12 novembre 2017 ore 10.15 – 12.15

Neoplasie neuroendocrine gastro-entero-pancreatiche (GEP-NEN): la risposta al trattamento ed il follow-up

Maria Vittoria Davì, Matteo del Pin, Nicola Fazio, Angelina Filice, Franco Grimaldi, Francesca Spada

Franco Grimaldi: conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag.17 del Regolamento Applicativo Stato-Regioni del 05/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Ipsen
- Novartis
- Italfarmaco

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag.17 del Regolamento Applicativo Stato-Regioni del 05/11/2009, il sottoscritto **dr. Nicola Fazio** dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Novartis

Ipsen

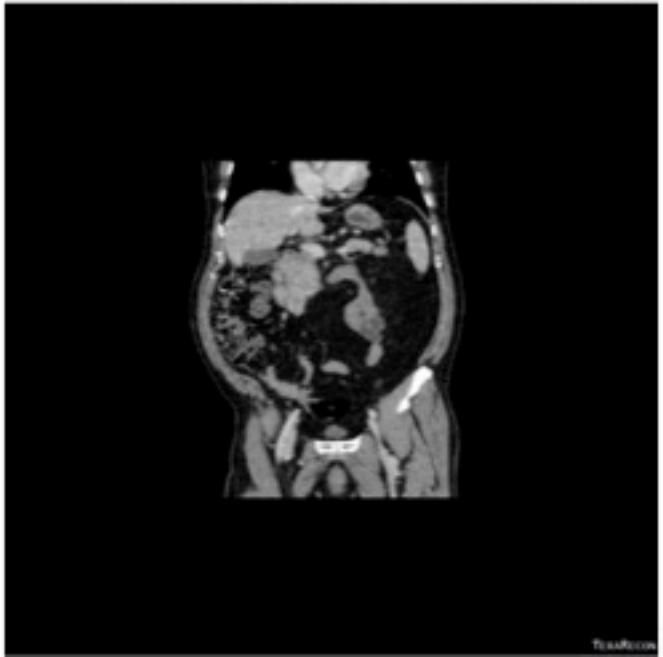
Pfizer

AAA

Caso clinico 1

Dragan, maschio, 59 anni

- Voluminoso pNEN, apparentemente non secernente, di recente riscontro TC (febbraio u.s.) in seguito a comparsa di lombalgia acuta.



… a livello della testa pancreatica-processo uncinato si apprezza lesione solida a contorni polilobati e margini netti, con intenso e disomogeneo enhancement di 66x50x68 mm … a livello epatico sono presenti 2 lesioni sospette per secondarietà delle dimensioni di 10 e 5 mm.

Caso clinico 1

Esame	*Risultato*	*Intervallo di normalità*
Cromogranina A	36 ng/ml	0 - 108
NSE	14,2 ng/ml	0,3 - 12
Glicemia	100 mg/dl	76-110
Calcio	10,6 mg/dl	8.4-10.7
Fosforo	2,3 mg/dl	2,4 – 4,5
PTH	80,7 pg/ml	11,1 - 79
IGF1	180 ng/ml	45 - 213
PRL	178,6 mUI/L	53 - 369
Cortisolo	397 nMol/L	150 - 650
TSH	1,9 microIU/ml	0,350 – 5,0
5-HIAA urinario	19 microMol/24 h	11 - 37

Caso clinico 1

Esegue visita chirurgica: ricovero in Day Hospital

Ecoendoscopia (6/4/2017):

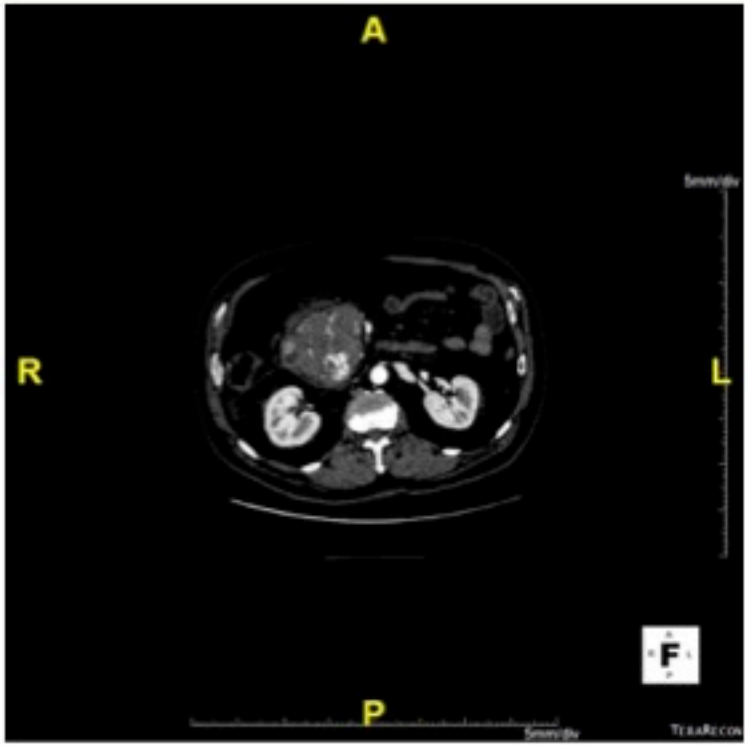
… a livello del processo uncinato esteso sino alla testa in regione retropapillare di grossolana neoformazione ovalare e lobulata ad ecostruttura debolmente iperecogena, con areole ipoanecogene centrali e margini regolari, di circa 65 mm. La lesione appare notevolmente vascolarizzata; all'elastografia presenta pattern hard in periferia, più soft nella porzione centrale.

Conclusioni: **Lesione solida del processo uncinato del pancreas di 65 mm di dimensioni** con aspetto ecografico compatibile in primis con NEN, anche se non può essere escluso altro (tumore pseudopapillare solido, linfoma). In attesa di conferma citologica.

Reperto citologico di **neoplasia neuroendocrina ben differenziata** con positività immunoistochimica per sinaptofisina, cromogranina, CD56, CK-MNF116 (negativi, CD 45 ed NSE).

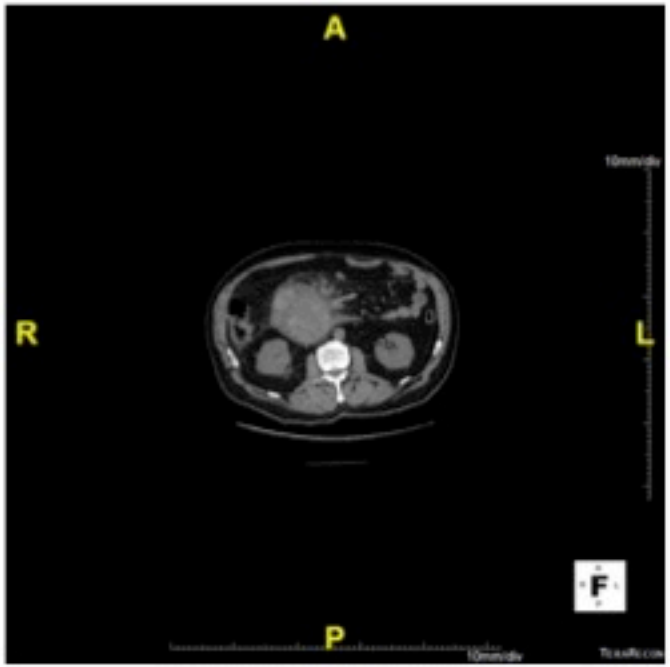
Indice proliferativo (Ki67) <1%.

Caso clinico 1

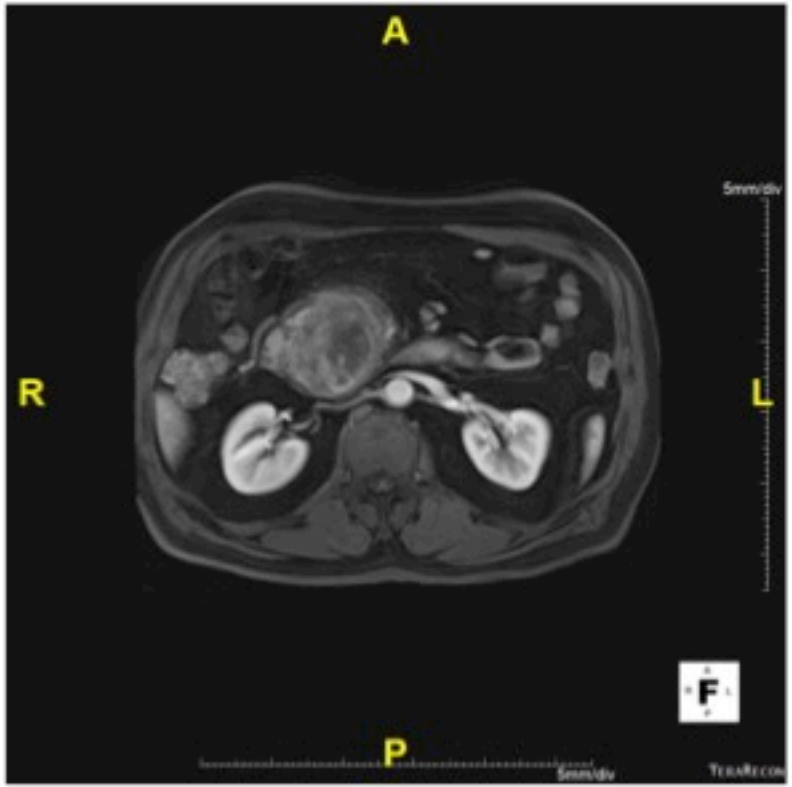


TC addome mdc (10/4/2017):

Complicanza della procedura: sanguinamento post Ecoendoscopia, viene eseguita embolizzazione



Caso clinico 1

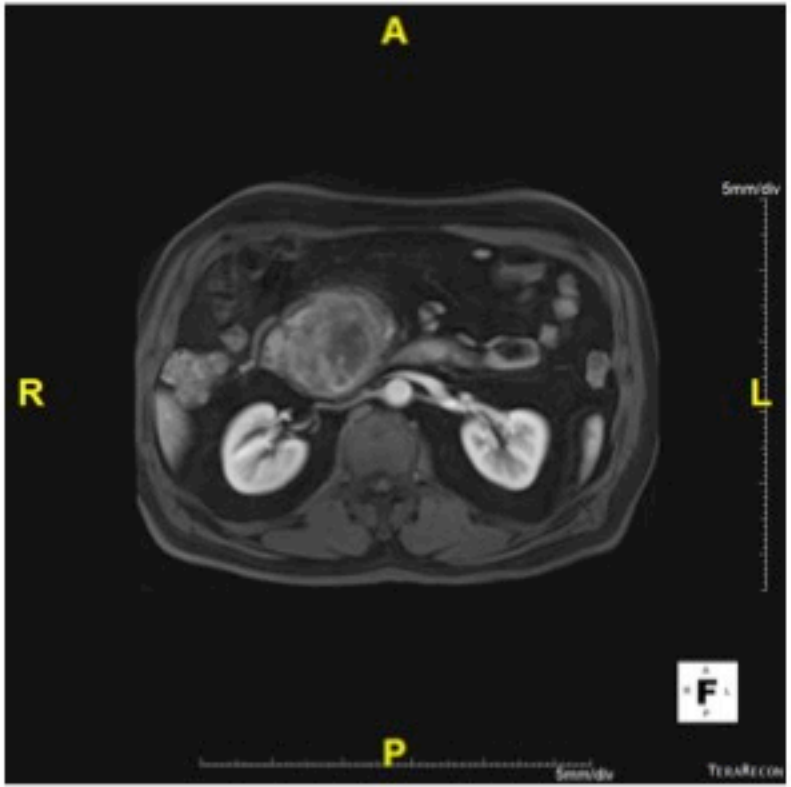


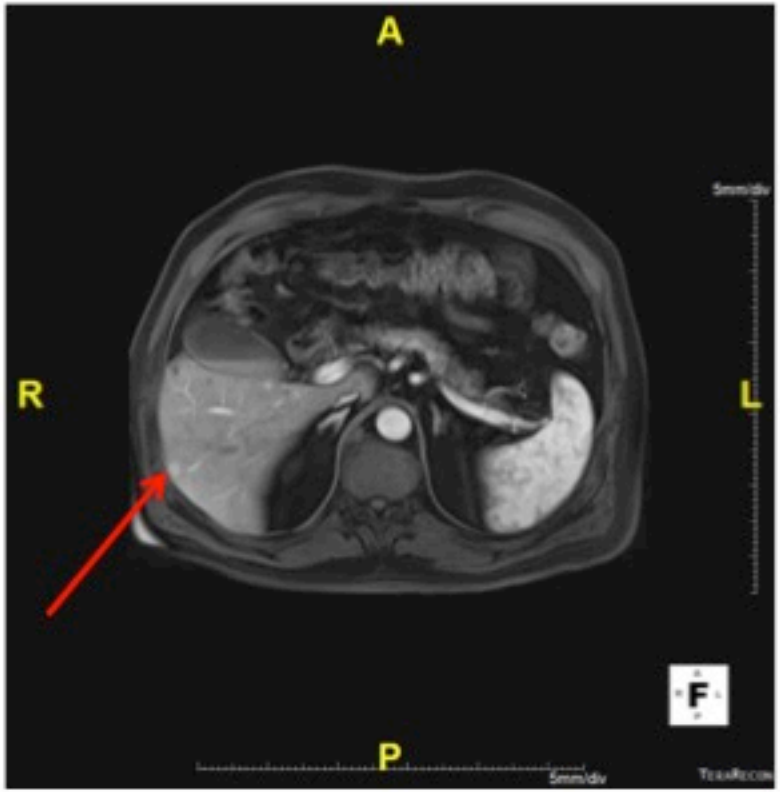
RMN addome mdc (8/5/2017):

Iniziale riassorbimento dell'ematoma.

… medialmente la vena mesenterica superiore nel suo tratto distale permane non riconoscibile, come da sua possibile trombosi.

Caso clinico 1





Giugno 2017: viene inviata in consulenza endocrinologica: NEN pancreatico NF

The initial characterization of a patient with NEN should be based on information concerning the disease status:

- The pathologic report is histology, grading (identifies both tumor morphology and proliferation rate).
- Tumor extension according to morphologic and functional imaging, hormone secretion
- Integrated with information on his/her performance status, comorbidities, recent clinical evolution, social role, and beliefs.

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Assessment of Response to Treatment and Follow-Up in Gastroenteropancreatic Neuroendocrine Neoplasms

F. Grimaldi, N. Fazio, et al 2017 submitted

NEN pancreatico NF

Quale imaging:

- Ecografia addome, CEUS, CT, RMN
- PET-TC Gallio 68, PET-TC 18-FDG?

Il ruolo del radiologo

La **TC con MdC, con studio trifasico dell'addome superiore** costituisce metodica imaging di base per i NET nella diagnosi, staging, sorveglianza e monitoraggio della terap

Table 1. CT diagnosis of NETs

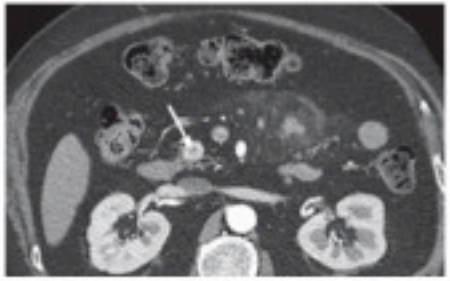
Type of NET	Mean sensitivity	Mean specificity	Mean detection rate	Patients/ studies	Ref.
NET disease	82 (77–85)	86 (71–85)		253/4	3–6
Pancreatic NET	82 (67–96)	96		119/2	10–11
Liver metastases			79 (73–94)	79/3	7–9
	84 (75–100)	92 (83–100)		342/5	3, 12–15
Extrahepatic abdominal soft tissue metastases	70 (60–100)	96 (87–100)		451/6	3, 12–15, 17
Bone metastases	61 (46–80)	99 (98–100)		337/3	3, 18,19
CT enteroclysis for small intestinal NETs	50	25		8/1	20
	85	97		219/1[a]	21

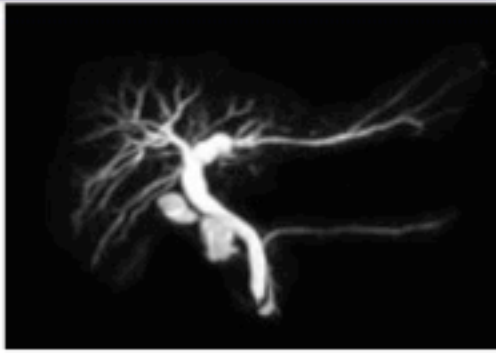
Data in the literature on the sensitivity, specificity and detection rate for NET diagnosis by CT. Figures are percentages with ranges in parentheses unless indicated otherwise. [a] Out of 219 patients included in the study, there were 19 subjects with small intestinal NETs.

Neuroendocrinology DOI: 10.1159/000471879

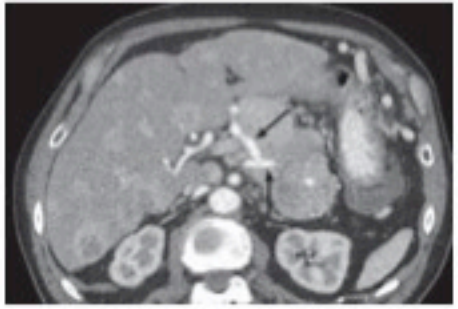
Il ruolo del radiologo

In TC i pNET funzionanti come l'insulinoma ed i pNET non funzionanti scoperti casualmente sono spesso piccoli e ben delimitati, in genere appaiono ben visibili ed ipervascolari nella fase arteriosa tardiva.





Gli altri pNET (gastrinoma, VIPoma, glucagonoma) e pNET non funzionanti solo in genere più grandi, con calcificazioni e con vascolarizzazione disomogenea (anche con aree di necrosi)



La TC inoltre permette di identificare la posizione del tumore rispetto al dotto pancreatico (MRCP?) e l'encasement vascolare, permette di valutare i linfonodi e le eventuali metastasi a distanza (soprattutto epatiche)

Neuroendocrinology DOI: 10.1159/000471879

Il ruolo del radiologo

La RM è superiore alla TC nel visualizzare le metastasi epatiche (MdC epatospecifico e DWI), metastasi cerebrali, ossee e nel visualizzare i tumori pancreatici (specie ipovascolari).

Table 2. MRI diagnosis of NETs

Type of NET	Mean sensitivity	Mean specificity	Mean detection rate	Patients/ studies	Ref.
Gastrinoma	70			122/1	28
Pancreatic NET	79 (54–100)	100	76 (61–95)	258/7	11, 29–34
Liver metastases	75 (70–80)	98		200/2	40, 41
Carcinomatosis			88 (81–91)	72/2	42, 43

Data in the literature on the sensitivity, specificity and detection rate for NET diagnosis by MRI. Figures are percentages with ranges in parentheses unless indicated otherwise.

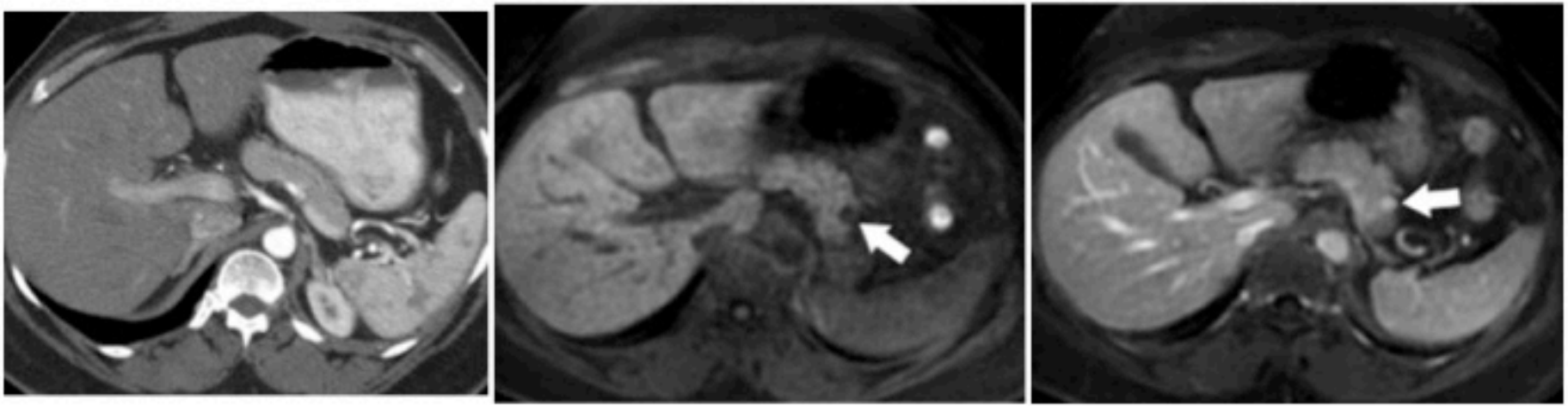
Neuroendocrinology DOI: 10.1159/000458155

Linee guida neoplasie neuroendocrine AIOM 2016

Neuroendocrinology DOI: 10.1159/000471879

Il ruolo del radiologo

La RM è superiore nel visualizzare le metastasi epatiche (MdC epatospecifico e DWI), metastasi cerebrali, ossee e nel visualizzare i tumori pancreatici (specie ipovascolari).



Radiology 2013;266: 38-61

Il ruolo del radiologo

L'ecografia transaddominale ha bassa sensibilità nell'individuare le lesioni pancreatiche (**CEUS?**), mal visualizza le aree di reazione desmoplastica addominale, non sempre visualizza tutto il fegato. Utile a volte come problem solving o come guida per procedure interventistiche

Table 3. US, EUS, IOUS and CEUS diagnosis of NETs

Type of NET and US method	Mean sensitivity	Mean specificity	Mean detection rate	Patients/ studies	Ref.
pNETs					
US			39 (17–76)	250/6	61–66
EUS			86 (75–97)	220/9	9, 62, 63, 66, 70–74
	86 (82–93)	92 (86–95)		149/3	67–69
IOUS			92 (74–96)	127/4	64, 66, 75, 76
Insulinoma					
EUS			86 (57–100)	250/12	63, 64, 72, 77–85
IOUS			92 (84–100)	264/9	66, 75, 76, 86–91
Duodenal tumors and lymph node metastases					
US			18	25/1	66
EUS			63	59/2	66
					72
Liver metastases					
US	88	95		131/1	12
CEUS	82			48/1	92

Data in the literature on the sensitivity, specificity and detection rate for NET diagnosis by US, EUS, IOUS and CEUS. Figures are percentages with ranges in parentheses unless indicated otherwise. US, ultrasonography; EUS, endoscopic ultrasonography; IOUS, intraoperative ultrasonography; CEUS, contrast-enhanced ultrasonography.

Linee guida neoplasie neuroendocrine AIOM 2016

Neuroendocrinology DOI: 10.1159/000471930

Il ruolo del radiologo

Ma cosa e come misurare?

Eur. J. Cancer, 2009, 45,228-247

Il ruolo del radiologo

Cosa e come misurare?

Table 4
Comparison between RECIST 1.0 and RECIST 1.1.

	RECIST 1.0	RECIST 1.1
Tumor burden	10 targets (5 per organ)	5 targets (2 per organ)
Lymph nodes	Measure like any other lesion	Measure short axis Define normal size
PD definition	20% increase in SLD	20% increase in SLD 5 mm in absolute increase
No measurable PD	Unequivocal	More details and examples
Functional imaging	Not included	FDG-PET considered in the evaluation of new lesions

Eur. J. Cancer, 2009, 45,228-247

Il ruolo del radiologo

Cosa e come misurare?

Table 5
Modified Choi criteria.

Response	Definition
CR	Disappearance of all lesions, no new lesions
PR	A decrease in size ≥10% and a decrease in tumor attenuation (HU) ≥15% on CT, no new lesions, no obvious progression of non-measurable disease
SD	Does not meet criteria for CR, PR, or PD; No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size ≥10% and does not meet criteria of PR by tumor attenuation; new lesions

Oncol. Lett., 2013, 6, 1707-1712

Il ruolo del radiologo

Cosa e come misurare?

