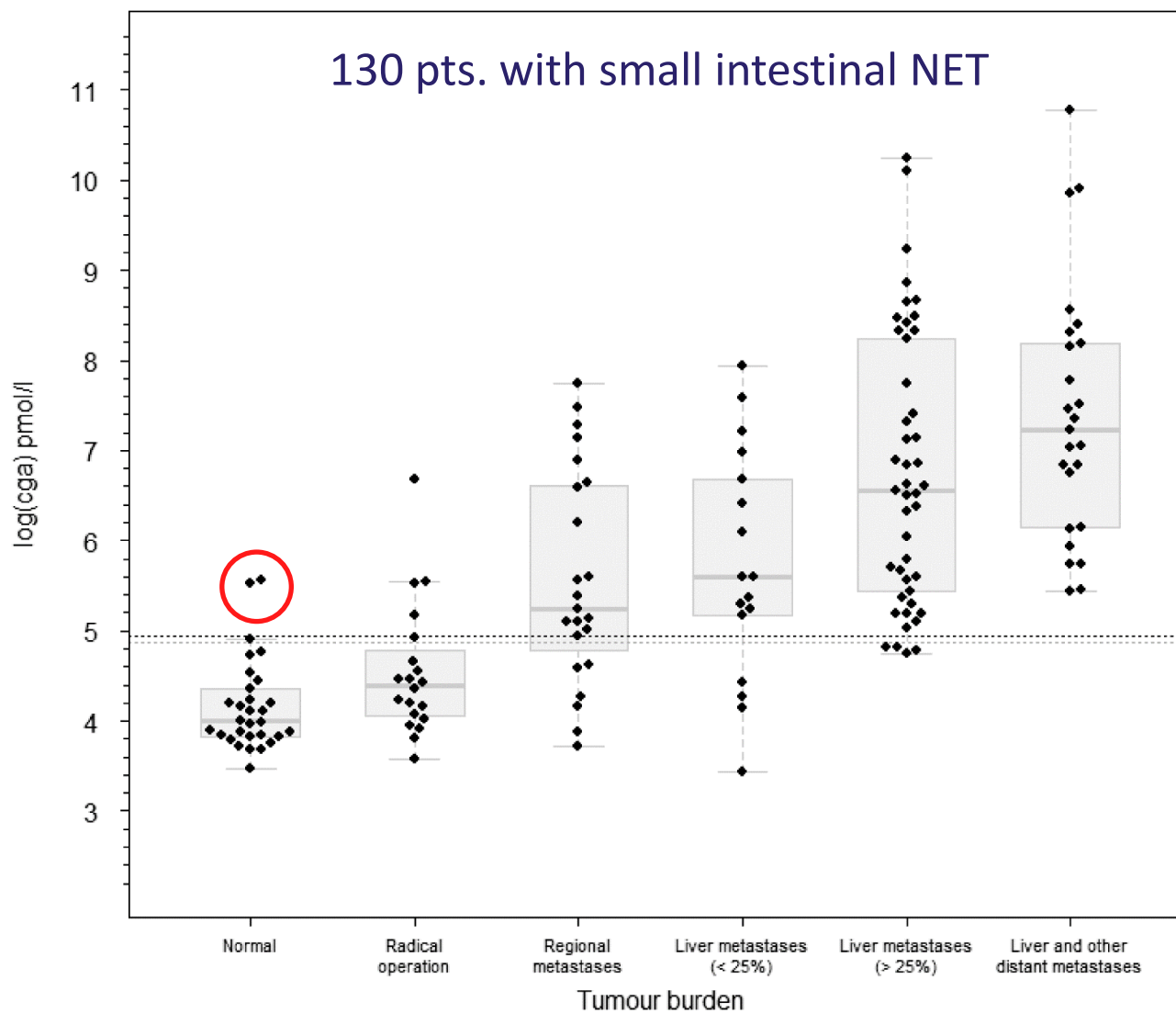
>3/4 of all NEN are diagnosed by histology or endocrine symptoms

If not

Diagnostic workup For small intestinal NEN

- p Chromogranin A
- s 5-HIAA (metabolite of serotonin)
- Thoraco-abdominal-pelvic CT (reveals liver metastases)

p Chromogranin A (RH assay)



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, antihypertensiva and other?
- unknown factors

1-2 weeks treatment stop



p Chromogranin A





diagnostics

Published: 29 October 2020



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} 

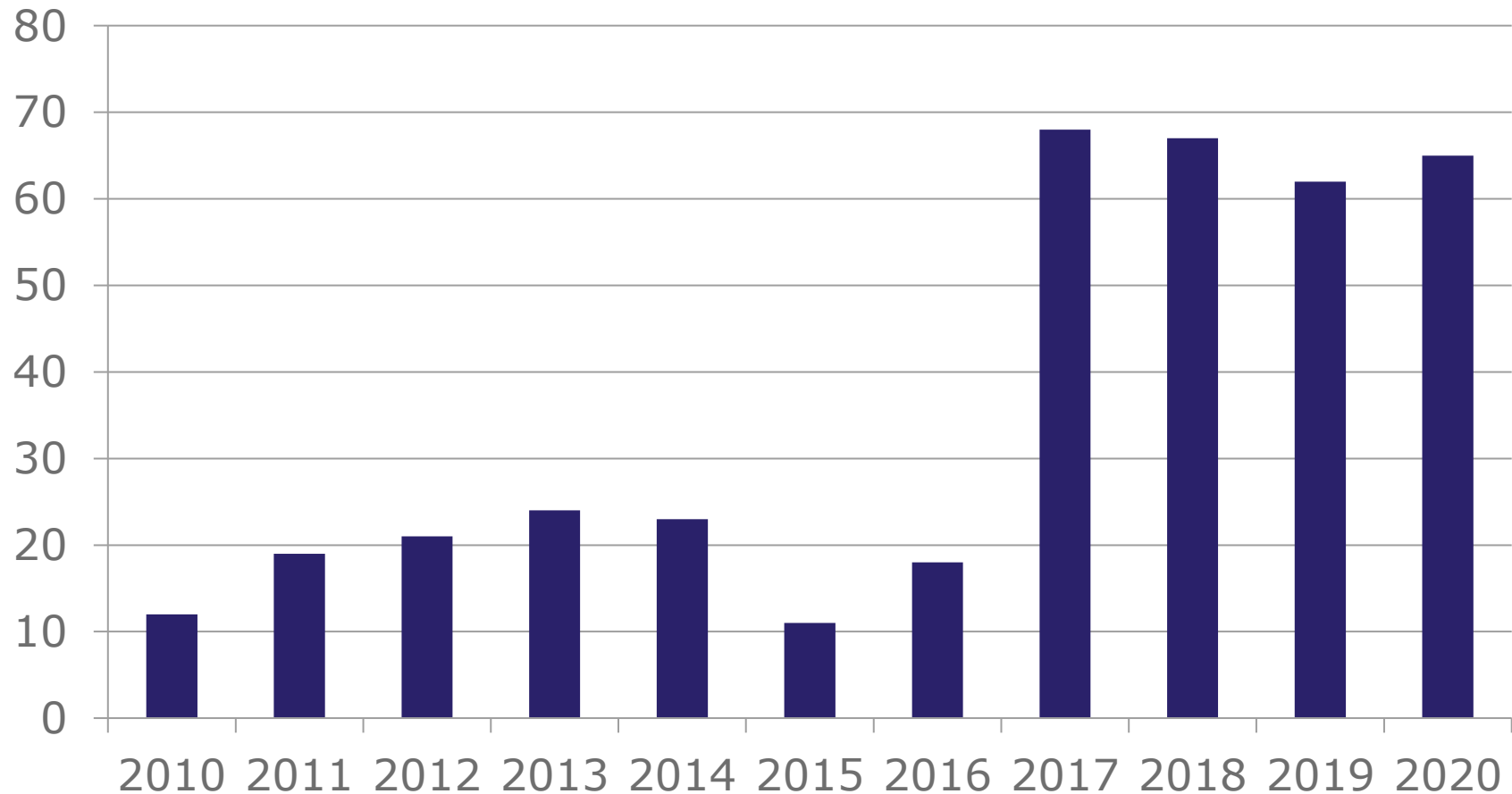
Trypsin cleavage chromogranin

2020, RH database:

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



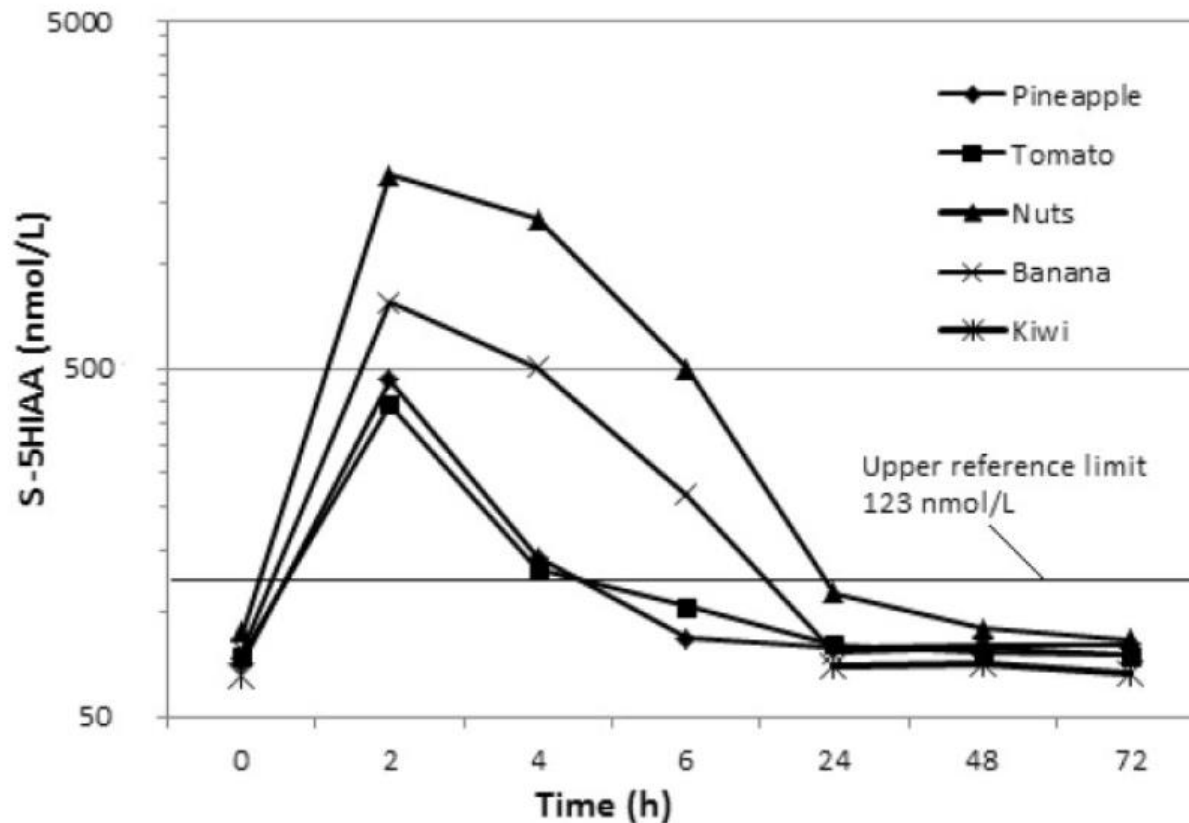
No. of pts. referred suspected for NET (elevated CgA) NET not found



s 5-HIAA

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

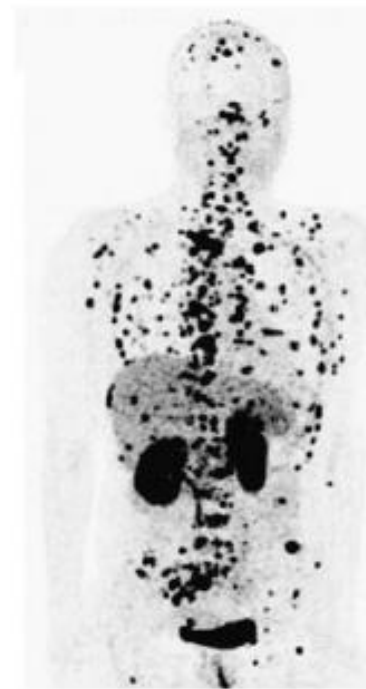
→ false positive elevation of the serotonin metabolite



