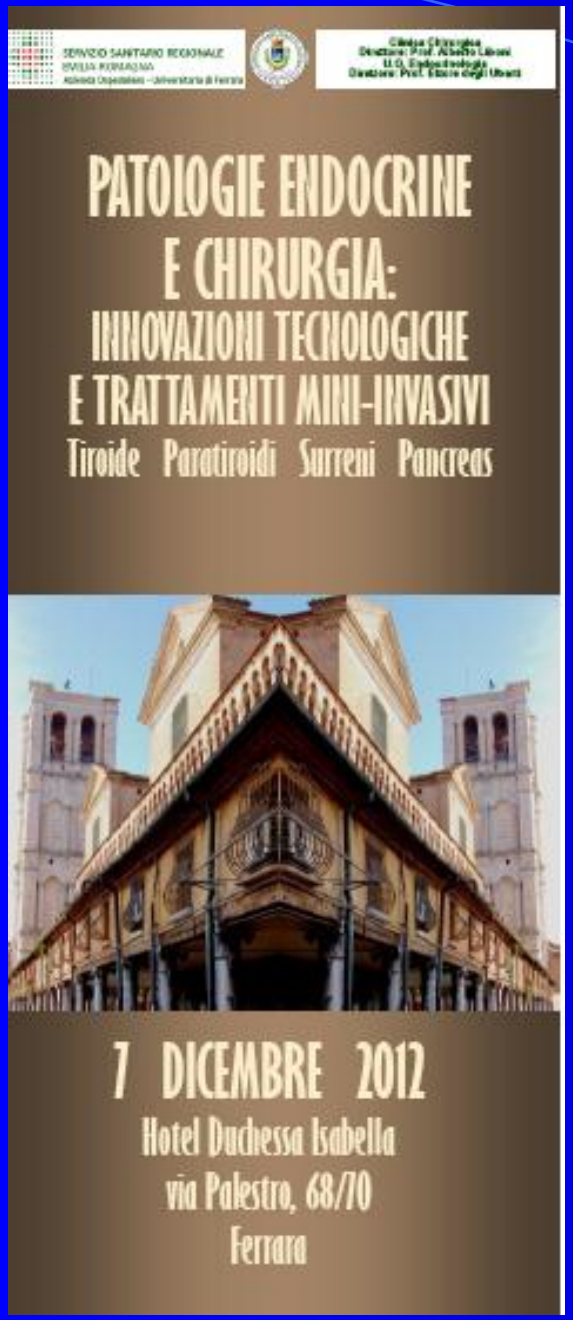

INQUADRAMENTO DIAGNOSTICO DEI TUMORI NEUROENDOCRINI DEL PANCREAS

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EFE 2012

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Tumori neuroendocrini pancreatici

Prevalenza 4-12 casi/milione di abitanti

- Non funzionanti (~ 40%)
- Funzionanti
  - Insulinoma (~26%)
  - Gastrinoma (~18%)
  - VIPoma (~5%)
  - Glucagonoma (~6%)
  - Somatostatinoma (~3%)
  - Tumori secernenti ormoni ectopici (~2%)
- Sporadici
- Associati a Neoplasie Endocrine di Tipo 1
  (40-100% dei pz con MEN1)
  spesso multiplo e non funzionante
  causa più frequente di morte nei pz MEN1

a Sdr. di von Hippel-Lindau
(12-20% dei pz con VHL)

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases

L'esperienza italiana

Età media 58.6±14.7 anni
F= 51.2 %, M= 48.8%

- ✓ Funzionanti: 73 (24.6%)
  - Insulinomi:53
  - Gastrinomi:15
  - Altre secrezioni: 5
- ✓ NON Funzionanti: 232 (75.4%)

➡ 115 casi (38.7%), diagnosi incidentale

Zerbi A et al. Am J Gastroenterol. 2010;105:1421

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Tumori neuroendocrini pancreatici

L'esperienza di Ferrara

casi: 40
M= 16 (40%) F= 24 (60%)
Età media alla diagnosi: 62 anni (range: 16-92 anni)

- ✓ Non funzionanti: 22 (55%)
- ✓ Funzionanti: 18 (45%) →
  - Insulinomi:10 (55.5%)
  - Gastrinomi:3 (16.6%)
  - Vipomi:2 (11.1%)
  - Glucagonomi: 1 (5.5%)
  - Tumori secernenti ormoni ectopici (calcitonina):2 (11.1%)

- ✓ Sporadici: 35 (87.5%)
- ✓ Associati a MEN1: 5 (12.5%)

