VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

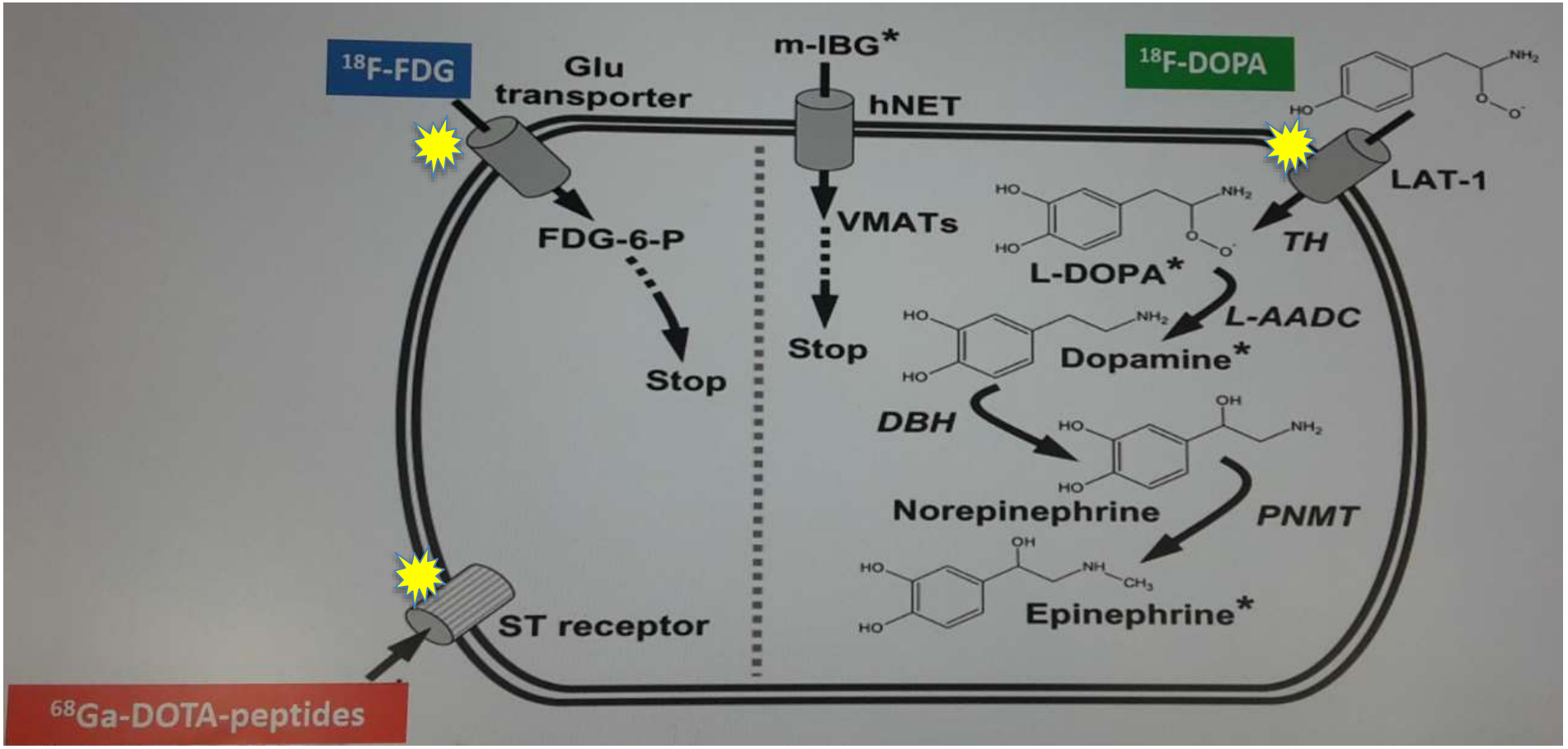
NEN Preceptorship

IEO
Istituto Europeo di Oncologia

Approccio diagnostico-terapeutico (TERAGNOSTICO) al paziente con NET gastro-intestinale Il Medico Nucleare

Chiara M. Grana
Divisione Medicina Nucleare
(Theragnostic Nuclear Medicine)
IRCCS, Istituto Europeo di Oncologia
Milano

Radiofarmaci PET: dove si legano?



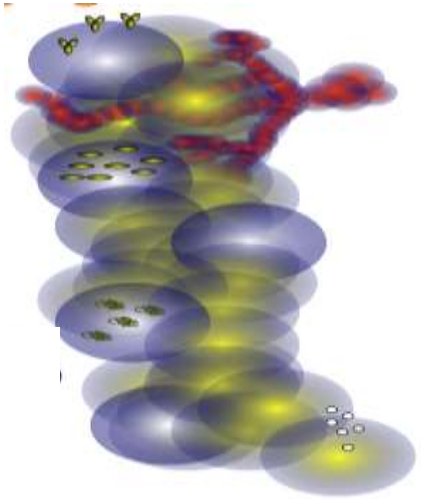
Molecular Imaging

"Molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast"

Weissleder R. *Radiology.* 1999;212(3):609-614.

Aims:

- **Earlier detection and characterization of disease ("molecular signature" prior to irreversible damage)** Ga-68-peptidi
- **Understanding of underlying biology** FDG PET
- **Selection of specific treatment option for targeted therapy** Ga-68-peptidi
- **Concept of THERANOSTICS nuclear medicine/molecular imaging ideally set for this dual role**



Manoharan, EANM 2016

combinazione di agenti per la **diagnosi e terapia** (nello stesso target)

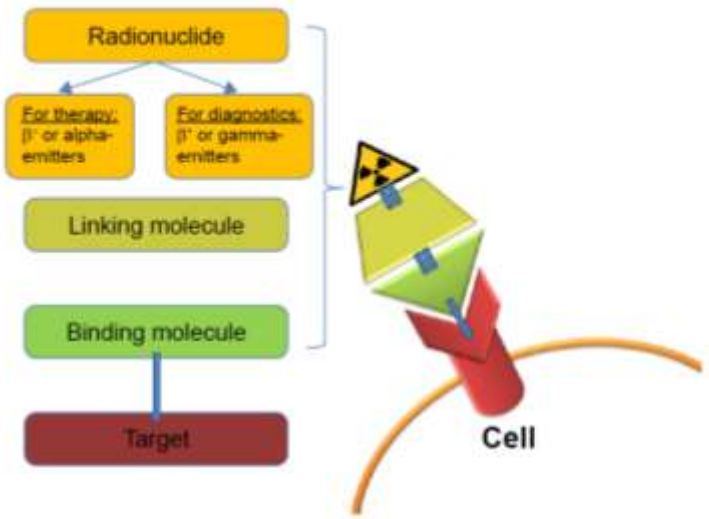


Figure 1 The theranostic principle in nuclear medicine involves combining diagnostic imaging and therapy with the same molecule, which is radiolabeled differently, or administered in other dosages. In case of radioiodine therapy (RAI), the radioisotope (^{131}I or ^{123}I) can be directly mediated by the sodium-iodide symporter in the thyroid cells. In other cases, it can be more complex. The image shows a simplified model of a radiopharmaceutical, which consists of a binding molecule that binds the target, and a linking molecule, which binds the radioisotope. Examples of such theranostic molecules are DOTA-TOC, DOTA-TATE, and PSMA-617.


OncoTargets and Therapy

Theranostics in nuclear medicine practice

This article was published in the following Dove Press journal:
OncoTargets and Therapy
3 October 2017
Number of times this article has been viewed

The link with the receptor and the internalization of the same Peptide, for Imaging & Therapy

^{68}Ga-DOTATATE/TOC → ^{177}Lu-DOTATATE/TOC

^{68}Ga-PSMA → ^{177}Lu-PSMA

$^{131/123}$I → ^{131}I

Eur J Nucl Med Mol Imaging (2014) 41:399–401
DOI 10.1007/s00259-013-2609-2

EDITORIAL

Nothing new under the nuclear sun: towards 80 years of theranostics in nuclear medicine

Frederik A. Verburg · Alexander Heinzel · Heribert Hänscheid · Felix M. Mottaghy · Markus Luster · Luca Giovanella

brain, normal growth, and metabolic balance.[9,31–33] In 1936, Dr Saul Hertz, director of the Thyroid Clinic in Massachusetts (1931–1943), developed the idea of administering radioactive iodine in patients with thyroid diseases. Iodine and external beam radiation were well-known tools in thyroid disease therapy, but the combination of these was a considerably innovative approach. This idea followed a few years of preclinical studies in collaboration with the Massachusetts Institute of Technology (MIT), where the first cyclotron for medical use had been built. The MIT Cyclotron produced 90% iodine-130 (^{130}I, half-life: 12 hours) and 10% iodine-131 (^{131}I, half time: 8 days). Subsequently, on March 31, 1941, Dr Hertz treated the first patient with radioiodine (^{130}I).[21,34,35]

The first radioiodine therapy (RAI) with ^{131}I in patients with thyroid cancer (TC) was undertaken by Seidlin et al in 1946.[36] This group studied the use of RAI in patients with metastatic thyroid carcinomas.[36,37] Seidlin et al also reported one of the first cases of acute myeloid leukemia after repeated RAI treatments.[7]

To date, ^{131}I is still the gold standard for the therapy and diagnosis of differentiated TC.[38] It is a low-cost nuclear reactor product from the neutron bombardment of tellurium-131. ^{131}I combines the characteristics of a beta (β^-, approximately 90% of the radiation, mean: 192 keV, mean tissue penetration: 0.4 mm) and gamma (approximately 10% of the radiation, mean: 383 keV) emitter. In this way, it irradiates

Table 1 Overview of theranostic agents

Theranostic molecule	Iodine	mIBG	SSA	PSMA-ligands	Benzamide/ arylcarboxamide
Target	Thyroid cancer cells	Neurosecretory granules	SSTR, especially the subtype SSTR2	PSMA	Melanin
Planar imaging/ SPECT or	^{131}I and ^{123}I	[^{131}I]I-mIBG, [^{123}I]I-mIBG	SSA labeled with indium-111	[^{123}I]I-MIP-1072	[^{123}I]I-BA52
PET	^{124}I	[^{124}I]I-mIBG	[^{68}Ga]Ga-DOTA-TATE [^{68}Ga]Ga-DOTA-TOC [^{68}Ga]Ga-DOTA-NOC	[^{68}Ga]Ga-PSMA-11 [^{68}Ga]Ga-PSMA-617	[^{18}F]F-ICF15002
Therapeutic agent	^{131}I	[^{131}I]I-mIBG	[^{177}Lu]Lu-DOTA-TATE [^{177}Lu]Lu-DOTA-TOC [^{90}Y]Y-DOTA-TOC [^{90}Y]Y-DOTA-TATE	[^{177}Lu]Lu-J591 [^{90}Y]Y-J591 [^{131}I]I-MIP-1095 [^{177}Lu]Lu-PSMA-617	[^{131}I]I-BA52 [^{131}I]I-ICF15002
Indication	Thyroid cancer	Neuroblastomas, pheochromocytomas, paragangliomas, medullary thyroid carcinomas, and other NEN	NEN, especially GEP-NEN	Metastatic prostate cancer	Metastatic melanoma

Abbreviations: mIBG, metaiodobenzylguanidine; SSA, somatostatin analogs; SSTR, somatostatin receptors; NEN, neuroendocrine neoplasia; GEP, gastroenteropancreatic system; SPECT, single photon emission computed tomography; PET, positron emission tomography.

I Tumori neuroendocrini…..

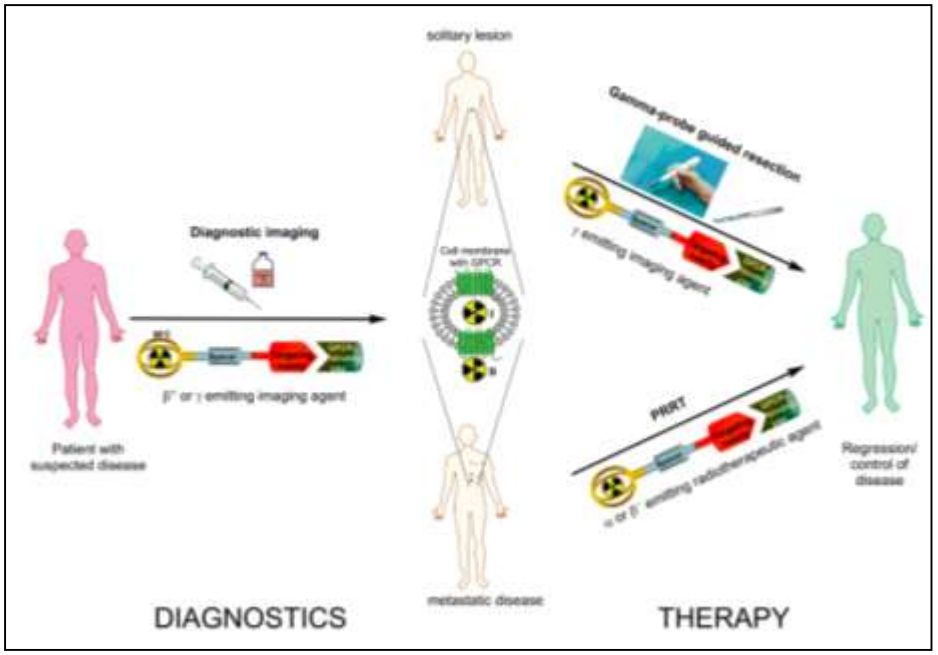
Hanno reso grande la Teragnostica

La Teragnostica ha valorizzato

I Tumori neuroendocrini (intestinali)

Radiofarmaci nella diagnosi e nella terapia dei NET

NET: presenza dei recettori → captazione dei peptidi



diagnosi
terapia

pharmaceuticals

Review

Current Status of Radiopharmaceuticals for the Theranostics of Neuroendocrine Neoplasms

Melpomeni Fani [1,*], Petra Kolenc Peitl [2] and Irina Velikyan [3]

