ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Diagnosis, Staging, Classification and Characterization of Neuroendocrine Tumours

The Clinician's role

Dr. Christos G. Toumpanakis MD PhD FRCP

Consultant in Gastroenterology/Neuroendocrine Tumours

Hon. Senior Lecturer University College of London

Neuroendocrine Tumour Unit - ENETS Centre of Excellence

ROYAL FREE HOSPITAL, London,UK

UCL

Royal Free London NHS
NHS Foundation Trust

The NET clinician should..

- Be aware of symptoms and signs of functional NETs
- Suspect the non-functional NETs
- Utilize properly the established NET biomarkers
- Be aware of new NET biomarkers
- Be aware and recognize NET heterogeneity
- Utilize a combination of imaging studies for better diagnosis and characterization of NETs

Diagnosis of NETs

- History and clinical examination
- Biochemical tests (Biomarkers)
- Imaging studies
  (for localization of primary and metastatic lesions)
- Histology - “ gold standard”

METASTATIC MIDGUT NETs
(in 30-40%) &
(in 5% of bronchial and 1% of pancreatic NETs)

a. " Carcinoid syndrome"

Flushing, diarrhoea,
bronchospasm, Carcinoid heart disease

- 20 – 30 % of patients with liver metastases
- 5% of patients with carcinoid syndrome do not have liver metastases

b. "Carcinoid crisis"

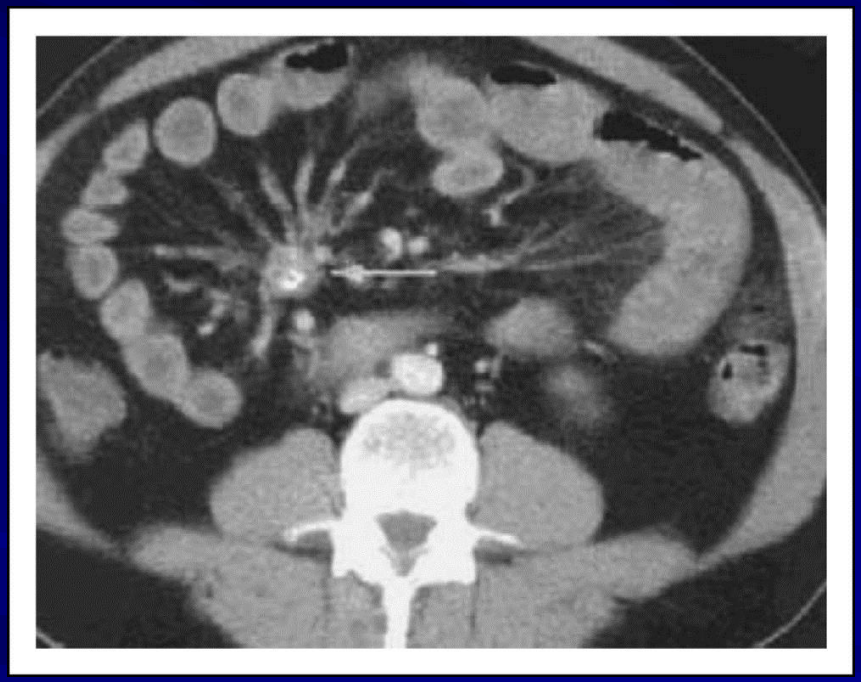
Severe symptoms of carcinoid syndrome + hypotension during procedures that involve GA, as well as in TAE, and when the patient is on inotropes

Carcinoid Heart Disease

- May develop in 20 % of patients, with carcinoid syndrome.
- Main cause of death in 40-50% of patients.
- Involves mainly the right valves of the heart.
- May be present even in asymptomatic patients.
- Valve replacement in a selected group of patients.

Battacharyya S , Toumpanakis C et al, AJC 2008

Mesenteric fibrosis in midgut NETs



- Episodes of sub-acute bowel obstruction
- Hydronephrosis
- Malnutrition
- Small bowel bacterial overgrowth
- Recurrent ascites & GI bleeding from ectopic varices

Differential Diagnosis - Flushing

Carcinoid Syndrome flushing

- Dry
- Intermittent
- Provoked by exercise, alcohol, and food-containing tyramines (eg, blue cheese,chocolate etc)
- Involves the face and upper trunk as far as the nipple line.

Flushing related to other causes

+ **Diarrhoea** ▸ **Other NETs** : medullary Thyroid carcinoma, pancreatic VIPoma

Wet flushing : Menopause

Constant flushing : alcoholism, polycythemia, and mitral valve disease

+ headaches : phaeocromocytoma or mastocytosis

+ rash features : rosacea, mastocytosis

Different causes of diarrhoea in small bowel NETs

- Hormone production (carcinoid syndrome)
- Steatorrhoea
- Bacterial overgrowth
- Bile acid malabsorption
- Mesenteric ischaemia

CLINICAL PRESENTATION (2)

Specific symptoms – Pancreatic NETs

Gastrinoma

- Recurrent/resistant to treatment peptic ulcers, not related to *H.pylori* & NSAIDs
- Chronic diarrhoea responding to PPIs

VIPoma

Chronic diarrhoea, hypokalaemia and dehydration

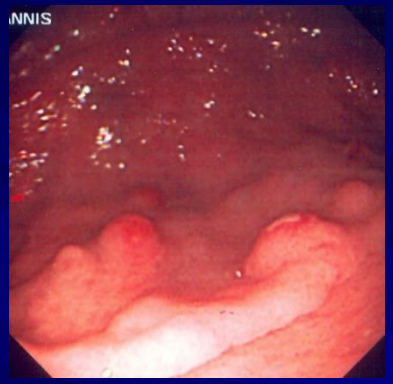
Insulinoma

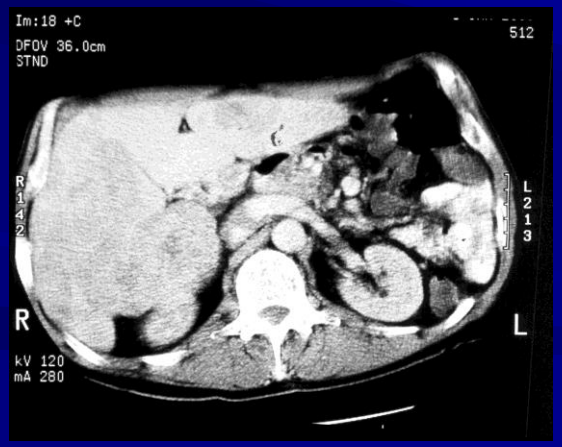
Fasting hypoglycaemia, low blood glucose, and improvement after administration of glucose (Whipple's triad)