- ✓ Carcinomi neuroendocrini: 20 (50%) → Con metastasi: 12 (66.6%)
- ✓ Tumori neuroendocrini: 15 (37.5%)
- ✓ Ad istologia non specificata: 5 (12.5%)

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

WORK-UP DIAGNOSTICO

Esame istologico
determinante per la strategia terapeutica

Markers immunoistochimici

Valutazione biochimica
Markers tumorali specifici e aspecifici

Imaging
Valutazione del tumore primario e della estensione della malattia

Kjell Öberg Clinics 2012;67(S1):109

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

LA DIAGNOSI SI BASA su

STORIA FAMILIARE

SEGNI E SINTOMI CLINICI

INDAGINI DI LABORATORIO

- PARAMETRI BIOCHIMICI -

INDAGINI DIAGNOSTICHE per IMMAGINI:

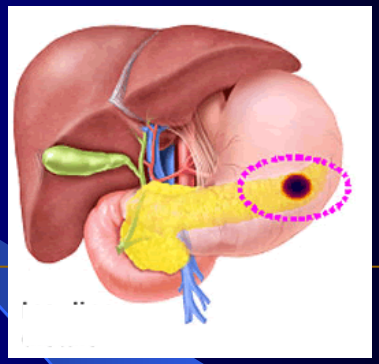
- Tomografia Computerizzata
- Risonanza Magnetica
- Ecografia
- Endoscopia
- Ecoendoscopia (EUS)
- Scintigrafia per SSR
- Angiografia

ISTOLOGIA

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

incidence ➔ 1-3/million population/year



- ➔ < 10% are malignant
- ➔ ~ 10% are multiple
- ➔ ~ 5% are associated with the MEN1 syndrome
- ➔ Tumor size ≥ 2 cm, Ki67 > 2% and various molecular features (chromosomal instability; chromosomal loss of 3p or 6q; chromosomal gain on 7q, 12q or 14q) all are predictors of metastatic disease, which is associated with decreased survival

Jensen RT et al Neuroendocrinology 2012;95:98

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Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

ages 40-45 years
females 60%

Clinical Presentation

The symptoms are due to the effects of hypoglycemia

on the CNS ➔ confusion, visual disturbances, headaches, behavioral changes, coma
on the adrenergic system ➔ sweating, tremor, palpitations, irritability

A recent increase in body weight is present in the majority of patients

The mean duration of symptoms at diagnosis is 3 years

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

DIAGNOSIS

- documented blood glucose levels ≤ 2.2 mmol/L (40 mg/dL)
- concomitant serum insulin levels ≥ 6 mU/L (≥ 36 pmol/L; ≥ 3 mU/L by ICMA)
- plasma/serum C-peptide levels ≥ 200 pmol/L
- serum proinsulin levels ≥ 5 pmol/L
- serum β-hydroxybutyrate levels ≤ 2.7 mmol/L
- absence of sulfonylurea (metabolites) in the plasma and/or urine

de Herder WW. Best Practice & Research Clinical Endocrinology & Metabolism 2007; 21,:33.

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

DIAGNOSIS

72-hour fast ➔ gold standard test

When the patient develops symptoms and the blood glucose levels are 2.2 mmol/L (40 mg/dL), blood is also drawn for C-peptide, proinsulin and insulin determinations

Failure of appropriate insulin suppression in the presence of hypoglycaemia substantiates an autonomously secreting insulinoma

de Herder WW. Best Practice & Research Clinical Endocrinology & Metabolism 2007; 21,:33.

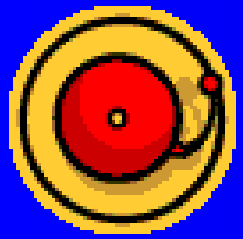
Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

DIAGNOSIS

Some of these tumours produce more proinsulin than insulin

PROINSULINOMA



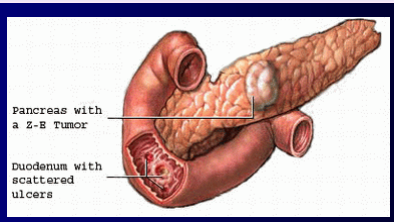
The diagnosis may be erroneously missed using only insulin ELISA, IRMA or ICMA

Insulin RIAs
generally have cross-reactivity with proinsulin
therefore do not produce these diagnostic problems

de Herder WW. Best Practice & Research Clinical Endocrinology & Metabolism 2007; 21,:33.

