



12th AME Italian Meeting Associazione Medici Endocrinologi
Italian Association of Clinical Endocrinologists
6th Joint Meeting with AAACE American Association of Clinical Endocrinologists
Bari, 7-10 November 2013



Bari,
7-10 novembre 2013

Meet the expert:

la sindrome da carcinoide

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Verona



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GI and NET Unit

IEO, Milano



Bari,
7-10 novembre 2013

Programma di oggi

Sindrome da carcinoide

✓ Ruolo dell'endocrinologo

- come fare la diagnosi
- come controllarla
- quando e come prevenire la crisi da carcinoide

✓ Ruolo dell'oncologo

- come controllare la crescita tumorale
- quando i farmaci biologici (nuovi trials)
- quando la chemioterapia

• GI-NETs (67%)



gastrointestinali
(GI-NET)

- **38% piccolo intestino (> ileali)**
- **S. da carcinoide tipica: ~30% ileali**
- Multicentrici nel 30% dei casi
- Maligni anche se Ki 67 \leq 2% e piccole dimensioni
- Eta' d'insorgenza: VI-VII decade

• NETs Toracici (25%)



tracheobronco
polmonari/timo

- **Carcinoide bronchiale tipico**
- **S.da carcinoide atipica: 1-3%**
- Ki 67 \leq 2%
- Metastasi < 15%
- Eta' d'insorgenza: V decade

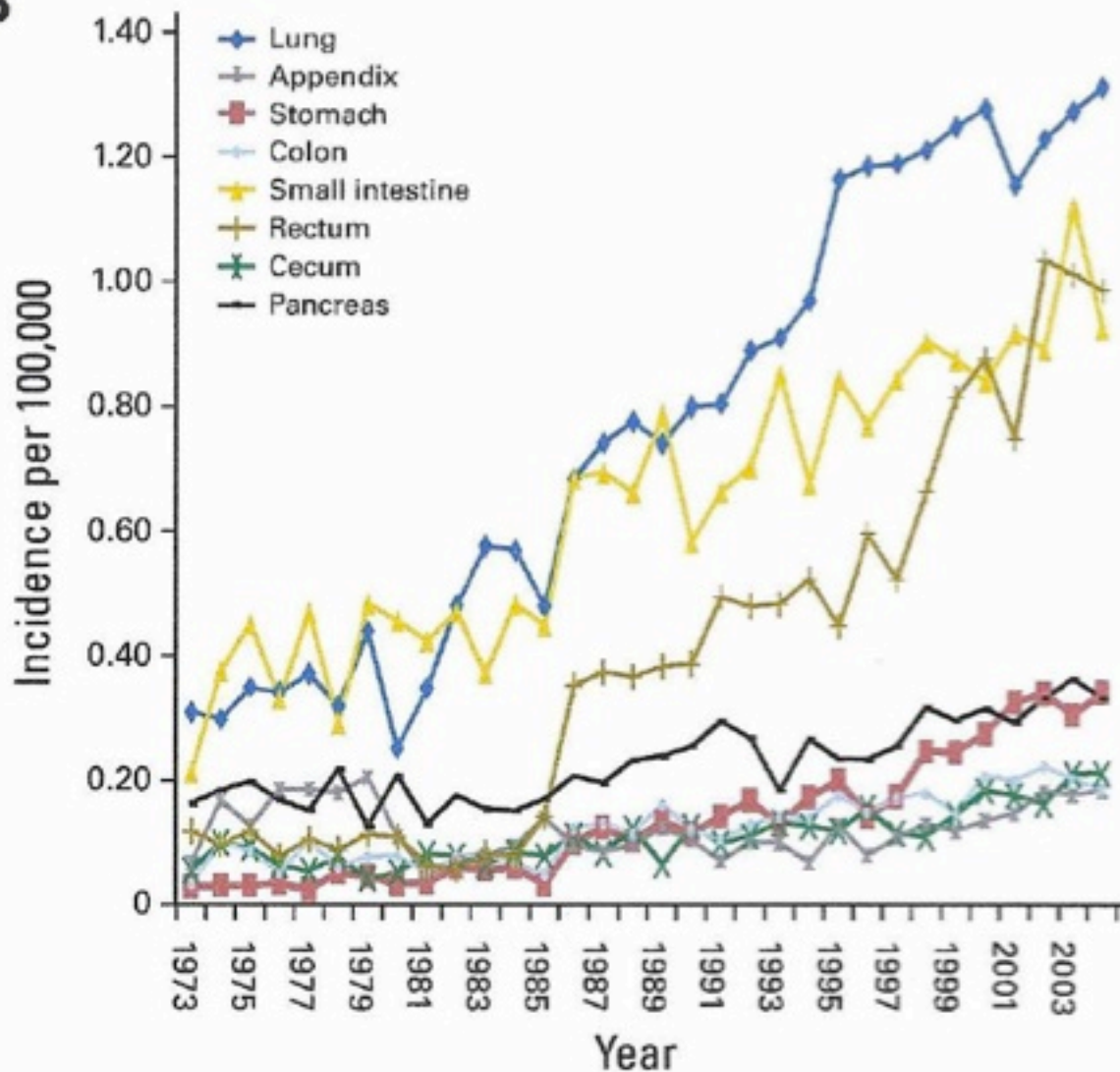
Epidemiologia dei carcinoidi (NETs)

(dati USA SEER)



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B



Polmone: 1.35:100.000
Ileo: 0.67:100.000
Retto: 0.86:100.000
Pancreas: 0.32:100.000

Autopsie:
pNETs 1,5%
NET ileo 1,2%

**Natural history of gastro-enteropancreatic
and thoracic neuroendocrine tumors. Data from a large
prospective and retrospective Italian Epidemiological Study:
The NET MANAGEMENT STUDY**

J Endocrinol Invest. 2012 Oct;35(9):817-23.

Figure 1. Incidence of NET per lustri intervals in the "Net management database" by site of primary tumor.

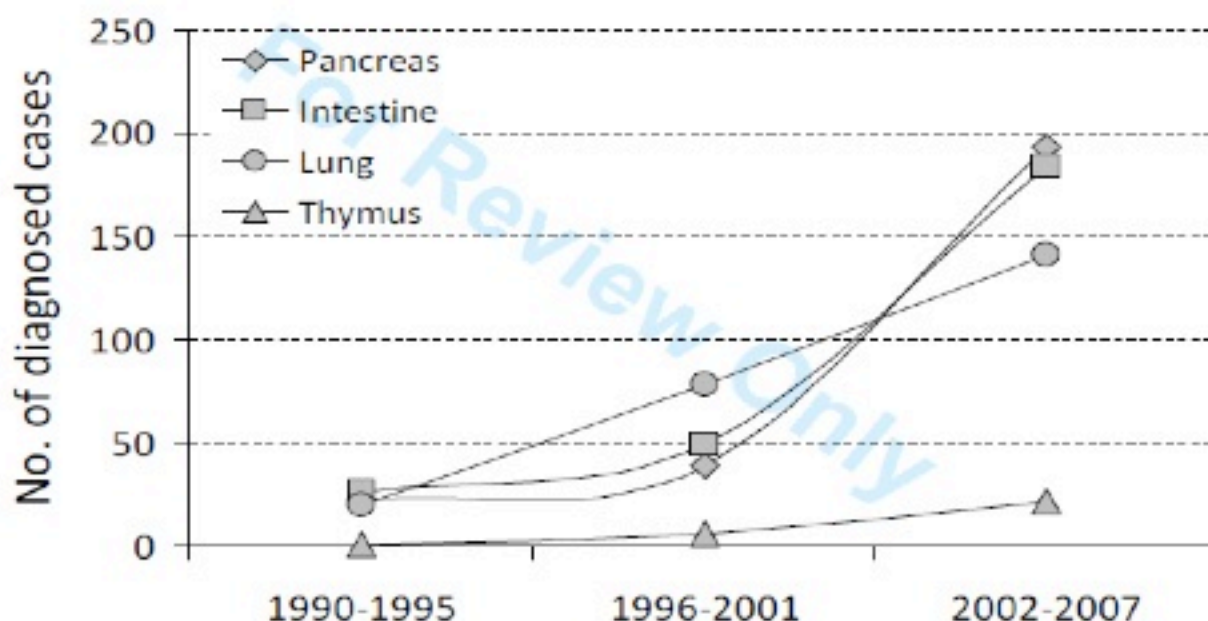
13 centri italiani

1203 NETs:

63% GEP

33% Thorax

4% Unknown



Classificazione WHO dei GEP-NET

WHO 1980	WHO 2000	WHO 2010
Carcinoide	Tumore endocrino ben differenziato (WDET) ^a	NET G1 (carcinoide) ^b
	Carcinoma endocrino ben differenziato (WDEC) ^a	NET G2 ^b
	Tumore endocrino poco differenziato/ carcinoma a piccole cellule (PDEC)	NEC (tipo a larghe cellule o a piccole cellule) ^{b,c}

Modificato da (1)

Prognosi dei pazienti



Buona



Negativa

Modificato da (2,3)

Criteria di *grading* istopatologico (1,4,5)

G1	<2 mitosi x 10 HPF e/o <2% Ki-67
G2	2-20 mitosi x 10 HPF e/o 3-20% Ki-67
G3	>20 mitosi x 10 HPF e/o >20% Ki-67

Elaborazione da (1,4,5)



TNM classification and disease staging

Jejunum-ileum



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- T1 Tumor invades mucosa or submucosa and size ≤ 1 cm
- T2 Tumor invades muscularis propria or size >1 cm
- T3 Tumor invades subserosa
- T4 Tumor invades peritoneum/other organs

- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

- M0 No distant metastases
- M1 Distant metastasis

Stage I	T1 N0 M0
Stage IIa	T2 N0 M0
IIb	T3 N0 M0
Stage IIIa	T4 N0 M0
IIIb	any T N1 M0
Stage IV	any T any N M1

AJCC/UICC: 2009

Sobin, Gospdarowicz, Wittekind. Wiley-Blackwell. 7thEdition; 2009

ENETS 2006

Rindi G et al. Virchows arch. 2006; 449: 395-441



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CARCINOIDE TIPICO

- morfologia da carcinoide
- <2 mitosi / 2 mm² (10 HPF) E
- no necrosi

CARCINOIDE ATIPICO

- morfologia da carcinoide
- 2-10 mitosi / 2 mm² (10 HPF) O
- necrosi (spesso puntiforme)

LCNEC (large cell neuroendocrine carcinoma)

- morfologia neuroendocrina
- >10 mitosi / 2 mm² (10 HPF) (mediana di 70/10 HPF)
- necrosi
- caratteristiche citologiche da NSCLC (nucleoli)
- elevato rapporto N/C
- positività per uno o più markers NE

SCLC (small cell lung cancer)

- cellule a piccola taglia
- scarso citoplasma / nuclei senza nucleolo
- >10 mitosi / 2 mm² (10 HPF) (mediana 80/10 HPF)