Glucagonoma

New onset of DM, weight loss and "migratory necrolytic erythema

CLINICAL PRESENTATION (2)
Non-*specific symptoms*



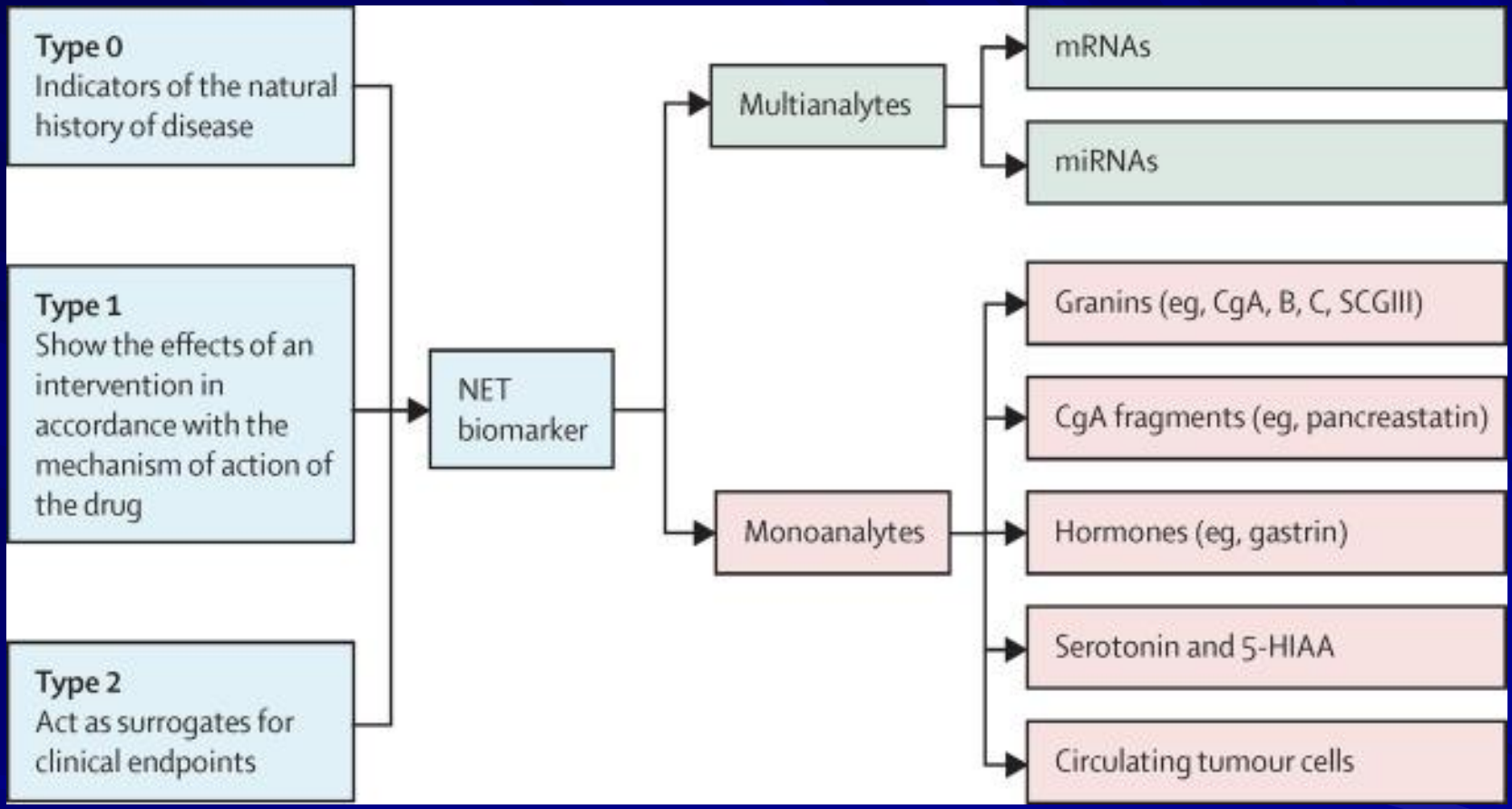


- Dyspepsia
- Chronic abdominal pain
- Weight loss
- Symptoms compatible with IBS
- Etc, etc.. So…

Tumours are diagnosed incidentally:

a. During surgery
b. During endoscopy
c. On imaging studies and guided biopsy of tumour lesions.

Categories of NET biomarkers



Monoanalytes: identify, with various degrees of sensitivity and specificity single biological hallmarks (secretion, tumour type)
Multianalytes: use multiple, simultaneous measurements of different parameters

Oberg et al, Lancet Oncol 2015

Biochemical tests (biomarkers) : Non-specific - Chromogranin-A (CgA)

- **Sensitivity : 60-90%**
- Correlate with tumour burden
- Early decrease of its levels may predict PFS and OS
- Independent factor of survival in midgut NETs

Not raised in:

- Small volume disease
- Rectal NETs
- Insulinomas
- Poorly differentiated NECs

May be raised in non-NETs situations:

- Chronic PPI use
- Atrophic gastritis
- IBD
- Renal failure
- Cirrhosis
- Other cancers

Specificity: 10 – 35 %

Yao JC, et al. J Clin Endocrin Metab. 2011
Modlin et al, Am J Gastroenterology 2015
Kidd et al, Curr Opin Endocrinol Diabetes Obes 2016

Biochemical tests (biomarkers) : Specific

SPECIFIC

a. 24hour urinary 5-HIAA
(metastatic midgut NETs)

Please note that : certain foods like bananas, avocados, aubergine, pinepapple, plums, walnuts and some drugs like paracetamol, fluorouracil, methysergide, naproxen and caffeine , may cause *false positive results*, whilst other drugs like levodopa or phenothiazines may cause *false negative results.*

b. Fasting gut hormones
(functioning pancreatic NETs)

(gastrin, VIP, somatostatin, insulin, glucagon)

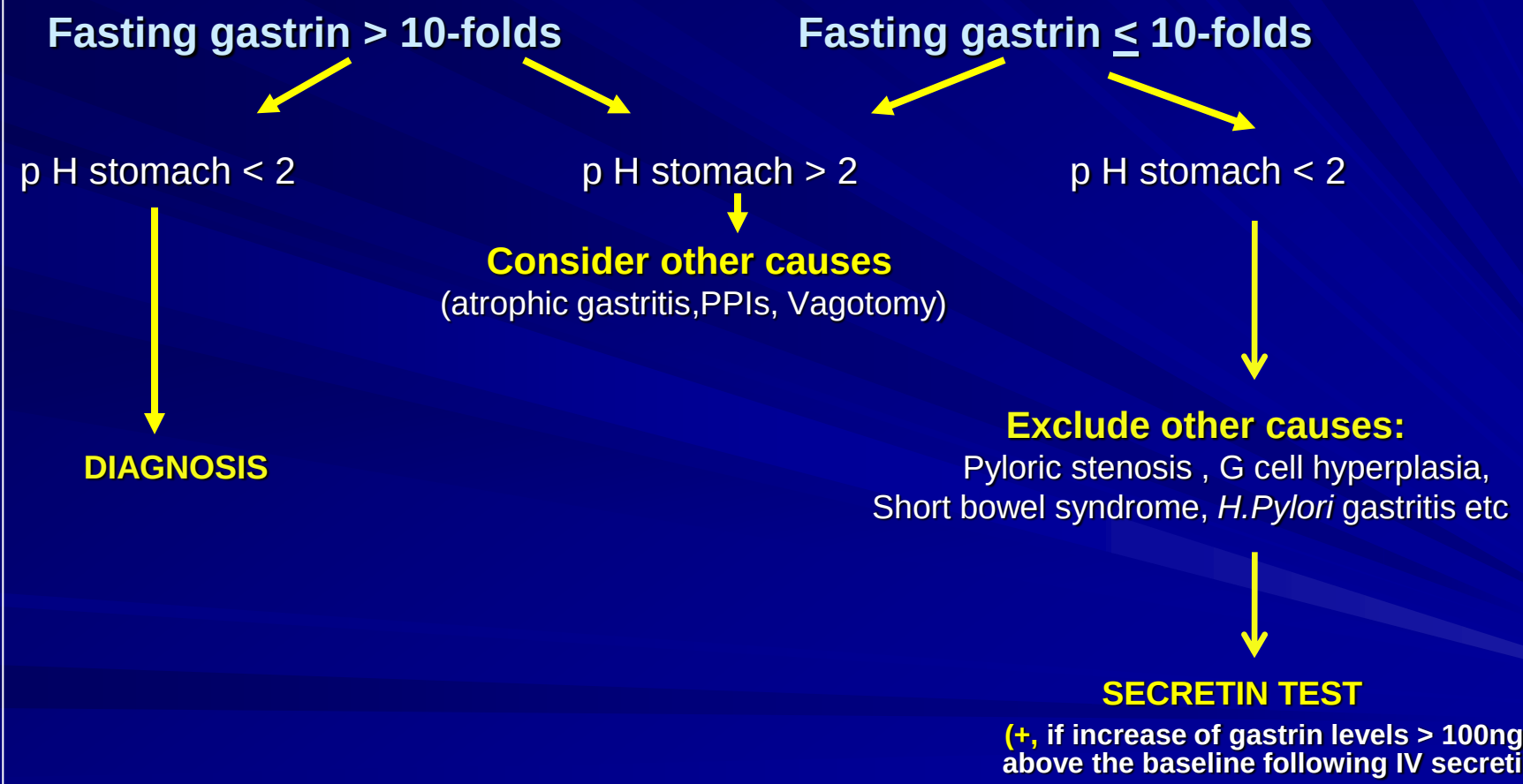
c. Role of Gastrin in differentiation of types of Gastric NETs