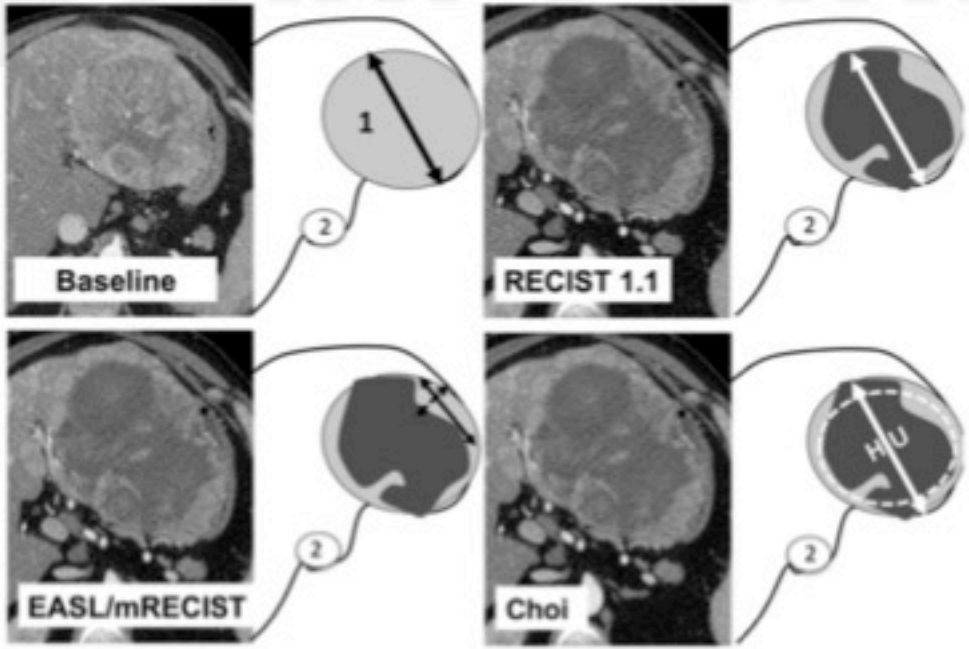
Table 6
mRECIST criteria.

Response	Definition
CR	Disappearance of any intratumor arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

J. Natl. Cancer Inst., 2008, 100, 698–711

Il ruolo del radiologo

Cosa e come misurare?



The Oncologist 2014;19:1–9

Il ruolo del radiologo

J. Endocrinol. Invest., 2014, 37, 875-909

La radiologia inoltre ha ruolo chiave nella gestione dei PZ sintomatici

Il ruolo del radiologo

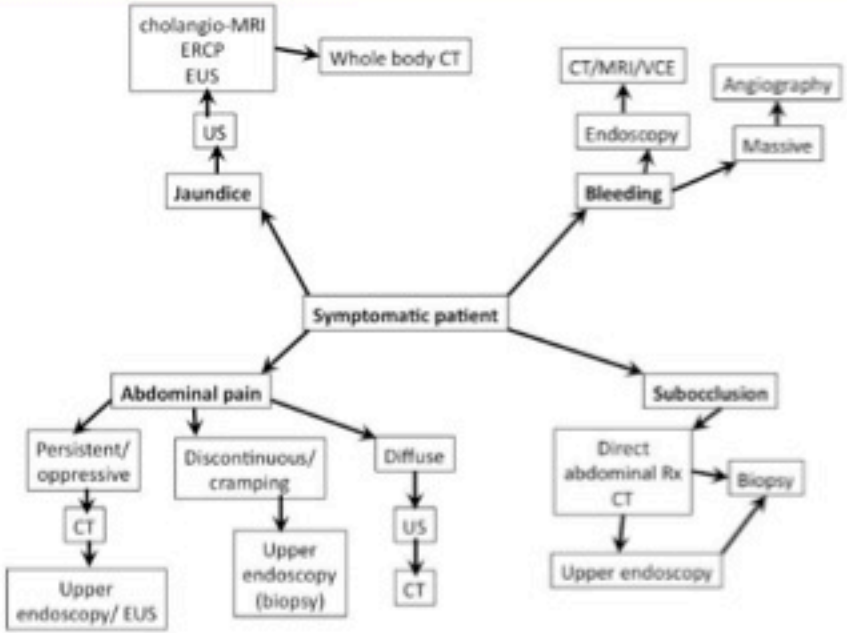


Figure 1
Selection of imaging modalities according to the type of symptoms

F. Grimaldi. Nicola Fazio, et al. Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Assessment of Response to Treatment and Follow-Up in Gastroenteropancreatic Neuroendocrine Neoplasms. submitted

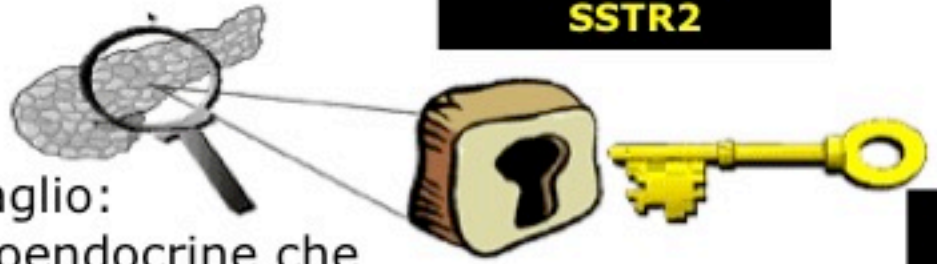
Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag.17 del Regolamento Applicativo Stato-Regioni del 05/11/2009, la sottoscritta **dr.ssa Angelina Filice** dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Commento del medico nucleare (Dott.ssa Angelina Filice)

Imaging medico-nucleare
Presupposti fisiopatogici

Sito di "aggancio" prevalente:
SSTR2



Bersaglio:
neoplasie neuroendocrine che esprimono recettori per la somatostatina

Analoghi della somatostatina

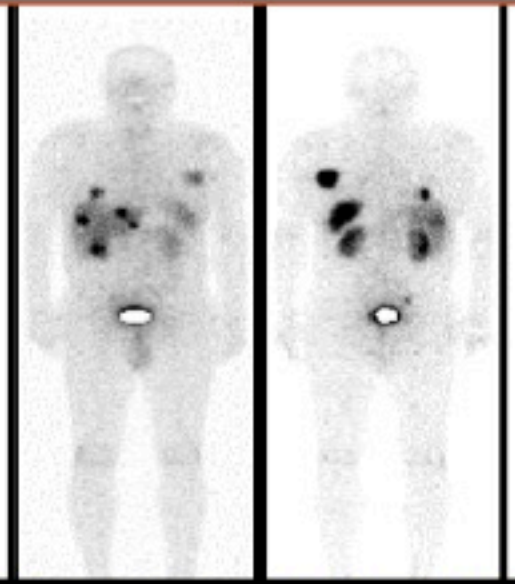
Densità di Espressione del SST-R2 nei Tumori GEP e ***Sensibilità dell'imaging con analoghi della somatostatina*** marcati

Gastrinoma	90-95%
Carcinoide	85-95%
VIP-oma	80-90%
Non-funzionanti	75-85%
Glucagonoma	70-80%
Insulinoma	50-60%

Metodiche

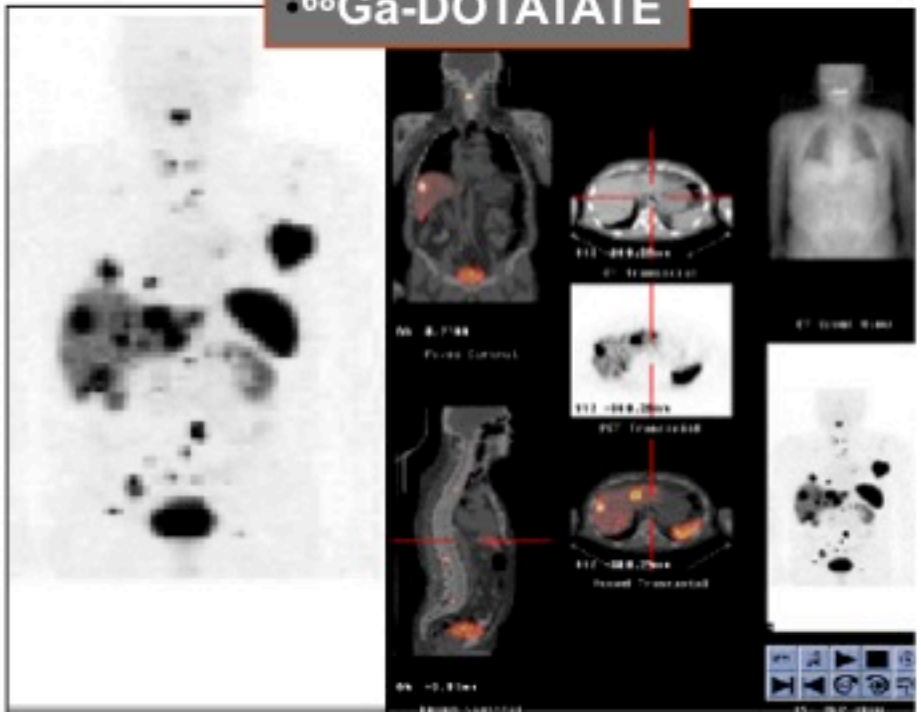
Scintigrafia, SPECT, SPECT/CT

- ^{111}In-Octreoscan



PET/CT

- ^{68}Ga-DOTATOC
- ^{68}Ga-DOTANOC
- ^{68}Ga-DOTATATE



Tumore neuroendocrino del tratto gastroenteropancreatico metastatico

^{111}In-Octreoscan and 68Ga-DOTA peptide PET/CT

- **Primary tumor localization and staging**
- **Restaging** (detection of residual, recurrent or progressive disease)
- **SSTR status evaluation** (patients with high positivity are more likely to respond to octreotide therapy)
- **Response** to therapy monitoring
- **Selection of patients for** peptide receptor radionuclide therapy (**PRRT**)

Bombardieri E Eur J Nucl Med 2010
Virgolini I Eur J Nucl Med 2010

ENETS Consensus Guidelines

Neuroendocrinology

Neuroendocrinology 2016;103:153–171
DOI: 10.1159/000443171

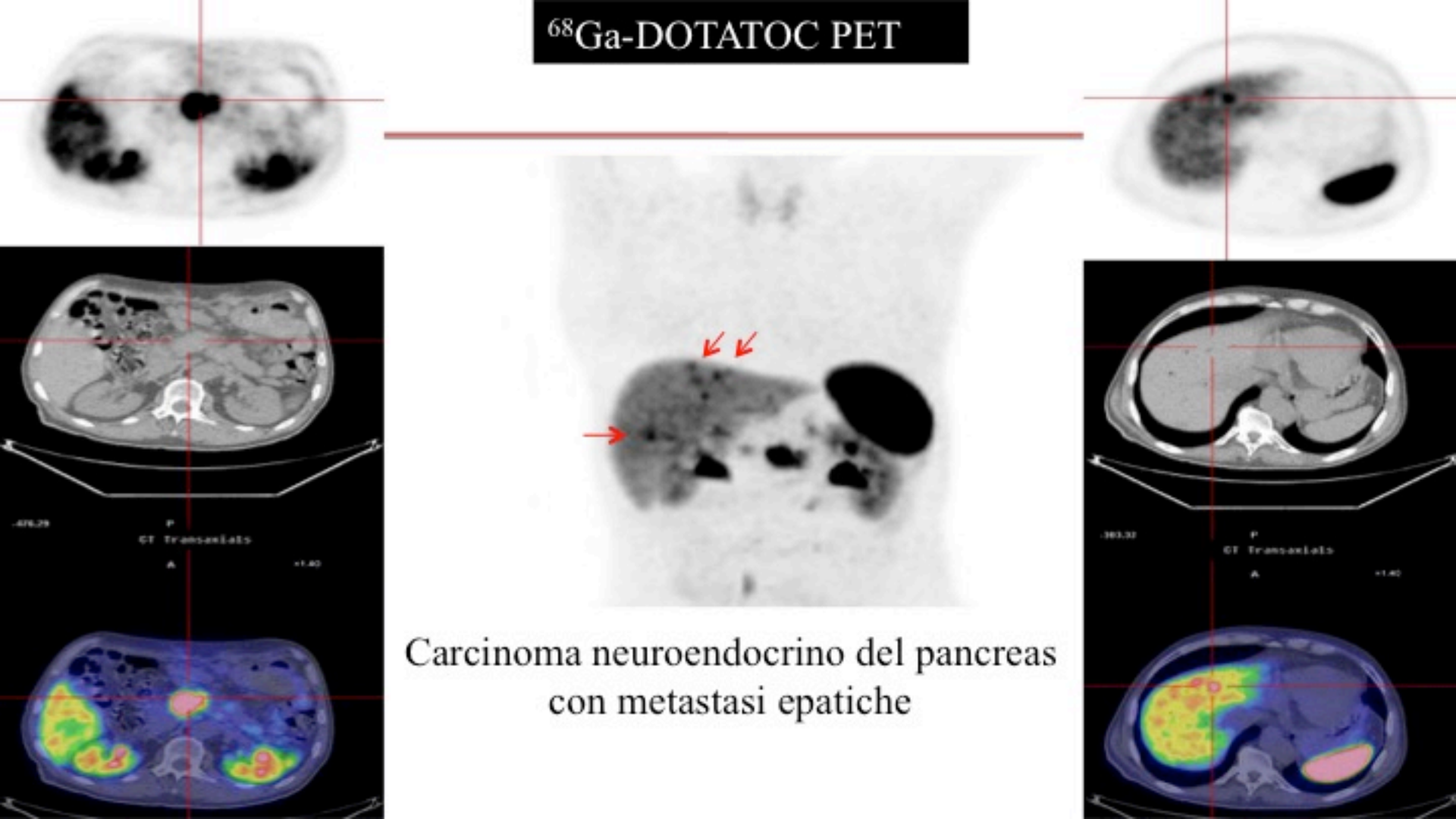
Published online: January 5, 2016

ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors

M. Falconi[a] B. Eriksson[b] G. Kaltsas[c] D.K. Bartsch[d] J. Capdevila[e] M. Caplin[f] B. Kos-Kudla[g] D. Kwekkeboom[h] G. Rindi[i] G. Klöppel[j] N. Reed[k] R. Kianmanesh[l] R.T. Jensen[m] all other Vienna Consensus Conference participants

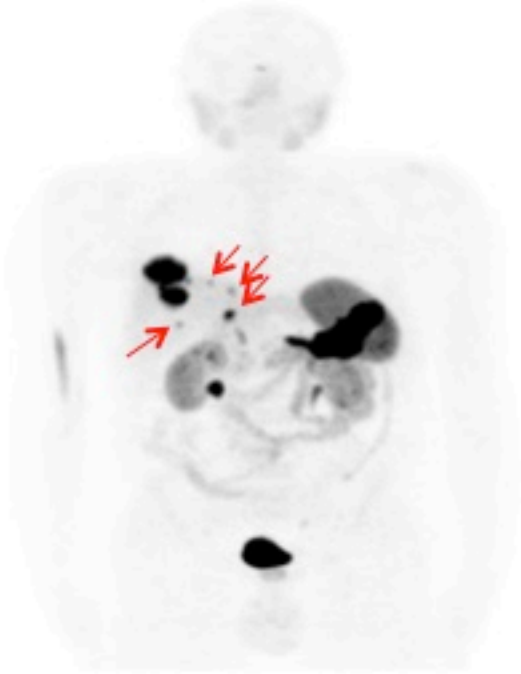
While somatostatin receptor scintigraphy (SRS) with SPECT remains useful in staging P-NETs, numerous studies have demonstrated that imaging with positron emission tomography with CT (PET/CT) with ^{68}Ga-labeled somatostatin analogues has the highest sensitivity for localizing P-NETs, as well as generally for other NETs, and also has a high specificity. In various studies on P-NETs, the sensitivity varied from 86 to 100% and the specificity from 79 to 100% for all P-NETs [80–89], except insulinomas, in which case the sensitivity was only 25% [90]. The consequence of these findings is that PET/CT is now the method of choice to fully stage and localize the extent of disease in patients with non-insulinoma P-NETs [83, 91]. ^{68}Ga-labeled somatostatin analogues have been shown to change the management (surgical, medical, staging) in 20–55% of all patients [87, 88, 92, 93] and, therefore, they should generally be used in patients with non-insulinoma P-NETs.

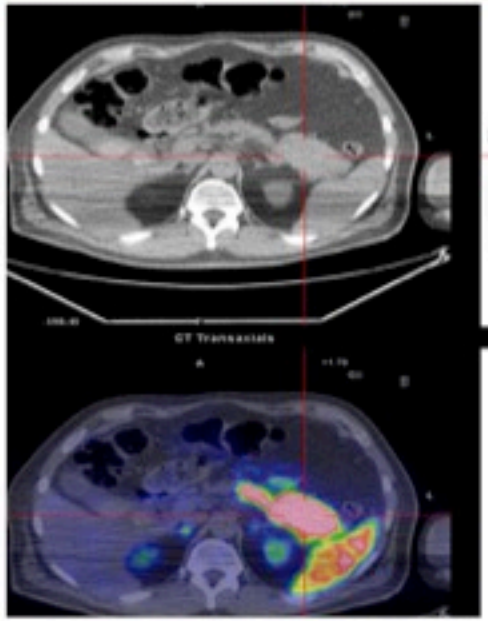
^{68}Ga-DOTATOC PET

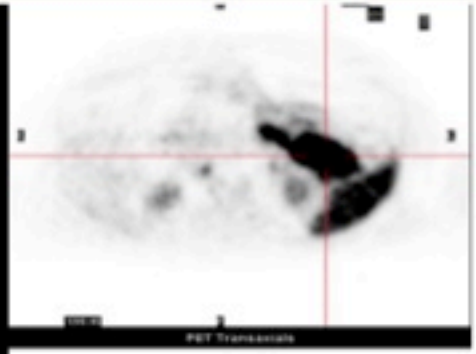


Carcinoma neuroendocrino del pancreas
con metastasi epatiche

^{68}Ga-DOTATATE PET/CT







M
67 aa

Riscontro occasionale in corso di esame ecotomografico addominale (per calcolosi della colecisti) di metastasi epatiche da ca neuroendocrino del corpo-coda del pancreas

Detection of unknown primary neuroendocrine tumours (CUP-NET) using ^{68}Ga-DOTA-NOC receptor PET/CT

Vikas Prasad · Valentina Ambrosini · Merten Hommann · Dieter Hoersch · Stefano Fanti · Richard P. Baum

Eur J Nucl Med Mol Imaging (2010) 37:67–77

Table 2 Comparison of the sensitivity of ^{68}Ga-DOTA-NOC PET/CT and CT alone for detection of the primary tumour and sites of metastases of neuroendocrine tumours

Site	^{68}Ga-DOTA-NOC PET/CT	CT
Primary tumour	35/59 (59%)	12/59 (20%)
Liver metastases	46/59 (78%)	38/59 (64%)
Lymph node metastases	30/59 (51%)	16/69 (27%)
Bone metastases	17/59 (29%)	8/59 (14%)
Lung metastases	3/59 (5%)	3/59 (5%)

Bone Metastases in Patients with Neuroendocrine Tumor: ^{68}Ga-DOTA-Tyr^3-Octreotide PET in Comparison to CT and Bone Scintigraphy

Daniel Putzer[1], Michael Gabriel[1], Benjamin Henninger[2], Dorota Kendler[1], Christian Uprimny[1], Georg Dobrozemsky[1], Clemens Decristoforo[1], Reto Josef Bale[2], Werner Jaschke[2], and Irene Johanna Virgolini[1]

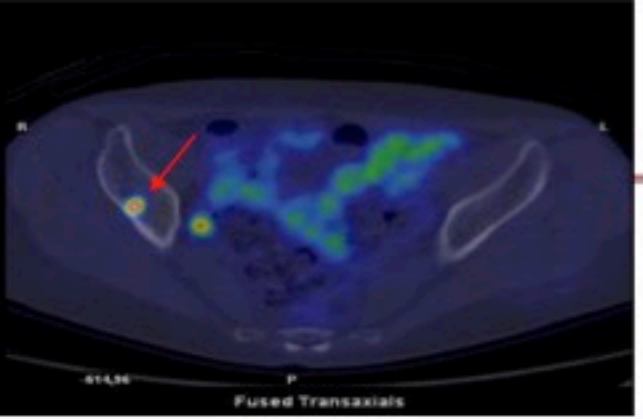
[1]*Department of Nuclear Medicine, Innsbruck Medical University, Innsbruck, Austria; and* [2]*Department of Radiology, Innsbruck Medical University, Innsbruck, Austria*

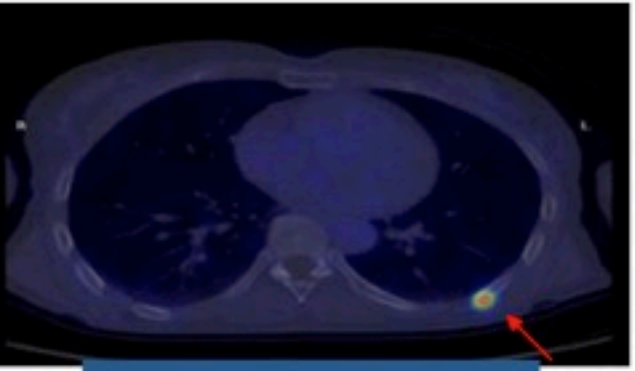
TABLE 2. Comparison of PET and CT in Detection of Bone Metastases from Neuroendocrine Tumor

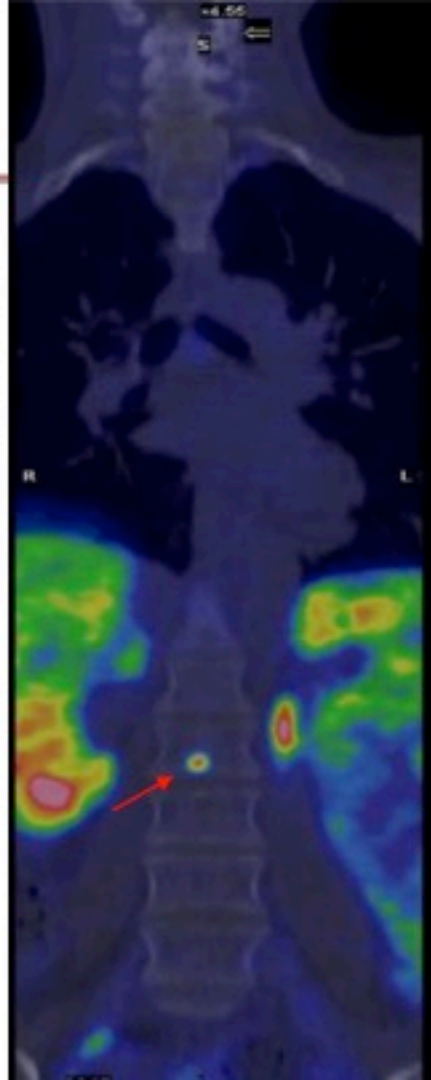
Parameter	^{68}Ga-DOTATOC PET (%)	CT (%)
Sensitivity	92 (37/38)	58 (22/38)
Specificity	97 (12/13)	100 (13/13)
Accuracy	96 (49/51)	69 (35/51)

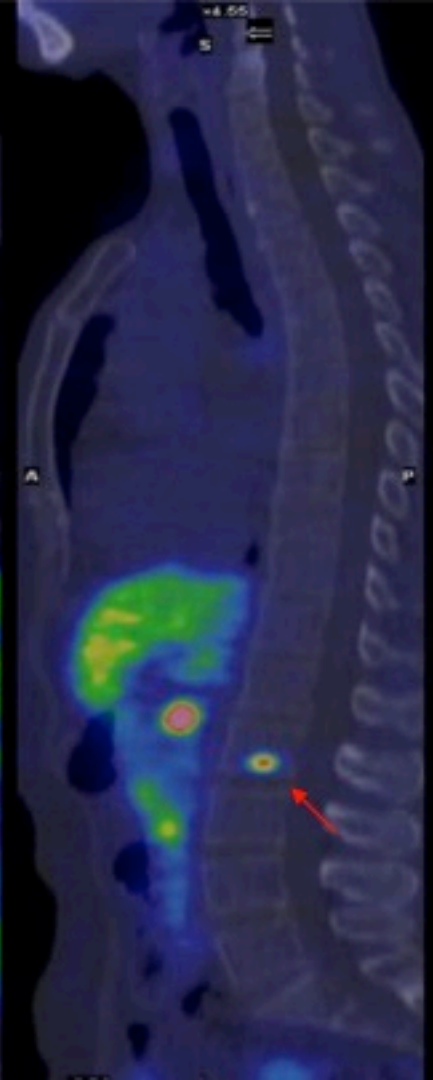
Numbers of patients are in parentheses.