1 Division of Radiopharmaceutical Chemistry, University Hospital of Basel, 4031 Basel, Switzerland; melpomeni.fani@usb.ch
2 Department of Nuclear Medicine, University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia; petra.peitl@kclj.si
3 Department of Medicinal Chemistry, Uppsala University, 751 23 Uppsala, Sweden; irina.velikyan@akademiska.se
* Correspondence: melpomeni.fani@usb.ch; Tel.: +41-61-556-58-91; Fax: +41-61-265-49-25

Academic Editor: Klaus Kopka
Received: 7 February 2017; Accepted: 9 March 2017; Published: 15 March 2017

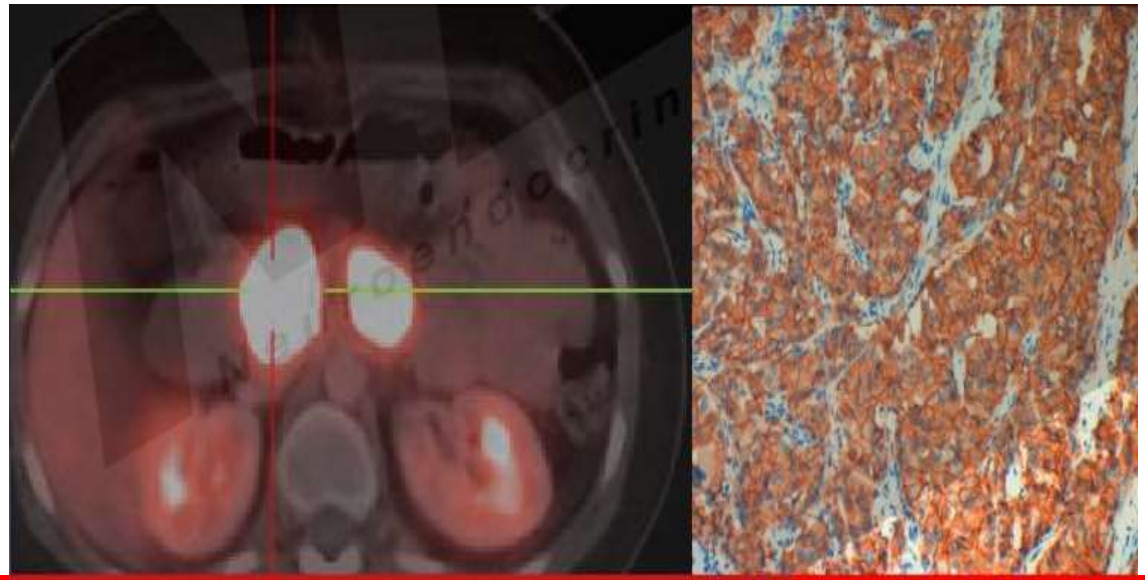
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-1846-5

Eur J Nucl Med Mol Imaging 2011 Sep;38(9):1659-68

Somatostatin receptor imaging using SUV on Ga-68 SSTR PET/CT results inaccurate estimation of the receptor density

Molecular imaging with ^{68}Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours

Daniel Kaemmerer · Luisa Peter · Amelie Lupp · Stefan Schulz · Jörg Sänger · Vikas Prasad · Harshad Kulkarni · Sven-Petter Haugvik · Merten Hommann · Richard Paul Baum

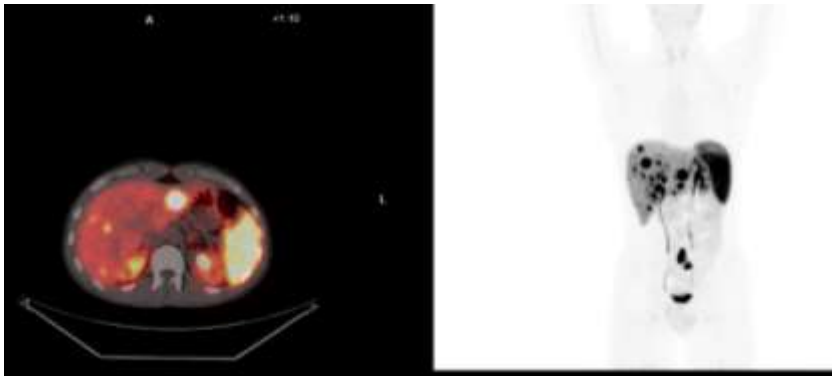


Ga-68 DOTA-SSTR PET/CT provides *in vivo* histopathology!

Imaging molecolare nei NET: obiettivi

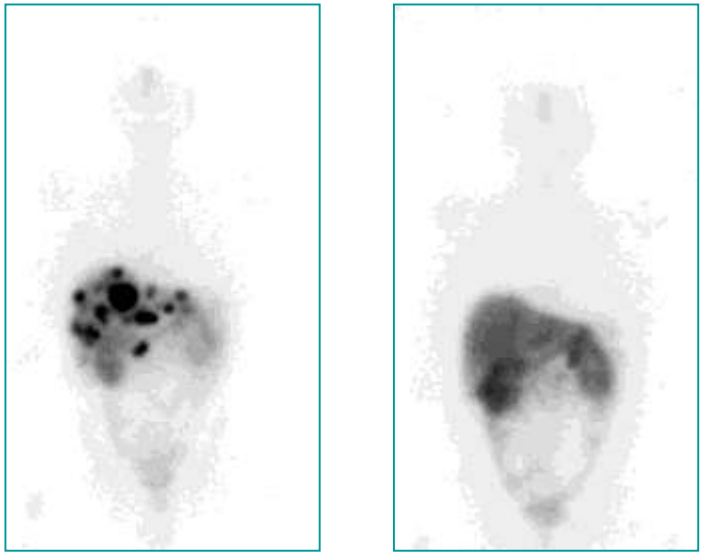
Staging – localization of primary tumours and detection of metastatic disease

Restaging – follow-up of patients with known disease to detect residual, recurrent or progressive disease



Patient selection for PRRT
Virgolini et al. Eur J Nucl Med Mol Imaging (2010) 37:2004–2010

Monitoring response to therapy (particularly PRRT) – is proposed but still needs to be further assessed and established as the change in receptor status does not necessarily indicate Treatment response and dedifferentiation with loss of receptors must be taken into account.



Dosimetry – post-PRRT dosimetry studies can be performed but this is limited to certain centres

Modifica del trattamento

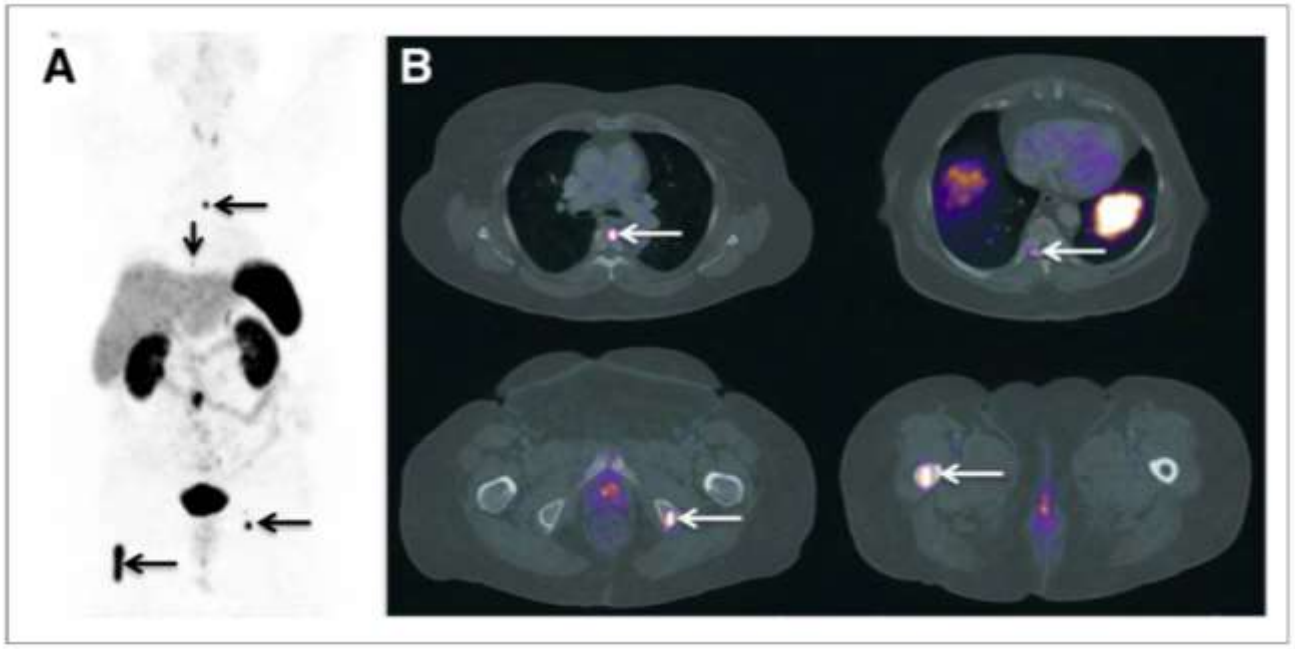


FIGURE 3. Upstaging of patient with history of small intestine NEN and 6.5-cm lesion within right proximal femur with benign appearance at prior MRI. (A) DOTATATE maximum-intensity-projection image revealed multiple mesenteric and pelvic, as well as multiple unexpected osseous, metastases (arrows). (B) On axial PET/CT, the unexpected soft-tissue and bone metastases were detected in more detail (arrows). Intended treatment was converted from surgery and octreotide to surgery, octreotide, and selective radiotherapy of bone metastases. (Adapted from (66).)

J Nucl Med 2017; 58:1718–1726

CONTINUING EDUCATION

Current Concepts in ^{68}Ga-DOTATATE Imaging of Neuroendocrine Neoplasms: Interpretation, Biodistribution, Dosimetry, and Molecular Strategies

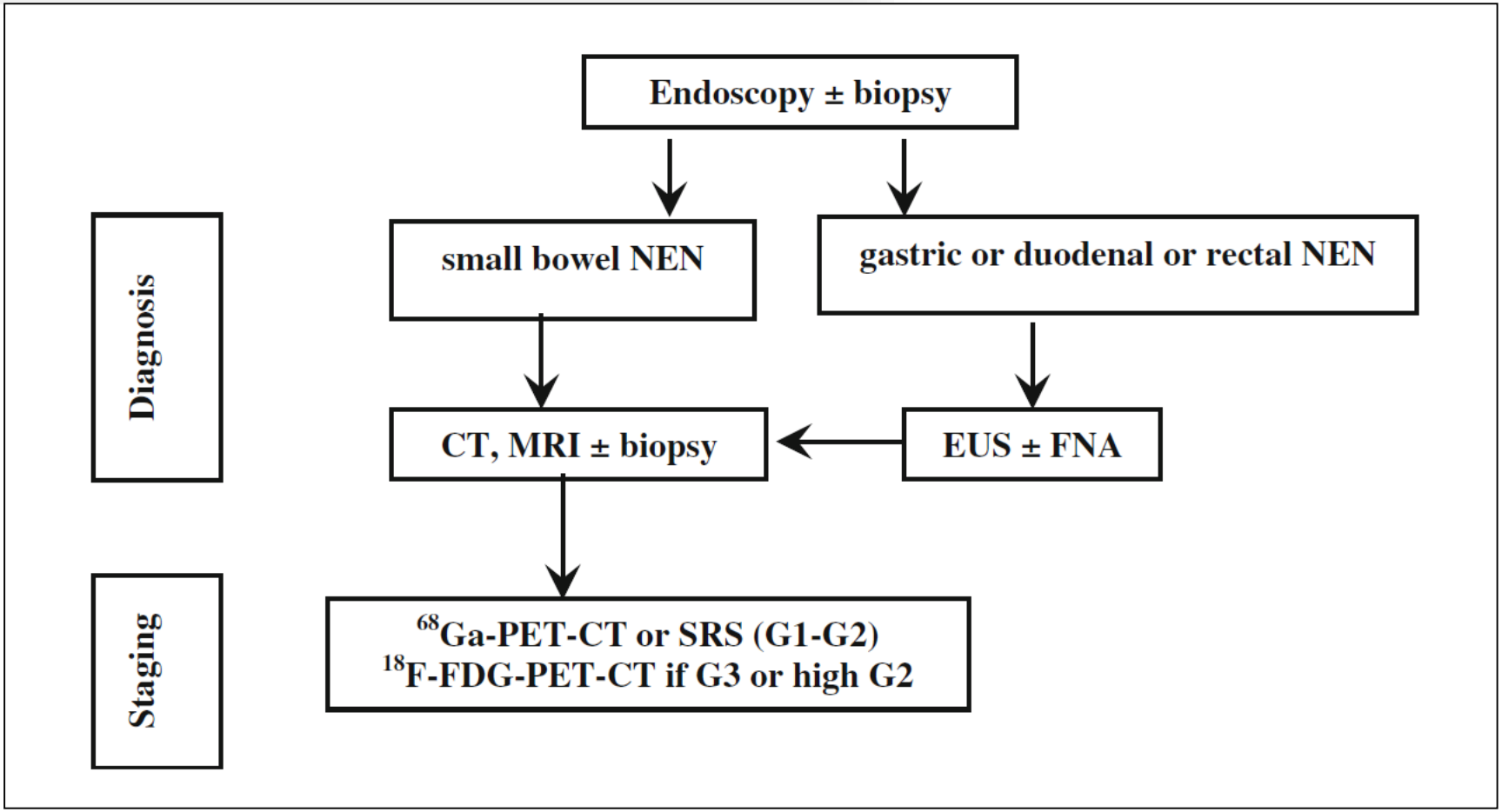
Lisa Bodei[1], Valentina Ambrosini[2], Ken Herrmann[3,4], and Irvin Modlin[5]

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 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



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

Attuali esami MNU

Scintigrafia convenzionale (Octreoscan; ^{111}In-pentetreotide)

