SESSIONE I

TUMORI NEUROENDOCRINI DEL TRATTO GASTRO-ENTERO-PANCREATICO

9.20 L'iter diagnostico: fondamentale il gioco di squadra

Cosa ci dice l'AME GEP-NET Statement?

Franco Grimaldi & Enrico Papini

Caso clinico: ipoglicemia spontanea

- **Test al digiuno +**
- **TC addome: lesione compatibile con NET pancreatico singolo**
- **Chirurgia**
  - Esame istologico: 2 tumori NET G1, Ki67 <1%, 18 mm e 5 mm, esprimenti recettori per somatostatina 2
  - Coesistono multiple lesioni di 1-5 mm, compatibili con "nesidioblastosi«
  - Test genetico per MEN1 negativo.
- Dopo 12 mesi **PET DOTA-NOC** : +++ a livello dell'istmo pancreatico, lesione di 13 mm
- Nuovo **test al digiuno**: + tardiva
- **Ecografia endoscopica:** presenza della lesione nota e di una ulteriore formazione di 10 mm, sempre nel corpo-istmo pancreatico.
- Discussione **multidisciplinare**: mancato accordo sul percorso terapeutico
- Si pone in **trattamento con octreotide LAR 30 mg**, 1 fl i.m. ogni 28 giorni .

Ipoglicemia spontanea: problemi diagnostici "step by step"

- Quando sospettare un iperinsulinismo endogeno
- Come confermarlo
- Come fare la diagnosi di localizzazione
- Esame citologico: utilità e limiti
- Quali indagini sul materiale operatorio
- Quando eseguire la valutazione genetica

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CONSENSUS STATEMENT

Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms

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Ipoglicemia spontanea: problemi diagnostici "step by step"

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A STEP BY STEP MULTIDISCIPLINARY APPROACH TO CLINICAL DIAGNOSIS

3.3.3 Spontaneous hypoglycemia

3.3.3.1 Clinical approach: when to suspect a GEP-NEN

Hypoglycemia (plasma glucose < 60 mg/dL on a venous blood sample) is an uncommon clinical problem in non-diabetic adults. The presence of symptoms reinforces the clinical relevance of this finding because some normal subjects may have an asymptomatic low glucose level after prolonged fasting. Symptoms may be due to sympathoadrenal activation ("adrenergic symptoms", i.e. sweating, shakiness, tachycardia, anxiety, hunger) and/or neuroglycopenia (weakness, dizziness, inappropriate behavior, altered concentration, confusion, blurred vision and, in extreme cases, coma and death)(227,228,229). Symptoms may present at a variable glucose level (generally as low as <55-60 mg/dL)(227,228,230,231).

Hypoglycemia may be due to several conditions beyond insulin-secreting tumors (232) (table 8).

Table 8
Differential diagnosis of hypoglycemia

Drugs	Insulin, oral hypoglycemic drugs Quinine, pentamidine, indomethacin, lithium More rarely: ACE-inhibitors, levofloxacin, trimethoprim-sulphamethoxazole, and heparin
Excessive alcohol consumption	Block of stored glucose release
Liver, kidney or heart failure	Depletion of substrates required for gluconeogenesis
Long-term starvation (anorexia nervosa)	Depletion of substrates required for gluconeogenesis
Non islet cell tumors	Excessive production of IGF-II that causes the use of too much glucose
Gastric surgery (post gastric bypass)	Accelerated transit and malabsorption
Hypoadrenalism and hypopituitarism	Deficiency of hormones that regulate glucose production
Insulin autoimmune hypoglycemia	

IPOGLICEMIA: CLASSIFICAZIONE

Tradizionale

Ipoglicemia a digiuno

vs

post-prandiale ("reattiva")

Sindrome post-prandiale

sintomi aspecifici, entro 4 h dal pasto, senza vera ipoglicemia

Nuova

- **Paziente in terapia o con malattie concomitanti**
- **Paziente in apparente benessere**
  - **Iperinsulinismo endogeno** (insulinoma, nesidioblastosi)
  - **Ipoglicemia autoimmune**
  - **Ipoglicemia factitia**

Diagnosi con Test al pasto misto

Test OGTT

Cause di ipoglicemia post-prandiale «documentata»: Insulinoma (esordio), nesidioblastosi primitiva o secondaria a bypass gastrico, autoimmune, factitia…..

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3.3.3.2 Work-up in the patient with suspected insulinoma

Biochemical assessment

Symptoms and/or signs suggesting hypoglycemia combined with a ≤55 mg/dL (3.0 mmol/liter) plasma glucose, a ≥ 3.0 μU/mL (18 pmol/liter) plasma insulin, a ≥0.6 ng/mL (0.2 nmol/liter) C-peptide, and a ≥ 5.0 pmol/liter proinsulin indicate endogenous hyperinsulinism (227.228.231). Exogenous insulin-induced hypoglycemia is always associated with low levels of C-peptide. In patients with insulinoma, proinsulin corresponds to about 70% of insulin immunoreactivity, whereas it is normally limited to 20%.