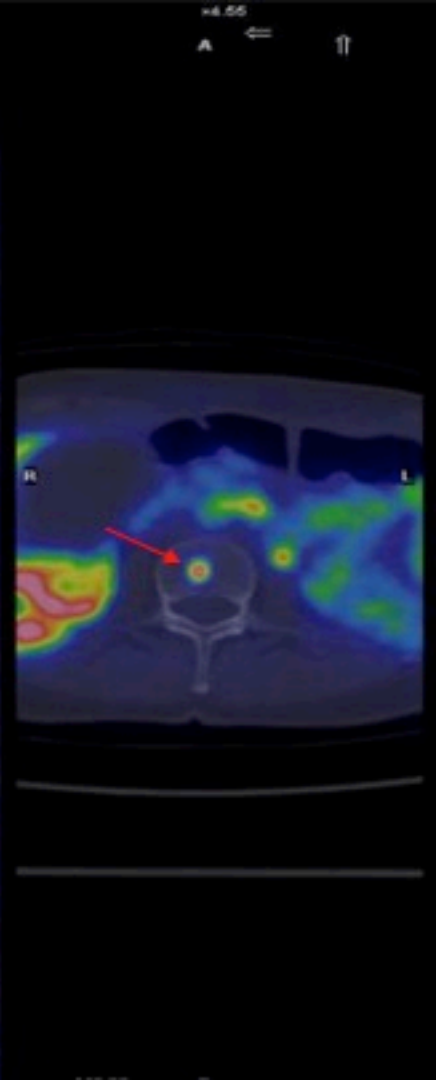
J Nucl Med 2009; 50:1214–1221











Metastasi scheletriche da NET pancreatico

^{68}Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Metaanalysis

Michael M. Graham[1], Xiaomei Gu[2], Timothy Ginader[3], Patrick Breheny[3], and John J. Sunderland[1]

J Nucl Med 2017; 58:1452–1458
DOI: 10.2967/jnumed.117.191197

1) Sensibilità e specificità

TABLE 2
Sensitivity and Specificity

Reference	*n*	True-positive	False-negative	True-negative	False-positive	Sensitivity	Specificity
Gabriel et al. (*8*)	84	69	2	12	1	97.2%	92.3%
Versari et al. (*9*)	19	12	1	5	1	92.3%	83.3%
Ruf et al. (*10*)	51	32	7	8	4	82.1%	66.7%
Mayerhoefer et al. (*11*)	55	32	1	18	4	97.0%	81.8%
Beiderwellen et al. (*12*)	8	4	1	3	0	80.0%	100.0%
Schraml et al. (*13*)	51	40	1	10	0	97.6%	100.0%
Venkitaraman et al. (*14*)	32	25	1	6	0	96.2%	100.0%
Frilling et al. (*15*)	52	52	0			100.0%	
Poeppel et al. (*19*)	40	40	0			100.0%	
Jindal et al. (*16*)	13	13	0			100.0%	
Kumar et al. (*17*)	20	20	0			100.0%	
Nakamoto et al. (*18*)	46	6	1			85.7%	

^{68}Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Metaanalysis

Michael M. Graham[1], Xiaomei Gu[2], Timothy Ginader[3], Patrick Breheny[3], and John J. Sunderland[1]

ITALIAN CHAPTER

J Nucl Med 2017; 58:1452–1458
DOI: 10.2967/jnumed.117.191197

2) Confronto ^{68}Ga-DOTATOC vs ^{111}In Octreotide

The sensitivity of ^{68}Ga-DOTATOC PET is definitely better than ^{111}In-octreotide SPECT imaging. In the 2 papers that directly compared the 2 approaches, the sensitivity for ^{68}Ga-DOTATOC on a per-lesion basis was 100% and for ^{111}In-octreotide 78%. In the

TABLE 5
^{68}Ga-DOTATOC Versus ^{111}In-Octreotide

		DOTATOC		Octreotide	
Reference	*n*	True-positive	False-negative	True-negative	False-positive
Hofmann et al. (*3*)	8	40	0	34	6
Buchman et al. (*24*)	27	70	0	52	18

3) Cambio nel management

review, 3 papers were found that reported change in management after ^{68}Ga-DOTATOC PET imaging. The pooled result reported change of management in 95 of 188 (51%), which clearly illustrates

Functional Imaging of Neuroendocrine Tumors With Combined PET/CT Using ^{68}Ga-DOTATATE (Dota-DPhe^{1},Tyr^{3}-octreotate) and ^{18}F-FDG

Irfan Kayani, FRCR[1]
Jamshed B. Bomanji, MD, PhD, FRCR[1]
Ashley Groves, MD[1]
Gerard Conway, MD[2]
Sveto Gacinovic, MD[1]
Thida Win, MD[3]
John Dickson, PhD[1]
Martyn Caplin, FRCP[4]
Peter Joseph Ell, FRCR, FRCP[1]

CANCER June 1, 2008 / Volume 112 / Number 11

TABLE 3
SUVmax of ^{68}Ga-DOTATATE and ^{18}F-FDG According to Tumor Grade

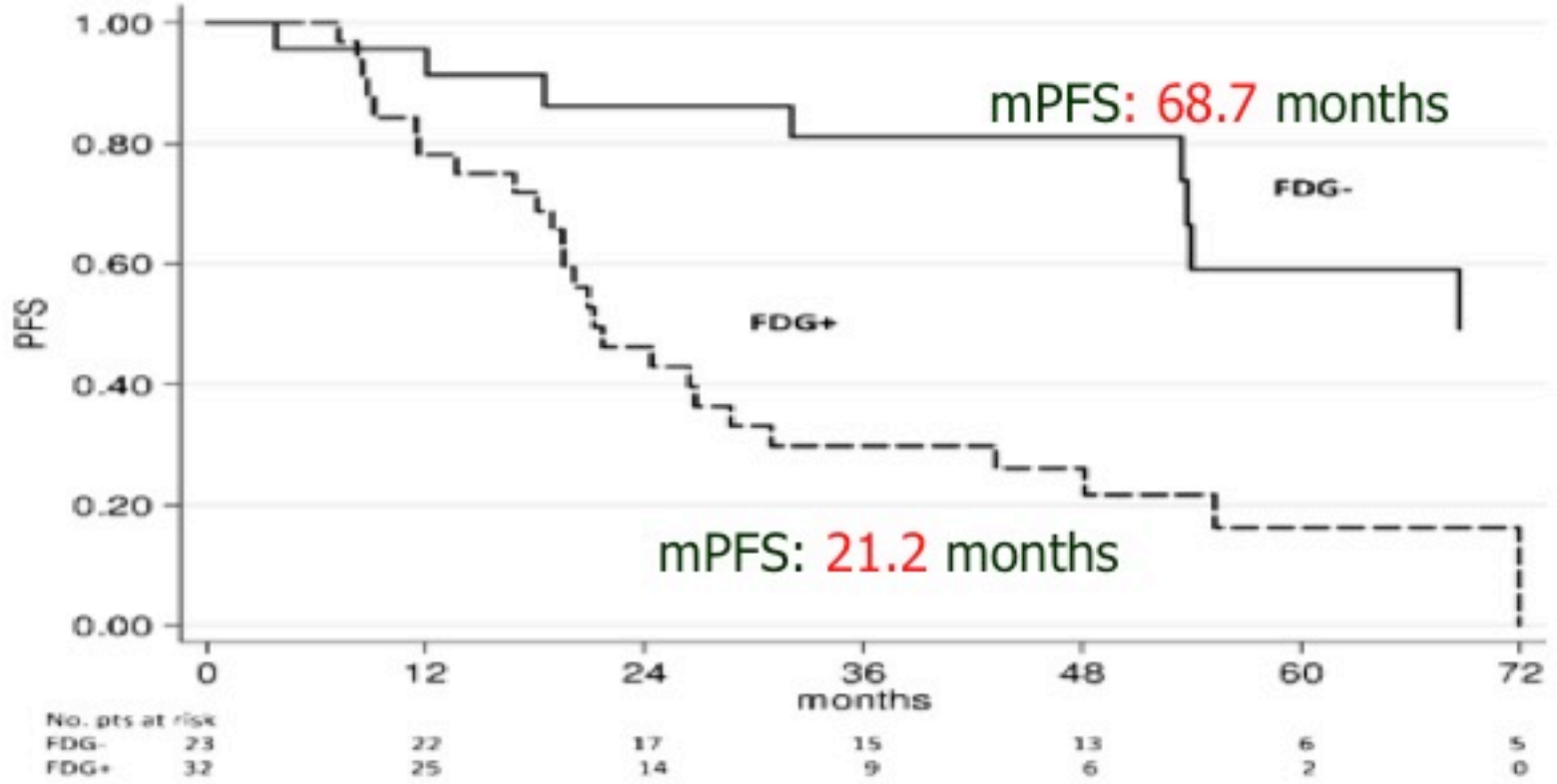
	^{68}Ga-DOTATATE	^{18}F-FDG	*P*
All NET	16.9 (1.6–50)	4.2 (1.4–16.4)	.005
Low-grade NET Ki67 index ≤2%	29 (3.3–45)	2.9 (1.5–12)	<.001
Intermediate NET Ki67 index 3%–20%	15.5 (1.8–50)	10.5 (2.0–13.9)	NS
High-grade NET Ki67 index >20%	4.4 (1.6–8.9)	11.7 (4.1–16.4)	.03

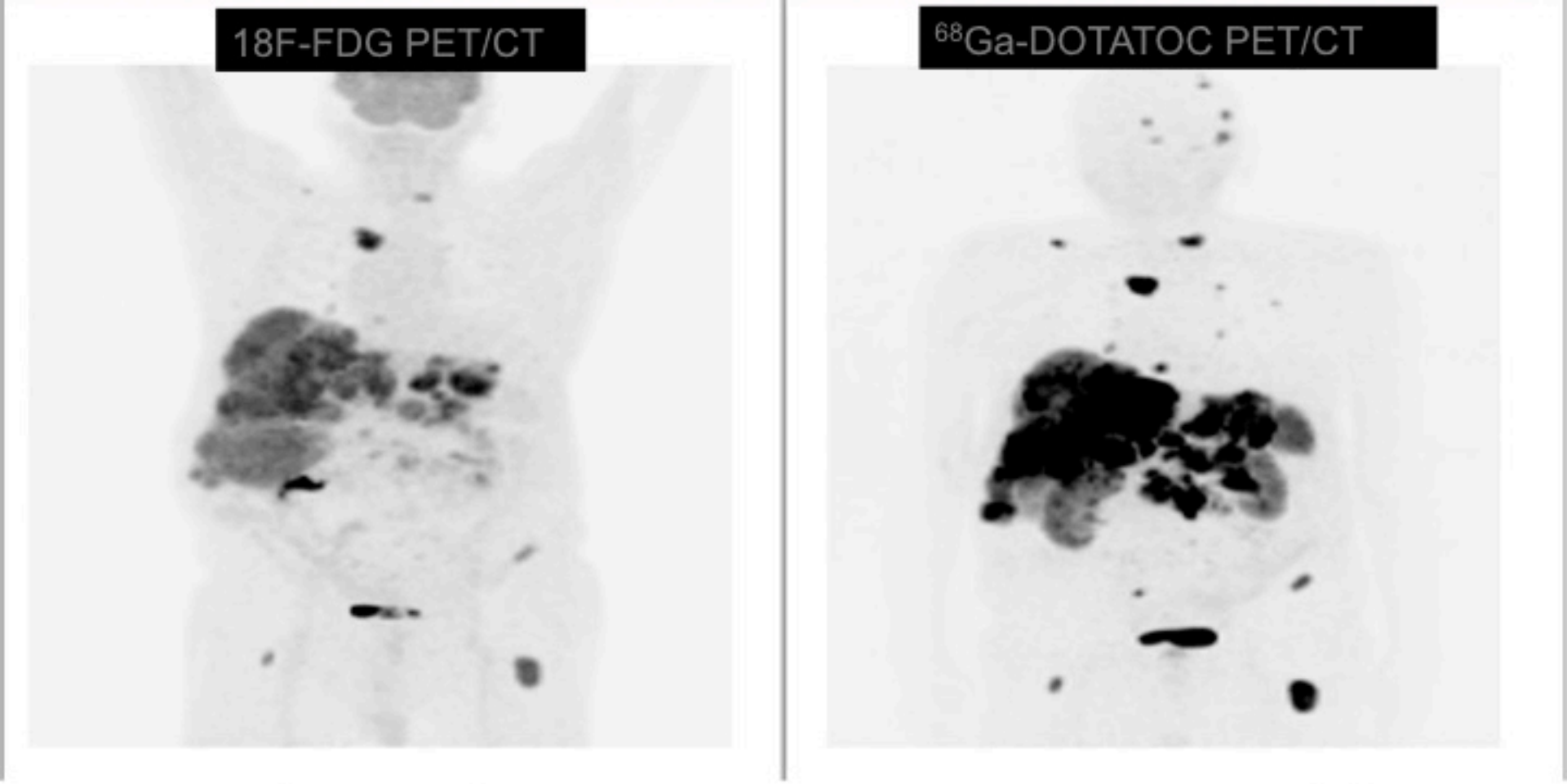
SUVmax is the median SUVmax with range in parentheses.
SUVmax indicates maximum standardized uptake value; NET, neuroendocrine tumor; ^{68}Ga-DOTATATE, ^{68}Ga-DOTA-[SCAP]D[R]Phe^{1},Tyr^{3}-octreotate; ^{18}F-FDG, ^{18}F-Fluorodeoxyglucose.

Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-D OTATATE

Maddalena Sansovini[1] · Stefano Severi[1] · Annarita Ianniello[1] · Silvia Nicolini[1] · Lorenzo Fantini[1] · Emilio Mezzenga[2] · Fabio Ferroni[3] · Emanuela Scarpi[4] · Manuela Monti[4] · Alberto Bongiovanni[5] · Sara Cingarlini[6] · Chiara Maria Grana[7] · Lisa Bodei[7] · Giovanni Paganelli[1]

Eur J Nucl Med Mol Imaging (2017) 44:490–499





GEP NET (Ki67 20%) con estesa metastatizzazione epatica e scheletrica

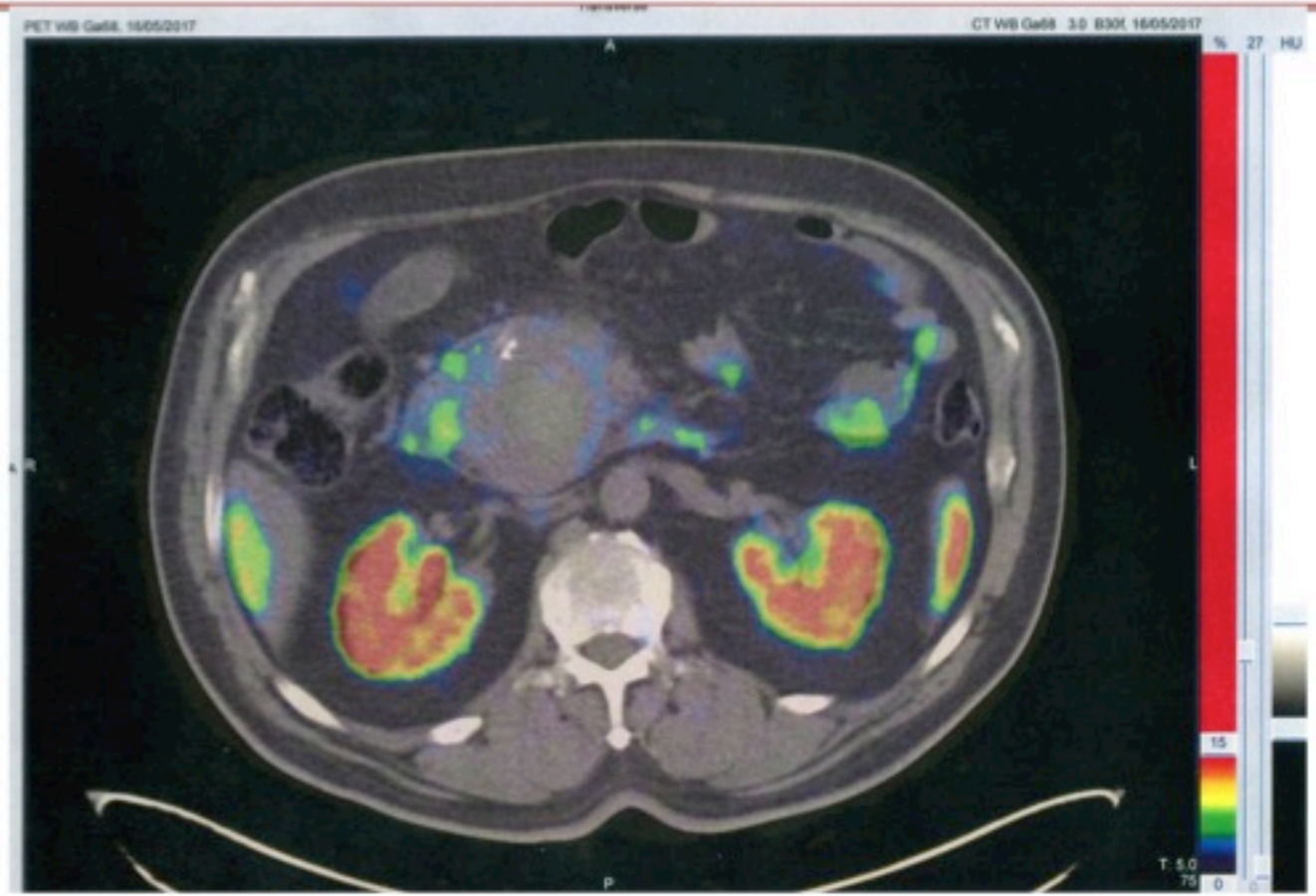
Caso clinico 1

Ricovero in DH Endocrinologico

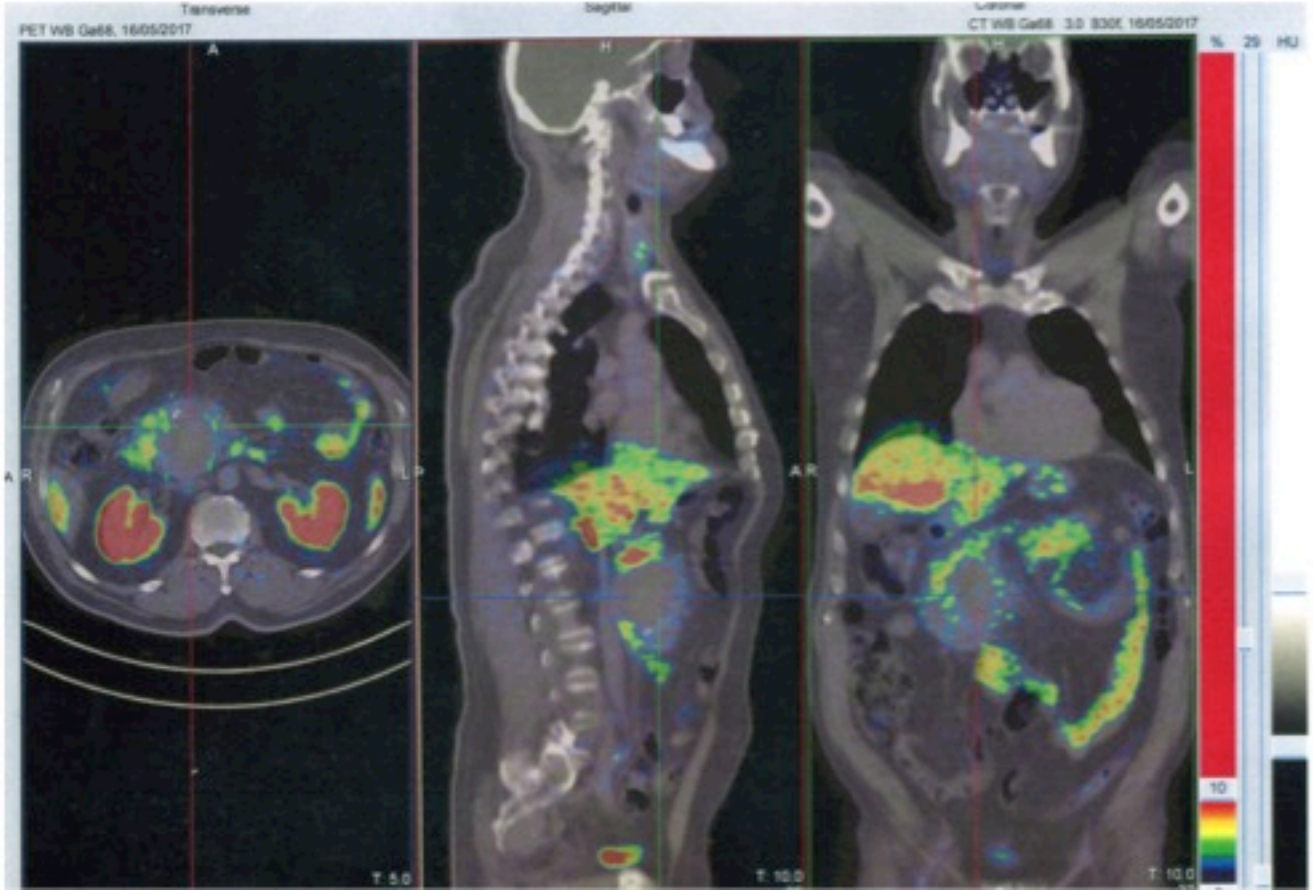
Giugno 2017 PET-TC 68-Gallio

Modesto, disomogeneo e non significativo uptake del tracciante recettoriale a livello della nota formazione di circa 7 cm a carico della testa-processo del pancreas compatibile con scarsa/assente densità recettoriale.

PET-TC 68-Gallio 16/5/2017



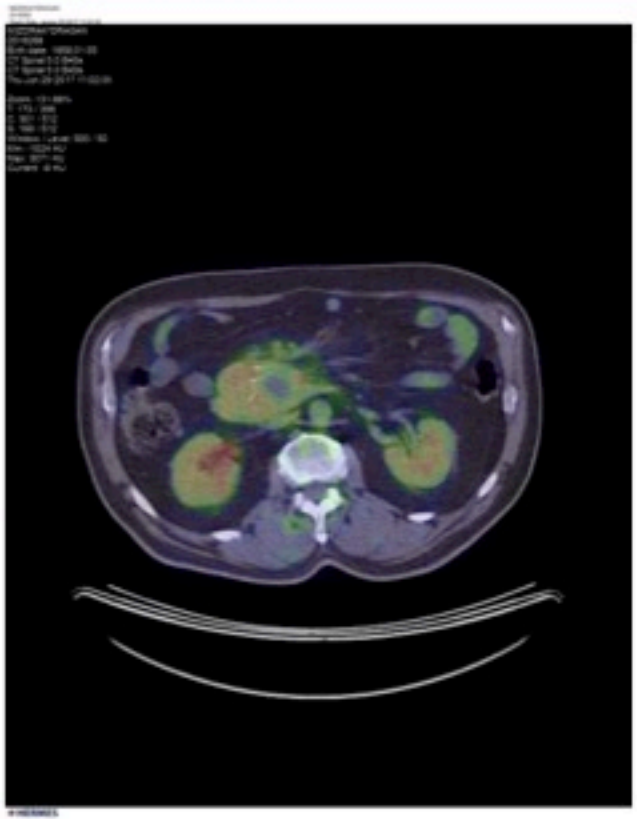
PET-TC 68-Gallio 16/5/2017

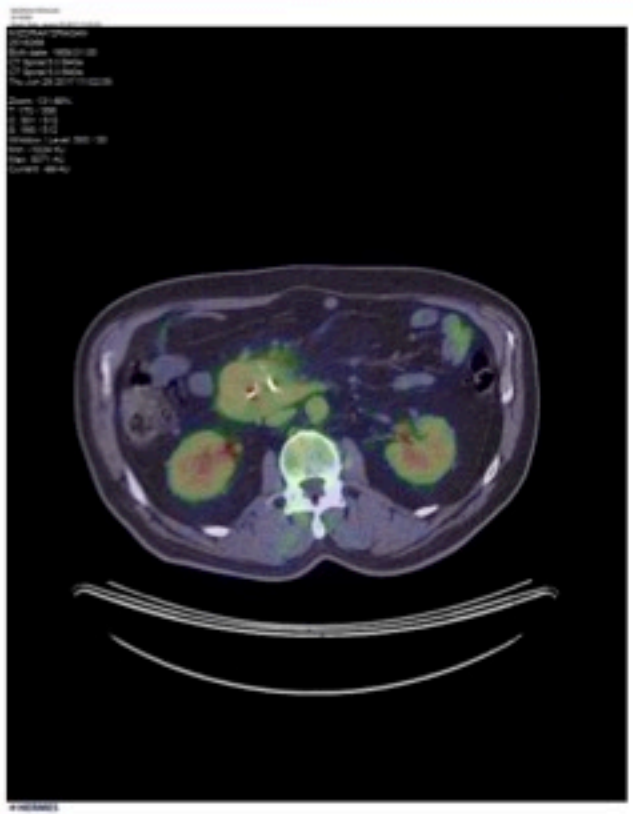


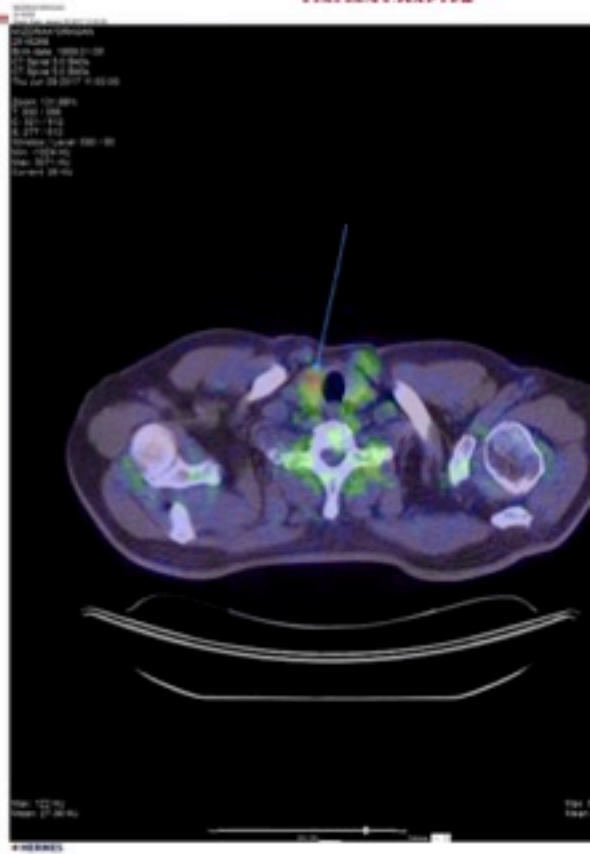
Caso clinico 1

- **PET-TC 18-FDG:** concentrazione del radiofarmaco in corrispondenza della testa del pancreas con gradiente metabolico non molto elevato (SUV: 5.8) ed in corrispondenza del lobo destro della tiroide sede di nodulo tiroideo (SUV: 5.6)
- **FNAB ecoguidato** in corrispondenza del nodulo ecograficamente sospetto, classe ecografica 3 AME/AACE 2016/ U4 British, dimensioni 11 mm, lesione follicolare Tir 3A; richiesta valutazione molecolare: BRAF (esone 15): mutazione p.V600E

Caso clinico 1: PET-TC 18-FDG







Nodulo tiroideo

Caso clinico 1

- Programmata biopsia epatica in data 06-07-2017 e 18-08-2017: le formazioni nodulari epatiche descritte all'RM non sono ecograficamente riconoscibili. Non si può procedere a biopsia.

