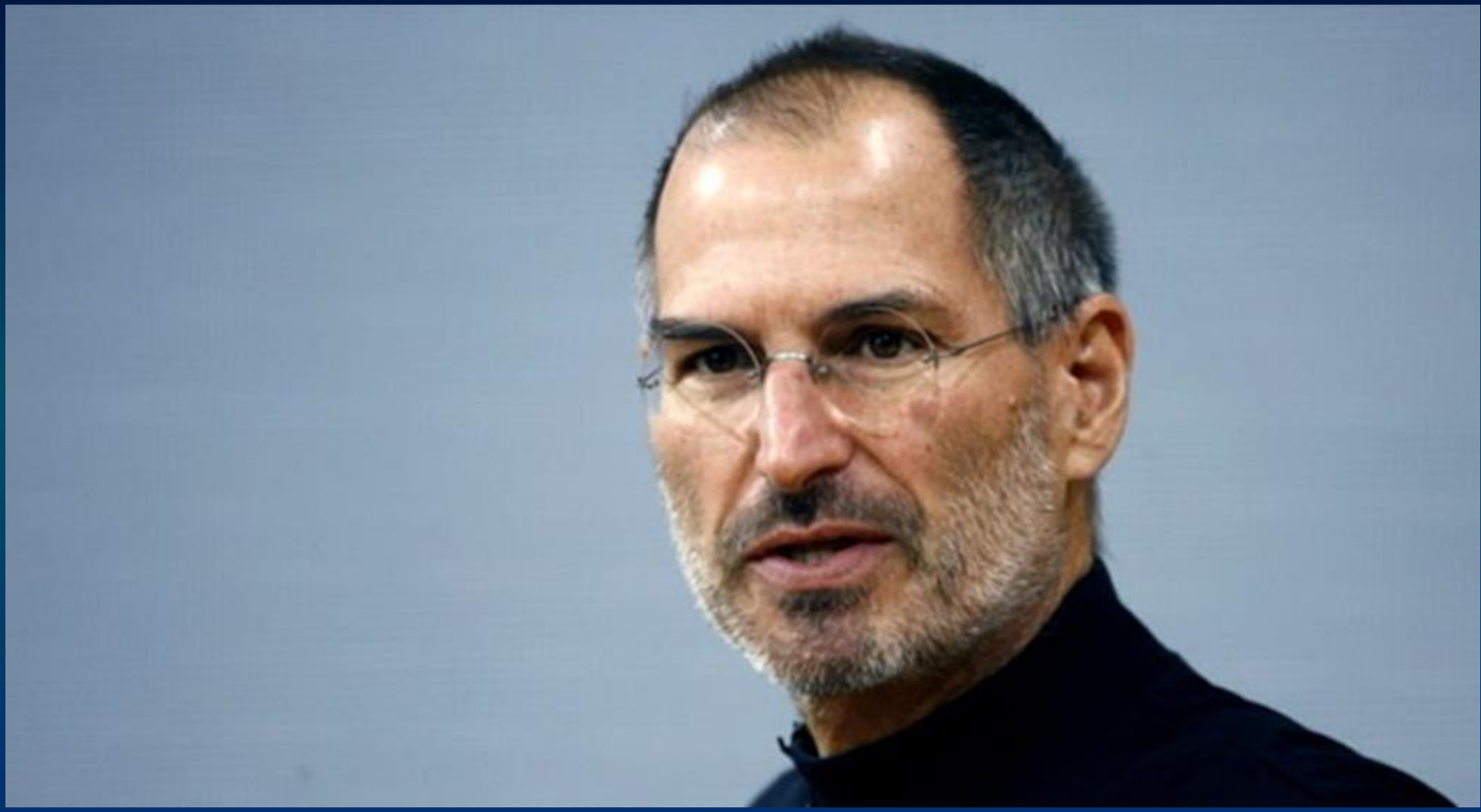
Nevroendokrin sykdom i tarm

Halfdan Sørbye, prof
Kreftavdelingen
Haukeland Univ sykehus
Bergen



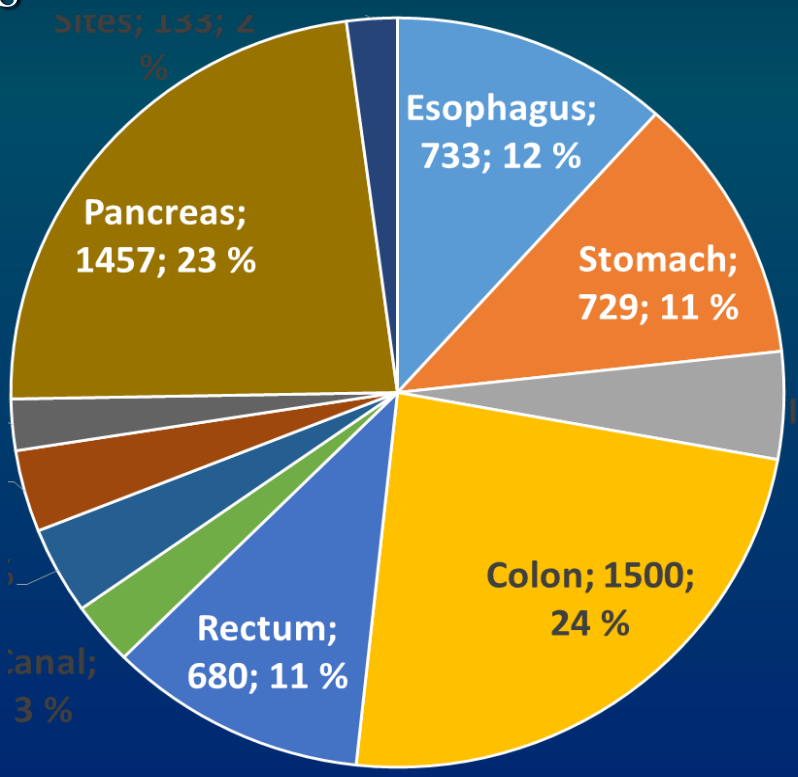
Nomenklatur

- NEN= neuroendokrine neoplasmer (alle)
- NET=neuroendokrin tumor (høyt differensiert)
- NEC= nevroendocrint carcinom (lavt differensiert)

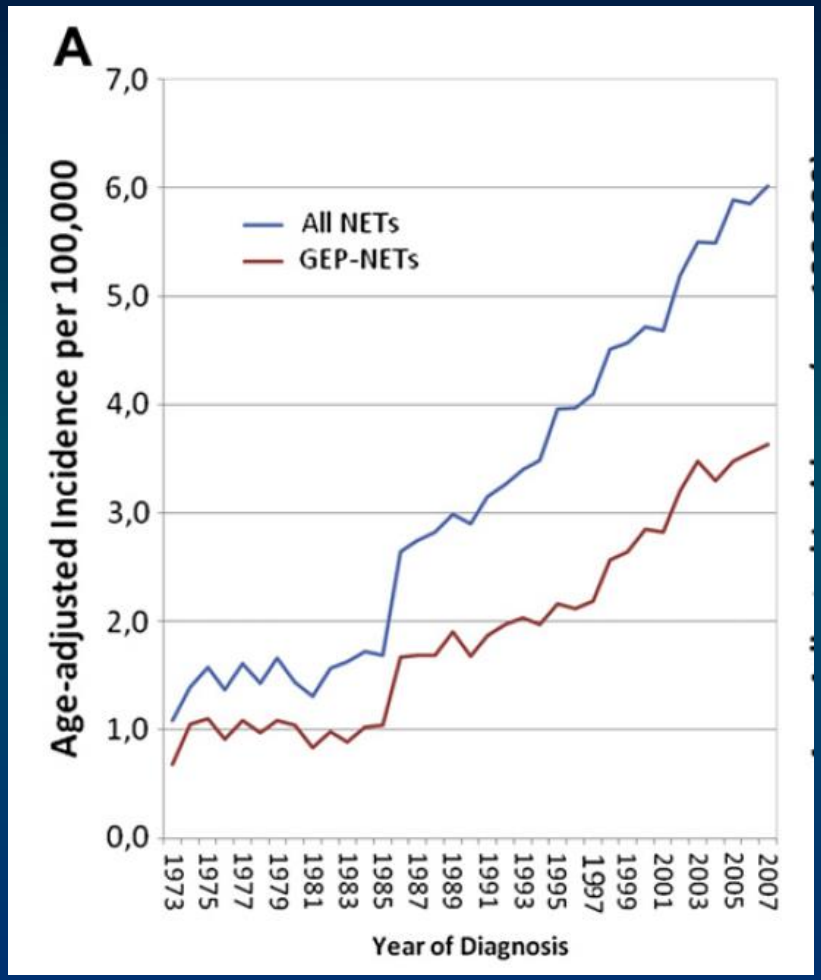
- Carcinoid begrepet prøver man å unngå å bruke
  - SI-NET, pan-NET

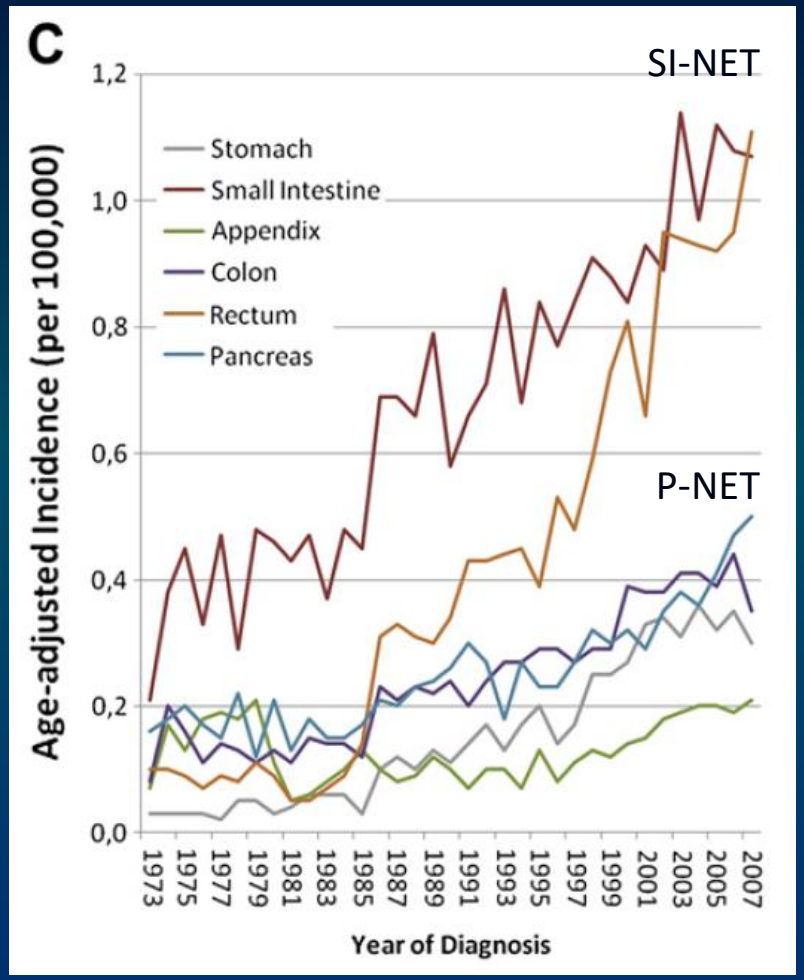
Nevroendocrine kreftsykdom

- Kan forekomme i alle organ
- Gastrointestinalt vanlig
  - NET (kaukasus) vanligst i rectum (polypper), tynntarm og pancreas
  - NEC: alle