Screening for MEN-1 in pNETs

- Ca
- PTH
- ? Pituitary hormones

Gastrin & Gastrinoma

- **PPIs should be discontinued for at least 10 days**



Jensen et l, Neuroendocrinology 2006

Insulin & Insulinoma

- Blood glucose $\leq$ 40 mg/dl
- Insulin levels $\geq$ 36 pmol /l
- C-peptide $\geq$ 200 pmol/l
- Pro-insulin levels > 5 pmol/l
- β- Hydroxybutyrate levels $\leq$ 2.7 mmol/l
- Absence of sulfonylurea metabolites in plasma and urine

72 h – Fast test

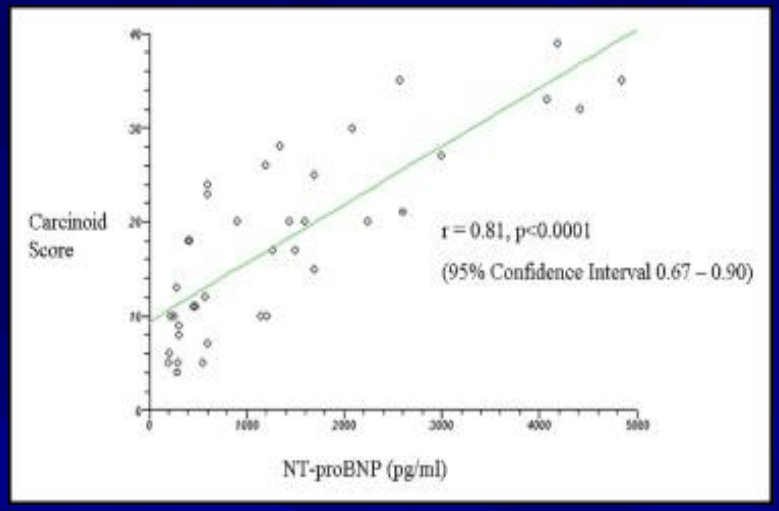
- When symptoms occur and if glucose is low: estimation of insulin, pro-insulin and C-peptide
- Usually diagnosis is made within the first 48h

Tucker at al, Br J Surgery 2006
De Herder et al, ENET guidelines, Neuroendocrinology 2006

Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease.

Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J.

Am J Cardiol. 2008 Oct 1;102(7):938-42



200 patients με with midgut NETs underwent cardiac ECHO and estimation of N-terminal pro-brain natriuretic peptide.

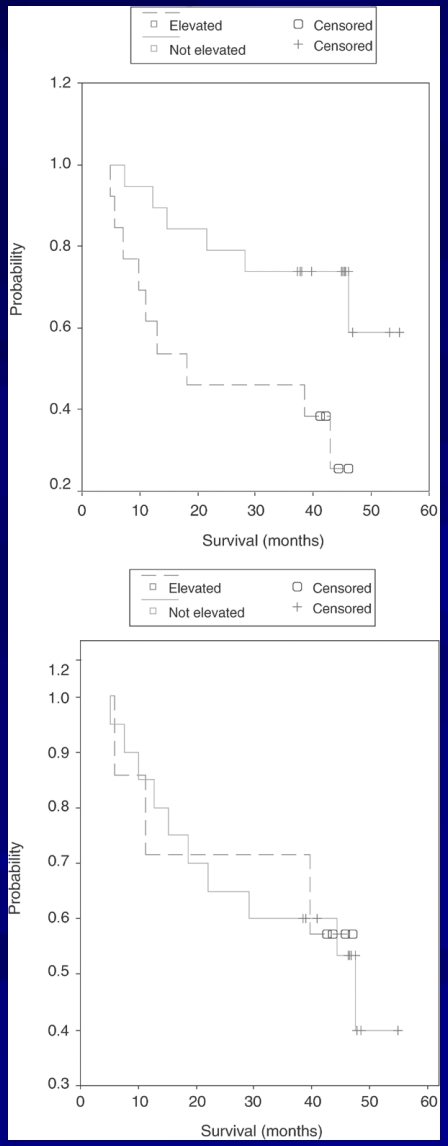
19.5% had ECHO findings consistent with CHD

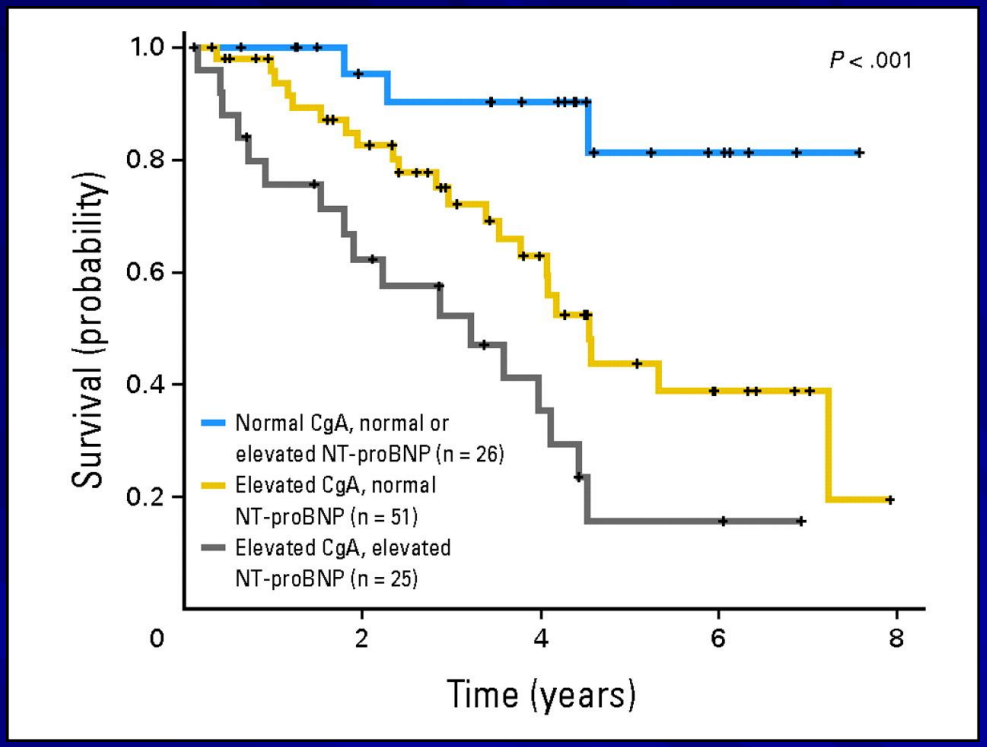
NT pro-BNP levels were significantly higher (p<0.001) in patients με carcinoid heart disease.

Sensitivity and specificity for "cut-off" level of 260pg/ml was 92% and 91%.

NT pro-BNP levels had positive correlation with CHD score (r:0.81, p<0.001) and NYHA scale (p<0.001)

NT pro-BNP as a predictor of survival

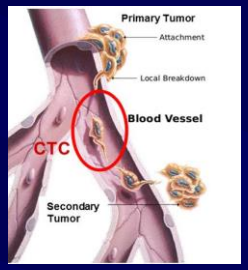




- Worse survival in raised levels.
- Patients with raised NT proBNP and CgA levels have a 16% survival probability in 5 years.