WHO 2004

Lung/Thymus NETs

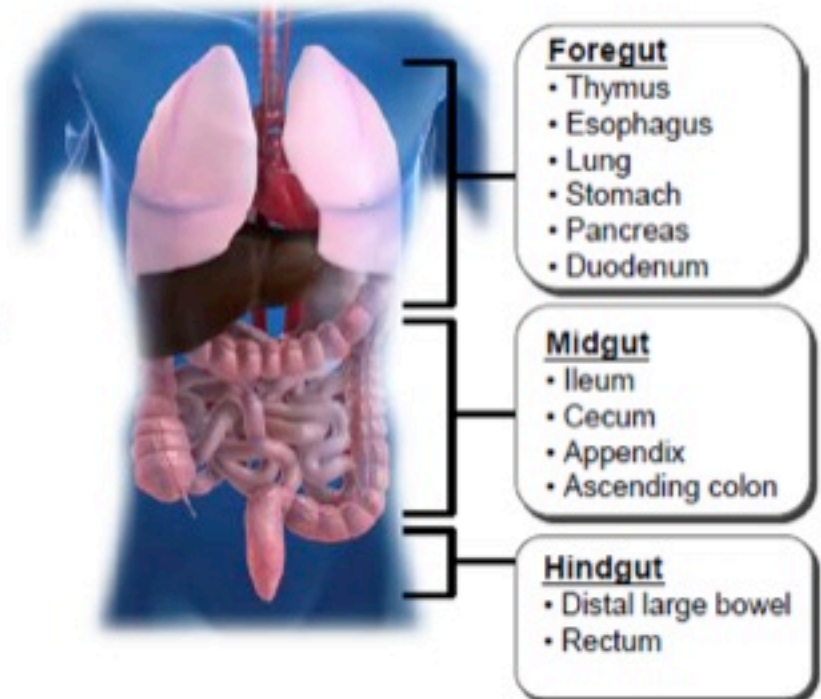
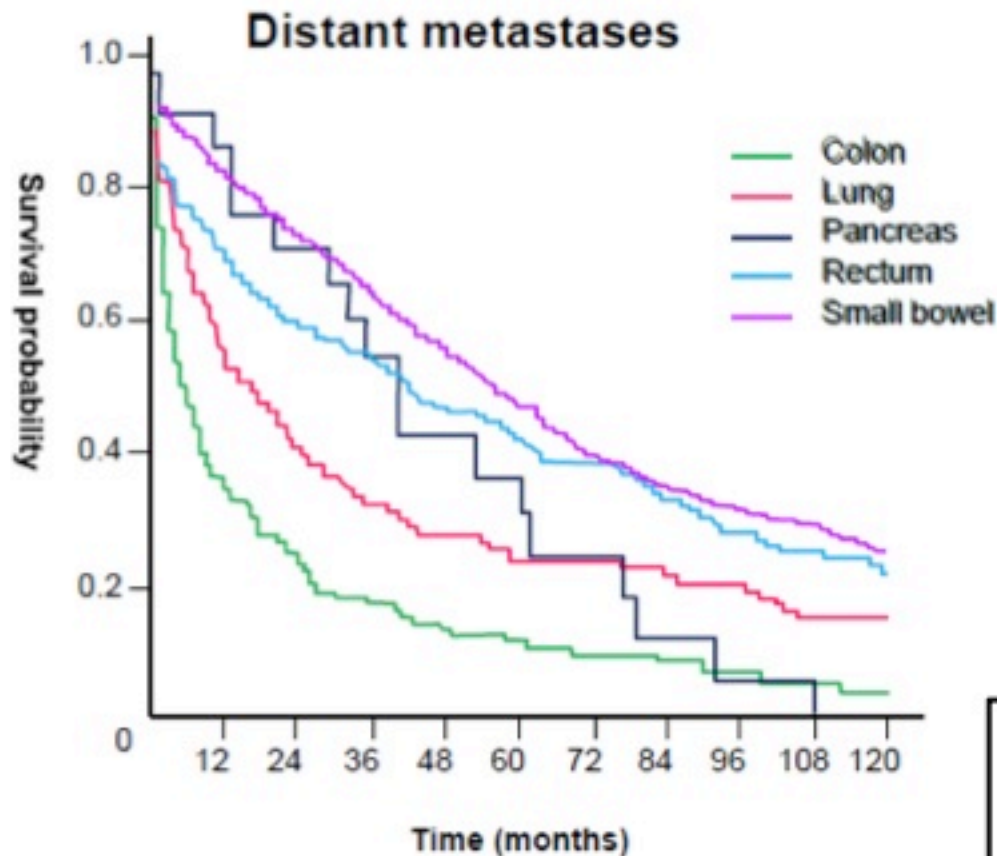
Lyon Travis WD, IARC Press, 2004

TNM UICC/AJCC, VII EDIZIONE 2010

STADIO 0	Tis	N0	M0
STADIO 1A	T1 a,b	N0	M0
STADIO 1 B	T2 a	N0	M0
STADIO II A	T2 b	N0	M0
	T1 a,b	N1	M0
	T2 a	N1	M0
STADIO II B	T2 b	N1	M0
	T3	N0	M0
STADIO III A	T1 a,b; T2 a,b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
STADIO III B	T4	N2	M0
	Ogni T	N3	M0
STADIO IV	Ogni T	Ogni N	M1

Primary Site Identifies Different Tumor Types

Organ of Origin and Survival



Median survival (months):

Ileum	56
Pancreas	24
Lung	16

Scarpa A, et al. Mod Pathol. 2010;23:824-33.

Yao JC, et al. J Clin Oncol. 2008;26:3063-72.



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Mediatori umorali della sindrome carcinoide

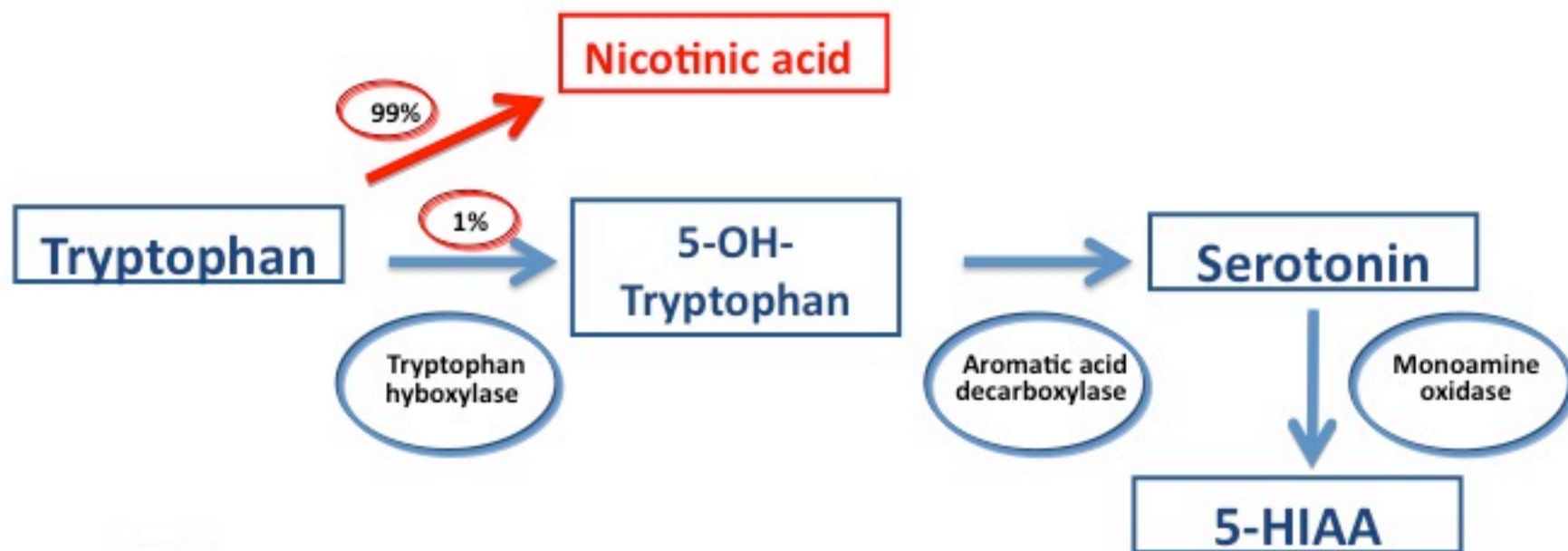
NET ileali

- Serotonina
- Callicreina
- Tachichinine

NET bronchiali/ gastrici

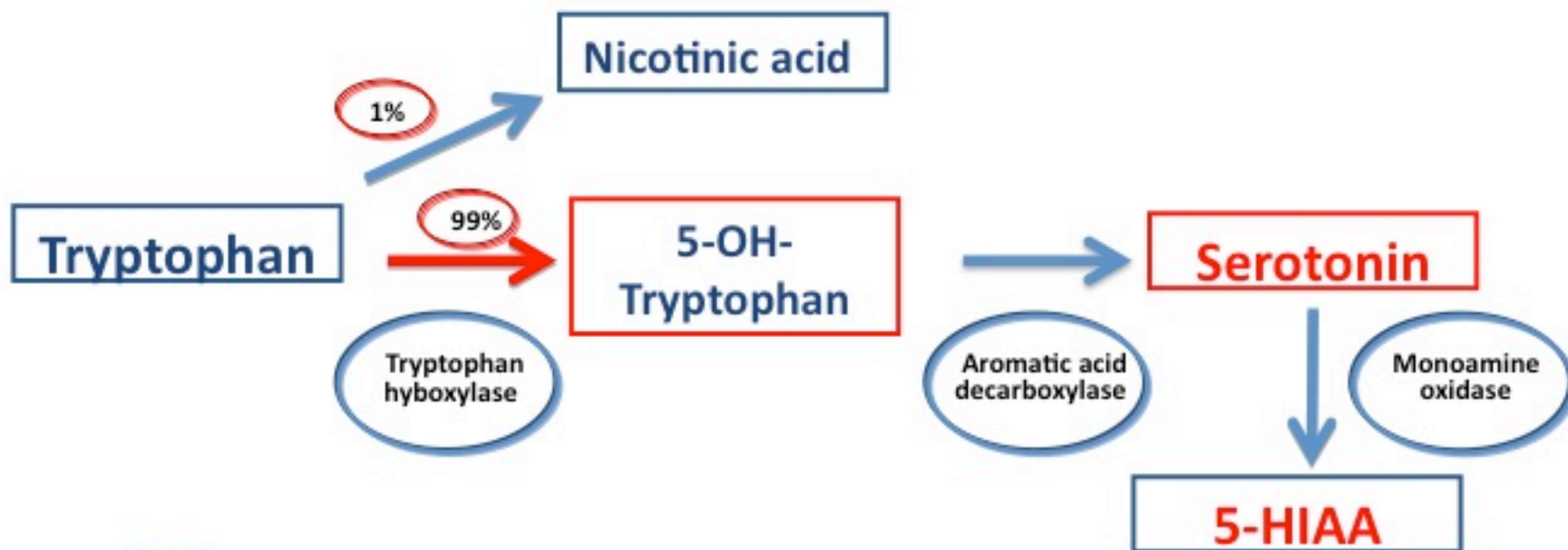
- Istamina
- 5-idrossitriptofano
- Prostaglandine