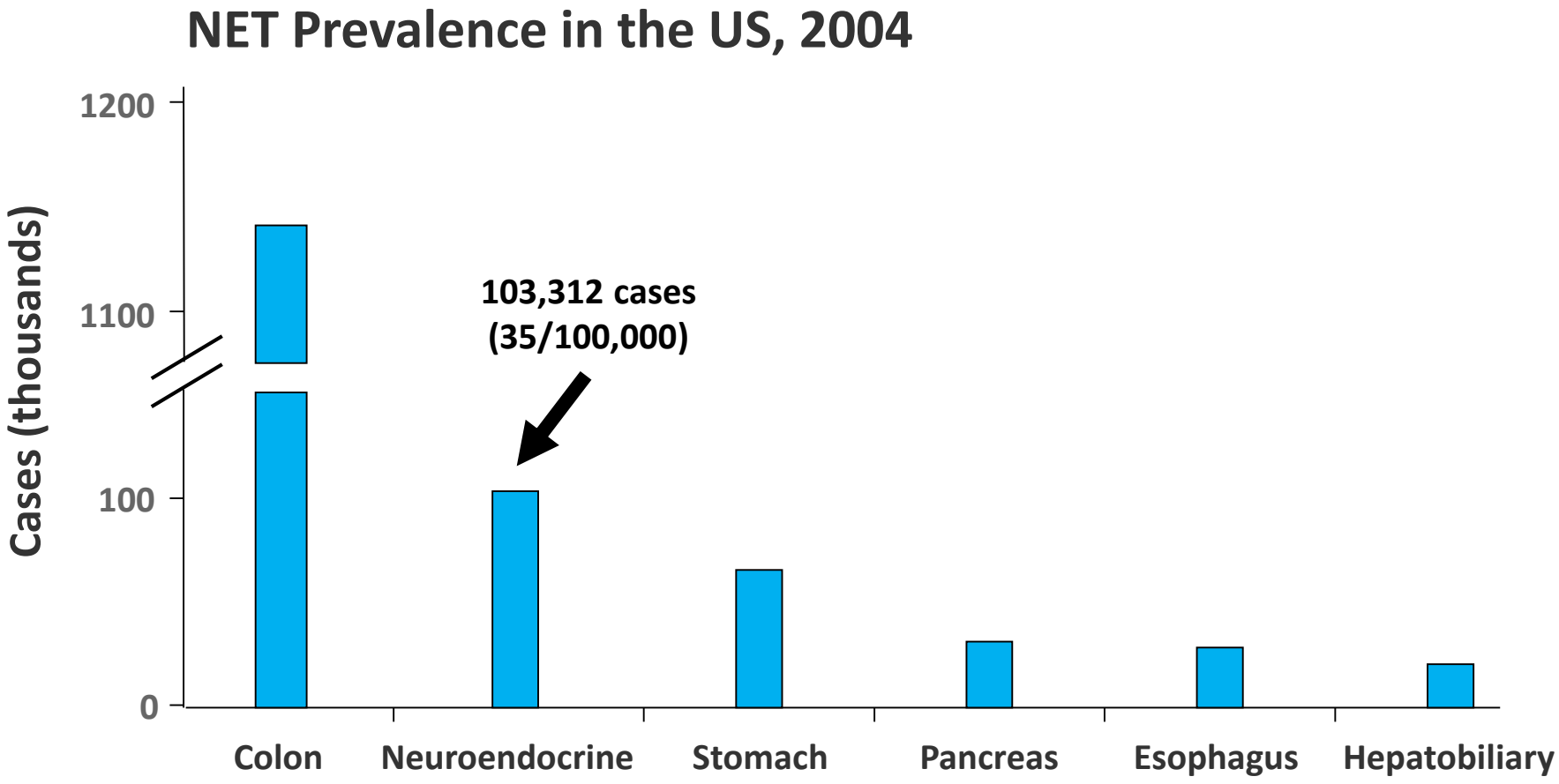
Epidemiology: Incidence





Lawrence, Endocrinol Metab Clin N Am 2011

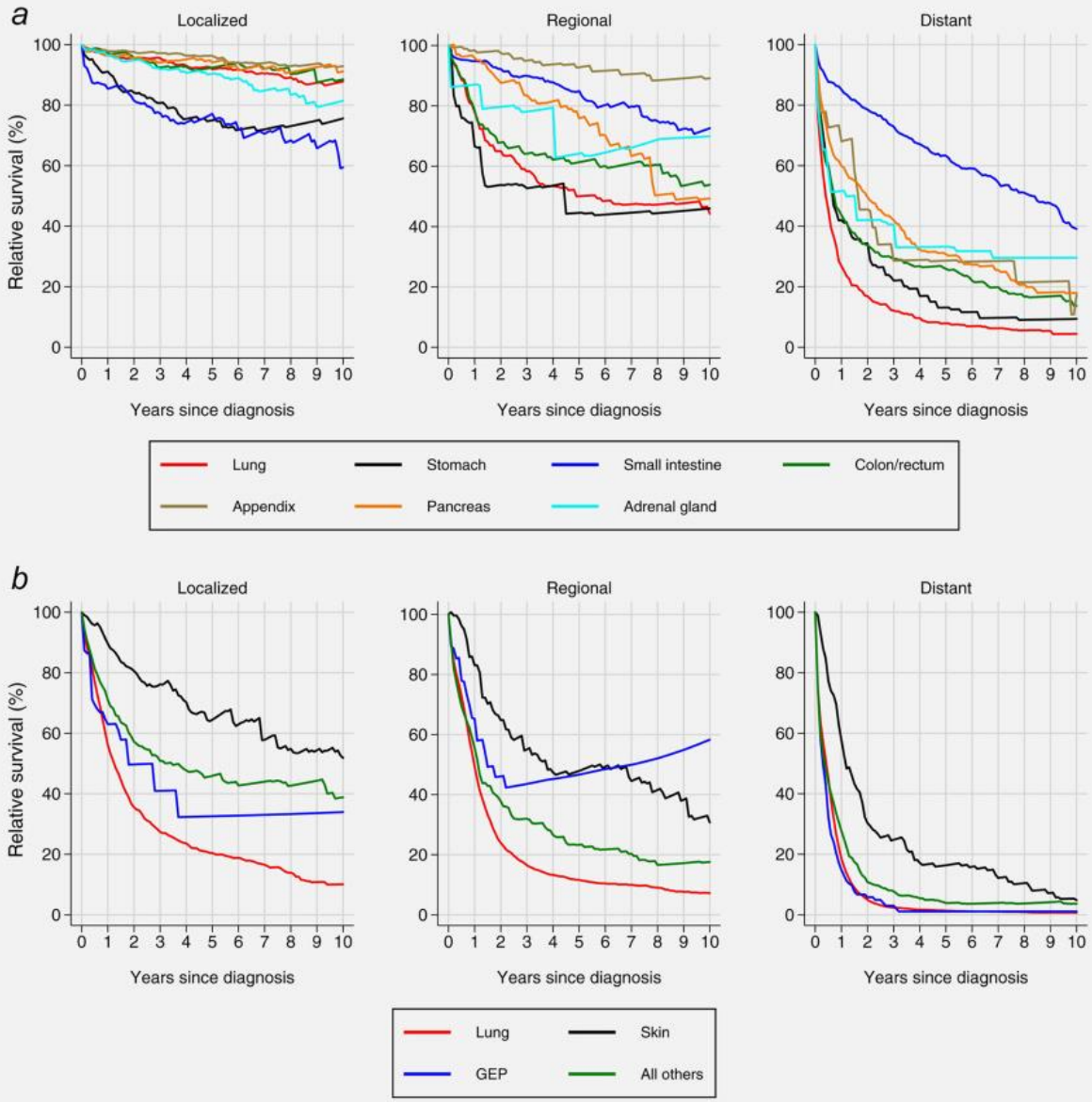
NETs Are Second Most Prevalent Gastrointestinal Tumor



Survival in neuroendocrine neoplasms; A report from a large Norwegian population-based study

NET

NEC



International Journal of Cancer, Volume: 142, Issue: 6, Pages: 1139-1147, First published: 30 October 2017, DOI: (10.1002/ijc.31137)

Small intestinal NET - Symptoms and signs

Abdominal pain

- Small intestinal obstruction (partial or complete)

Diarrhoea

- Partial small intestinal obstruction

Weight loss

Often found incidentally during operation for intestinal obstruction
Asymptomatiske liver metastases CUP

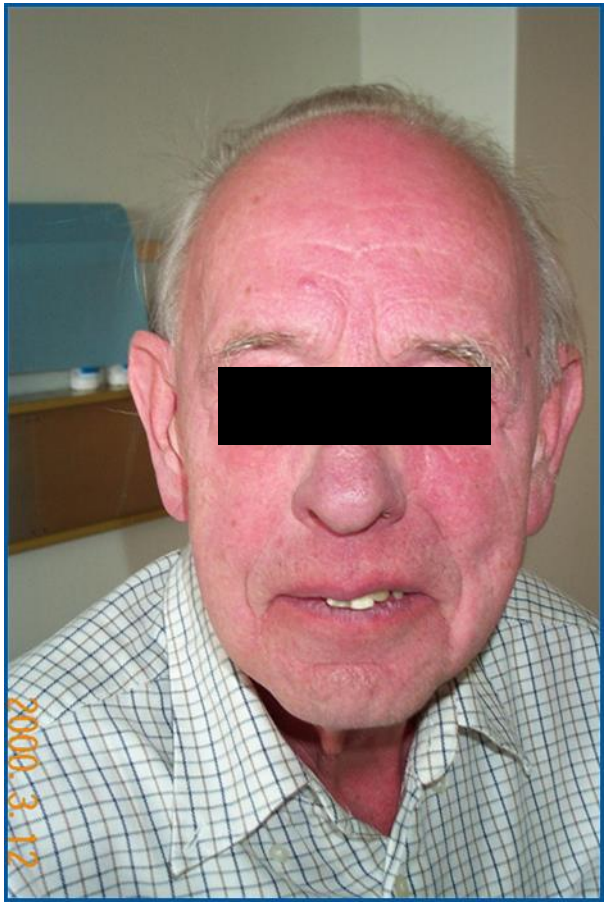
Mean delay from onset of symptoms until diagnosis 3-5 years.