Zuetenhorst et al, Br J Cancer, 2004
Korse et al, J Clin Oncol 2009

Circulating Tumor Cells (CTCs) as prognostic markers in neuroendocrine tumors

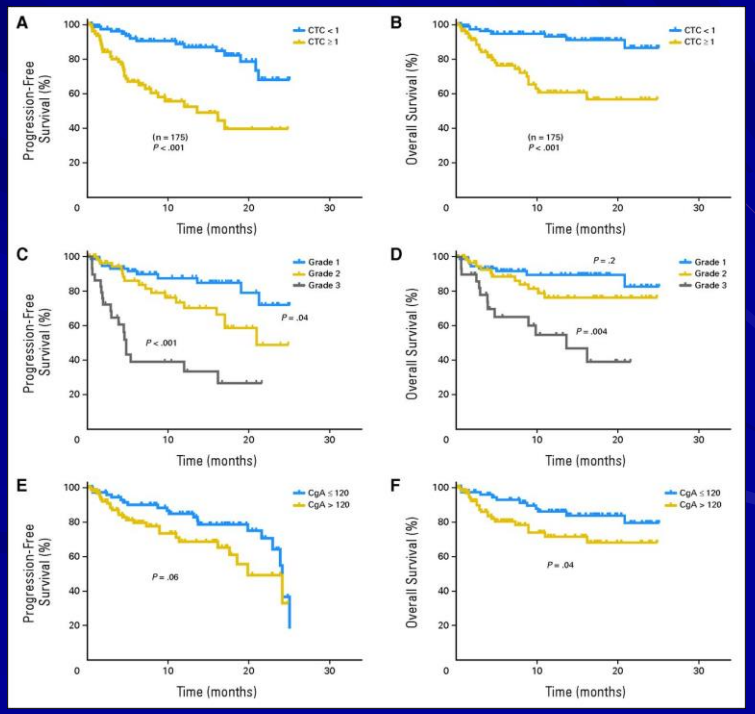


Khan MS, Kirkwood A, Tsigani T, Garcia-Hernandez J, Hartley JA, Caplin ME, Meyer T.

Neuroendocrine Tumour Unit, ENETS Centre of Excellence,Royal Free Hospital,

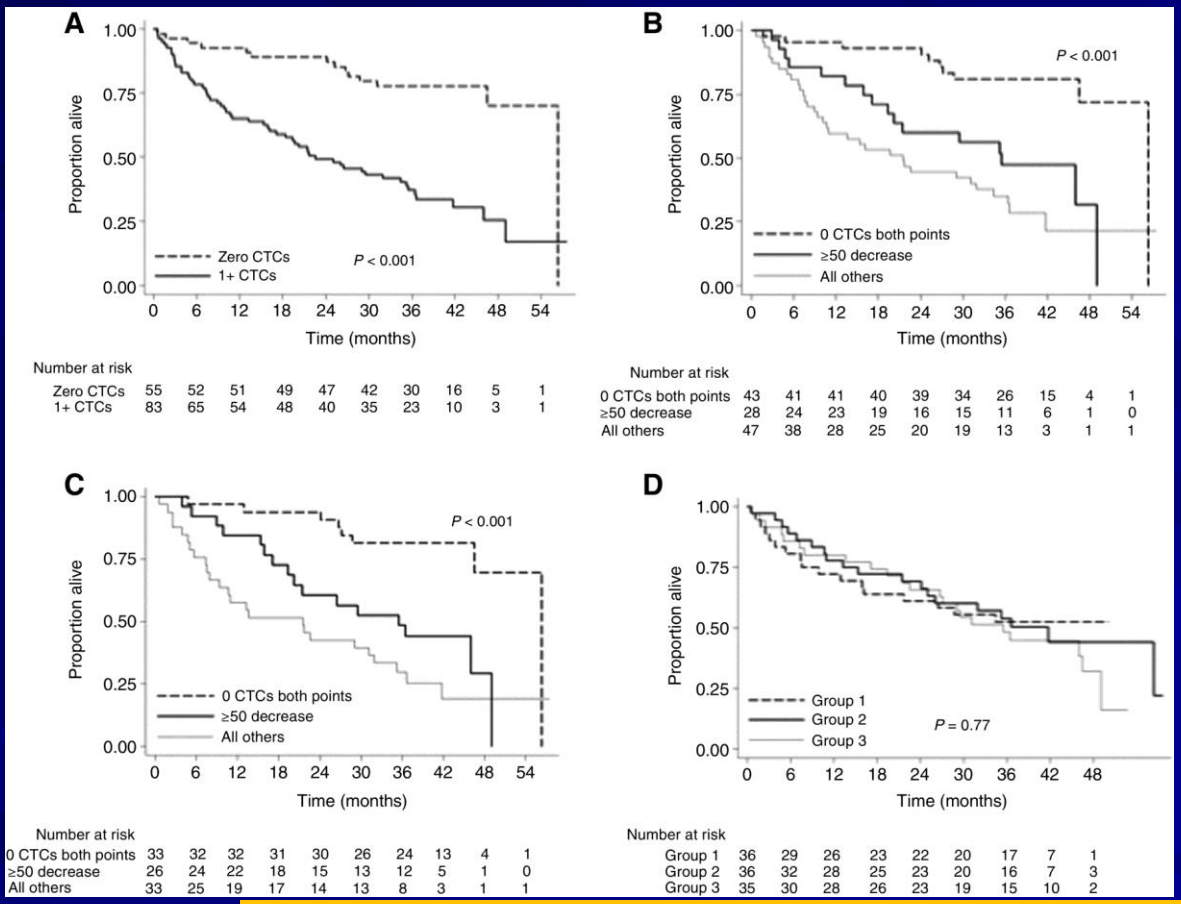
J Clin Oncol. 2013 Jan 20;31(3):365-72

- Presence of CTCs was associated with increased burden, increased tumor grade, and elevated serum chromogranin A .
- The presence of ≥ one CTC was associated with worse PFS and overall survival.
- Within tumor grades, presence of CTCs was able to define a poor prognostic subgroup.
- CTCs are a promising prognostic marker for patients with NETs and should be assessed in the context of clinical trials with defined tumor subtypes and therapy.



Early Changes in Circulating Tumor Cells Are Associated with Response and Survival Following Treatment of Metastatic Neuroendocrine Neoplasms

Khan et al, Clin Cancer Research 2016



- 138 patients with metastatic NENs (G1/G2) commencing therapy were prospectively recruited .

First post-treatment time point (PT1) : 3–5 weeks

0 CTCs at PT1 : only 4% progressed

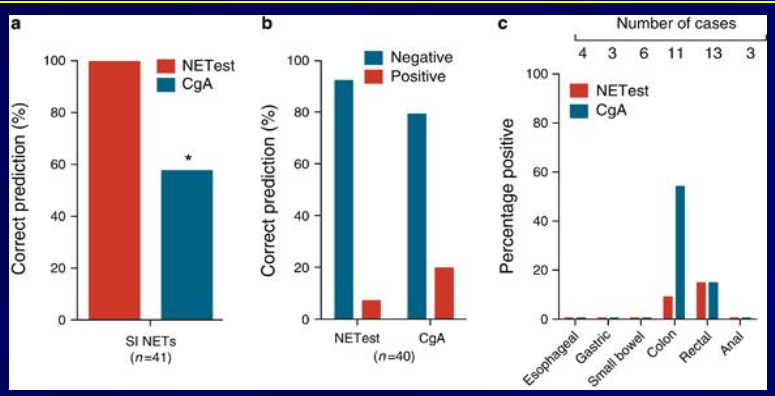
> 8 CTCs at PT1 : 65% progressed

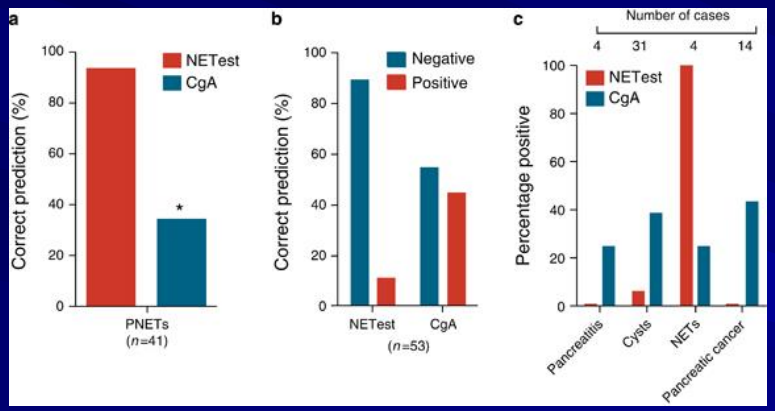
CTCs No	Median Survival mo
0	Not reached at 54
1-8	31.2
>8	10.8

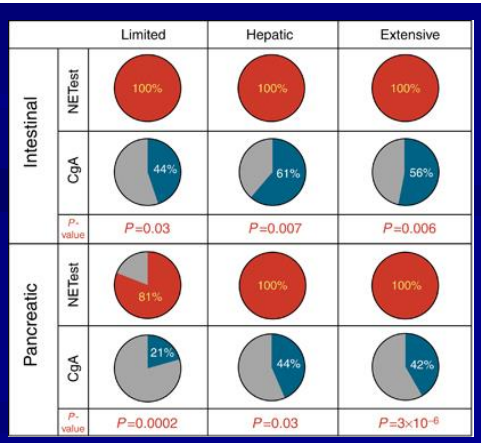
Early post-treatment CTC change is associated with radiologic response and survival, presenting an opportunity to explore biomarker-led sequencing studies in patients with NENs.