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA



incidence ➔ 0.5–2/million population/year

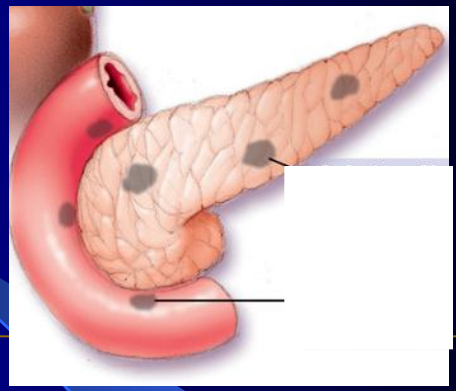
- According to WHO 2010 gastrinomas are NET G1-G2, usually >1 cm, showing local invasion and/or proximal lymph node metastases
- Liver metastases occur much more frequently with pancreatic gastrinomas (22–35%) than duodenal gastrinomas (0–10%)
- Pancreatic gastrinomas are generally large in size (mean 3.8 cm, 6% < 1 cm), duodenal gastrinomas are usually small (mean 0.93 cm, 77% < 1 cm)
- While the pancreatic gastrinomas may occur in any portion of the pancreas, duodenal gastrinomas are predominantly found in the first part of the duodenum including the bulb
- At surgery, 70–85% of gastrinomas are found in the right upper quadrant (duodenal and pancreatic head area), the so-called 'gastrinoma triangle'

Immunohistochemically, almost all gastrinomas stain for gastrin

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA



MEN 1

- 20–30% of patients with ZES
- Duodenal tumors are usually (70–100%) responsible for the ZES
- Duodenal tumors are almost always multiple
- Histologically, most gastrinomas are well differentiated and show a trabecular and pseudoglandular pattern
  Their proliferative activity (i.e. the Ki67 index) varies between 2 and 10%, but is mostly close to 2%