Symptoms and signs

Carcinoid syndrome seen in 10-15% of patients with small intestinal tumors

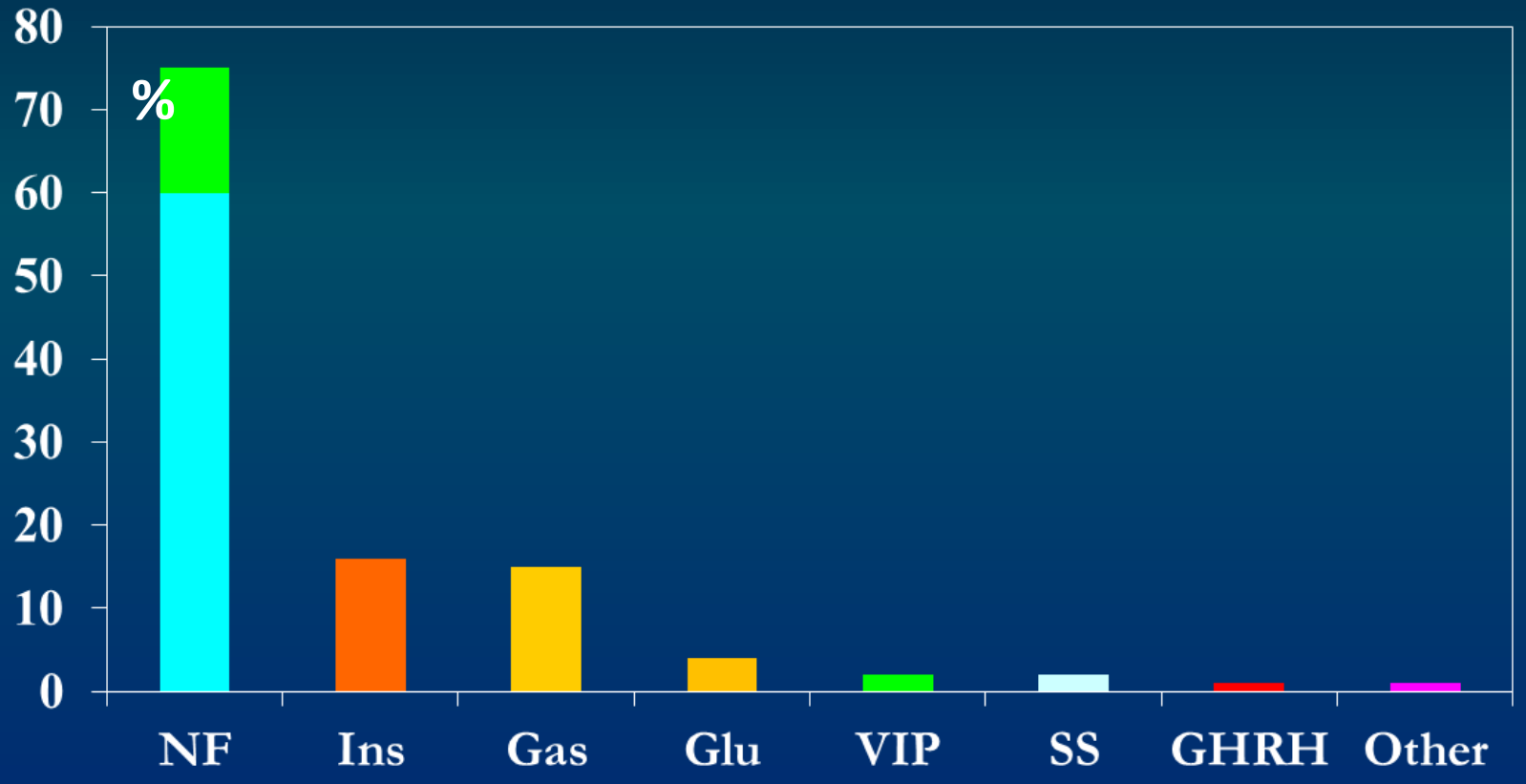
Hormones eliminated in liver – symptoms first at liver metastasis (some exceptions)

- Flushing
- Diarrhea, up to 10-12x daily
- Carcinoid heart disease – right-sided heart failure
- Bronchial wheezing



Neuroendocrine tumors of the pancreas

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



WHO classification, Neuroendocrine neoplasms

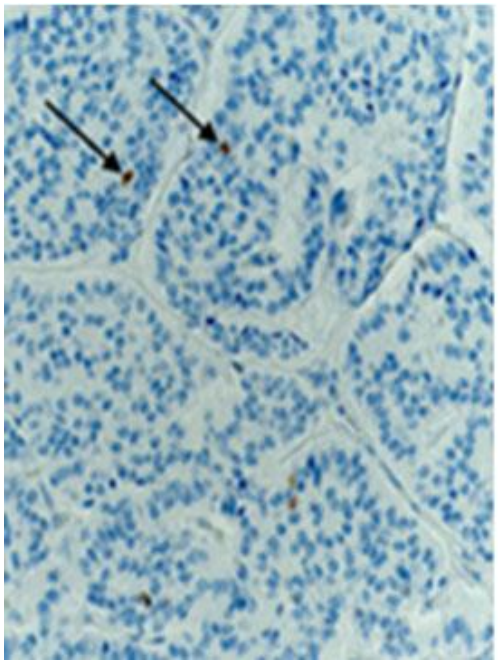
- Neuroendocrine tumour, G1
  - Well differentiated morphology
  - Ki-67 index ≤ 2%
- Neuroendocrine tumour, G2
  - Well differentiated morphology
  - Ki-67: 3-20%
- Neuroendocrine tumour, G3
  - Well differentiated morphology
  - Ki-67: 3-20% or mitotic index: 2-20

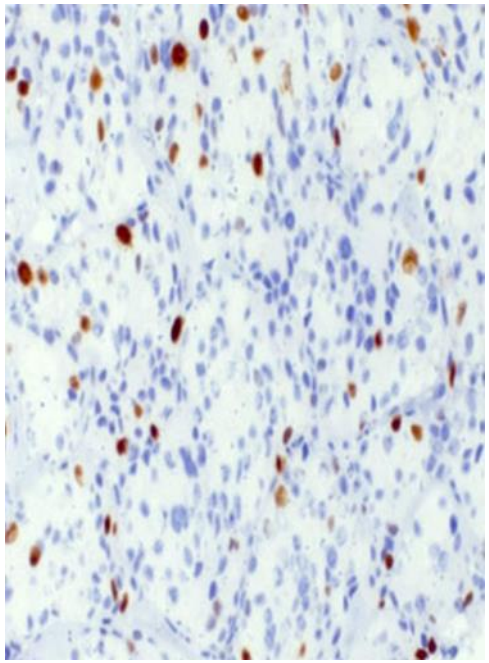
LOW GRADE

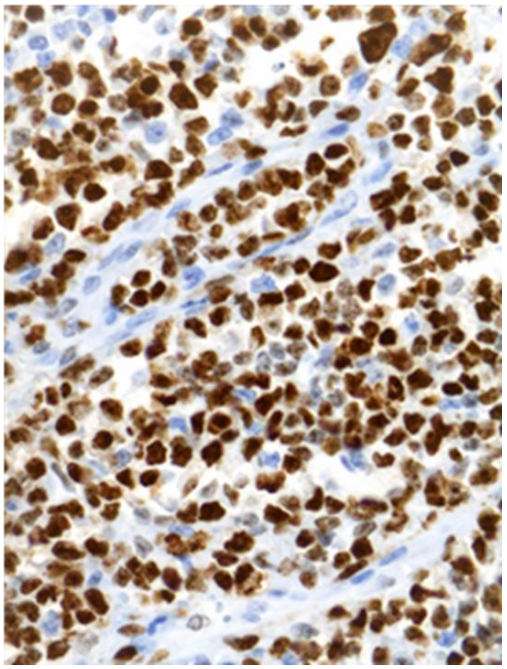
- Neuroendocrine carcinoma (NEC) G3
  - Ki-67 > 20% Poorly differentiated morphology, small cell type
  - Poorly differentiated morphology, large cell type

HIGH GRADE

Ulike sykdommer







	G1	G2	G3
Modersvulst	**Tynntarm**	**Pancreas**	**Mage-tarm**
Ki-67	**1-2%**	**5-10%**	**>20 %. Ofte 70-90%**
Differensiering	**Høyt**	**Høyt**	**Lavt**
mOS stage 4 Medically treated	**10-12 år**	**3-4 år**	**11 m**

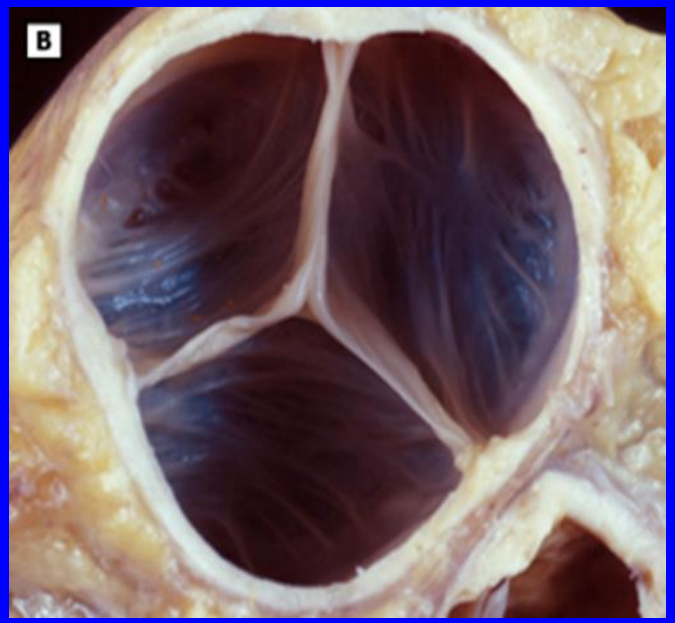
Tumormarkører NET

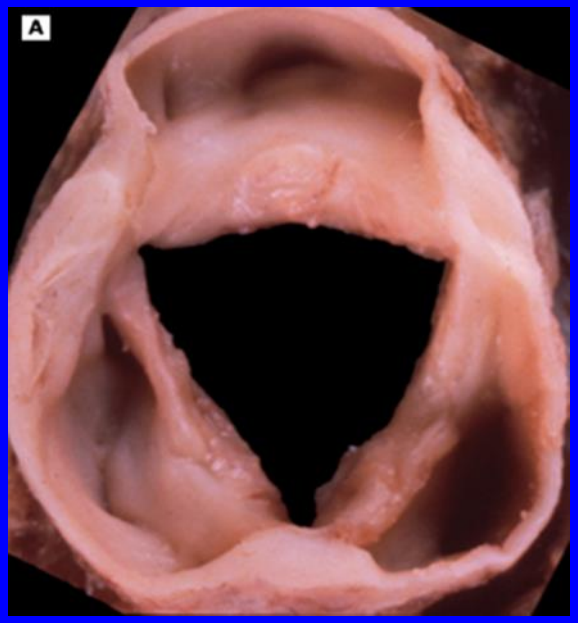
- Chromogranin A
  - Neuroendocrine kreftceller, granula som skilles ut
  - Diagnostisk- serumprøve
  - Forhøyet ved nyresvikt, PPI
- 5HIAA serotonin nedbrytningsprodukt
  - Serum us- tidl døgnurin
  - oftest ved tynntarms NET, sjeldent pan NET, aldri rectum
  - Bør være lave for å unngå skade av hjerteklaffene.
  - Vanligste dødsårsak tidligere carcinoid hjertesykdom

Pro BNP

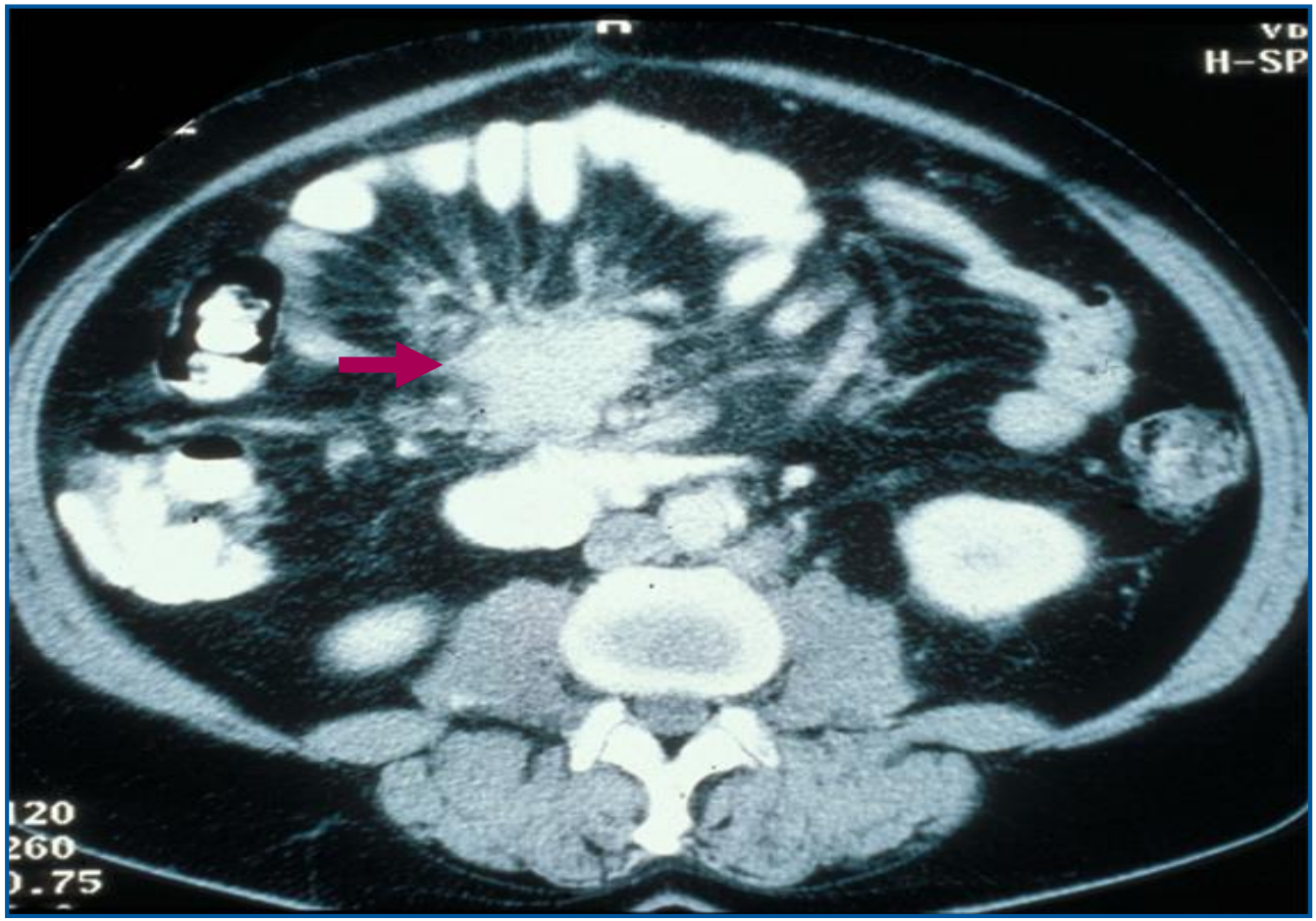
- Påvist sammenheng mellom proBNP og carcinoid hjertesykdom (>300)
- Pasienter med NET fra tynntarm og levermetastaser bør testes med proBNP