From monoanalytes to multianalytes…

MAAA PCR-based test (NETest)





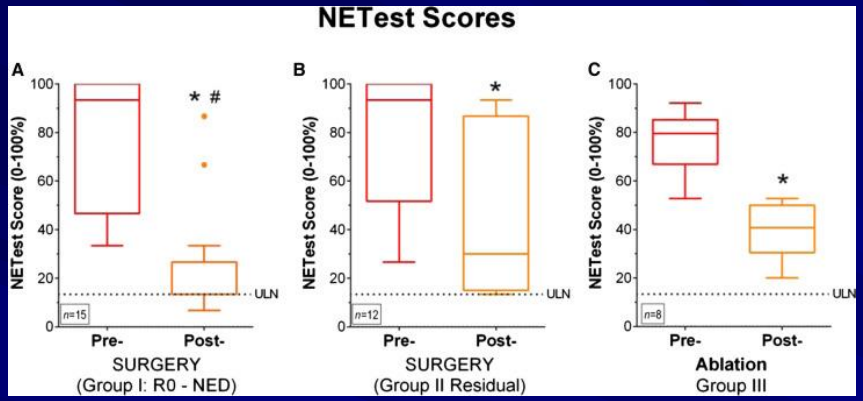


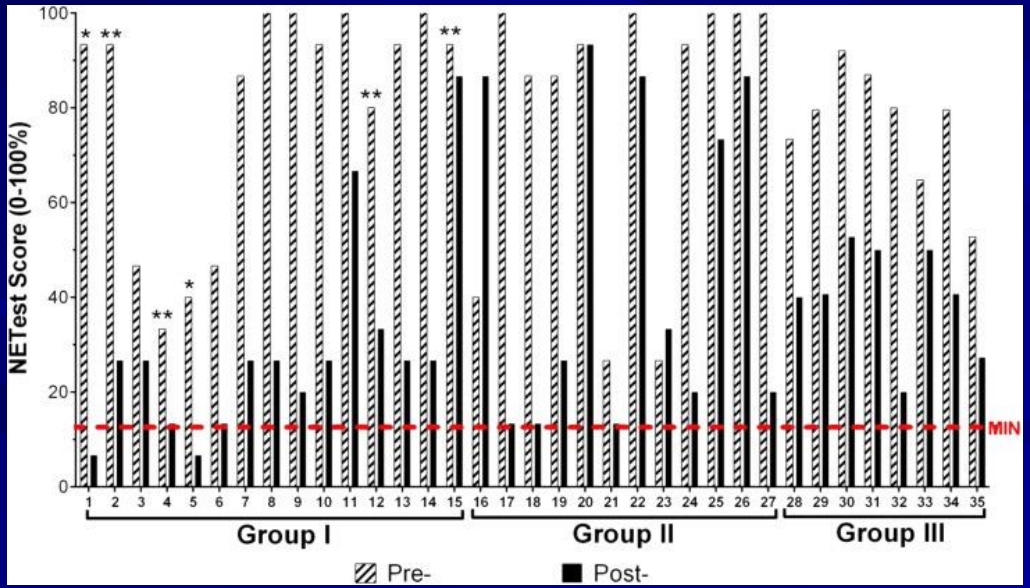
- Multianalyte with Algorithm Analysis Assay.
- Using gene microarray-based approaches of both malignant NET tissue and blood, **a PCR-based 51 marker signature (multigene test)** was developed.
- High sensitivity (85–98%) and specificity (93–97%) for the detection of intestinal and p NETs in circulating blood.
- Not affected by age, gender, ethnicity, fasting or PPIs.
- **A NET score (0–8)** is derived from the PCR data.
- Values ranged from 0 to 8; a value of >2 is a positive tumor score.

Modlin et al, Am J Gastroenterol 2015

NETest – potential clinical applications

Can it define the effectiveness of operative resection and loco-regional [TA(C)E, RFA] treatments?

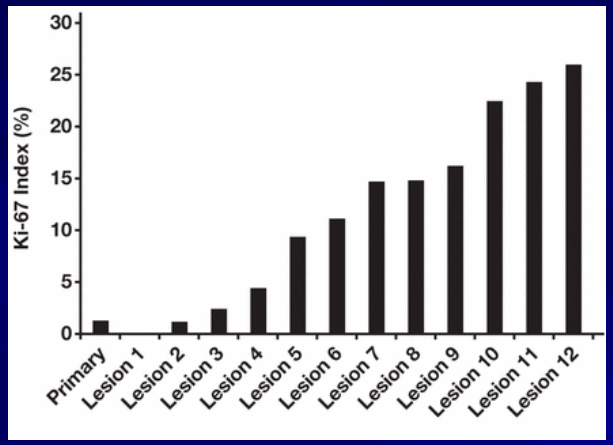


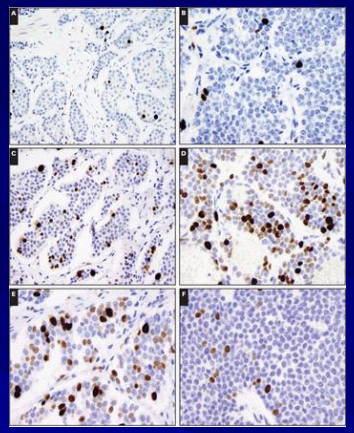


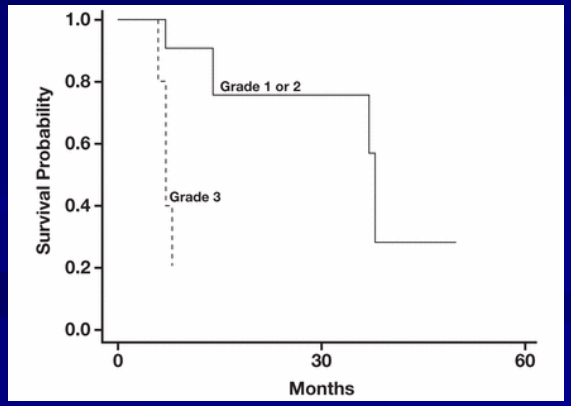
- 35 patients with GEP-NET (mainly G1 & G2) were included.
- Surgery was performed in 27 (1) to remove primary tumor, including loco-regional lymph nodes (*n* = 21); (2) for debulking (*n* = 4); and (3) for suspicion of NET
- 8 subjects had loco-regional treatments (TAE = 3, TACE: 3, RFA = 3) for hepatic metastases
- The NETest was scaled as minimal activity risk <14%, low activity risk 14–47%, and high activity risk >47%.
- Surgery significantly reduced scores in each of these groups .
- **4 (27%) developed disease recurrence loco-regionally at 6 months identified by imaging (^{68}Ga-somatostatin receptor-based PET). At 1 month after surgery, all 4 patients exhibited increased NETest scores (median, 30%; range 13-87%).**
- For group III, the pre-ablation NETest scores were elevated (76.2 ± 4.4%) and reduced after treatment.