  Si consiglia follow-up RMN

- Richiesta **consulenza genetica**

- Inizia analogo della somatostatina: **Lanreotide Autogel 120 mg/ 28 gg**

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag.17 del Regolamento Applicativo Stato-Regioni del 05/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Novartis

Commento dell'endocrinologo

Maria Vittoria Davi'
UOS di Endocrinologia
Policlinico Universitario
GB Rossi AOUI VERONA

ENETS *Center of Excellence*

Valutazione iniziale: ruolo dell'endocrinologo

- ✓ Alcuni **NET "non funzionanti" (NF)** solo apparentemente sono tali: una accurata raccolta anamnestica riesce talvolta a far emergere sintomi correlati a **sindrome ormonale** (s. da carcinoide, s. di Cushing ectopica, ecc) o talvolta possono diventare **funzionanti (F)**
- ✓ Inoltre alcuni **NET NF e/o F** possono associarsi a **patologie endocrine** che possono sfuggire all'oncologo o al chirurgo
- ✓ Importanza **dell'anamnesi familiare**: parenti di I grado con endocrinopatie o calcolosi renale
- ✓ Interpretazione di alterazioni di **marker biochimici/ormonali**, eventuale esecuzione di test diagnostici (al digiuno, secretina, calcio gluconato ...).
- ✓ **Nel caso clinico:** lieve iperparatiroidismo normocalcemico associato a NET pancreas: MEN1?

Valutazione iniziale: ruolo dell'endocrinologo nella possibile associazione con forme ereditarie

Clinical Practice Guideline

Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

J Clin Endocrinol Metab 97: 2990–3011, 2012

MEN1: MANIFESTAZIONI CLINICHE

Type (chromosome location)	Tumors (estimated penetrance)	Gene, most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%)	*MEN1*
	Enteropancreatic tumor (30–70%): gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20–55%), glucagonoma (<1%), VIPoma (<1%)	83/84, 4-bp del (~4%) 119, 3-bp del (~3%) 209–211, 4-bp del (~8%) 418, 3-bp del (~4%) 514–516, del or ins (~7%) Intron 4 ss, (~10%)
	Pituitary adenoma (30–40%): prolactinoma (20%), somatotropinoma (10%), corticotropinoma (<5%), nonfunctioning (<5%)	
	Associated tumors: adrenal cortical tumor (40%), pheochromocytoma (<1%), bronchopulmonary NET (2%), thymic NET (2%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (8%)	

Neuro endocrinology

Original Paper

Neuroendocrinology 2011;94:58–65
DOI: 10.1159/000326364

Received: September 9, 2010
Accepted after revision: February 21, 2011
Published online: April 5, 2011

ITALIAN CHAPTER

Presentation and Outcome of Pancreaticoduodenal Endocrine Tumors in Multiple Endocrine Neoplasia Type 1 Syndrome

Maria Vittoria Davi[a] Letizia Boninsegna[b] Luca Dalle Carbonare[a] Marco Toaiari[a]
Paola Capelli[c] Aldo Scarpa[c, d] Giuseppe Francia[a] Massimo Falconi[b]

31 pz con MEN1 e NET pancreatico-duodenali (PD-NET):
16 NF, 6 insulinomi, 9 ZES

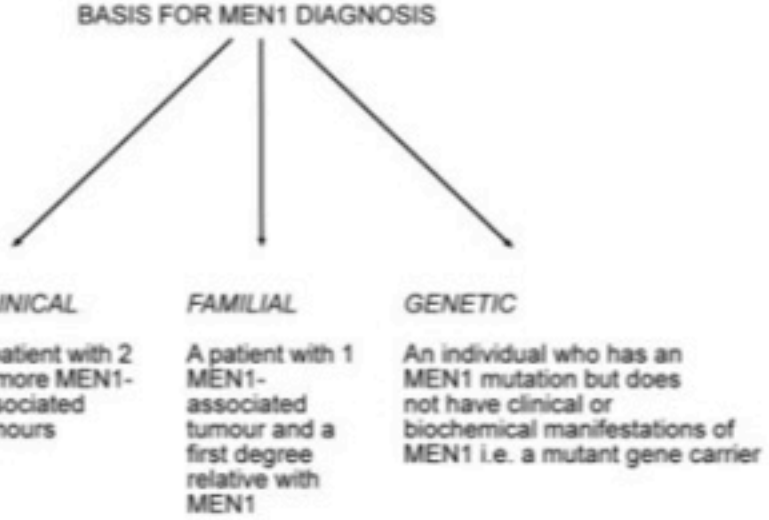
✓16 pz (52%): diagnosi di MEN1 per PD-NET

✓15 pz (94%) già presente IPERPARATIROIDISMO I non diagnosticato (asintomatico nel 60%)

Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

Rajesh V. Thakker, Paul J. Newey, Gerard V. Walls, John Bilezikian, Henning Dralle, Peter R. Ebeling, Shlomo Melmed, Akihiro Sakurai, Francesco Tonelli, and Maria Luisa Brandi

J Clin Endocrinol Metab 97: 2990–3011, 2012



Screening/Follow up NEN/MEN1

TABLE 2. Suggested biochemical and radiological screening in individuals at high risk of developing MEN1

Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NET			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yr)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 yr)

J Clin Endocrinol Metab 97: 2990–3011, 2012

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag.17 del Regolamento Applicativo Stato-Regioni del 05/11/2009, il sottoscritto **dr. ssa Francesca Spada** dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

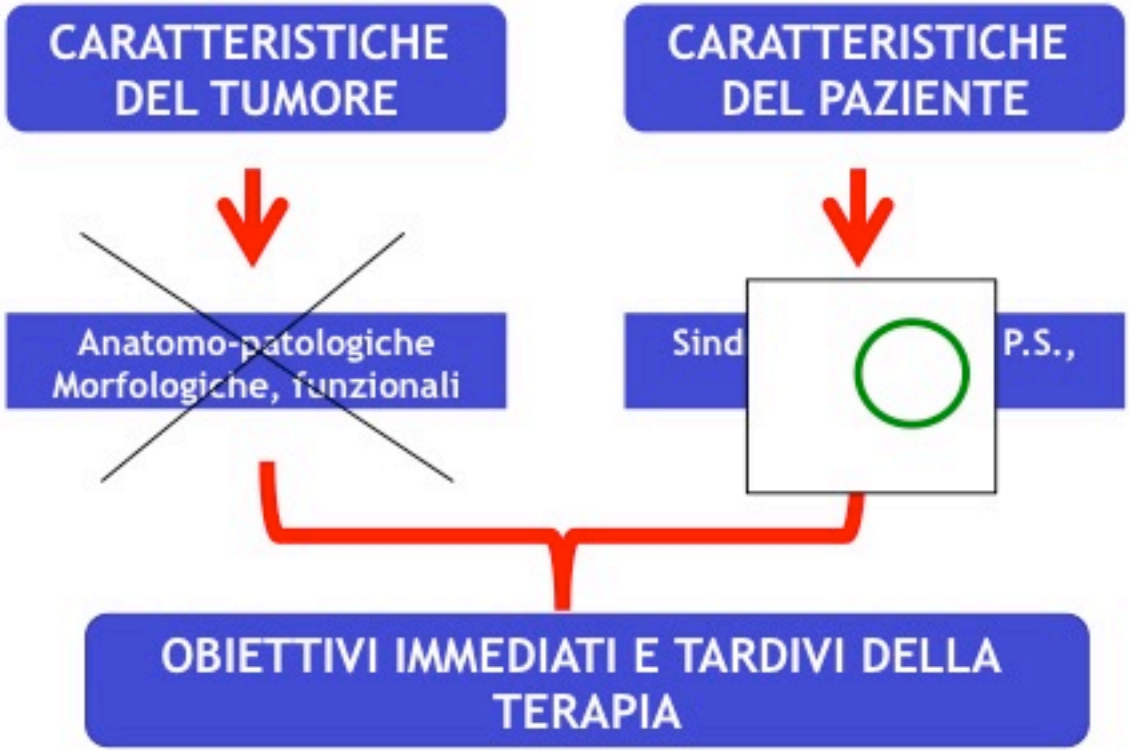
Novartis

Ipsen

PanNET NF: algoritmo diagnostico

1. **Diagnosi: sospetta, probabile, certa**
   - TC febbraio 2017
   - EUS aprile 2017
   - FNA aprile 2017
2. **Stadiazione e caratterizzazione**
   - Caratterizzazione morfologica
   - Caratterizzazione funzionale
3. **Strategia terapeutica**
   - Obiettivi (immediati e tardivi)

PanNET NF: strategia terapeutica



PanNET NF: strategia terapeutica

J Endocrinol Invest (2014) 37:875–909
DOI 10.1007/s40618-014-0119-0

POSITION STATEMENT

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

Franco Grimaldi · Nicola Fazio · Roberto Attanasio · Andrea Frasoldati · Enrico Pag
Roberto Baldelli · Debora Berretti · Sara Bianchetti · Giancarlo Bizzarri · Marco Ca
Nadia Cremonini · Anna Crescenzi · Maria Vittoria Davì · Angela Valentina D'Elia ·
Stefano Pizzolitto · Annibale Versari · Michele Zini · Guido Rindi · Kjell Öberg

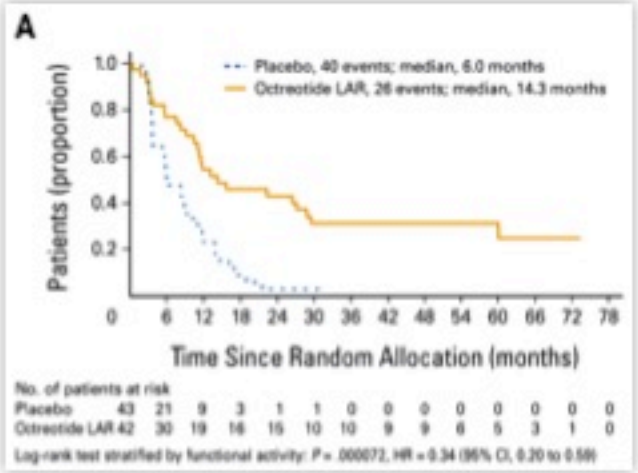
1. Stadiazione sistemica
2. Evolutività radiologica

We recommend chest-abdomen MDCT as the routine morphologic imaging modality for the detection and staging of GEP-NENs.
We recommend MRI when the evaluation of bone and CNS is required. In all the other cases MRI should be used as a second-line imaging study, when MDCT is not conclusive or contraindicated.
We suggest CEUS or MRI for a better characterization of liver involvement.

We recommend the use of SSTR functional imaging for localization and staging of G1-G2 GEP-NENs.
We recommend PET/CT with ^{68}Ga-labeled SA as the procedure of choice. When not available, ^{111}In-pentetreotide (Octreoscan®) scintigraphy may be used.
We recommend against the routine use of ^{18}F-FDG PET/CT.
We suggest ^{18}F-FDG PET/CT for staging high grade (G3) and selected G2 GEP-NENs.

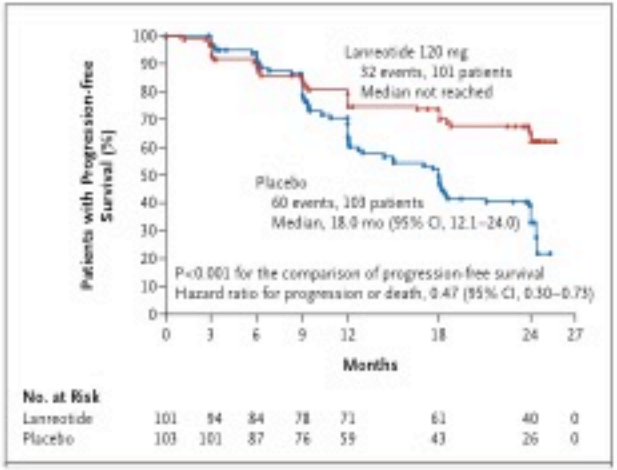
Analoghi della somatostatina

PROMID



TTP: 14,3 VS. 6 mo

CLARINET



PFS: NR VS. 18 mo

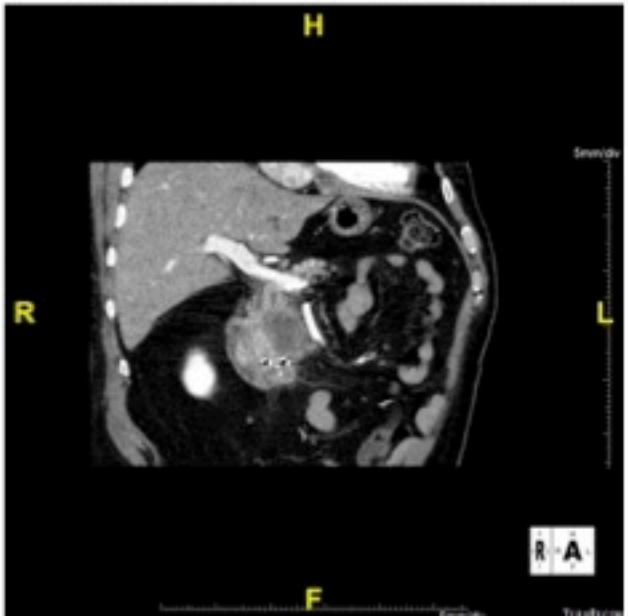
Rinke A. et al, JCO 2009; Caplin M. et al. NEJM 2014

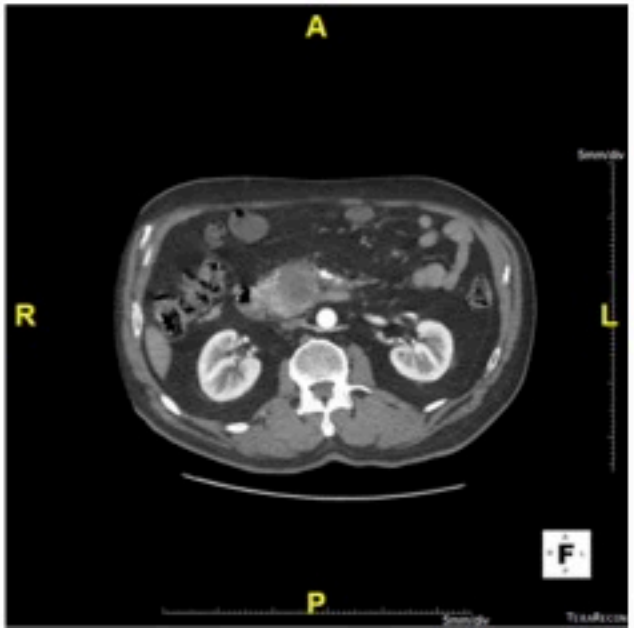
LG AIOM/ITANET 2017

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
Alta	Nei pazienti con NET enteropancreatico non funzionante, non rapidamente progressivo, con basso Ki67 ed esprimenti i recettori della somatostatina, Octreotide e Lanreotide dovrebbero essere presi in considerazione (1,2).	**Positiva forte**

Il chirurgo decide di eseguire intervento chirurgico per VLP

In considerazione delle dimensioni e della contiguità con l'arteria mesenterica, non esegue exeresi della lesione pancreatica, ma biopsia di una lesione epatica, visualizzabili 11 lesioni comprese tra 5 e 10 mm





04-10-2017 Referto della biopsia epatica:

Parenchima epatico con area subcapsulare di proliferazione epiteliale con modesta atipia, con positività immunoistochimica per sinaptofisina, cromogranina, CD56, PAX8 +, negativa per TTF-1. Indice proliferativo (Ki67) <2%.

Interdisciplinary Discussion

What treatment/follow up?

Regione Autonoma Friuli Venezia Giulia - Servizio Sanitario Regionale
Azienda Sanitaria Universitaria Integrata di Udine
Presidio Ospedaliero "Santa Maria della Misericordia" di Udine
Percorso neuroendocrino

VALUTAZIONE MULTIDISCIPLINARE

nome **DRAGAN** data di nascita **05/01/1958** (**MAS**)
Codice Fiscale Medico curante
Comune residenza

ID n° *PNEnd* ***79***

Valutazione

Data Meeting **18/10/2017**
Proponente Endocrinologia

Conclusioni e programma

Conclusioni del meeting: Controllo TC ed Entero-TC a 4 mesi al fine per di valutare eventuale progressione al fine di intreprendere trattamento con everolimus.

Nel frattempo prosegue l'iter ORL per tiroidectomia totale con linfoadenomectomia del sesto livello ed esplorazione cervicale per paratiroidi.

Indicazioni e commenti: Vedi paragrafo conclusioni del meeting.

Presenti al meeting

Dott. Grimaldi Franco
Dott. Capobianco Decio
Dott. Giacomuzzi Francesco
Dott.ssa Carpentieri Maria
Dott.ssa Cipri Claudia
Dott.ssa Ermacora Paola
Prof. Uzzau Alessandro
Dott. Parisi Giuseppe
Dott.ssa Berretti Debora
Dott.ssa Kora Elda

endocrinologo (3), medico nucleare, oncologo (2), chirurgo, gastroenterologa

Il compilatore
Dott. Franco Grimaldi

La presente scheda deve intendersi quale orientamento diagnostico terapeutico del gruppo multidisciplinare; la decisione finale spetta al medico referente del caso, dopo visita e discussione con il/la paziente.

Quale follow up diagnostico – terapeutico ?

Quesiti:

Terapia medica:

- Analoghi della somatostatina?
- Everolimus?

Ulteriori indagini:

- Quali?,
- Quando?

Neuro endocrinology

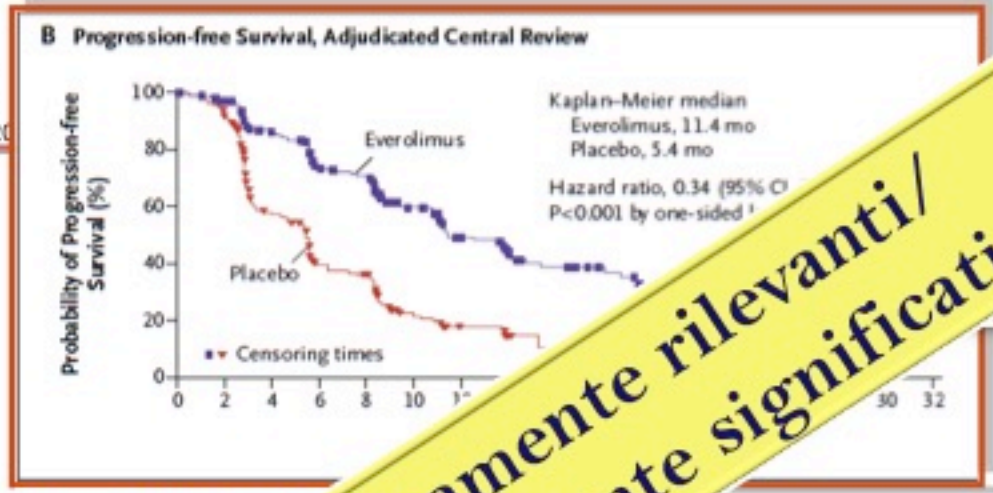
Neuroendocrinology
DOI: 10.1159/000455155

Received: November 6, 2015
Accepted after revision: January 31, 2017
Published online: February 17, 2017

ITALIAN CHAPTER

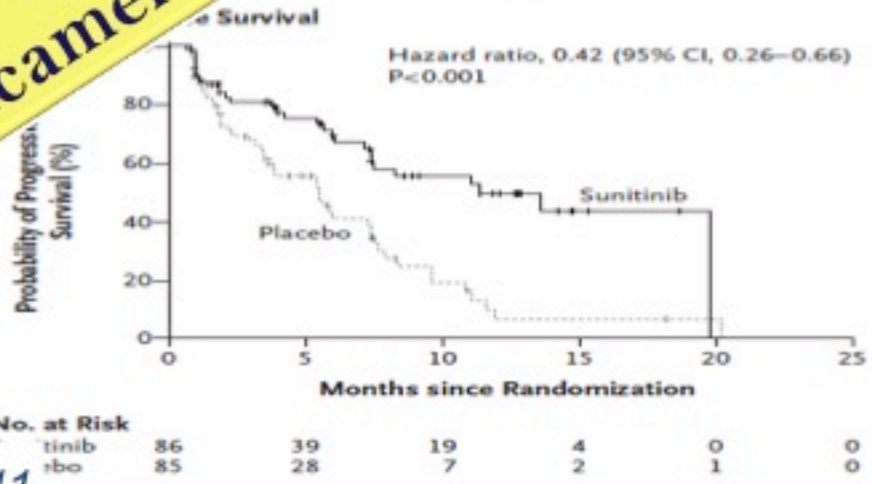
ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Pancreas										
Insulinoma solitary G1–G2 NET[n]	resected	yes	once 3–6 m	yes[d]	fasting BS insulin C-peptide pro-insulin	no	no	no		fasting test performed if symptoms recur; EUS may be required if recurrence is suspected
Insulinoma localized or metastases G1–G2 NET[n]	nonresected	yes	3–6 m	yes[d]	fasting BS insulin C-peptide pro-insulin	no	3–6 m	12 m[e]		EBUS may be required if progression is suspected
Gastrinoma G1–G2	resected	yes	3–6 m	yes	gastrin, B_{12}, Ca^{2+}, PTH		6–12 m	12–24 m[e]		gastric pH measurement or secretin test may be performed if symptoms recur; EUS may be required if recurrence is suspected
Gastrinoma G1–G2	nonresected	yes	3–6 m	yes	gastrin, B_{12}, Ca^{2+}, PTH		3–6 m	12–24 m[e]		EUS may be required if progression is suspected
Functional pNET G1–G2 localized or metastases[n]	resected/ nonresected	yes	3–6 m	yes	relevant tumor hormones[f]	no	3–6 m	12–24 m[e]		EUS may be required if recurrence or progression is suspected
Nonfunctional pNET G1–G2[n]	resected/ nonresected	yes	3–6 m	yes	none	no	3–6 m	12–24 m[e]		EBUS may be required if recurrence or progression is suspected
pNET G3 NEC/ NET[n]	resected/ nonresected	yes	3 m	yes[d]	if functioning relevant tumor hormones[f]	no	2–3 m	12 24 m[e,f]	12 24 m[f]	EBUS may be required if recurrence or progression is suspected



Yao, NEJM

Clinicamente rilevanti/ statisticamente significativi



Raymond, NEJM 2011

Caso clinico 2

- Signor Roberto, 69 anni.