Carcinoid heart disease



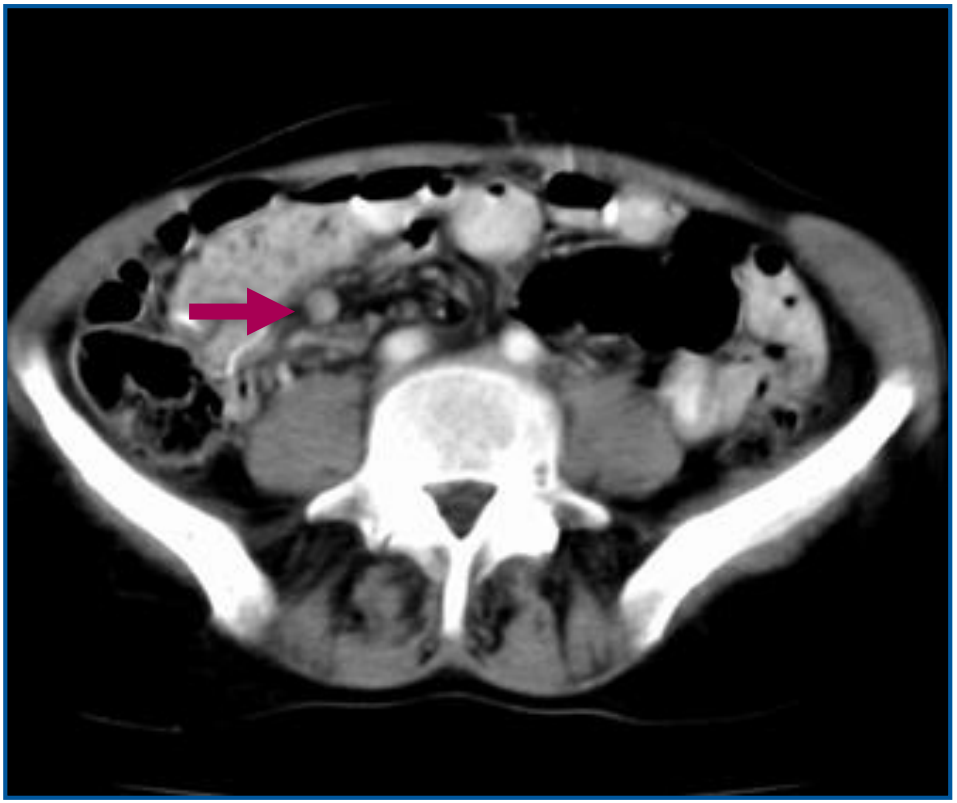


CT scan Desmoplastic reaction due to mesenteric lymph node metastases and fibrosis

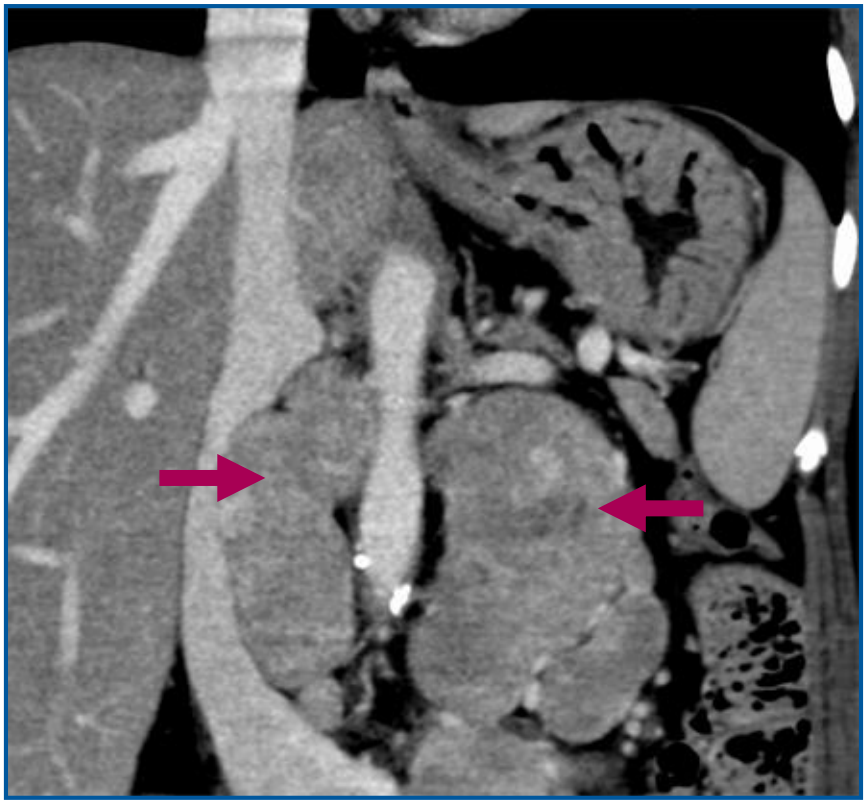


CT scan

Mesenteric lymph node mets.

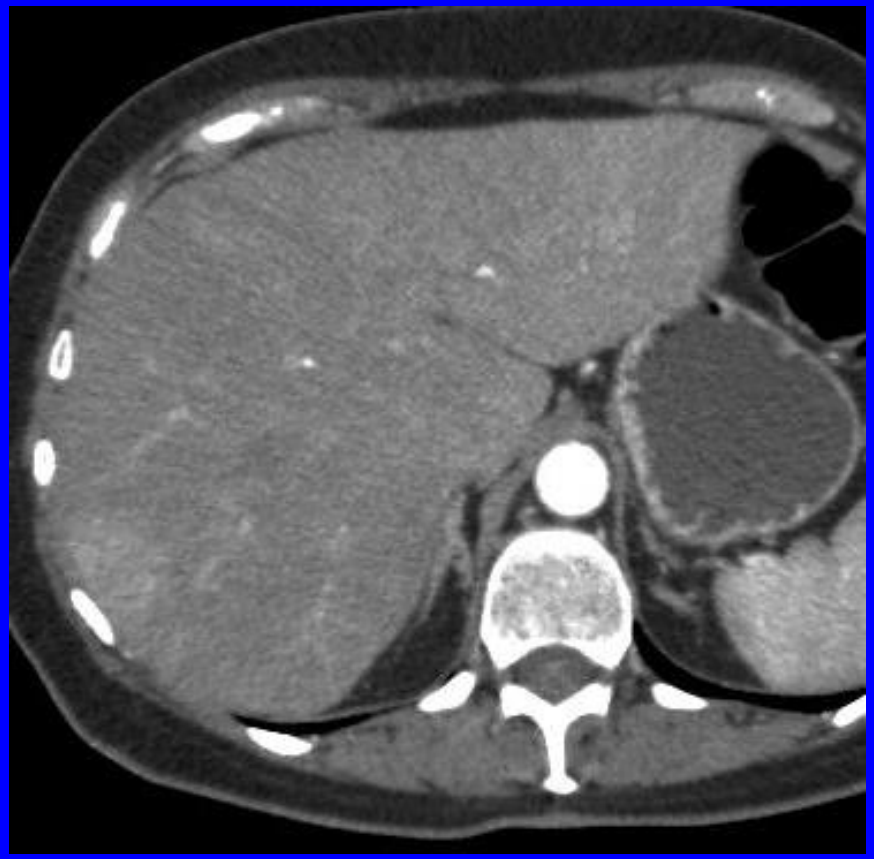


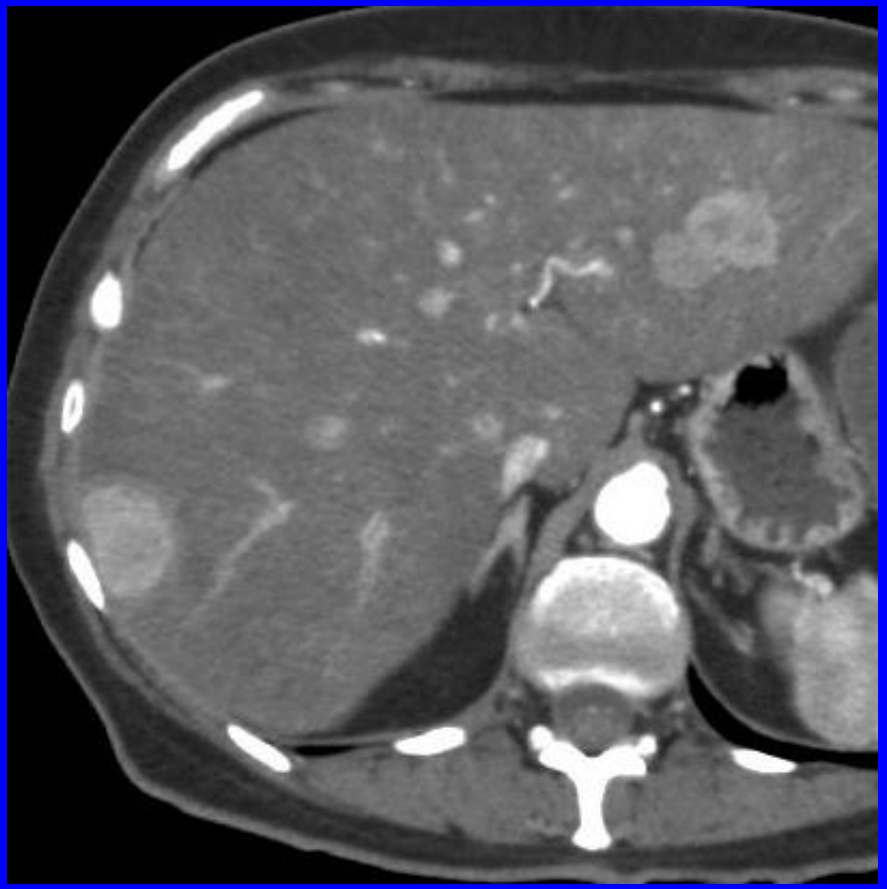
Retroperitoneal lymph node mets.