Modlin et al, Surgery 2016

NET heterogeneity





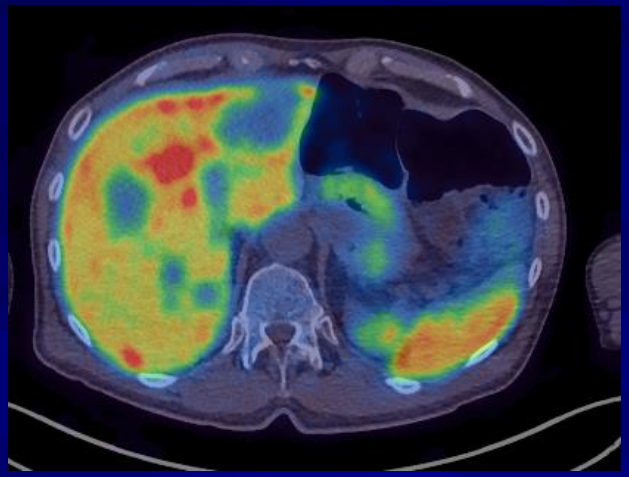


- Intra-tumoural phenotypic heterogeneity is frequently observed in GEP-NETs.
- Most primary small bowel NETs are G1 tumours (Ki67<2%).
- However, when these tumors metastasize to the liver, they may become highly proliferative.
- More than two-thirds of the patients who had G1 primary tumor developed G2 or G3 liver metastases.

Chi et al, Am J Clin Pathol, March 2015

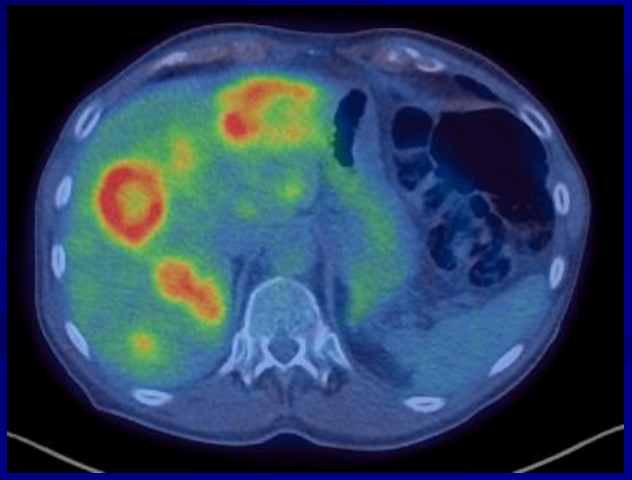
Combination of PETs for NET heterogeneity

Ga68

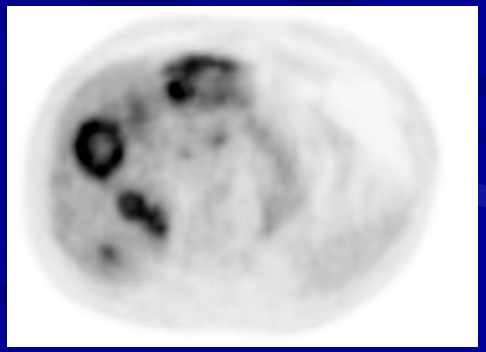


Ga68

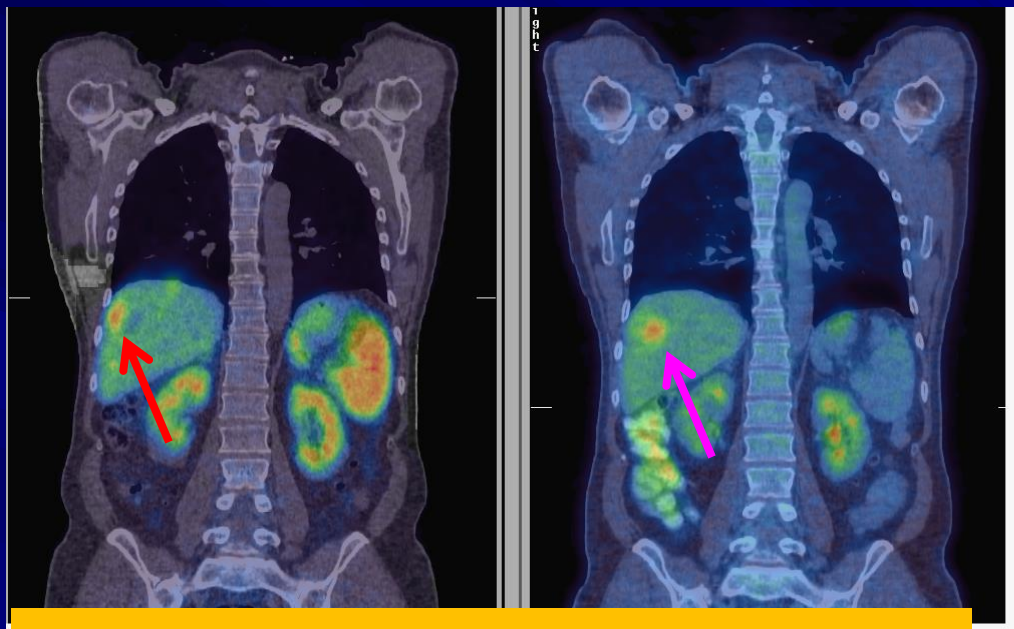
FDG



FDG

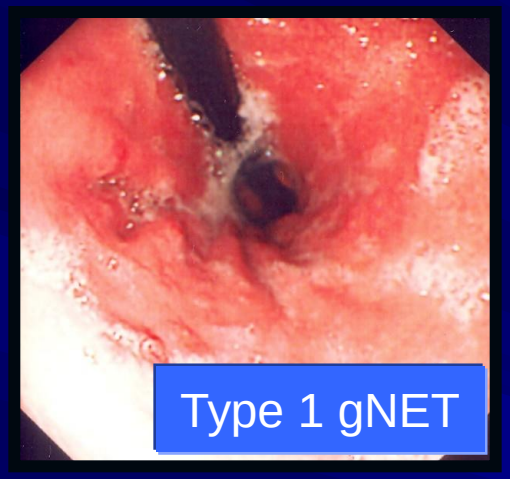


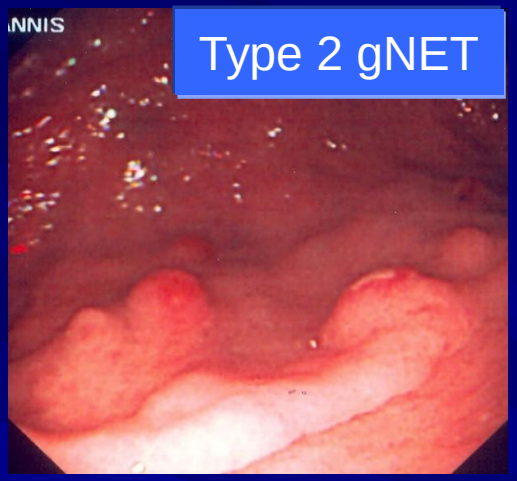
Hepatic metastases from NET (68Ga-octreotate PET, left) and from colorectal cancer (FDG-PET,right) in the same patient