Serotonin synthesis



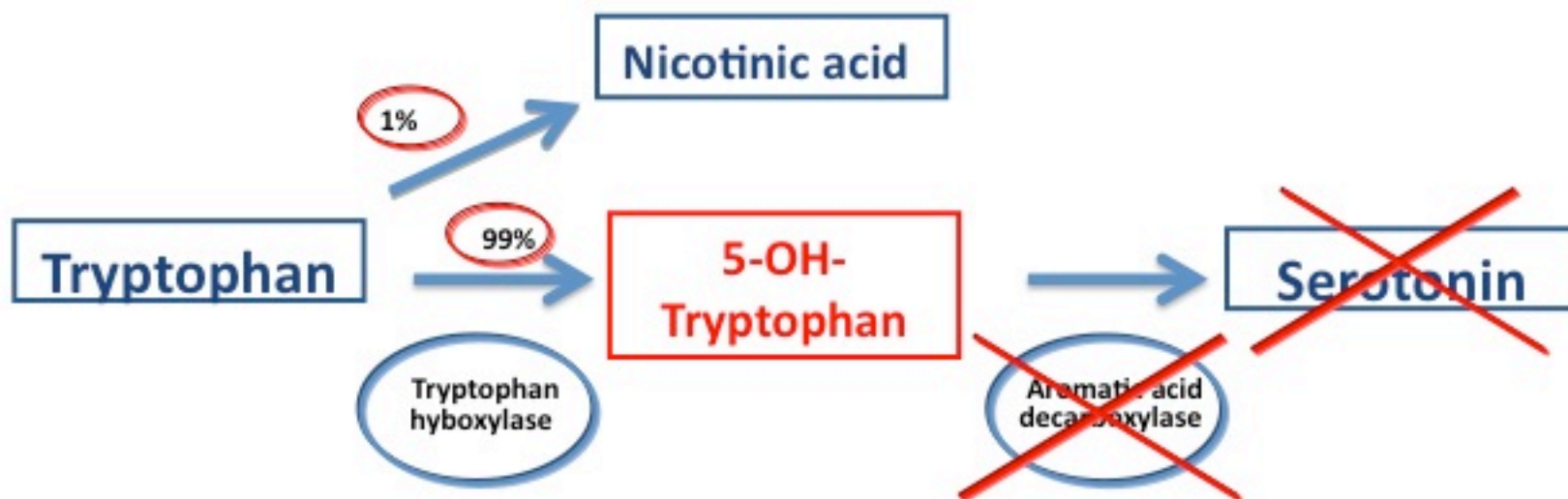
Normal subject

Serotonin synthesis



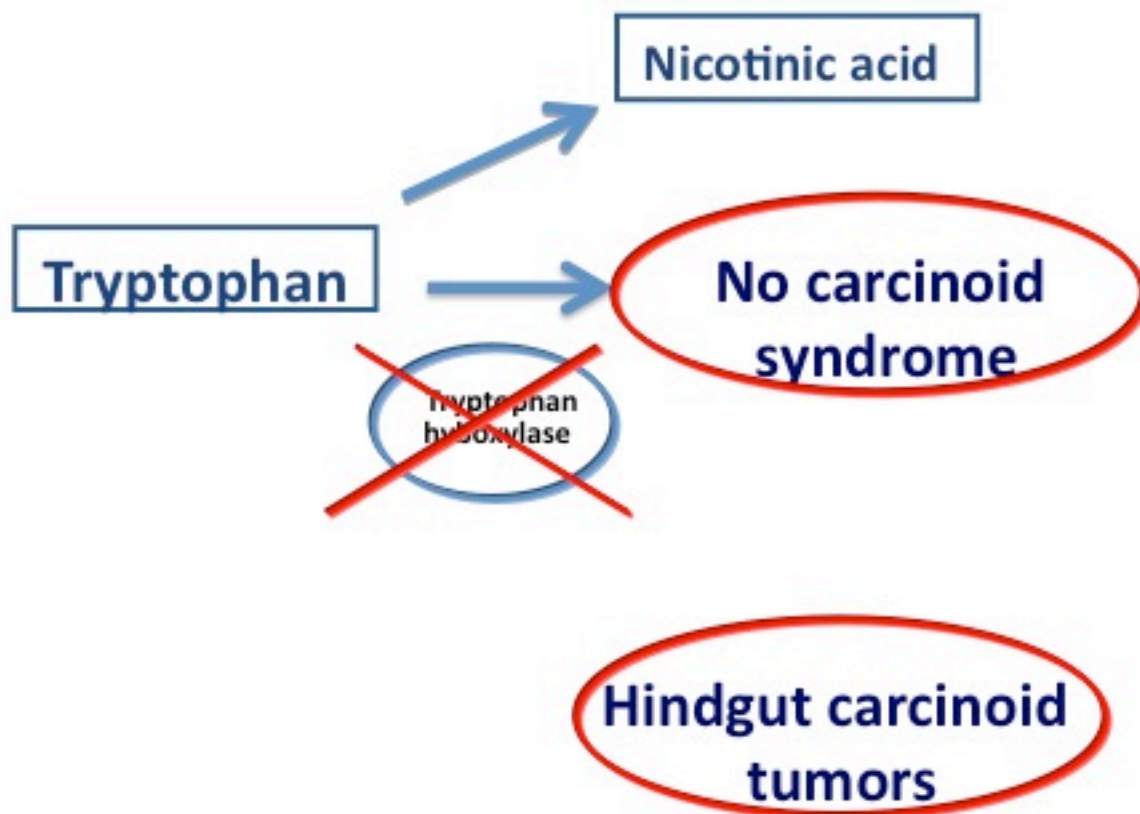
Ileal carcinoid tumors

Serotonin synthesis



**Foregut carcinoid
tumors**

Serotonin synthesis





Sindrome da carcinoide (sc)



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SC TIPICA (95%):

- 18-30% NET digiuno-ileali
+ mts epatiche**
- <5% mts retroperitoneali o carcinoide ovarico
- flushing (viso, collo, torace)
- diarrea
- crampi e dolore addominale
- broncospasmo
- pellagra
- scompenso cardiaco ds da alterazioni fibrotiche delle valvole cardiache ds

SC ATIPICA (5%): **NET gastrici e bronchiali**

- flushing prolungato
- teleangectasie, acrocianosi
- edema e iperemia oculare
- broncospasmo
- Ipotensione

CRISI DA CARCINOIDE

- ipotensione (rara ipertensione)
- tachicardia
- broncospasmo
- diarrea
- alterazioni neurologiche

Alcol, alcuni cibi, stress fisico e metale, infezioni possono scatenare una crisi !!



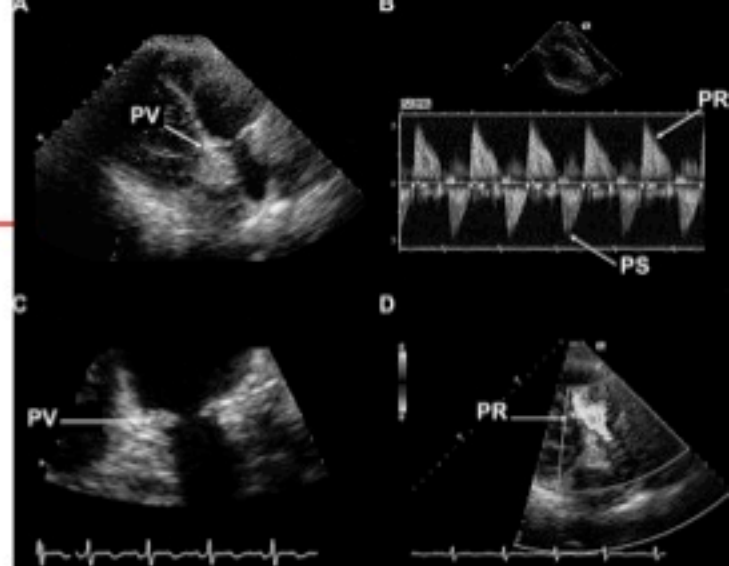
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Table 7
Differential diagnosis of flushing

Drugs	All vasodilators, calcium channel blockers, morphine and other opiates, etc
Menopause	Associated with sweating
Mastocytosis	Flushing lasting longer than CS, may be accompanied by headache, dyspnea, palpitations, abdominal pain and diarrhea
Medullary thyroid carcinoma	Associated with diarrhea in patients with advanced disease
Pheochromocytoma	Rare, but it may occur after a paroxysm of hypertension, tachycardia and palpitations and is preceded by pallor

Cardiopatia da carcinoide

- 25-50% nei pz con s da carcinoide
- Scompenso cardiaco ds e' causa di morte nel 30-50% dei casi
- Fibrosi a placche delle valvole ds
- Eta', livelli di 5-HIAA, insufficienza tricuspидale predittori di mortalita'
- Screening ecocardiogramma
- Considerare sostituzione valvolare in pz in controllo ormonale e stabilita' di malattia e prima di TACE e chirurgia epatica





Caso clinico

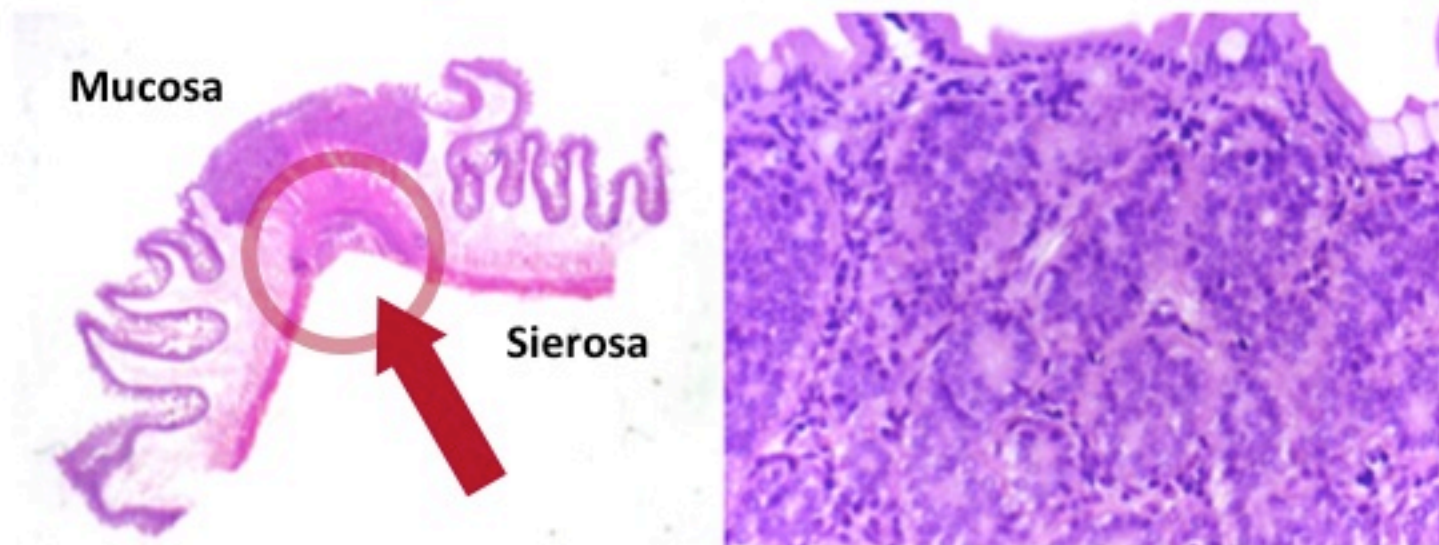


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- **F, 48 anni**
- **Agosto 2008:** ricovero in chirurgia per addome acuto
- Nelle ultime settimane stipsi ostinata e dolore addominale

- **A. pat remota:** negli ultimi 2 anni diarrea (8/10 scariche/die) alternata a stipsi e episodi di dolore crampiforme localizzato in mesogastrio e ipocondrio ds.
- **Ecografia addome:** multipli angiomi epatici
- **Colonscopia:** negativa
- **Visita gastroenterologica:** diagnosi di colon irritabile, prescritta terapia sintomatica

Esame istologico

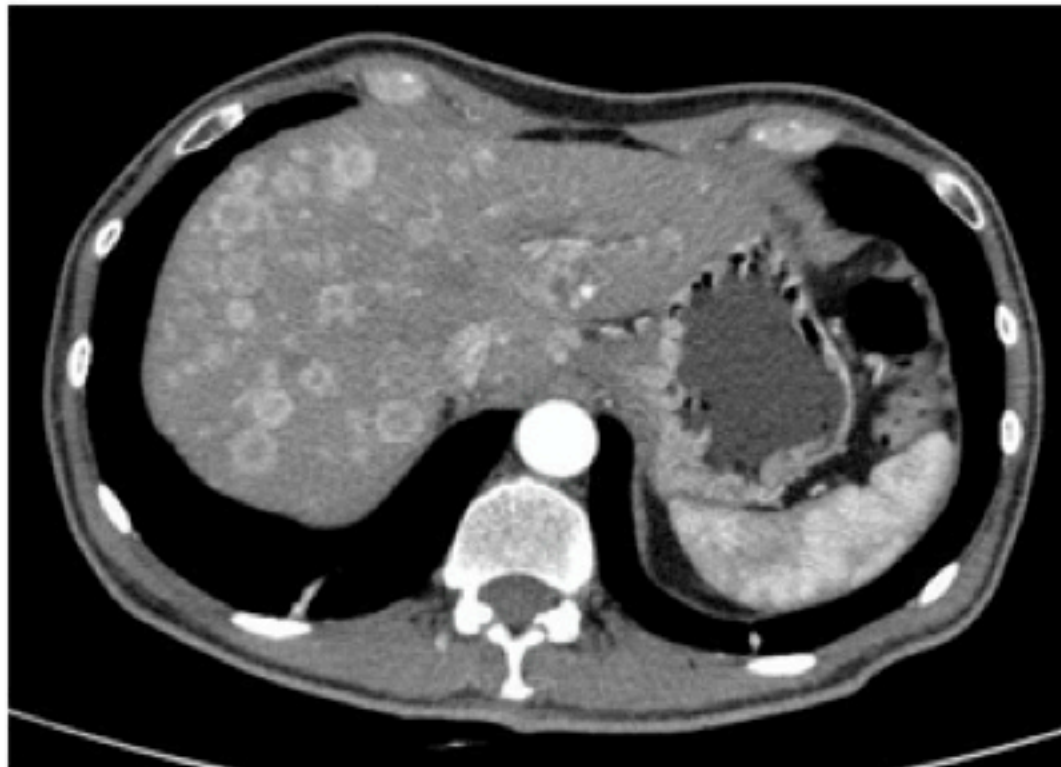


NET G1 (Ki67 1%) ileale multifocale infiltrante la parete fino alla sierosa con
invasione del tessuto adiposo
N+: 3/4 linfonodi periviscerali