Jensen RT et al Neuroendocrinology 2012;95:98

EFE 2012

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA

Clinical Presentation

sporadic gastrinomas
ages 48-55 years
males 54-56%

All of the symptoms

except those late in the disease course

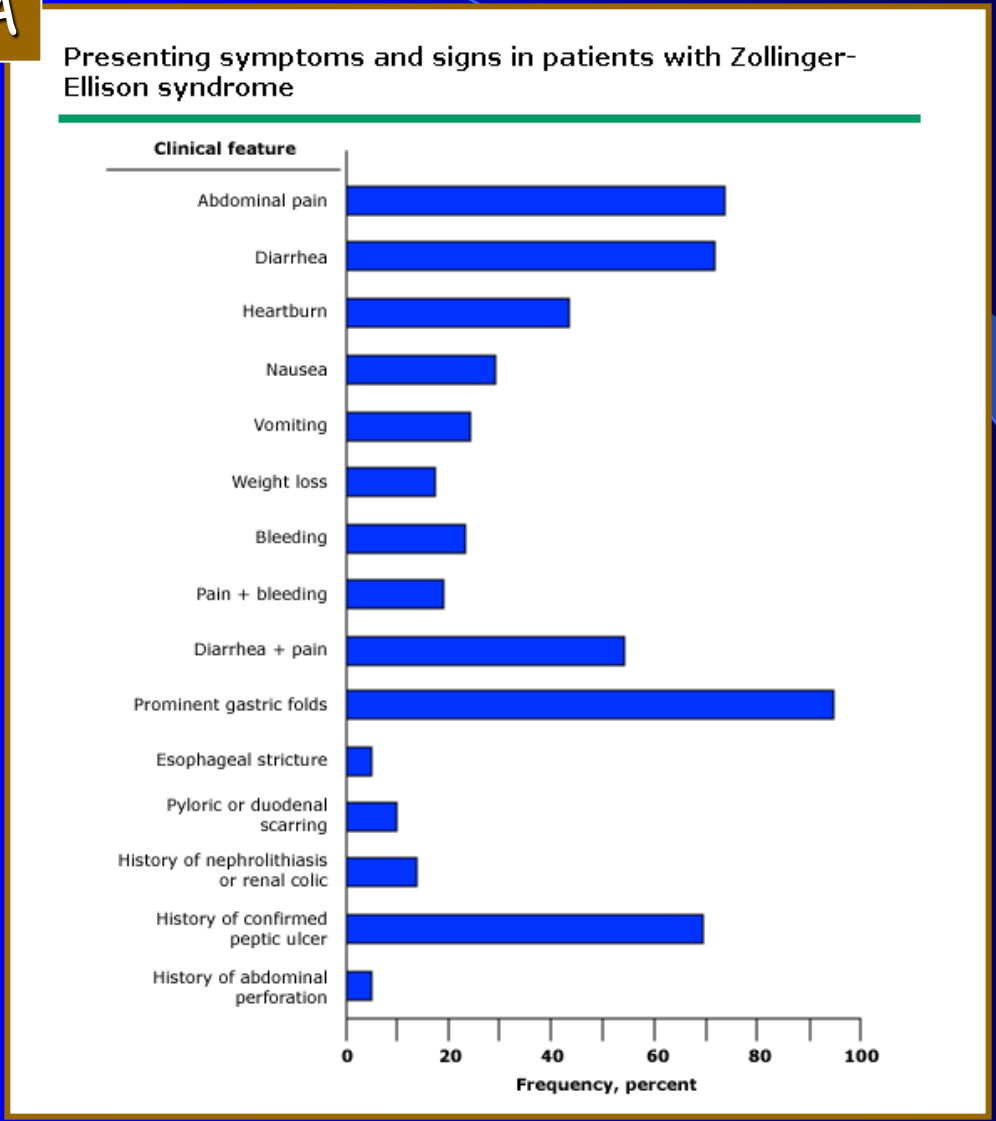
are due to gastric acid hypersecretion

The mean delay in diagnosis from the onset of symptoms is 5.2 years

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA



Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA

DIAGNOSIS

- Fasting serum gastrin concentration
- Secretin stimulation test
- Gastric acid secretion studies

Several other tests have also been described that may still have an adjunctive role, particularly when secretin is unavailable

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA

DIAGNOSIS

Fasting serum gastrin (FSG)

physiologic level < 100 pg/mL
is elevated in > 98% of all ZES patients
alone does not establish the diagnosis because of the many other causes of hypergastrinemia

Cause of hypergastrinemia

with hypochlorhydria/achlorhydria

- chronic atrophic fundus gastritis
often associated with pernicious anemia

with normal or slightly increased gastric acid secretion

- renal insufficiency
- massive small bowel resection
- G-cell hyperplasia
- gastric outlet obstruction
- retained gastric antrum

Jensen RT et al Neuroendocrinology 2012;95:98

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Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA

DIAGNOSIS

Fasting serum gastrin (FSG)

FSG level ≥ 1000 pg/mL
gastric pH ≤ 2

but

in 2/3 of patients with the ZES
FSG level >150 and < 1000 pg/mL

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

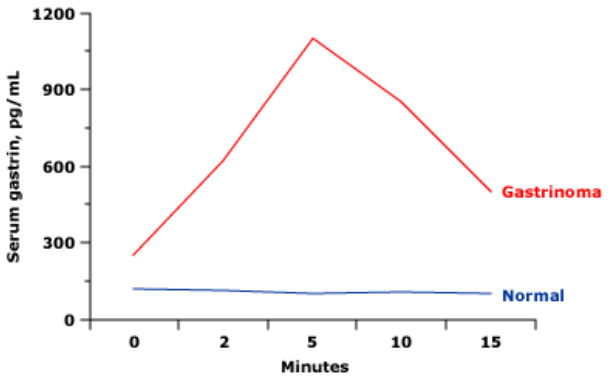
GASTRINOMA

DIAGNOSIS

Secretin stimulation test

Purpose
To diagnose gastrinoma (Zollinger-Ellison syndrome).
Preparation
Subject should be fasting on the day of study. Acid suppressive medications should be discontinued well in advance to avoid effects on gastrin release.*
Method
Baseline blood samples are taken five minutes and immediately prior to (time -5 minutes and 0 minutes) secretin administration. Secretin (0.4 mcg/kg) is given IV over a 30-second period. Serum samples are taken at two and five minutes after injection, and then at five-minute intervals for 20 minutes.
Contraindications
Secretin testing should not be performed in patients with acute pancreatitis.
Interpretation
Baseline serum gastrin in patients with gastrinoma is greater than 150 pg/mL. A positive secretin stimulation test demonstrates a quick and substantial increase in serum gastrin (by more than 200 pg/mL) and occurs in over 85 percent of patients with proven gastrinoma.
Note
Achlorhydria or profound hypochlorhydria can result in increased fasting serum gastrin levels and an exaggerated response to IV secretin stimulation. Proton pump inhibiting medications should be discontinued five days before the test and patients placed on a H2 receptor antagonist, which should be discontinued 24 hours prior to testing.

* Some authorities recommend that proton pump inhibitors should not be discontinued because of the risk that patients with severe disease may develop acute complications such as bleeding and perforation (see text).



Marked hypersecretion of gastrin occurs after the administration of secretin in a patient with a gastrinoma (Zollinger-Ellison syndrome) compared to the lack of response in normal subjects.