Blood and urine assays for sulfonylureas will detect factitious hypoglycemia caused by these drugs. Pituitary and adrenal function tests are useful to rule out hypoadrenalism and hypopituitarism (227,228,230,238).

We recommend against the use of biochemical markers as the initial diagnostic step for potential GEP-NEN patients.

We recommend the determination of the appropriate biochemical marker only after the diagnosis or strong clinical suspicion of GEP-NEN. The panel of markers should take into account the clinical picture and local availability/expertise.

We recommend considering all possible clinical and analytical interfering factors in presence of elevated serum or urinary levels of GEP-NEN markers. The determination should be repeated, if possible, after their timely withdrawal.

Diagnosi differenziale delle sindromi ipoglicemiche da iperinsulinismo

Indagine	Insulinoma	Insulina Esogena	Sulfaniluree	Ipoglicemia Autoimmune
Insulina	++	+++	+++	+++
C-peptide	+++	-	+++	+++
Proinsulina	+++	-	+++	+++
Ac anti insulina	-	-/+	-	++
β idrossi-buttirato	-	-	-	-

Biochimica della nesidioblastosi: analoga all'insulinoma

Tumore extrapancreatico (produzione IGF-II): ↓Insulina e ↓ C-Peptide

Caso clinico: problemi diagnostici step by step nel sospetto di insulinoma

- Quando sospettare un iperinsulinismo endogeno
- **Come confermarlo**
- Come fare una diagnosi di localizzazione
- Esame citologico: utilità e limiti
- Quali indagini sul materiale operatorio
- Quando eseguire la valutazione genetica

DIAGNOSI BIOCHIMICA DI INSULINOMA

Test al digiuno per 72 h (gold standard):

- ↓ **Glicemia < 55*** mg/dL (3 mmol/L)
- ↑ **Insulina ≥ 3** µU/mL (≥18 pmol/L) (precedente 6 µU/mL)
- ↑ **C-peptide ≥ 0,6** ng/mL (0,2 nmol/L)

- **Screening per sulfaniluree**: negativo
- **Negatività anticorpi anti-insulina**
- **Pro-Insulina** ≥ 5 pmol/L (rara produzione solo di pro-insulina).
- **Beta-idrossi-butirrato** ≤ 2,7 mmol/L

Attenzione ai valori dei Reflettometri ….

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Provocative tests

Biochemical diagnosis is based on lack of suppression of endogenous insulin secretion by hypoglycemia (239) and inappropriately elevated insulin level during hypoglycemia is the diagnostic key point. In 95% of cases the diagnosis is achieved only during prolonged fasting (up to 72 h) inducing symptomatic hypoglycemia (240). The test should be performed on inpatients under close supervision and with regular control of glycaemia and mental status. A ≥3 μU/mL (≥18 pmol/L) insulin value, in the presence of glucose level <55 mg/dL has recently been proposed as diagnostic cut-off (223). Plasma β-hydroxybutyrate levels ≤2.7 mmol/liter may confirm the diagnosis, demonstrating the suppressive effect of insulin on ketogenesis even during a protracted fasting (231).

At the end of the 72h fasting test, in the absence of hypoglycemia, the use of stimulation tests was proposed (231). Stimulation tests, e.g. tolbutamide, glucagon or calcium, are not recommended because they may induce a prolonged and refractory hypoglycemic condition, but long-term fasting can be finished after 72 hours with bicycle test.

I test di stimolo al termine del digiuno sono sconsigliati per il rischio di ipoglicemie protratte e severe.
Considerare il test al cicloergometro.

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We recommend the simultaneous evaluation of blood glucose, insulin and C-peptide to detect endogenous hyperinsulinemia in all patients with spontaneous hypoglycemia.
We recommend a prolonged fasting test (up to 72 h) in patients referred for a previous hypoglycemic episode who are free of symptoms at the moment of medical examination.
We recommend against the use of stimulation tests for the diagnosis of insulinoma.
We recommend the use of localization tests (CT/CEUS and EUS) only after the biochemical diagnosis of insulinoma.