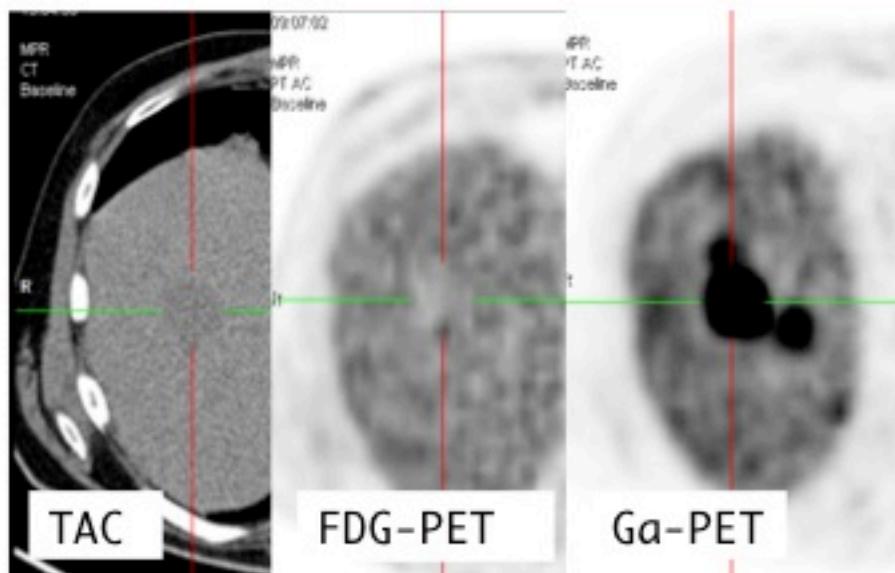
Stadiazione post-chirurgica (sett 2008)



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- **RMN addome con mdc:** multiple lesioni epatiche disomogenee suggestive per metastasi.
- **FNAB:** metastasi of NET ileale (Ki 67 <2%)



- FDG-PET: **negativa**
- Ga-PET: **positiva**

- **Markers tumorali:**

5-HIAA: 80 mg/24h (v.n. .2-8)

CgA: > 541 U/L (v.n. <17)



Marker specifico: ACIDO 5-IDROSSI-INDOLACETICO



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5-HIAA URINARIO

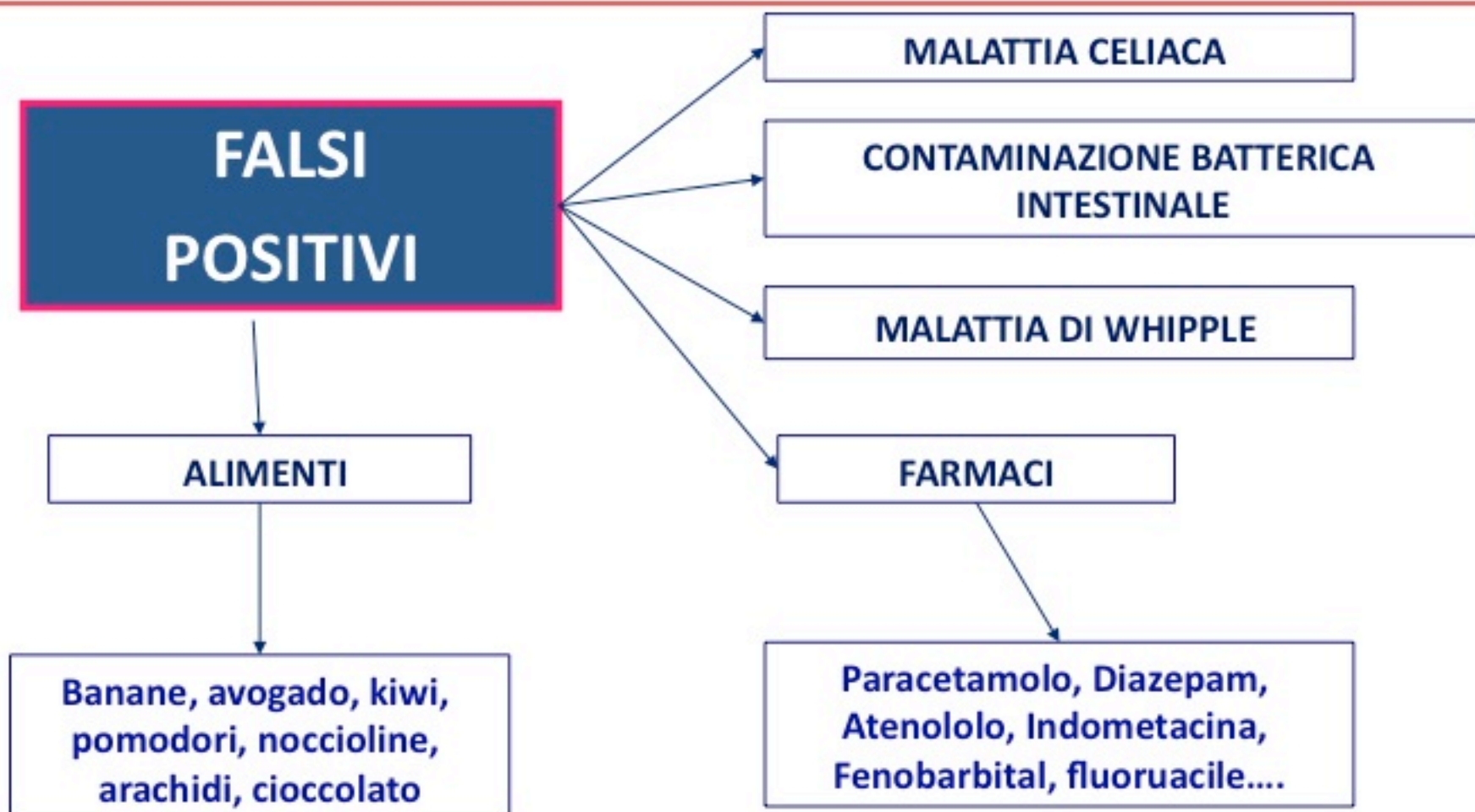
n. v. = 2- 8 mg/24 h

cut-off > 20 mg/24 h

SENSIBILITA' >90%

SPECIFICITA' 90%

ACIDO 5-IDROSSI-INDOLACETICO





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Serotonina

**La determinazione della serotonina sierica e' meno
sensibile e specifica del 5-HIAA
varia considerevolmente durante il giorno a seconda
dell'attivita' fisica e lo stress
pertanto non e' raccomandata**



Marker aspecifico: cromogranina A



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- ✓ Glicoproteina acida localizzata nei granuli di secrezione
- ✓ Non e' utile nella diagnosi, poco specifica
- ✓ I livelli correlano con l'estensione di malattia
- ✓ Utile monitoraggio in corso di terapia

Attenzione ai falsi +:

PPI

INSUFFICIENZA EPATICA, RENALE

GASTRITE ATROFICA

MALATTIE INFIAMMATORIA INTESTINALE

IPERTENSIONE ARTERIOSA

STRESS....



Carcinoidi - Imaging



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RADIOLOGICO

- US
- CT
- RMN

ENDOSCOPICO

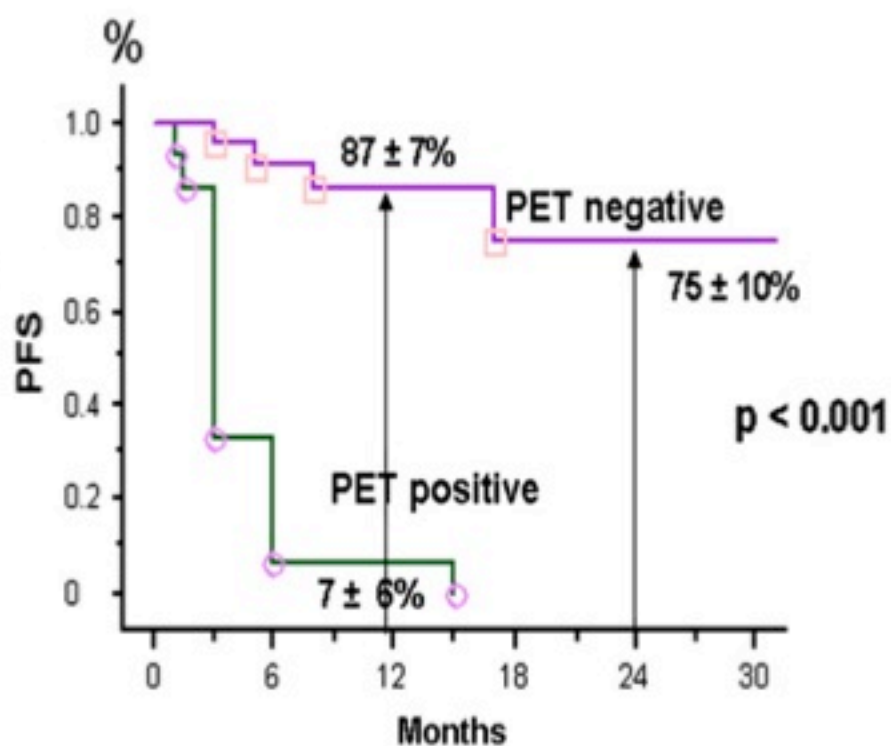
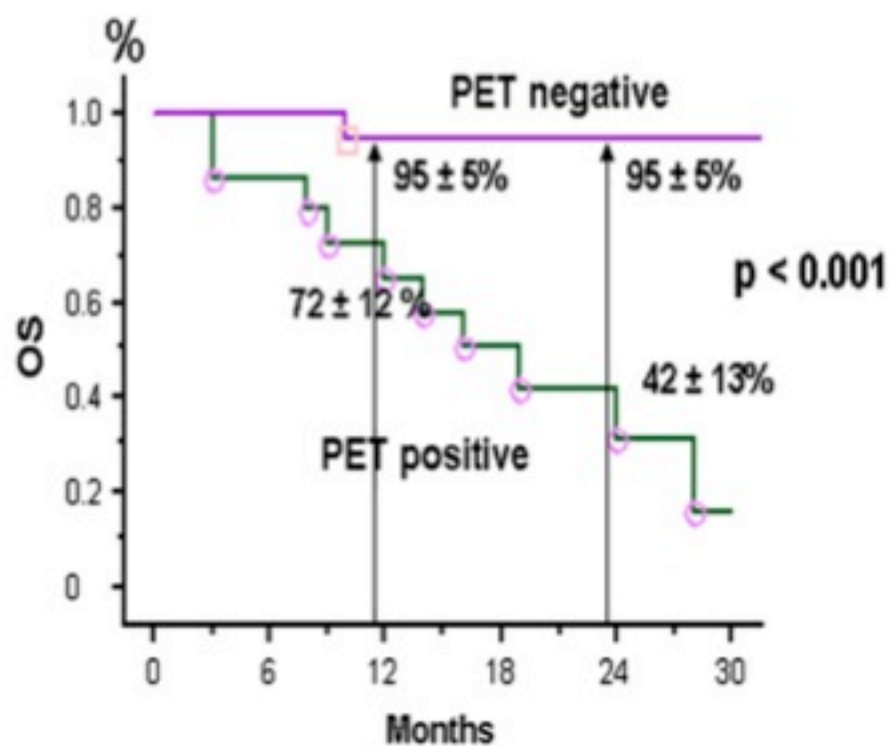
- Entero/colonscopia
- Broncoscopia
- Videocapsula

MEDICO-NUCLEARE

- OCTREOSCAN
- Ga⁶⁸-DOTATOC PET-CT
- (¹⁸FDG-PET)

- ✓ Visualizza SSTR2/SSTR5
- ✓ Staging
- ✓ Strategia terapeutica

La **FDG-PET** ha significato prognostico negativo





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....tornando al caso clinico....

- Paziente di 49 anni in assenza di comorbilità'
- **Metastasi epatiche Ga-PET ++, FDG-PET -, Ki 67 <2%, da carcinoide ileale asportato con sindrome ormonale**

WHO: NET G1, ENETS TNM: IV STADIO

COSA FARE?



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Qual'è la vostra scelta?