PET/CT

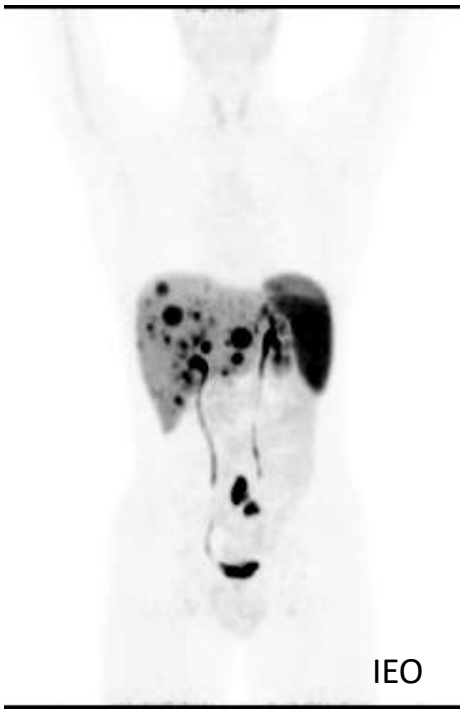
^{68}Ga-DOTATOC

^{18}F-DOPA

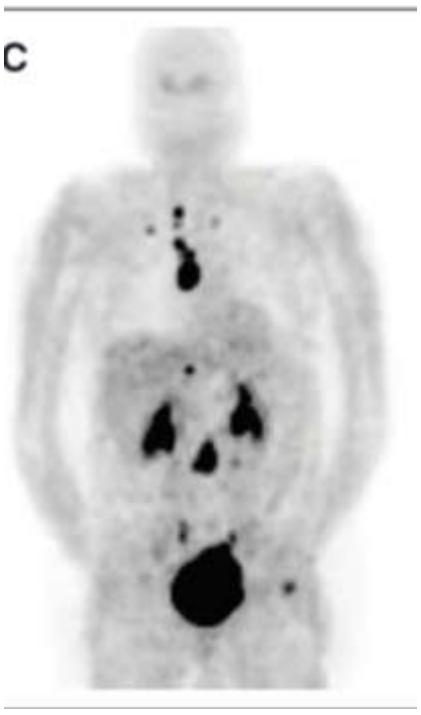
^{11}C-HTP

P-NET

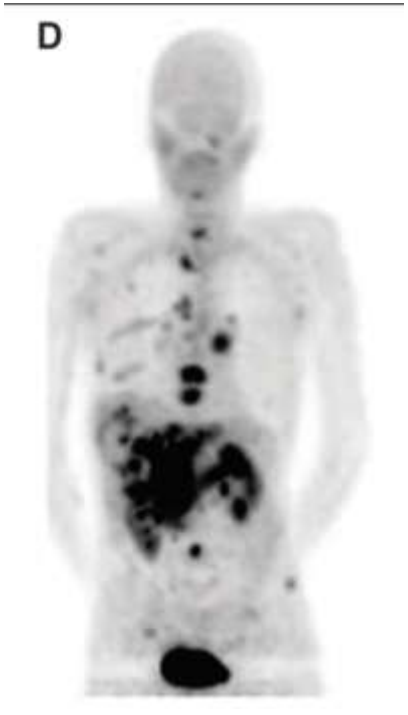
SI-NET



SI-NET



P-NET



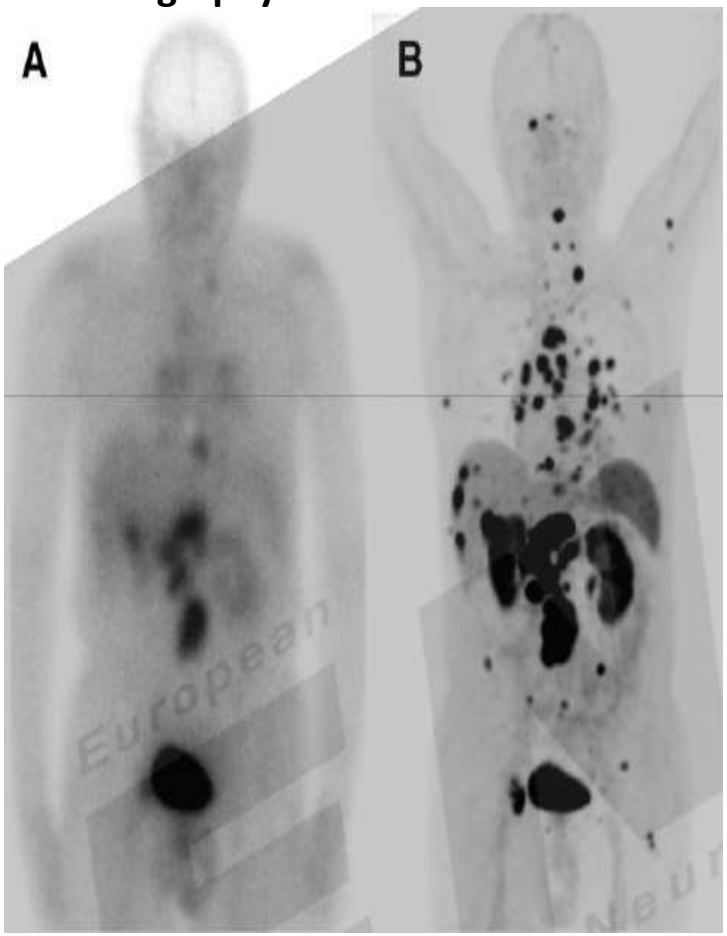
Paganelli et al, E J Nucl Med, 2001

Koopmans et al, JCO 2008

SSTR scintigraphy using SPECT with In-111 pentetreotide

In-111 pentetreotide SSTR scintigraphy

Ga-68 DOTATATE PET MIP



Patient with metastatic low-grade cecal NEN

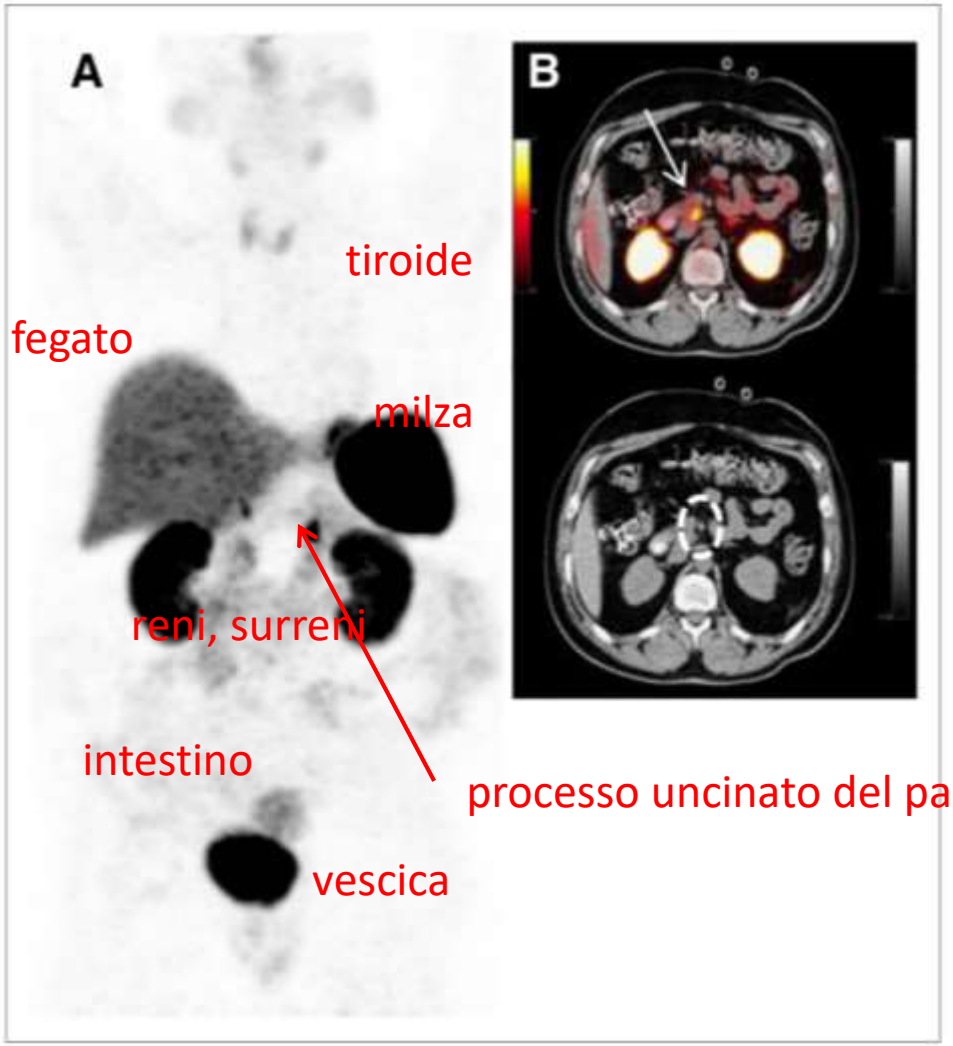
Deroose et al. JNM 2016.

Table 1. Advantages of SSTR PET/CT Over Conventional Scintigraphy.
↑↑ sensitivity: <5mm lesion characterization
↑ specificity
Fully tomographic (3D)
Multi-slice CT near universal
↓ uptake time: 45-60 min vs. 24-48 hrs
↓ imaging time: 12-15 min vs. 45-60 min
Quantitative
↓↓ radiation dose to patient
In-house on demand production

Hofman et al. Discovery Med 2012

PET/CT con Ga-68-peptidi, immagine normale

(K05)
Pancreatic Uptake in Ga-68 DOTATATE PET in a Series of Small Bowel Neuroendocrine Neoplasms: Metastasis, New Primary or Just Physiological Uptake?



Captazione fegato e milza → SSA

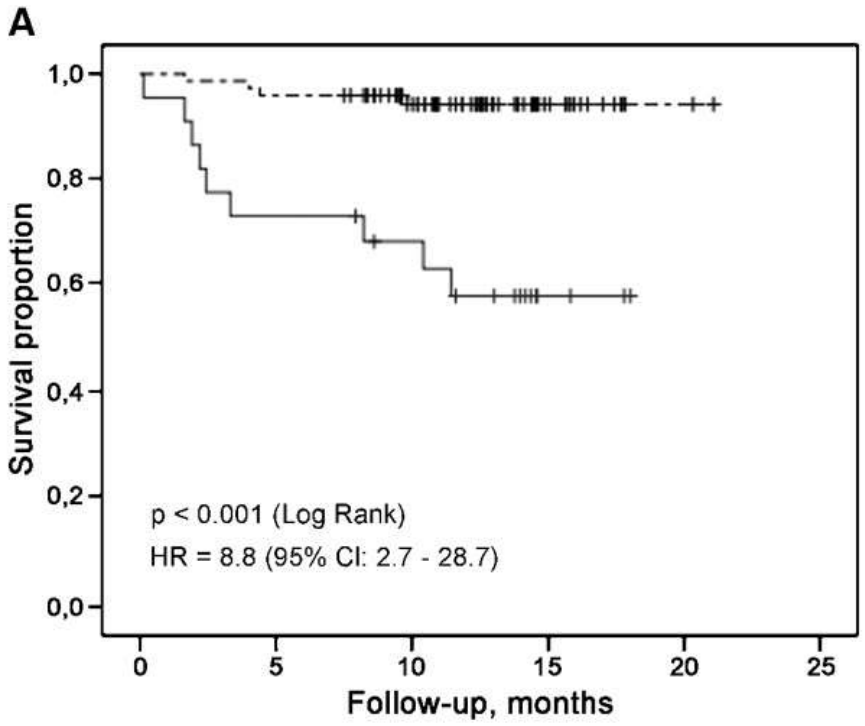
J Nucl Med 2017; 58:1718–1726

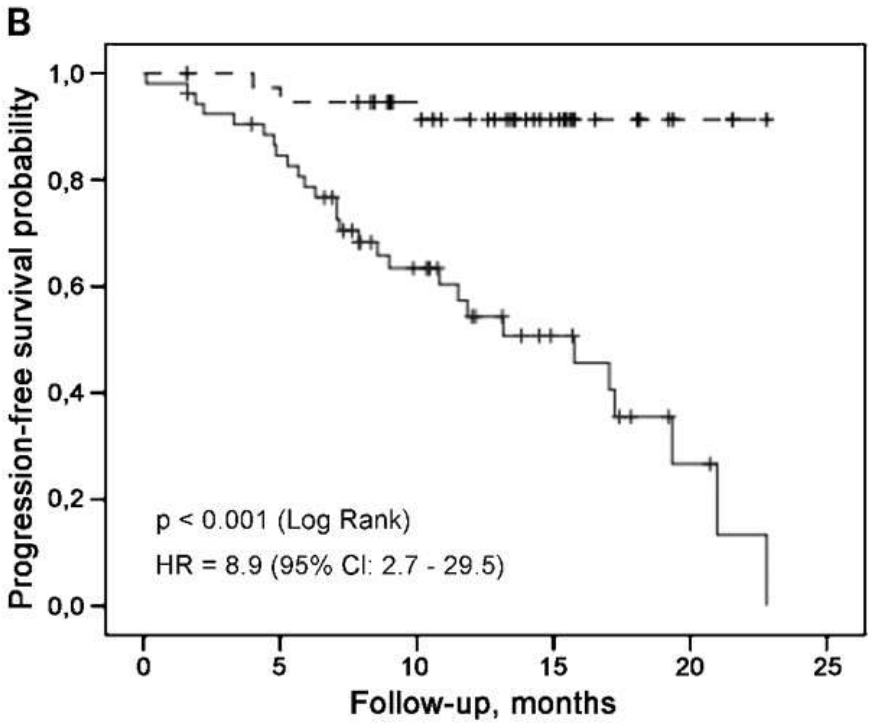
CONTINUING EDUCATION

Current Concepts in ^{68}Ga-DOTATATE Imaging of Neuroendocrine Neoplasms: Interpretation, Biodistribution, Dosimetry, and Molecular Strategies

Lisa Bodei[1], Valentina Ambrosini[2], Ken Herrmann[3,4], and Irvin Modlin[5]

^{18}F-FDG:
dobbiamo parlarne ancora?