Anamnesi:

- Diverticolosi del sigma
- Prostatectomia totale per ca. prostata (2015)

➢ Nel corso del follow-up oncologico urologico (marzo 2016) riscontro ecografico con successiva conferma TC di focalità epatiche non captanti alla PET-TC con 18-FDG

Caso clinico 2

- Esordio sintomatico con diarrea cronica dall'autunno 2016 (alvo: 20 scariche/die).

- Seguito in Gastroenterologia: indagini colturali, gastroscopia e colonscopia risultate negative.

- Maggio 2017: Cromogranina: 92.440 ng/ml
- Giugno 2017: Cromogranina ulteriore incremento

Caso clinico 2

Esame 28-06-2017	*Risultato*	*Intervallo di normalità*
Cromogranina	**121.520 ng/ml**	**0 - 108**

Caso clinico 2

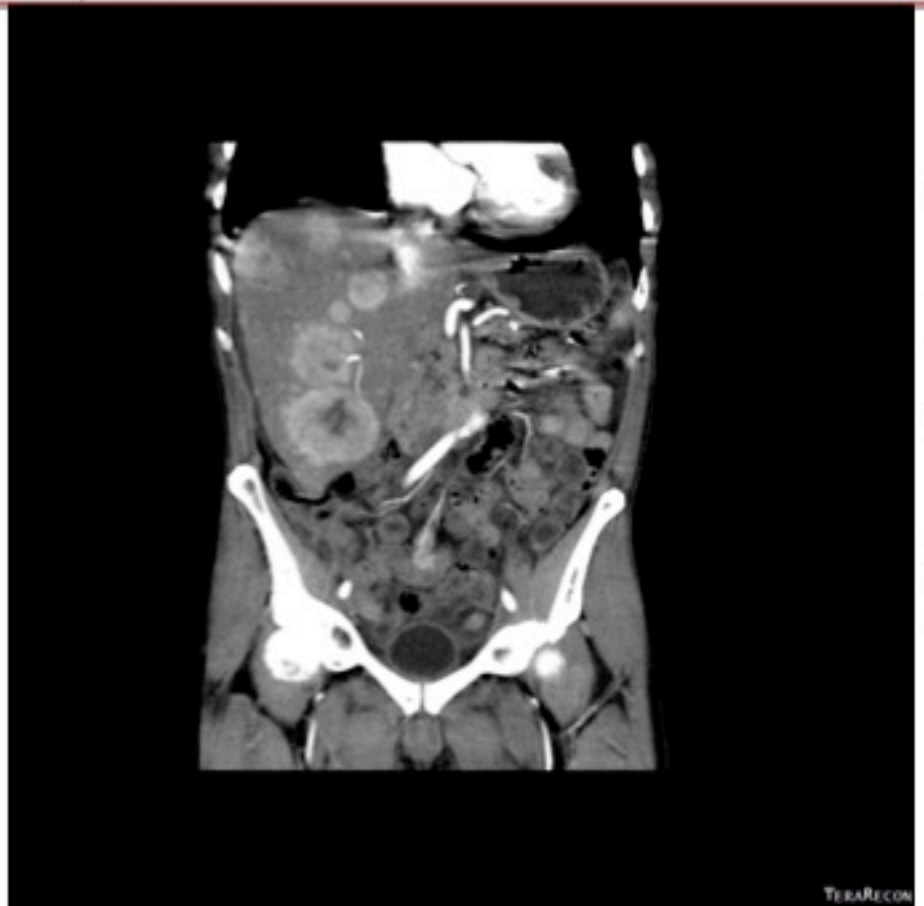
- Fine Giugno 2017 il gastroenterologo richiede consulenza endocrinologica

- **Ricoverato in Day Hospital Endocrinologico, si richiede:**
  - dosaggio **acido 5-OH-indol acetico**
  - **TC addome e TC torace** eseguita 05-07-2017
  - **PET/TC Gallio 68** eseguita 13-07-2017
  - **visita cardiologica ed ecocardiografia:** sintomatologia suggestiva per coinvolgimento cardiaco da sindrome da carcinoide (segni da scompenso destro)

Caso clinico 2

Esame *28-06-2017*	*Risultato*	*Intervallo di normalità*
5-HIAA urinario	**1764 microMol/24 h**	**11 - 37**

Caso clinico 2



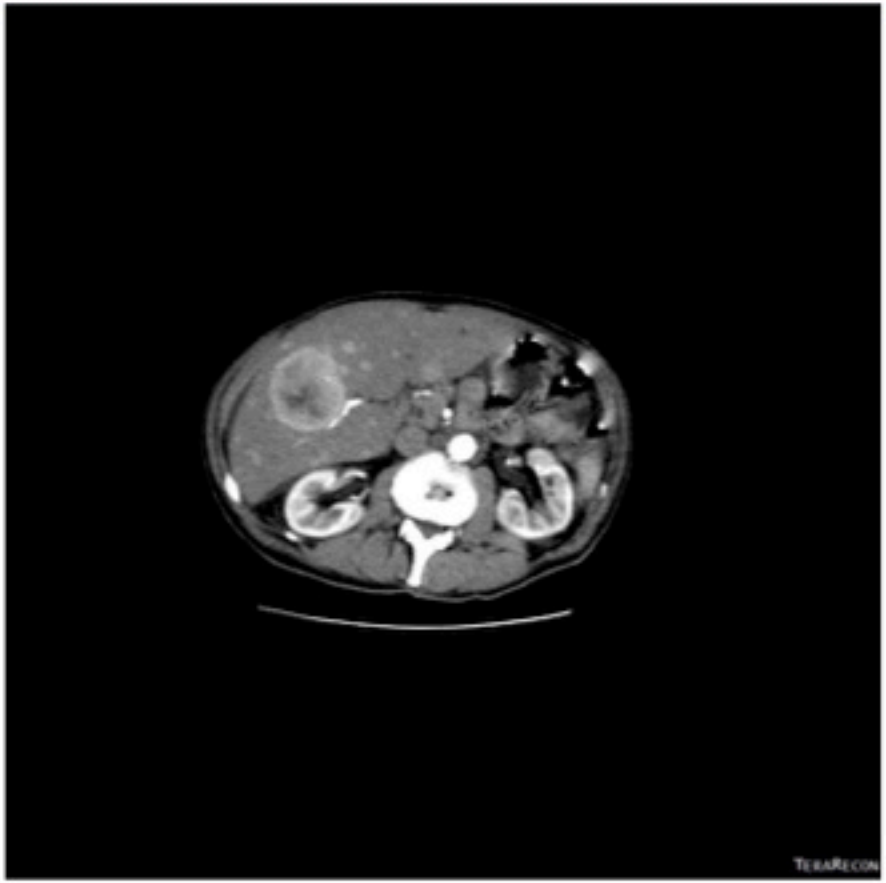
TAC addome:

nel ventaglio mesenterico si riconosce **tessuto solido ipervascolare**, dimensioni: 2,4 cm in continuità/adeso senza piano adiposo di clivaggio con la parete di un'ansa intestinale a carattere di tenue.

Caso clinico 2

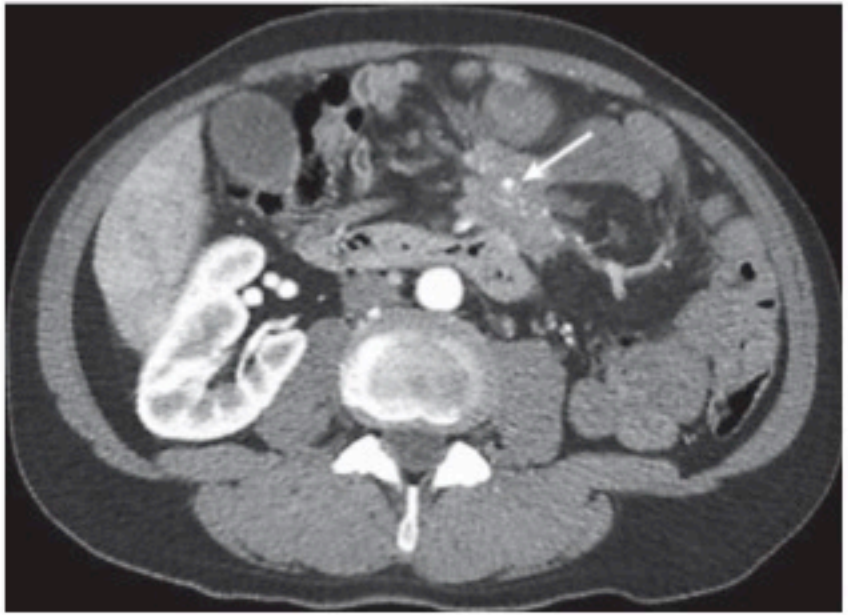
TAC addome:

In ambito epatico: **plurime lesioni focali ipervascolari** preferenzialmente di natura secondaria, a carico di entrambi i lobi, le maggiori con componente centrale ipodensa come da colliquazione, localizzate VII (circa 7,7 x 7,5 cm), V (circa 6,3 x 5,4 cm) e VI (circa 6,7 x 6,6 cm) segmento



Il ruolo del radiologo

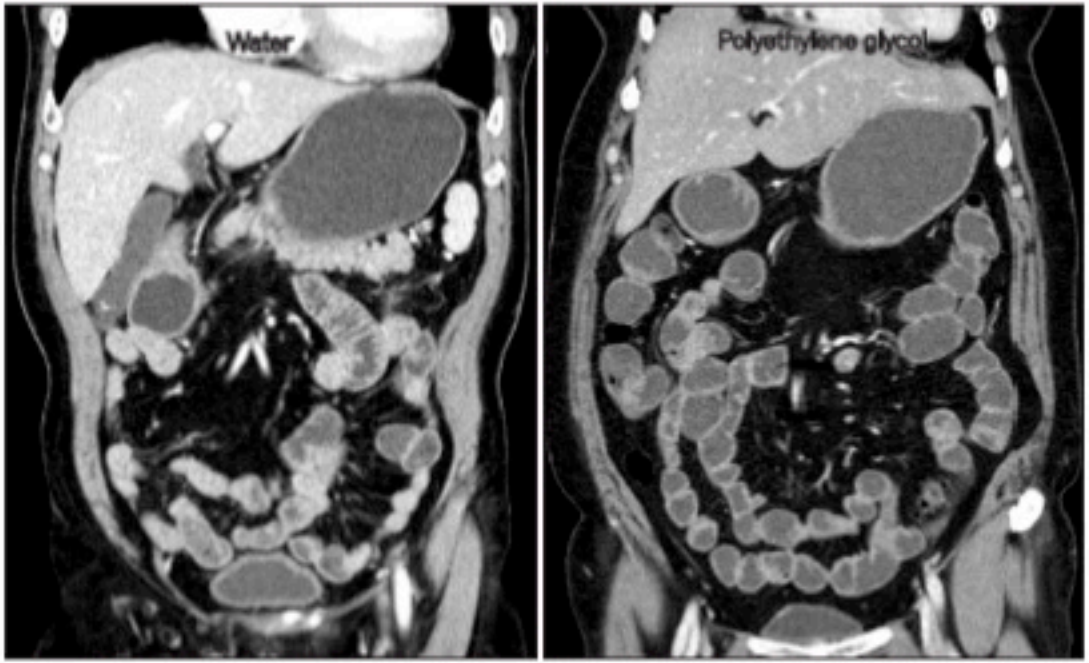
Nei SI-NENs spesso in TC é più facile visualizzare le metastasi mesenteriche che possono indurre reazione desmoplastica (portando a ostruzione intestinale o encasement dei vasi con alterazione della circolazione) rispetto al tumore primitivo



Neuroendocrinology DOI: 10.1159/000471879

Il ruolo del radiologo

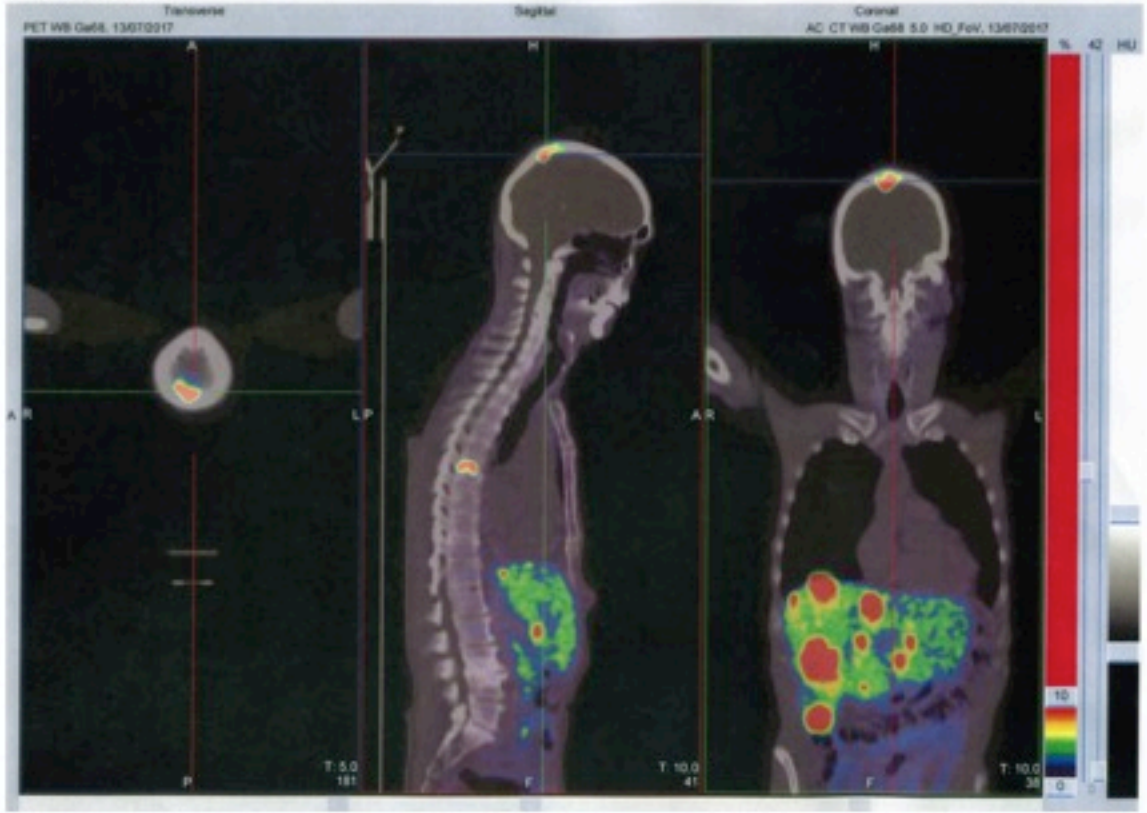
Per la visualizzazione del tumore primitivo può essere utile l'entero-TC o entero-RM. Enterografia (MdC per os) o enteroclisi (MdC con sondino) sono comparabili. Sensibilità molto alta per entrambe (100-86%). Specificità 96-98%. In TC esame più breve e meno artefatti da movimento. Bassa l'accuratezza nel visualizzare multifocalità (riscontrabile nel 20-30% dei casi).



Neuroendocrinology DOI: 10.1159/000464292

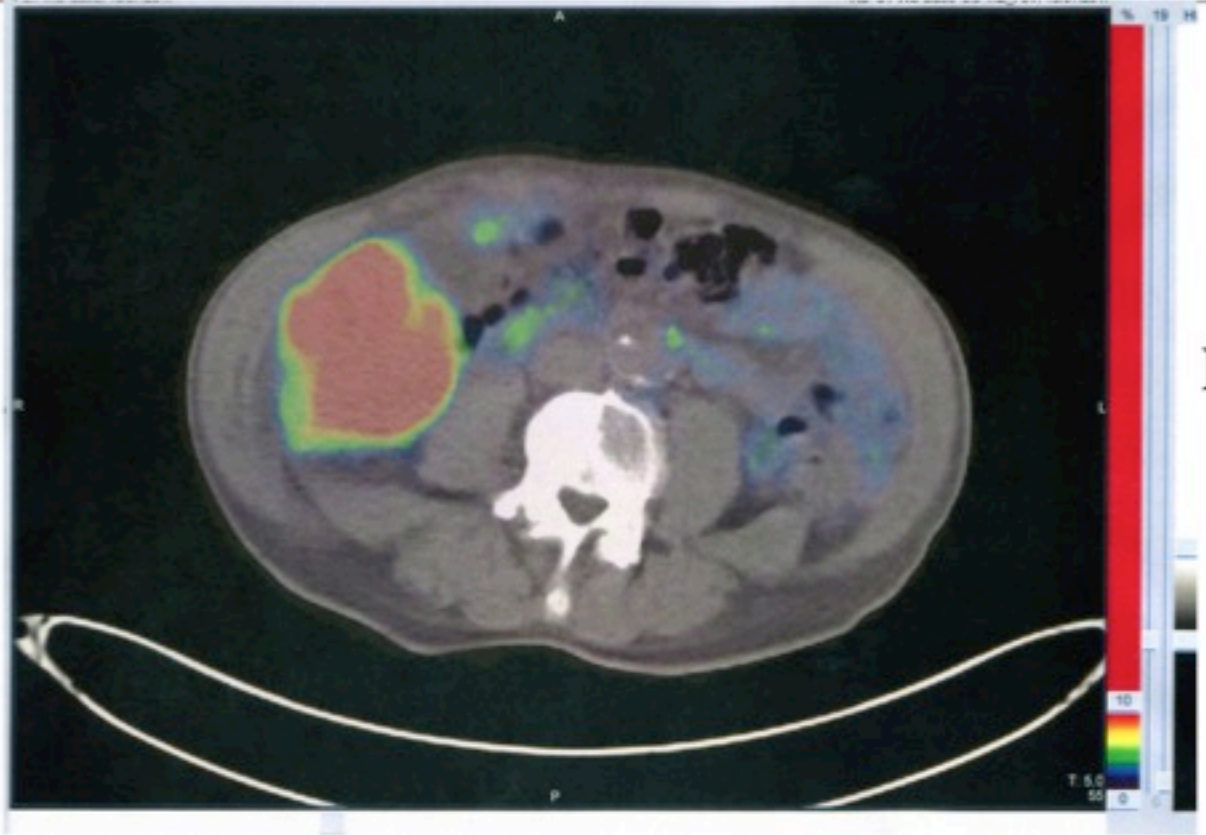
Neuroendocrinology 2016;103:125–138 Linee guida neoplasie neuroendocrine AIOM 2016

In ambito epatico, si apprezza un diffuso sovvertimento di tutto parenchima per la presenza di numerose neoformazioni intensamente fissanti il radiofarmaco, le maggiori delle quali presentano un core necrotico-colliquato.
In ambito scheletrico, si documentano due lesioni ipercaptanti di significato ripetitivo: una a livello della teca cranica (regione parietale superiore sinistra a livello dell'apice) l'altra in corrispondenza del soma di D7.



PET Gallio 68

All'analisi delle immagini si apprezza un'area di intensa captazione del radiofarmaco in corrispondenza della formazione solida posta in regione ipogastrica, in corrispondenza del ventaglio mesenterico, che sembra essere adesa a un'ansa intestinale (pacchetto linfonodale? lesione primitiva?). Più cranialmente rispetto a questo reperto, si osserva inoltre una focale captazione del tracciante che si proietta a livello del colon ascedente (piano passante per il margine inferiore di L5). Tutti i reperti sovramenzionati sono suggestivi per malattia ad elevata espressione dei recettori della somatostatina.

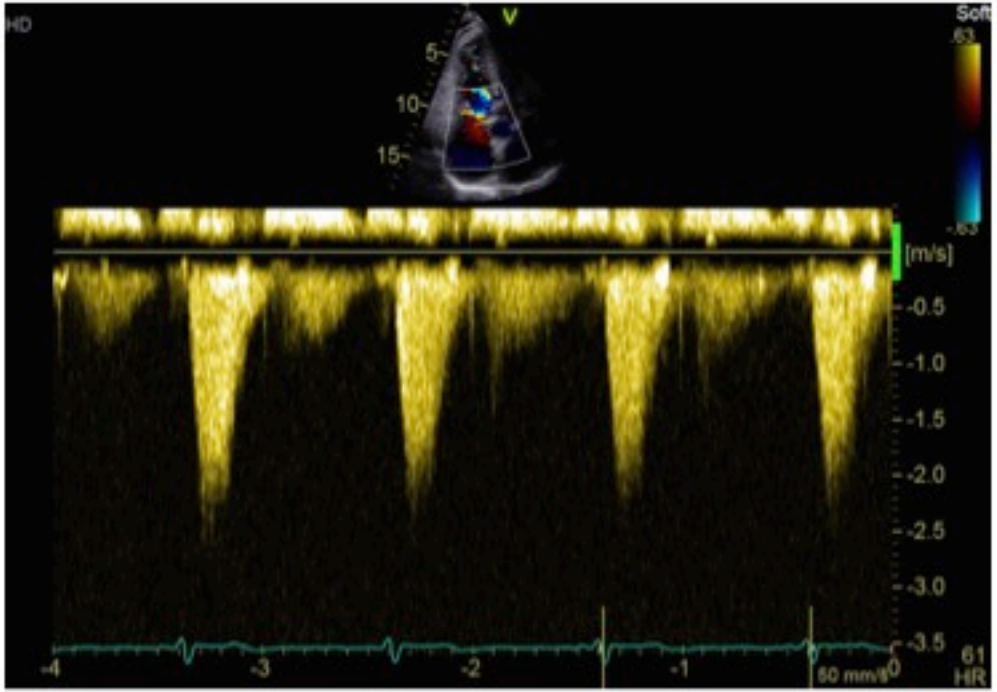


PET Gallio 68

Cardiopatia da carcinoide

- Valutazione cardiologica
- Ecocardiografia

L'immagine indica il segnale doppler del rigurgito tricuspidale che appare di forma triangolare, compatibile con **valvulopatia tricuspidale con rigurgito di grado severo, con segni di scompenso destro.**



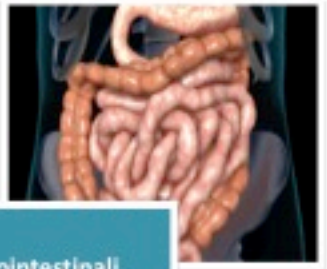
Inizio terapia

3 settimane dopo la presa in carico, inizia terapia con analoghi della somatostatina:

- **Octreotide LAR 30 mg/28 gg previa induzione con Octreotide s.c.**
- Ottima risposta clinica e bioumorale: riduzione della diarrea: 20 --> 6 scariche/die

Carcinoidi associati a sindrome

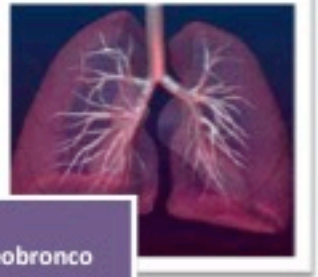
- **GI-NETs (67%)**



gastrointestinali (GI-NET)