UpToDate

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Functional pancreatic endocrine tumor (PET) syndromes

Name	Biologically active peptide(s) secreted	Incidence (new cases/10^6 population/year)	Tumor location	Malignant %	Associated with MEN-1, %	Main symptoms/signs
A. Most common functional PET syndromes						
Insulinoma	insulin	1–3	pancreas (>99%)	<10	4–5	hypoglycemic symptoms (100%)
Zollinger-Ellison syndrome	gastrin	0.5–2	duodenum (70%); pancreas (25%); other sites (5%)	60–90	20–25	pain (79–100%); diarrhea (30–75%); esophageal symptoms (31–56%)
B. Established rare functional PET syndromes (RFTs)						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	vasoactive intestinal peptide	0.05–0.2	pancreas (90%, adult); other (10%, neural, adrenal, periganglionic)	40–70	6	diarrhea (90–100%); hypokalemic (80–100%); dehydration (83%)
Glucagonoma	glucagon	0.01–0.1	pancreas (100%)	50–80	1–20	rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%)
Somatostatinoma	somatostatin	rare	pancreas (55%); duodenum/jejunum (44%)	>70	45	diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%)
GRHoma	growth hormone-releasing hormone	unknown	pancreas (30%); lung (54%); jejunum (7%); other (13%)	>60	16	acromegaly (100%)
ACTHoma	ACTH	rare	pancreas (4–16% all ectopic Cushing's)	>95	rare	Cushing's syndrome (100%)
PET causing carcinoid syndrome	serotonin? tachykinins	rare (43 cases)	pancreas (<1% all carcinoids)	60–88	rare	same as carcinoid syndrome above
PET causing hypercalcemia (PTHrp-oma)	PTHrp; others unknown	rare	pancreas (rare cause of hypercalcemia)	84	rare	abdominal pain due to hepatic metastases, symptoms due to hypercalcemia
Possible rare functional PET syndromes						
PET secreting calcitonin	calcitonin	rare	pancreas (rare cause of hypercalcitonemia)	>80	16	diarrhea (50%)
PET secreting renin	renin	rare	pancreas	unknown	no	hypertension
PET secreting luteinizing hormone	luteinizing hormone	rare	pancreas	unknown	no	anovulation, virilization (female): reduced libido (male)
PET secreting erythropoietin	erythropoietin	rare	pancreas	100	no	polycythemia
PET secreting IF-II	insulin-like growth factor II	rare	pancreas	unknown	no	hypoglycemia

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Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Nonfunctional Pancreatic Neuroendocrine Neoplasms

ENETS Consensus Guidelines

Minimal Consensus Statements on Clinical Presentation and Prognosis

NF pancreatic NETs were formerly thought to present as large tumors, with signs and symptoms related to the tumor burden; however, more recent data reveals that these tumors increased incidence appears related to smaller incidental tumors. At first diagnosis the incidence of liver metastases ranges from 32 to 73%. The median overall survival of NF pancreatic NETs is 38 months with a 5-year survival rate of 43%. The presence of distant metastases and the degree of differentiation are the most powerful predictor of poor survival.

Falconi M et al.Neuroendocrinology 2012;95:120

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Nonfunctional Pancreatic Neuroendocrine Neoplasms

Symptoms and signs

- abdominal pain (35–78%)
- weight loss (20–35%)
- anorexia and nausea (45%)
- intra-abdominal hemorrhage (4–20%)
- jaundice (17–50%)
- palpable mass (7–40%)

In rare cases
in both familiar and more rarely sporadic in NF-NENs
the tumor may become functional during the
clinical course and present hormonal symptoms

Falconi M et al.Neuroendocrinology 2012;95:120

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Nonfunctional Pancreatic Neuroendocrine Neoplasms

ENETS Consensus Guidelines

Minimal Consensus Statement on Laboratory Tests

CgA is a recommended tumor marker, while the sensitivity and specificity of meal-stimulated PP are controversial. PP may be useful for early detection of pancreatic tumors in MEN-1. Extensive hormonal screening is not justified unless the patient during follow-up starts presenting hormonal symptoms.