Radiologi

- CT, 2-fase
- Spesifikk radiologisk NET protokoll
- Dobbel mengde kontrast





DOTATOC-PET: NET spesifikk, somatostatin-2 reseptorer

Bruk

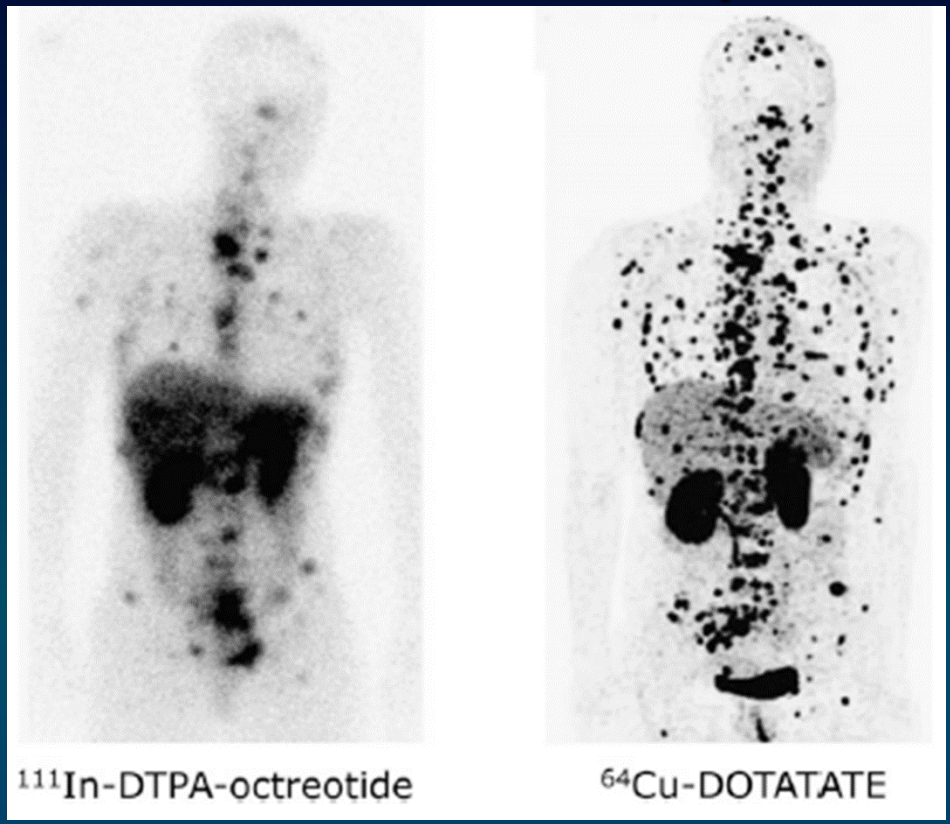
Diagnostisk

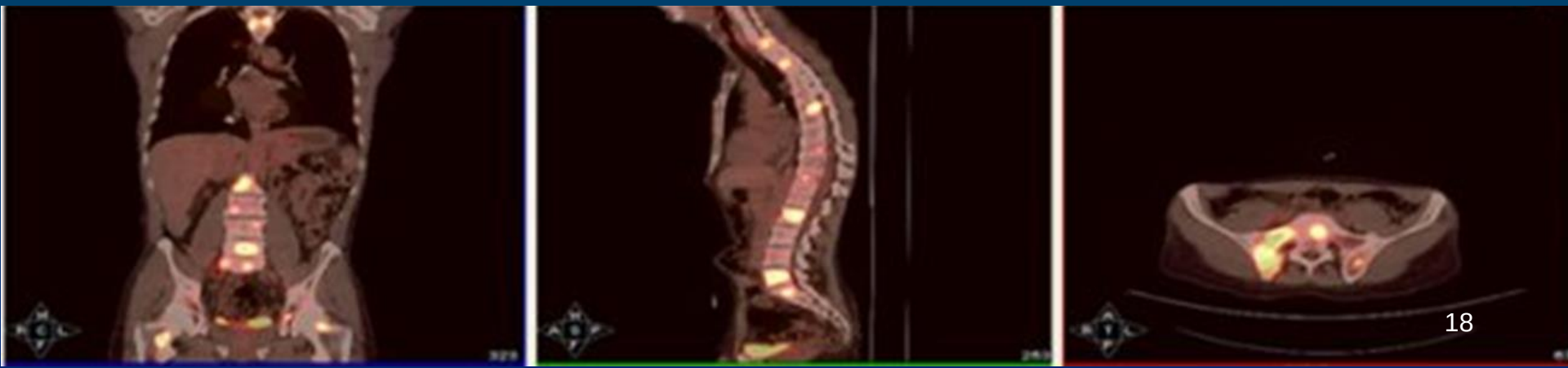
Tas pre-operativt

kartlegging utbredelse

+ follow-up tid

- Diagnose av tilbakefall
- Aktuell for PRRT
- Lever transplantasjon utred





Histologi

- Alltid biopsi; FNAC ikke godt nok
- Chromogranin A + Synaptofycin
- Ki-67 i hot spots
- Differensiering: høyt =NET, lavt =NEC

- Alle pasienter med lite differensiert adenocarcinom i GI skal rutinefarges på synaptofysin og CgA

Nevroendocrin tumor i tynntarm

Kirurgi

- Fjerning av primærtumor med lymfeknute spredning, unngå senere avklemming av tarm eller obstruksjon av blodårer.
- Slutt med fjerning av ikke-symptomatisk primærtumor ved ikke operabel metastatisk sykdom (Daskalakis JAMA Oncol 2018)

CONCLUSIONS AND RELEVANCE: Prophylactic up-front LRS conferred no survival advantage in asymptomatic patients with stage IV SI-NETs. Delayed surgery as needed was comparable in all examined outcomes and was associated with fewer reoperations for intestinal obstruction. The value of a priori LRS in the presence of distant metastases is challenged and needs to be elucidated in a randomized clinical study.

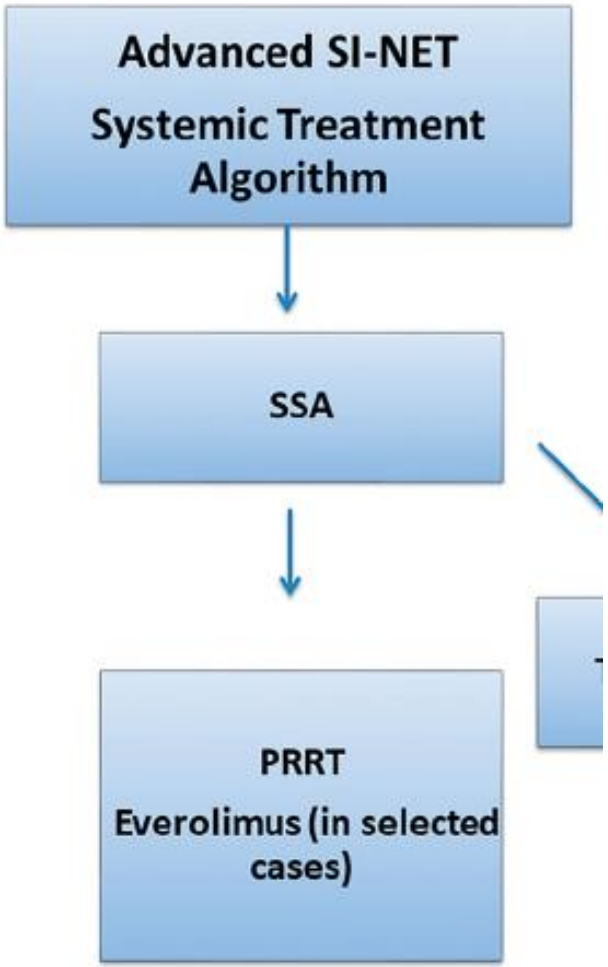
- Levermetastase kirurgi: alltid mere enn synlig på MR
- Levertransplantasjon: Ki67 < 10%, ingen x-tra hepatisk sykdom ved DOTATOC-PET, stabil sykdom 12 m.

Adjuvant behandling ?

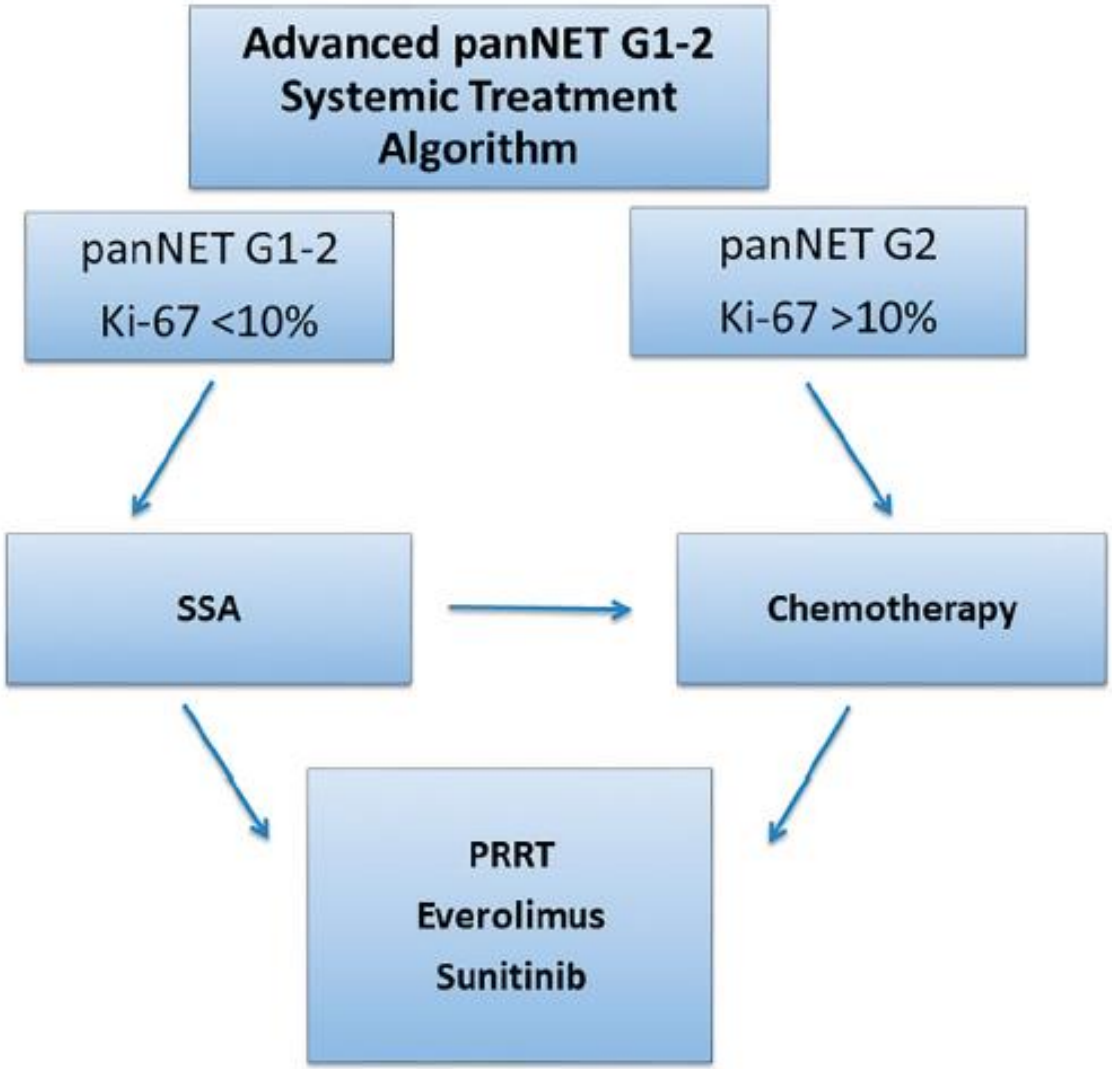
- Ikke anbefalt for NET G1-G3 uansett primær tumor.