I test di localizzazione devono essere condotti solo dopo la diagnosi biochimica di iperinsulinismo endogeno

Caso clinico: problemi diagnostici step by step nel sospetto di insulinoma

- Quando sospettare un iperinsulinismo endogeno
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Imaging

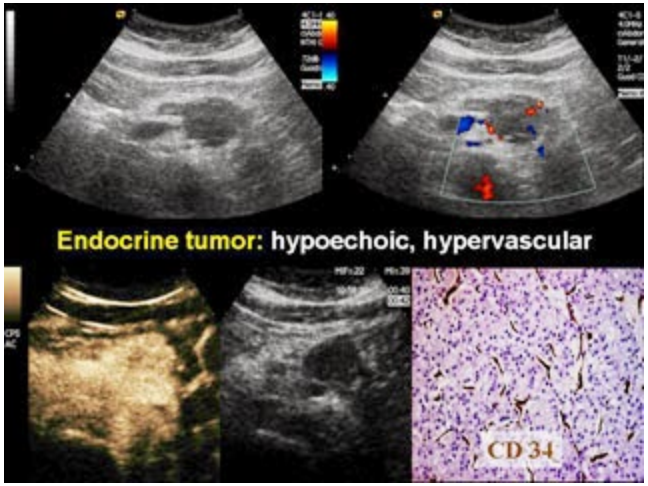
In all patients with a confirmed biochemical diagnosis, imaging is indicated to localize the tumor (241).
Since 80% of insulinomas are less than 2 cm in size, they are frequently missed by high-resolution transabdominal US (50% sensitivity), while EUS is more sensitive (77%) and should be preferred (242). Helical or multislice CT and MRI offer a comparable (82-94%), but incomplete, sensitivity (243,244). Selective arteriography has an 82% sensitivity and a 95% specificity.
Due to small size and/or lack of SSTR2 expression in 50% of insulinoma (151), SSTR-related imaging plays a minor role than morphological imaging. DOPA-PET has been proposed as an alternative tool (245). Radiolabelling with ^{111}In-labeled glucagon-like peptide-1 receptors agonist (^{111}In-DOTA-exendin-4) is a promising technique, still not routinely used (246).

Ecografia trans-addominale: scarsa sensibilità
Ecoendoscopia: sensibilità buona
TAC multistrato e RM: sensibilità molto buona ma non completa
SSTR-imaging: risultati incostanti
DOPA-PET: alternativa efficace, in corso di definizione
111-In-DOTA-exendin-4: in corso di sperimentazione

Ecografia trans addominale (US)

- Non invasiva
- non espone a radiazioni
- poco costosa
- anatomicamente precisa.

Il mezzo di contrasto vascolare aumenta la sensibilità dell'esame.
Il color Doppler identifica e localizza le formazioni vascolari vicine in previsione chirurgica.



Da Dr. Rosario Gulizia, Studio Ecografico, Pavia

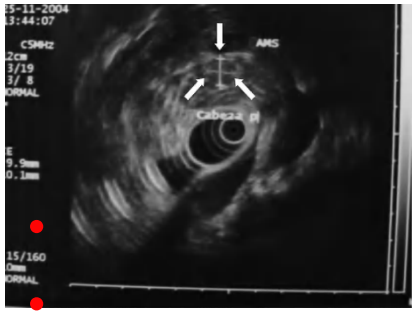
LIMITI: estrema dipendenza dall'operatore, habitus del paziente (molti pazienti con insulinoma sono in sovrappeso).

Review Article

Pancreatic insulinoma: current issues and trends

Dennis Vaidakis, John Karoubalis, Theodora Pappa, George Piaditis and George N Zografos

Athens, Greece



ECOENDOSCOPIA

La testa del pancreas è scansionata con la sonda posizionata nel duodeno, il corpo e la coda vengono scansionati tramite lo stomaco.

- La tecnica è sensibile nel dimostrare piccoli tumori nella testa del pancreas (che può essere impalpabile in chirurgia) e linfoadenopatia regionale. Utile in previsione di chirurgia mini-invasiva.

- **LIMITI**: lesioni nella coda del pancreas, valutazione imprecisa di malignità, scarsa identificazione delle lesioni peduncolate e debole differenziazione dei tumori omogenei al circostante parenchima

- Ecografia intraoperatoria **= IOUS** per decidere il tipo di procedura durante la chirurgia. Mandatoria nel sospetto lesioni multiple. L'ecografia intraoperatoria laparoscopica identifica >85% delle lesioni.