Falconi M et al.Neuroendocrinology 2012;95:120

EFE 2009

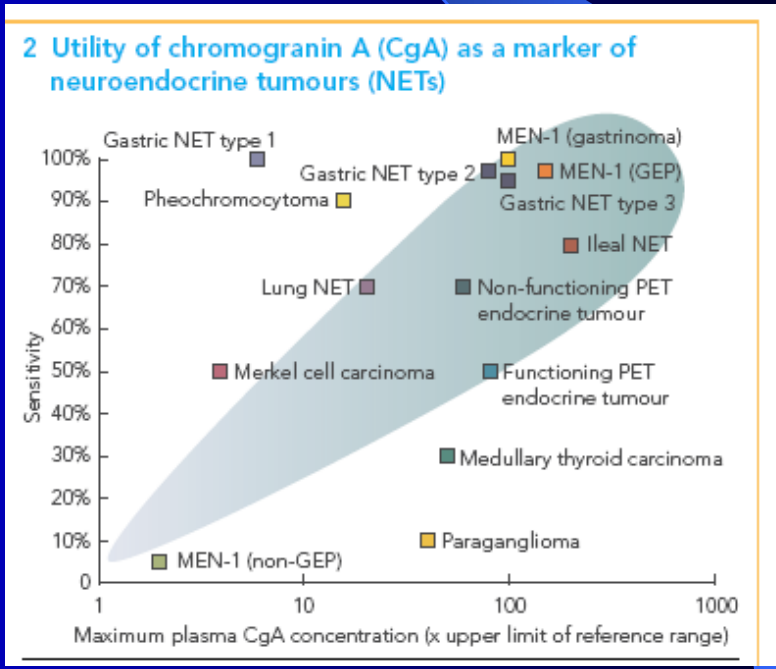
Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Chromogranin A

- is the best general neuroendocrine serum marker available in all NETs
- may be useful to indicate tumour progression and response to treatment

False positives

- chronic renal, liver and heart failure
- essential hypertension
- inflammatory bowel disease
- diarrhoea
- chronic atrophic gastritis
- proton pump inhibitors
- pancreatic and small-cell lung cancer
- some prostate carcinomas



Modlin IM et al MJA 2010; 193: 46
de Herder WW. Best Practice & Research Clinical Endocrinology & Metabolism 2007; 21,:33.

EFE 2009

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Nonfunctional Pancreatic Neuroendocrine Neoplasms

Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors

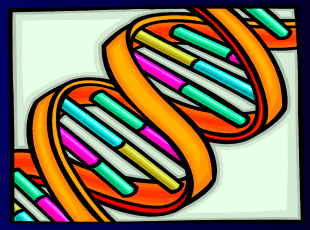
68 patients (28 functioning, 40 non functioning)

The combined assessment of CgA and PP leads to a significant increase in the diagnosis of pancreatic NETs with an increasing in sensitivity from 68% to 93%

Panzuto F et al. J Endocrinol Invest. 2004;27:6

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Pancreatic Neuroendocrine Neoplasms



ENETS Consensus Guidelines

Genetic Study for MEN1 and Other Inherited Syndromes Associated with p-NETs

If the family history is positive for MEN1, suspicious clinical or laboratory data for MEN1 are found or multiple tumors are present raising the possibility of MEN1, then MEN1 genetic testing should be considered. Genetic testing for MEN1 should include sequencing of the entire gene and its splice variants. If genetic testing is considered, genetic counseling should be performed, prior to testing [11, 84, 85].

If clinical features suggest von Hippel-Lindau disease (VHL), tuberous sclerosis or NF-1, appropriate gene testing should be considered after genetic counseling [11].

Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Diagnosis

Tumor localization studies are necessary to

- determine whether surgical resection is indicated
- localize the primary tumor
- determine the extent of the disease
  (metastatic disease the liver or distant sites)
- assess changes in tumor extent with treatments

Jensen RT et al Neuroendocrinology 2012;95:98

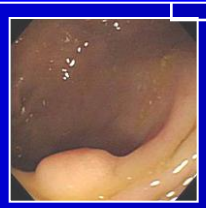
Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Diagnosis

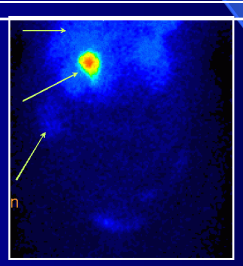
Localization studies

- MRI

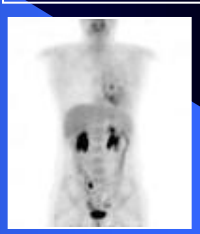
- Endoscopy



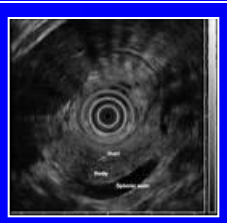
- SSR scintigraphy



- PET

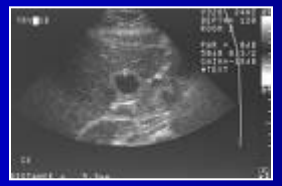


- Endoscopic ultrasound

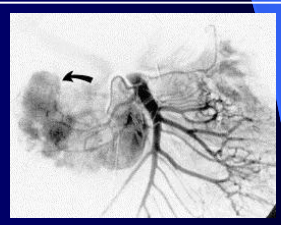


- CT

- Ultrasound



- Selective angiography



Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

Diagnosis

ENETS Consensus Guidelines

Localization studies

Ultrasound, CT, and MRI are positive in 10–40% of cases

Endoscopic US is positive in 70–95% of all cases if an experienced endoscopist is available and is thus is the imaging study of choice if the other non-invasive studies are negative