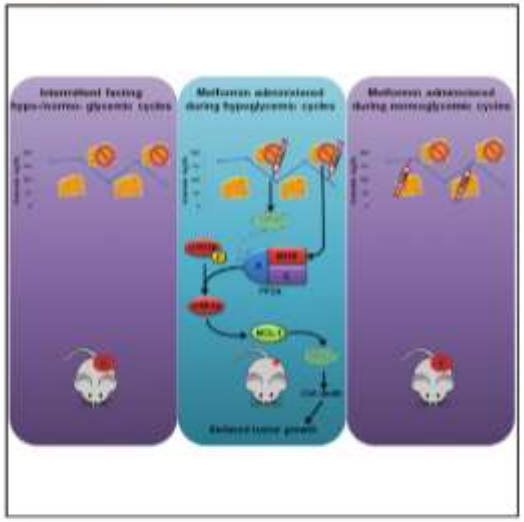


Binderup T et al. Clin Cancer Res 2010

Cancer Cell

Combination of Hypoglycemia and Metformin Impairs Tumor Metabolic Plasticity and Growth by Modulating the PP2A-GSK3β-MCL-1 Axis

Graphical Abstract



Authors

Mohamed Elgendy, Marco Cirò, Amir Hosseini, ..., Wolfram Weckwerth, Marco Foiani, Saverio Minucci

Correspondence

mohamed.elgendy@univie.ac.at (M.E.), saverio.minucci@ieo.it (S.M.)

In Brief

Elgendy et al. show that metformin administered during the fasting period synergizes with 24-h feeding/fasting cycles to suppress tumor growth. Inhibition of CIP2A by metformin and upregulation of B56δ by low glucose activates PP2A toward GSK3β leading t reduced pro-survival protein MCL-1 and cell death.

Highlights

- Metformin plus fasting-induced hypoglycemia synergistically reduces tumor growth
- PP2A-GSK3β-MCL-1 axis mediates the synergistic cytotoxicity of the combination
- Simultaneous CIP2A inhibition and B56δ upregulation dictate combination specificity

Tumor cells may adapt to metabolic challenges by alternating between glycolysis and oxidative phosphorylation (OXPHOS). To target this metabolic plasticity, we combined intermittent fasting, a clinically feasible approach to reduce glucose availability, with the OXPHOS inhibitor metformin. In mice exposed to 24-h feeding/fasting cycles, metformin impaired tumor growth only when administered during fasting-induced hypoglycemia. Synergistic anti-neoplastic effects of the metformin/hypoglycemia combination were mediated by glycogen synthase kinase 3β (GSK3β) activation downstream of PP2A, **leading to a decline in the pro-survival protein MCL-1, and cell death.** Mechanistically, specific activation of the PP2A-GSK3β axis was the sum of metformin-induced inhibition of CIP2A, a PP2A suppressor, and of upregulation of the PP2A regulatory subunit B56δ by low glucose, leading to an active PP2A-B56δ complex with high affinity toward GSK3β.

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Peptide receptor radionuclide therapy for patients with advanced pancreatic neuroendocrine tumors

John Ramage[a], Boris G. Naraev[b], Thorvardur R. Halfdanarson[c,*]

[a] Kings Health Partners Neuroendocrine Centre, London, UK
[b] Banner MD Anderson Cancer Center, Gilbert, AZ, USA
[c] Mayo Clinic Cancer Center, Rochester, MN, USA

PET/CT ^{18}F-FDG

PET/CT ^{68}Ga-DOTA-peptide

…less uptake occurs on SSTR imaging of G3 tumors, and for this reason G3 NEC are generally imaged with 18F-FDG PET.

Use of 18F-FDG PET has also been proposed alongside Gallium-68 SSTR imaging, in G2 NET with a Ki-67 >10%, for its role in identifying patients with tumors that are more likely to progress.

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2017; 7(5): 1149-1158. doi: 10.7150/thno.18068

Research Paper

Dual Somatostatin Receptor/FDG PET/CT Imaging in Metastatic Neuroendocrine Tumours: Proposal for a Novel Grading Scheme with Prognostic Significance

David LH Chan, Nick Pavlakis, Geoffrey P Schembri, Elizabeth J Bernard, Edward Hsiao, Aimee Hayes, Tristan Barnes, Connie Diakos, Mustafa Khasraw, Jaswinder Samra, Enid Eslick, Paul J Roach, Alexander Engel, Stephen J Clarke and Dale L Bailey

Table 1. The categories of NETPET grading descriptors (the colour scheme corresponds to the colours assigned in the flowchart) with green indicating that PRRT may be a potential therapy, amber indicating that PRRT may or may not be useful as a mono-therapy, and red indicating that PRRT alone is unlikely to be an effective therapy).

NETPET Grade	SSTRI scan status	FDG scan status	Description of target lesion – the single lesion most FDG avid relative to SSTRI (no. of lesions with this characteristic)	Secondary Characteristic
P0	-	-	N/A	-
P1	+	-	N/A	-
P2a	+	+	FDG less avid than SSTRI (1-2 lesions)	-
P2b	+	+	FDG less avid than SSTRI (3+ lesions)	-
P3a	+	+	FDG equivalent to SSTRI (1-2 lesions)	-
P3b	+	+	FDG equivalent to SSTRI (3+ lesions)	-
P4a	+	+	FDG greater than SSTRI (1-2 lesions)	-
P4b	+	+	FDG greater than SSTRI (3+ lesions)	-
P4b	+	+	FDG +ve / SSTRI –ve (1 lesion)	With 1 additional lesion FDG > SSTRI
P5	+	+	FDG +ve / SSTRI –ve (1 lesion)	With 2+ additional lesions FDG > SSTRI
P5	+	+	FDG +ve / SSTRI –ve (2+ lesions)	
P5	-	+	N/A	

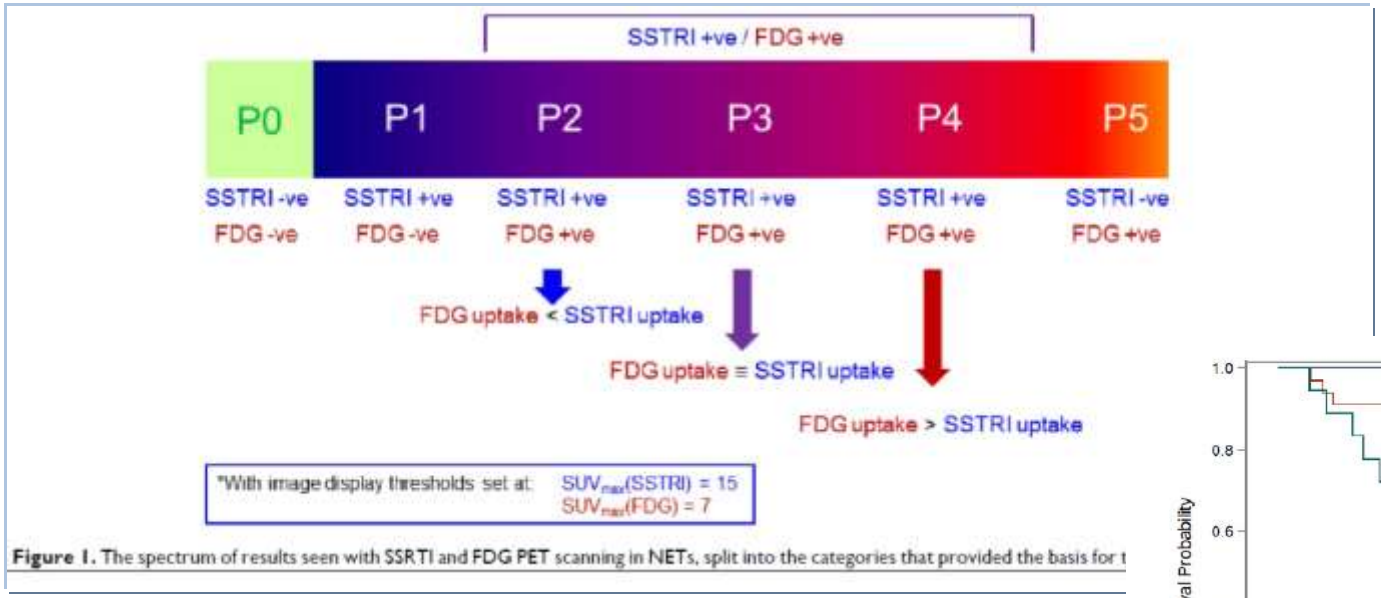


Figure 1. The spectrum of results seen with SSRTI and FDG PET scanning in NETs, split into the categories that provided the basis for t

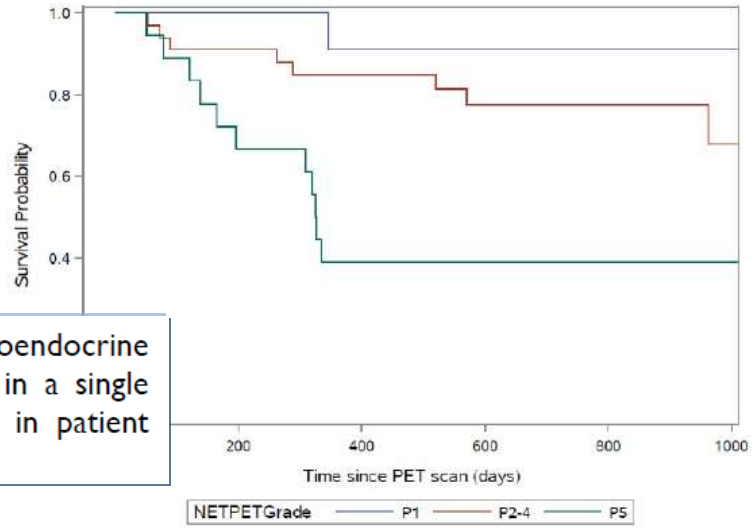


Figure 5. Kaplan-Meier curves for the NETPET subjects grouped as P1 (N=11), P2-P4 (N=33) and P5 (N=18).

Conclusions: The NETPET grade has promise as a prognostic imaging biomarker in neuroendocrine tumours. It permits the capturing of the complexity of dual radiotracer imaging in a single parameter which describes the subjects' disease and is readily amenable to use in patient management and further research.

F-18 Fluorodihydroxyphenylalanine (18F-DOPA)

F-18 FDOPA PET/CT has been successfully used for NEN imaging.

Once internalized via the sodium-independent system L, **F-18 FDOPA is decarboxylated to F-18-dopamine, transported, and stored in cellular neurosecretory granules.**

High sensitivity in low-grade ileal NEN, and can be helpful for tumor localization and staging.

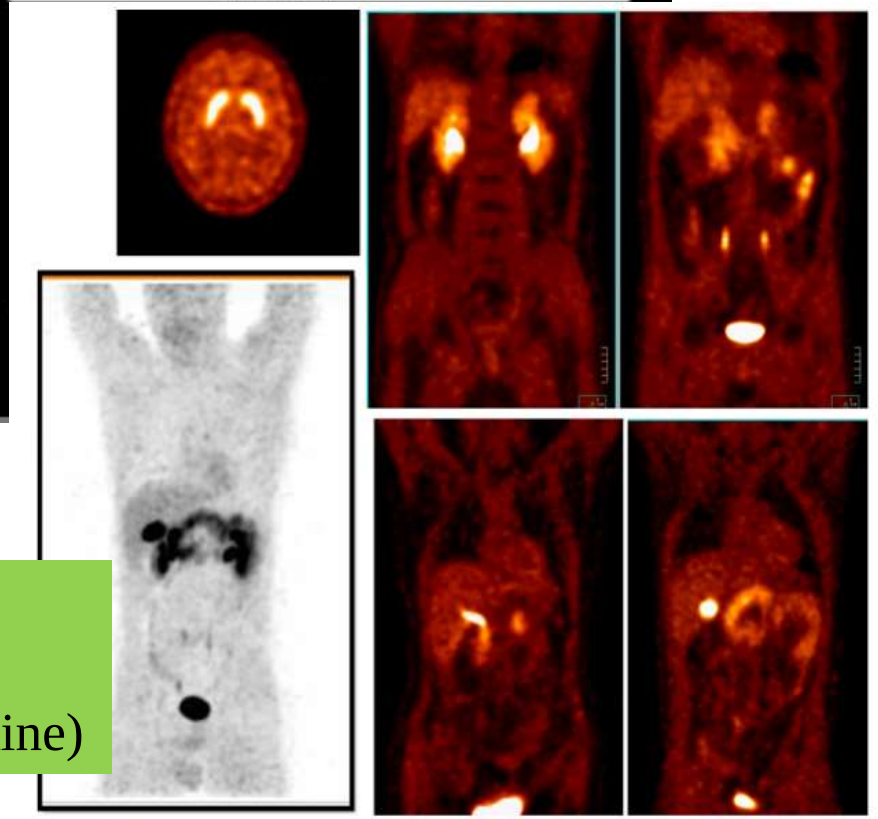
The increased activity of aromatic L-amino acid decarboxylase, involved in tumoral biosynthesis of serotonin, explains this high sensitivity in carcinoids.

It has low sensitivity (25%) in high-grade GEP NEN and NETs arising from the foregut and hindgut.

Deroose et al. JNM 2016

P-NET imaging: PET with ^{18}F-DOPA

Locally advanced P-NET

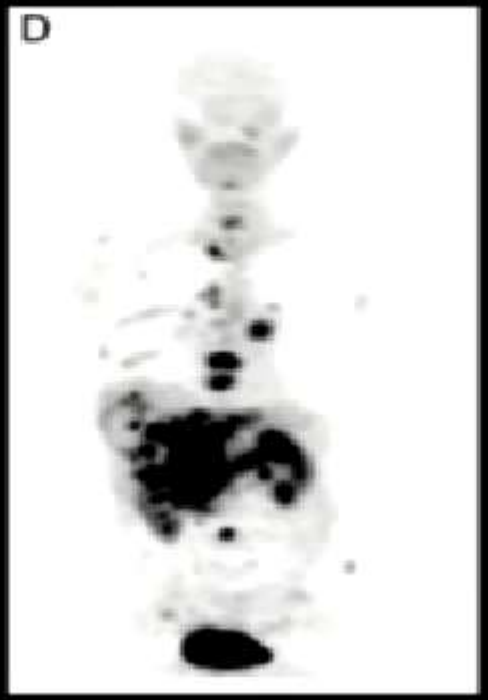


Utile quando SSR imaging negativo
Alta sns nei "carcinoidi"
(metabolismo elevato delle varie amine)

Fig. 1. Normal distribution of ^{18}F-DOPA including high activity in the urinary excretion system as well as high accumulation in the gallbladder and bile ducts; intermediate or low ^{18}F-DOPA uptake is seen in the striatum, myocardium, liver and pancreas; only minimal uptake is evident in the normal adrenal medulla.