SRS/Octreoscan

- Immagini tomografiche SPECT, in previsione di PRRT

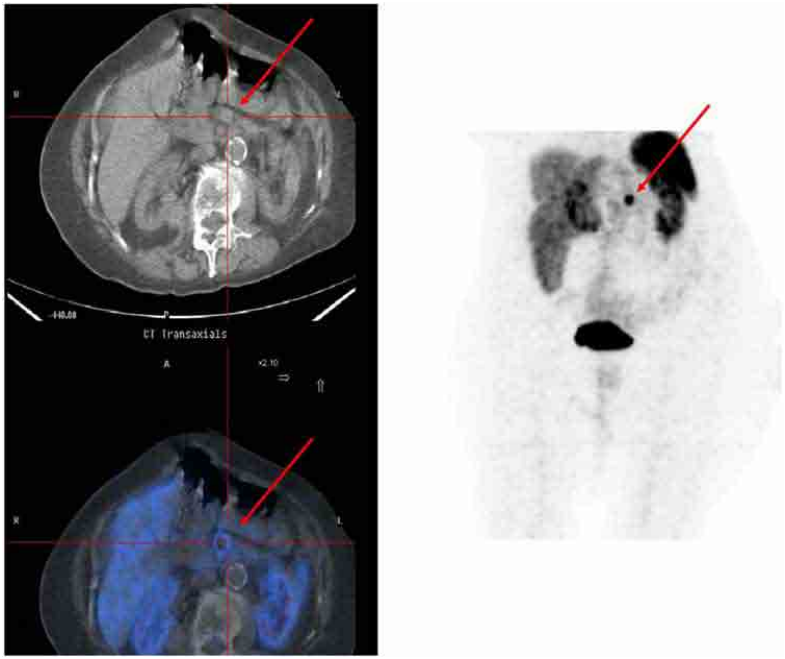
- **Falsi Positivi**: aree di flogosi, captazione aumentata dalla colecisti, contaminazione cutanea.

- **Falsi Negativi**: lesioni sub- centimetriche, uso contemporaneo di analogo “freddo”, mancata espressione recettoriale.

Gli insulinomi benigni spesso non esprimono SSTR e 1/3 degli insulinomi non hanno recettori per il 2 e 5.

PET con DOTA peptidi

- (DOTATOC o DOTANOC o DOTATATE, analoghi della somatostatina) marcati con Gallio68
- Elevata affinità per SSTR2 (anche 3 per DOTANOC)
- **FP**: captazione fisiologicamente aumentata al processo uncinato per > concentrazione di recettori



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Arteriography combined with selective calcium stimulation.
Calcium is able to stimulate insulin release from neoplastic tissue but not from normal islets. Hence, the catheterization of the arterial branches of the celiac system and the measurement of insulin in the blood sampled from hepatic veins during selective intra-arterial calcium injection localizes the pancreatic area nesting the tumors in 88-100% of cases (34,247,248). This test is cumbersome, expensive and poorly available. Accordingly, it should be reserved only to selected, biochemically-proved cases with negative imaging studies.

- **In casi selezionati, con diagnosi biochimica accertata ma imaging costantemente negativo, eseguire: arteriografia selettiva del tripode con stimolo con calcio.**
- **Definizione dell'area pancreatica comprendente la lesione nella assoluta maggioranza dei casi.**
- **Costo, durata, impegno tecnico, discomfort: elevati.**

Algoritmo di localizzazione “step by step”

- Iniziare con **TC multistrato o con RMN** (che offre nelle lesioni piccole una migliore definizione).
- Alternativa possibile (allergici a mdc o IRC): **Contrast-enhanced US**: sensibilità alta anche se non sovrapponibile alla TC.
- Considerare **Ecoendoscopia** (consente la tipizzazione della lesione con esame citologico e immunocitochimica).

Se esami precedenti negativi o in previsione di terapia non chirurgica (PRRT in lesione già sospetta per malignità):

- indagini funzionali: **PET Ga68 (**solo in seconda linea: **Octreoscan)** che definiscono lo ‘standard of care’ dei GEP NEN (localizzazione, caratterizzazione, stadiazione, ri-stadiazione).
- **PET metaboliche:** solo se le precedenti sono inconclusive.

Algoritmo di localizzazione “step by step” (2)

In caso di iperinsulinismo endogeno **accertato** e di studio di immagine persistentemente negativo:

- **Angiografia selettiva** (arteria gastroduodenale, mesenterica superiore, splenica): positiva nel 60% casi
- Dopo **stimolo intraarterioso** con gluconato di calcio: positiva nell’88%-100% se combinata a dosaggio di insulina su prelievo venoso dalle sovraepatico.

Prospettive?

- Analoghi radio marcati di GLP1 – exendina 4 (sovraespressione di recettori GLP1 nell’insulinoma).