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

- **NETs Toracici (25%)**

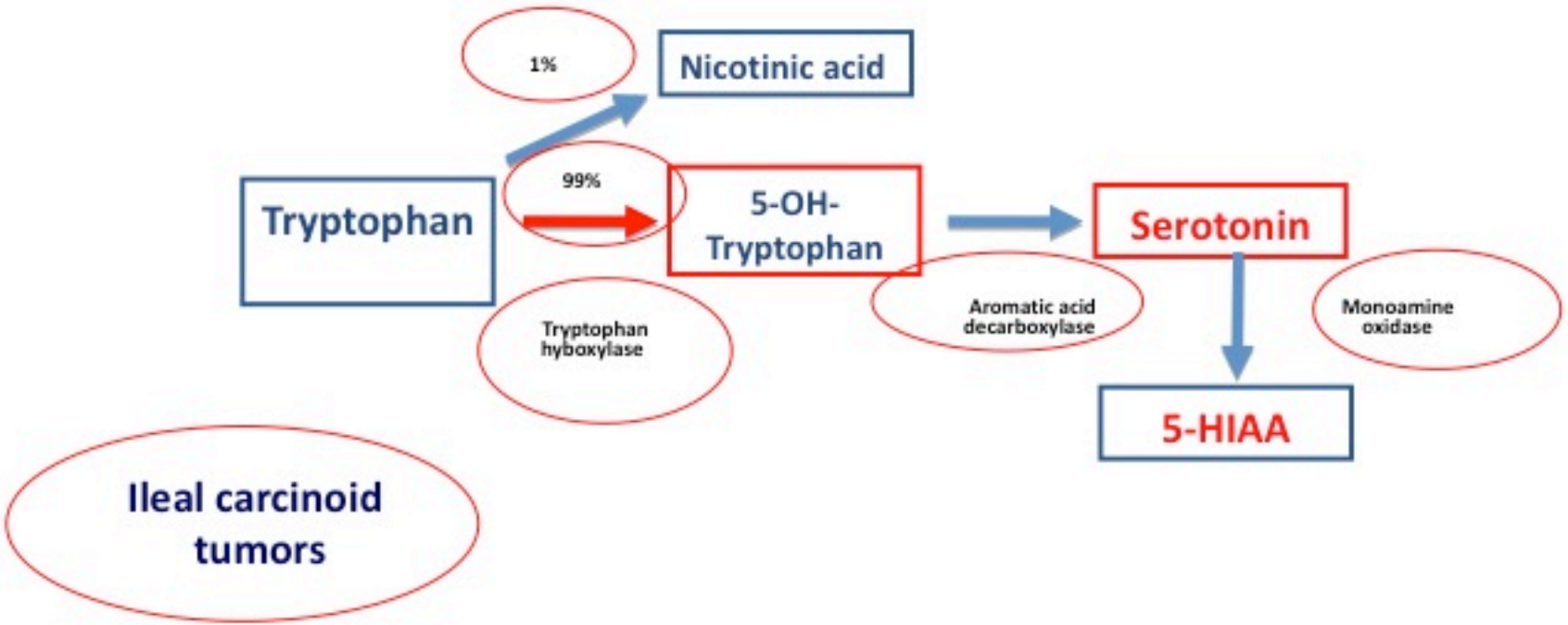


tracheobronco polmonari/timo

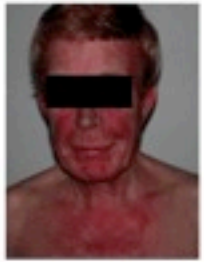
- **Carcinoide bronchiale tipico**
- **S. da carcinoide atipica: 1-3%**
- Ki 67 ≤ 2%
- Metastasi < 15%
- Età d'insorgenza: V decade

Modlin IM Cancer 2003, Yao JC JCO 2008
Modlin IM Lancet Oncol 2008

Serotonin synthesis



Sindrome da carcinoide (sc)



SC TIPICA (95%):

18-30% NET digiuno-ileali
+ mts epatiche

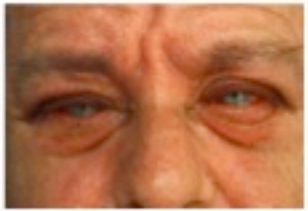
< 5% mts retroperitoneali o carcinoide ovarico

- 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



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

CRISI DA CARCINOIDE

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

Gestione della sindrome cardiaca da carcinoide: ruolo dell'endocrinologo

ITALIAN CHAPTER

- 40-50% nei pz con s. da carcinoide (20% dopo introduzione AS)
- Fibrosi a placche delle valvole ds
- Scompenso cardiaco destro è causa di morte nel 30-50% dei casi
- Età, livelli di 5-HIAA, insufficienza tricuspidale predittori di mortalità
- Ecocardiogramma: gold standard x diagnosi e follow up
- NT-proBNP: valore diagnostico e prognostico

(J Am Coll Cardiol 2017;69:1288-304)

5-HIAA urinario

- Marker specifico della sindrome da carcinoide
- Dosaggio della serotonina non è più raccomandato
- > Elevato nella cardiopatia da carcinoide (predittore di progressione)

Valori normali = 2- 8 mg/24 h; 10-42 µmol/24 h

cut-off x la diagnosi di SC > 20 mg/24 h; 100 µmol/24 h

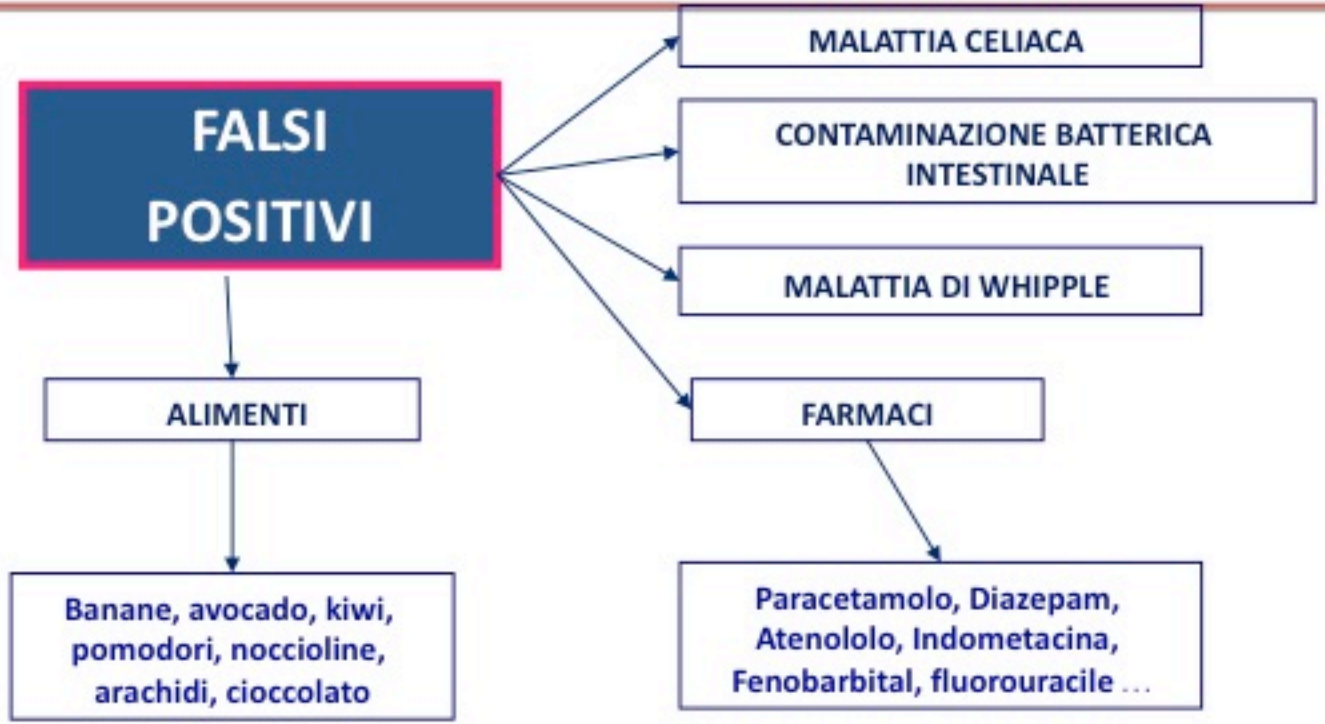
> 300 µmol/24 h (60 mg/24 h) rischio di sviluppo di cardiopatia

SENSIBILITA' > 90%

SPECIFICITA' 90%

O'Toole D, 2009 ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biochemical markers Neuroendocrinology 90 194–202.

ACIDO 5-IDROSSI-INDOLACETICO



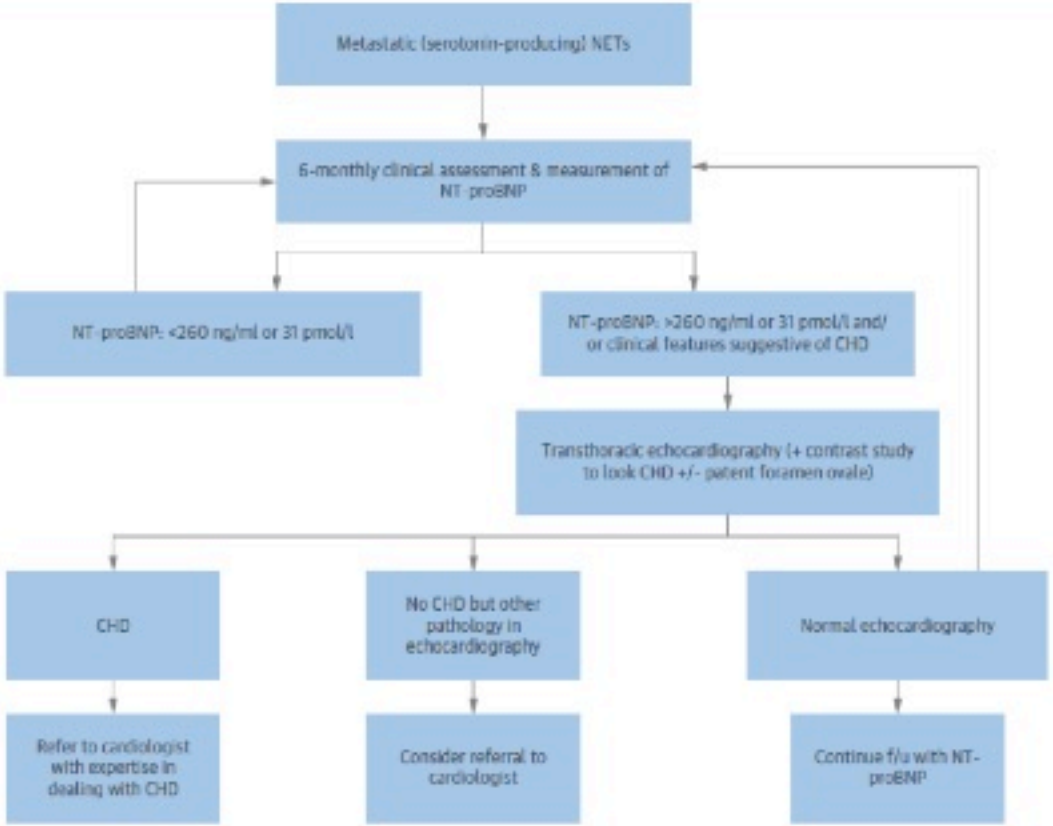
NT-proBNP

- **Marker della cardiopatia/scompenso cardiaco** (diagnosi e follow up)
- Cut-off: 260 pg/ml (31 pmol/l) (sensibilità 92%, specificità 91%)
- Valore prognostico di sopravvivenza
- Da dosare ogni 1 o 2 anni
- In associazione ad ecocardiogramma

CrgA e cardiopatia da carcinoide

- Sensibilità del 100% e specificità del 30% nel predire la cardiopatia da carcinoide
- Non indicata nello screening della cardiopatia da carcinoide ma nella valutazione della progressione del NET

FIGURE 2 Proposed Algorithm for the Screening and Investigation of CHD



This graphic provides an algorithm for how patients with metastatic (serotonin-producing) neuroendocrine tumors (NETs) should be screened and assessed for carcinoid heart disease (CHD), including, importantly, when to refer to cardiology. f/u = follow-up; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

(J Am Coll Cardiol 2017;69:1288-304)

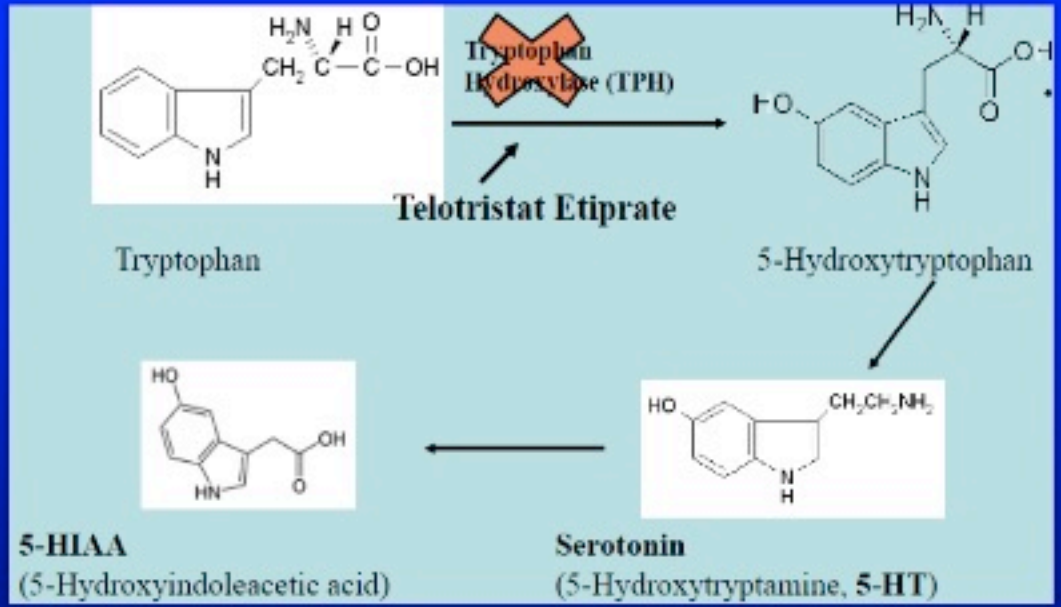
Trattamento della cardiopatia da carcinoide

Terapia dello scompenso cardiaco: trattamento personalizzato

- **Analoghi della somatostatina di 1^ scelta** per il controllo della sindrome da carcinoide e per prevenire la progressione della cardiopatia;
- **Nelle forme refrattarie: aumento della dose di SA**, aggiunta di Interferone, PRRT, **Telotristat;**
- **TAE e chirurgia epatica**: cautela nelle forme avanzate di cardiopatia
- **Terapia cardiochirurgica** in casi selezionati

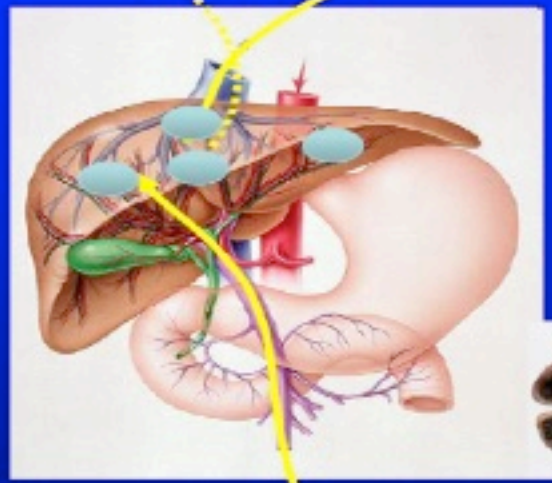
(J Am Coll Cardiol 2017;69:1288-304)

Telotristat etiprate: Mode of action



TPH catalyzes
the first step of serotonin
synthesis

In addition to SSA, telotristat etiprate inhibits serotonin production and alleviates symptoms



Serotonin ↓

hormonal syndrome

flushing, diarrhoea.....

5-HIAA↓

Urine

NET-Cell

Tryptophan

Tryptophan-Hydroxylase

Telotristat etiprate

5-Hydroxytryptophan (5-HTP)

Serotonin (5-HT)

Serotonin ↓

SSTR

SSA

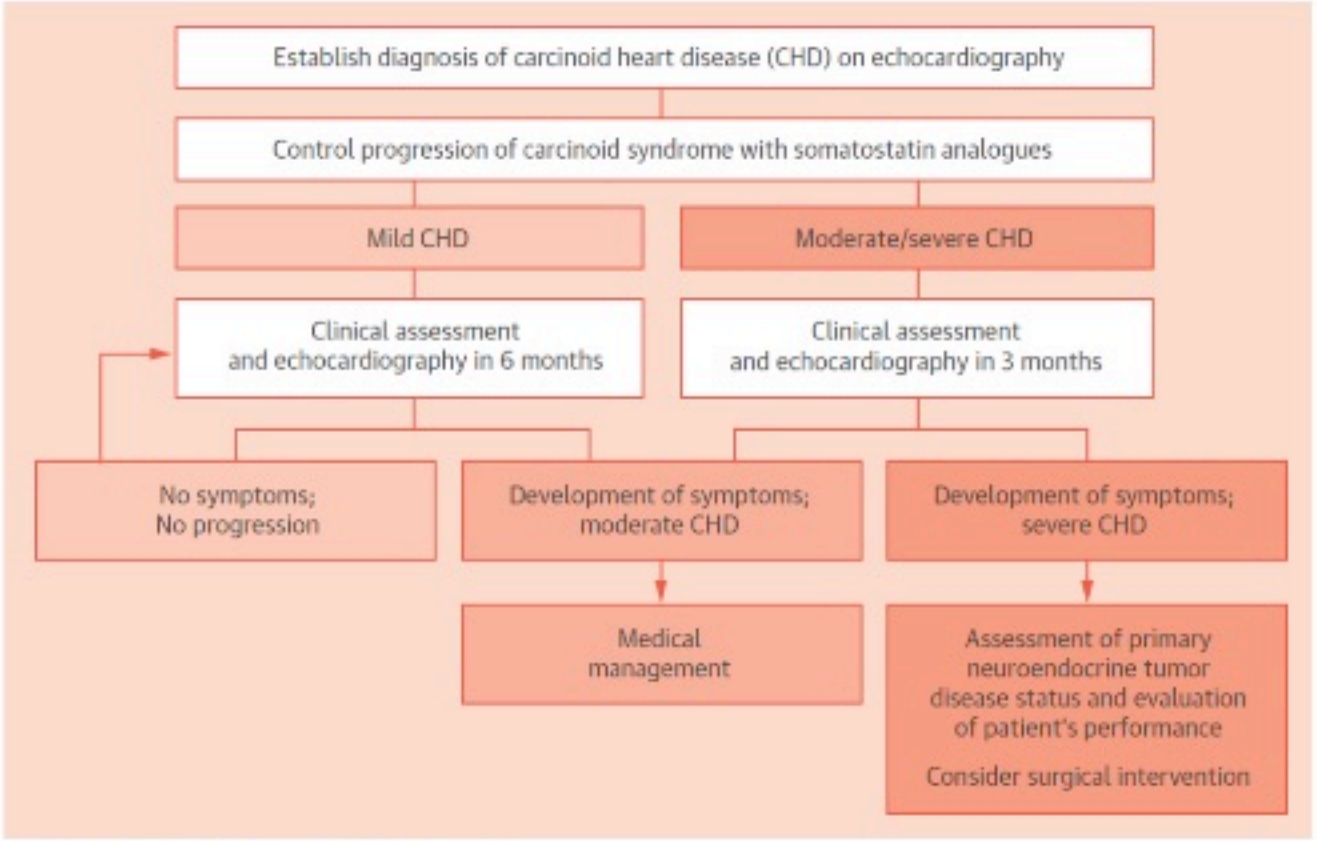
5-HIAA: 5-hydroxyindole acetic acid

SSA somatostatin analogue

SSTR somatostatin receptor

Adapted from: Kronenberg H, et al, eds. Williams Textbook of Endocrinology. 11th ed. 2008:1823-1824 and Van der Horst-Schrivers A, et al.Neuroendocrinology. 2004;80(suppl 1):28-32.

CENTRAL ILLUSTRATION Management Algorithm for Patients With CHD



Davar, J. et al. J Am Coll Cardiol. 2017;69(10):1288–304.

28-07-2017

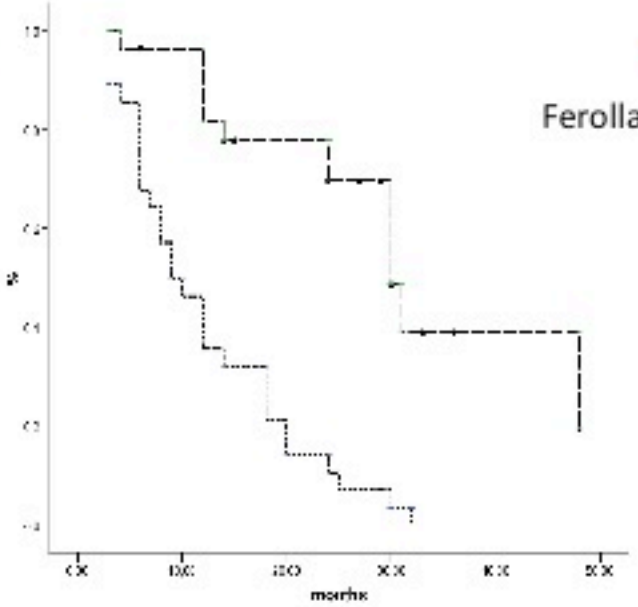
Biopsia epatica, previa preparazione medica, con octreotide 10 fl in 250 cc fisiologica: quadro compatibile con metastasi da NEN a partenza verosimilmente intestinale: positività immunoistochimica per cromogranina A, sinaptofisina, CDX-2, serotonina, CD56, MNF116, CAM5,2, Ki67 < 1%

Caso clinico 2

- Si modifica la terapia dell'analogo riducendo l'intervallo di somministrazione per ottimizzare la risposta clinica (normalizzare l'alvo) e biochimica; in previsione della chirurgia per escludere la presenza di una subocclusione del tenue, vista la presenza di sintomatologia dolorosa addominale saltuaria riferita dal paziente
- 27-09-2017: **CgA: 12.700 ng/ml** (121.520)

  Acido-5 OHIA: 327 uMol/24 h (1764)
- **Sostituzione dell'Octreotide LAR 30 mg/28 gg con Lanreotide Autogel 120 mg/21 gg (vedi scheda tecnica: indicazioni posologia octreotide)**
- Ulteriore miglioramento clinico (**alvo: 3 scariche/die**)

Time to tumor progression after standard dose OCT-LAR treatment (point line) and high dose OCT-LAR treatment (dashed line) (p<0.0001)

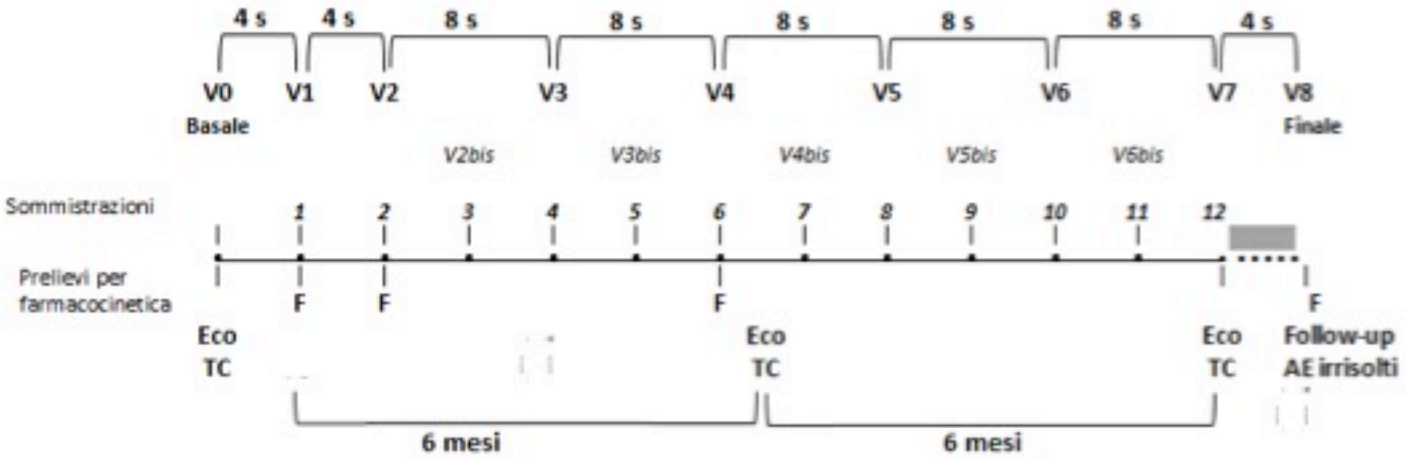


Ferolla P, Faggiano A, Grimaldi F, et al., 2010

Conclusion: In patients with NET in progressive disease during standard OCT-LAR dose, **a dose of 30 mg every 21 days induced control of hypersecretion-related clinical syndrome and/or re-stabilization of tumor size** in relevant percentage of cases.

Studio spontaneo, di fase II, multicentrico, prospettico, in aperto con singolo braccio di trattamento. Lanreotide 180 mg/28 giorni (2 iniezioni da 90 mg)

Scientific objective	To evaluate the **Safety** of Lanreotide treatment at higher dosage of administration in NET patients in progression during standard therapeutic treatment schedule with SSAs.
Study description	Phase II, multicenter, prospective, open label, single arm study. Patients with NET in treatment with LAN 120mg/28days or OCT 30mg/28days in presence of disease progression (symptomatic, biochemical or RECIST criteria) will be shifted to receive Lanreotide 180mg every 28 days.
Sample size	**35 patients/ 10 centers – Promoter/Coordinator: Prof Diego Ferone (Genova)**



CLARINET Forte

*Efficacy and safety of **lanreotide Autogel® 120 mg administered every 14 days** in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with **lanreotide Autogel® 120 mg administered every 28 days***

Primary Endpoint	• Progression-free survival (PFS),according to RECIST v1.0 criteria
Secondary Endpoints	• Time to progression; Overall survival; Overall response rate (ORR); Disease control rate (DCR); Best overall response ; Change in tumor biomarker concentrations from baseline; Symptom control (diarrhea, flushing); Quality of life and safety

Caso clinico 2

- **Il paziente è in attesa di intervento chirurgico** programmato per fine novembre nel sospetto di una subocclusione

- Post chirurgia: valutata l'ottima risposta agli analoghi freddi ed all'esito della PET con Gallio 68, verrà programmata la **terapia radiorecettoriale**

- **Valutare eventuale intervento cardiochirurgico** per la valvulopatia tricuspidale di grado severo

TERAPIA PERI-OPERATORIA

TABLE 7 Perioperative Management

1. Admission of a patient ≥48 h before surgery
2. Commencement of an octreotide infusion at the dosage of 50 μg/h administered 12 h before the procedure, throughout the operation, and 48 h after the operation, and increased to 100-200 μg/h, if necessary
3. Coordination of perioperative management by members of the multidisciplinary team

Quale follow up diagnostico-terapeutico?