Imaging

Abdomial CT

^{64}Cu -DOTATATE PET/CT



^{64}Cu -DOTATATE

Imaging

General imaging methods

- Endoscopy
- EUS
- External US + biopsy
- CT
- MRI
- **^{18}F -FDG PET**

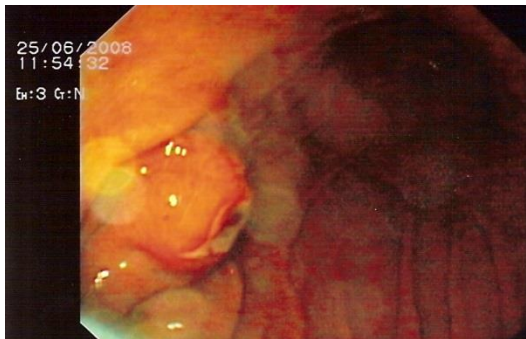
Specific NEN imaging methods

- ^{111}In -Octreotide scintigraphy (obsolete)
- ^{131}I -MIBG scintigraphy (obsolete)
- **^{68}Ga -DOTATOC PET**
- **^{64}Cu -DOTATATE PET**
- ^{18}F -L-DOPA PET (obsolete)
- ^{11}C -5-HTP PET (?)

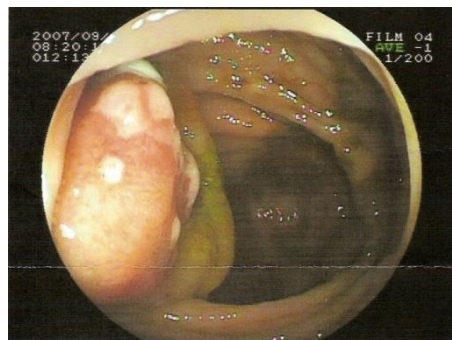
Endoscopy

- Gastroscopy
- Colonoscopy
- Capsule endoscopy
- Endoscopic US (+ FNA)
- Balloon-endoscopy

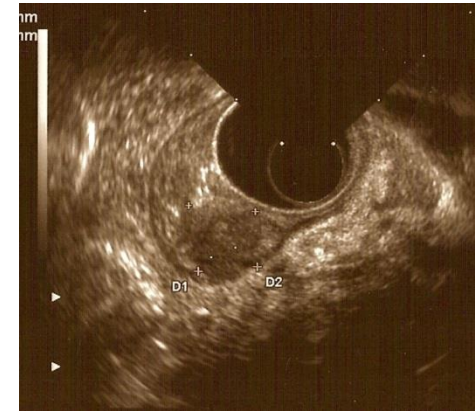
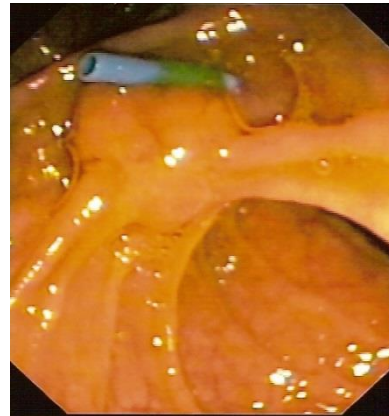
Gastric type III NET



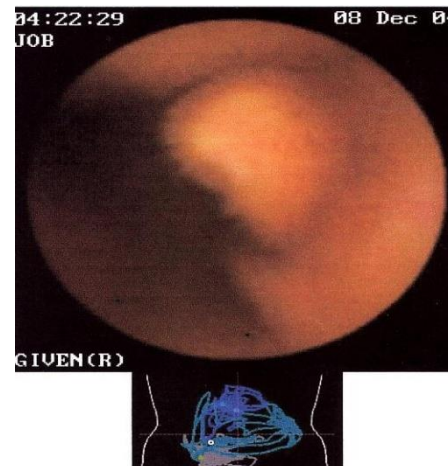
NEC in the coecum



Duodenal somatostatinoma at the ampulla of Vater



Ileal NET (carcinoid)



CT imaging

- 2-3 phase
- multi-slice
- organ dedicated

CT-scan in NEN

Homogeneous arterial enhancement and washout in venous phase

Liver mets. from pancreatic NEN



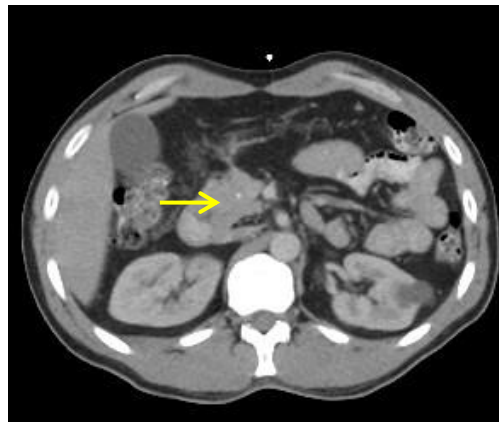
Node mets. from ileal NEN



Pancreatic NEN



Pancreatic insulinoma



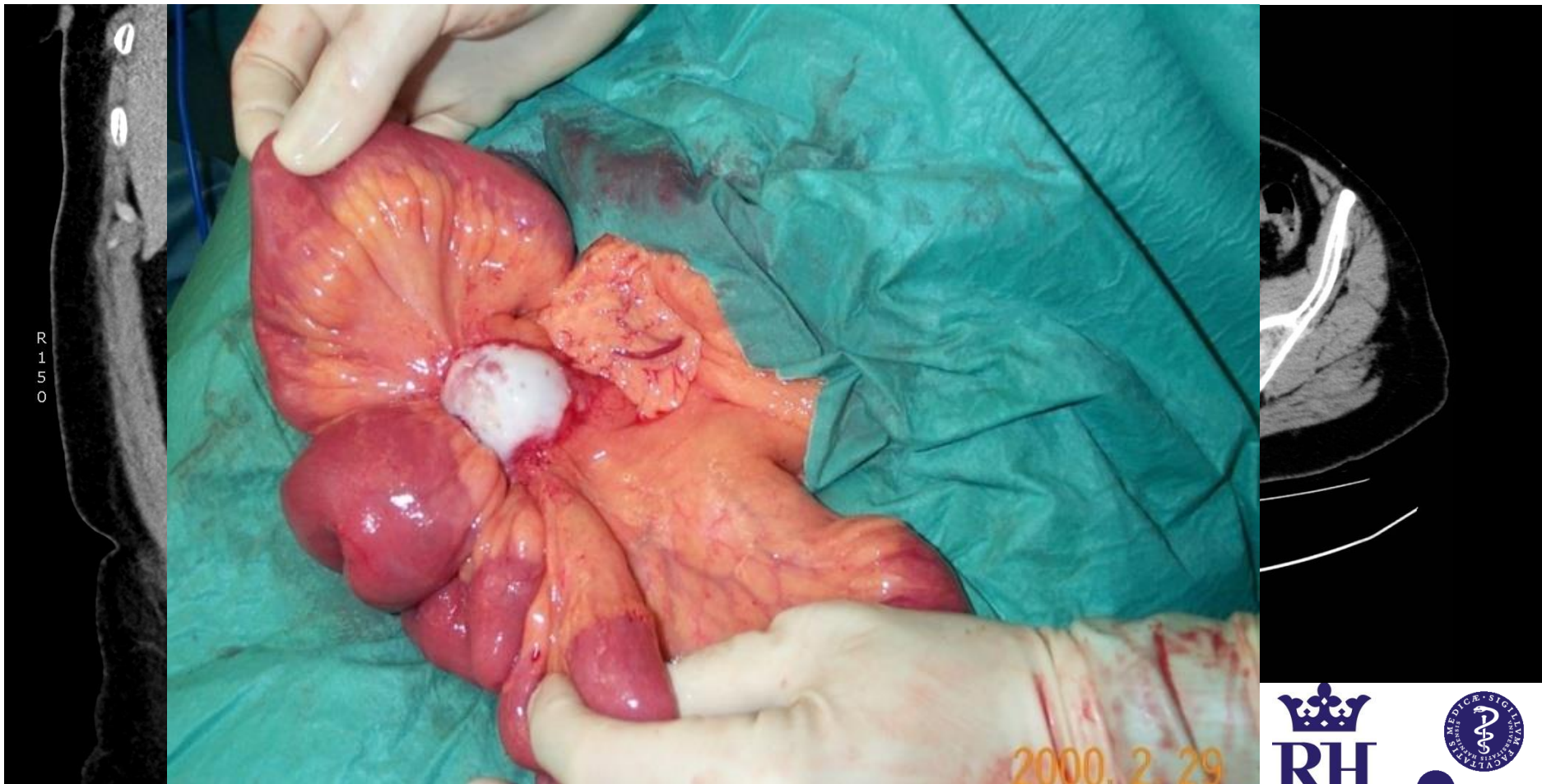
Duodenal gastrinomas



CT imaging

Small intestinal NET and mesenteric node metastases

Mesenteric tumor masses and mesenteric fibrosis: Desmoplastic reaction



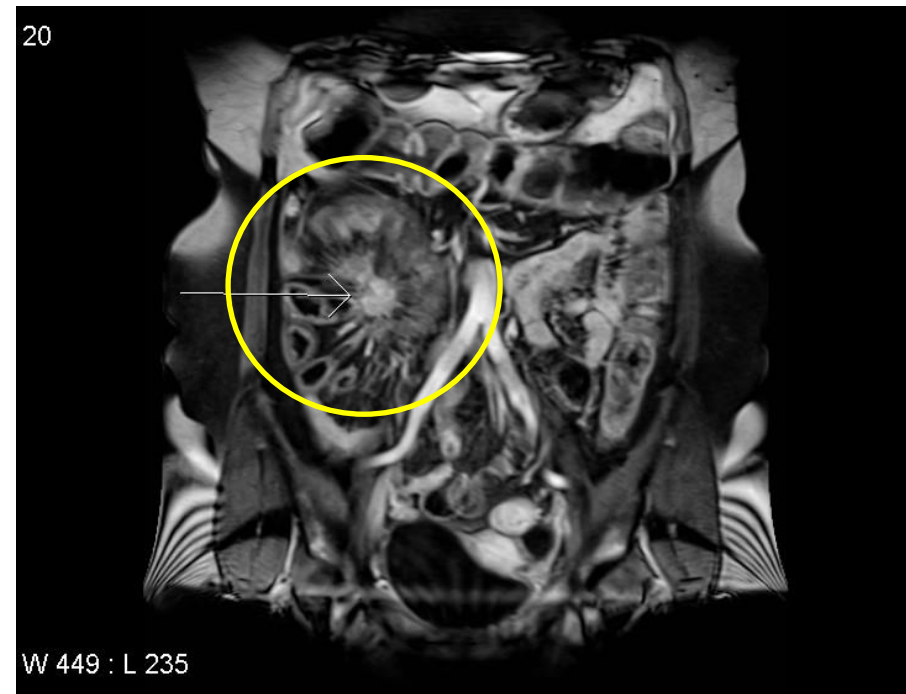
CT imaging

Vascular encasement

due to lymph node metastases and fibrosis at the mesenteric root
causing occlusion of the mesenteric vessels