Selective angiography is positive in 60% of cases
if combined with hepatic venous sampling for insulin after intra-arterial calcium administration it is positive in 88–100% of cases

Intraoperative ultrasound is essential for localizing the insulinoma at surgery

Jensen RT et al Neuroendocrinology 2012;95:98

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Inquadramento diagnostico dei tumori neuroendocrini del pancreas

INSULINOMA

Diagnosis

ENETS Consensus Guidelines

Localization studies

SRS is positive in only 50% of cases ➔low density or lack of somatostatin receptors that bind octreotide with high affinity (sst2, sst5)

18 F-FDG PET imaging is disappointing ➔low proliferative potential

Promising results have been obtained using PET/CT with 11 C-5-HTP, and 68 Ga-DOTATOC

Insulinomas have been shown to overexpress GLP-1 receptors and it has been shown that radiolabeled GLP-1 analogues can localize the insulinoma

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

GASTRINOMA

Diagnosis

ENETS Consensus Guidelines

Localization studies

Most recommend initially a UGI endoscopy with careful inspection of the duodenum followed by a mdCT or MRI and SRS

If these studies are negative and surgery is being considered,
EUS should be performed which will detect most pancreatic gastrinomas, but misses up to 50% of duodenal tumors
If results are still negative (< 10%), selective angiography with secretin stimulation and hepatic venous gastrin sampling should be considered

Intraoperative ultrasound and routine duodenotomy for duodenal lesions preferably preceded by transillumination of the duodenum should be done in all patients at surgery

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Jensen RT et al Neuroendocrinology 2012;95:98

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

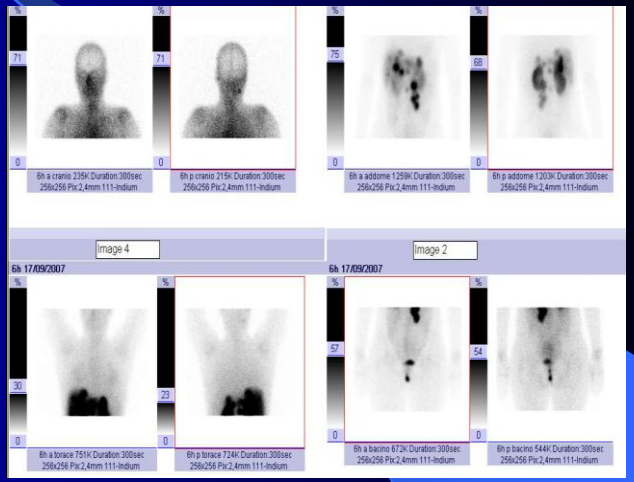
GASTRINOMA

ENETS Consensus Guidelines

Diagnosis

Localization studies

SRS is the best study to initially stage the disease and detects both liver and distant metastases
SRS misses 50% of tumors <1 cm



Bone metastases occur in up to 1/3 of patients with LM and should be sought in all patients by using SRS and an MRI of the spine

18 F-FDG PET imaging is disappointing ➔low proliferative potential
Promising results have been obtained using PET/CT with 11 C-5-HTP, 18 F-DOPA, 68 Ga-DOTATOC

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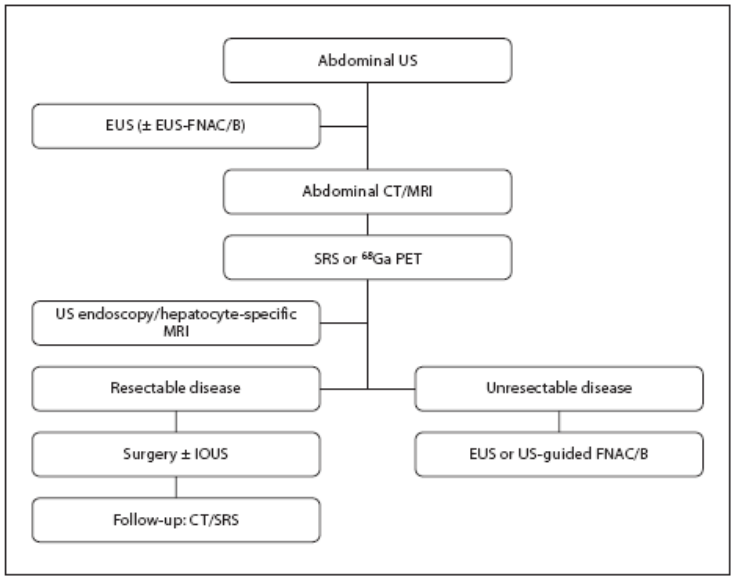
Jensen RT et al Neuroendocrinology 2012;95:98