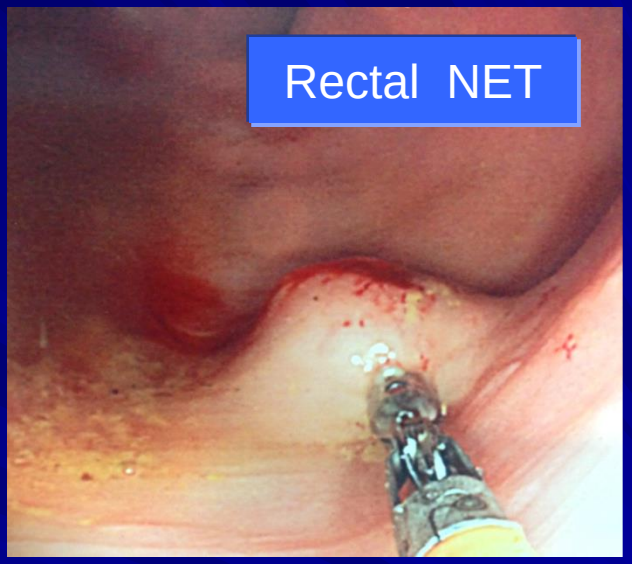


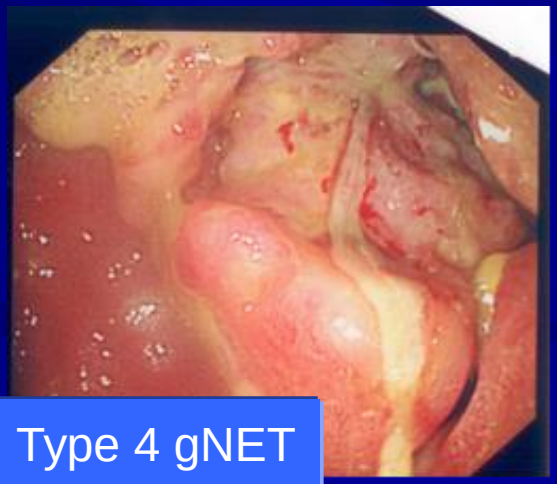
Use of Molecular Imaging to Differentiate Liver Metastasis of Colorectal Cancer Metastasis From Neuroendocrine Tumor Origin.
Desai et al, J Clin Gastroenterology 2010

The role of upper and lower GI endoscopy for diagnosis of NETs









The surrounding mucosa should be ALWAYS biopsied especially in gastric NETs

Endoscopic Ultrasound & Wireless small bowel capsule endoscopy

Endoscopic Ultrasound

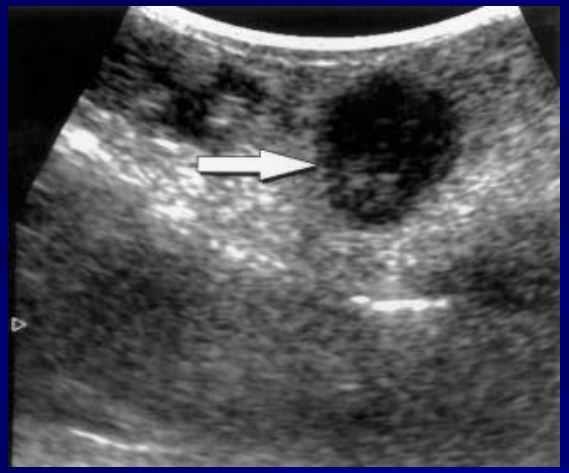
- Sensitivity :
  - 94% in insulinomas
  - 90% in pancreatic gastrinomas
- Can assess depth of invasion of stomach, duodenal, rectal wall

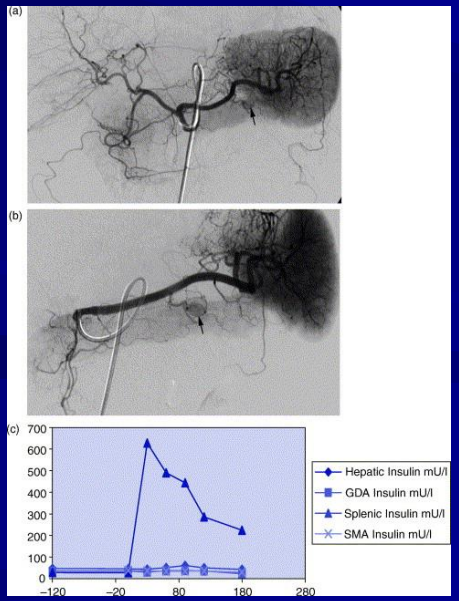
Wireless small bowel capsule endoscopy

May have a role for detection of occult small bowel NETs and ectopic varices

Jensen, Neuroendocrinology 2004
Tucker et al, Br J Surg 2006
Rondonotti et al, Endoscopy 2008

Other interventional techniques



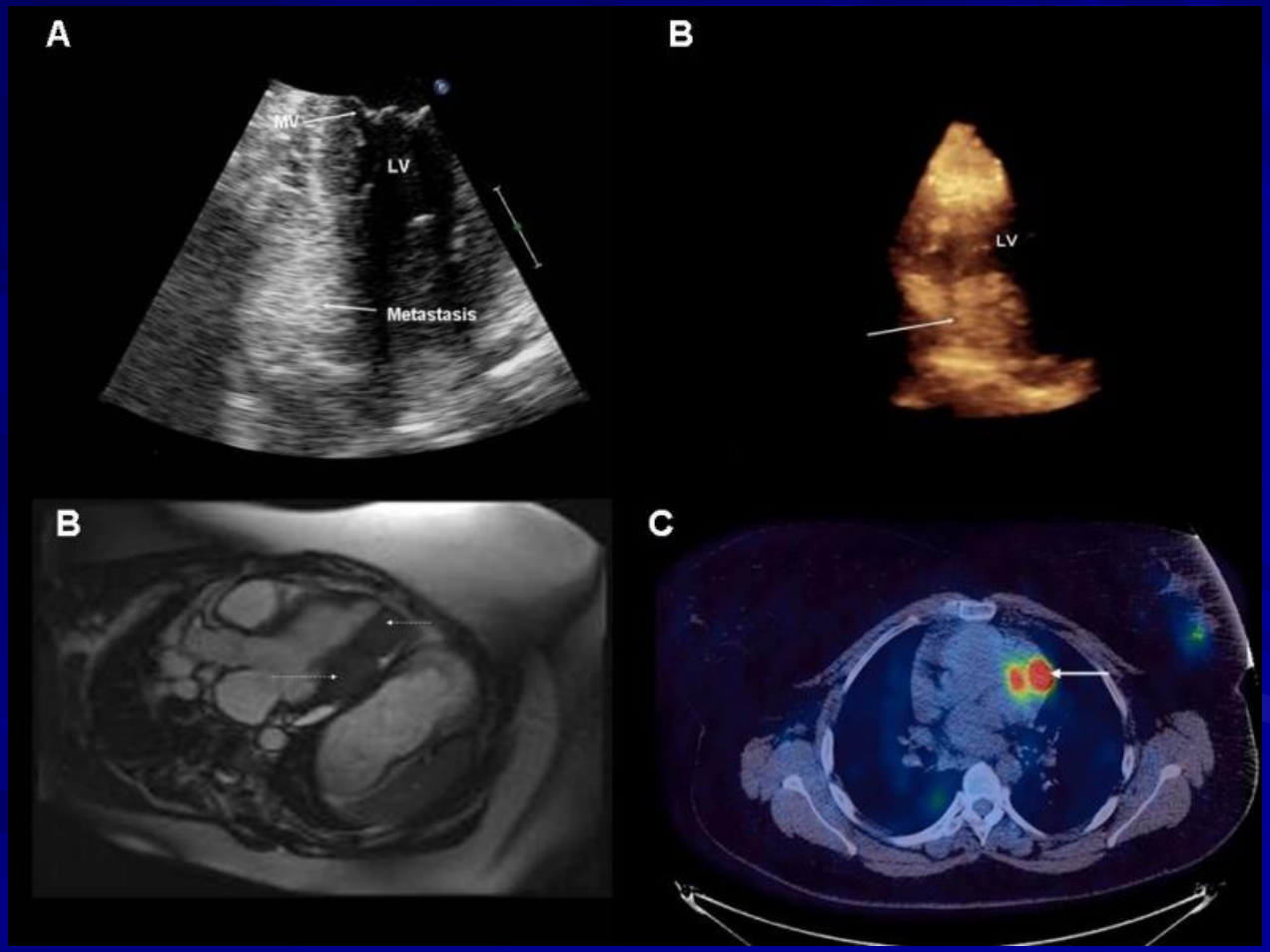


- **Intraoperative Ultrasound**
  Sensitivity : 95%
  Very useful in duodenal gastrinomas