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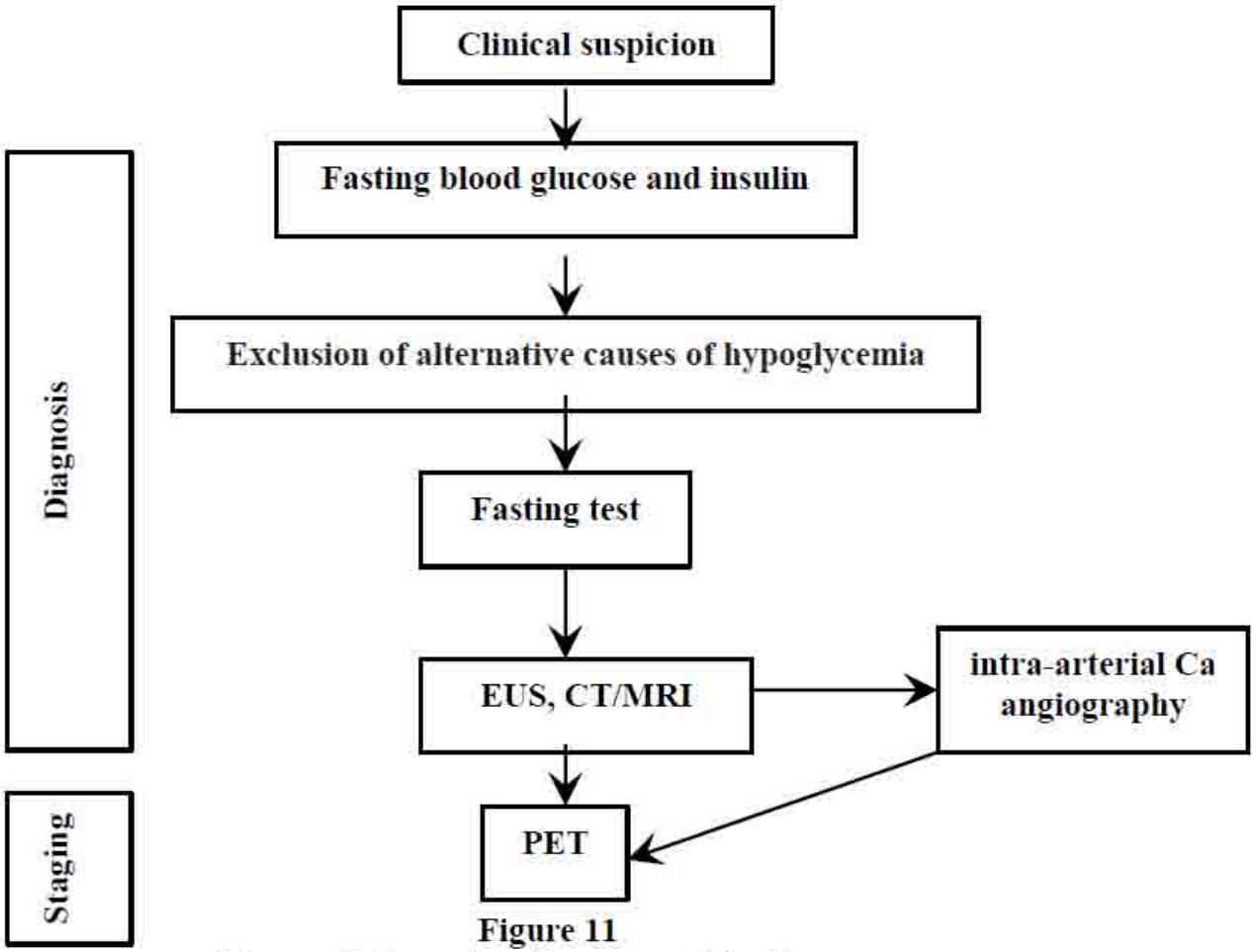

Figure 11
Diagnostic flow-chart for suspected insulinoma

Caso clinico: problemi diagnostici step by step nel sospetto di insulinoma

- Quando sospettare un iperinsulinismo endogeno
- Come confermarlo
- Come fare una diagnosi di localizzazione
- Esame citologico: utilità e limiti
- Come eseguire la stadiazione preoperatoria
- Quali indagini sul materiale operatorio
- Quando eseguire la valutazione genetica

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Cytology is gaining a major role for the diagnosis in duodeno-pancreatic tumors. The endoscopic ultrasonography (EUS) fine needle aspiration (FNA) technique appears reliable, with a reported specificity of about 75%, sensitivity of 87.5%, accuracy of 89%, positive predictive value (PPV) of 93%, and negative predictive value (NPV) of 60% [29,30,31].

La citologia su FNA in corso di EUS ha una elevata accuratezza diagnostica nel confermare la diagnosi di GEP NET, soprattutto se coniugata con le colorazioni immunocitochimiche.

La citologia ha scarso valore predittivo nel distinguere i NET pancreatici a basso da quelli a intermedio grado di malignità (G1 dai G2).