Nonfunctional Pancreatic Neuroendocrine Neoplasms

ENETS Consensus Guidelines

Suggested algorithm of different diagnostic options for the identification, typing and staging of non-functioning pancreatic NENs.

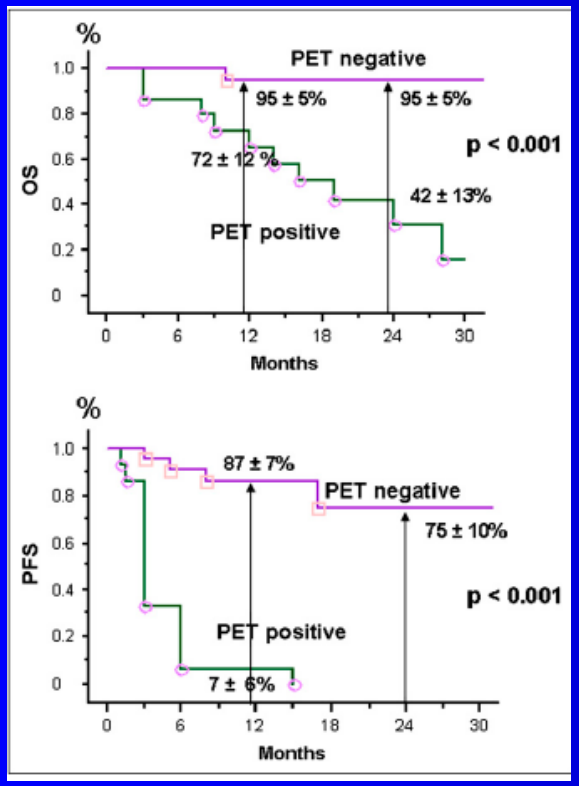


Minimal Consensus Statement on Imaging

US combined with state-of-the-art contrast-enhanced CT/MRI (including MRCP) is recommended. The decision whether to use CT or MRI depends on the preference, skill and expertise of the radiologist and the availability of the different techniques at each institution. Somatostatin receptor scintigraphy has been the mainstay single-screening method for extrahepatic disease manifestation although PET using ^{68}Ga and ^{18}F-DOPA appears to be challenging and may give better resolution and detect more lesions. Patients with small NF pancreatic NETs may be assessed using EUS, and EUS-FNAB has shown good results in confirming a diagnosis. Contrast-enhanced US appears to improve characterization of NET liver metastases and CE-EUS may prove effective in characterizing pancreatic NETs.

Inquadramento diagnostico dei tumori neuroendocrini del pancreas

Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors



Garin E et al. J Nucl Med 2009; 50: 858

18F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors

Translational Relevance

Neuroendocrine (NE) tumors are a heterogeneous group of neoplasms with great variability in clinical outcome. This requires accurate diagnostic techniques for precise staging and choice of therapy. Today, the grading of NE tumors is mainly based on the immunohistochemical determination of the proliferation marker, Ki67. However, pathologic examination on biopsy or resected specimens may not be representative of the whole tumor burden, and whole-body noninvasive alternatives are warranted. In this study, we show a high prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for predicting the survival of patients with NE tumors. The prognostic value of FDG-PET was compared with the value of traditional markers for NE tumors, such as proliferation index, computed tomography–verified liver metastases, and plasma chromogranin A levels. FDG-PET and Ki67 index were the only independent predictors of overall survival. This observation suggests FDG-PET as a valuable noninvasive supplement or alternative to grading based on the proliferation index as well as for detection of disease progression.

Binderup T et al.Clin Cancer Res.2010;16:978

The use of FDG PET appears promising in disease prognostication possibly influencing aggressiveness of management

Tan EH & Tan EH World J Clin Oncol 2011;2: 28

CONCLUSIONS

Careful evaluation of clinical symptoms and appropriate use of diagnostic tools are needed in order to achieve a correct management of patients with neuroendocrine pancreatic tumors

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