P-NET imaging: PET with ^{11}C-HTP

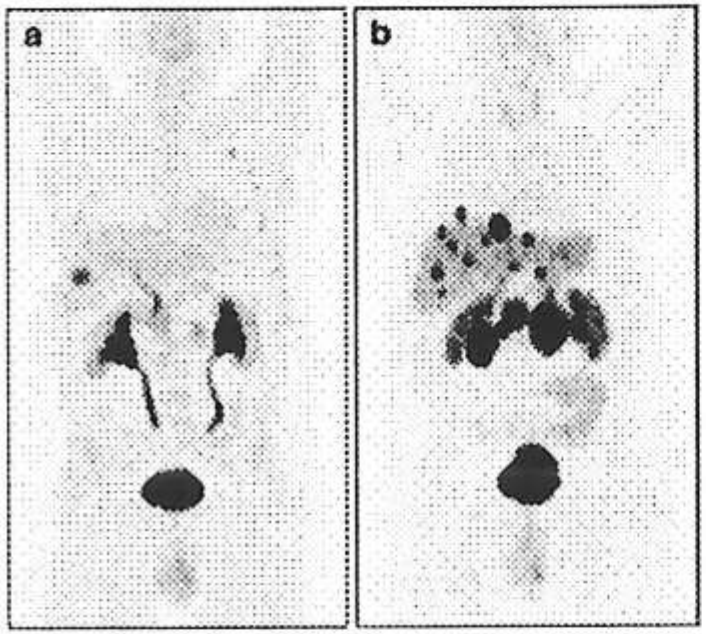
P-NET with diffuse liver, lymph node and skeletal metastases



MIP image

^{11}C-5-HTP è un precursore della serotonina → nei NET
Utile quando SSR imaging negativo
Alta sns nel pancreas (non c'è saturazione di serotonina)
→Captazioni fisiologiche (pancreas, vie urinarie);
→ premedicazione con Carbidopa (aum uptake)
→ con ciclotrone

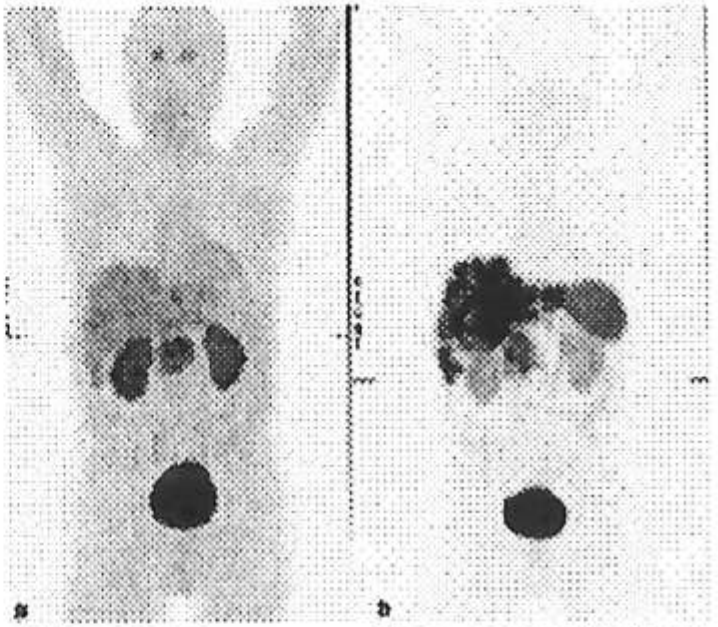
^{68}Ga-DOTA-peptides or ^{18}F-DOPA in NETs?



^{18}F-DOPA ^{68}Ga-DOTANOC

^{68}Ga-DOTANOC is accurate and offers advantages compared to ^{18}F-DOPA (more lesions and primary location; 13 pts)

Ambrosini V. et al. Eur J Nucl Med Mol Imaging 2008



^{18}F-DOPA ^{68}Ga-DOTATATE

^{68}Ga-DOTATATE clearly superior to ^{18}F-DOPA (96 vs 56% sensitivity), which could be a second choice

Haug A. et al. Eur J Nucl Med Mol Imaging 2009

^{68}Ga-PET gives therapeutic indications!

SRI: correlazione con la risposta alla PRRT

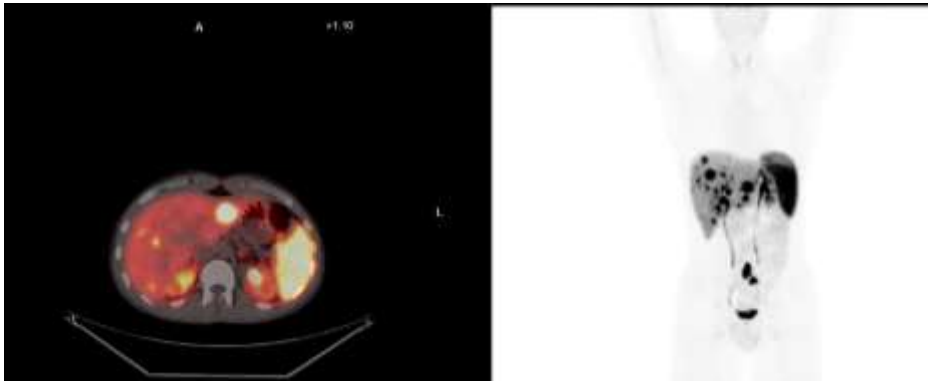
Ga-68-SSA-PET

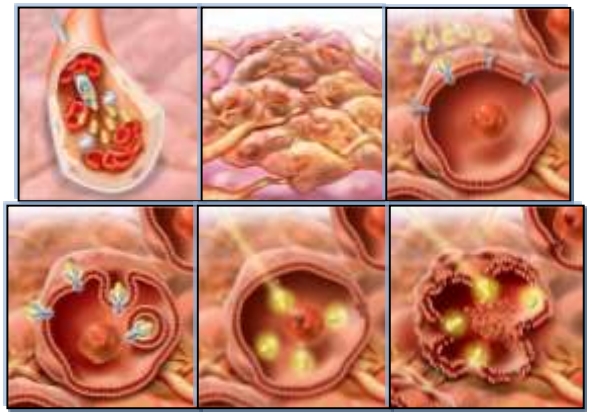
Elevata concentrazione
di radioattività

Alta dose al tumore

Captazione
elevata

Risposta



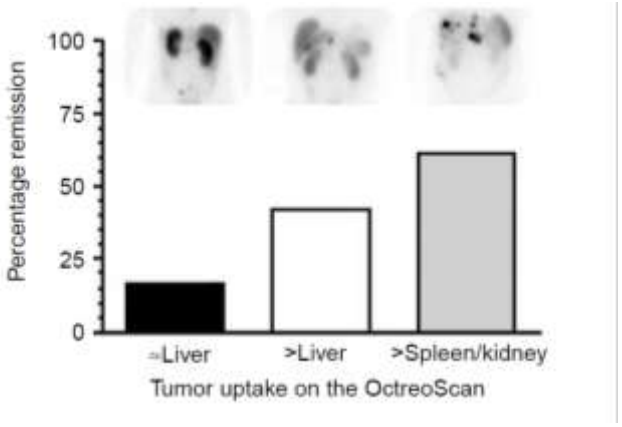


REVIEW

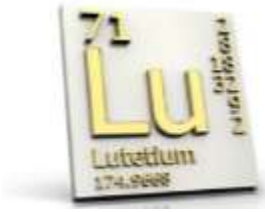
Endocrine-Related Cancer (2010) **17** R53–R73

Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors

Dik J Kwekkeboom[1], Boen L Kam[1], Martijn van Essen[1], Jaap J M Teunissen[1], Casper H J van Eijck[2], Roelf Valkema[1], Marion de Jong[1], Wouter W de Herder[3] and Eric P Krenning[1]



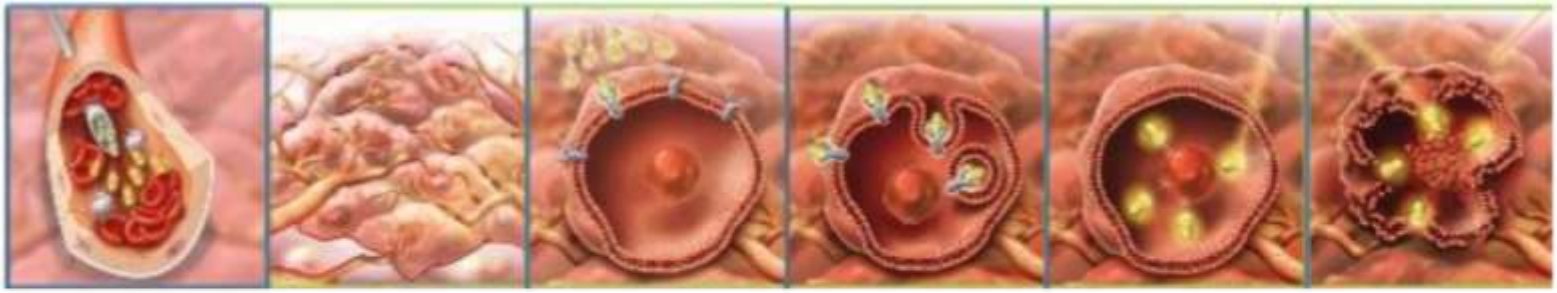
Perché il ^{177}Lutezio nella terapia ?



"Lutetium", un elemento che fa parte della famiglia delle 17 terre rare (dei quali 15 lantanidi) dal nome Latino di Parigi (Lutetia) poiché il suo scopritore, Georges Urbain, fu professore alla Sorbonne nel 1907 al tempo della sua scoperta.

Molecular Formula:
177Lu
Monoisotopic mass:
176.943756 Da
Physical Half Life:
6.65 days

Radiation ß-(Emax in KeV):
175 (12,3%) 380 (9%) 497 (78,7%)
y (E in KeV): 208 (11%) 113 (6%)
Specific activity:
>500 GBq/mg
Activity concentration:
80 GBq/ml at activity reference time



Somministrazione endovenosa

Captazione e concentrazione nel sito NET

Legame con i recettori (SSTR2) sovraespressi nei NET

Internaliz zazione nelle cellula

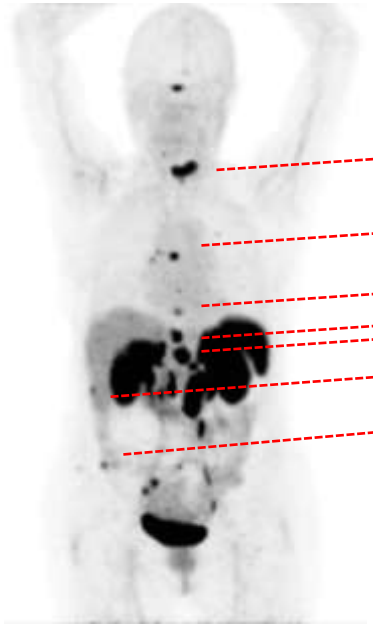
Rilascio delle dose di radiazioni beta

Effetto radioterapico tramite il danno delle strutture cellulari «critiche»

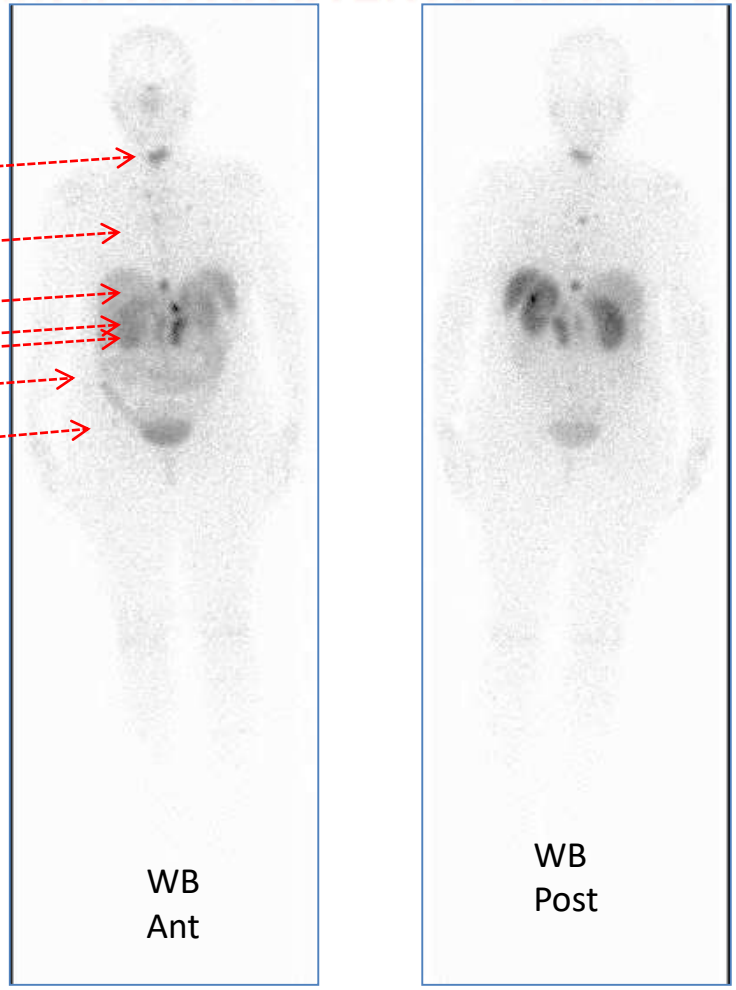
^{68}Ga-DOTATOC PET vs. ^{177}Lu-DOTATATE/TOC

Liver, LN and bone mets from ileal G1 NET (Ki67 <1%). Status post ileocolectomy; SSA ongoing