- NEC anbefalt adjuvant

Nordic guidelines advanced disease

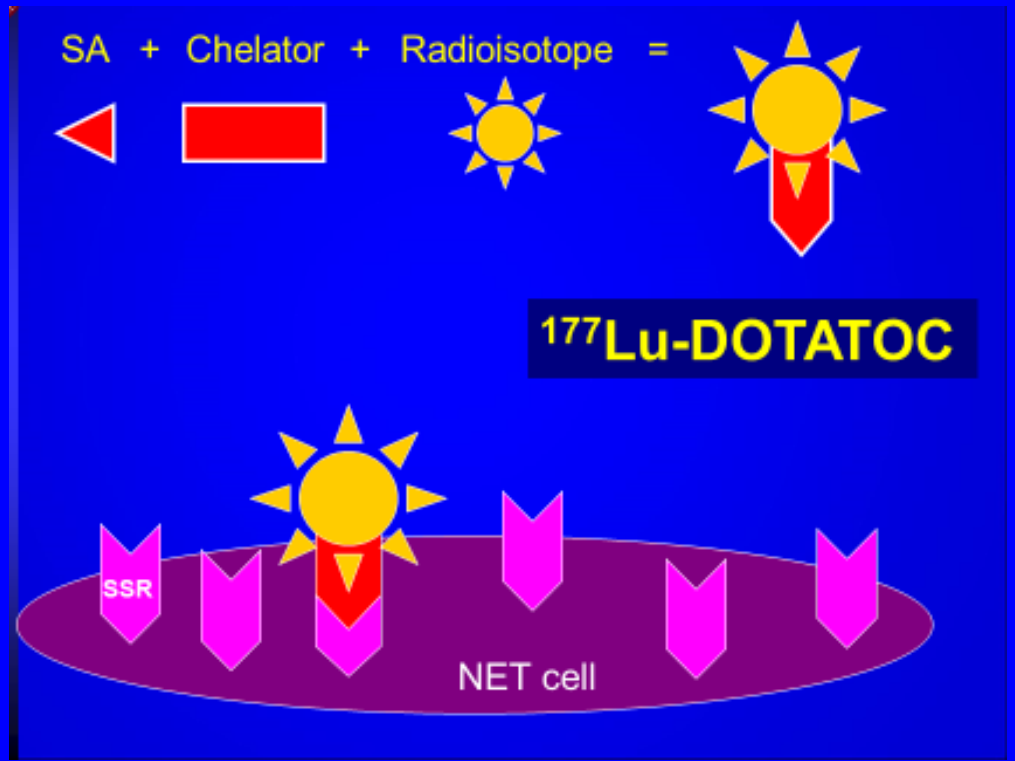


Somatostatin analoger: Sandostatin LAR, Ipstyl, Octreoanne


Advanced panNET G1-2
Systemic Treatment
Algorithm
panNET G1-2
Ki-67 <10%
panNET G2
Ki-67 >10%
SSA
Chemotherapy
PRRT
Everolimus
Sunitinib

Radioaktiv isotopbehandling

- Peptide reseptor radionukleotide terapi (PRRT).
- Radioaktiv kilde, 177-Lutetium med octreotide.
- Må ha høyt opptak på DOTATOC- PET
- 4 behandlinger med 8 ukers mellomrom.



Progression-Free Survival

N = 229 (ITT)

Number of events: 91

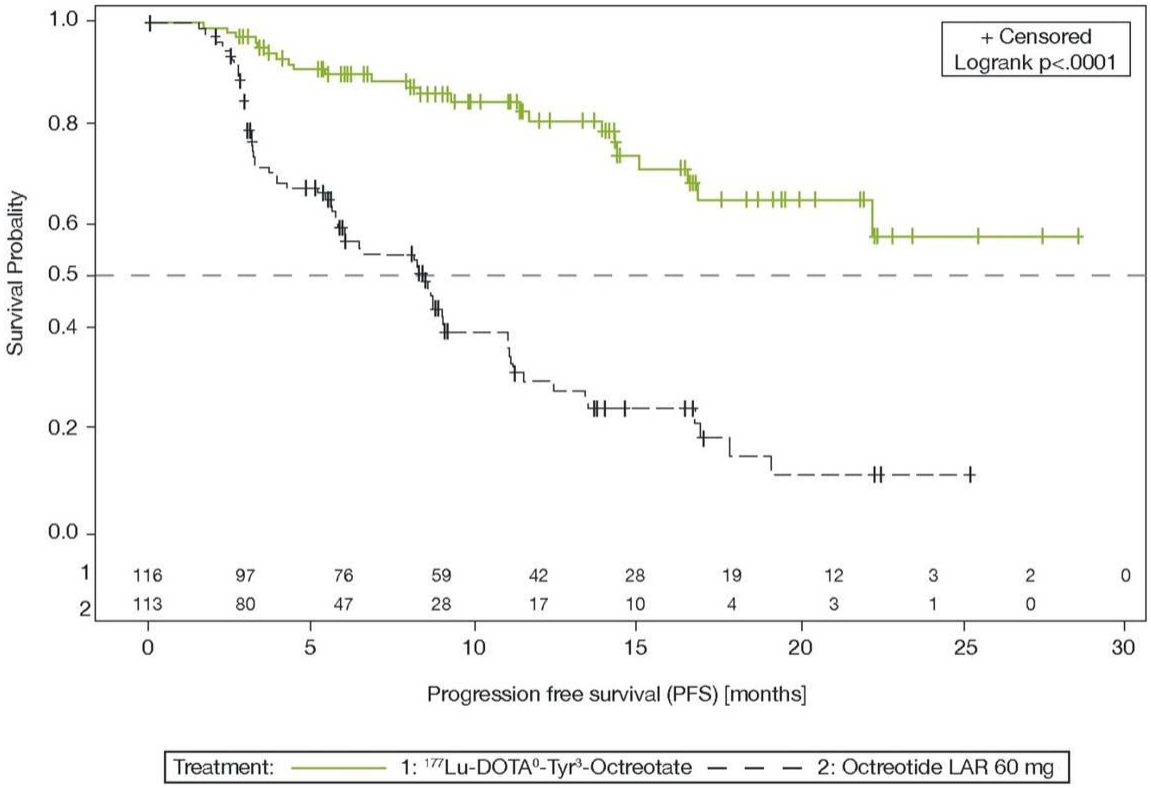
^{177}Lu-Dotatate: 23

Oct 60 mg LAR: 68

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

79% reduction in the risk of disease progression/death

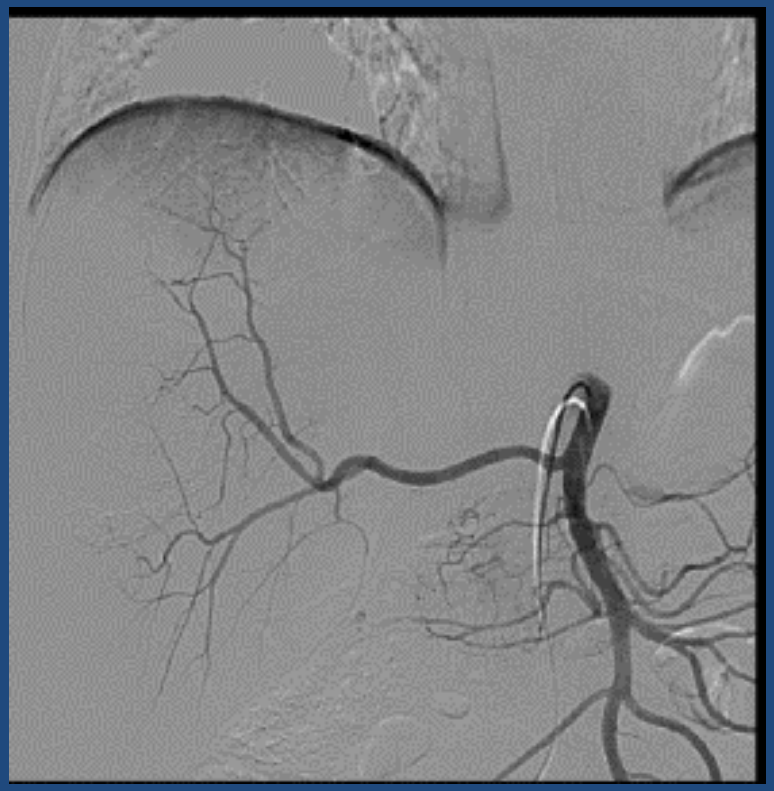
Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months

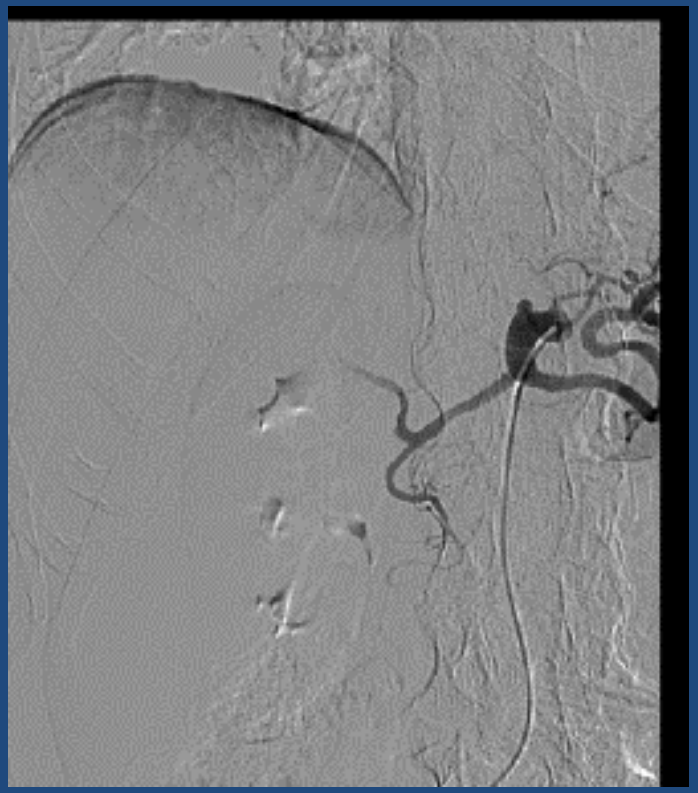


All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Embolisering

Ved negativ DOTATOC PET
Lever dobbel blodforsyning, cancer lever mest på arteriell forsyning.
Injeksjon av plastkuler til halve leveren