- **Quesiti:**
  - Proseguire con analoghi della somatostatina
  - Intervento cardiochirurgico per la valvulopatia tricuspidale
  - **Terapia radiorecettoriale**
  - Altre terapie ?
  - **Controllo a lungo termine: quale imaging e timing**

Neuro endocrinology

ENETS Consensus Guidelines

Neuroendocrinology 2016;103:172–185
DOI: 10.1159/000443167

Published online: January 5, 2016

ITALIAN CHAPTER

Table 1. Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/–	G1	midgut	+	low tumor burden
Lanreotide	+/–	G1/G2 (–10%)	midgut, pancreas	+	low and high (>25%) liver tumor burden
IFN-alpha 2b	+/–	G1/G2	midgut		if SSTR negative
STZ/5-FU	+/–	G1/G2	pancreas		progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/–	G2	pancreas		progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/–	G1/G2	lung		atypical carcinoid and/or SSTR negative
			pancreas		insulinoma or contraindication for CTX
			midgut		if SSTR negative
Sunitinib	+/–	G1/G2	pancreas		contraindication for CTX
PRRT	+/–	G1/G2	midgut	+ (required)	extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin§/ etoposide	+/–	G3	any		all poorly differentiated NEC

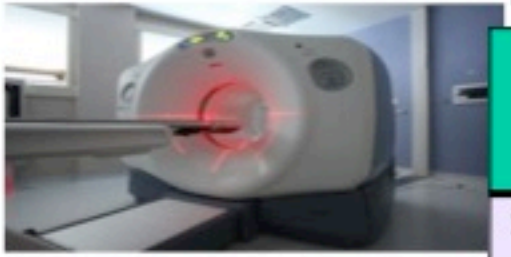
CAP = Capecitabine; TEM = temozolomide. * ≤6–12 months. § Cisplatin can be replaced by carboplatin.

^{111}In-Octreoscan and ^{68}Ga-DOTA peptide PET/CT

- Primary tumor localization and staging
- Restaging (detection of residual, recurrent or progressive disease)
- SSTR status evaluation (patients with high positivity are more likely to respond to octreotide therapy)
- Response to therapy monitoring
- Selection of patients for peptide receptor radionuclide therapy (PRRT)

Bombardieri E Eur J Nucl Med 2010
Virgolini I Eur J Nucl Med 2010

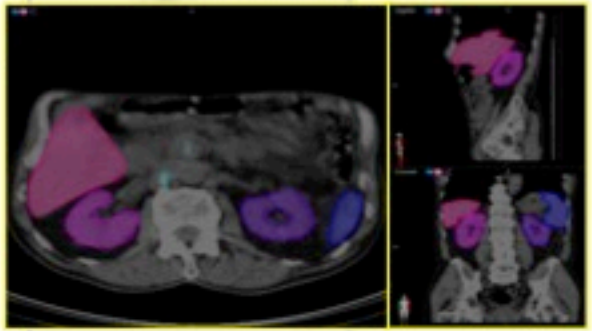
TERANOSTICA: dalla Diagnosi al Trattamento



	β- (Mev)	γ (Kev)	T1/2 (days)
^{177}Lu	0.49	110-210	6.7
^{90}Y	2.27		2.7

DOTA-TOC/TATE

Terapia
^{90}Y / ^{177}Lu

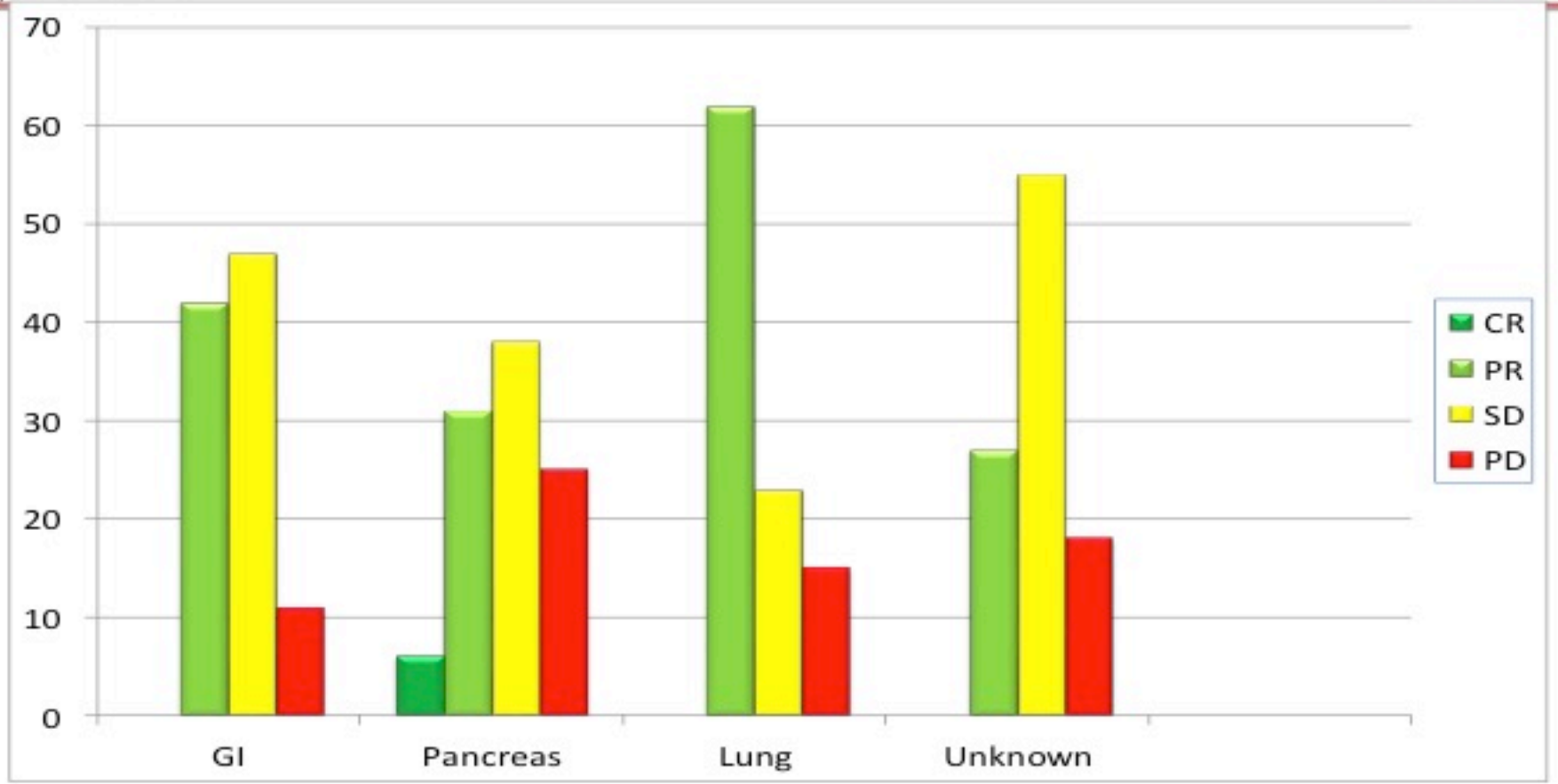


Peptide Receptor Radionuclide Therapy (PRRT)

Author	Year	Radiopharmaceutical	N° Pts.	Primary NET	Response (%)				
					CR	PR	MR	SD	PD
Waldherr	2001	90Y-DOTATOC	41	GEP+lung	2	22	12	49	15
Waldherr	2002	90Y-DOTATOC	39	GEP+lung	5	18	-	65	11
Valkema	2006	90Y-DOTATOC	58	GEP	0	9	12	61	19
Kwekkeboom	2008	177Lu-DOTATATE	310	GEP	2	28	16	35	20
Bodei	2011	177Lu-DOTATATE	51	GEP+lung	2	27	26	27	18
Filice	2012	90Y/177Lu-DOTATOC	59	GEP+lung	2	40	-	40	18
Vinjamuri	2013	90Y-DOTATOC	57	GEP+lung	-	25	-	47	28
Mariniello	2015	90Y/177Lu DOTATOC	117	Lung	0	13	13	41	33

PRRT 59 pts

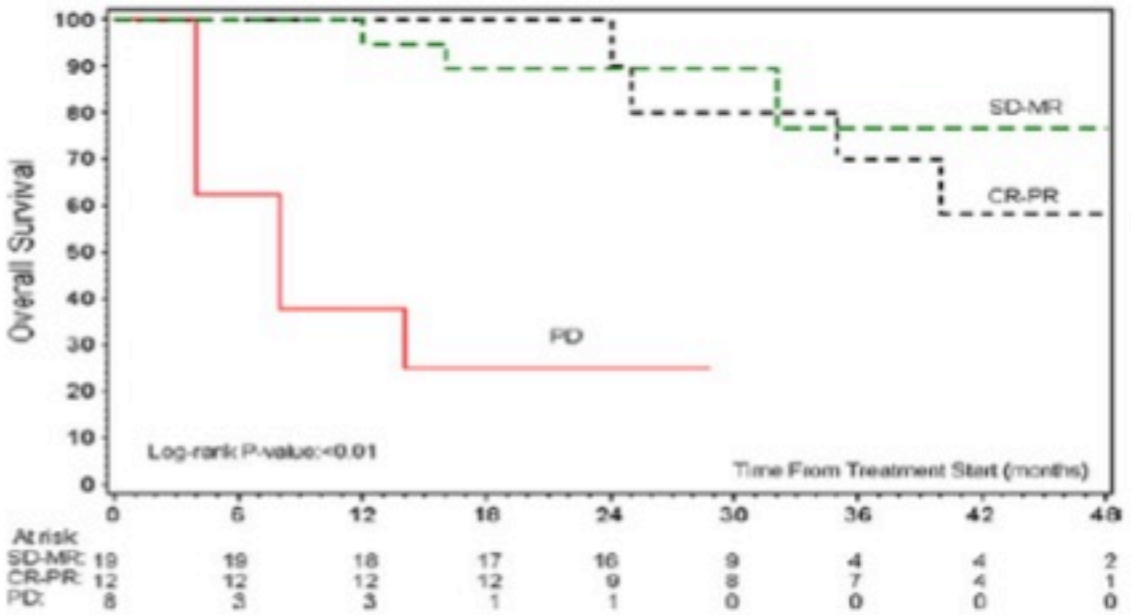
A. Filice et al, J of Oncology 2012



Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study

Lisa Bodei · Marta Cremonesi · Chiara M. Grana · Nicola Fazio · Simona Iodice · Silvia M. Baio · Mirco Bartolomei · Dario Lombardo · Mahila E. Ferrari · Maddalena Sansovini · Marco Chinol · Giovanni Paganelli

Fig. 5 Overall survival in progressing patients at baseline. From a prognostic point of view, stabilizations and objective responses showed the same survival probability



ITALIAN CHAPTER

GEP–NETs UPDATE

Radionuclide therapy in neuroendocrine tumors

Wouter A van der Zwan, Lisa Bodei[1], Jan Mueller-Brand[2], Wouter W de Herder, Larry K Kvols[3] and Dik J Kwekkeboom

Correspor

European Journal of Endocrinology 2015

Table 3 Long-term toxicity in patients with neuroendocrine tumors, treated with different radiolabeled somatostatin analogs.

Center (reference)	Ligand	*n*	FU	Toxicity		
				Creatinine	MDS	Leukemia
Milan (13)	[^{90}Y-DOTA^0,Tyr^3]octreotide	40	19	10% Grade 1	0	0
Basel (14)	[^{90}Y-DOTA^0,Tyr^3]octreotide	41	15	0	0	0
Basel (15, 41)	[^{90}Y-DOTA^0,Tyr^3]octreotide	39	6	3% Grade 2	0	0
Multicenter (1)	[^{90}Y-DOTA^0,Tyr^3]octreotide	58	18	3% Grade 4	1	0
Basel (16)	[^{90}Y-DOTA^0,Tyr^3]octreotide	31	12	12.9% Grade 3/4[a]	0	0
Copenhagen (3)	[^{90}Y-DOTA^0,Tyr^3]octreotide	53	17	0	1	0
Basel (8)	[^{90}Y-DOTA^0,Tyr^3]octreotide	1109	23	9.2% Grade 3/4[a]	1	1
Rotterdam (5)	[^{177}Lu-DOTA^0,Tyr^3]octreotate	504	19	0.4% Grade 4	3	0
Milan (10)	[^{177}Lu-DOTA^0,Tyr^3]octreotate	51	29	24% Grade1	0	0

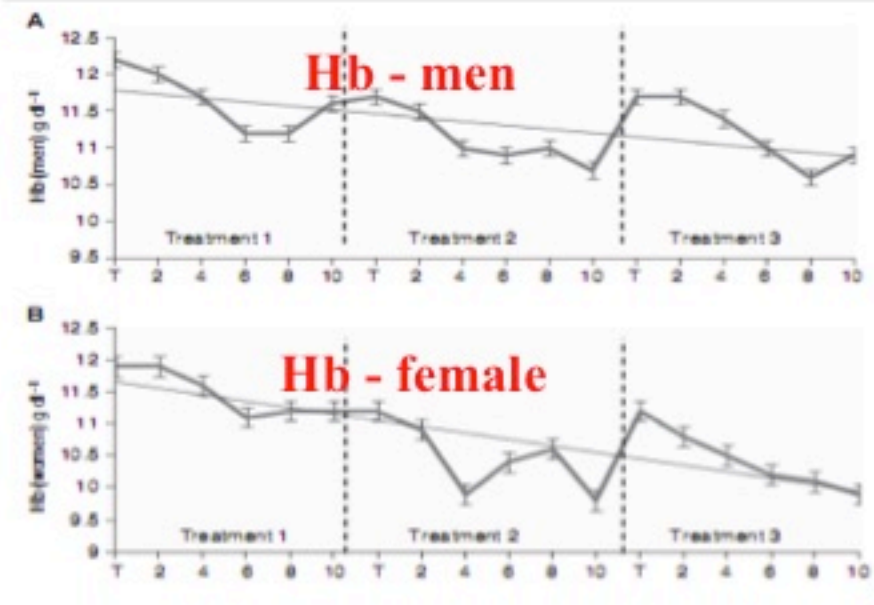
FU, follow-up; MDS, myelodysplastic syndrome. Grades pertain to World Health Organization (WHO) classification.
[a]Toxicity based on glomerular filtration rate.

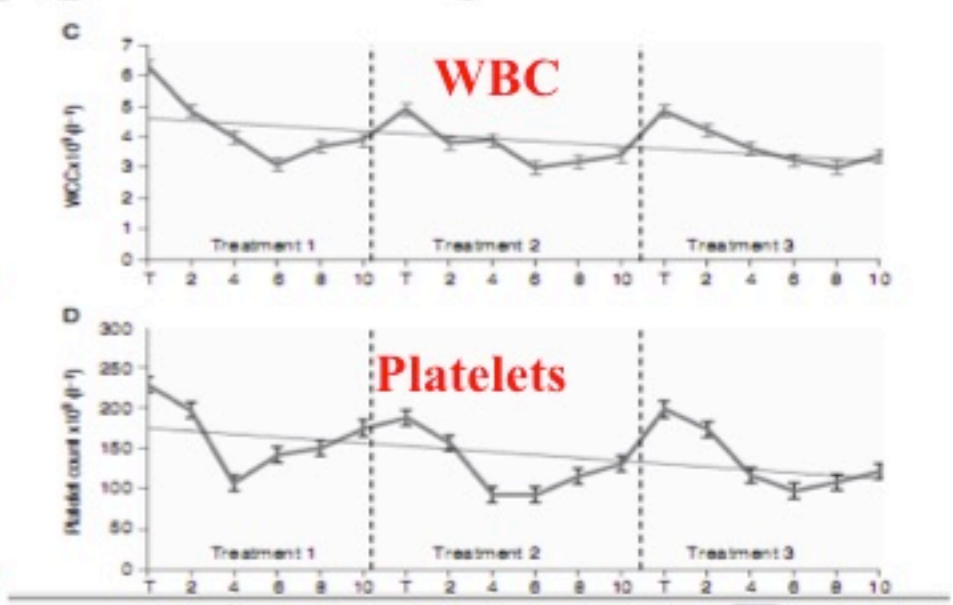
British Journal of Cancer (2013) 108, 1440–1448

Peptide receptor radionuclide therapy with ^{90}Y-DOTATATE/^{90}Y-DOTATOC in patients with progressive metastatic neuroendocrine tumours: assessment of response, survival and toxicity

S Vinjamuri[1,8], T M Gilbert[2,8], M Banks[3], G McKane[1], P Maltby[1], G Poston[3], H Weissman[4], D H Palmer[5], J Vora[6], D M Pritchard[7] and D J Cuthbertson[*,2]

PRRT - Hematological toxicity





Roma, 9-12 novembre 20

Terapia Radiorecettoriale

Protocollo DOTATER1

Procedura di Reggio Emilia

ITALIAN CHAPTER

Esami ematologici ogni 15 giorni

Esami ematologici ogni mese

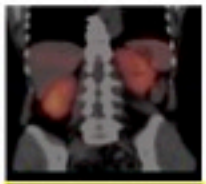
Follow up

0 2 4 6 8 10 3 12

mesi

Valutazione durante PRRT
177Lu-DOTATOC
SPECT/CT

PET basale
CT o RM



Studio
Dosimetrico

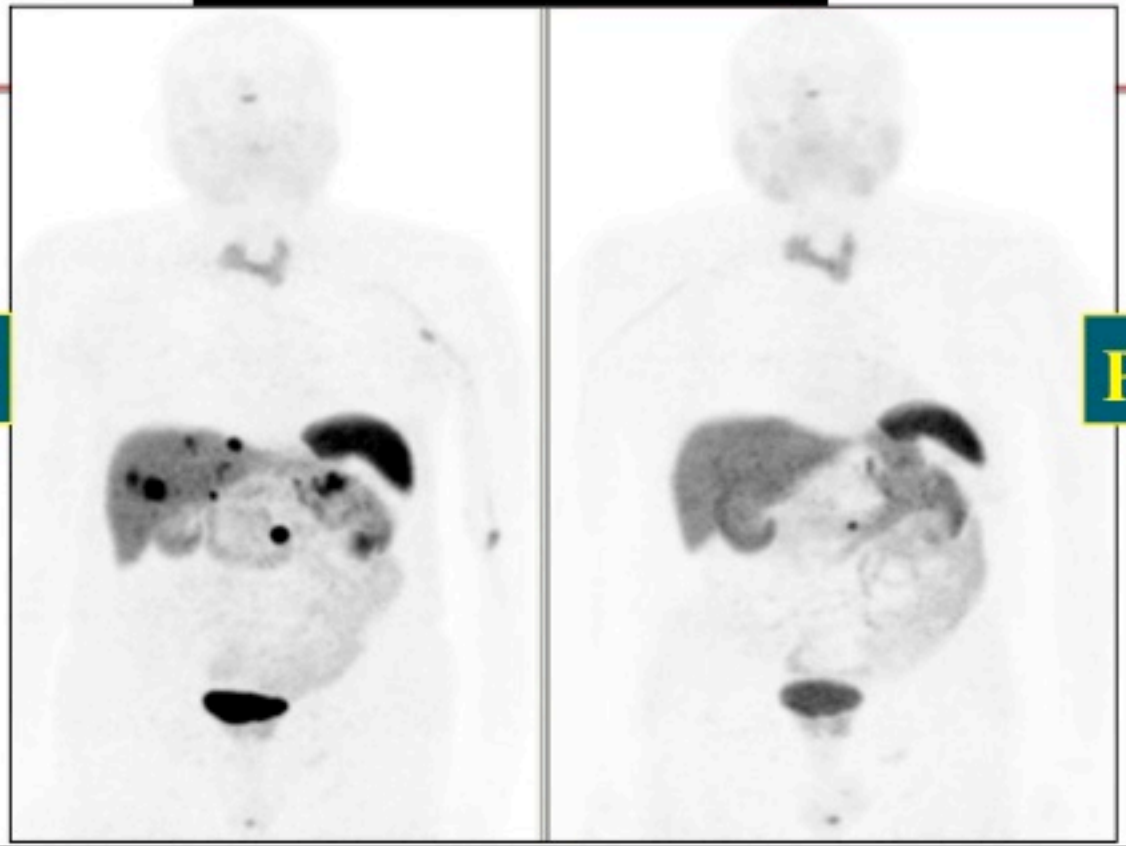
STOP
trattamento

PET ,
CT /RM

PET ,
CT /RM

^{68}Ga-DOTATATE PET/CT

Pre-terapia



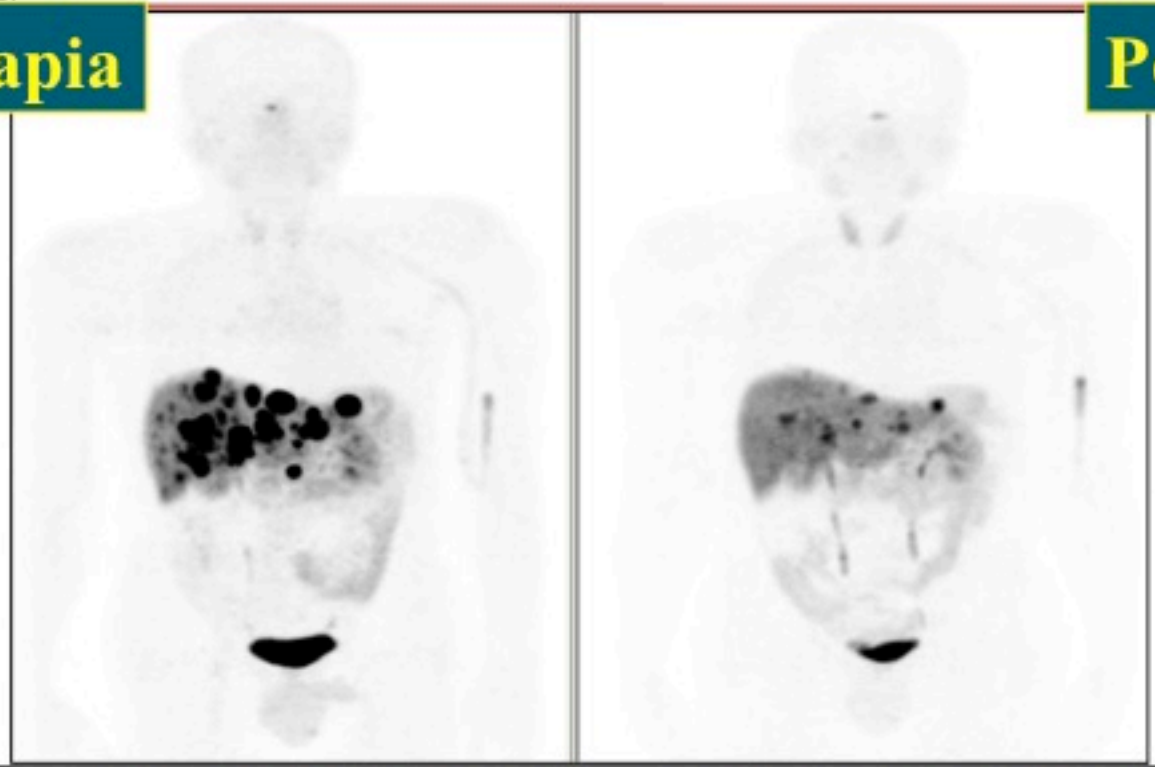
Post-terapia

M, 73 y: NET pancreatico con metastasi epatiche
2 cicli di 90Y e 4 cicli di 177Lu. PR