1. Solo terapia medica con analoghi della somatostatina
2. + Terapia radiometabolica con ^{90}Y -dotatoc o ^{177}Lu -dotatate
3. + TAE/TACE
4. Chemioterapia

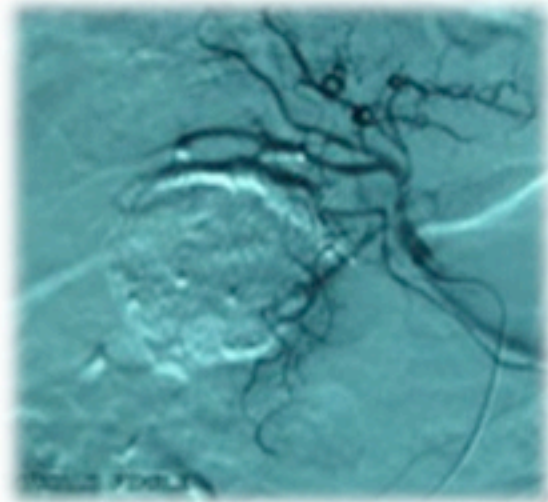
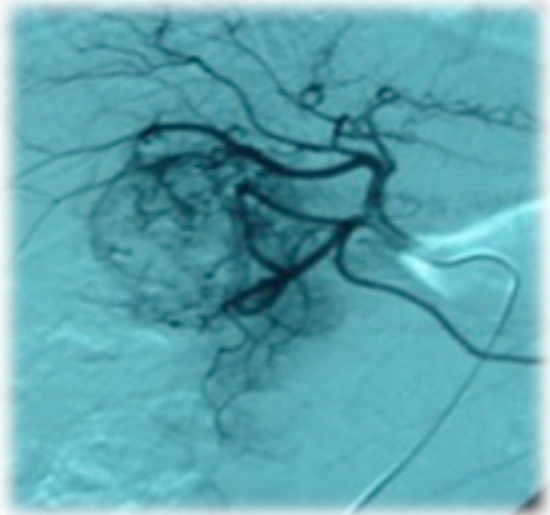


Cosa e' stato deciso dal team multidisciplinare



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- **Octreotide LAR 30** mg im/28 gg per controllo sintomi
- **Chemo-embolizzazione** (2 sedute con dacarbazina) per controllo sintomi + crescita tumorale





Progressione epatica (Apr 2009)



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TC stadiazione : ...aumento delle dimensioni e numero delle lesioni epatiche bilateralmente

- 4 cicli di **PRRT** con ^{177}Lu -DOTATATE (341 mCi) con risposta parziale e controllo della sindrome
- 2013: 4 anni dopo, continua **octreotide LAR 30 mg/28 gg**

ENETs Guidelines 2012

**NETs ileali sindromici con metastasi epatiche,
G1-G2, primitivo resecato,
assente malattia extraepatica**

**Mts epatiche UNI/
BILOBARI**

**Mts epatiche
DIFFUSE**

Chirurgia ±
RFA

TAE/TACE

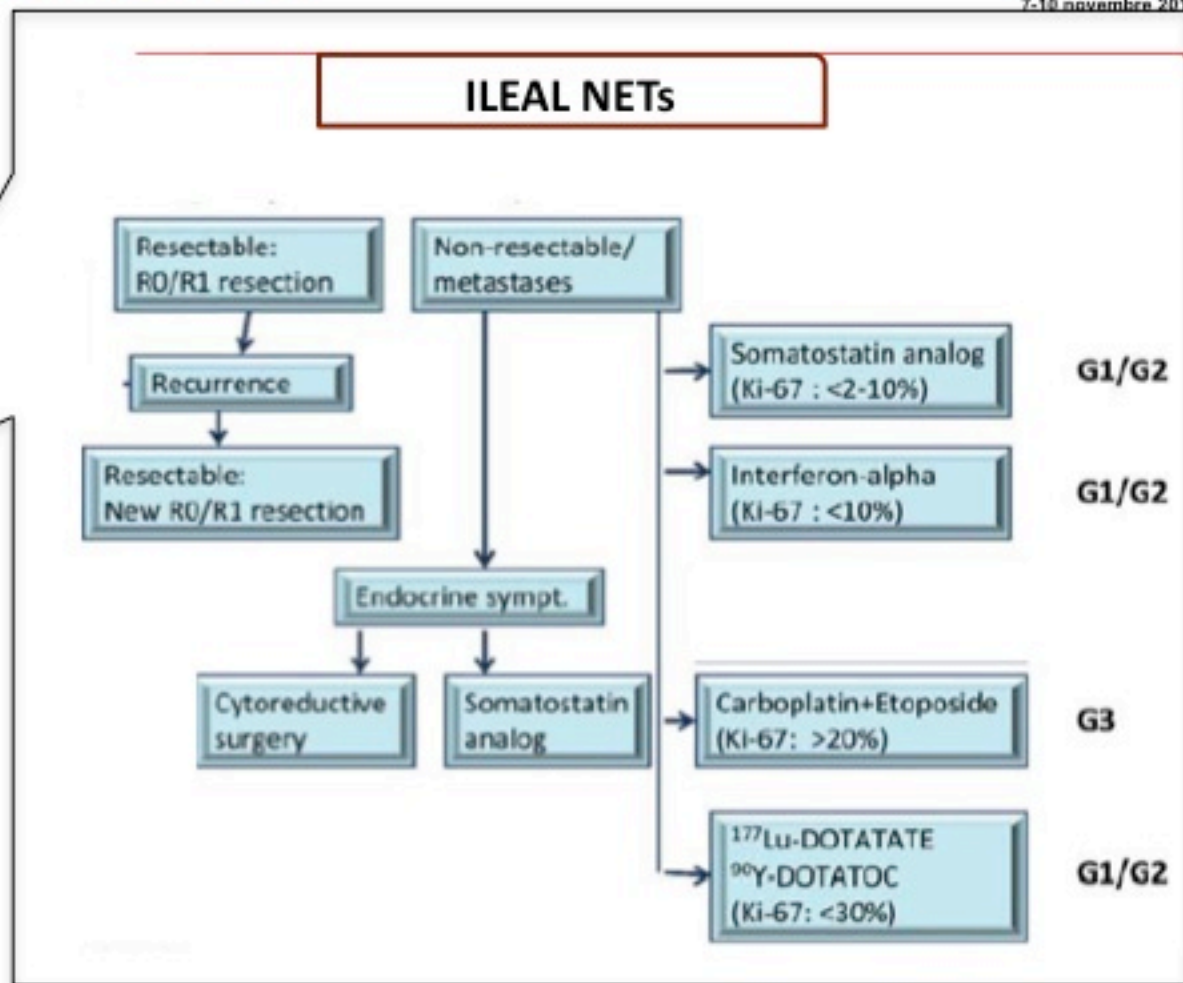
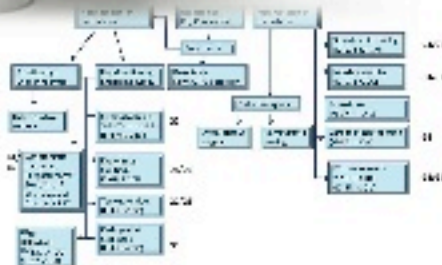
SSA (IFN)
PRRT
(everolimus)

Casi
selezionati:
Trapianto

ESMO guidelines 2012



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Somatostatin Analogues in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors

THIERRY DELAUNOIT, MD; JOSEPH RUBIN, MD; FLORENCE NECZYPORENKO, MD; CHARLES ERLICHMAN, MD;
AND TIMOTHY J. HOBDAJ, MD



Study	n	Response	Stable Disease	Progressive Disease	Death	Quality of Life
Delvaunot et al (2005)	10	67.3%	100%	0%	0%	Improved
Rubin et al (2005)	10	67.3%	100%	0%	0%	Improved
Neczyporenko et al (2005)	10	67.3%	100%	0%	0%	Improved
Erlichman et al (2005)	10	67.3%	100%	0%	0%	Improved
Hobday et al (2005)	10	67.3%	100%	0%	0%	Improved
Total	50	67.3%	100%	0%	0%	Improved

Study	n	Response	Stable Disease	Progressive Disease	Death	Quality of Life
Delvaunot et al (2005)	10	0%	7%	0%	0%	No Change
Rubin et al (2005)	10	0%	7%	0%	0%	No Change
Neczyporenko et al (2005)	10	0%	7%	0%	0%	No Change
Erlichman et al (2005)	10	0%	7%	0%	0%	No Change
Hobday et al (2005)	10	0%	7%	0%	0%	No Change
Total	50	0%	7%	0%	0%	No Change

Risposta sintomatica → 67.3 - 100%

Risposta obiettiva → 0 - 7%

Malattia stabile → 40 - 87.5%



OCTREOTIDE LAR

TABLE 2. Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors*

Reference	No. of patients	Agent	Dosage	Response (%)			
				OR	SD	BR	SR
Ricci et al, ²¹ 2000	15	Long-acting octreotide	20 mg/mo			41	82
Shojamanesh et al, ²⁶ 2002	15	Long-acting octreotide	20-30 mg/mo	6	47	NR	NR
Tomassetti et al, ²⁵ 1998	16	Long-acting octreotide	20 mg/mo	0	87.5	81	100
Rubin et al, ¹¹ 1999	26 vs 22/20/25	Octreotide vs long-acting octreotide	300-900 µg/d (total dose) vs 10/20/30 mg/mo	NR	NR	NR	58 vs 67/71/62

Symptoms response → 71 - 100%

LANREOTIDE

Ricci et al, ²⁹ 2000	25	Prolonged-release lanreotide	30 mg every 14 d			42	65
Scherubl et al, ²¹ 1994	18	Prolonged-release lanreotide	30 mg every 10-14 d			NR	86/42/50, F/D/A
Tomassetti et al, ²⁵ 1998	18	Prolonged-release lanreotide	30 mg every 10 d			NR	100
Ruszniewski et al, ³⁰ 1996	39	Prolonged-release lanreotide	30 mg every 14 d	0	NR	18	39/30, F/D
Wymenga et al, ¹⁷ 1999	55	Prolonged-release lanreotide	30 mg every 14 d	6	81	38	42

Symptoms response → 30 - 100%



Procedure a rischio di crisi da carinoide



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- ✓ Chirurgia
- ✓ Chemio/embolizzazione epatica
- ✓ Ablazione termica con radiofrequenza
- ✓ Terapia radiometabolica con SA



CARCINOID CRISIS INDUCED BY RECEPTOR RADIONUCLIDE THERAPY WITH ^{90}Y -DOTATOC IN A CASE OF LIVER METASTASIS FROM BRONCHIAL NEUROENDOCRINE TUMOR.

M.V. Davi¹, L.Bodei², G.Francia¹, M. Bartolomei², C.Oliani³, L.Scilanga¹, M.Falconi⁴, G. Paganelli², M. Ferdeghini⁵

OCTREOTIDE S.C.

TABLE 2. Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors*

Reference	No. of patients	Agent	Dosage	Response (%)			
				NR	NR	BR	SR
Arnold et al, ¹⁴ 1996	52	Octreotide	200 µg 3 times daily			74	NR
Maton et al, ²⁰ 1989	107	Octreotide	Various doses			79.4	67.3
Kvols et al, ²³ 1987	22	Octreotide	150-500 µg 3 times daily			68.2	100
Ruszniewski et al, ²² 1993	4	Octreotide	200 µg twice daily	NR	NR	75	100
Eriksson et al, ²⁸ 1990	14	Octreotide	100 µg twice to 3 times daily	28.6	21.4	28.6	NR
Eriksson & Oberg, ²⁷ 1993	19	Octreotide	100 µg twice daily	NR	31.6	31.6	NR
di Bartolomeo et al, ¹⁵ 1996	58	Octreotide	500-1000 µg 3 times daily	3	46.5	77	73
Saltz et al, ¹³ 1994	34	Octreotide	250 µg 3 times daily	0	50		71†

Iniziare almeno 1 h prima della procedura:

Octreotide 50-100 µg/h ev infusione continua per 24-72 hrs

Octreotide 100-500 µg/sc ogni 8 h per almeno 3 gg





Terapie locoregionali delle metastasi epatiche NETs G1/G2



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Risposta parziale/completa

Tipo di procedura	Sintomatica	Biochimica	Radiologica	Durata della risposta sintomatica	5-yr Survival
TACE/TAE	70-100%	50-90%	30-50%	14-20 mesi	40-83 %
RFA	70-80%			12 mesi	
SIRT	-	55%	50-60%		

- Controindicazioni:**
- trombosi portale
 - insufficienza epatica
 - anastomosi biliari (resezione sec. Whipple)
 - severe comorbilita'

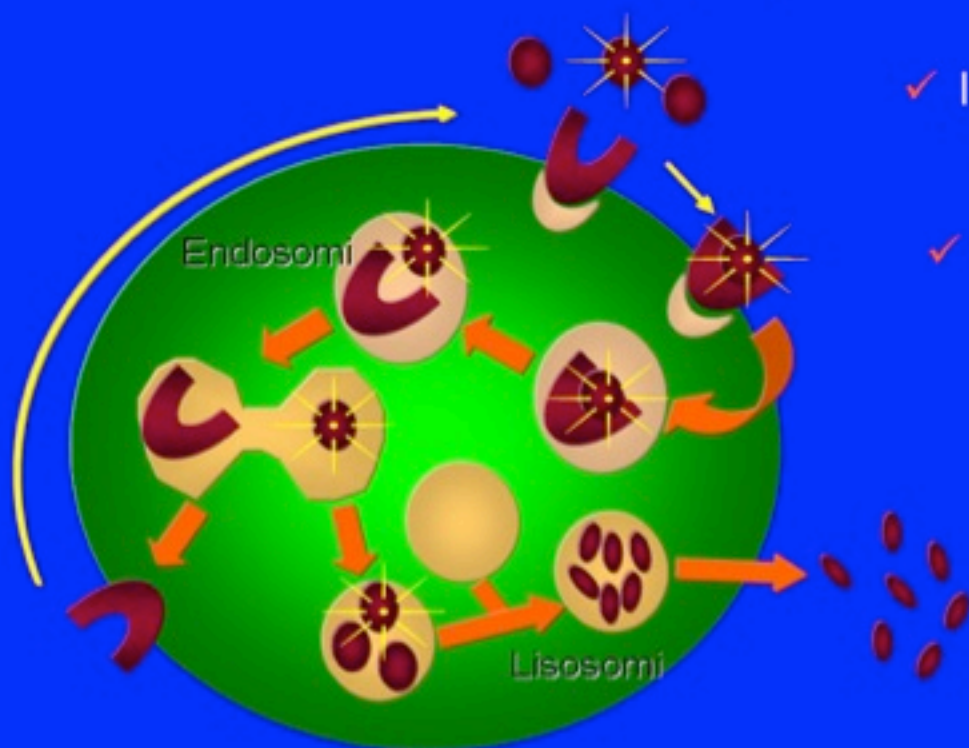
Eriksson J, World J Surg 2008; 32: 930-938.