^{68}Ga-DOTATOC



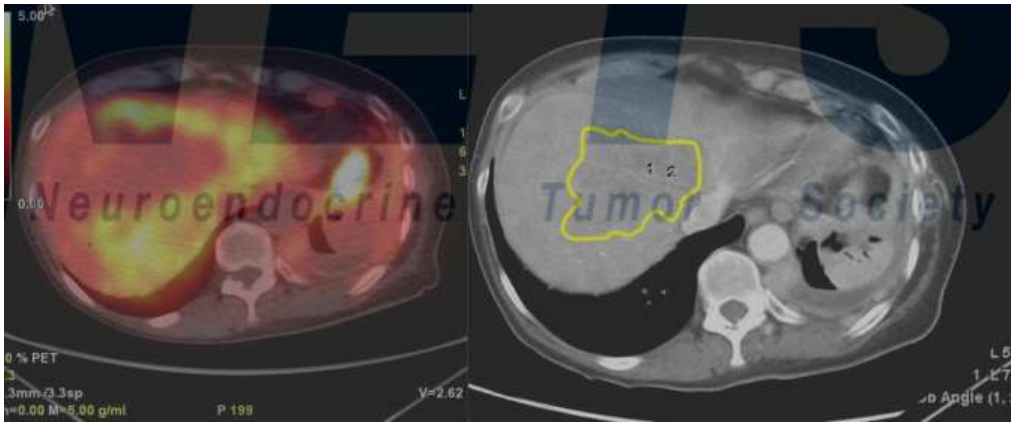
^{177}Lu-DOTATATE/TOC scan (4.5 GBq)



PRRT sempre indicata?

carcinoide atipico bronchiale,

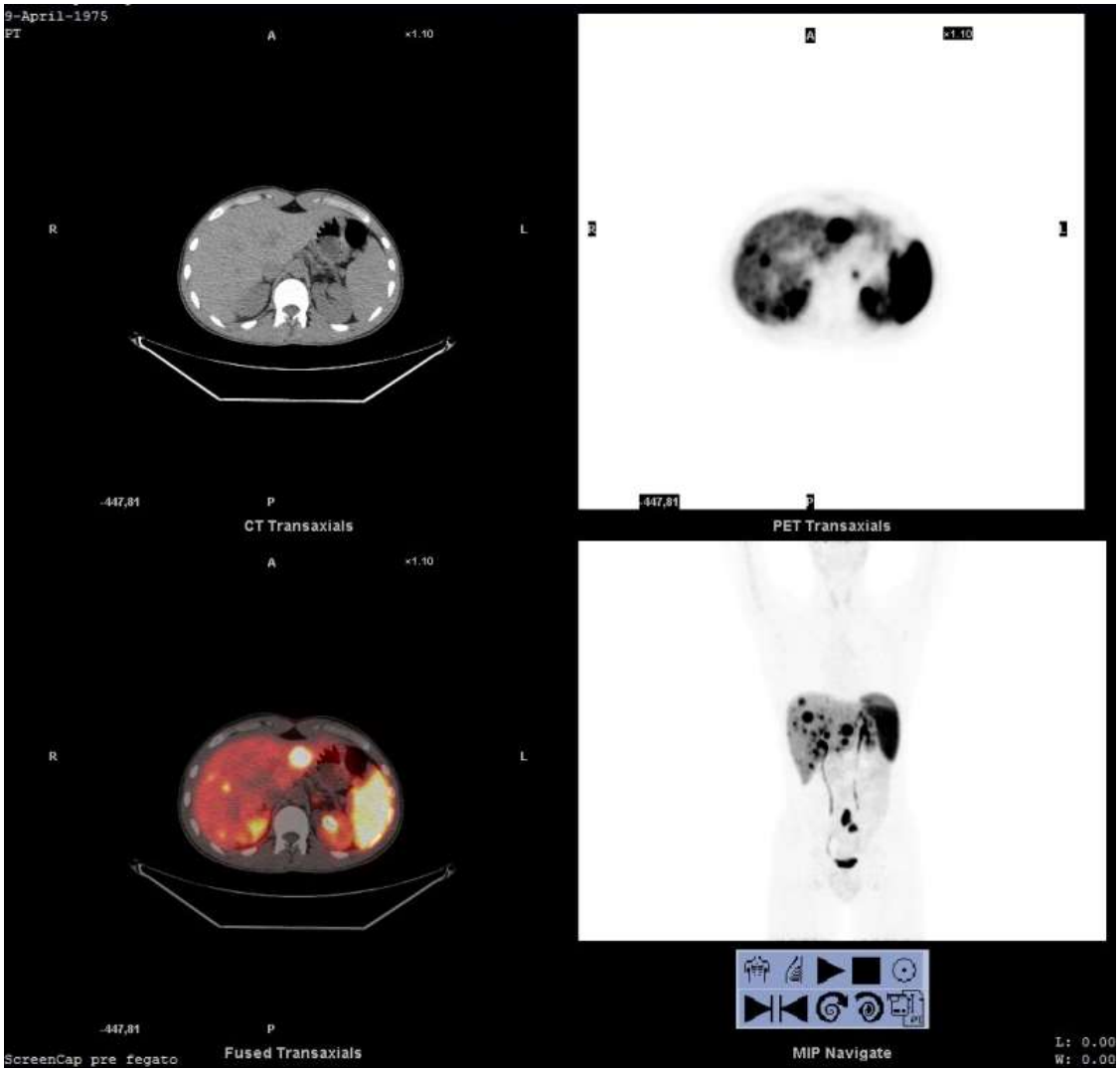
mts ossee e ln, epatiche



No uptake, no PRRT

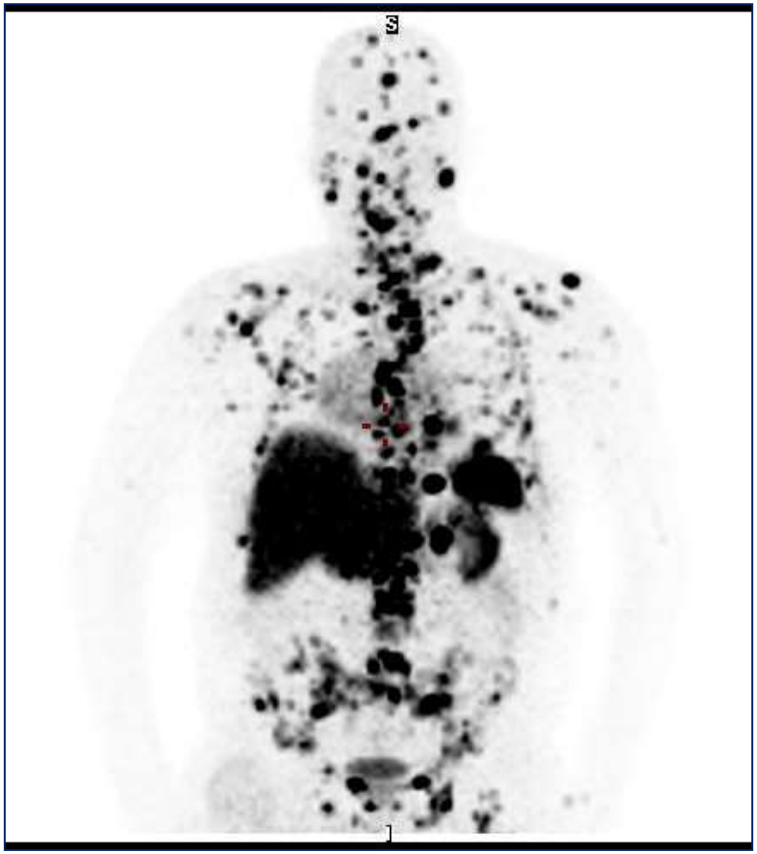
Courtesy of ENETS

Intensa captazione; ok per PRRT



T, SUV 28,2

Captazione intensa: è sempre indicata la PRRT?



ECOG 2, perdita peso

compromissione funzionalità ematologica basale

Dosimetria sfavorevole sull’osso

La storia autorizzativa della PRRT (Lutathera)

IAEA International Atomic Energy Agency

EANM

SNMMI Society of Nuclear Medicine and Molecular Imaging

FDA U.S. Food & Drug Administration

AIOM

ENETS European Neuroendocrine Tumor Society

SERIE GENERALE

Anno 159° - Numero 245

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Sabato, 20 ottobre 2018

SI PUBBLICA TUTTI I GIORNI NON FESTIVI

SERIE GENERALE

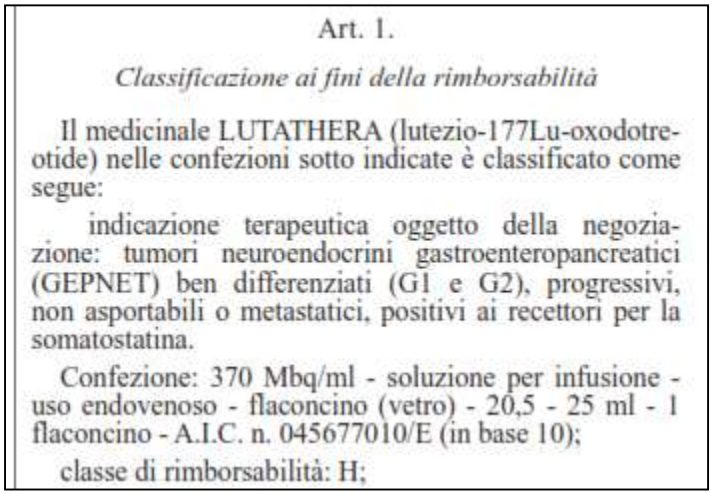
Anno 160° - Numero 75

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Venerdì, 29 marzo 2019

SI PUBBLICA TUTTI I GIORNI NON FESTIVI



Art. 1.

Classificazione ai fini della rimborsabilità

Il medicinale LUTATHERA (lutezio-177Lu-oxodotreotide) nelle confezioni sotto indicate è classificato come segue:

indicazione terapeutica oggetto della negoziazione: tumori neuroendocrini gastroenteropancreatici (GEPNET) ben differenziati (G1 e G2), progressivi, non asportabili o metastatici, positivi ai recettori per la somatostatina.

Confezione: 370 Mbq/ml - soluzione per infusione - uso endovenoso - flaconcino (vetro) - 20,5 - 25 ml - 1 flaconcino - A.I.C. n. 045677010/E (in base 10);

classe di rimborsabilità: H;

RegioneLombardia

Regione Lombardia - Giunta
DIREZIONE GENERALE WELFARE
PROGRAMMAZIONE POLO OSPEDALIERO
FARMACO, DISPOSITIVI E HTA

Protocollo G1.2019.0015603 del 24/04/2019

AI DIRETTORI GENERALI ATS

AI DIRETTORI GENERALI ASST

AI DIRETTORI GENERALI FONDAZIONI IRCCS DI DIRITTO PUBBLICO

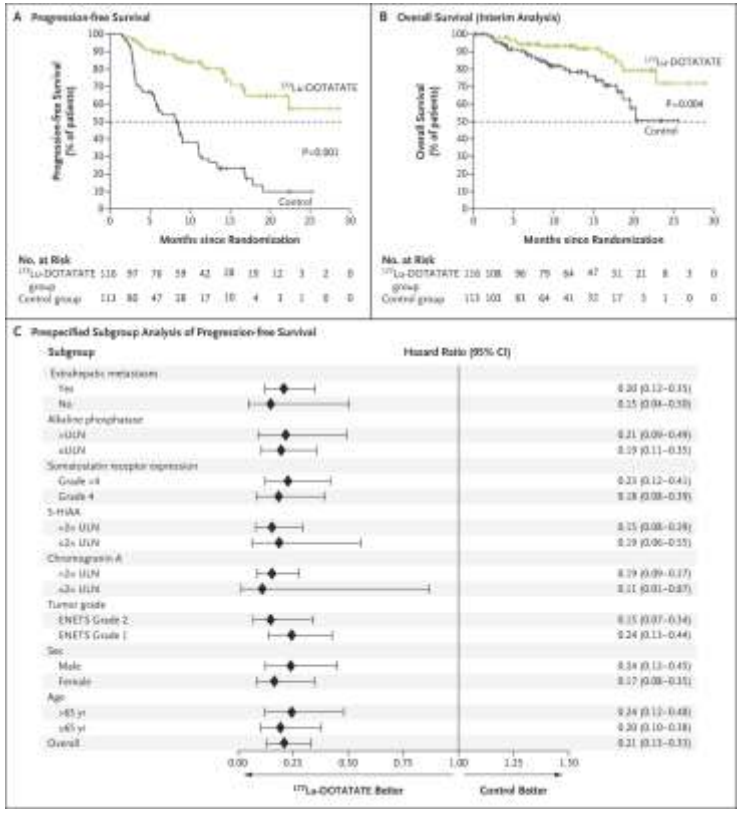
AI LEGALI RAPPRESENTANTI IRCCS PRIVATI - OSPEDALI CLASSIFICATI - CASE DI CURA ACCREDITATE

Segretario regionale AIOP Associazione Italiana
Via Timavo, 24
20124 MILANO (MI)
Email: aioplombardia@cert.aconet.it

SEGRETARIO REGIONALE ANISAP
Via Missori, 9
20900 MONZA (MB)
Email: amministrazione@anisap-lombardia.com

NETTER -1 and beyond

First international, multicenter, randomized, controlled study, PRRT + SSAs vs Octreotide LAR 60mg
Subjects: inoperable, SSTR positive, midgut NET, progressive with Octreotide LAR 30mg



^{177}Lu-Dotatate was safe and more effective than Octreotide 60 mg:

- PFS (Not Reached vs 8.5 months, p<0.0001)
- ORR (13% vs 4%, p=0.0008)
- OS (not reached vs. 27.4 months, interim analysis; p=0.0043)

Conclusion: ^{177}Lu-Dotatate demonstrated significant prolongation in PFS compared with high-dose octreotide LAR in patients with advanced, progressive midgut NET, regardless of baseline liver tumor burden, elevated ALP, or the presence of a large target lesion.