Arterial encasement
intestinal ischemia

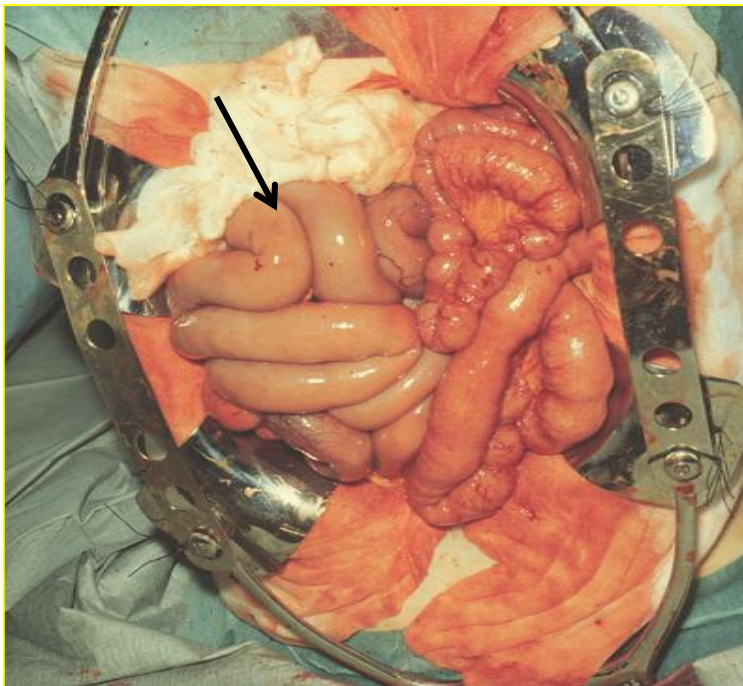


Venous encasement
intestinal edema

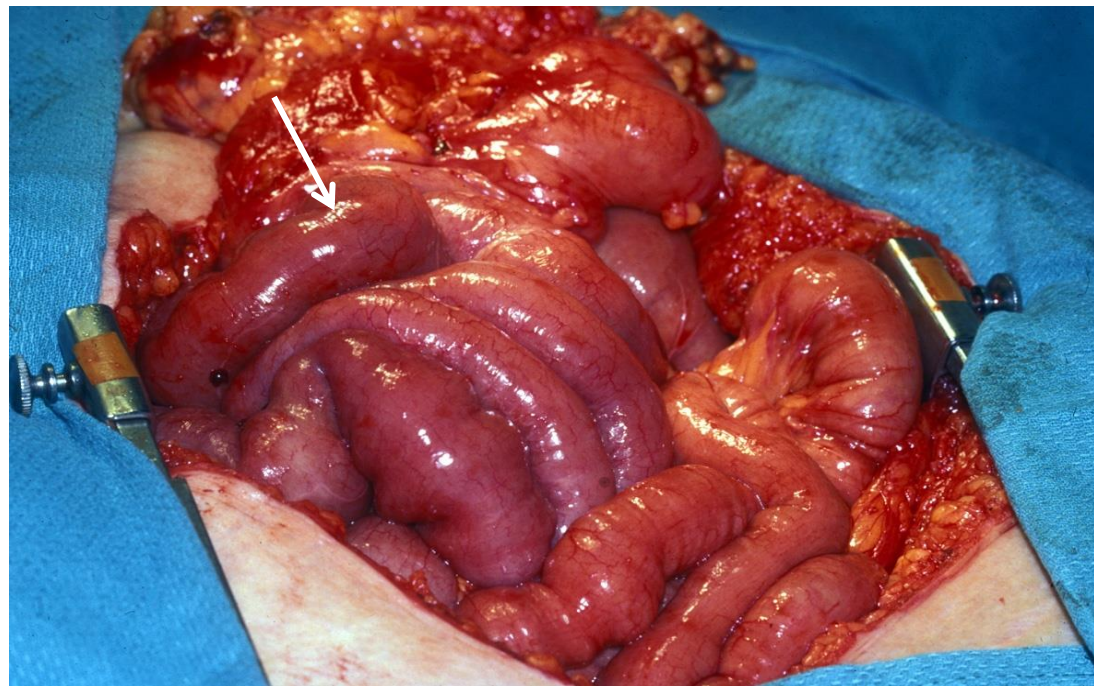
CT imaging

Vascular encasement

due to lymph node metastases and fibrosis at the mesenteric root
causing occlusion of the mesenteric vessels



Arterial encasement
intestinal ischemia



Venous encasement
intestinal edema

MR imaging

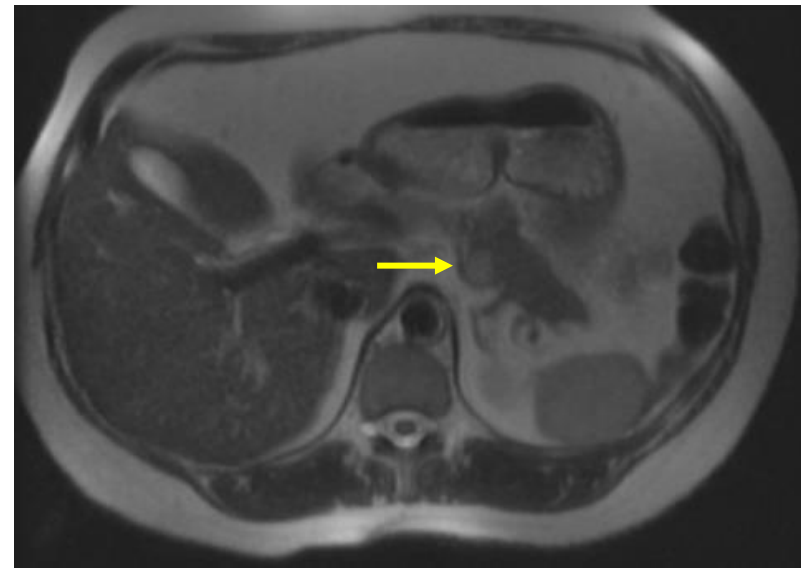
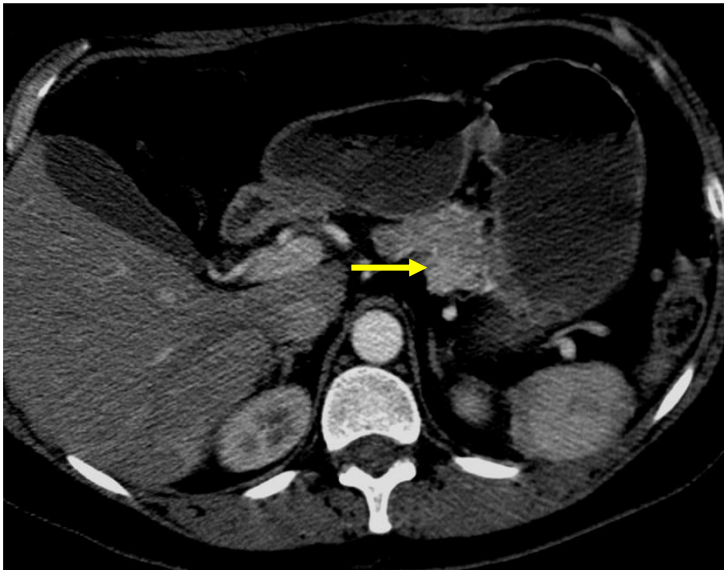
Diffusion or T2-weighted imaging

MRI more sensitive than CT-scan for pancreatic NEN, liver metastases and rectal NEN

But often less available

Indication for use

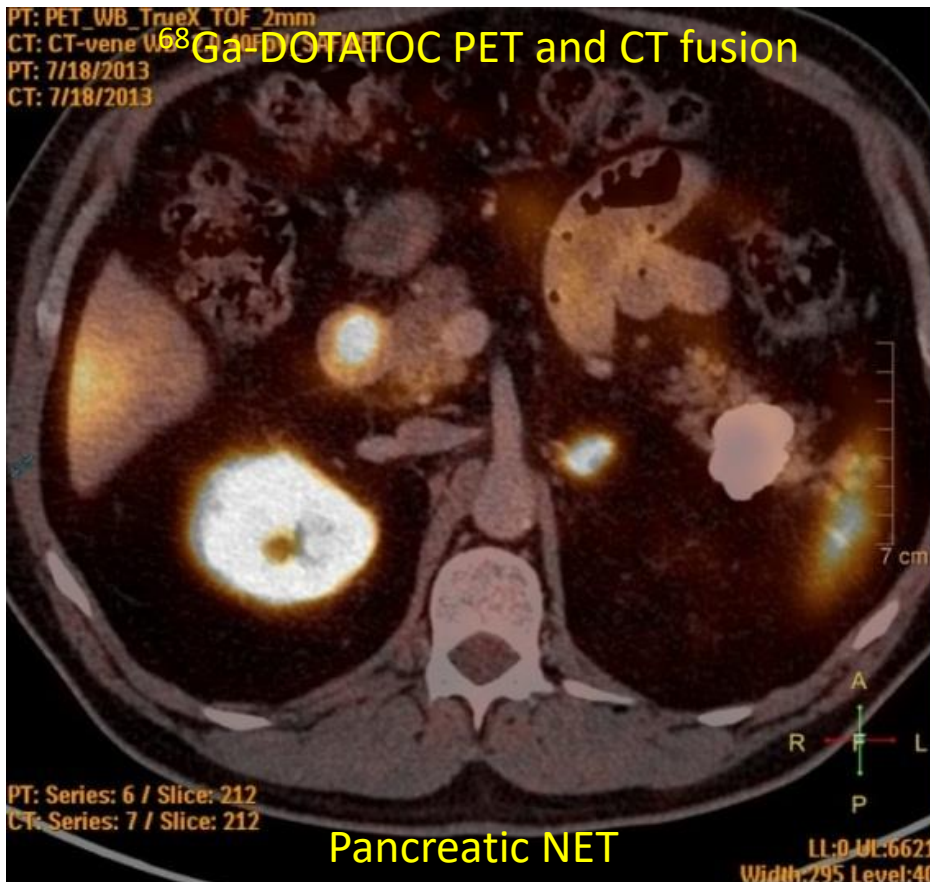
CT inconclusive or negative; planning of hepatic surgery; allergy to contrast media; reduced kidney function; young patients having several scans over years



SRS, US and (CT) negative, but insulinoma localized by MRI

Somatostatin receptor imaging (SRI)

- > 90% of GEP NET express somatostatin SSR-2
- SS-analogs have high affinity for somatostatin SSR-2



Generator generated; Cyclotron not required

Purpose

- Detection of tumor and metastases
- Tumor staging (whole body scan)
- Diagnosis of recurrence
- Eligibility for PRRT
(SUVmax or Krenning scale)

Sensitivity

Dependent on tumor size
and SSR-2 density at tumor

- | | |
|--------------|------|
| • NET | >90% |
| • Insulinoma | <25% |
| • NEC | <50% |

Specificity

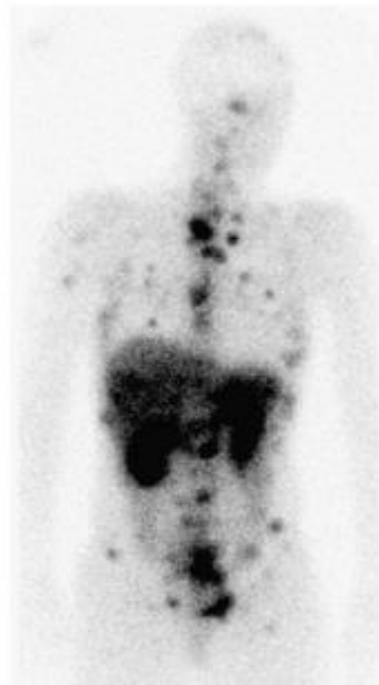
- | | |
|-------|--------|
| • All | 80-90% |
|-------|--------|

Somatostatin receptor imaging (SRI)

^{68}Ga -PET and ^{64}Cu -PET is superior to ^{111}In -Octreotide scintigraphy (SPECT)

^{64}Cu -PET is superior to ^{68}Ga -PET in head-to-head comparison

Prospective head-to-head comparison of 112 NEN



^{111}In -DTPA-octreotide



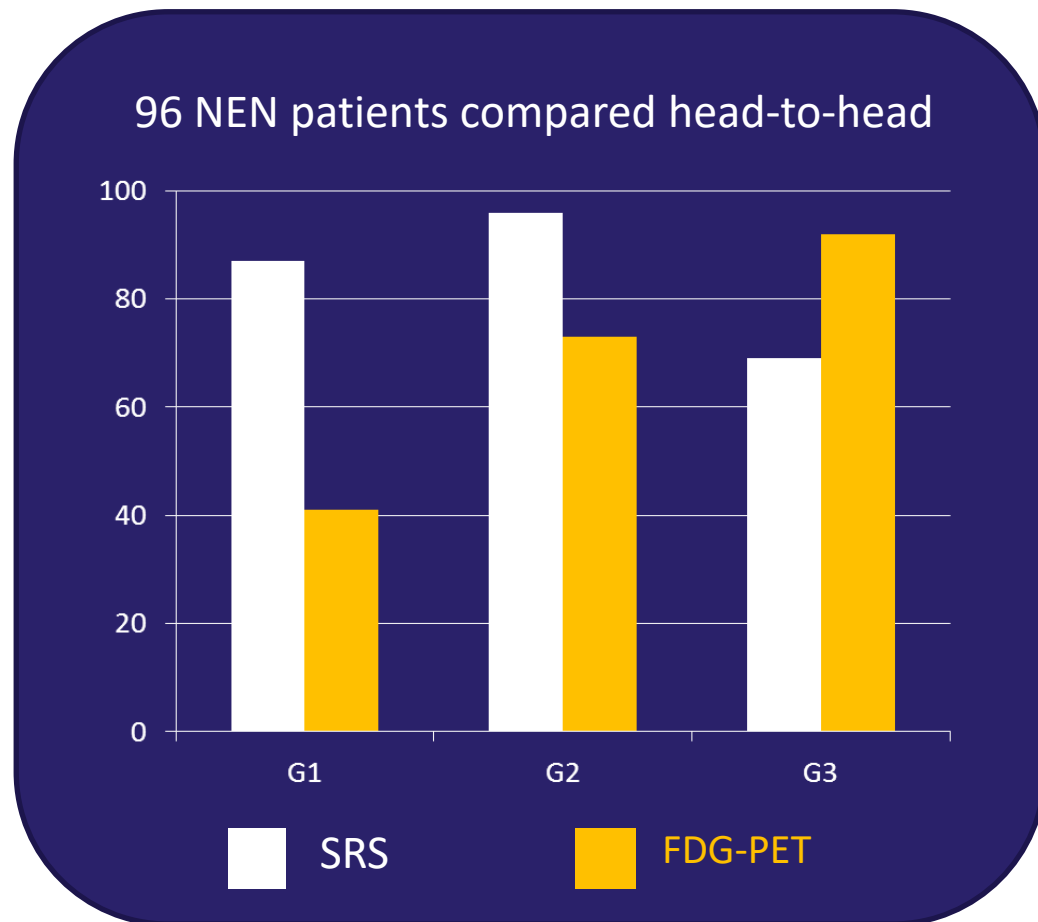
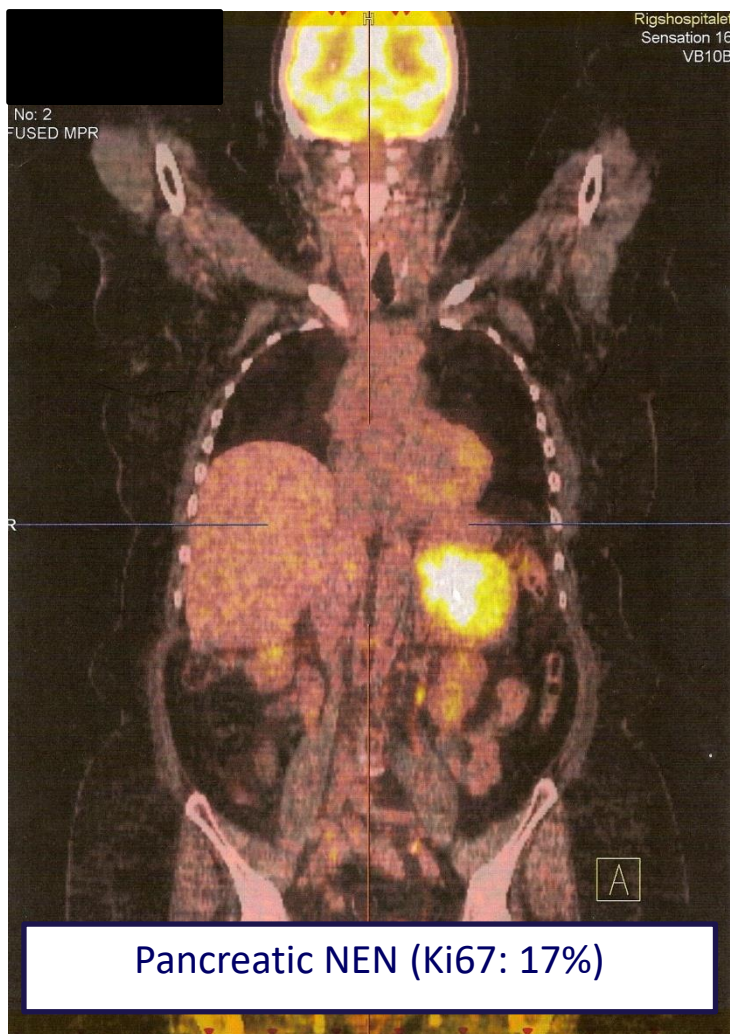
^{64}Cu -DOTATATE

- revealing more foci
- longer half-life
- less radiation

Johnbeck, J Nucl Med 2017;58:451-457

^{64}Cu -PET Cyclotron generated

Pfeifer, J Nucl Med 2013 & 2015;56:847-854

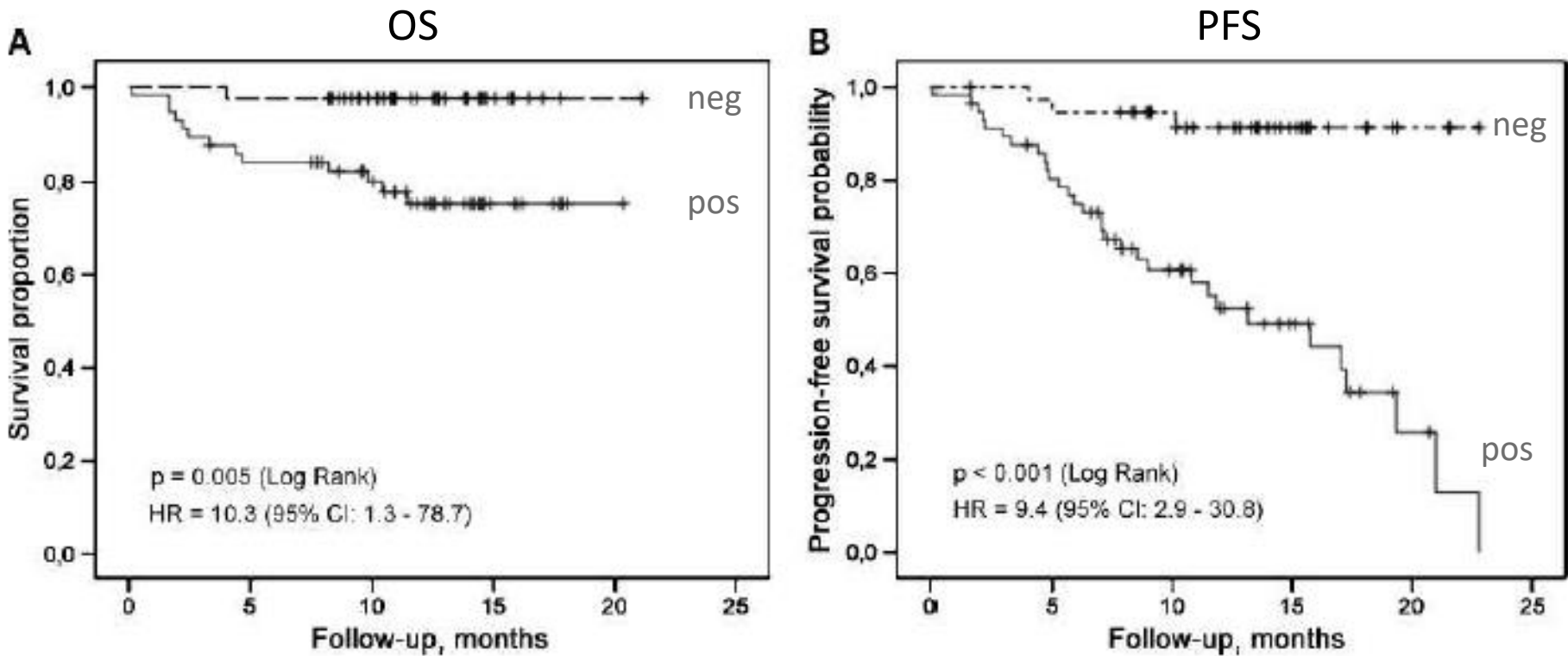
^{18}F -FDG-PET

Binderup, J Nucl Med 2010;51:704-712

^{18}F -FDG-PET as a prognostic marker

OS and PFS based on pos. or neg. FDG-PET (2 years FU)

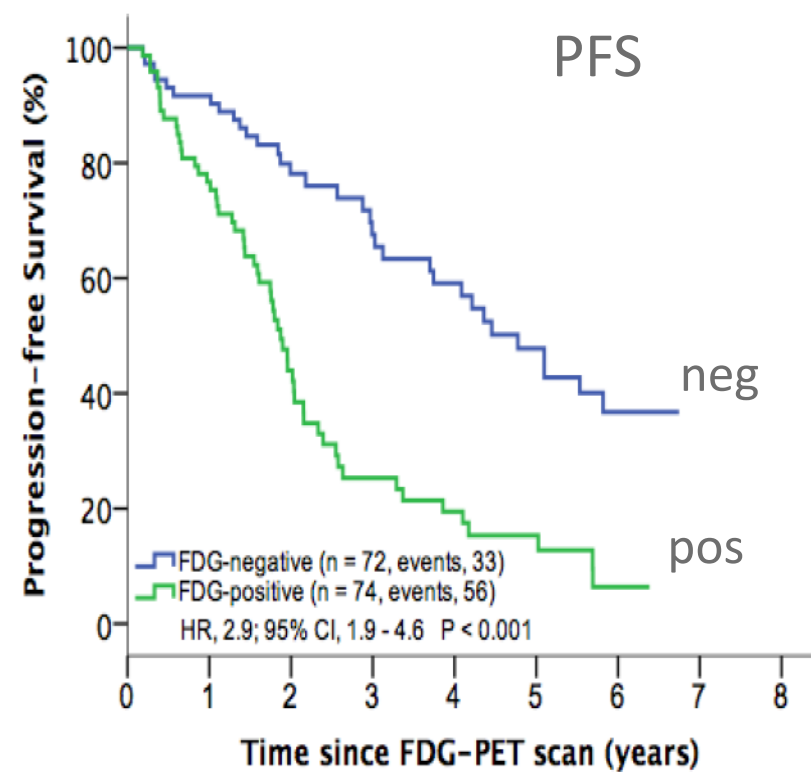
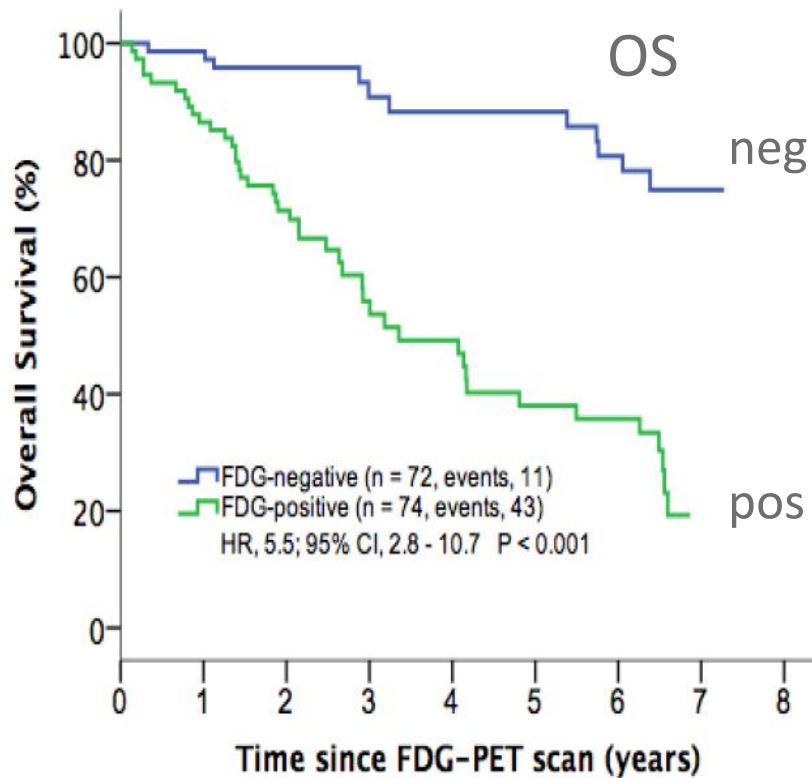
NET G1, NET G2, NET G3 and NEC



^{18}F -FDG-PET as prognostic marker

OS and PFS based on pos. or neg. FDG-PET

NET G1 + G2



Case

Patient opereres for ileus på X-sygehus.

Årsag: Tumor afklemmende tyndtarmen.

Tyndtarmsresektion.

Histologi: Neuroendokrin tumor

Hvad ønsker du af yderligere oplysninger fra patolog?

Hvilke blodprøver ønsker du?

Hvilke andre undersøgelser vil du foretage?

Hvad er vigtigst at du foretager dig?

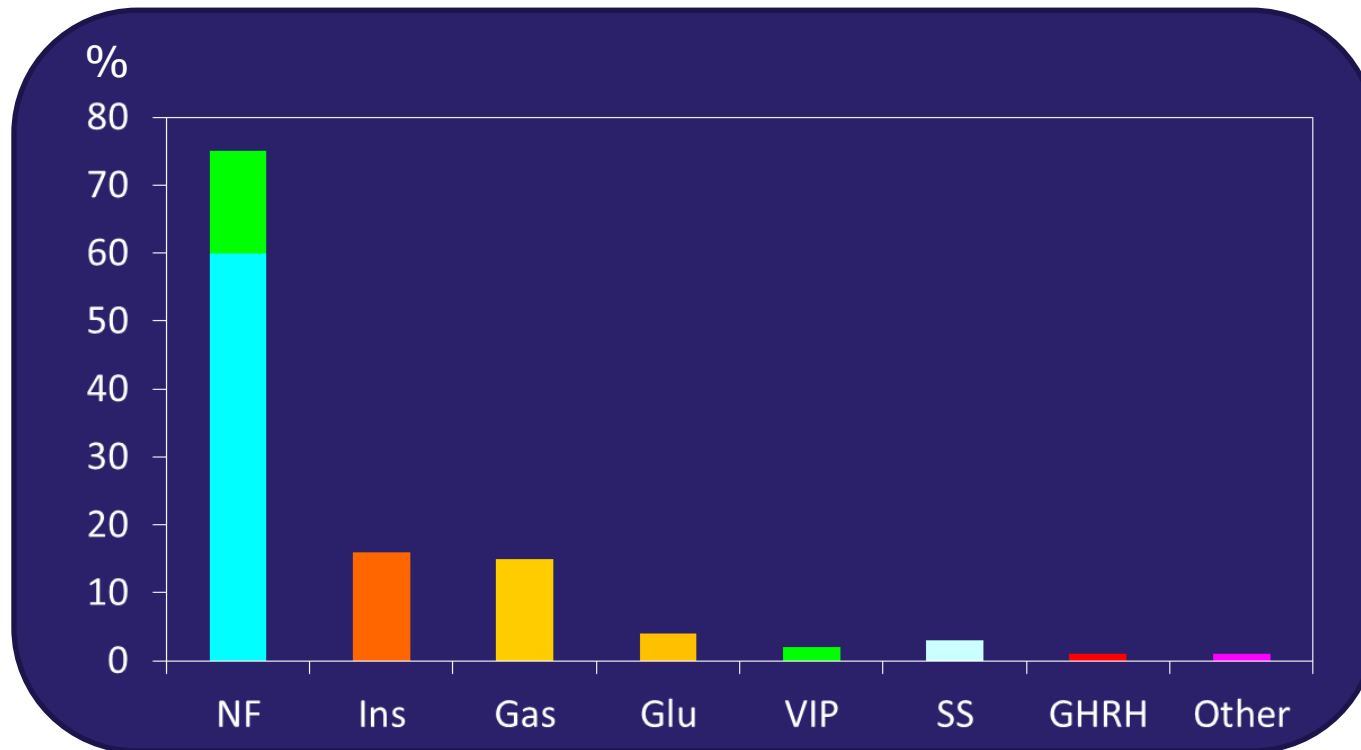
Henvise til NET Center

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)



Neuroendocrine neoplasms of the pancreas (and duodenum)

Etiology

- **80-90 % Sporadic**
- **10-20 % Multiple endocrine neoplasia 1 (MEN-1)**
 - Duodenal gastrinomas and pancreatic NET (multiple)
- **<5 % von Hippel Lindau disease (vHL)**
 - Non-functioning pancreatic NET (>90%)
- **<1% neurofibromatosis type 1 (von Recklinghausen)**
 - Duodenal somatostatinomas

Rare functioning pancreatic NE tumors

Clinical manifestations

- **Glucagonomas**

- necrolytic migratory erythema, stomatitis, glossitis, diabetes
- anemia, fatigue, weight loss, thrombosis, hypoaminoacidemia (zinc)

Somatostatin analog treatment



Non-functioning pancreatic NEN

- 50-60 years, f = m
- 70 - 80% of NE pancreatic tumors
- well to poorly differentiated
- mostly G2 and G3 NEN
- >60% large (>50 mm), aggressive behaviour
- >80% N1 and/or M1 disease at diagnosis
- 5-year survival: 30-65%

Clinical manifestations

- symptoms related to tumor mass and metastases
- none, found by incident

Pancreatic NET incidentalomas

With improved imaging more often hypervascular NET <1-2 cm in size are found by incident

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

Benign behaviour ?

Observation or Resection ?

Tendency toward observation even in younger patients

Resection only if growing or > 2cm

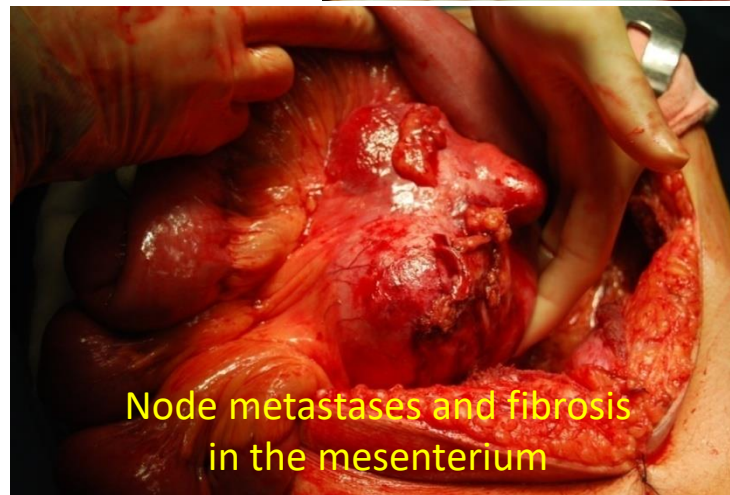
Neuroendocrine neoplasms of the small intestine

Clinical manifestations

Incidence: 1.0 - 1.7 / 100.000 / year

Related to primary tumor

- None
- Abdominal discomfort (for years)
- Diarrhoea
due to partial bowel obstruction or ischemia
- Small bowel obstruction
- Intestinal ischemia or infarction
- Malnutrition
- Gastrointestinal bleeding
- Intussusception
- Abdominal mass



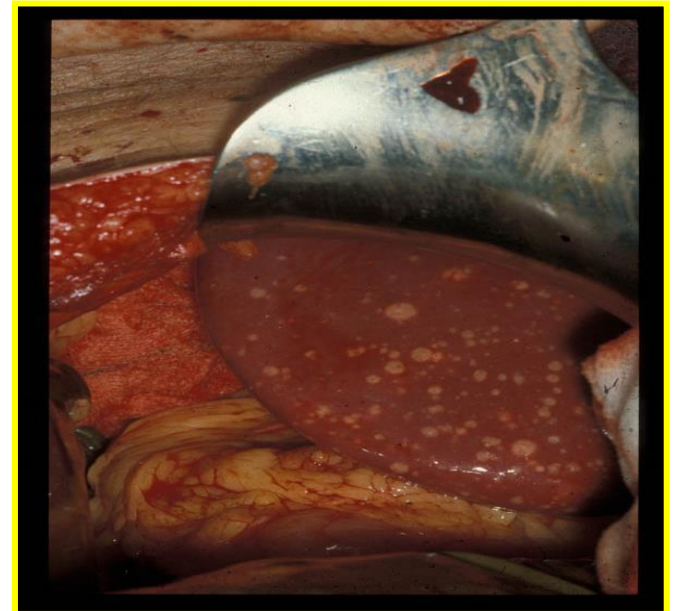
Neuroendocrine neoplasms of the small intestine

Clinical manifestations

Related to metastatic and advanced disease

Carcinoid syndrome

- Incidence: 0.40 - 0.65 / 100.000 / year
- 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



Hvad er carcinoid syndrom ?

Neuroendocrine neoplasms of the small intestine

Carcinoid syndrome

Clinical manifestations

Vasomotor symptoms (90%)

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

Right-sided heart failure (<15%)

- Endocardial fibrosis
- Pulmonary stenosis
- Tricuspid insufficiency
- Tricuspid stenosis
- Mostly both valves are affected

Increased intest. motility (80%)

- Diarrhoea
- Borborygmia
- Abdominal pain

Bronchial constriction (<10%)

- Astma

**Øget svedtendens er ikke
en del af carcinoid syndrom**

Neuroendocrine neoplasms of the small intestine

Carcinoid syndrome

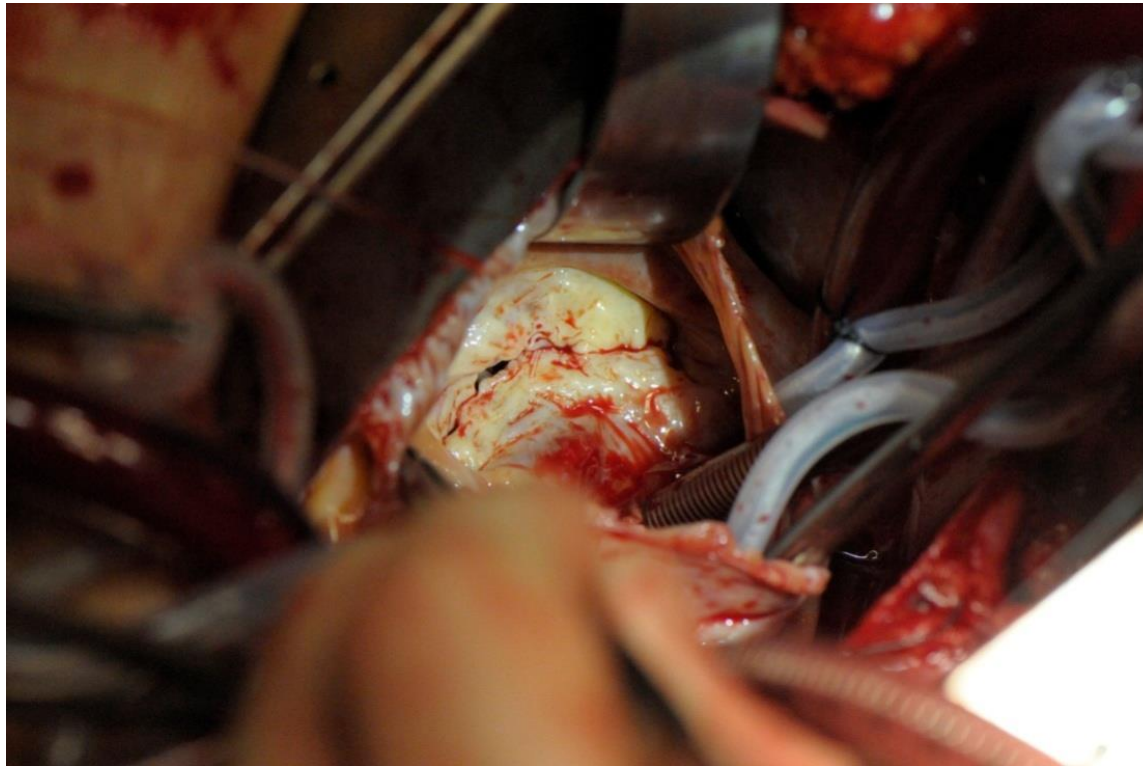
Facial flushing



Neuroendocrine neoplasms of the small intestine

Carcinoid syndrome

Tricuspid valve fibrosis and insufficiency



- echocardiography
- plasma Pro-BNP

Take home message

Alle NEN skal henvises til NET Center

Øget svedtendens er ikke et symptom på NET og bør ikke medføre en bestemmelse af p Chromogranin A

P Chromogranin A kan/må ikke anvendes til screening for NET med mindre der er stærke indicier for NET (pos CT, MRI mv.)

p CgA skal udgå af “rutine diagnostiske blodprøveskemaer” på diagnostiske enheder, endokrinologiske og gastroenterologiske afd.

Hvis der skal foretages p 5-HIAA bestemmelse bør pt. informeres om føderestriktioner



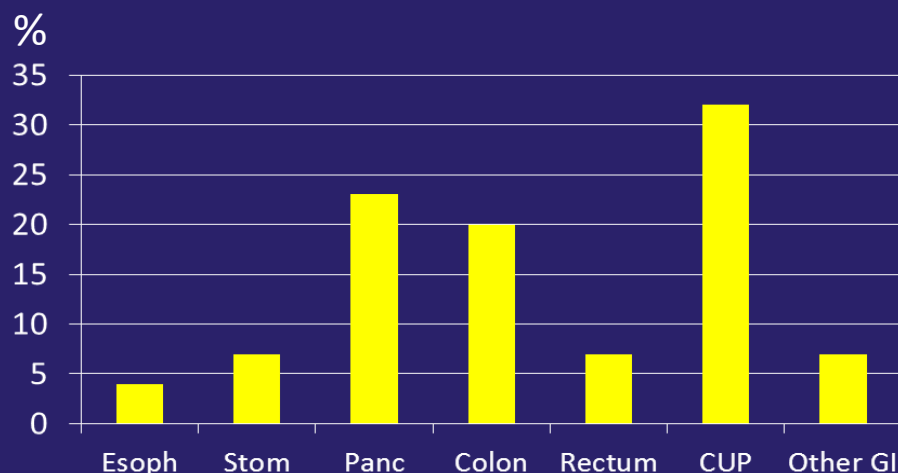
Neuroendocrine Carcinomas G3

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

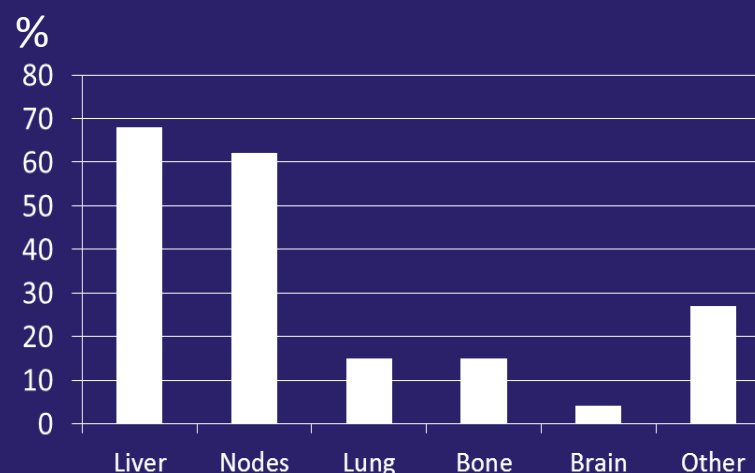
Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

Period
2000-2009

H. Sorbye^{1*}, S. Welin^{2,†}, S. W. Langer^{3,†}, L. W. Vestermark⁴, N. Holt⁵, P. Osterlund⁶, S. Dueland⁷, E. Hofslø⁸, M. G. Guren⁹, K. Ohrling¹⁰, E. Birkemeyer¹¹, E. Thiis-Evensen¹², M. Biagini¹³, H. Gronbaek⁵, L. M. Soveri⁶, I. H. Olsen¹⁴, B. Federspiel¹⁵, J. Asmus¹⁶, E. T. Janson^{2,‡} & U. Knigge^{14,‡}



Primary site



Metastases

original article

Annals of Oncology 24: 152–160, 2013
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305例进展期胃肠道神经内分泌癌 (WHO G3) 患者治疗和生存的预测及预后因素: NORDIC NEC研究

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. Vestermark⁴, N. Holt⁵, P. Osterlund⁶, S. Dueland⁷, E. Hofslø⁸, M. G. Guren⁹, K. Ohrling¹⁰, E. Birkemeyer¹¹, E. This-Evensen¹², M. Biagini¹³, H. Gronbaek⁵, L. M. Soveri⁸, I. H. Olsen¹⁴, B. Federspiel¹⁵, J. Assmus¹⁶, E. T. Janson^{2,†} & U. Knigge^{14,‡}

¹Department of Oncology, Haukeland University Hospital, Bergen, Norway; ²Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ³Department of Oncology, Rigshospitalet, University of Copenhagen; ⁴Department of Oncology, Odense University Hospital, Odense; ⁵Department of Oncology and Medical V, Aarhus University Hospital, Aarhus, Denmark; ⁶Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; ⁷Department of Oncology, Oslo University Hospital, Radium Hospital, Oslo; ⁸Department of Oncology, St Olavs Hospital, University of Trondheim, Trondheim; ⁹Department of Oncology, Ullevål Hospital, Oslo University Hospital, Oslo, Norway; ¹⁰Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; ¹¹Department of Oncology, Stavanger University Hospital, Stavanger; ¹²Department of Gastroenterology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; ¹³Department of Pathology, Odense University Hospital, Odense; Departments of ¹⁴Surgery C; ¹⁵Pathology, Rigshospitalet, University of Copenhagen, Denmark; ¹⁶Center for Clinical Research, Haukeland University Hospital, Bergen, Norway

曹彦硕 译 王晰程 审校

背景: 由于胃肠道神经内分泌癌 (WHO G3) (GI-NEC) 相关研究有限, 我们回顾性分析了相关临床资料, 以期明确进展期GI-NEC患者的预测及预后标志物。

患者与方法: 回顾性收集2000~2009年在12家北欧医院诊断为进展期GI-NEC患者的数据。

结果: 252例接受姑息性化疗的患者中位生存期为11个月, 53例仅接受最佳支持治疗 (BSC) 的患者中位生存期为1个月。一线化疗的缓解率达31%, 且33%的患者获得疾病稳定。通过受试者操作特征 (ROC) 分析, 将Ki-67<55%视为与缓解率相关的最佳临界值。与Ki-67≥55%的患者相比, Ki-67<55%的患者缓解率较低 (15% vs 42%, $P<0.001$), 但总生存期较长 (14个月 vs 10个月, $P<0.001$)。铂类方案未影响患者的缓解率或生存结局。生存结局最重要的不良预后因素包括较差的体力状态 (PS)、原发性结直肠肿瘤以及血小板或乳酸脱氢酶 (LDH) 水平升高。

结论: 进展期GI-NEC患者应立即考虑接受化疗。体力状态、原发性结直肠肿瘤以及血小板或LDH水平升高是生存的预后因素。Ki-67<55%的患者对于以铂类为基础的化疗缓解率较低, 但生存期更长。研究数据表明, 也许不能将所有的GI-NEC作为一种单一的疾病来考虑。

关键词: 化疗, 胃肠道肿瘤, 神经内分泌癌, 神经内分泌肿瘤, 预测因素, 预后因素

*Correspondence to: Prof. H. Sorbye, Department of Oncology, Haukeland University Hospital, 5021 Bergen, Norway. Tel: +47 55972010; Fax: +47 55972046; E-mail: halfdan.sorbye@helse-bergen.no

[†]Shared second authorship.

[‡]Shared last authorship.

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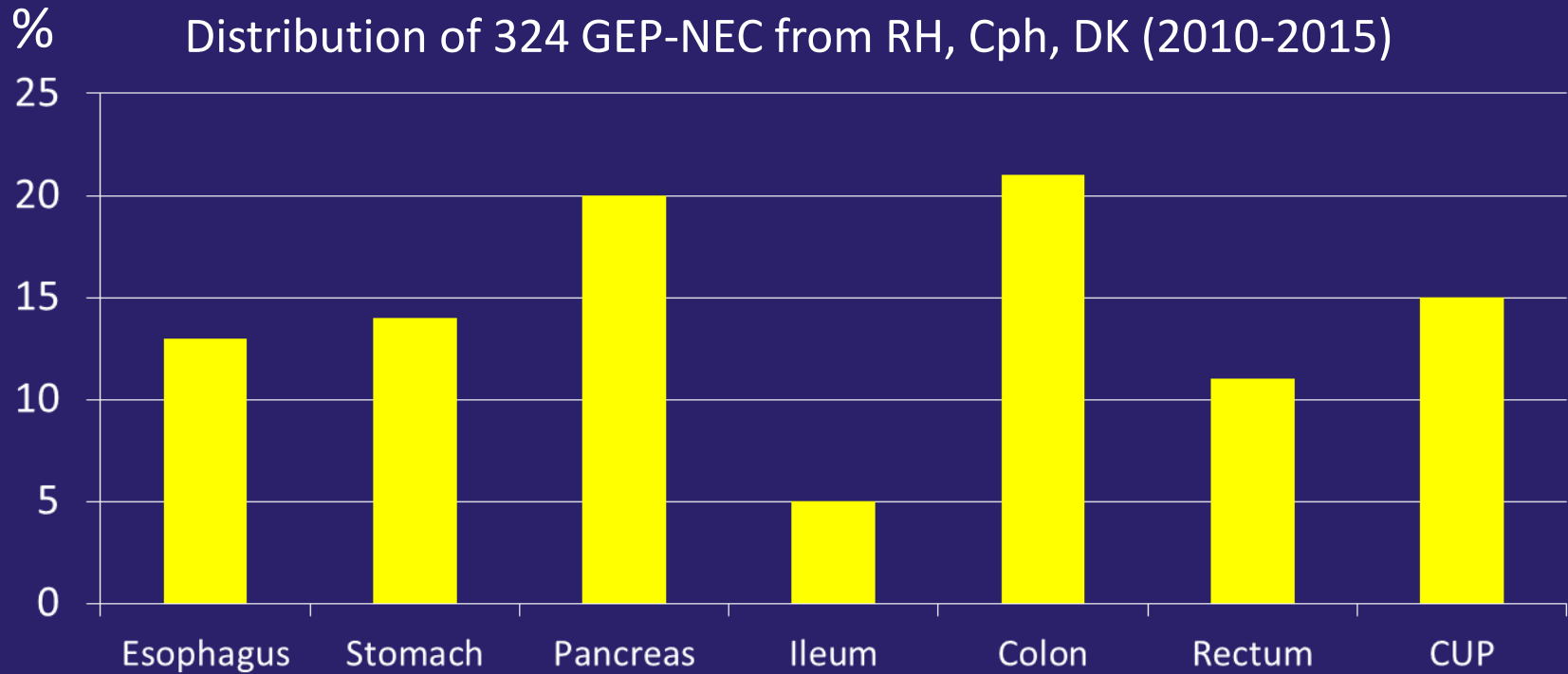
引言

肺外神经内分泌癌 (NEC) 最常见于胃肠道^[1,2], 在高达30%的病例中无法明确原发肿瘤部位^[3]。以前将这些肿瘤



Neuroendocrine Carcinomas G3

2010-15 RH, yearly incidence of NEC: app. 2.16/100.000.



Hvad er den mediane overlevelse for metastaserende GEP-NEC ?

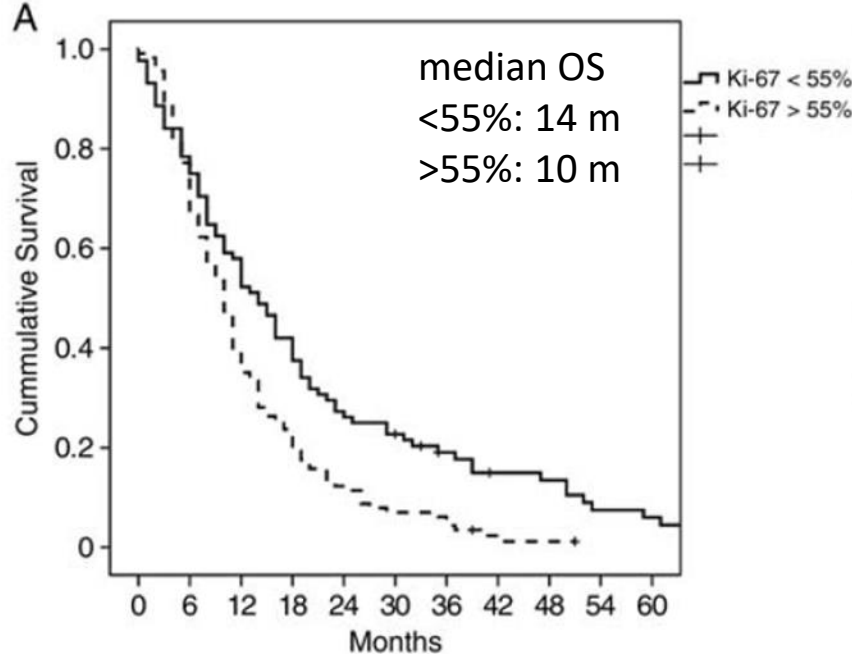
Neuroendocrine Carcinomas G3

1. line chemotherapy: Etoposide + Cis-/Carboplatin

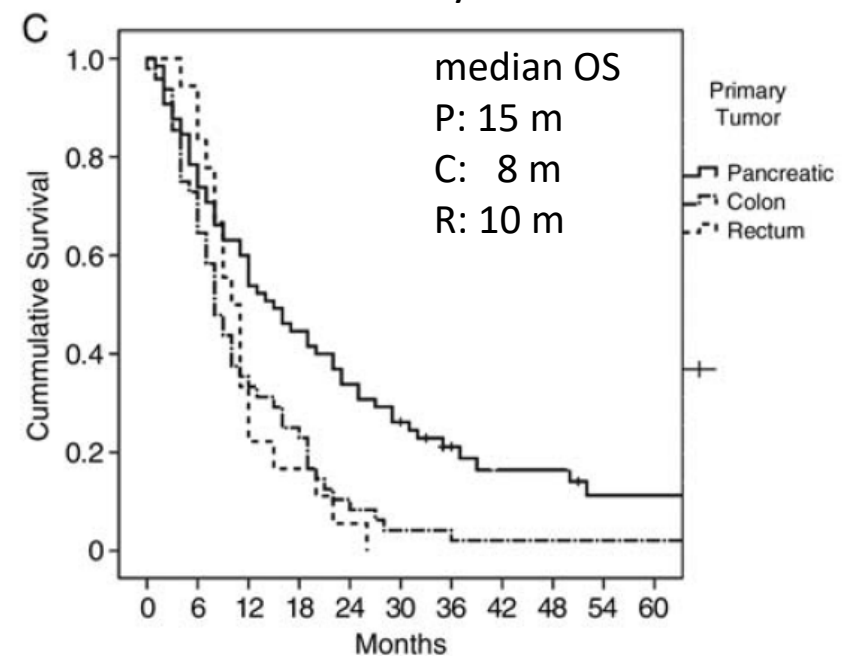
PFS: 4 months

OS: 11 months

Ki67 index



Primary



If untreated – OS: 1 month

Bør kirurgi overvejes ved NET G3 and NEC ?

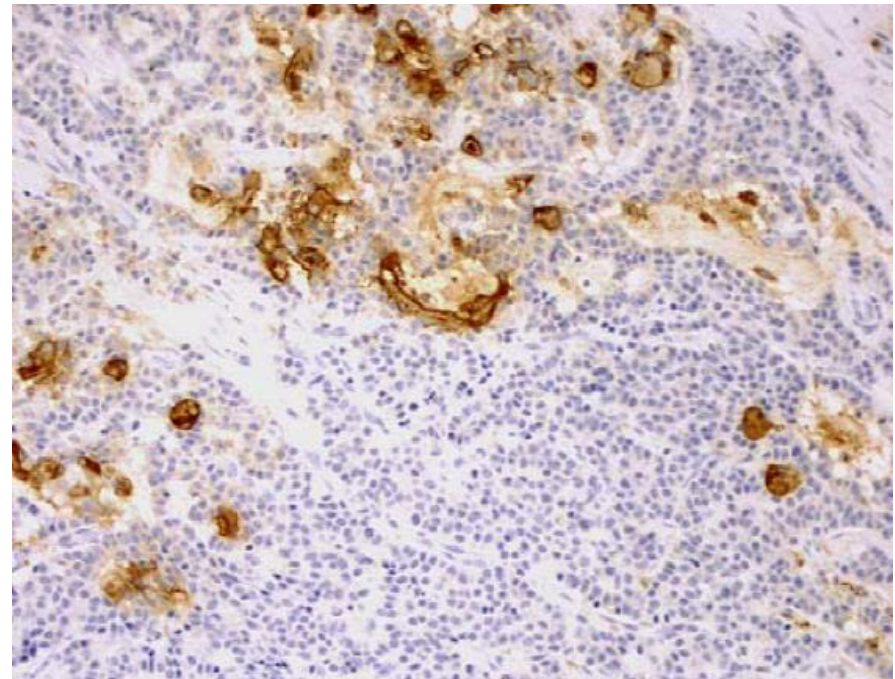
og i så fald til hvilke patienter ?

“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

MiNEN (mixed neuroendocrine non-neuroendocrine carcinomas) MANEC (mixed adeno-neuroendocrine carcinomas)

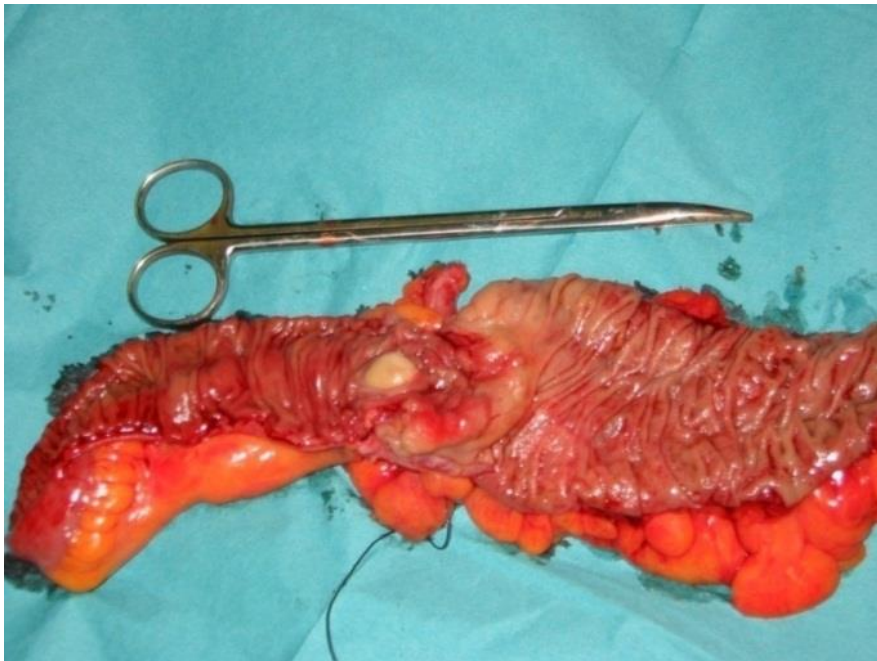
- > 30% of each component – Ki67 >20% in NEC component
- Seen with increased frequency
- Primary tumor
 - Esophagus
 - Stomach
 - Colon-Rectum
 - Pancreas
- Metastases from one or both components
 - frequent at diagnosis
 - may develop at follow-up
- Adenocarcinomas with neuroendocrine differentiation



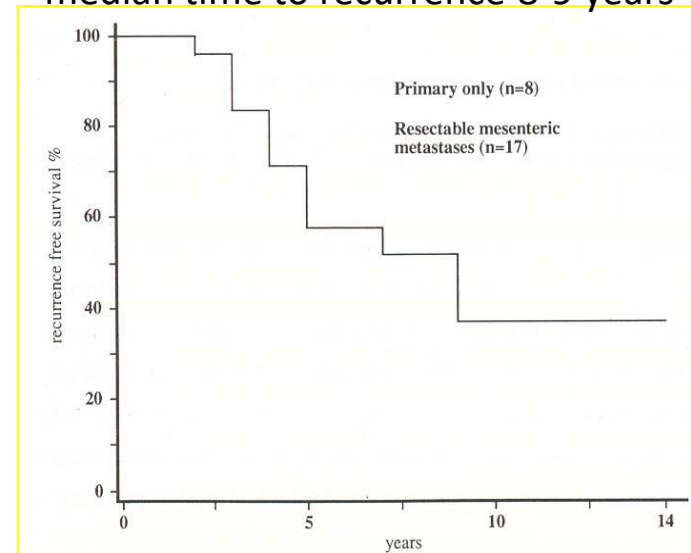
Treatment – Surgery in NEN

Surgery is the only curative treatment

- Surgery should always be considered as first line therapy; at diagnosis and at recurrence – even in NEC G3 and MiNEN

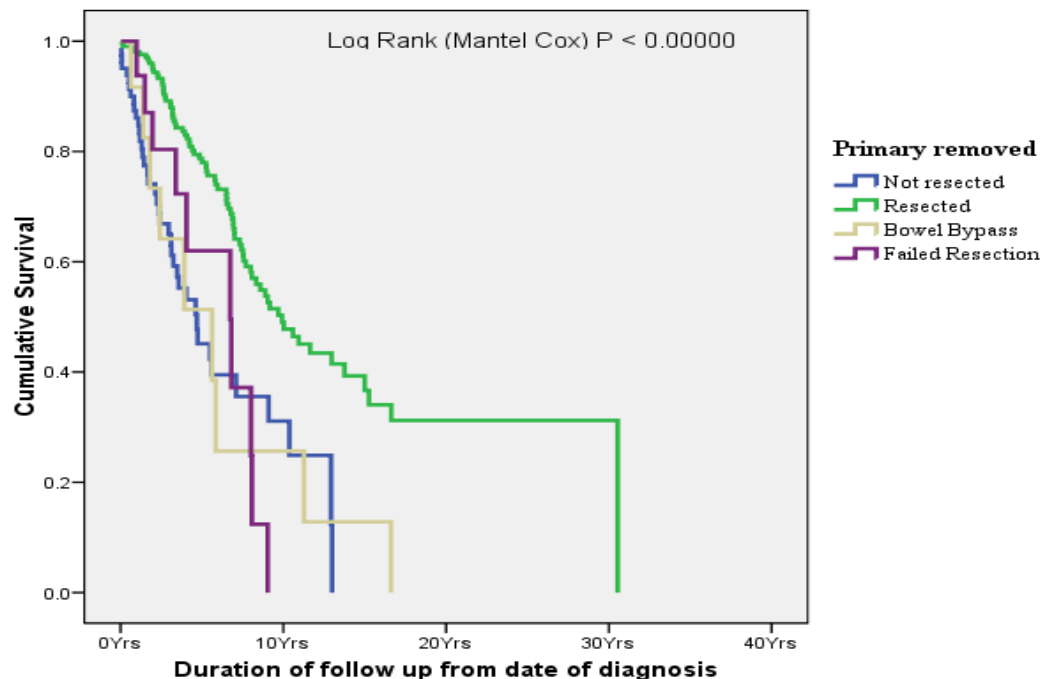


In pts. considered radically operated, tumor recurs in many median time to recurrence 8-9 years



Treatment – Surgery for NEN

- Pancreatic NET: T4, N1, M1 stage or involvement of portal or mesenteric vessels does not exclude surgery - if R0/R1 resection can be obtained
- pNET <1-2 cm (MEN-1, VHL): no surgery, but close surveillance in selected cases
- Small intestinal NET: Resection of the primary and mesenteric metastases should be considered, even in the presence of liver metastases to prevent bowel obstruction (and prolong survival ?)



Retrospective studies

BIAs

”the best pts. are operated”

Treatment – Surgery for NEN

Neuroendocrine liver metastases

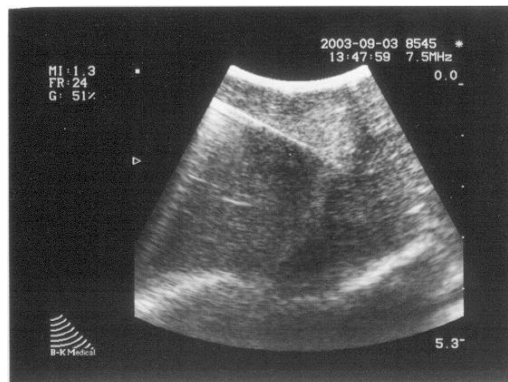
Indications

- Curative intent (possible in <10 %)
- Palliative intent - debulking (possible in 10 %)
 - reduce hormone related symptoms
 - reduce local pain
 - prolong survival

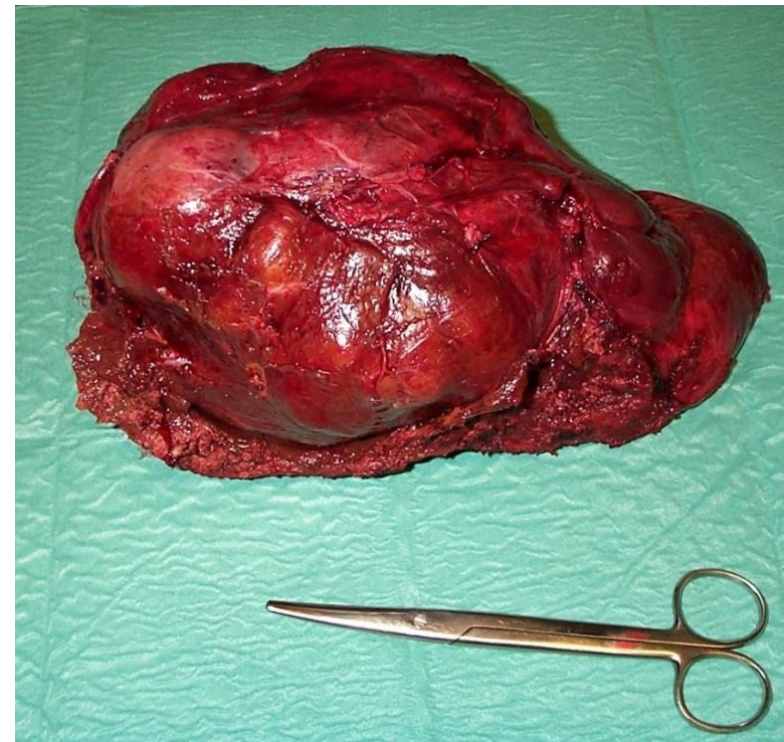
Effect of treatment

- Symptom relief: >90%
- Tumor recurrence/progression: 90%
- Prolong median OS: 50-95 months

RFA



Right hemihepatectomy



Rigshospitalets NET Center

Rigshospitalets NET-Center blev i december 2009
Internationalt akkrediteret og certificeret som Centre of Excellence
af the European Neuroendocrine Tumor Society (ENETS) og GSG
blandt de første 6 NET-centre i Europa

Royal Free Hospital, London
Erasmus Univ. MC., Rotterdam
Hospital Beaujon, Paris

University Hospital, Uppsala
Charité Hospital, Berlin
Rigshospitalet, København



International re-akkreditering og re-certificering as CoE 2012, 2015 og 2018