Mazzaglia PJ, Surgery 2007; 142: 10-19

Vogl TJ, Eur J Radiol 2009; 72: 517-528

Kennedy AS, Am J Clin Oncol 2008; 31: 271-279

Internalizzazione recettore-mediata del radiopeptide



✓ Irradiazione della
cellula tumorale

✓ Meccanismo di
"cross-fire"



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PRRT nei GEP-NETs: risultati

$^{90}\text{Yttrium}$ and $^{177}\text{Lutetium}$ DOTATOC o DOTATATE

Risposta obiettiva	Stabilizzazione	Tempo medio alla progressione
30-40%	50%	30-40 mesi

Risposte superiori nei NETs pancreatici vs ileali

Kwekkeboom DJ, J Clin Oncol 2008; 26: 2124–2130

Kwekkeboom DJ, ENETS Guidelines, Neuroendocrinology 2009; 90: 220–226.



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PRRT for metastatic carcinoid refractory to octreotide PFS

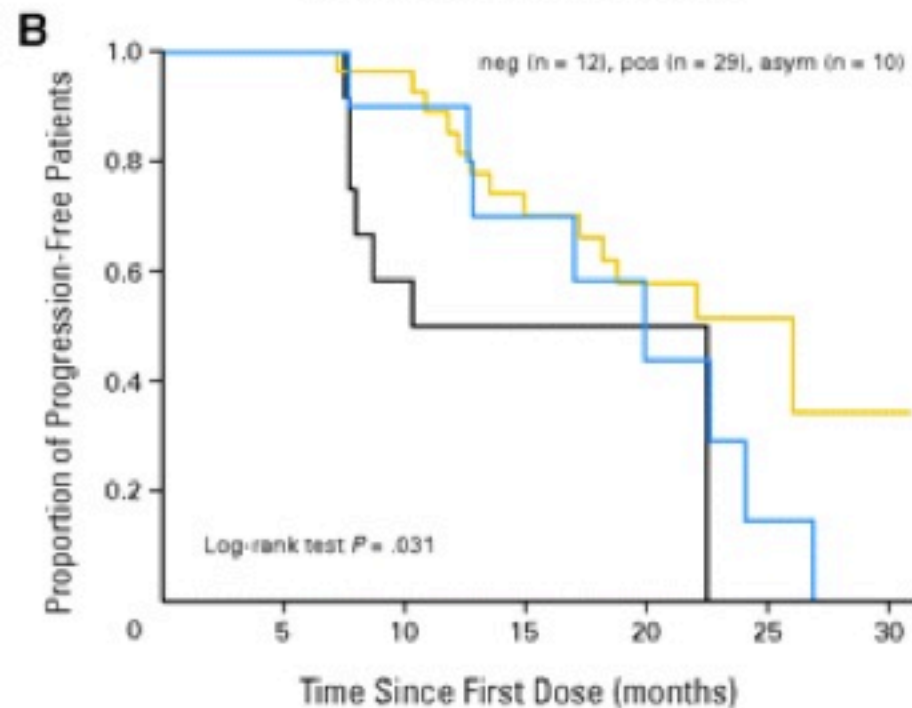
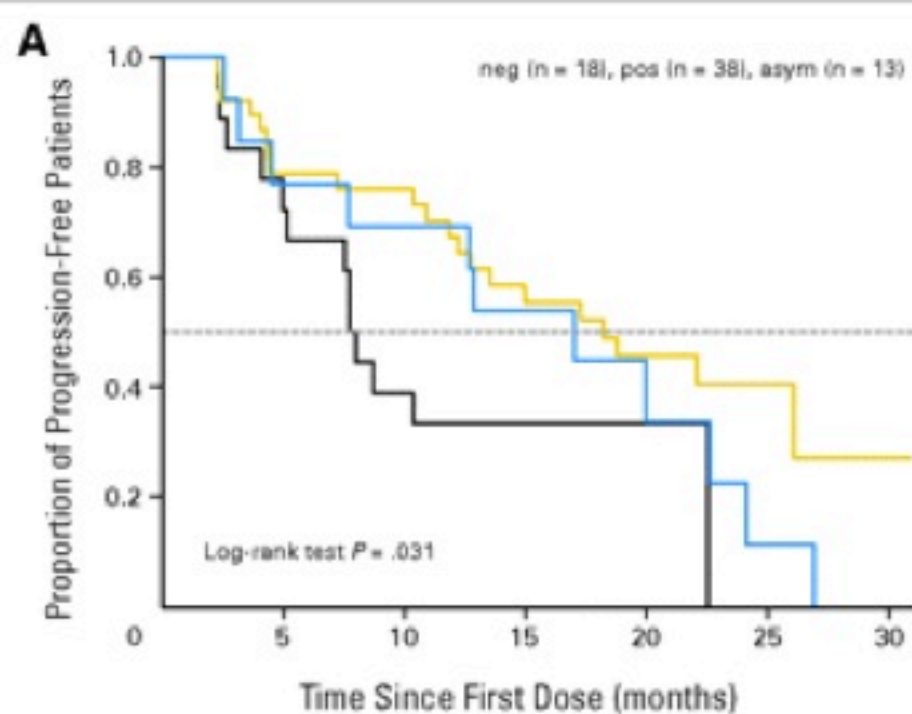
18,2 months: 38 pts with durable diarrhea
improvement

7,9 months: 18 pts without diarrhea
improvement

p=0,03

90Y-edotreotide treatment improved
symptoms associated with malignant carcinoid
among subjects with no treatment
alternatives. Treatment was well-tolerated and
had an acceptable expected AE profile.

*Bushnell DL, et al.
J Clin Oncol 28:1652-1659. 2010*





Favorable prognostic factors for PRRT



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- High uptake on the Octreoscan
- Karnofsky performance score >70 %
- Moderate tumor load

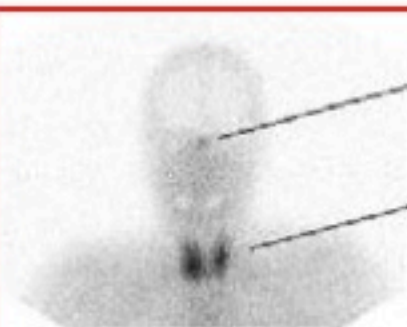
PRRT should be started during the earliest possible stage of disease progression



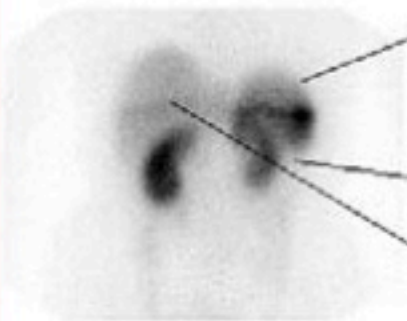
TOXICITY



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- No important effect on pituitary function
- No important effect on thyroid function
- Common: mild bone marrow suppression



- Common: Lymphocytopenia
- Rare: MDS, Leukemia
- Rare: Kidney impairment
- Rare: Liver toxicity

Progressione epatica (Apr 2009):

TC stadiazione : ...aumento delle dimensioni e numero delle lesioni epatiche bilateralmente

- 4 cicli di **PRRT** con ^{177}Lu -DOTATATE (341 mCi) con risposta parziale e controllo della sindrome
- 2013: 4 anni dopo, continua **octreotide LAR 30 mg/28 gg**

...**ma in caso di ulteriore progressione di malattia quale sara' il passo successivo?**



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PROSPETTIVE PRESENTI E FUTURE....

Nicola Fazio



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.....QUALE TRATTAMENTO PER I NETs POLMONARI?

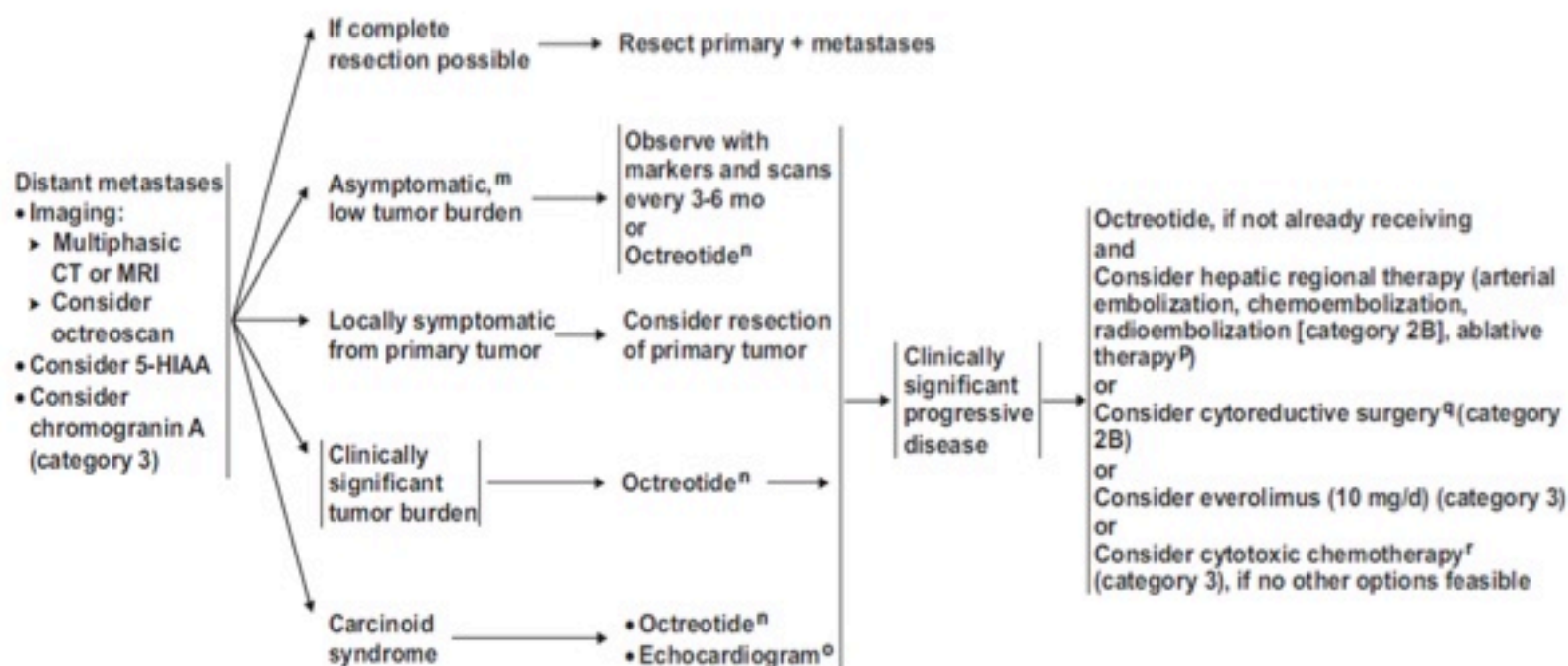


Trattamento dei NET toracici metastatici o localmente avanzati secondo le linee guida NCCN 2011

NCCN National Comprehensive Cancer Network[®] NCCN Guidelines™ Version 1.2011
Carcinoid Tumors

[NCCN Guidelines Index](#)
[Neuroendocrine TOC](#)
[Discussion](#)