Impact of Liver Tumor Burden, Alkaline Phosphatase Elevation, and Target Lesion Size on Treatment Outcomes With ^{177}Lu-Dotatate: An Analysis of the NETTER-1 Study

Jonathan Strosberg[1], Pamela L. Kunz[2], Andrew Hendifar[3], James Yao[4], David Bushnell[5], Matthew H. Kulke[6], Richard P. Baum[7], Martyn Caplin[8], Philippe Ruszniewski[9], Ebrahim Delpassand[10], Timothy Hobday[11], Chris Verslype[12], Al Benson[13], Rajaventhan Srirajaskanthan[14], Marianne Pavel[15], Jaume Mora[16], Jordan Berlin[17], Enrique Grande[18], Nicholas Reed[19], Ettore Seregni[20], Giovanni Paganelli[21], Stefano Severi[21], Michael Morse[22], David C. Metz[23], Catherine Ansquer[24], Frédéric Courbon[25], Adil Al-Nahhas[26], Eric Baudin[27], Francesco Giammarile[28], David Taieb[29], Erik Mittra[30], Edward Wolin[31], Thomas M. O'Dorisio[5], Rachida Lebtahi[8], Christophe M. Deroose[12], Chiara M. Grana[32], Lisa Bodei[33], Kjell Öberg[34], Berna Degirmenci Polack[35], Beilei He[35], Maurizio F. Mariani[35], Germo Gericke[35], Paola Santoro[35], Jack L. Erion[35], Laura Ravasi[35], Eric Krenning[36] on behalf of the NETTER-1 study group.

Ma c’è qualcos’altro di nuovo?

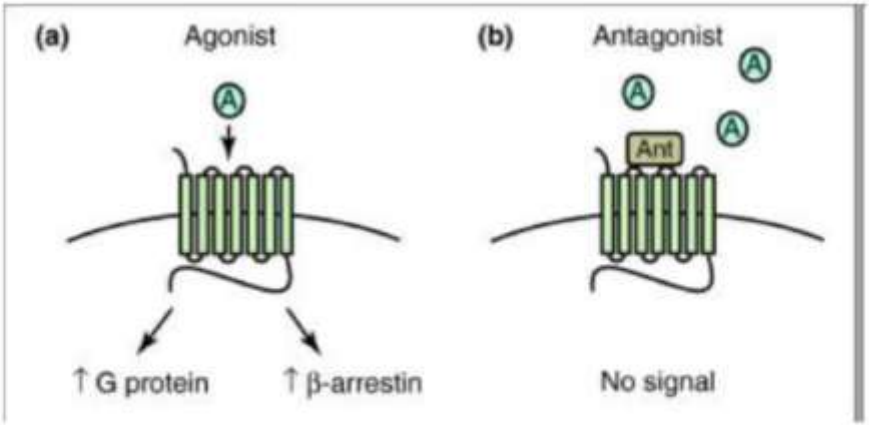
Antagonisti radiomarcati dei recettori per la somatostatina

Sono la più recente e promettente innovazione nel "molecular imaging" e nella PRRT per i NET's

Possono rappresentare con ogni probabilità il futuro dell'imaging e del trattamento dei tumori «sstr-positive».

Further developments in the field…

The importance of the vector



Antagonists instead of Agonists

Somatostatin Receptor Antagonist

Higher Bmax (binding site)
Higher tumor uptake

Longer tumor retention time
Higher renal uptake

Ginj. M. et al. PNAS 2006

Fani M. et al. JNM 2012

Wild D. et al. JNM 2014

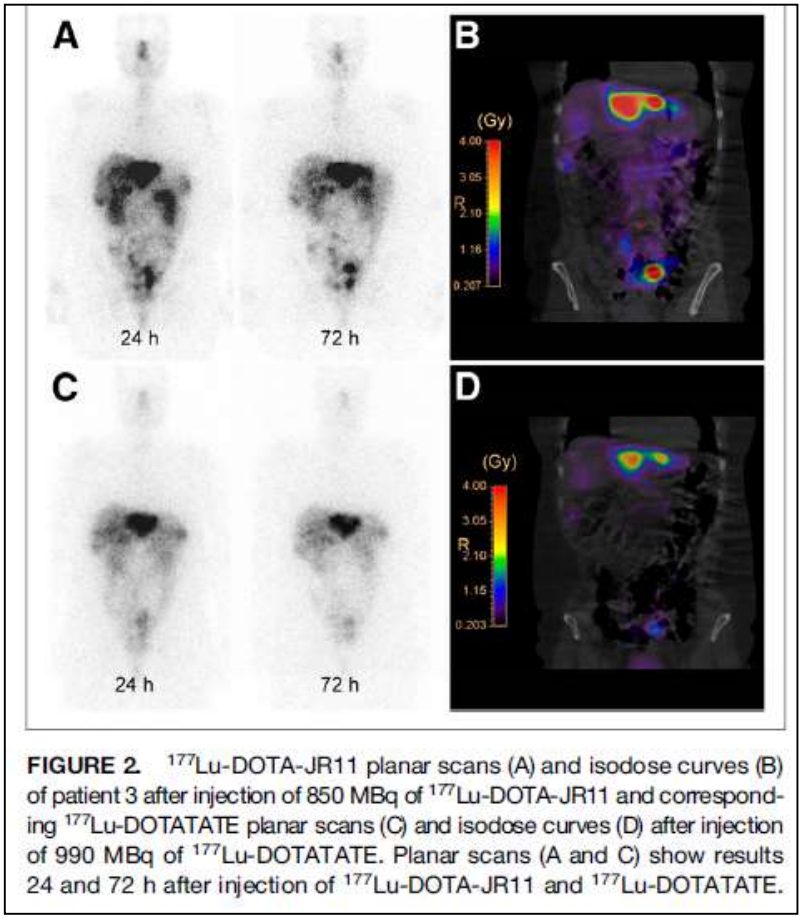


FIGURE 2. ^{177}Lu-DOTA-JR11 planar scans (A) and isodose curves (B) of patient 3 after injection of 850 MBq of ^{177}Lu-DOTA-JR11 and corresponding ^{177}Lu-DOTATATE planar scans (C) and isodose curves (D) after injection of 990 MBq of ^{177}Lu-DOTATATE. Planar scans (A and C) show results 24 and 72 h after injection of ^{177}Lu-DOTA-JR11 and ^{177}Lu-DOTATATE.

Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study

J Nucl Med 2014; 55:1248–1252

Damian Wild[1,2], Melpomeni Fani[1,2], Richard Fischer[3], Luigi Del Pozzo[1], Felix Kaul[1,2], Simone Krebs[1], Richard Fischer[1], Jean E.F. Rivier[4], Jean Claude Reubi[5], Helmut R. Maecke[1,6], and Wolfgang A. Weber[1,6,7]

Migliore rapporto T/nonT
→ Migliore sensibilità

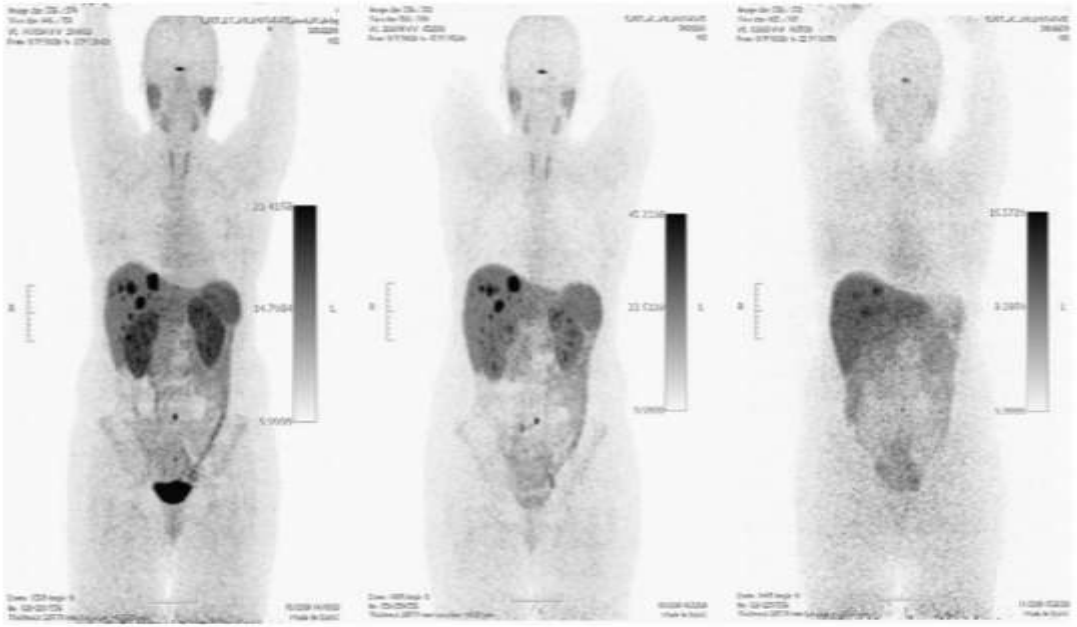


FIGURE 1. ^{64}Cu-DOTATATE PET (maximum-intensity projections) at 1, 3, and 24 h in same patient with gastroenteropancreatic NET with liver metastases.

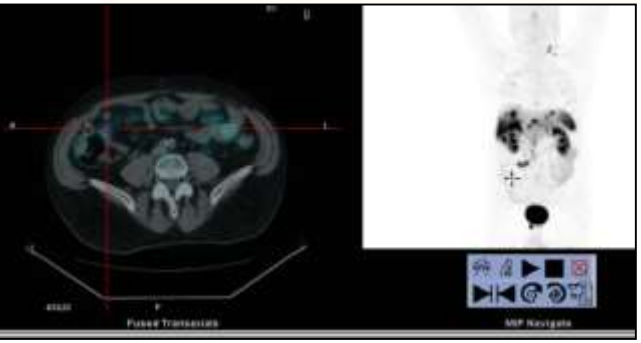
Clinical PET of Neuroendocrine Tumors Using ^{64}Cu-DOTATATE: First-in-Humans Study

Andreas Pfeifer[1–3], Ulrich Knigge[2–4], Jann Mortensen[1,3], Peter Oturai[1,3], Anne Kiil Berthelsen[1,3], Annika Loft[1,3], Tina Binderup[1–3], Palle Rasmussen[5], Dennis Elema[5], Thomas Levin Klausen[1,3], Søren Holm[1,3], Eric von Benzon[1,3], Liselotte Højgaard[1,3], and Andreas Kjaer[1–3]

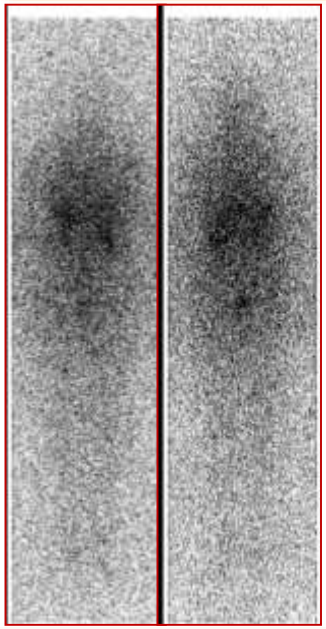
[1]*Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen, Denmark;* [2]*Cluster for Molecular Imaging, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark;* [3]*ENETS Center of Excellence for Neuroendocrine Tumors, Copenhagen, Denmark;* [4]*Department of Surgical Gastroenterology C, Rigshospitalet, Copenhagen, Denmark; and* [5]*Hevesy Laboratory, DTU-Risø, Roskilde, Denmark*

Johnbeck CB et al. J Nucl Med 2017

1. Uptake in the tumour (PET/CT with ^{68}Ga-DOTATOC)



2. Radiopharmaceutical administration before surgery (^{90}Y-DOTATOC)



Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

First ex vivo validation of a radioguided surgery technique with β-radiation.

E. Solfaroli Camillocci, M. Schiariti, V. Bocci, A. Carollo, G. Chiodi, M. Colandrea, F. Collamati, M. Cremonesi, R. Donnarumma, M.E. Ferrari, P. Ferroli, F. Ghielmetti, C.M. Grana, C. Mancini Terracciano, M. Marafini, S. Morganti, M. Patanè, G. Pedroli, B. Pollo, L. Recchia, A. Russomando, M. Toppi, G. Traini, R. Faccini

3. Lesion evaluation after surgical remove by the probe

Radiation detected by the probe

Confirmed by histology

Qualche commento…

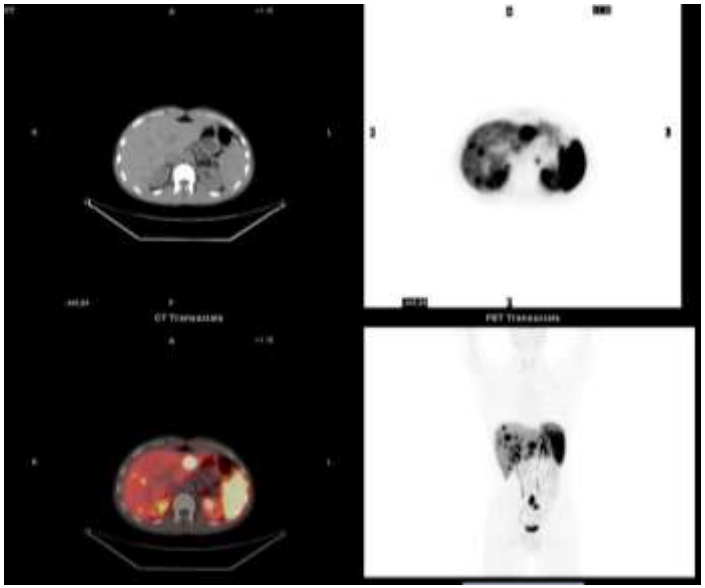
Caso clinico: midgut

Uomo, 37 aa; dolori addominali e flushing

→eco, TC: lesioni epatiche e piccoli linfonodi

→**Biopsia: mts da tumore NE,** Ki-67 4%.

→**Ottobre 2008 Ga-68-DOTATOC PET/CT**:
Multiple lesioni epatiche, sst2-5 + ln e intestino



→ **SSA**

→**Gennaio 2009 resezione ileale: tumore NE** Ki-67: 5%N+

→ **PRRT alternata a TAE**

→ **PR e poi SD, marzo 2019 ultimo controllo**

Follow up, 2014 and 2016 e 2019

Nel follow up: PET/CT con Ga-68-DOTATOC? TC total-body? RM addome?