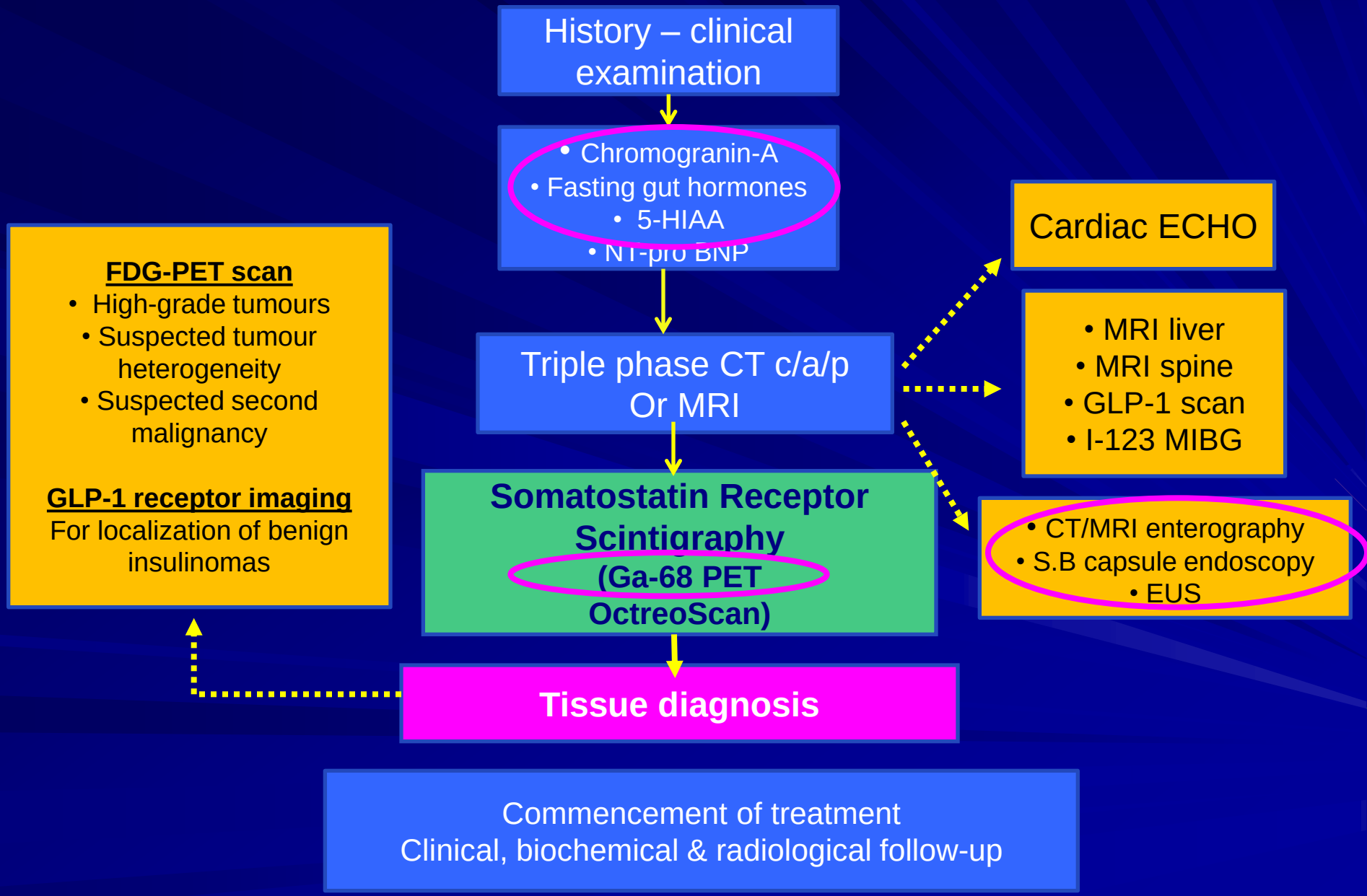
- **Selective angiogram with Ca**
  Rarely used
  > 90% sensitivity in revealing small pancreatic gastrinomas & insulinomas

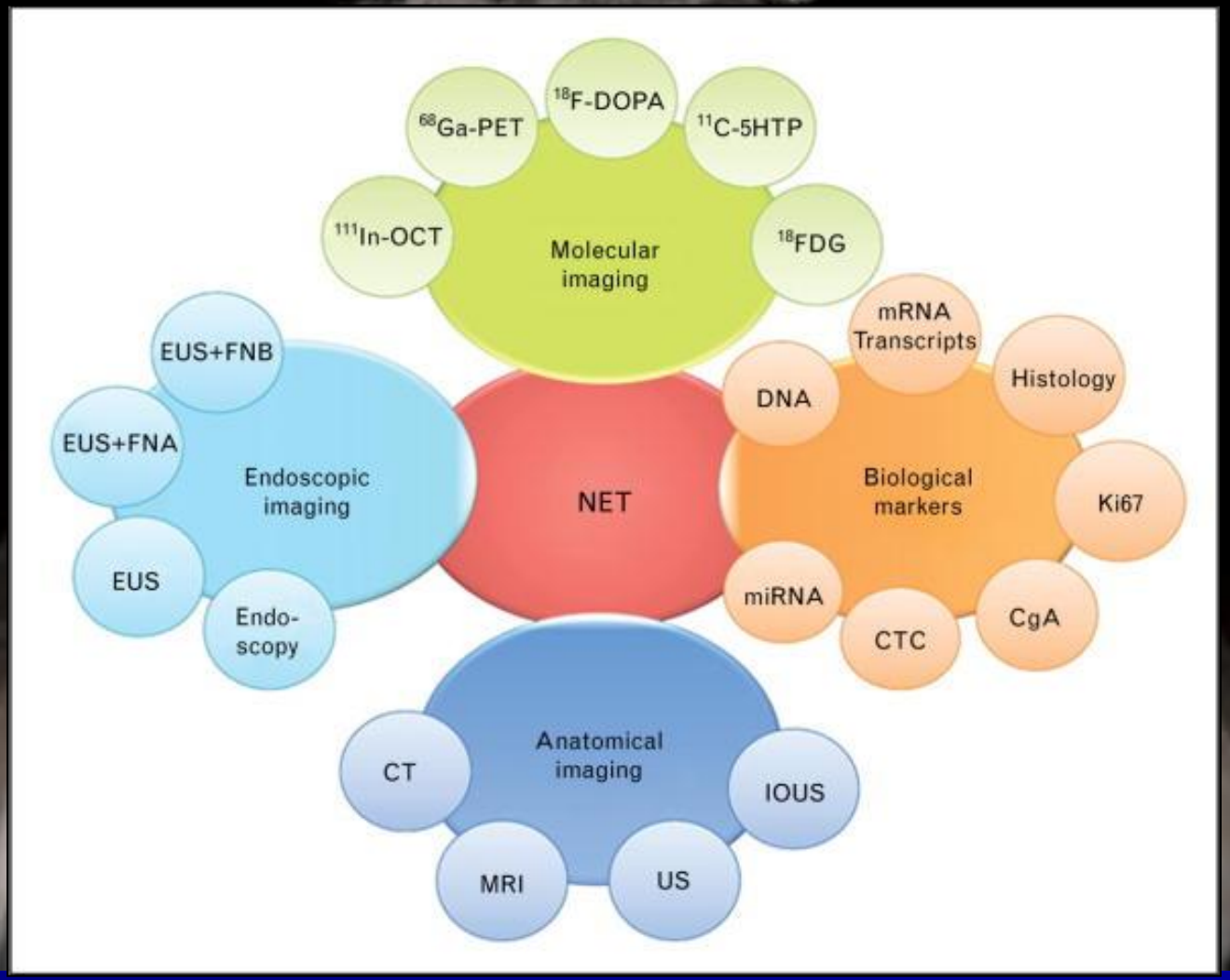
Jackson, Best Pract Clin Endocrinol Metabol 2005

Combination of diagnostic techniques to confirm cardiac metastases



Diagnostic algorithm




^{68}Ga-PET
^{18}F-DOPA
^{11}C-5HTP
^{111}In-OCT
Molecular imaging
^{18}FDG
EUS+FNB
EUS+FNA
Endoscopic imaging
EUS
Endo-scopy
NET
mRNA Transcripts
Histology
DNA
Biological markers
Ki67
miRNA
CgA
CTC
Anatomical imaging
CT
IOUS
MRI
US


Thank you