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^b





PRRT

- Lung NET vs Total NET -



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Autore	Radiofarmaco	Sede	N° pz	RC+RP RECIST
Valkema	^{90}Y -DOTATOC	GEP	58	9%
Kwekkeboom	^{177}Lu -DOTATATE	GEP	310	30%
Waldherr	^{90}Y -DOTATOC	Polmone	7	30%
		Mista	41	44%
Waldherr	^{90}Y -DOTATOC	Polmone	3	0%
		Mista	39	23%
Bodei	^{177}Lu -DOTATATE	Polmone	5	40%
		Mista	51	29%
Filice	^{90}Y -/ ^{177}Lu -DOTATOC	Polmone	13	62%
		Mista	59	42%

Tempo medio alla progressione: 30-40 mesi

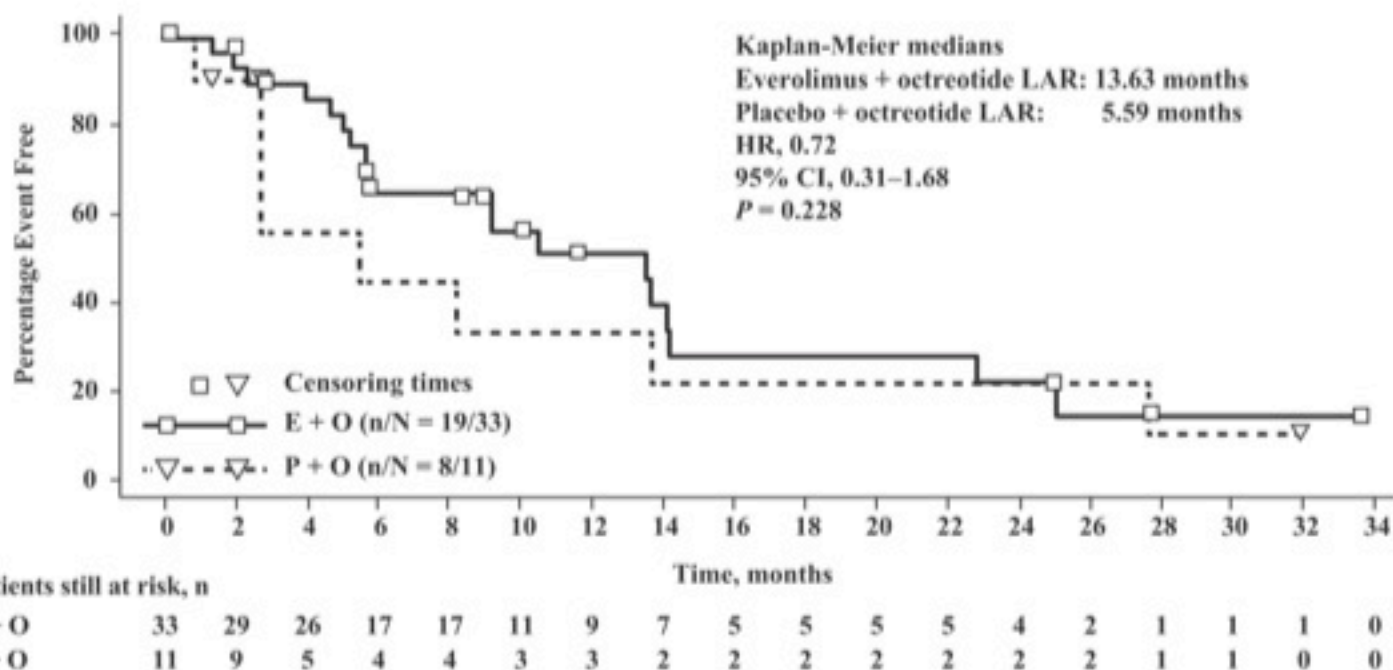


PFS in RADIANT-2

- Lung NET vs Total NET -

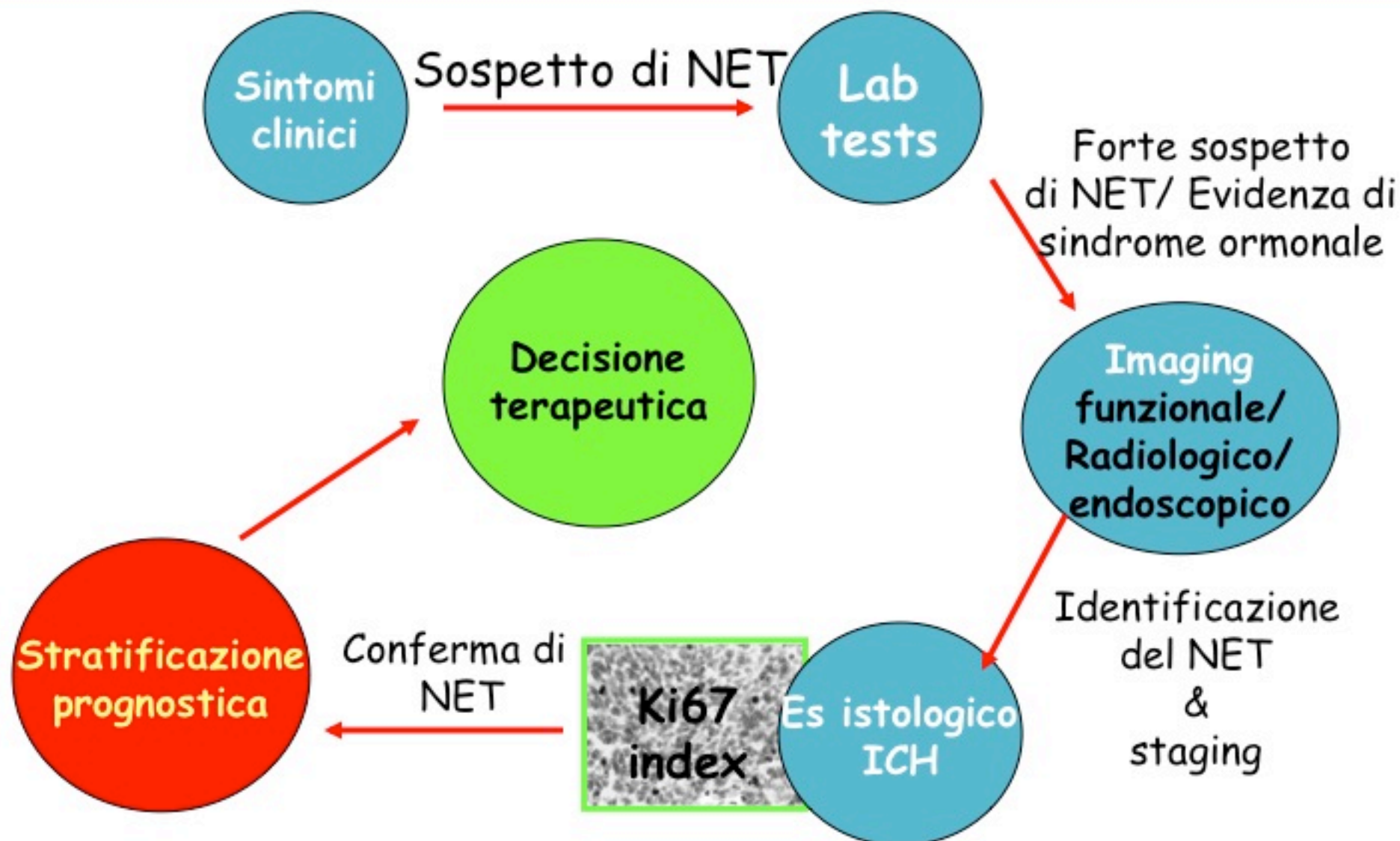


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	N°	Eve + SSA	Plac + SSA	Δ T	p
Lung NET	44 pz	13,6 mo	5,6 mo	8 mo	0,228 (NS)
Total NET	429 pz	16,4 mo	11,3 mo	5,1 mo	0,026 (NS)

Il percorso diagnostico dei carcinoidi





XII congresso nazionale AME VI Joint meeting with AACE

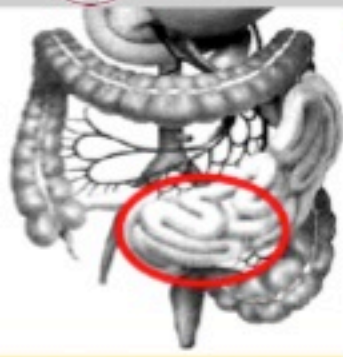


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La sindrome da carcinoide

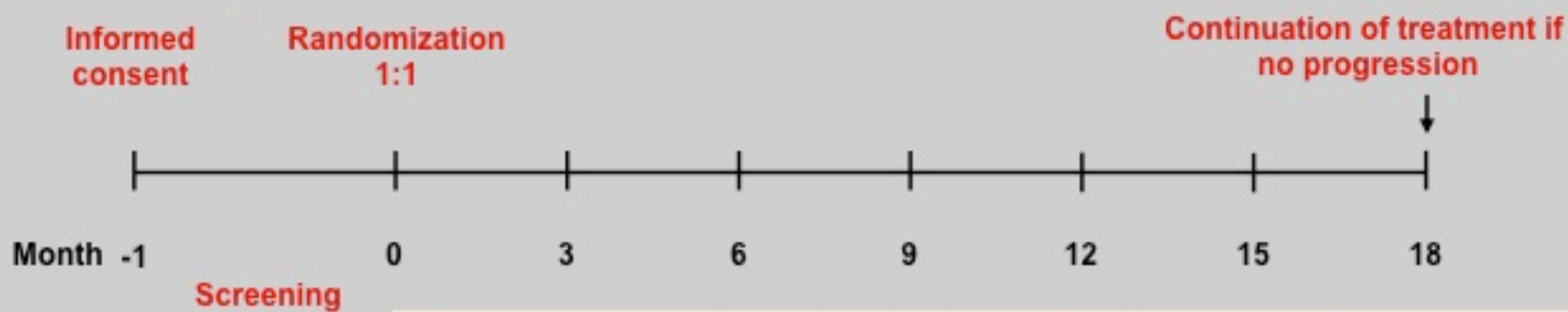
Dottor Nicola Fazio

PROMID trial: design



Octreotide LAR 30 mg i.m. every 4 weeks

Placebo i.m. every 4 weeks



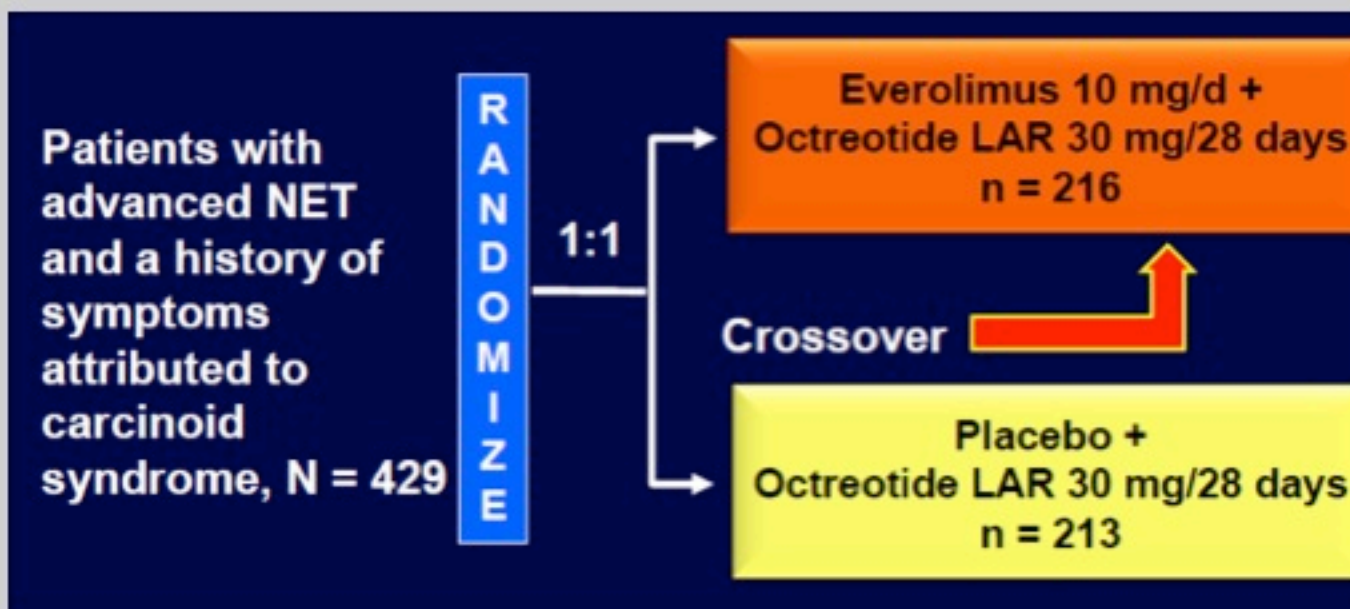
Primary endpoint: time to tumor progression

- Midgut
- 1° line
- Functioning or non-functioning

Rinke, JCO 2009

Only patients tolerating flushing without intervention or responding to treatment with loperamide or cholestyramine in case of diarrhea were included.

RADIANT-2 trial





RADIANT-2 trial: inclusion criteria



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Patients with advanced NET and a history of secretory symptoms

- Advanced low- or intermediate-grade NET
- Radiologic progression (not necessarily RECIST-based) in the proceeding 12 months
- History of secretory symptoms (flushing **and/or** diarrhea)
- Presence of measurable disease (RECIST v1.0)
- Prior antitumour therapy allowed (prior OCT LAR not mandatory)
- WHO PS \leq 2



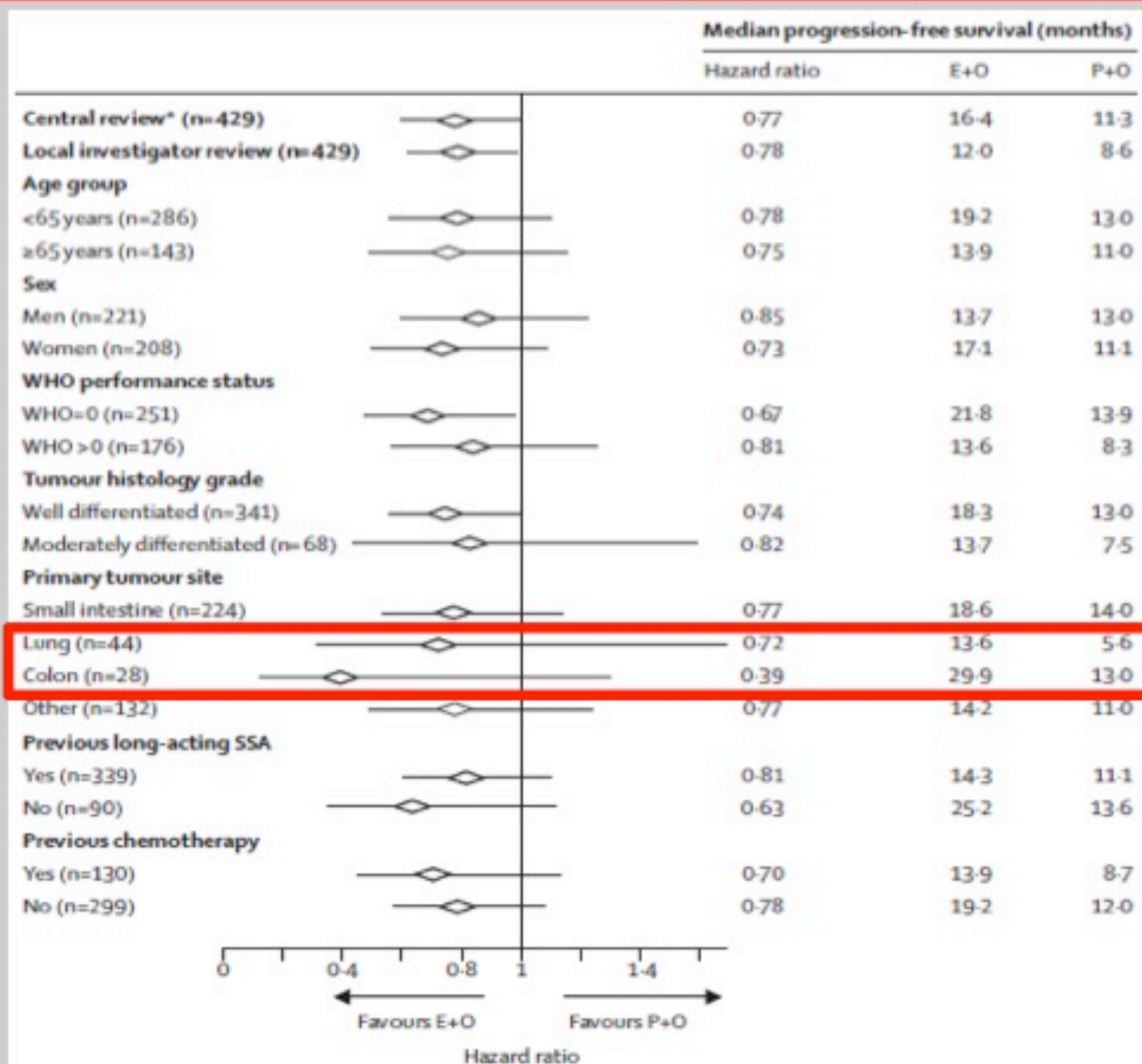
RADIANT-2 trial: population



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	Everolimus plus octreotide LAR group (n=216)	Placebo plus octreotide LAR group (n=213)
Median age, years (range)	60 (22–83)	60 (27–81)
Number of women	119 (55%)	89 (42%)
Number of men	97 (45%)	124 (58%)
WHO performance status*		
0	118 (55%)	140 (66%)
1	84 (39%)	62 (29%)
2	14 (6%)	10 (5%)
Primary site of cancer		
Small intestine	111 (51%)	113 (53%)
Lung	33 (15%)	11 (5%)
Colon	14 (6%)	14 (7%)
Pancreas	11 (5%)	15 (7%)
Liver	7 (3%)	11 (5%)
Other	40 (19%)	48 (23%)
Missing	0	1 (0.5%)

RADIANT-2 trial: subgroups





Casi clinici - 1



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	Paz. A	Paz. B
genere	F	F
anni	71	70
Anno diagnosi	2011	1989
primitivo	ileo	ileo
sindrome	si	si
grado	manca	manca
Ki67	2%	manca
SRS / PET-Ga	++	++
M+ epatiche	sincrone	sincrone
M+ extra-epatiche	sincrone	no



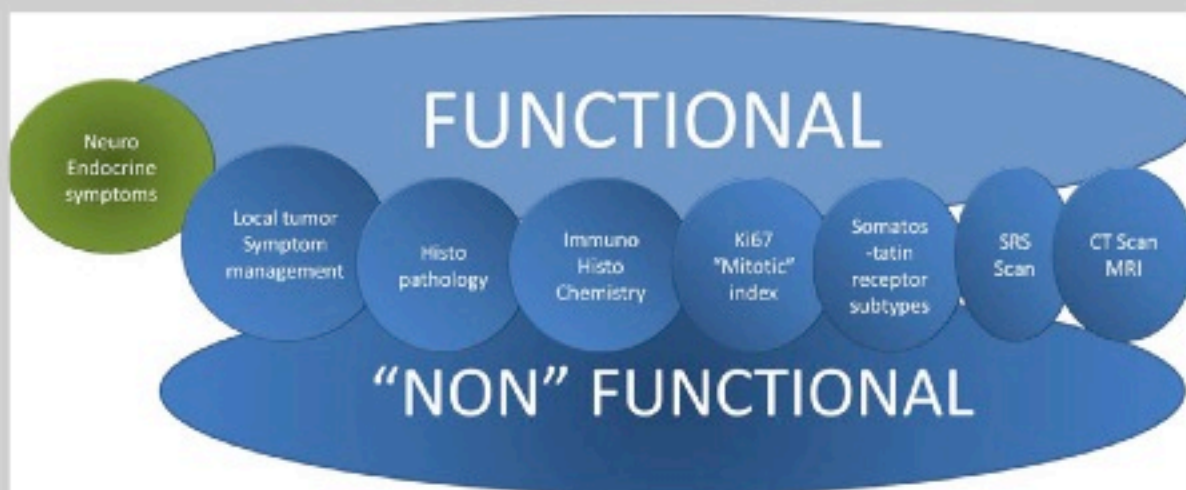
Casi clinici - 2



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	Paz. A	Paz. B
genere	F	F
anni	71	70
Cardiopatìa all'esordio	si	no
SSA	si	si
Stato attuale neoplasia	Rapida PD radiologica, funzionale, clinica	Lenta PD radiologica, funzionale e clinica
Stato attuale cardiopatìa	Netta progressione	Stenoin suff. aortica

Functioning / non-functioning NETs



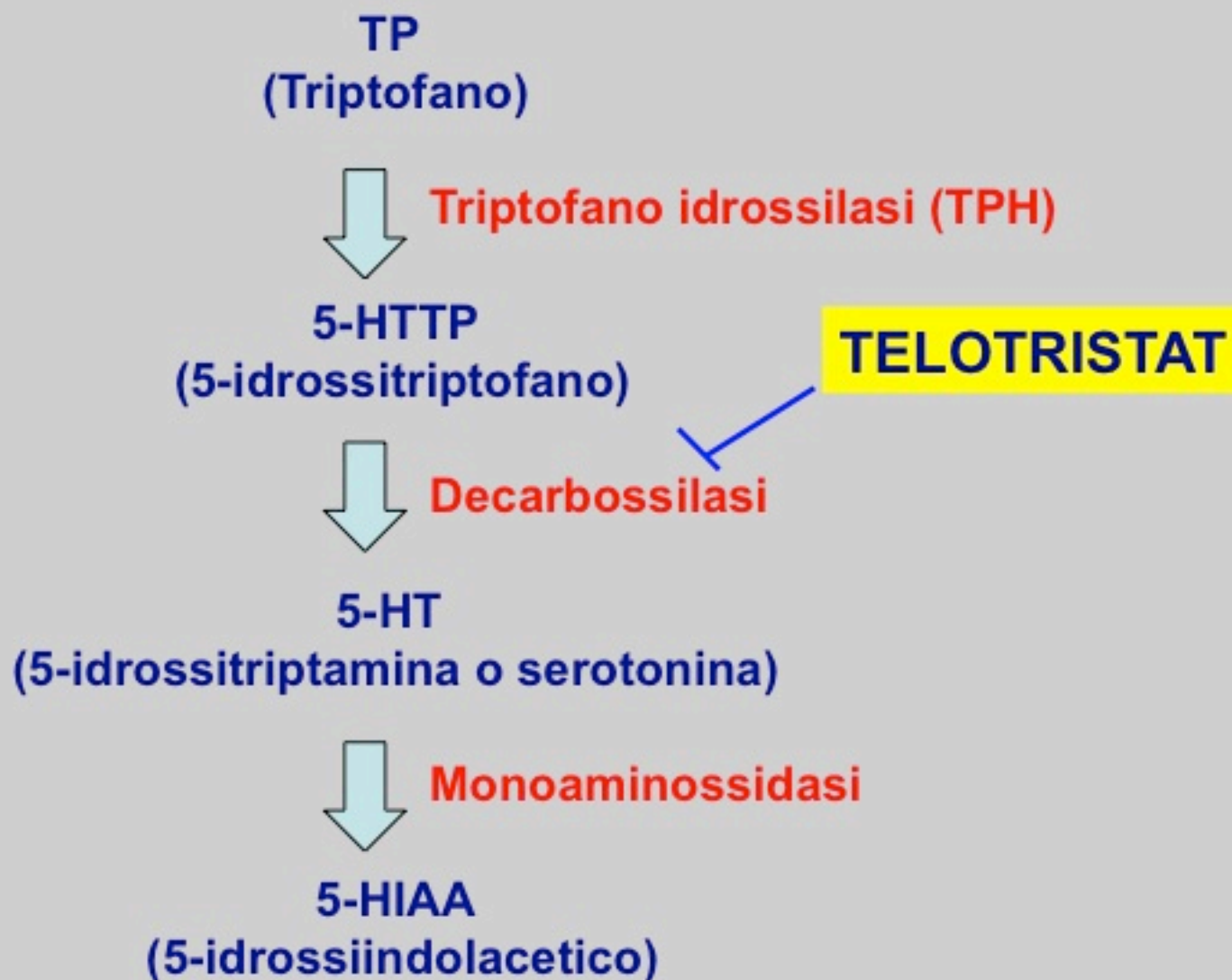
It therefore seems apparent that the consideration of NENs as functional or nonfunctional is an archaic clinical concept that should be discarded.



Triptofano / Serotonina



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7-10 novembre 2013





Giornata mondiale dei NET



Bari,
7-10 novembre 2013

THINK ZEBRA



Bologna 10 Novembre 2013
Giornata Mondiale dedicata ai tumori neuroendocrini