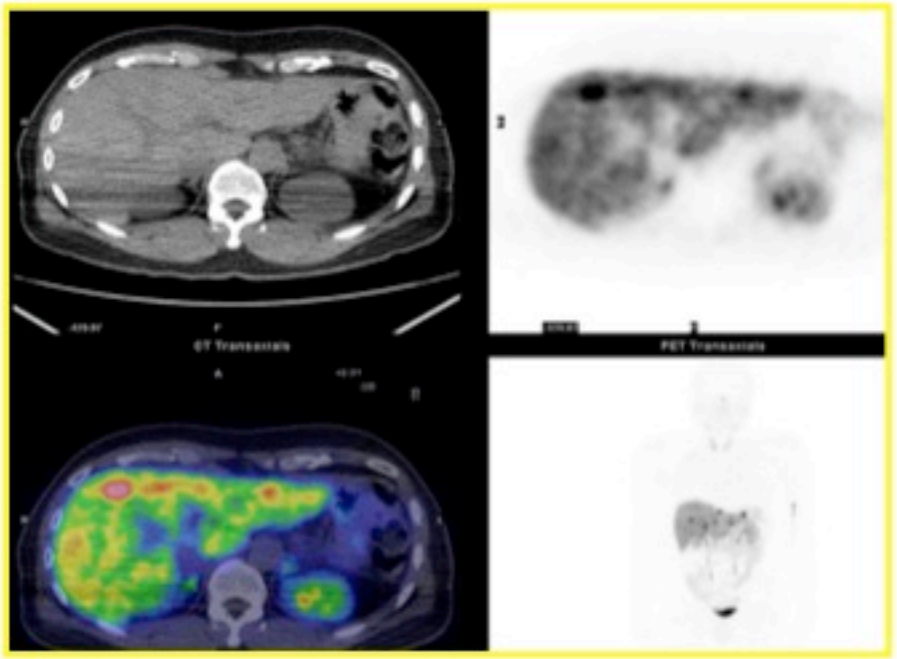
^{68}Ga-DOTATOC PET/CT

Pre-terapia

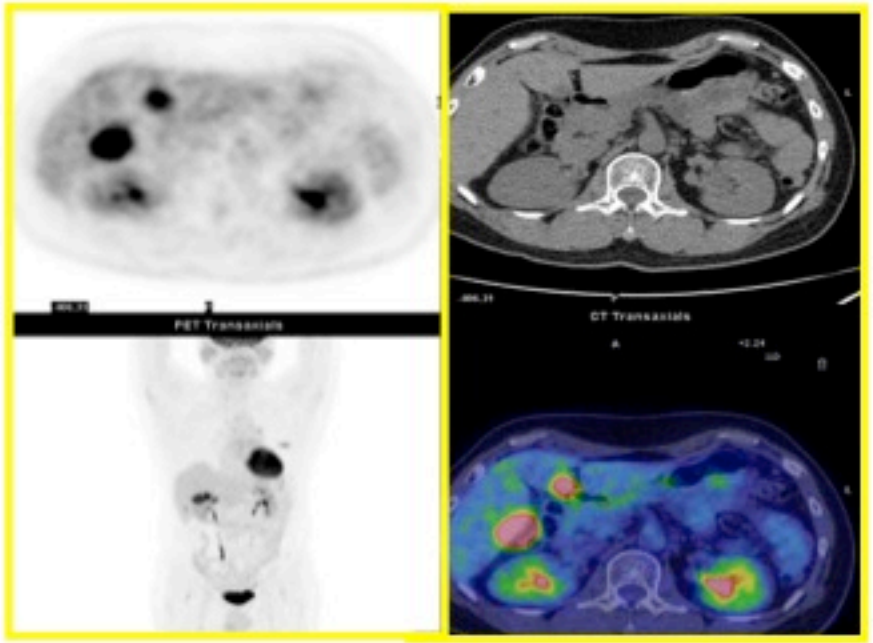
Post-terapia



M, 56 aa: NET pancreatico con metastasi epatiche
4 cicli di 90Y e 1 ciclo di 177Lu. PR

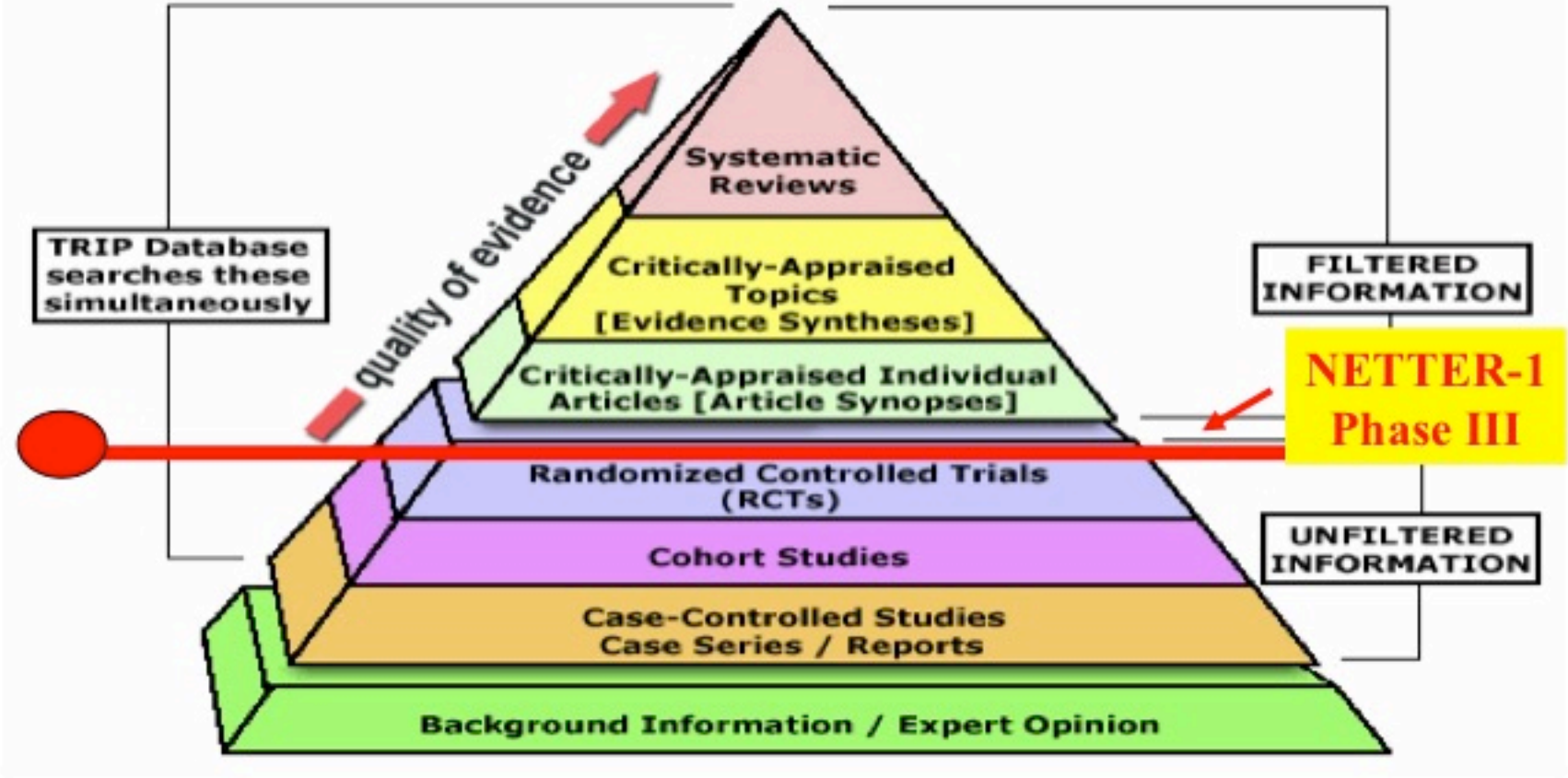


68Ga-DOTATOC



FDG-PET/CT

PRRT and EBM


TRIP Database searches these simultaneously
quality of evidence
Systematic Reviews
Critically-Appraised Topics [Evidence Syntheses]
Critically-Appraised Individual Articles [Article Synopses]
Randomized Controlled Trials (RCTs)
Cohort Studies
Case-Controlled Studies
Case Series / Reports
Background Information / Expert Opinion
FILTERED INFORMATION
NETTER-1 Phase III
UNFILTERED INFORMATION

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

NETTER -1 Study Objectives and Design

Aim

Evaluate the **efficacy and safety** of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60 mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, **midgut NET**, progressive under Octreotide LAR 30 mg (label use)

Design

International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments

Progression free survival (Recist criteria) every 12 weeks

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

- n = 111: 4 administrations of 7.4 GBq of ^{177}Lu-Dotatate every 8 weeks + SSAs (symptoms control)
- n = 110: Octreotide LAR (high dose - 60mg every 4 weeks[1])

5 Years follow up

1. FDA and EMA recommendation

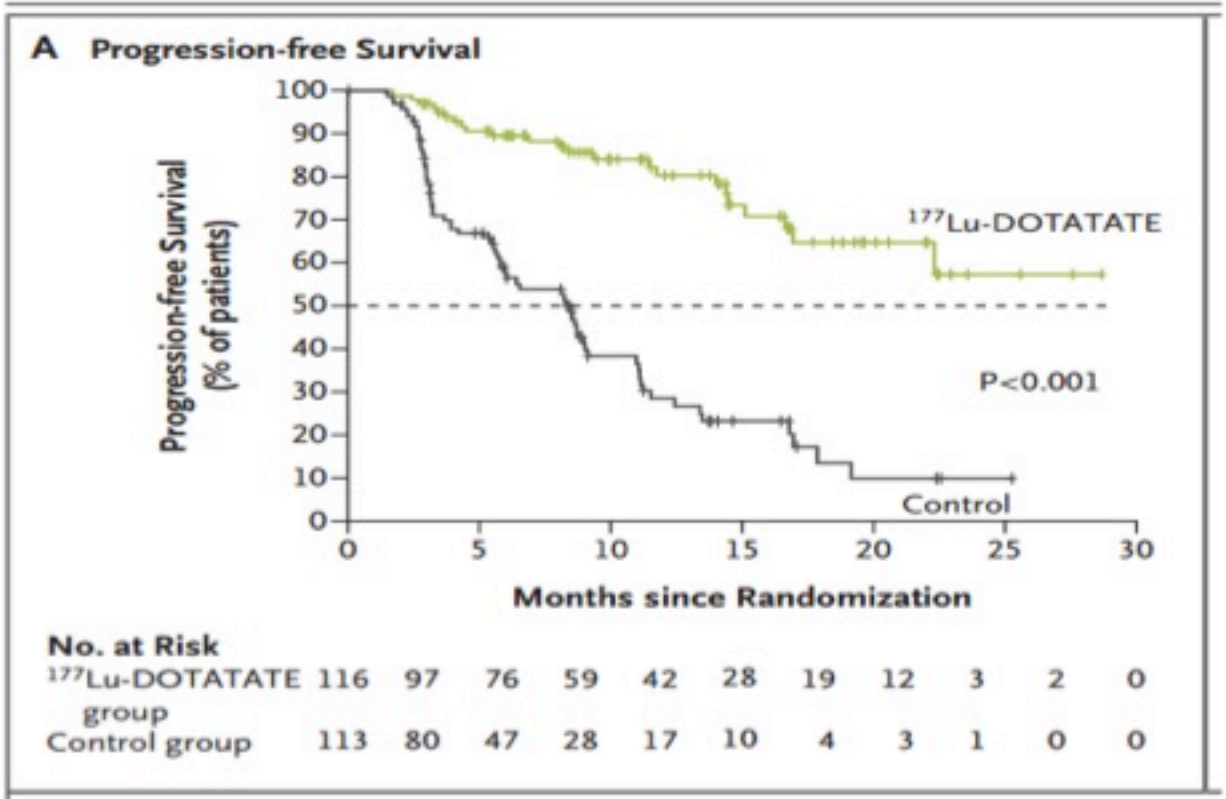
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

J Strosberg et al
N Engl J Med 2017;376:125-35

ITALIAN CHAPTER

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors



79% reduction in the risk of disease progression/death

Estimated Median PFS in the ^{177}Lu-Dotatate arm **≈ 40 months**

Median PFS
Control arm: 8.4 months

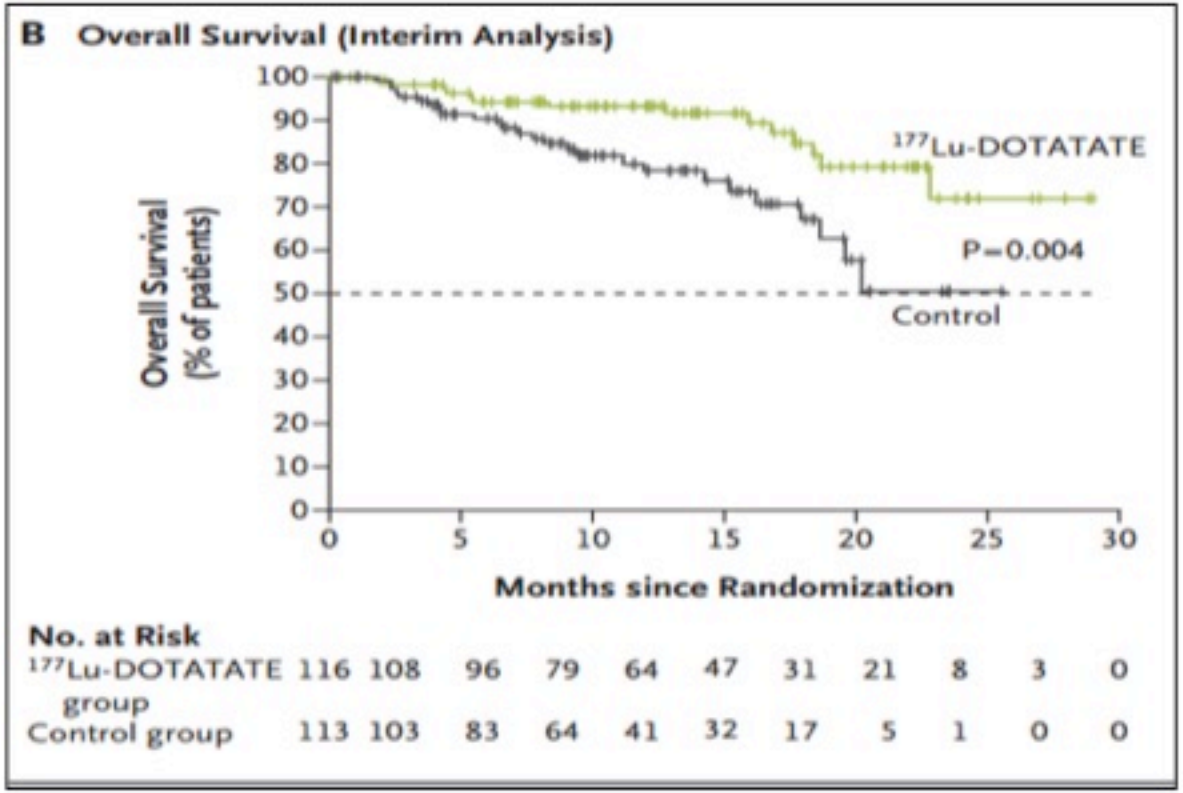
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

J Strosberg et al
N Engl J Med 2017;376:125-35

ITALIAN CHAPTER

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J Strosberg et al
N Engl J Med 2017;376:125-35

Table 3. Overview of Adverse Events (Safety Population).*

Event	^{177}Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher's exact text.

Neuro endocrinology

ENETS Consensus Guidelines

Neuroendocrinology 2016;103:172–185
DOI: 10.1159/000443167

Published online: January 5, 2016

ITALIAN CHAPTER

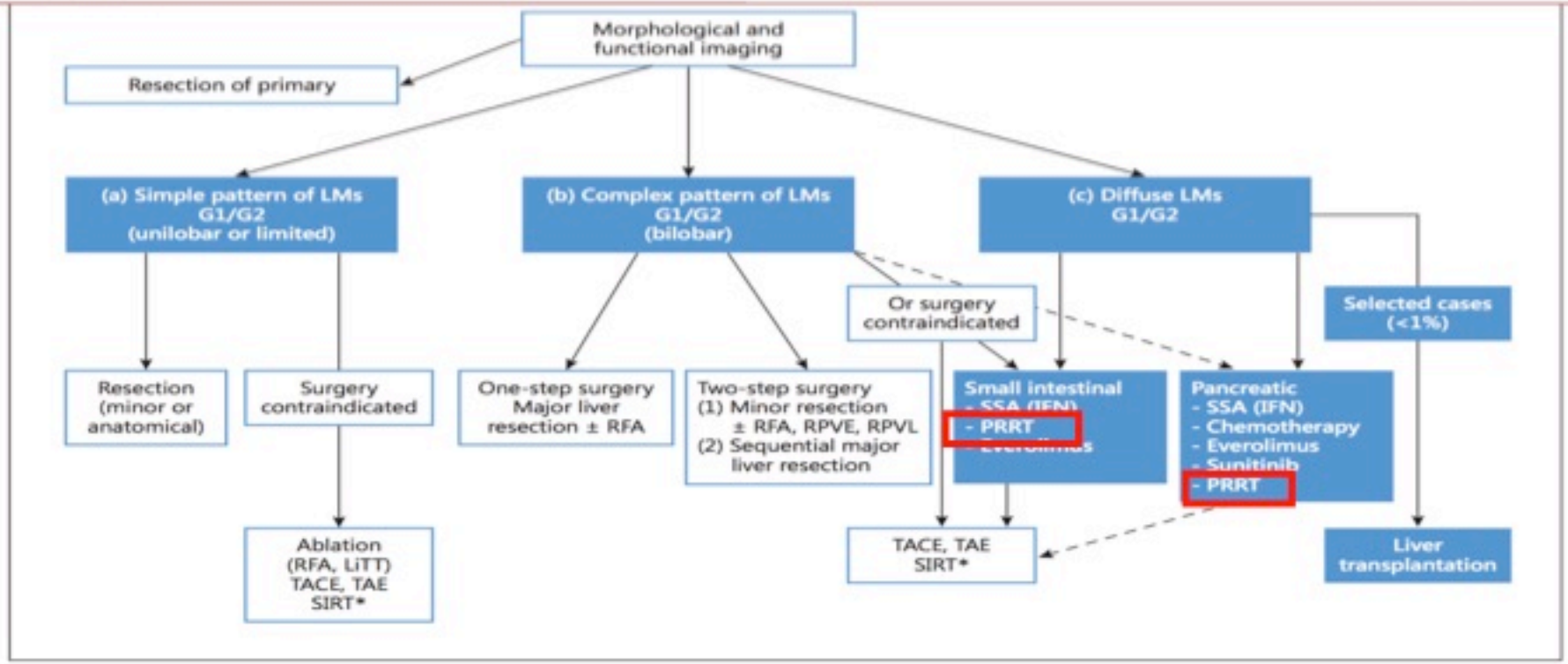


Fig. 1. Management of liver metastases without extrahepatic disease in G1/G2 NEN. * SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Treatment choice

Patient

PS

Comorbidity

- QoL
- Late toxiciy

AGE

Treatment availability

Logistic

Clinical Trials

Regulatory Authorities

AIFA Agenzia Italiana del Farmaco

Disease

Grade – Ki67
SSr expression
Functionality

AIM of Treatment

- Syndrome control
- Tumour growth control -> Disease Cronicization

Cardiotossicità dei farmaci utilizzati nei NEN

Farmaco	Cardiotossicità
Octreotide	Non segnalata
Lanreotide	Non segnalata
Everolimus	Ipertensione , dislipidemia ACE inibitori (angioedema) CYP3A4, PgP (diltiazem > esp) Scompenso congestizio (< 1%)
Sunitinib	CYP3A4 Ipertensione severa (4-12%) Ischemia miocardica (>1/100) < LVEF (2-4%) > QT (1.1%)
Temozolomide	Ipopotassiemia
Capecitabina	Aritmia, torsione di punta, bradicardia, angina, infarto miocardico acuto, insufficienza cardiaca, cardiomiopatia

Neuro-endocrinology

Neuroendocrinology
DOI: 10.1159/000455155

Received: November 6, 2015
Accepted after revision: January 24, 2017
Published online: February 17, 2017

ITALIAN CHAPTER

ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation

Table 1. Tumor-specific recommendations for follow-up (in most cases life-long)

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Small intestine										
G1–G2	curatively resected	yes	6–12 m	yes	5-HIAA	no	6–12 m	24 m[e]		
G1–G2	residual tumor or metastases	yes	3–6 m	yes	5-HIAA	no	3–6 m	12 m[e]		in patients with carcinoid syndrome: NT-pro-BNP and echocardiography at least yearly
G3 NEC/ NET	resected/ nonresected	yes	3 m	yes[d]	relevant tumor hormones[i]	no	2–3 m	12–24 m[e,f]	12–24 m[l]	in patients with carcinoid syndrome: NT-pro-BNP and echocardiography at least yearly

J Endocrinol Invest (2014) 37:875–909
DOI 10.1007/s40618-014-0119-0

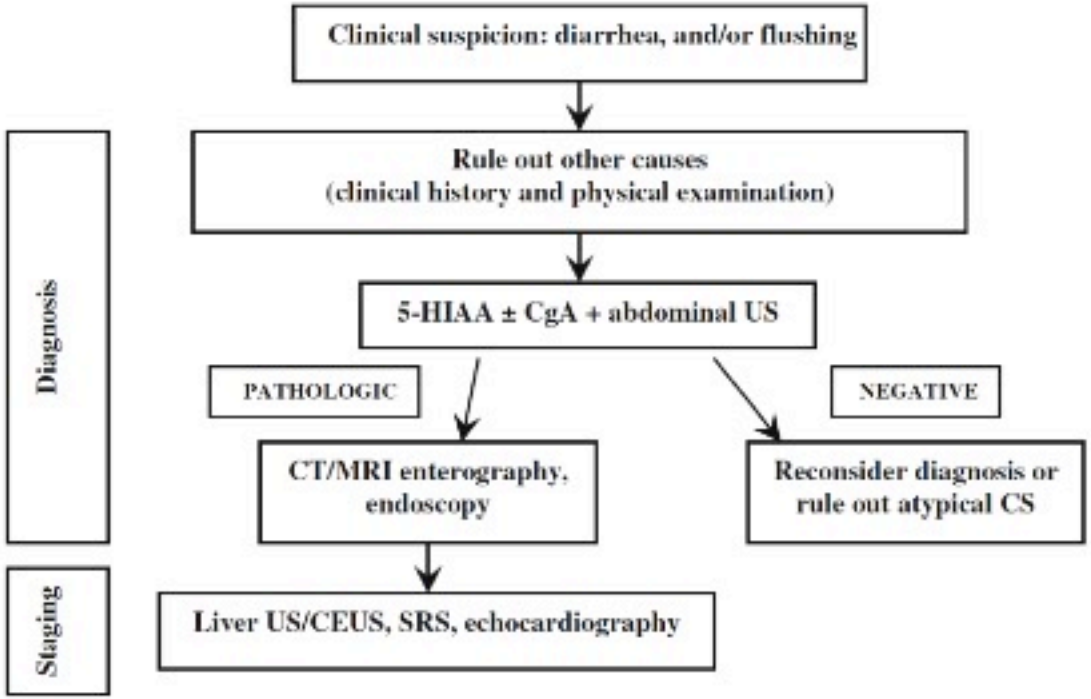
2014

POSITION STATEMENT

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

Franco Grimaldi · Nicola Fazio · Roberto Attanasio · Andrea Frasoldati · Enrico Papini · Francesco Angelini · Roberto Baldelli · Debora Berretti · Sara Bianchetti · Giancarlo Bizzarri · Marco Caputo · Roberto Castello · Nadia Cremonini · Anna Crescenzi · Maria Vittoria Davì · Angela Valentina D'Elia · Antongiulio Faggiano · Stefano Pizzolitto · Annibale Versari · Michele Zini · Guido Rindi · Kjell Öberg

Fig. 9 Diagnostic flow-chart for suspected carcinoid syndrome



2017

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Assessment of Response to Treatment and Follow-Up in Gastroenteropancreatic Neuroendocrine Neoplasms

Franco Grimaldi[1*], Nicola Fazio[2*], Roberto Attanasio[3], Andrea Frasoldati[4], Enrico Papini[5], Nadia Cremonini[6], Maria Vittoria Davì[7], Luigi Funicelli[8], Sara Massironi[9], Francesca Spada[2], Vincenzo Toscano[10], Annibale Versari[11], Michele Zini[4], Massimo Falconi[12], Kjell Öberg[13]

Endocrine, Metabolic & Immune Disorders - Drug Targets, 2017 submitted

SOC Endocrinologia e Malattie del Metabolismo
Nutrizione Clinica

SOS Diabetologia

Endocrinologia

Nutrizione Clinica