SIRT

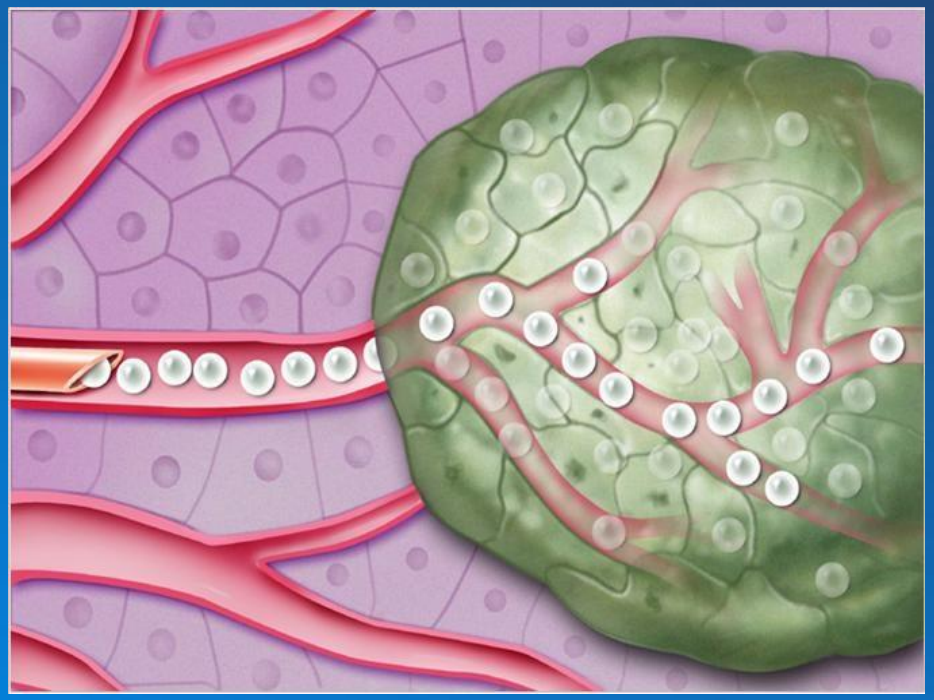
^{90}Yttrium Microsphere Therapy

Dels embolisering dels lokal stråling

Indikasjoner

- Metastaser i lever
- Neg. DOTATOC PET

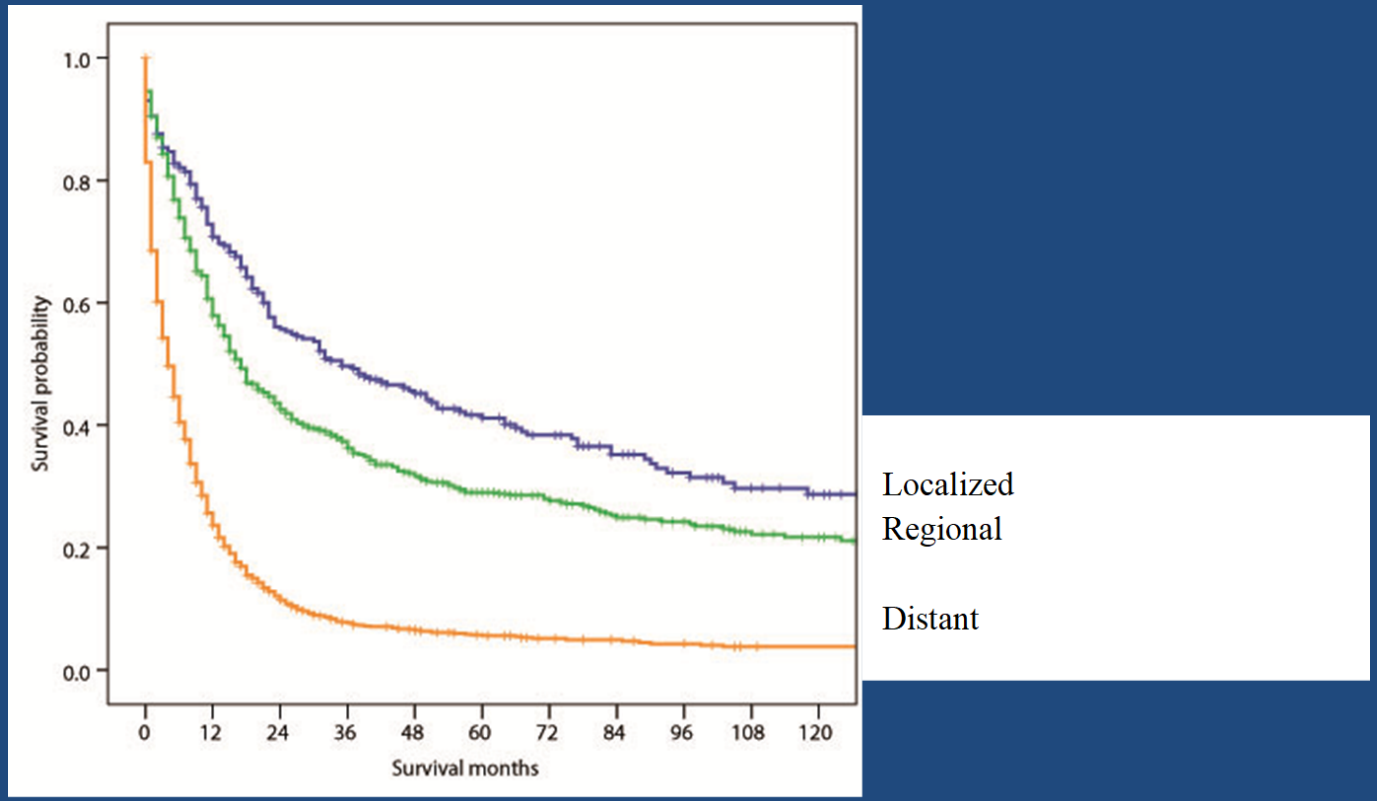
Pris et problem mtp takster



Surgery in NEC.

Diagnosen ofte etter kirurgisk inngrep- biopsi viste lite differensiert adenocarcinoma.

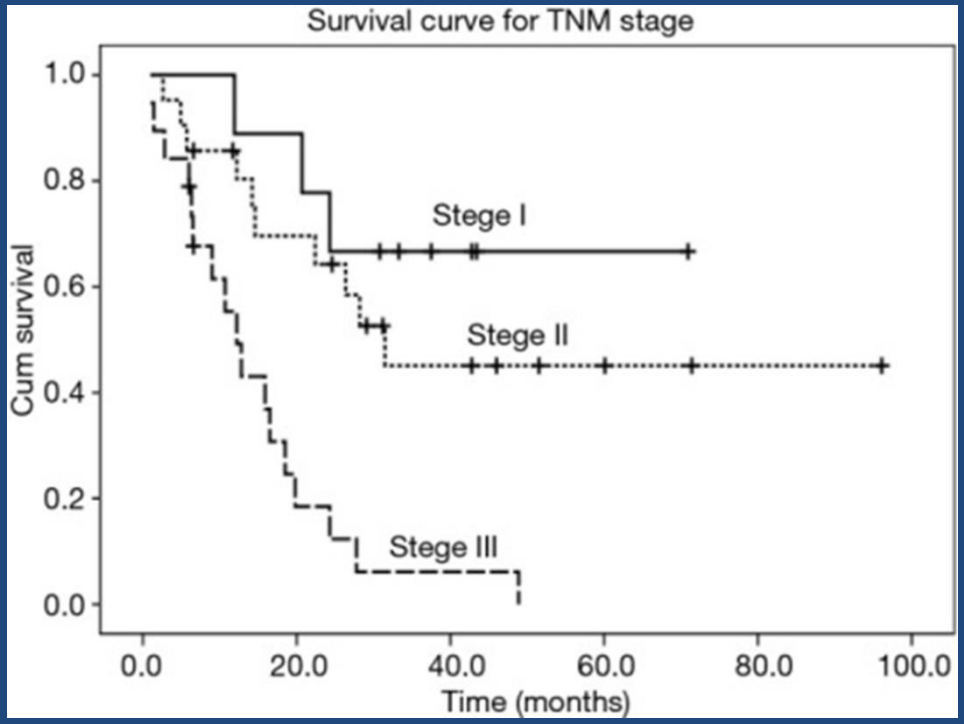
NEC: Ta FDG-PET før planlagt radikal kirurgisk behandling, ofte okkulte metastaser



Esophageal NEC

- Chemoradiation probably better than surgery
- Surgery vs CRT: N1 disease (mOS 12 vs 45 m)

[Meng MB, et al. Radiother Oncol 2013; 106:317]



Surgery for esophageal NEC

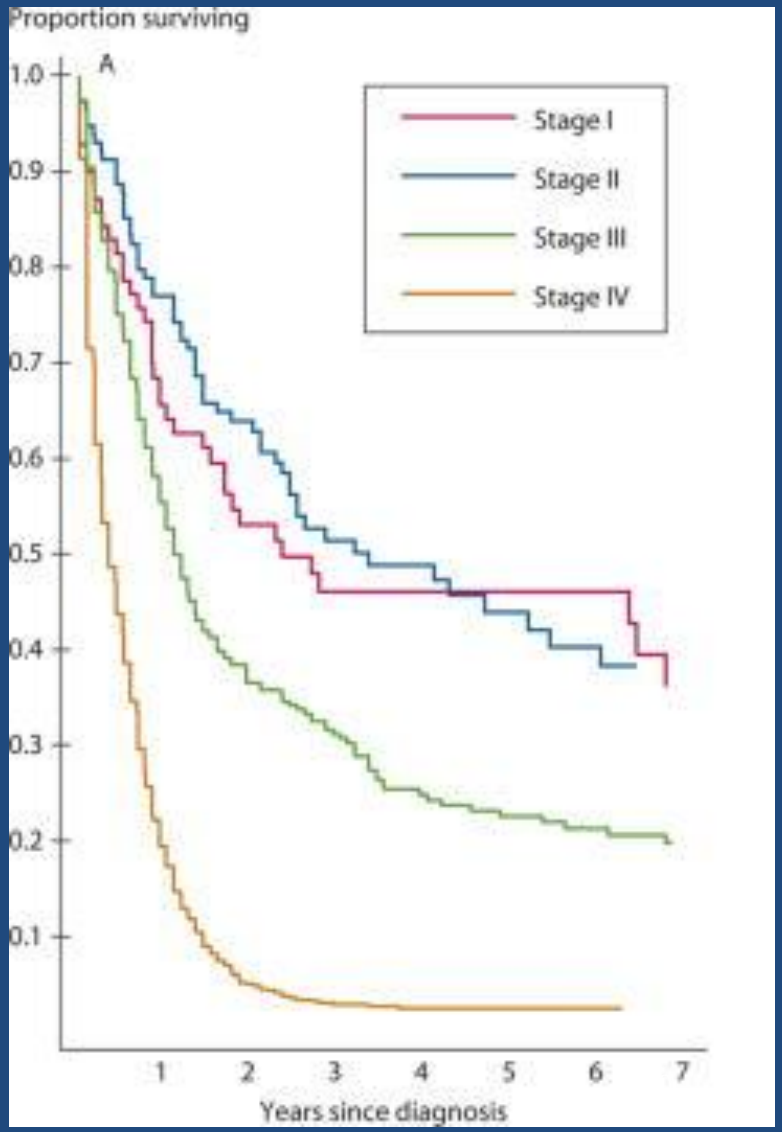
Deng HY et al. J Thorac Dis. 2016 8:1250-6.

Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis.

Shafqat H: Dis Colon Rectum. 2015 58:294-303.

Surgery in 440/502 (88%) Stage I-III.

	Neuroendocrine carcinoma		
Subgroup	*N*	*Median survival, months (95% CI)*	*Relative survival at 5 y, (95% CI)*
All cases	1367	7.1 (7.0–8.0)	16.3% (13.8–19.1)
Stage			
I	70	28.0 (17.1–81.1)	57.4% (41.0–70.7)
II	115	40.0 (27.0–72.0)	56.4% (37.7–71.4)
III	317	13.1 (11.0–16.0)	26.3% (20.0–33.0)
IV	791	4.0 (3.1–5.1)	3.0% (1.9–4.7)



Adjuvant treatment

- 4–6 cycles of cis/carboplatin and etoposide are recommended.

Ta ny FDG-PET før oppstart adjuvant behandling

Gastroentreopancreatic Neuroendocrine carcinoma (NEC)

Metastatic disease: urgent referral to oncologist

Much worse prognosis than adenocarcinoma

See an oncologist within a week or not at all.

Palliative chemotherapy mOS 11 m vs 1 m not given.

Rectal NET Nordic Guidelines (ETE)

- Rectal NETs <2 cm can often be radically resected by endoscopic procedures. Before attempts on endoscopic resection, EUS is recommended in tumours >0.5–1 cm to investigate the depth of tumour growth.
- Invasion into the muscularis propria is a contraindication for endoscopic removal.
- Follow-up : Patients with radically resected G1 polyps <1 cm do not need further surveillance.

Appendix carcinoid Nordic Guidelines (ETE)

Right-sided hemicolectomy not indicated for R0 resected tumours <1cm regardless of risk factors.

Risk factors: invasion of mesoappendix >3 mm, vascular invasion, lymphatic invasion, Ki67>10%.

R0 resected tumours 1–2 cm with the presence of two or more risk factors: right-sided hemicolectomy with lymph node dissection.

If the tumour size is >2 cm, DOTATOC-PET is recommended, followed by right-sided hemicolectomy.

Right-sided hemicolectomy if spread to regional lymph nodes irrespective of size.

Goblet celle carcinoid i appendix

- Ikke en nevroendocrine tumor/cancer
- Mye mer aggressiv tumor
- Behandles som et adenocarcinom !

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Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Nordic guidelines 2021 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms

Eva Tiensuu Janson, Ulrich Knigge, Gitte Dam, Birgitte Federspiel, Henning Grønbaek, Peter Stålberg, Seppo W. Langer, Andreas Kjaer, Johanna Arola, Camilla Schalin-Jäntti, Anders Sundin, Staffan Welin, Espen Thiis-Evensen & Halfdan Sorbye

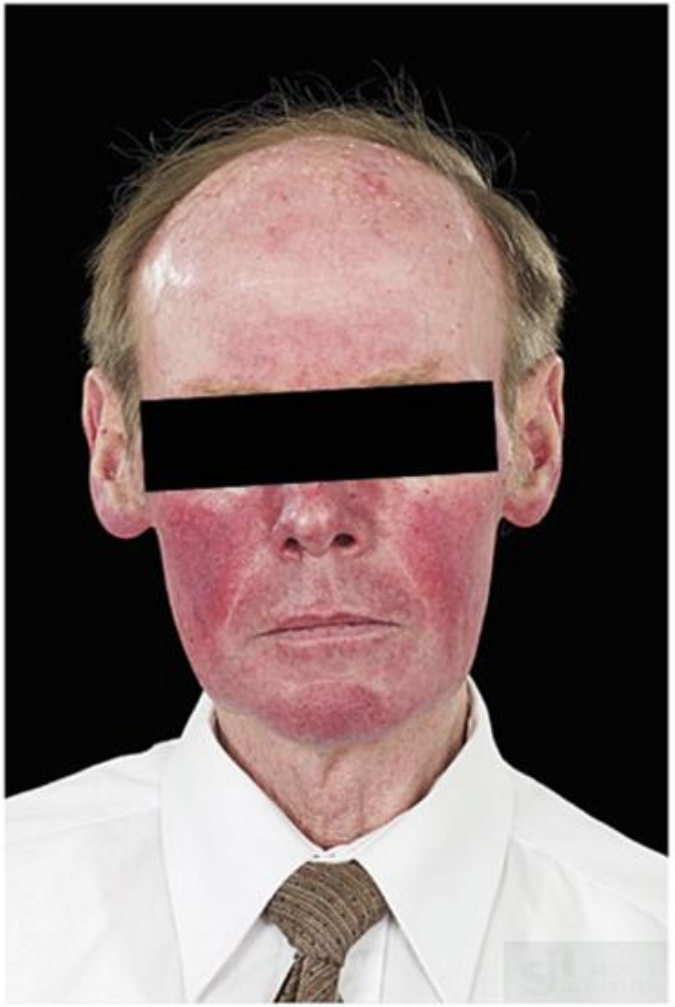
To cite this article: Eva Tiensuu Janson, Ulrich Knigge, Gitte Dam, Birgitte Federspiel, Henning Grønbaek, Peter Stålberg, Seppo W. Langer, Andreas Kjaer, Johanna Arola, Camilla Schalin-Jäntti, Anders Sundin, Staffan Welin, Espen Thiis-Evensen & Halfdan Sorbye (2021) Nordic guidelines 2021 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms, Acta Oncologica, 60:7, 931-941, DOI: 10.1080/0284186X.2021.1921262

Hvorfor nyttig å kunne noe om NET

- Mann født 1937
- 4-5 års sykehistorie med hetetokter og diare (8-10 x dgl). Økende plager.
- Utredet av gastromedisiner, coloskopi; inflammatorisk tarmsykdom.
- 5 cm stor tumor i lever, langsomt voksende, MR/CT; konkludert med FNH (unge kvinner?)

A

B

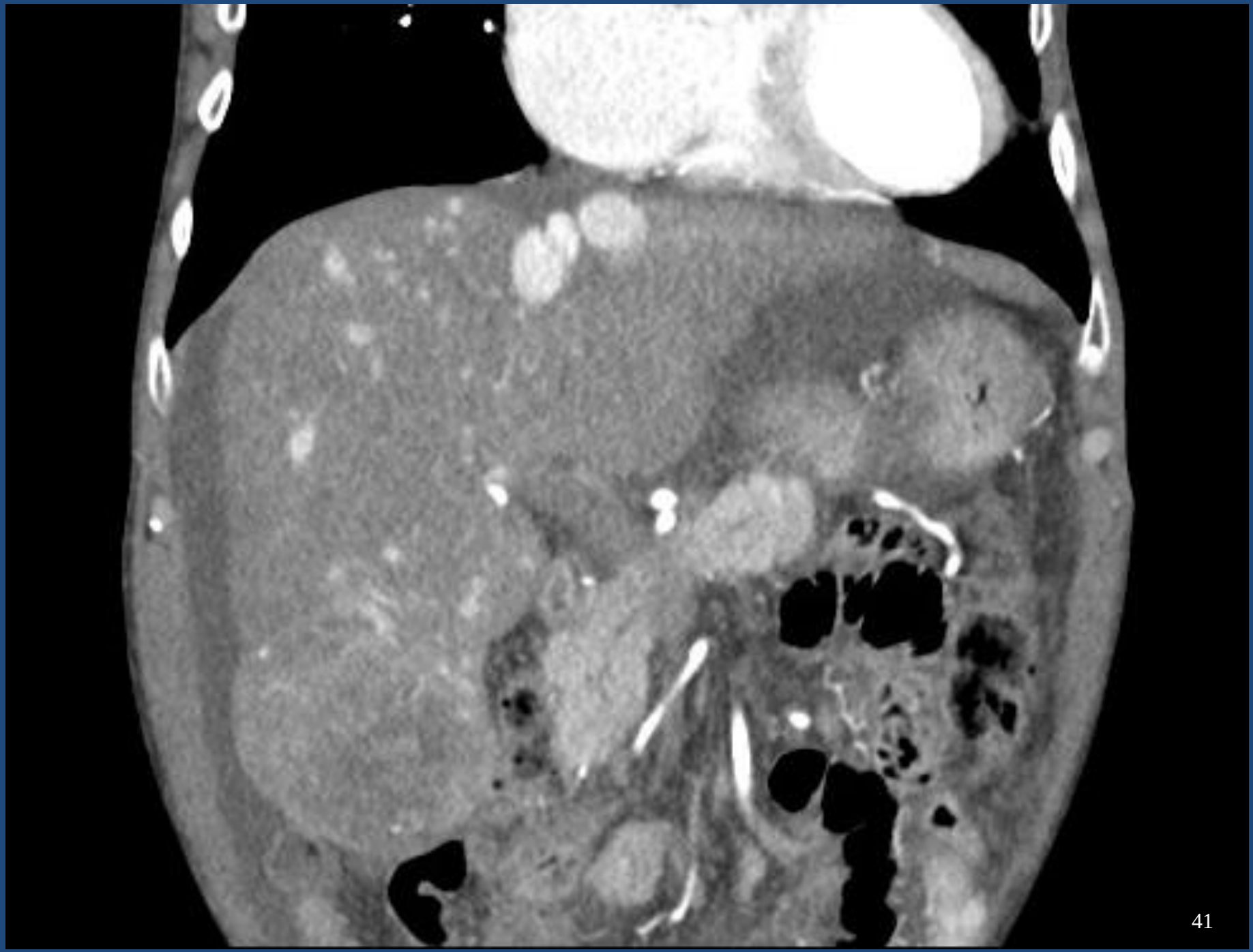


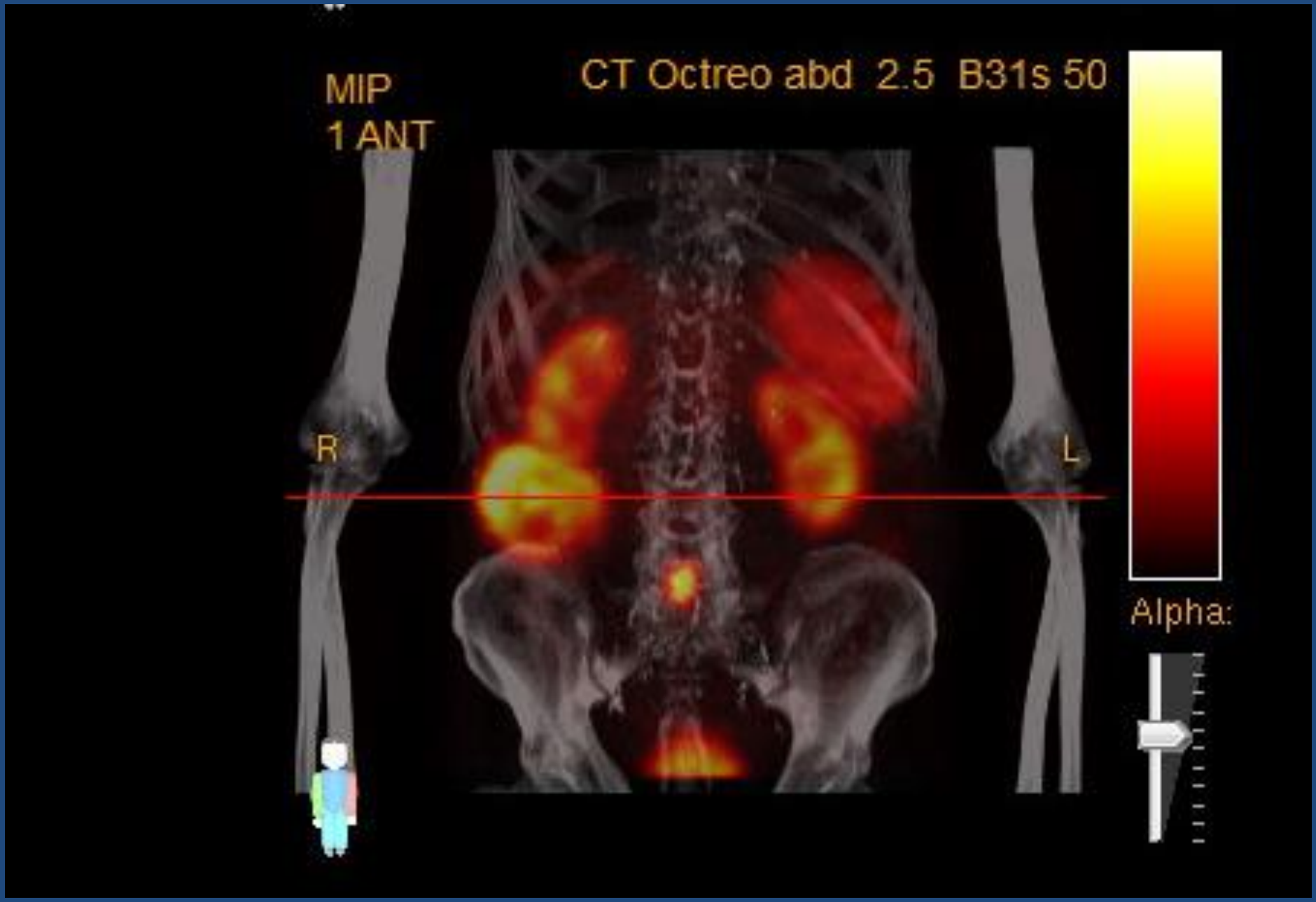
Hvorfor….

- Hjertesvikt utvikling, pleuravæske og ascitis.
- Utredning hos kardiolog.
- Vegetasjoner på hø klaffer

- Kardiologen stilte diagnosen med to prøver.

- Vegetasjoner på hø klaffer= carcinoid hjertesykdom?
- U-5HIAA: 696 (UNL 41)
- S-CgA: 74 (UNL 2)
- Tynntarmscarcinoid med levermetastaser.
- Delay: alvorlig carcinoid hjertesvikt, avslått for klaffe kirurgi.Oppdaget før: forventet levetid 10-12 år. Døde etter 8 mnd pga hjertesvikt.





DOTATOC PET