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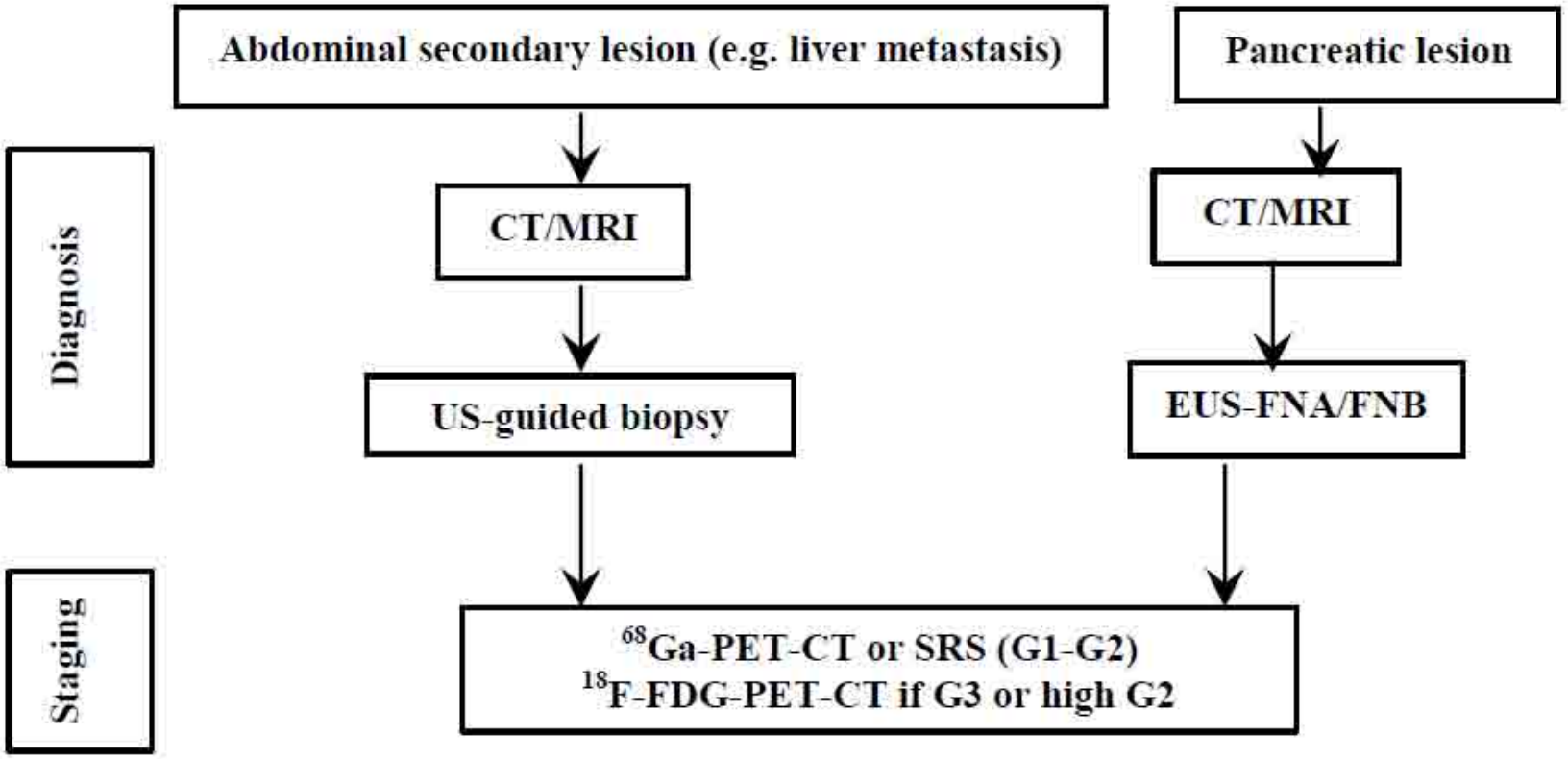

Figure 3
Diagnostic flow-chart for GEP-NEN suspected at morphological imaging

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2.1.2 Immunohistochemistry (IHC) and molecular biology techniques

Neuroendocrine differentiation: Synaptophysin (a small vesicle-associated marker) and Chromogranin A (CgA, a large secretory granule-associated marker) are useful IHC markers for the diagnosis of NENs. In NEC the staining for both these markers is required to confirm the diagnosis, because CgA may be negative [15]. Routine IHC staining for peptide hormones and bioamines is not recommended. Other neuroendocrine markers, such as PGP.9.5, NSE, CD56, NSP-55, are of questionable specificity and clinical usefulness.

- **Sinaptofisina e Cromogranina A sono i due marcatori che consentono la conferma diagnostica di NEN.**
- **Nei NEC è indispensabile l'esecuzione di ambedue i marcatori per la possibile negatività della CgA.**
- **La colorazione di routine per ormoni peptidici è opportuna solo in caso di chiaro indirizzo diagnostico.**

Caso clinico: problemi diagnostici step by step nel sospetto di insulinoma

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- **Quali indagini sul materiale operatorio**
- Quando eseguire la valutazione genetica

CLASSIFICAZIONE PATOLOGICA

1.4 CLASSIFICATION

In the last ten years WHO has repeatedly revised the pathologic classification of GEP-NETs (table 1)[16].

Table 1
WHO classifications of GEP-NETs

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	Well-differentiated endocrine tumor Well-differentiated endocrine carcinoma Poorly differentiated endocrine carcinoma/ small-cell carcinoma	Neuroendocrine tumors • NET G1 (Grade 1) • NET G2 (Grade 2) Neuroendocrine carcinoma • NEC G3 (Grade 3): o large cell NEC o small cell NEC
II. Mucocarcinoid III. Mixed carcinoid-adenocarcinoma forms	Mixed exocrine-endocrine carcinoma	Mixed adeno-neuroendocrine carcinoma (MANEC)
IV. Pseudotumor lesions	Tumor-like lesions	Hyperplastic and preneoplastic lesions

WHO 2010

DEFINIZIONE DEL GRADING

1.4.1 Grading assessment

The grade of a tumor is the primary predictor of its clinical outcome. Grading is based on the proliferation rate of the tumor, as assessed by the Ki-67 cell labeling and by the mitotic count (number of mitosis x 10 high power fields - HPF) (table 2) [15,16,17,18,19,20,21,22,23].

Table 2
Grading system for GEP-NETs
(adapted from 19)

	Ki-67 index (%)*	Mitotic count/10 HPF**
NET G1	≤2	<2
NET G2	3-20	2-20
NET G3	>20	>20

- *assessed by MIB-1 labeling in at least 2000 tumor cells in high nuclear density ("hot spot") areas
- **10 HPF = 2 mm^2, at least 50 optical fields in high density mitotic areas

Visual estimates are currently used as the standard technique for evaluating both Ki-67 and the mitotic count [24,25]. Several areas should be assessed within the tumor to reduce the risk of evaluation bias due to intratumoral heterogeneity. Densely stained regions ("hot spots") should be preferentially evaluated. Results from these areas should be reported as a single percentage reflecting the highest identified count [16,21,22].

Fattore più importante nel predire l'outcome clinico
Basato sul Ki-67 e sulla conta mitotica

STAGING: TNM (AJCC) / ENETS

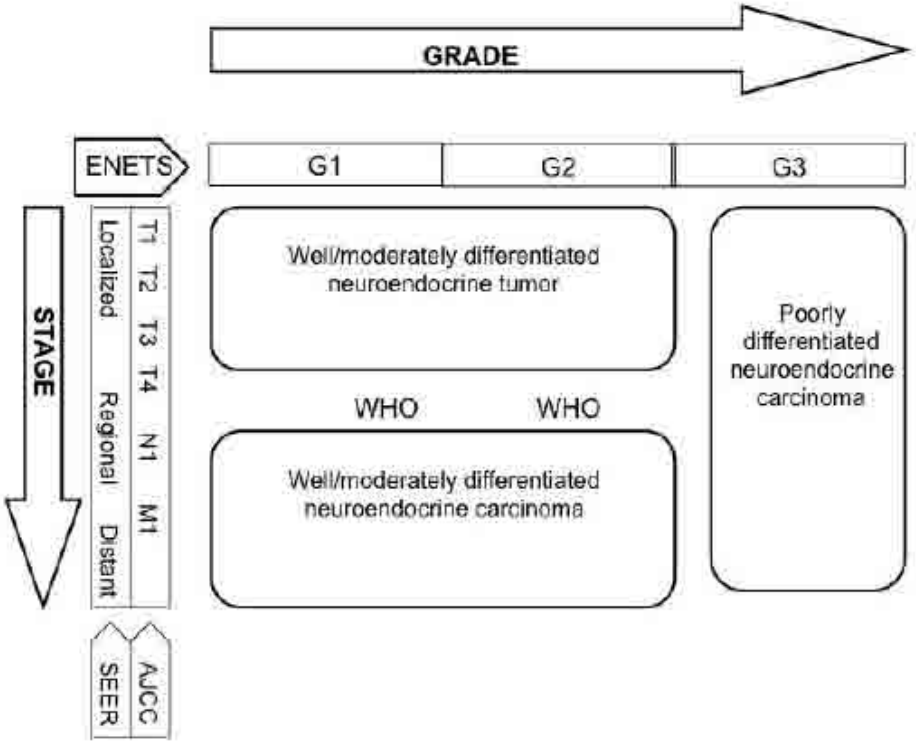

Figure 1
Integrated pathologic and biologic classification (*modified from 15*)

1.4.2 Pathologic staging

GEP-NETs are staged according to tumor size, site of origin, and locoregional or distant spreading [21,22,23]. The staging information is integrated with the 2010 WHO classification to stratify the prognostic risk and optimize the therapeutic and follow-up strategies (figure 1).

DATI ESSENZIALI DEL REFERTO ANATOMO-PATOLOGICO

The **minimum pathology data set** for resected specimens (both primary and metastatic) should include [36]:

- Site;
- Diagnosis (e.g. pure neuroendocrine neoplasm);
- Differentiation (i.e. well or poor);
- Proliferation (i.e. G1 or G2 or G3).

We recommend histology as the diagnostic standard, cytology if histology is not available.
We recommend classification according to WHO 2010.
We recommend grading according to Ki-67 index and/or mitotic count.
We recommend staging according to AJCC/UICC TNM and ENETS.

- **Sede**
- **Diagnosi**
- **Grado di differenziazione (buona o scarsa)**
- **Ki-67 e/o Conta mitotica (G1,G2 o G3)**

Caso clinico: problemi diagnostici step by step nel sospetto di insulinoma

- Quando sospettare un iperinsulinismo endogeno
- Come confermarlo
- Come fare una diagnosi di localizzazione
- Esame citologico: utilità e limiti
- Quali indagini sul materiale operatorio
- **Quando eseguire la valutazione genetica**

INQUADRAMENTO GENETICO

2.1.4 Genetic assessment

Approximately 5-10% of GEP-NENs have a hereditary background as part of tumor susceptibility syndromes: Multiple endocrine neoplasia Type 1 (MEN-1), Von Hippel-Lindau disease (VHL), Neurofibromatosis Type 1 (von Recklinghausen disease, NF1) and the Tuberous Sclerosis Complex (TSC). All are inherited autosomal dominant disorders [37].

MEN-1. GEP-NENs are the second most common manifestation of MEN-1, reported in 30-70% of cases in different series (mostly non-functioning – NF)[38,39]. A germ-line *MEN-1* mutation is identifiable in about 80-90% of familial cases [40] and in about 42% of sporadic cases [41]; in approximately 10% of patients, arise de novo without any family history [42]. *MEN-1* mutation testing should be offered to index cases and to their first-degree relatives, even if asymptomatic [39]. Genetic counseling is recommended [39]. The family members who carry the *MEN-1* mutation require routine surveillance for early detection of endocrine tumors, whereas those who do not carry the mutation can be reassured. When molecular genetic testing is not available, individuals at risk should undergo routine evaluation: due to the high penetrance (~100%) and early onset of primary hyperparathyroidism [43], serum calcium and PTH measurement should be used as the first-line tests. No genotype/phenotype correlations have been demonstrated in MEN-1 syndrome [44,45].

- **Considerare la possibilità di una MEN-1 nel paziente con insulinoma**
- **Eseguire in primo luogo, vista l'alta penetranza nella MEN-1 dell'iperparatiroidismo, la determinazione di Calcemia e PTH**
- **Completare con la determinazione di PRL e IGF-1.**

INQUADRAMENTO GENETICO (2)

We recommend germ-line DNA testing only in presence of a family history or clinical findings suggestive of MEN-1 or VHL. Genetic testing should include mutational screening and sequencing. A preliminary genetic counseling is needed.
We suggest the routine determination of serum calcium and PTH levels in patients with duodeno-pancreatic NEN as a first-line screening for MEN-1.
We recommend against routine somatic (tumor tissue) DNA testing.

- La ricerca di mutazioni germinali deve essere condotta di routine solo in caso di storia familiare o di reperti clinici o di laboratorio suggestivi per MEN-1
- Non è raccomandata la ricerca di routine di mutazioni somatiche (su tessuto tumorale).

INQUADRAMENTO GENETICO

Box 4

***Insulinoma** (236,237)*

Insulinoma is a NEN arising from insulin-secreting cells in pancreatic islets. Other hormones and metabolites (gastrin, ACTH, glucagon, hCG, somatostatin, and 5-HIAA) may be also secreted from this neoplasm.

About 90% of insulinomas are benign. In rare cases neither a single nor multiple tumors can be identified and the syndrome depends on diffuse beta-cell hyperplasia. In malignant forms with liver metastases, a 16-26 months survival is to be expected. Only 5% of all insulinomas are associated with MEN-1; in case of multiple insulinomas (near 10%), MEN-1 prevalence raises to 50%.

- **Solo il 5% degli insulinomi singoli è parte di una MEN-1**
- **Questa percentuale sale fino al 50% in caso di lesioni multiple**
- **Lo studio genetico è indicato in caso di coesistente iperparatiroidismo primitivo o di adenoma ipofisario e in caso di insulinomi multipli.**

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CONSENSUS STATEMENT

Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms

AME CONSENSUS STATEMENT

" a document developed by an independent panel of experts, usually multidisciplinary, convened to review the research literature for purpose of advancing the understanding of an issue, procedure, or method"

Grazie per l'attenzione

(e scusateci per le inevitabili lacune e per i limiti)