KEY POINTS: 1

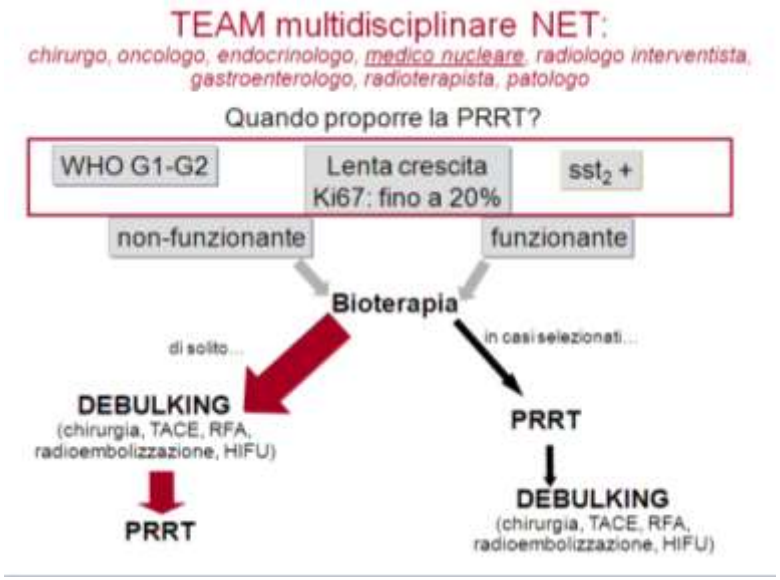
THE PATIENT:

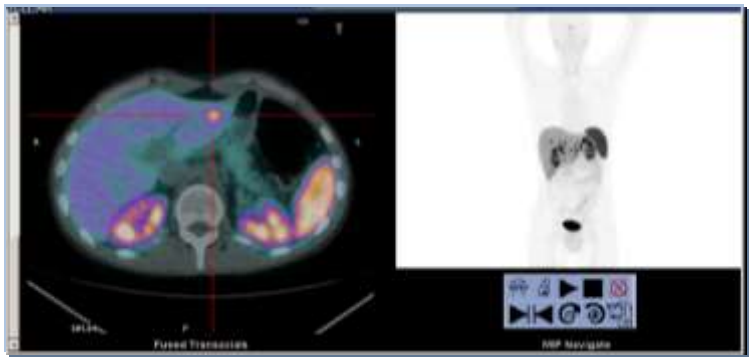
Neuroendocrine tumors: receptor evaluation IN VIVO

Morphological and functional imaging – staging

Patient's preference and convenience

Multidisciplinary tumor board to write a therapeutic path





Eur J Nucl Med Mol Imaging (2017) 44:490–499
DOI 10.1007/s00259-016-3533-z

ORIGINAL ARTICLE

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

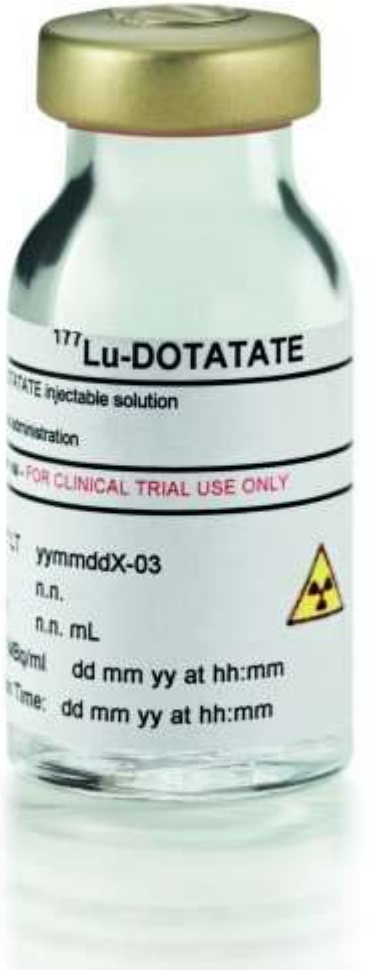
Maddalena Sansovini[1] · Stefano Severi[1] · Annarita Ianniello[1] · Silvia Nicolini[1] · Lorenzo Fantini[1] · Emilio Mezzenga[1] · Fabio Ferroni[1] · Emanuela Scarpi[2] · Manuela Monti[1] · Alberto Bongiovanni[3] · Sara Cingarlini[4] · Chiara Maria Grana[1] · Lisa Bodei[1] · Giovanni Paganelli[1]

KEY POINTS: 2

PRRT:

- Clinical evaluation
- Lab examinations
- Syndrome control
- Radioprotection
- Follow up
- Is it available?

NEWS????



KEY POINTS: 3

FOLLOW UP:

- Clinical evaluation
- Lab examinations
- QoL
- Morphological and functional evaluation
- **Always discuss in a Multidisciplinary Tumor Board**

Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: Possible indications for a multimodal approach

Emilio Bertani, MD,[a] Nicola Fazio, MD,[b] Edoardo Botteri, PhD,[c] Antonio Chiappa, MD, FACS,[a] Massimo Falconi, MD,[d] Chiara Grana, MD,[c] Lisa Bodei, MD,[c] Davide Papis, MD,[a] Francesca Spada, MD,[b] Barbara Bazolli, MSc,[c] *and* Bruno Andreoni, MD,[a] *Milan and Ancona, Italy*

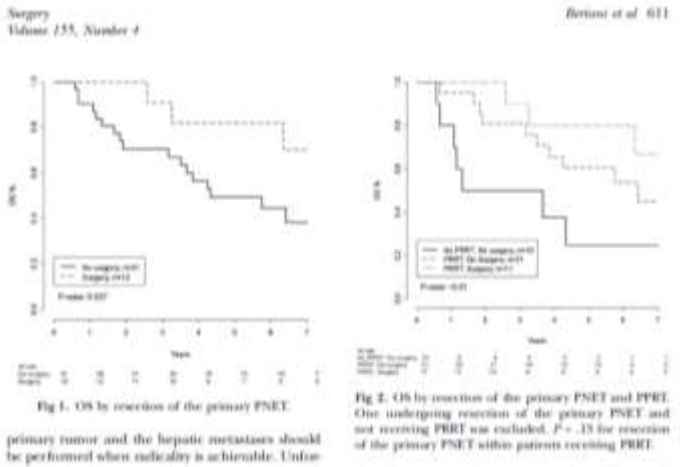


Fig 1. OS by resection of the primary PNET.

primary tumor and the hepatic metastases should be performed when radicality is achievable. Unfor-

Fig 2. OS by resection of the primary PNET and PPRT. One undergoing resection of the primary PNET and not receiving PRRT was excluded. $P = .15$ for resection of the primary PNET within patients receiving PRRT.

→ New theragnostic approaches, new modalities

JNM The Journal of NUCLEAR MEDICINE

Theranostic Concepts: More Than Just a Fashion Trend—Introduction and Overview

Ken Herrmann, Steven M. Larson and Wolfgang A. Weber

J Nucl Med. 2017;58:1S-2S.
Doi: 10.2967/jnumed.117.199570

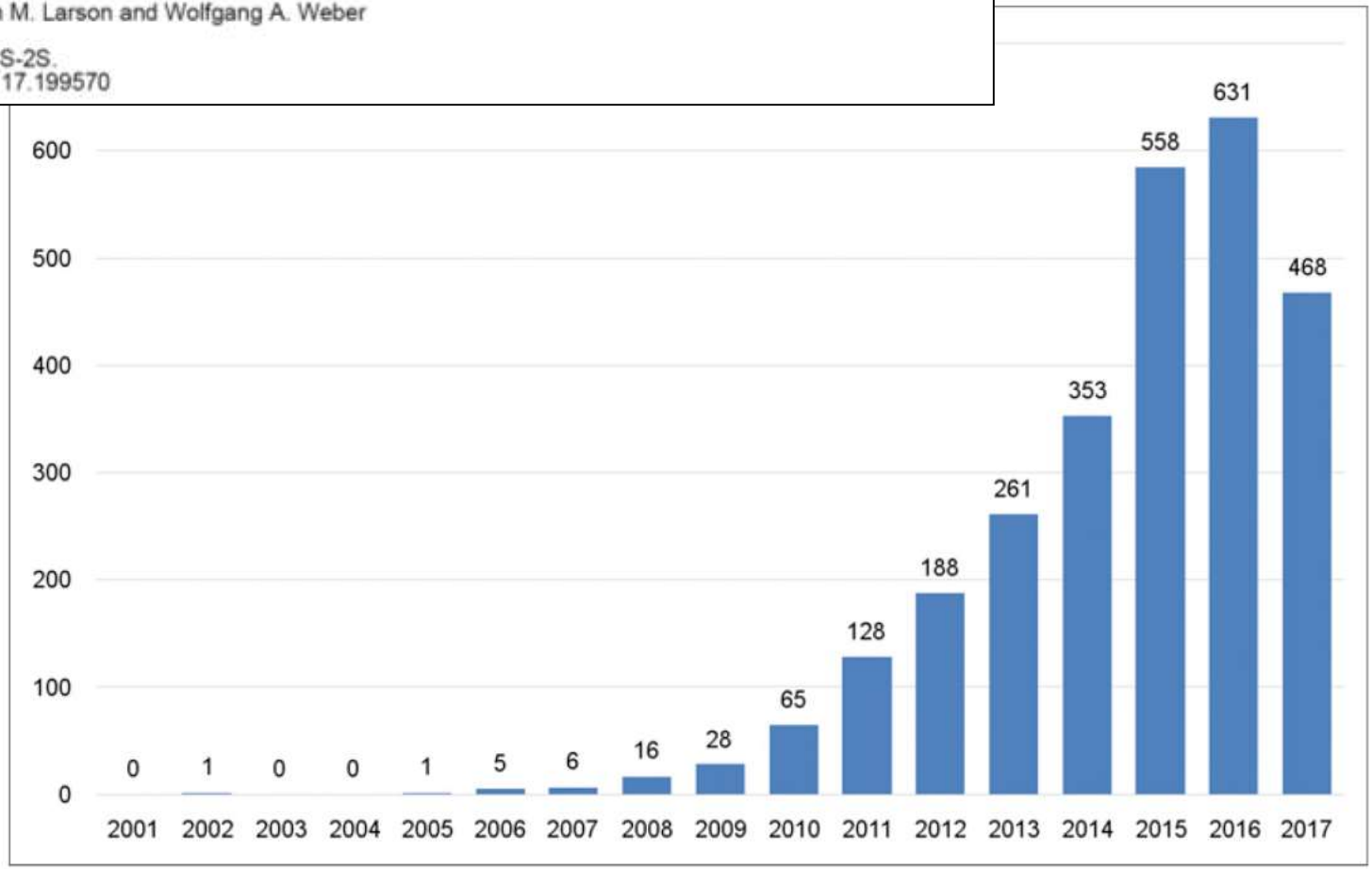


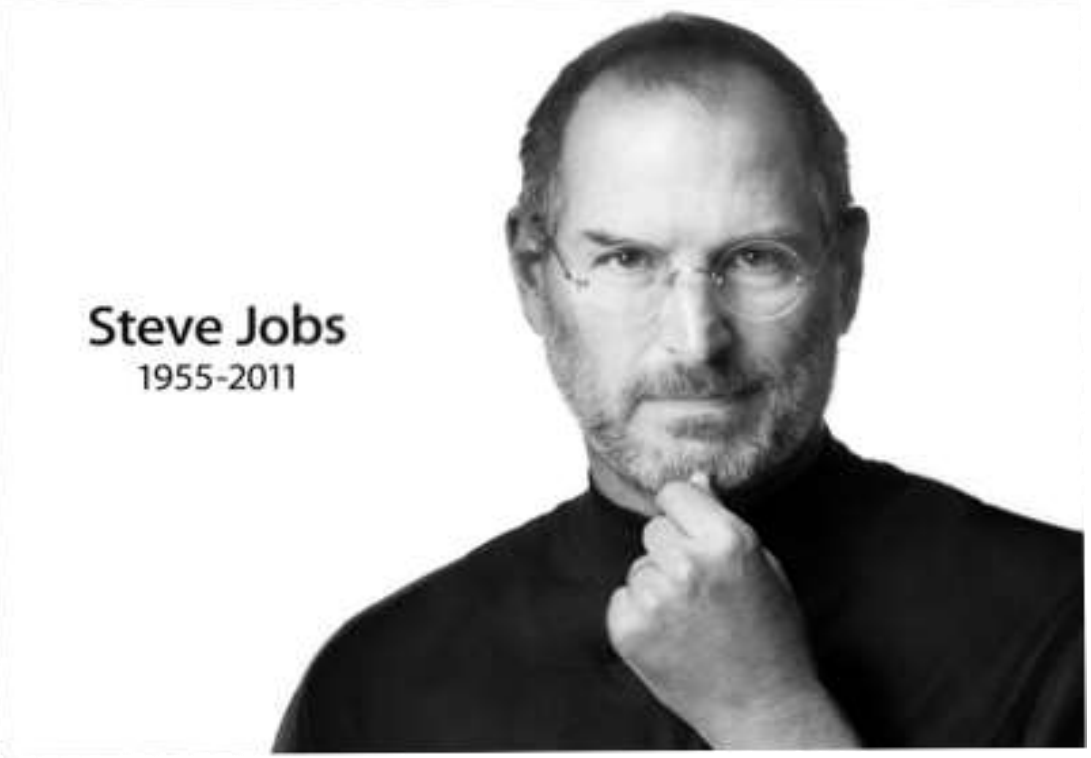
FIGURE 1. PubMed-derived number of publications including the term *theranostic* or *theragnostic* during each year from 2001 to 2017 (search performed July 16, 2017).

Functional imaging is fundamental for diagnosis, staging and follow up, as an integration to morphologic imaging

To date, PET techniques, especially receptor PET with ^{68}Ga-peptides, are the tools to provide invaluable biologic and clinical information:

- As theranostics
- To define the right treatment for the right patient at the right time at the right dose → personalized medicine

C'è qualcosa di nuovo sotto il sole nucleare…….



Think different.

VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia