Società Medico Chirurgica di Ferrara dal 1846

Con il patrocinio di:

Università degli Studi di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

sie Società Italiana Endocrinologia

It.a.net

Il Percorso del paziente con neoplasia neuroendocrina nella provincia di Ferrara

La terapia radiometabolica

Stefano Panareo

Medicina Nucleare Ferrara

s.panareo@ospfe.it

Imaging medico nucleare dei NET: *i radiocomposti*

1) Sintesi, immagazzinamento, e rilascio di ormoni

- ^{11}C-idrossi-**efedrina** (**HE**) **β+**
- ^{123}I-**metaiodo-benzil-guanidina** (**MIBG**) ***γ***

2) Produzione di amine e polipeptidi (APUD system)

- ^{11}C-idrossi-**triptofano** (**HTP**) **β+**
- ^{18}F-diidrossi-**fenilalanina** (**DOPA**) **β+**

3) Esprimono recettori per la somatostatina: sstr

- **^{68}Ga-DOTA -NOC -TOC -TATE** (**octapeptidi**) ***β+ emettitori***
- **^{111}In-DTPA-octreotride-** (**Octreoscan®**) ***γ emettitore***
- ^{99m}Tc-EDDA-HYNIC-TOC-scan

4) Composti metabolici non specifici

- ^{18}F-fluorodesossiglucosio (**FDG**) **β+**

UTILITA' E INDICAZIONI DELLE INDAGINI RECETTORIALI MEDICO-NUCLEARI NEI NET

^{111}In-DTPA-Octreotide (Octreoscan®) SPECT/CT
^{68}Ga-DOTA -NOC -TOC -TATE (octapeptidi) PET/CT

1) **DIAGNOSI, RICERCA PRIMITIVO E STADIAZIONE**

2) **INDICAZIONE ALLA TERAPIA CON ANALOGHI DELLA SOMATOSTATINA "FREDDI" O "RADIOMARCATI" PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)**

3) **VALUTAZIONE DELLA RISPOSTA ALLA TERAPIA**

4) **RISTADIAZIONE: malattia residua, recidivante, in progressione**

5) **INFORMAZIONI PREDITTIVE E PROGNOSTICHE**

^{111}In-DTPA-octreotide - Octreoscan®
Scintigrafia planare e SPECT/CT

- **Farmaco approvato in farmacopea e commercializzato: STANDARD DI RIFERIMENTO**

- **Acquisizione a 4 e 24 ore (48 ore)**

- **Corrispondenza molecolare con gli analoghi freddi della somatostatina per terapia**

- Non necessari tomografo PET, generatore e modulo di sintesi del radiofarmaco

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

- Migliore **risoluzione spaziale e rapporto tumore/fondo** della **PET** vs **scintigrafia planare e SPECT**

- Migliore **fissazione**: inferiore nel **fegato** e nell'**intestino**

- **"patient friendly" (1h** vs 4-24h**)**

- **Dosimetria e costi favorevoli**

- **Farmaci sperimentali**: protocolli di ricerca. **TOC**: farmacopea EU PREPARAZIONE GALENICA OFFICINALE

Potenziali vantaggi della
PET/CT con Ga-DOTA-peptidi vs Octreoscan®

Costi inferiori

Eur J Nucl Med Mol Imaging. 2011 Sep 17. [Epub ahead of print]

Cost comparison of (111)In-DTPA-octreotide scintigraphy and (68)Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours.

Table 6 Comparison of the total costs of ^{111}In-DTPA-octreotide scintigraphy and SPECT/CT and ^{68}Ga-DOTATOC PET/CT

	Octreotide scan	Per patient (n=22)	DOTATOC PET/CT	Per patient (n=29)
I.1 Staff costs	13 × 110.09 € 9 × 100.19 €=2332.88 €	106.04 €	29 × 88.79 €=2574.91 €	88.79 €
II.1 Proportionate investment costs and costs for disposables	22 € × 720.47=15,850.34 €	720.47 €	29 × 459.67 €=13,330.43 €	459.67 €
Total costs (without supplementary imaging tests)	18,183.22 €	826.51 €	15,905.34 €	548.46 €
I.2 Staff costs for supplementary imaging tests	10 × 41.63 € (MRI) 11 × 36.70 € (CT) = 820 €	37.27 €	2 × 41.63 € (MRI) = 83.26 €	2.87 €
II.2 Proportionate investment costs and costs for disposables for supplementary imaging tests	10 × 244.76 € (MRI) 11 × 24.51 € (CT) = 2717.21 €	123.51 €	2 × 244.76 € (MRI) = 489.52 €	16.88 €
Total costs for supplementary imaging	3537.21 €	160.78 €	572.78 €	19.75 €

^{68}Ga-DOTA-Tyr^{3}-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT

Michael Gabriel[1], Clemens Decristoforo[1], Dorota Kendler[1], Georg Dobrozemsky[1], Dirk Heute[1], Christian Uprimny[1], Peter Kovacs[2], Elisabeth Von Guggenberg[1], Reto Bale[2], and Irene J. Virgolini[1]

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

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 48 • No. 4 • April 2007

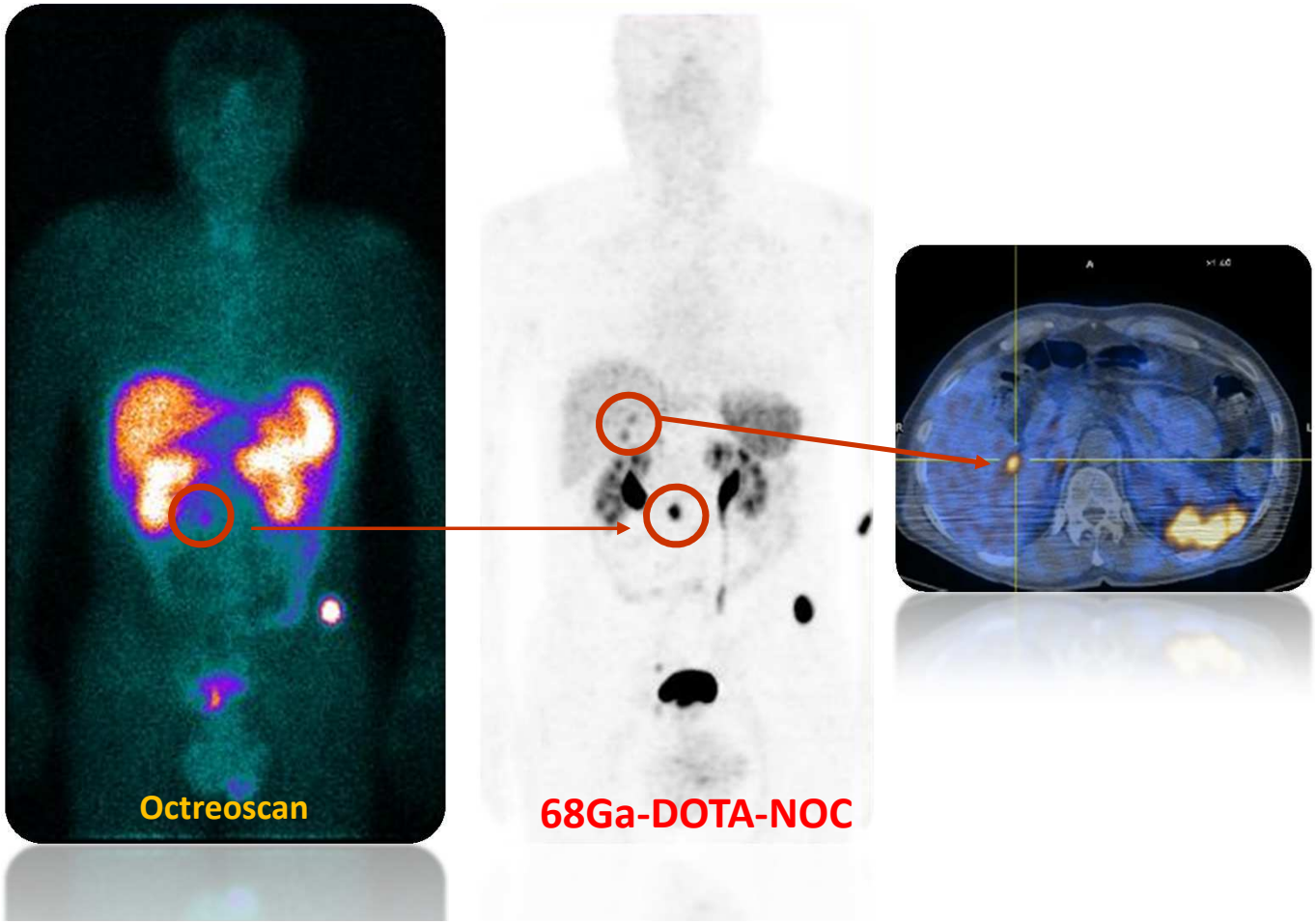
TABLE 5

Comparison of 3 Imaging Modalities: PET, SPECT, and CT

Parameter	PET (%)	SPECT (%)	CT (%)
Sensitivity	97 (69/71)	52 (37/71)	61 (41/67)
Specificity	92 (12/13)	92 (12/13)	71 (12/17)
Accuracy	96 (81/84)	58 (49/84)	63 (53/84)

Number of patients is in parentheses.

Potenziali vantaggi della
PET/CT con 68Ga-DOTA-peptidi vs 111In-pentetreotide Octreoscan®



^{68}Ga DOTA -NOC -TOC -TATE **PET/CT**
~~^{111}In-DTPA-Octreotide **SPECT/CT**~~

+

^{18}F-FDG PET/CT

Quale ruolo riveste?

Carcinoide

Scenario clinico	**Categoria di appropriatezza**
stadiazione	Inappropriato
follow up	Inappropriato

Tumori neuroendocrini

Scenario clinico	**Categoria di appropriatezza**
stadiazione	Inappropriato
valutazione della risposta al trattamento al termine della terapia	Inappropriato

^{68}Ga DOTA -NOC -TOC -TATE **PET/CT**
~~^{111}In-DTPA-Octreotide **SPECT/CT**~~

+

^{18}F-FDG PET/CT

Quale ruolo riveste?

ISSN 1591-223X
DOSSIER 157-2007

FDG-PET in oncologia

Criteri per un uso appropriato

2018

Carcinoide

Scenario clinico	**Categoria di appropriatezza**
stadiazione	Inappropriato
follow up	Inappropriato

Tumori neuroendocrini

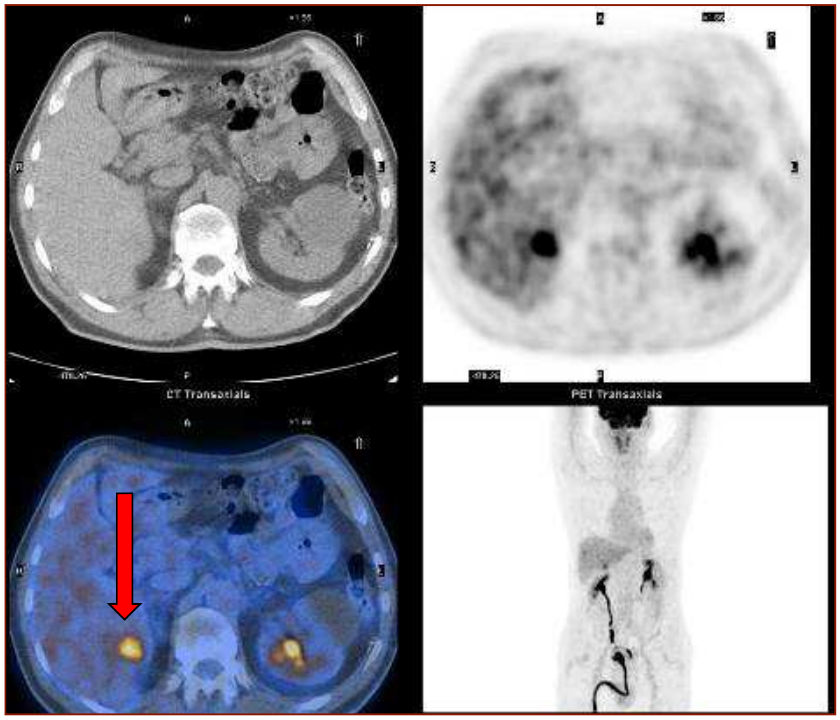
Scenario clinico	**Categoria di appropriatezza**
stadiazione	Inappropriato
valutazione della risposta al trattamento al termine della terapia	Inappropriato

APPROPRIATO

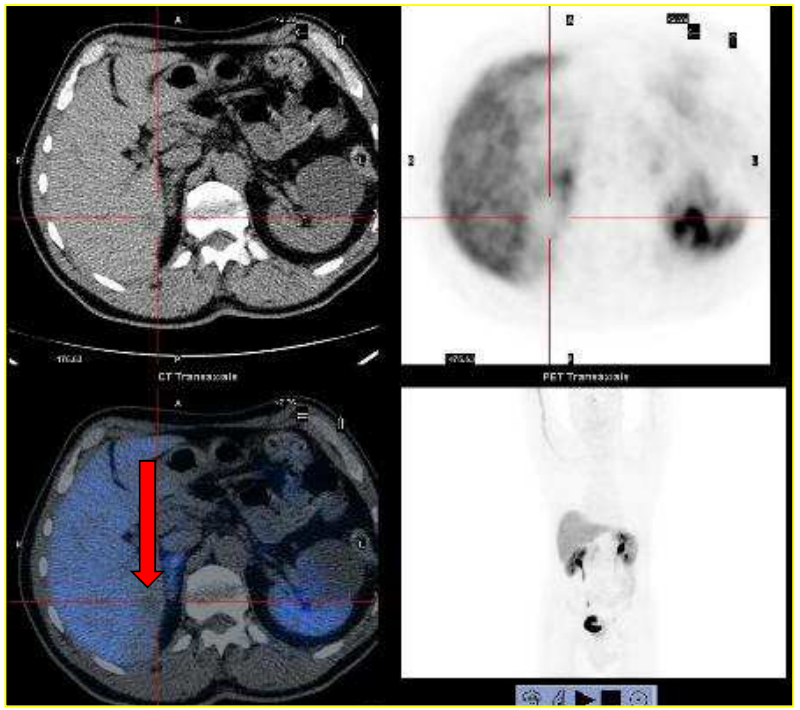
Ga68-DOTA e 18F-FDG

Metastasi epatiche da NET dell’ileo Ki67 20%

18F-FDG

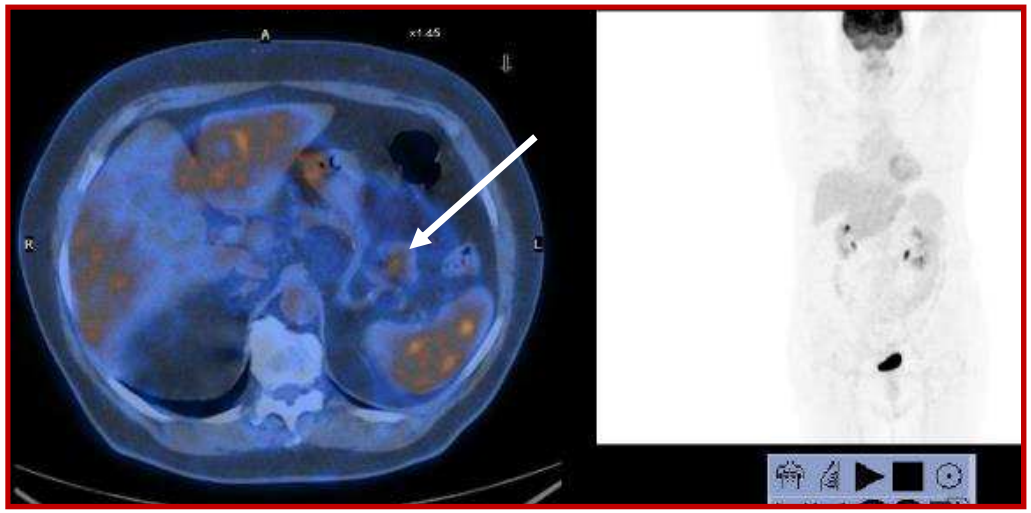


Ga68 DOTA TOC

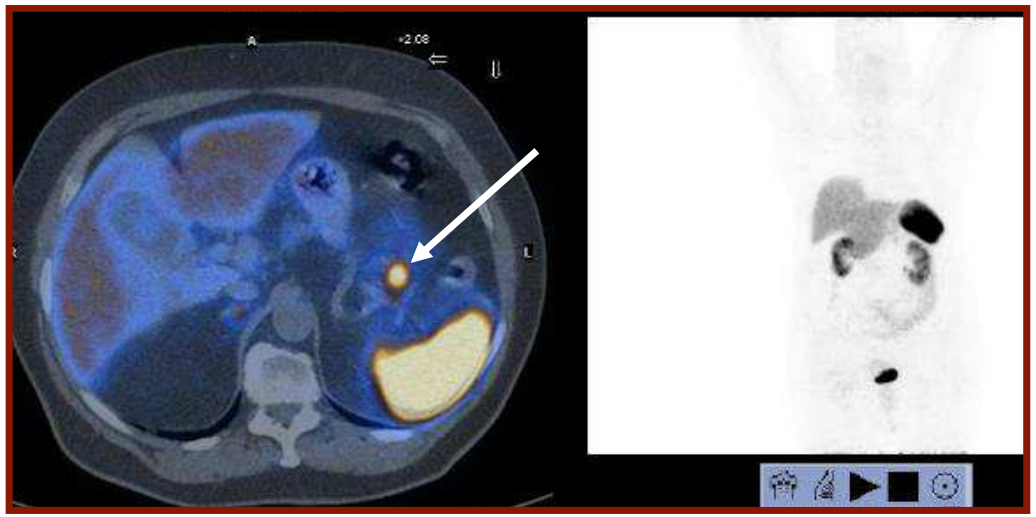


Lesione della coda del pancreas Ki67 = 4 %

18F-FDG



Ga68 DOTA-TOC



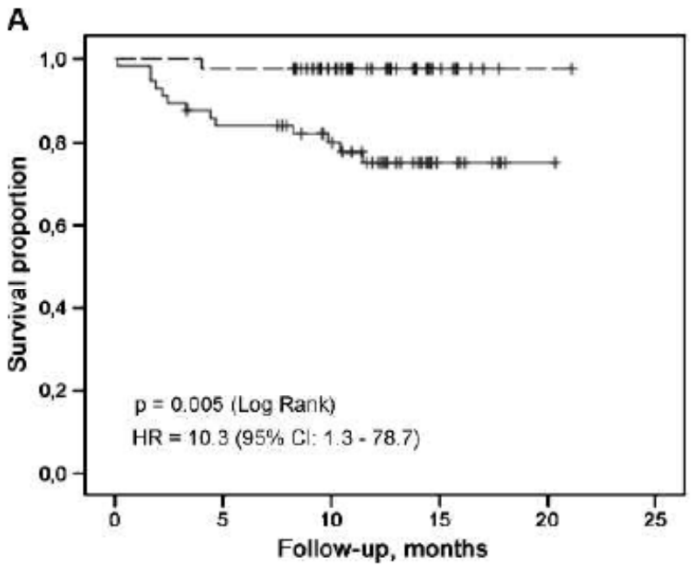
^{18}F-FDG PET/CT: VALORE PROGNOSTICO

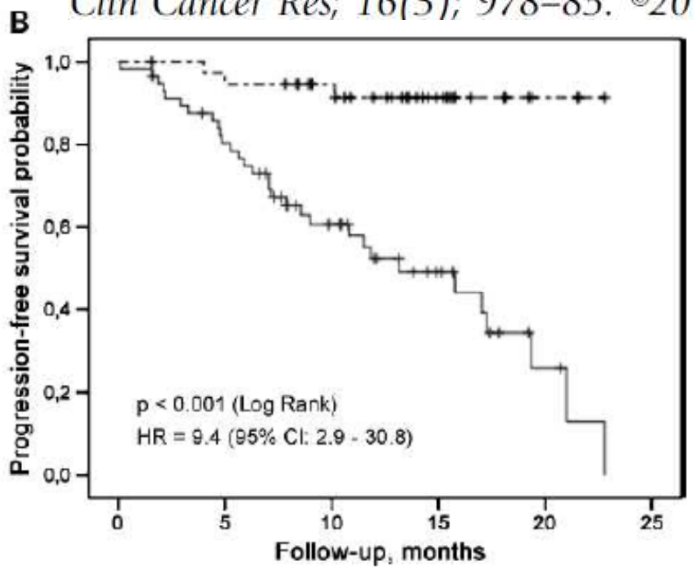
^{18}F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors

Tina Binderup[1,2], Ulrich Knigge[2,3], Annika Loft[1], Birgitte Federspiel[4], and Andreas Kjaer[1,2]

Clin Cancer Res; 16(3); 978–85. ©2010

OS





PFS

^{18}F-FDG PET positiva → probabile progressione di malattia

Diagnostica medico nucleare nei NET: Considerazioni

- Octreoscan® utilizzato solo in Strutture MedNucl senza PET

- **Elevata accuratezza** della **^{68}Ga-DOTA-peptidi PET/CT** nella stadiazione e ristadiazione dei **NET ben differenziati**.

- **L'imaging recettoriale PET o SPECT fornisce informazioni essenziali per indirizzare alla terapia con analoghi freddi o analoghi radiomarcati (PRRT) e per valutare la risposta alla terapia.**

- **FDG PET/CT** fornisce valide informazioni prognostiche.

I radiofarmaci analoghi della Somatostatina

DIAGNOSTICS + THERAPY = THERANOSTICS

	DIAGNOSTICA SPECT	DIAGNOSTICA PET	TERAPIA (PRRT) Peptide Receptor Radionuclide Therapy	
RADIOISOTOPO	^{111}In	^{68}Ga	^{90}Y	^{177}Lu
CHELANTE	DTPA	DOTA	DOTA	DOTA
LIGANDO RECETTORIALE ANALOGO DELLA SOMATOSTATINA	Octreotide *Octreoscan®*	NOC TOC TATE	TOC	TATE TOC

Terapie medico nucleari	Rf/dispositivi industriali	Rf/dispositivi sperimentali
Ipertiroidismo	^{131}I	
Carcinoma differenziato della tiroide	^{131}I	
Tumori dell'asse dell'asse simpatico-adrenergico	➲[^{131}I-MIBG]➲	
Metastasi scheletriche	⇩^{89}Sr (Metastron®) ⇩ ^{53}Sm-EDTMP (Quadramet®) ^{223}Ra (Xofigo®)	
Tumori solidi ematologici	⇩ ^{90}Y-CD20 (Zevalin®)	
Tumori epatici	^{90}Y-microsfere (Sirtex®) ^{90}Y-microsfere (TheraSphere®) ^{166}Ho-microsfere(QuiremSpheres®)	
Patologia flogistico-degenerativa delle articolazioni	➲[^{90}Y/^{169}Er/^{186}Re-colloidale]➲	
Tumori del sistema endocrino diffuso (PRRT)	^{177}Lu-OXODOTREOTIDE (Lutathera®) *registr. AIFA 04/2019*	^{177}Lu-DOTATOC ^{90}Y-DOTATOC
Tumori della prostata CR (PRLT)		^{177}Lu-PSMA-617
Altre terapie		Molecole marcate con ^{64}Cu o con α-emettitori (^{225}Ac o ^{213}Bi)

La storia della PRRT

- **1973** - somatostatin first isolated by Roger Guillemin
- **1987** - octreotide synthesis
  - scintigraphy with ^{123}I-octreotide
- **1991** - ^{111}In-octreotide first employed
- **1992** - five G-protein coupled somatostatin receptors (SSR_{t1-5}), identified and cloned
- **1993** - ^{111}In-octreotide registered (OctreoScan®)
- **1994** - first PRRT with high-dose ^{111}In-octreotide
- **1996** - first ^{90}Y-octreotide PRRT
- **2000** - first ^{177}Lu-octreotate PRRT
- **2012** - phase III registration trial of ^{177}Lu-octreotate
- **2014** - **first-in human experience with ^{213}Bi-DOTATOC (α-emitter)**
- **2017** - phase III pubblication trial of ^{177}Lu-octreotate (Netter1)
- **2019** - Lutathera® registered and available on the radiopharmaceuticals market

	DOTATOC	DOTATATE
^{90}Y	^{90}Y-DOTATOC	^{90}Y-DOTATATE
^{177}Lu	^{177}Lu-DOTATOC	^{177}Lu-DOTATATE

FENET-2016
(attivo dal 07/2018)

Netter1: il primo studio di fase 3 (1)

The NEW ENGLAND JOURNAL of MEDICINE

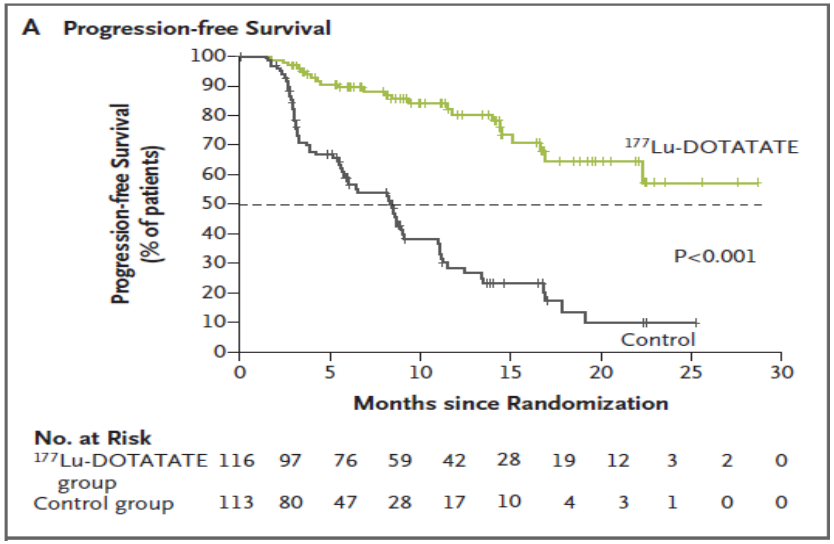
ORIGINAL ARTICLE

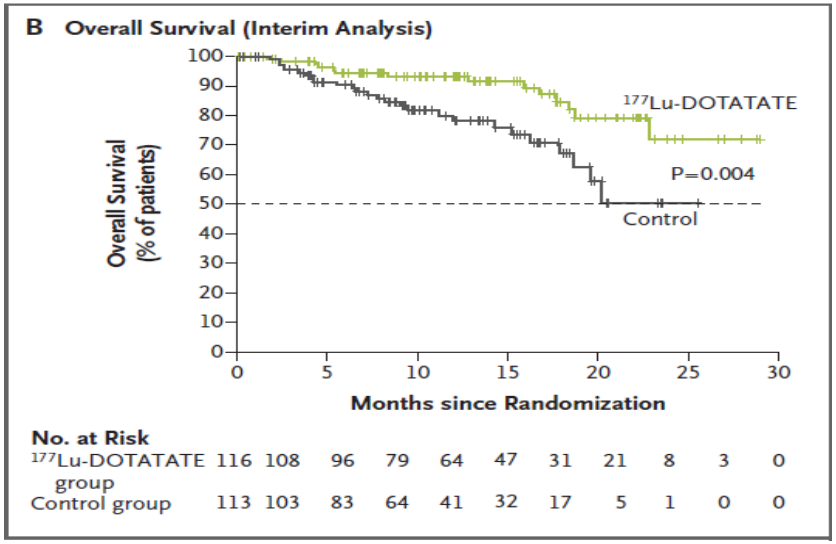
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

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*

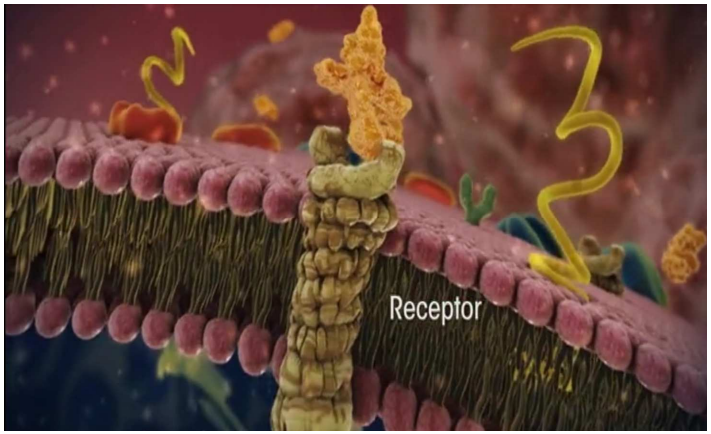
METHODS

We randomly assigned 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors to receive either ^{177}Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (^{177}Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol; a prespecified interim analysis of overall survival was conducted and is reported here.





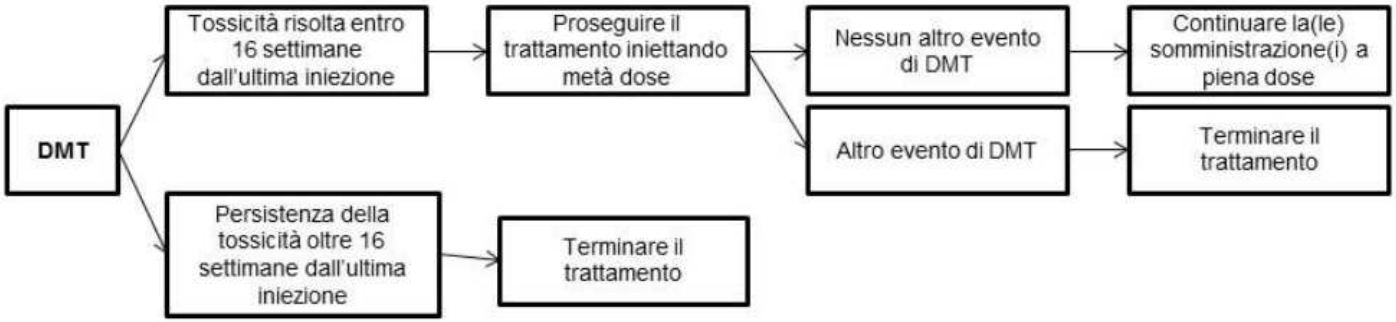
Netter1: il primo studio di fase 3 (2)



Indicazioni terapeutiche: Lutathera® è indicato in pazienti adulti per il trattamento di tumori neuroendocrini gastroenteropancreatici (NET-GEP) ben differenziati (G1 e G2), progressivi, non asportabili o metastatici, positivi ai recettori per la somatostatina.

Posologia: consiste in **4 infusioni da 7.400 MBq ciascuna**. L'intervallo consigliato tra una somministrazione e la successiva è di 8 settimane, estensibile fino a 16 settimane in caso di **T**ossicità **M**odificante la **D**ose (**DMT**).

Figura 1. Schema delle istruzioni per modificare la dose



www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 24), pp: 16932-16950

Research Paper

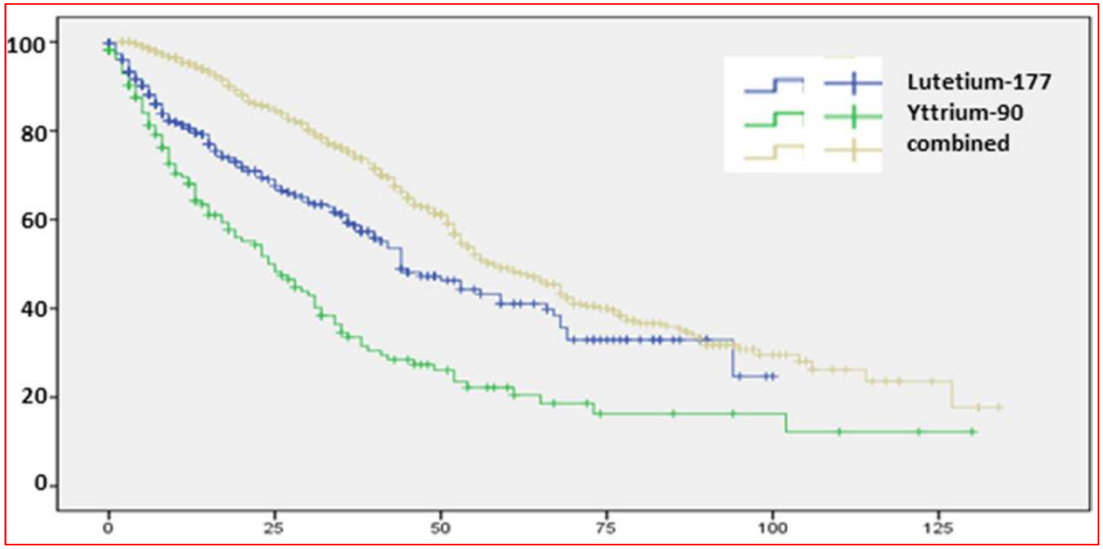
Results and adverse events of personalized peptide receptor radionuclide therapy with ^{90}Yttrium and ^{177}Lutetium in 1048 patients with neuroendocrine neoplasms

Richard P. Baum[1], Harshad R. Kulkarni[1], Aviral Singh[1], Daniel Kaemmerer[2], Dirk Mueller[1], Vikas Prasad[3], Merten Hommann[2], Franz C. Robiller[4], Karin Niepsch[1], Holger Franz[5], Arthur Jochems[6], Philippe Lambin[6,7] and Dieter Hörsch[8]

Personalizzazione della dose

Trattamento combinato ^{117}Lu/^{90}Y

OS



Number at risk:						
Total	1048	561	262	103	28	5
Lutetium-177	378	142	49	19	1	0
Yttrium-90	157	58	21	6	4	1
combined	513	361	192	78	23	4

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 24), pp: 16932-16950

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Bassa tossicità

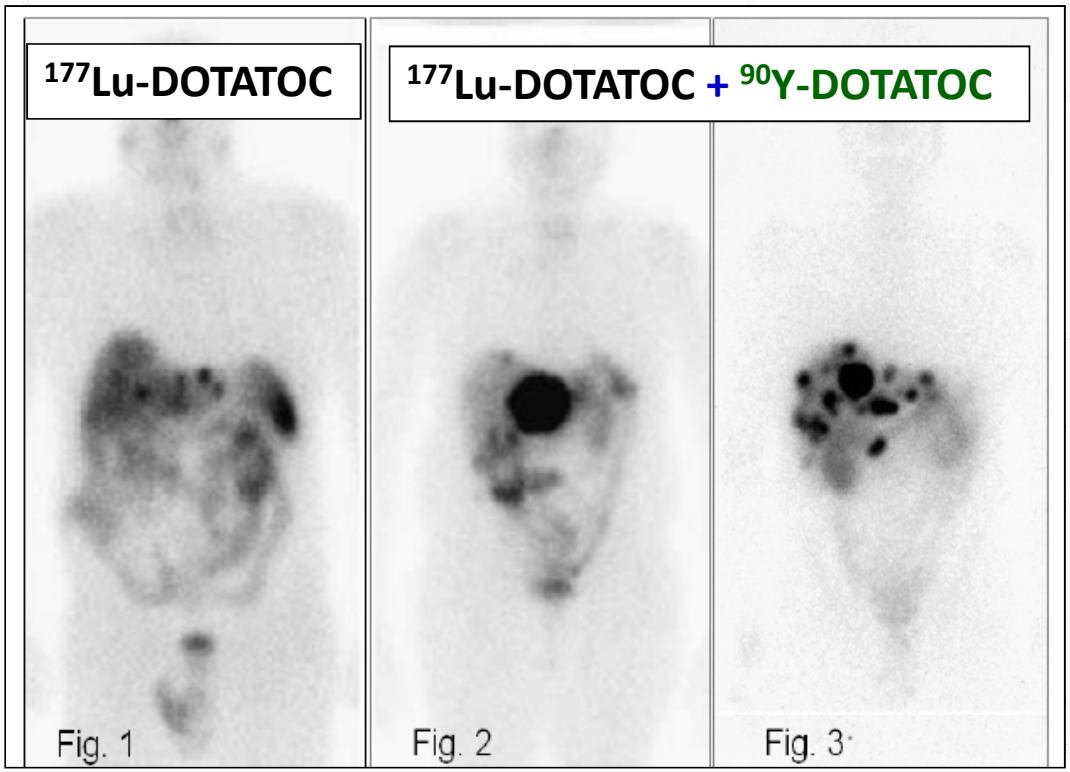
Table 3: Number of patients with adverse events according to CTCAE criteria

Before first PRRT (1048)				
	Normal, G1, G2	G3	G4	No information
Leucocytes	1047 (99.9%)	0	0	1
Thrombocytes	1047 (99.9%)	0	3	1
Hemoglobin	1040 (99.2%)	3	3	1
Chronic kidney disease	1040 (99.2%)	1	2	4 (0.3%)
According to treatment cycles (3692)				
	Normal, G1, G2	G3	G4	No information
Leucocytes	3680 (99.6%)	8 (0.2%)	0	4 (0.1%)
Thrombocytes	3679 (99.6%)	1	8 (0.2%)	4 (0.1%)
Hemoglobin	3666 (99.2%)	10 (0.2%)	7	9 (0.2%)
Chronic kidney disease	3664 (99.2%)	7 (0.1%)	7 (0.2%)	14 (0.3)

FENET-2016
Codice EUDRACT number 2016-005129-35

Studio clinico di fase II

Principal investigator: ***Dott. Mirco Bartolomei***
SC di Medicina Nucleare e Terapia Radiometabolica
Azienda Ospedaliero-Universitaria di Ferrara
via Aldo Moro, 8 – 440128 Ferrara
Telefono: 0532-236082



Teranostica

- ^{68}Ga-DOTATOC
- ^{177}Lu-DOTATOC (3.7-5.5 GBq/cycle)
- ^{90}Y-DOTATOC (1.9-2.8 GBq/cycle)

(d) dosimetria previsionale e di verifica

1° livello terapeutico (5 cicli)	
^{177}Lu-DOTATOC (d)	^{177}Lu-DOTATOC (d)
^{177}Lu-DOTATOC	^{90}Y-DOTATOC
^{177}Lu-DOTATOC	^{177}Lu-DOTATOC
^{177}Lu-DOTATOC	^{90}Y-DOTATOC
^{177}Lu-DOTATOC (d)	^{177}Lu-DOTATOC (d)
2° livello terapeutico (3 cicli)	
^{177}Lu-DOTATOC	^{90}Y-DOTATOC
^{177}Lu-DOTATOC	^{90}Y-DOTATOC
^{177}Lu-DOTATOC	^{90}Y-DOTATOC

Dove dobbiamo gestire il paziente affetto da NET?

NOVEMBER 2010 • jop.ascopubs.org

Multidisciplinary Care

TAILORED CURE is mandatory!

Multidisciplinary Reference Centers: The Care of Neuroendocrine Tumors

By Simron Singh, MD, and Calvin Law, MD

Odette Cancer Center, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada

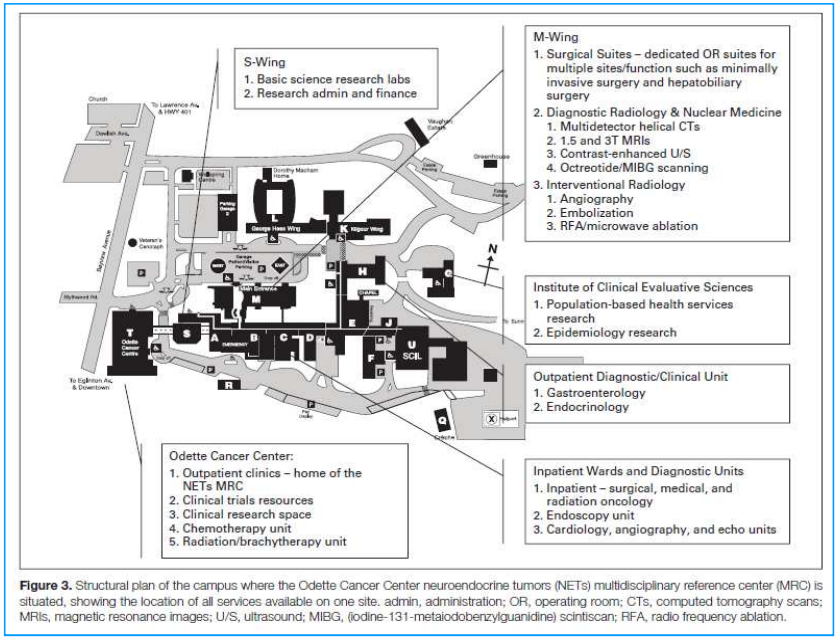
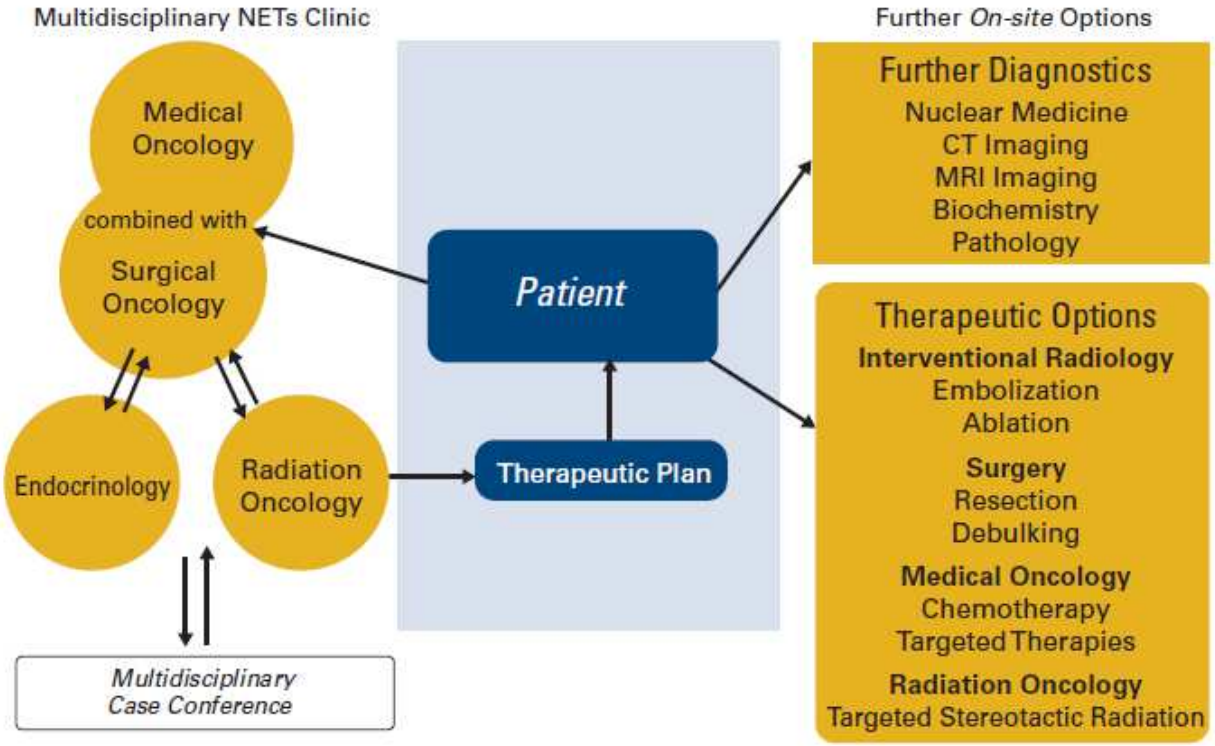


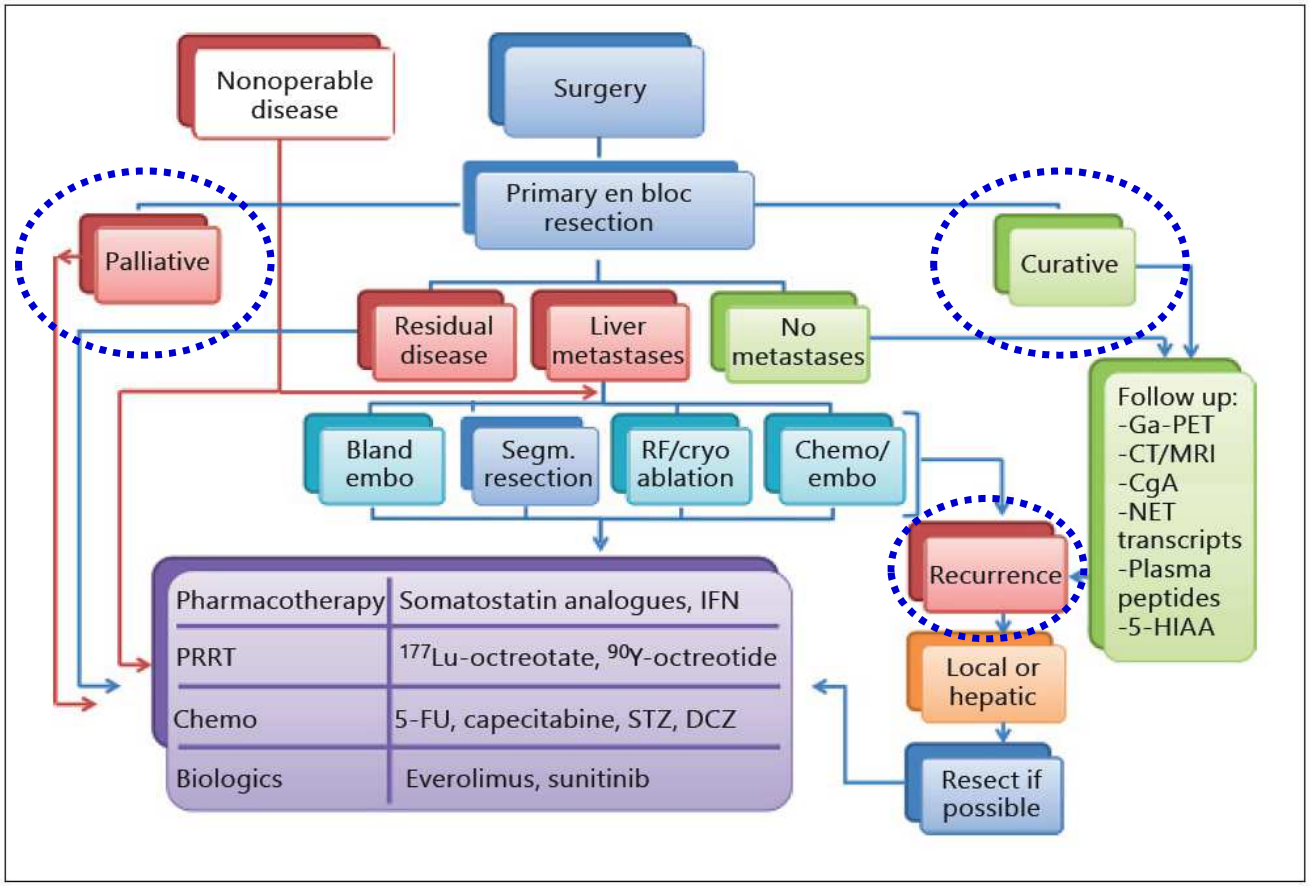
Figure 3. Structural plan of the campus where the Odette Cancer Center neuroendocrine tumors (NETs) multidisciplinary reference center (MRC) is situated, showing the location of all services available on one site. admin, administration; OR, operating room; CTs, computed tomography scans; MRIs, magnetic resonance images; U/S, ultrasound; MIBG, (iodine-131-metaiodobenzylguanidine) scintiscan; RFA, radio frequency ablation.



Team-working method must be standardized

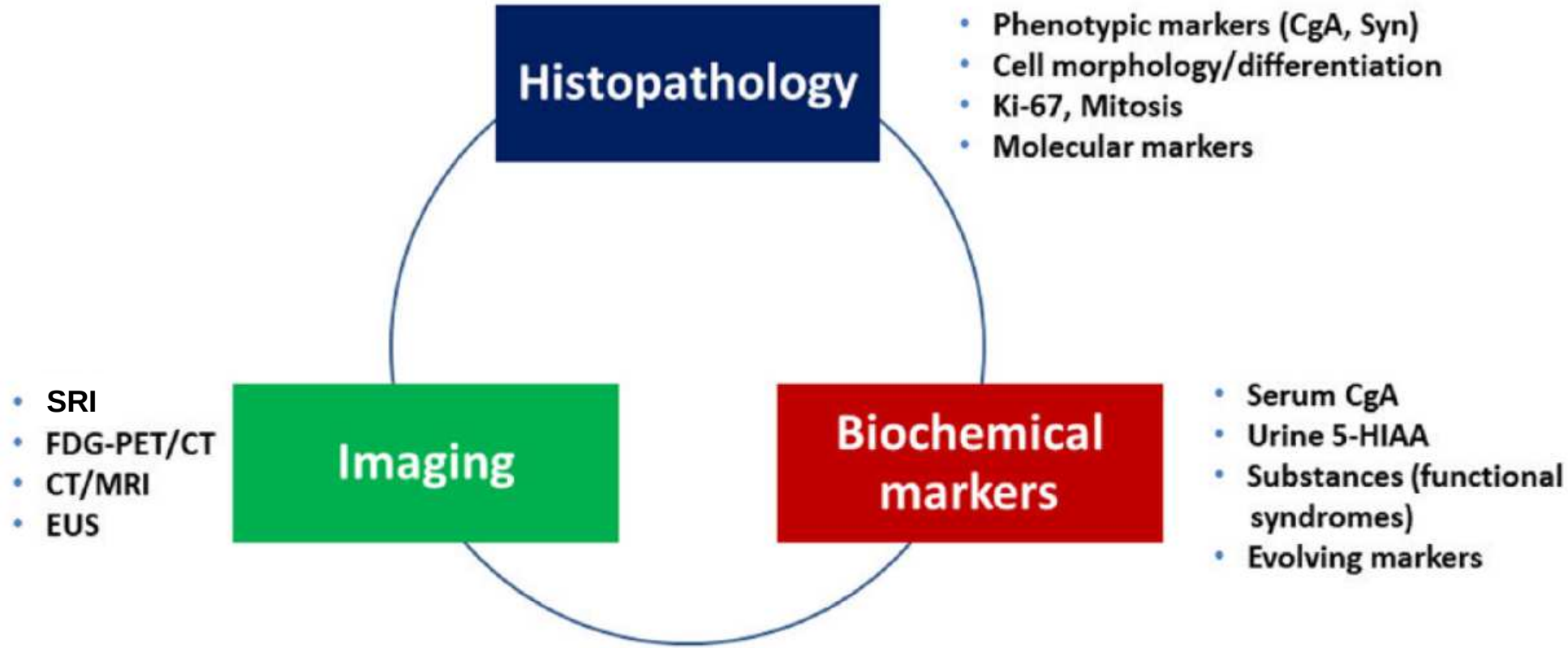
Come dobbiamo gestire il paziente affetto da NET? (1)

What is the purpose of the treatment?

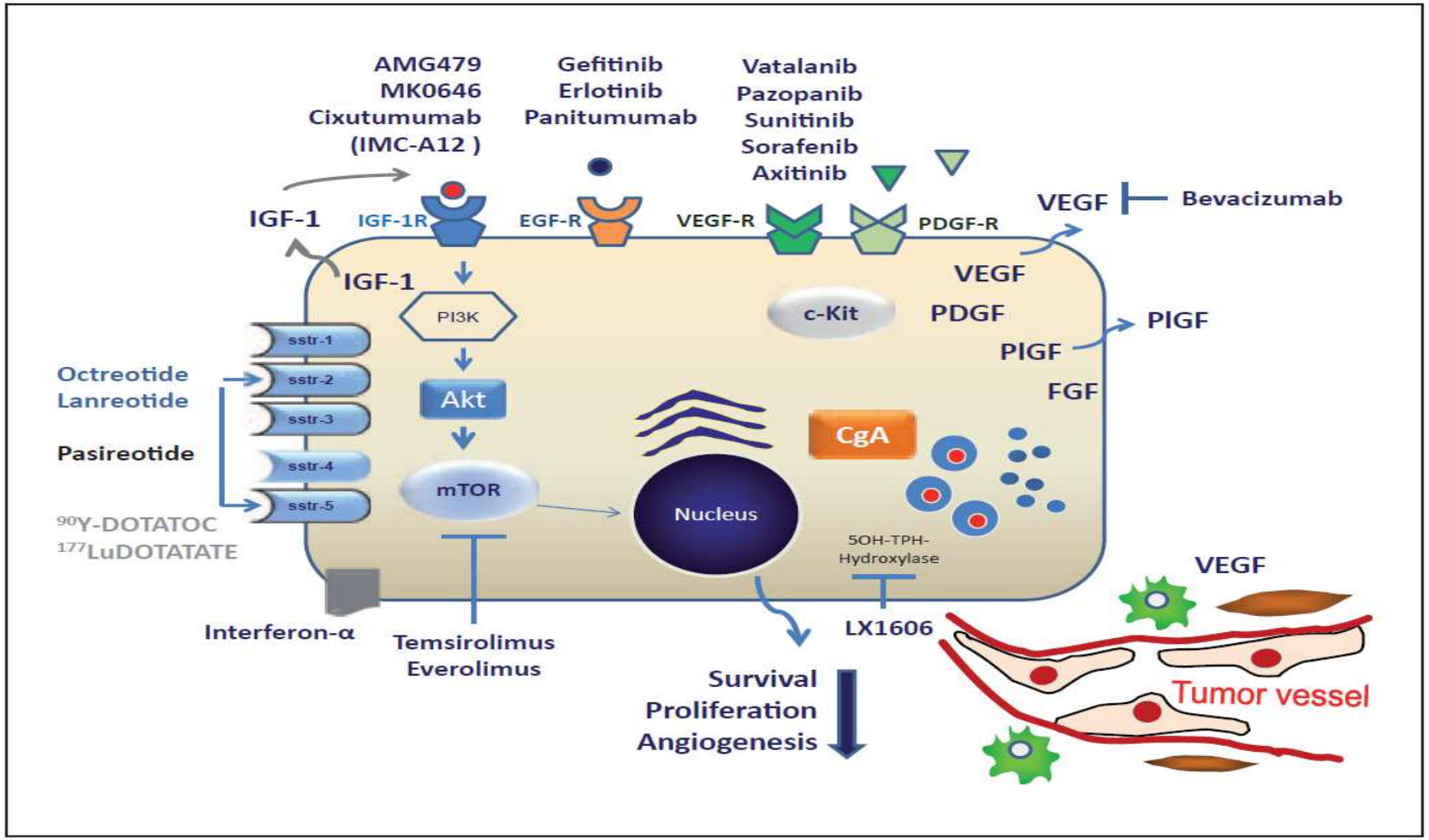


Weber HC et al. (2013)

Come dobbiamo gestire il paziente affetto da NET? (2)



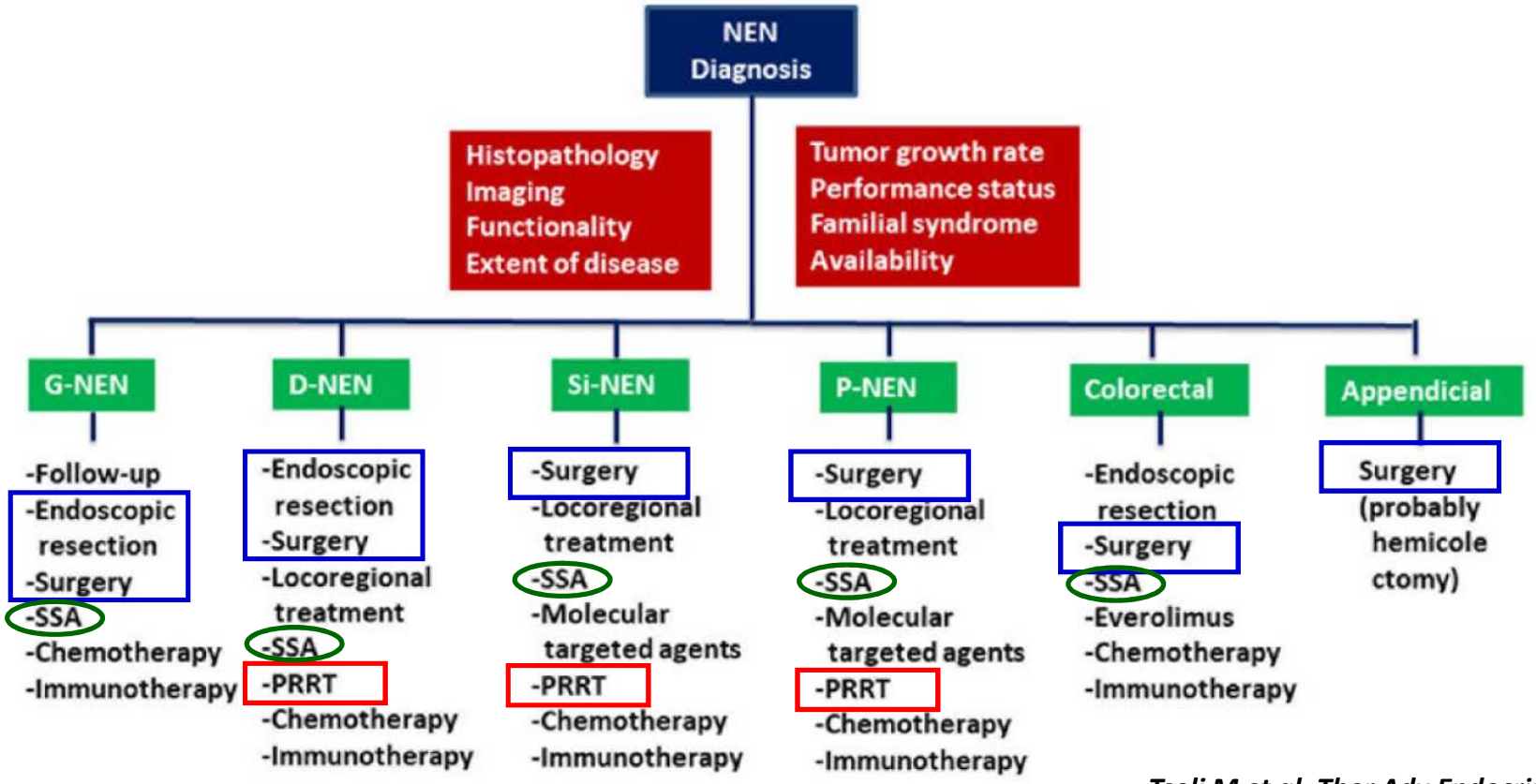
Come dobbiamo gestire il paziente affetto da NET? (3)



NET express a variety of receptors that may induce activating or inhibitory signaling

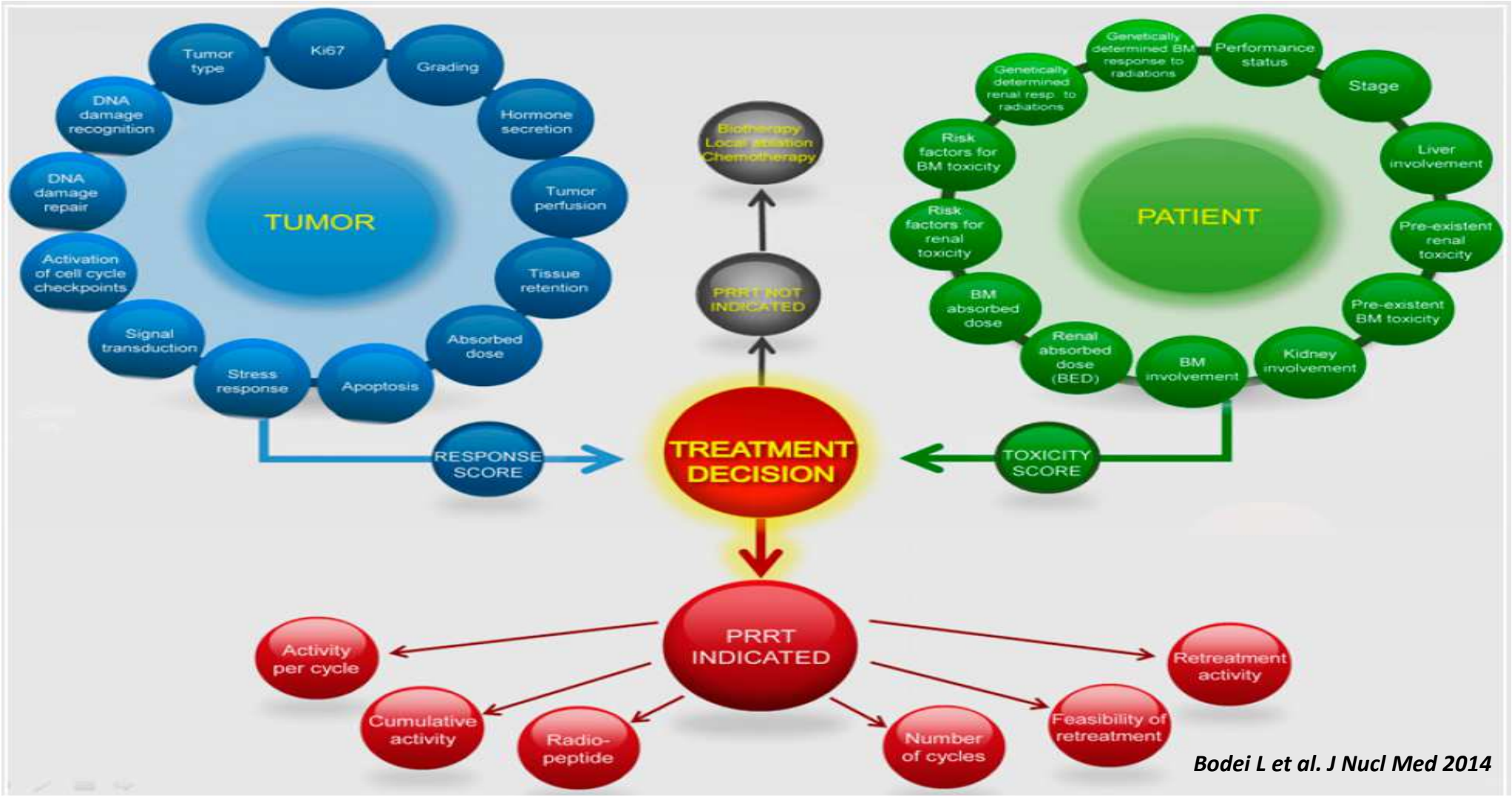
Come dobbiamo gestire il paziente affetto da NET? (4)

What is the sequence of treatment?



Tsoli M et al. Ther Adv Endocrinol Metab 2019

Nel paziente candidato a PRRT come procediamo?



Bodei L et al. J Nucl Med 2014

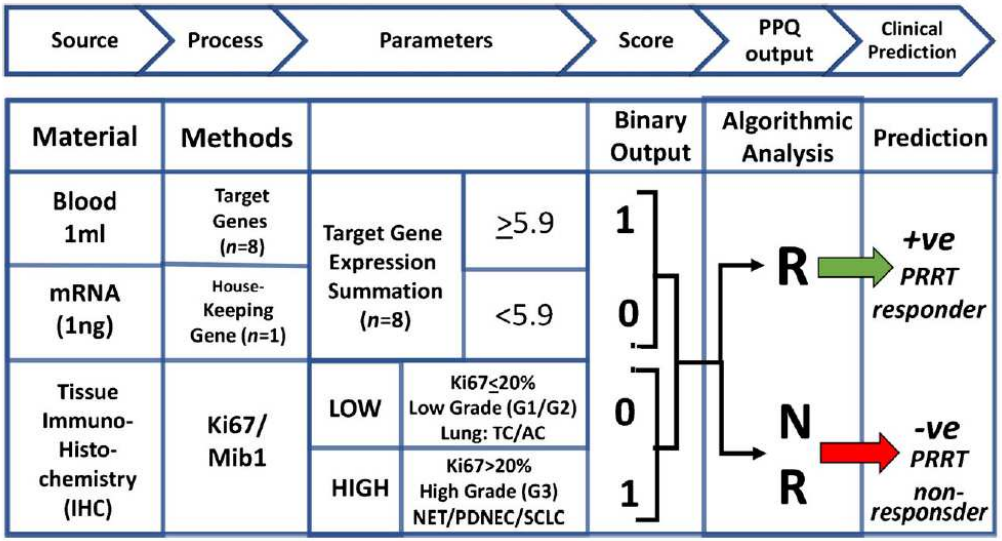
La selezione del paziente candidato a PRRT (1)

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:1155–1169
https://doi.org/10.1007/s00259-018-3967-6

ORIGINAL ARTICLE

PRRT genomic signature in blood for prediction of ^{177}Lu-octreotate efficacy

Lisa Bodei[1,2] · Mark S. Kidd[3] · Aviral Singh[4] · Wouter A. van der Zwan[5] · Stefano Severi[6] · Ignat A. Drozdov[3] · Jaroslaw Cwikla[7] · Richard P. Baum[2,4] · Dik J. Kwekkeboom[2,5] · Giovanni Paganelli[6] · Eric P. Krenning[2,8] · Irvin M. Modlin[2,9]



PRRT predictive quotient (PPQ) which stratifies PRRT **responders** from **non-responders**

Conclusion

The **PPQ** derived from circulating NET specific genes and tumor grade prior to the initiation of therapy is a highly specific predictor of the efficacy of PRRT with an **accuracy of 95%**.

PPQ for standardization of PRRT-enrollment?

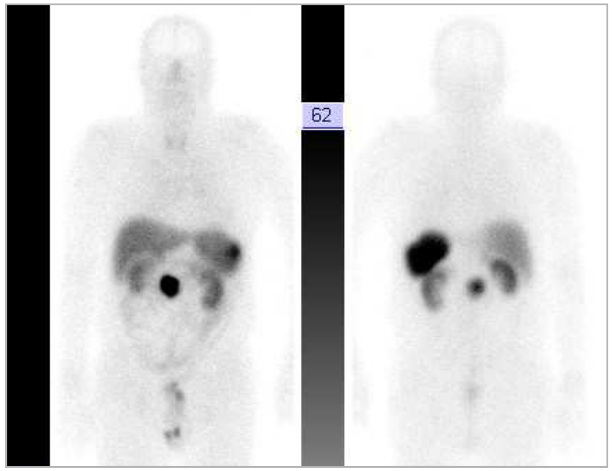
La selezione del paziente candidato a PRRT (2)

#008 (M-68aa)
Pancreas

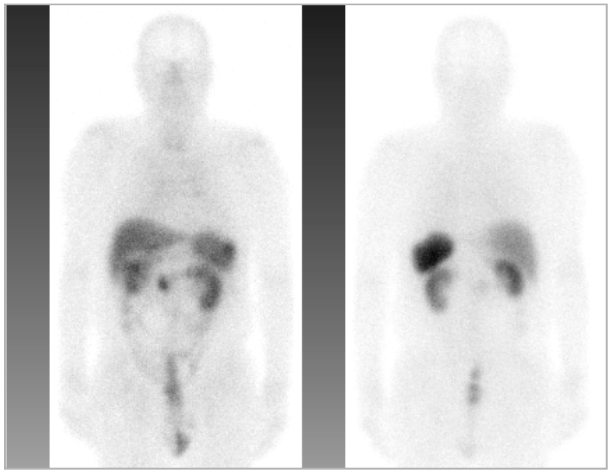
Ki67= 18%

G2

FDG PET +--
SUV 5.4



I cycle



V cycle

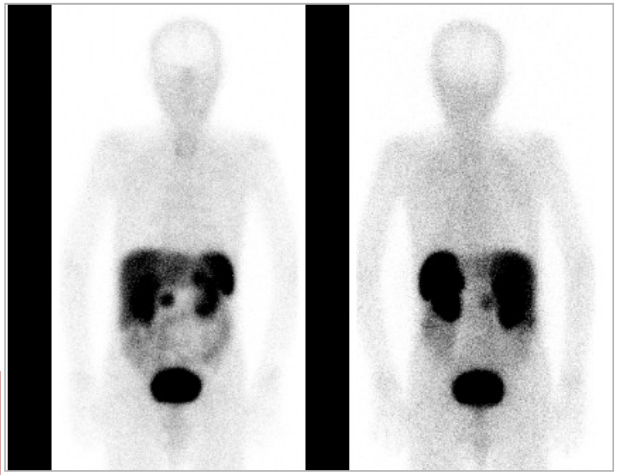
RESPONDER

#010 (M-65aa)
Pancreas

Ki67= 15%

G2

FDG PET +--
SUV 4.8



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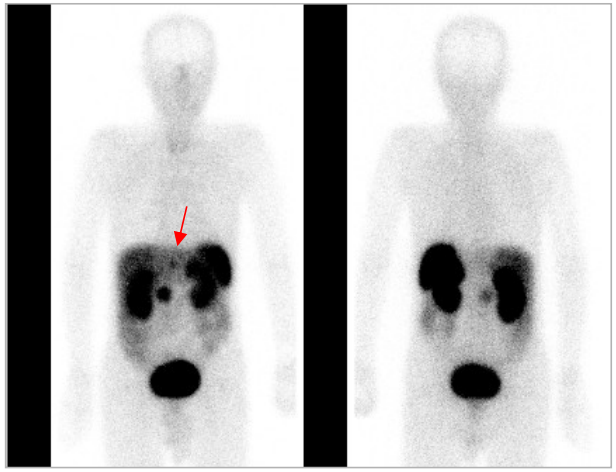


V cycle

NON-RESPONDER

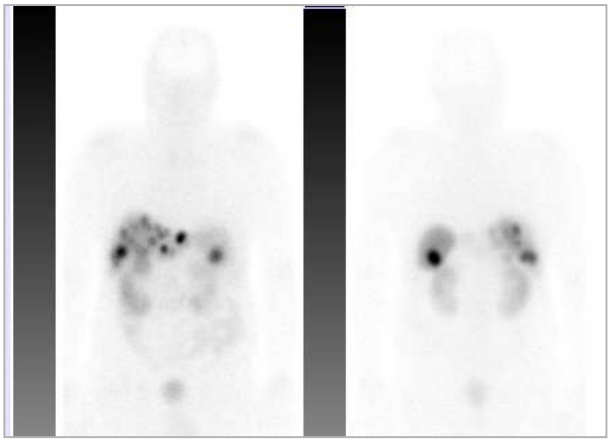
La selezione del paziente candidato a PRRT (3)

#014 (M-75aa)
Pancreas
(Tail) no Surg

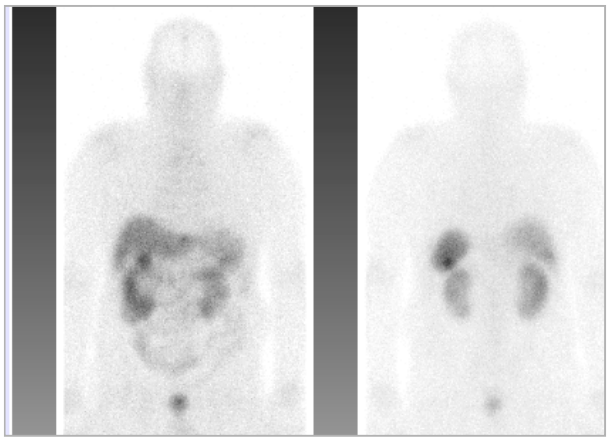
Ki67= 4%

G2

FDG PET ++-
SUV 8.4



I cycle



V cycle

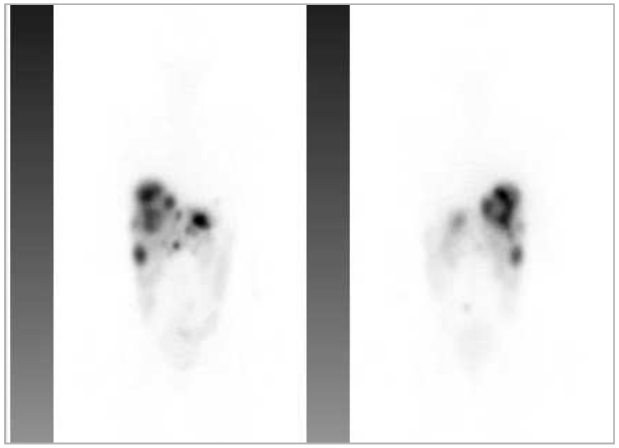
RESPONDER

#009 (F-61 aa)
Pancreas
(H-M-T) Surg

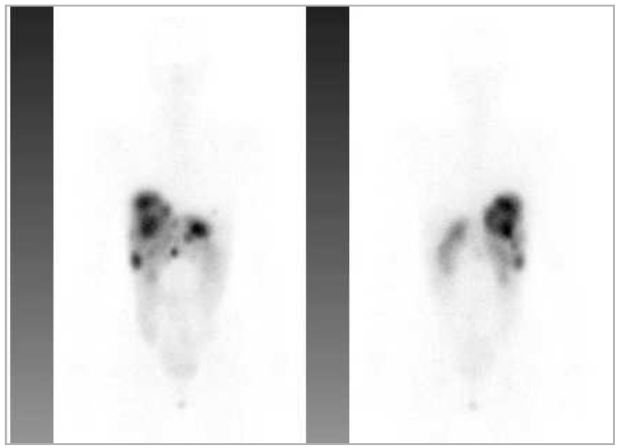
Ki67= 2-4%
liver **5-7%**

G2

FDG PET ++-
SUV n.a.



I cycle



V cycle

NON-RESPONDER

Dosimetria (1)

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2426–2441
https://doi.org/10.1007/s00259-018-4044-x

REVIEW ARTICLE

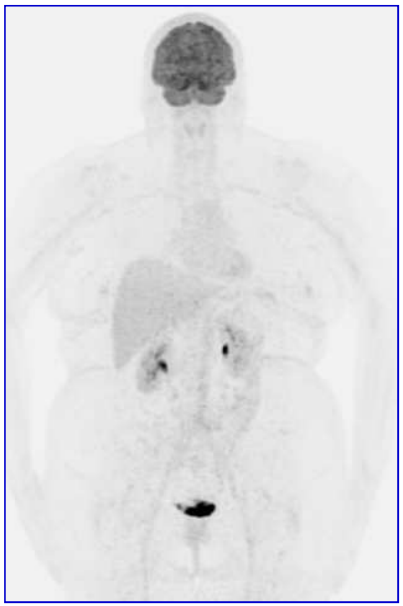
Correlation of dose with toxicity and tumour response to ^{90}Y- and ^{177}Lu-PRRT provides the basis for optimization through individualized treatment planning

Marta Cremonesi[1] · Mahila Esmeralda Ferrari[1] · Lisa Bodei[2] · Carlo Chiesa[3] · Anna Sarnelli[4] · Cristina Garibaldi[1] · Massimiliano Pacilio[5] · Lidia Strigari[6] · Paul Eugene Summers[1] · Roberto Orecchia[1] · Chiara Maria Grana[1] · Francesca Botta[1]

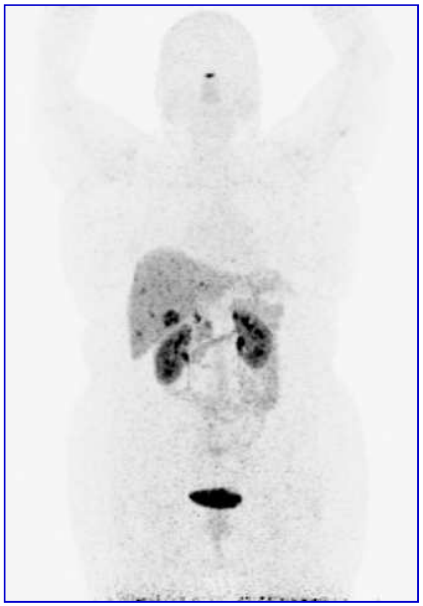
#003 (F-62aa)
PNET corpo-coda moderatamente differenziato
mts epatiche e scheletriche sincrone
(D: feb 2017)

Indice di proliferazione:
- Ki67: 20% (G2) sulla lesione pancreatica
- Ki67: 35% (G2) sulla maggiore lesione epatica

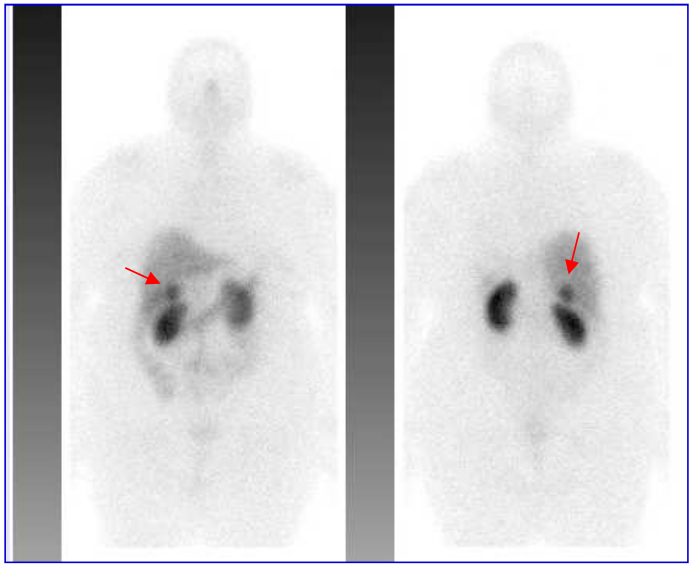
Terapie eseguite prima della PRRT:
- **Chemioterapia adiuvante** (mag-ott 2017) con risposta parziale a livello epatico e scheletrico
- **Intervento chirurgico** di spleno-pancreasectomia distale (gennaio 2018) e biopsia epatica con **Ki67: 6%**



PET con ^{18}F-FDG



PET con ^{68}Ga-DOTATOC



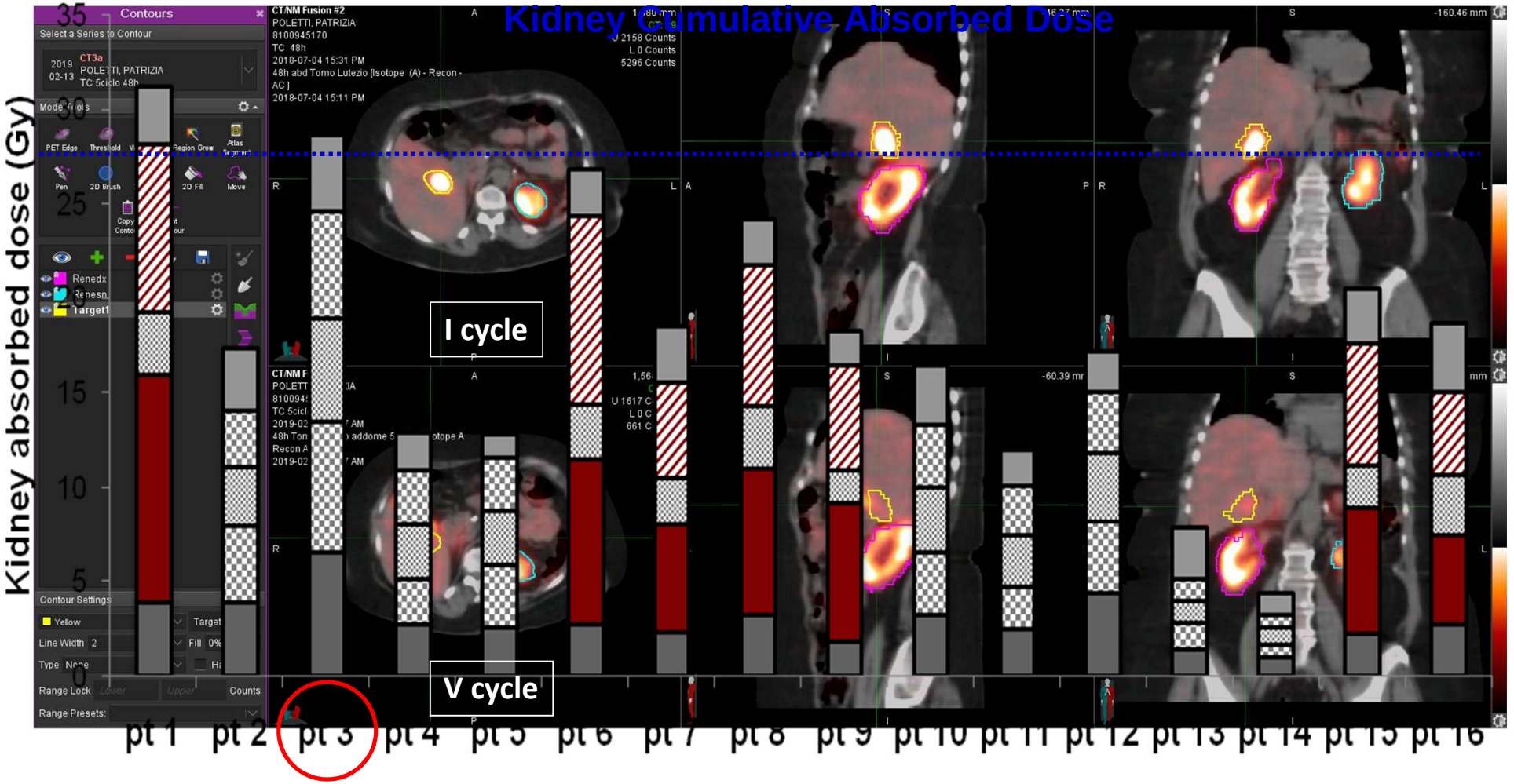
3.7.18 – I cycle: 5.5 GBq ^{177}Lu-DOTATOC

Perchè fare la dosimetria?

- Dosimetria per ottimizzare la PRRT con trattamento personalizzato per avere garanzie terapeutiche
- Dosimetria per ridurre gli «undertreatment»
- Dosimetria per contenere la tossicità (renale e midollare)

Renal AD: 7.6 Gy

Dosimetria (2)



Dosimetria (3)

Long-Term Hematotoxicity After Peptide Receptor Radionuclide Therapy with ^{177}Lu-Octreotate

Amir Sabet[1], Khaled Ezziddin[1], Ulrich-Frank Pape[2], Hojjat Ahmadzadehfar[1], Karin Mayer[3], Thorsten Pöppel[4], Stefan Guhlke[1], Hans-Jürgen Biersack[1], and Samer Ezziddin[1]

[1]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [2]Department of Hepatology and Gastroenterology, Charité, Campus Virchow Clinic, University Medicine Berlin, Berlin, Germany; [3]Department of Medicine, University Hospital Bonn, Bonn, Germany; and [4]Department of Nuclear Medicine, University Hospital Essen, Essen, Germany

Myelosuppression may be the dose-limiting toxicity in peptide receptor radionuclide therapy (PRRT). The aim of this study was to investigate the incidence, severity, and reversibility of long-term hematotoxicity in a large cohort of patient undergoing PRRT with ^{177}Lu-octreotate for metastatic neuroendocrine tumors. The impact of potential risk factors, including initial cytopenia, advanced bone metastatic disease, previous chemotherapy, and cumulative administered activity, and the protective effects of splenectomy were of particular interest.

PRRT-Induced Toxicities

Relevant hematotoxicity	Incidence per patient No.	Incidence per patient %	Incidence per cycle No.	Incidence per cycle %
Leukopenia	13	6.4	17	2.7
Grade 3	12	5.9	16	2.5
Grade 4	1	0.5	1	0.2
Thrombocytopenia	10	4.9	11	1.7
Grade 3	5	2.5	6	0.9
Grade 4	5	2.5	5	0.8
Anemia	7	3.4	7	1.1
Grade 3	7	3.4	7	1.1
Grade 4	0	0	0	0
Total	23	11.3	29	4.6

According to CTCAE.

^{177}Lu-PRRT: ≤ 29.6 GBq

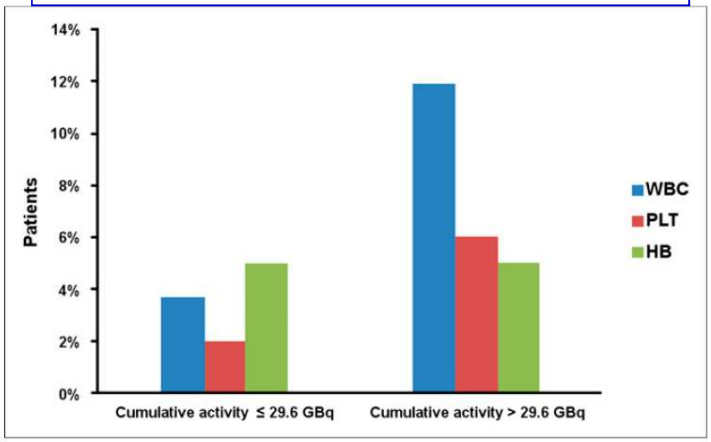
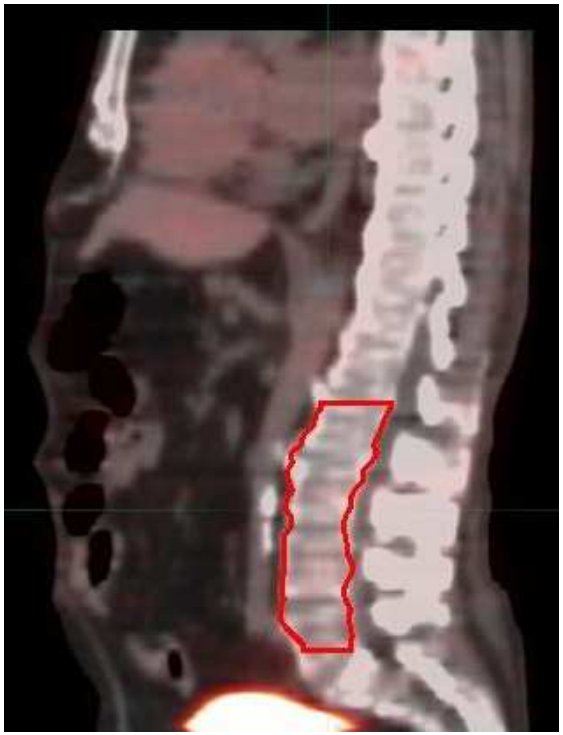


FIGURE 2. Incidence of significant hematotoxicity in patients receiving cumulative administered activities of less than or equal to 29.6 GBq (≤800 mCi) and greater than 29.6 GBq (>800 mCi). HB = hemoglobin; PLT = platelets; WBC = white blood cells.

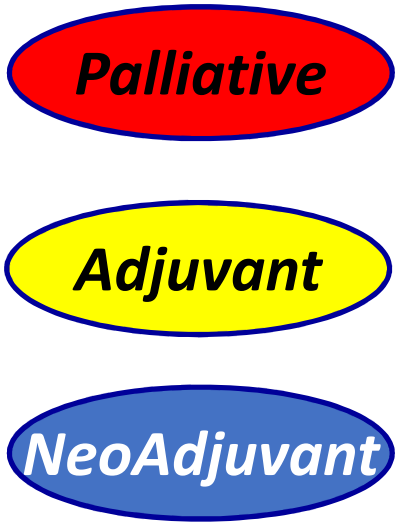


Possibili presentazioni cliniche nei NET

Presentazione clinica del paziente candidato a PRRT

I quadri clinici di presentazioni più frequenti relativi ai pazienti affetti da NET possono essere riassunti in base alla localizzazione e diffusione della malattia:

- **Presentazione 1**: presenza del tumore primitivo e concomitanti lesioni secondarie diffuse a livello loco regionale e/o a livello epatico e/o a livello extraepatico (per esempio: scheletro);
- **Presentazione 2**: pregressa asportazione del tumore primitivo con residue lesioni secondarie diffuse a livello loco regionale e/o a livello epatico e/o a livello extraepatico (per esempio: scheletro);
- **Presentazione 3**: presenza di lesioni secondarie diffuse a livello loco regionale e/o a livello epatico e/o a livello extraepatico (per esempio: scheletro) da tumore primitivo non noto;
- **Presentazione 4**: presenza di tumore primitivo non operabile in assenza di lesioni secondarie;
- **Presentazione 5**: presenza esclusiva di lesioni secondarie epatiche in paziente con tumore primitivo asportato o non noto.

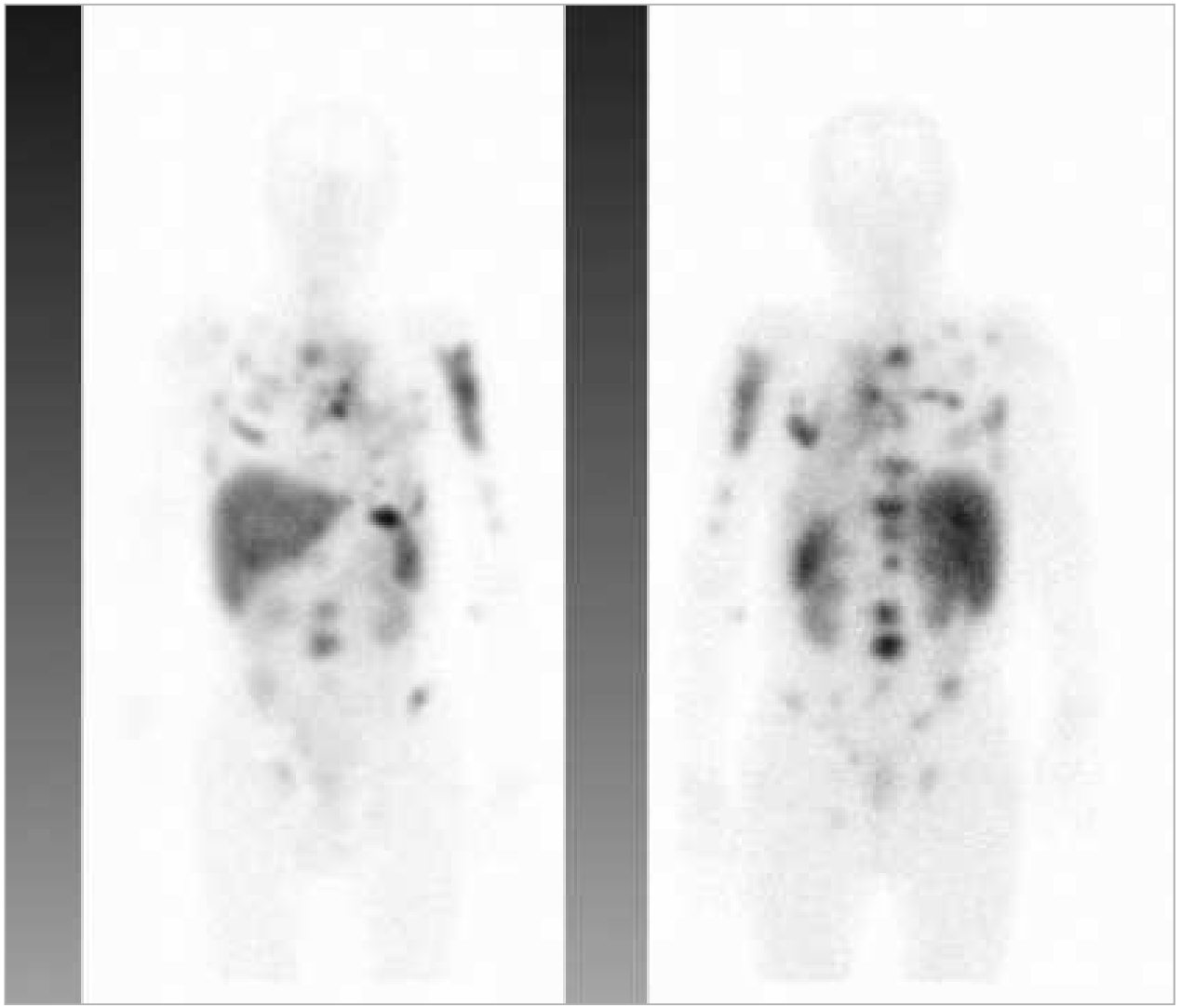


Palliative

 # 037 (M-65aa)
Carcinoide atipico polmonare
mts linfonodali e scheletriche
(D: feb 2013)

Indice di proliferazione:
- Ki67: 37% (G3)
- FDG PET ++-

Terapie eseguite prima della PRRT:
- **Chirurgia**
- **SSA**
- **Chemioterapia adiuvante (cisP+VP16)**
- **RT omero sx, C5**
- **Chemioterapia (TMZ)**

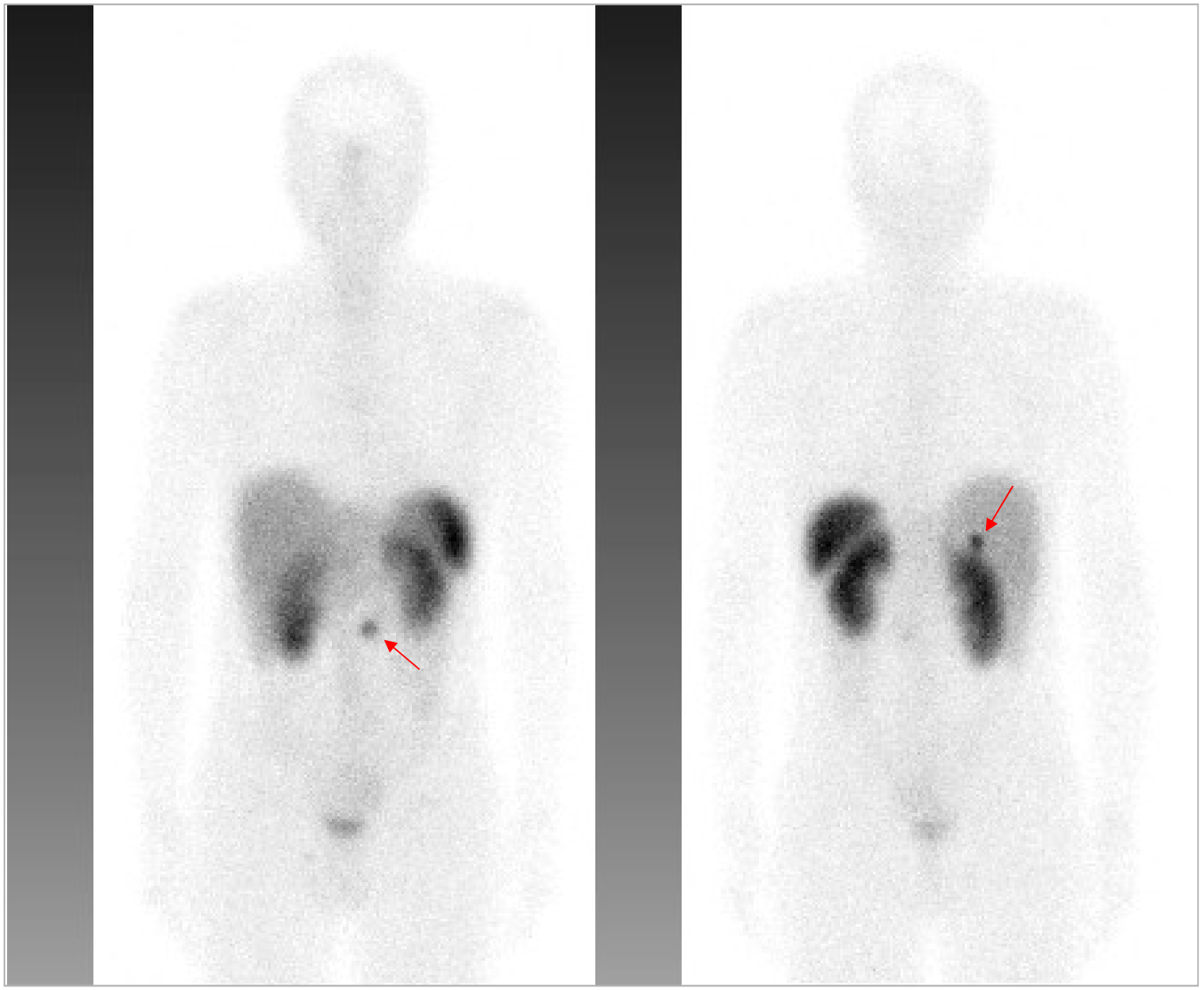


Adjuvant

#050 (M-45aa)
NET testa pancreas ben differenziato
mts linfonodali e scheletriche
(D: dic 2017)

Indice di proliferazione:
- Ki67: 4% (G2)
- FDG PET ---

Terapie eseguite prima della PRRT:
- **Chirurgia (DCP) gen 2018**
- **SSA**

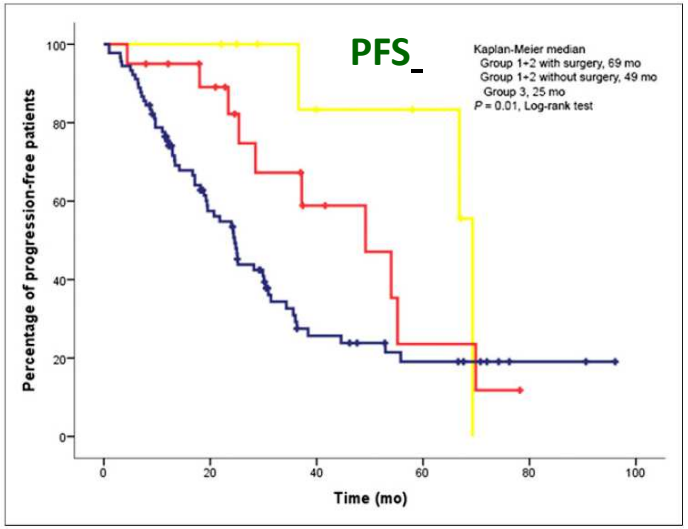


Il ruolo neoadiuvante della PRRT (1)

J Nucl Med 2015

Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Esther I. van Vliet[1], Casper H. van Eijck[2], Ronald R. de Krijger[3], Elisabeth J. Nieveen van Dijkum[4], Jaap J. Teunissen[1], Boen L. Kam[1], Wouter W. de Herder[5], Richard A. Feelders[5], Bert A. Bonsing[6], Tessa Brabander[1], Eric P. Krenning[1], and Dik J. Kwekkeboom[1]



*Surgery, 2017_*

Contents lists available at ScienceDirect

Surgery

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

Peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms

Stefano Partelli [a], Emilio Bertani [b], Mirco Bartolomei [c], Carolina Perali [a], Francesca Muffatti [a], Chiara Maria Grana [d], Marco Schiavo Lena [e], Claudio Doglioni [e], Stefano Crippa [a], Nicola Fazio [f], Giuseppe Zamboni [g], and Massimo Falconi [a,*]

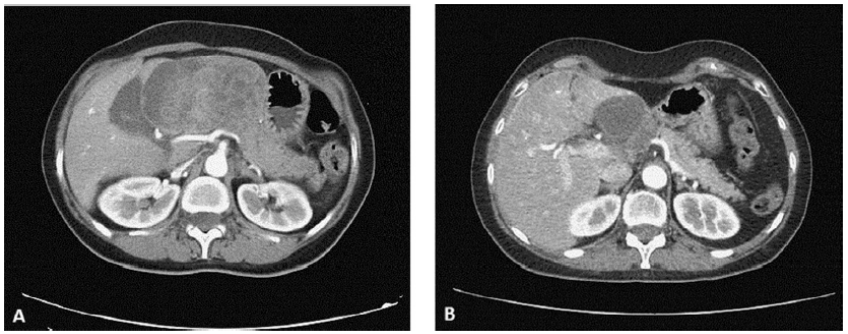


Fig. 1. Pretreatment (*A*) and follow-up CT 2 months after the end of 5 cycles of 90Y-DOTATOC (*B*) in a 59-year-old patient with a large PanNEN G2. Patient who presented at initial diagnosis with an enormous, resectable PanNEN, underwent distal pancreatectomy after neoadjuvant 90Y-DOTATOC.

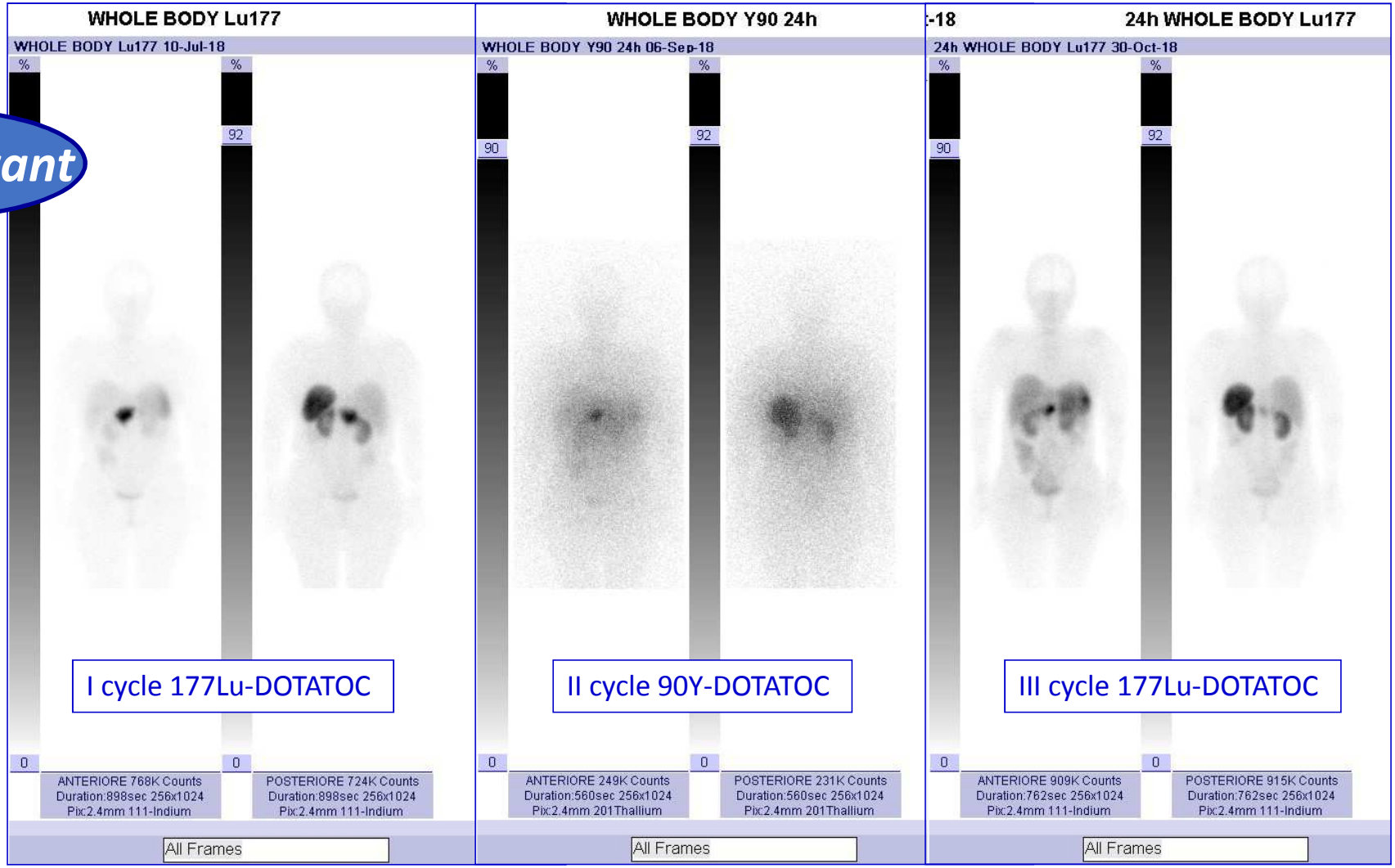
Il ruolo neoadiuvante della PRRT (2)

NeoAdjuvant

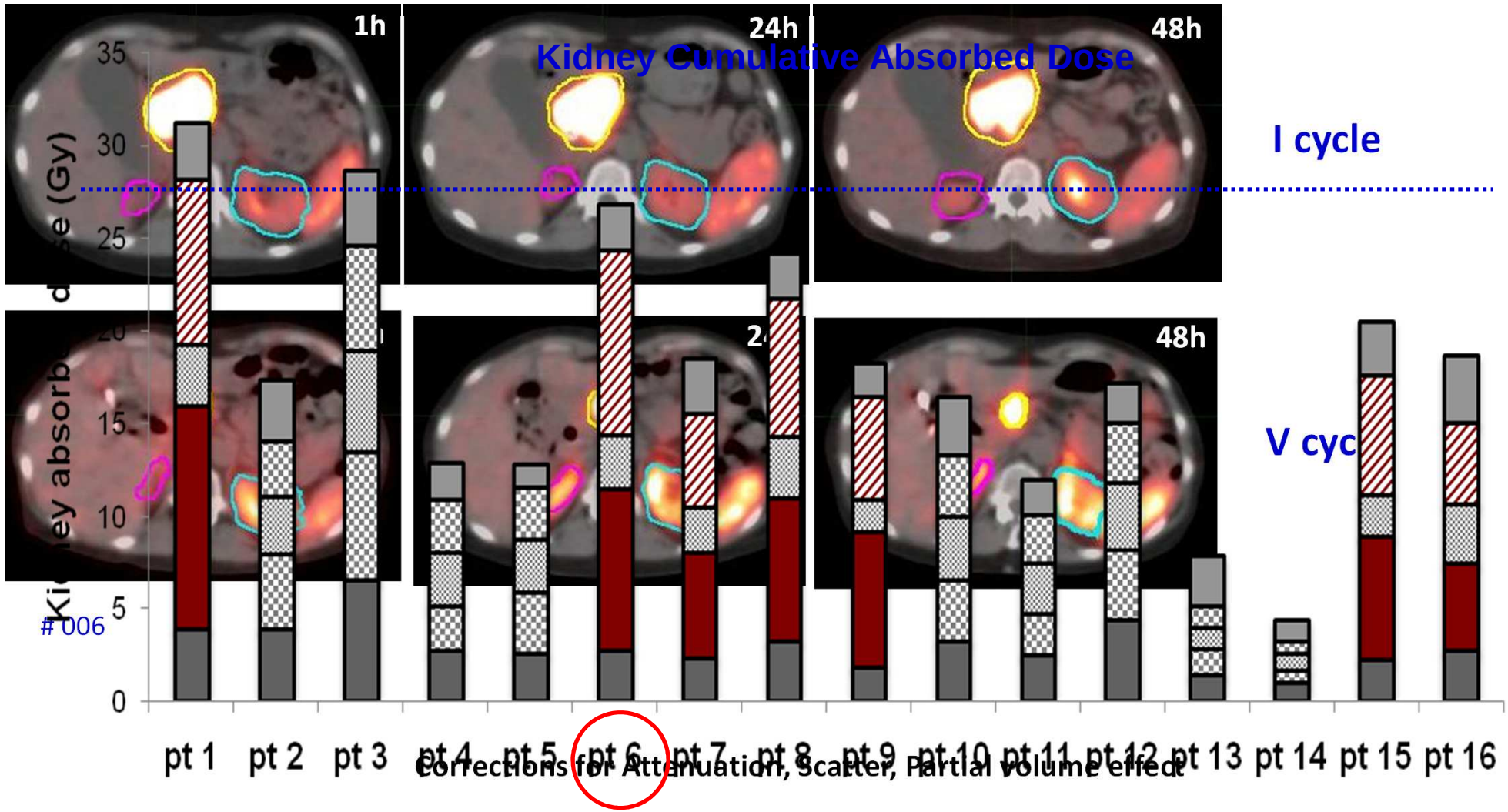
#006 (F-52aa)

NET testa pancreas

- Ki67: 15%
- G2
- FDG PET ++-



Il ruolo neoadiuvante della PRRT (3)



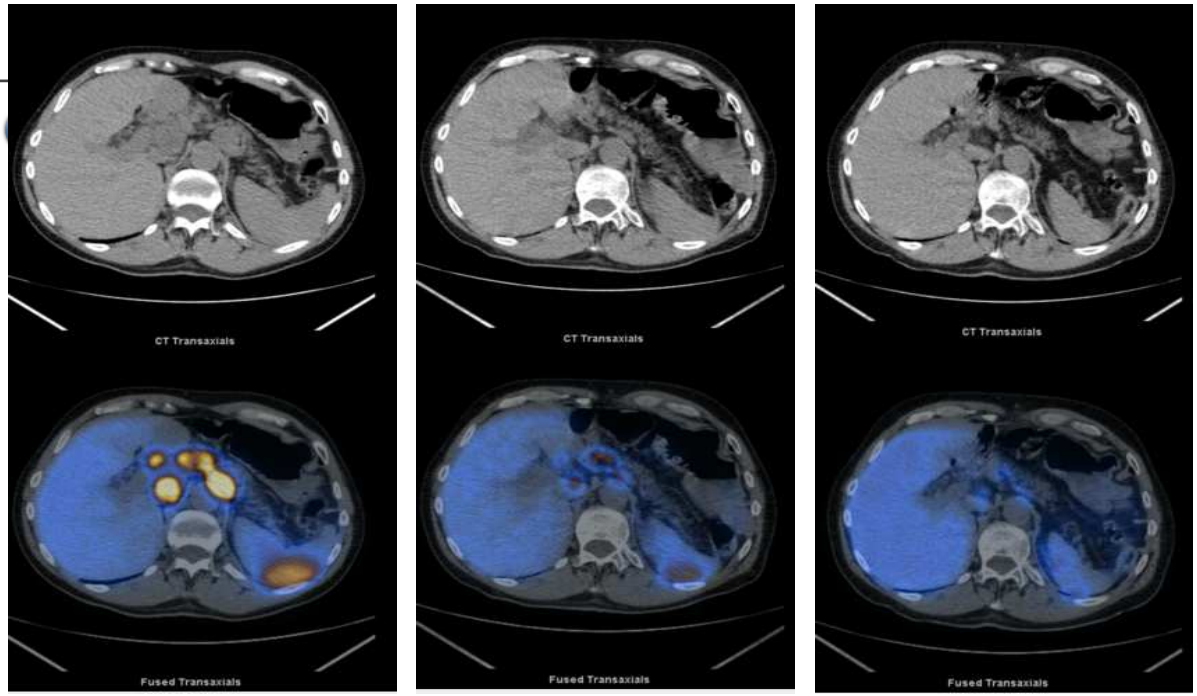
Come valutare la risposta alla PRRT?

Annals of Nuclear Medicine
https://doi.org/10.1007/s12149-018-1316-2

ORIGINAL ARTICLE

The RECIST criteria compared to conventional response evaluation after peptide receptor radionuclide therapy in patients with neuroendocrine neoplasms

Terje Løitegård[1] · Dag T. Berntzen[2] · Espen Thiis-Evensen[1]



Quality of Life

PERCIST → non validati

RECIST

Mismatch between morphologic and functional imaging

^{68}Ga-DOTANOC PET-CT → PR/CR

mdc-CT → SD

Validated PERCIST could improve standardization of PRRT-response evaluation

PRRT: futuri ambiti di studio e validazione

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-4158-1

ORIGINAL ARTICLE

Salvage peptide receptor radionuclide therapy with [^{177}Lu-DOTA,Tyr^3] octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours

W. A. van der Zwan[1] · T. Brabander[1] · B. L. R. Kam[1] · J. J. M. Teunissen[1] · R. A. Feelders[2] · J. Hofland[2] · E. P. Krenning[3] · W. W. de Herder[2]

Received: 20 May 2018 / Accepted: 5 September 2018

Retreatment with PRRT

Endocrine-Related Cancer (2011) **18** 595–602

Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases

Clemens Kratochwil, Ruben López-Benítez[1], Walter Mier, Sabine Haufe, Berend Isermann[2], Hans-Ulrich Kauczor[1], Peter L Choyke[3], Uwe Haberkorn and Frederik L Giesel

Hepatic intra-arterial PRRT

Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients

Jingjing Zhang*, Harshad R. Kulkarni*, Aviral Singh, Karin Niepsch, Dirk Müller, Richard P. Baum#

JNM, August 16, 2018

PRRT in Grade 3

CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 27, Number 9, 2012

DOI: 10.1089/cbr.2012.1276

Phase I-II Study of Radiopeptide ^{177}Lu-Octreotate in Combination with Capecitabine and Temozolomide in Advanced Low-Grade Neuroendocrine Tumors

Phillip G. Claringbold,[1] Richard A. Price,[2] and J. Harvey Turner[3]

PRRT in combination with other drugs

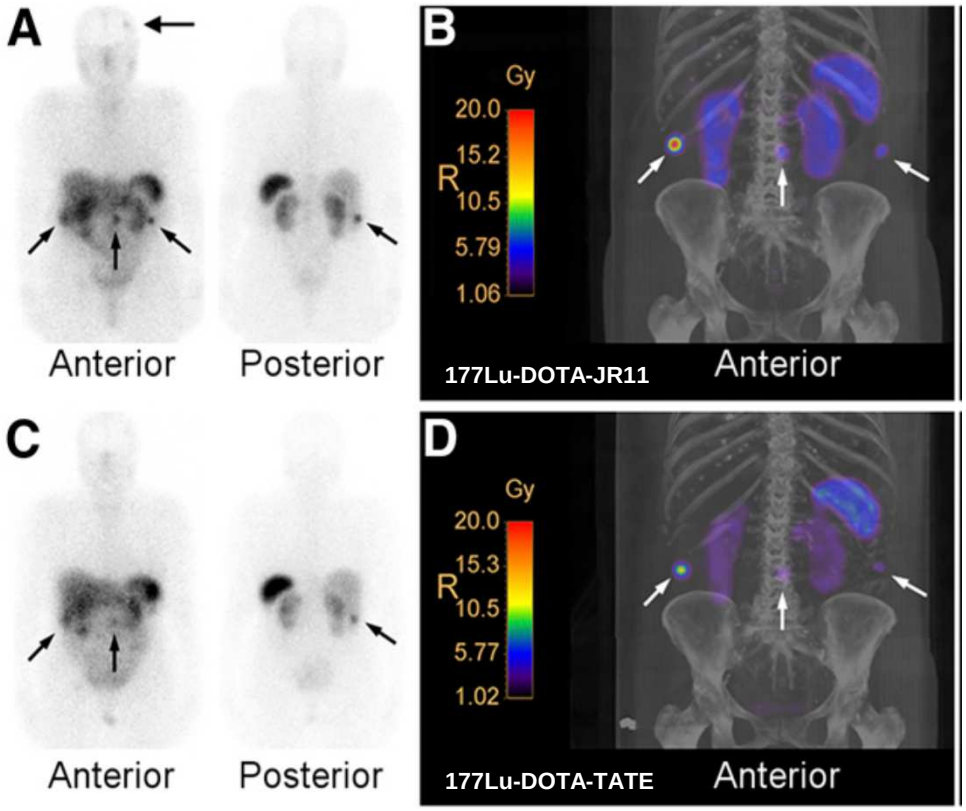
Radiofarmaci futuri (1)

Somatostatin Receptor Antagonists for Imaging and Therapy

Melpomeni Fani[1,2], Guillaume P. Nicolas[1,3], and Damian Wild[1,3]

J Nucl Med 2017; 58:61S–66S

[1]Division of Nuclear Medicine, University Hospital Basel, Basel, Switzerland; [2]Division of Radiopharmaceutical Chemistry, University Hospital Basel, Basel, Switzerland; and [3]Center for Neuroendocrine and Endocrine Tumors, University Hospital Basel, Basel, Switzerland



Antagonist
In-DOTA-BASS§
In-DOTA-JR11‖
Ga-DOTA-JR11‖ (Ga-OPS201)
Ga-NODAGA-JR11‖ (Ga-OPS202)
Lu-DOTA-JR11‖ (Lu-OPS201)

^{68}Ga/^{177}Lu-OPS202

- **better tumor uptake**
- **better image contrast *(T/nonT ratio)***
- **higher sensitivity**
- **potential higher efficacy in PRRT**

Radiofarmaci futuri (2)

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-014-2857-9

ORIGINAL ARTICLE

^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience

C. Kratochwil · F. L. Giesel · F. Bruchertseifer · W. Mier · C. Apostolidis · R. Boll · K. Murphy · U. Haberkorn · A. Morgenstern

α-emitters

Received: 31 March 2014 / Accepted: 3 July 2014

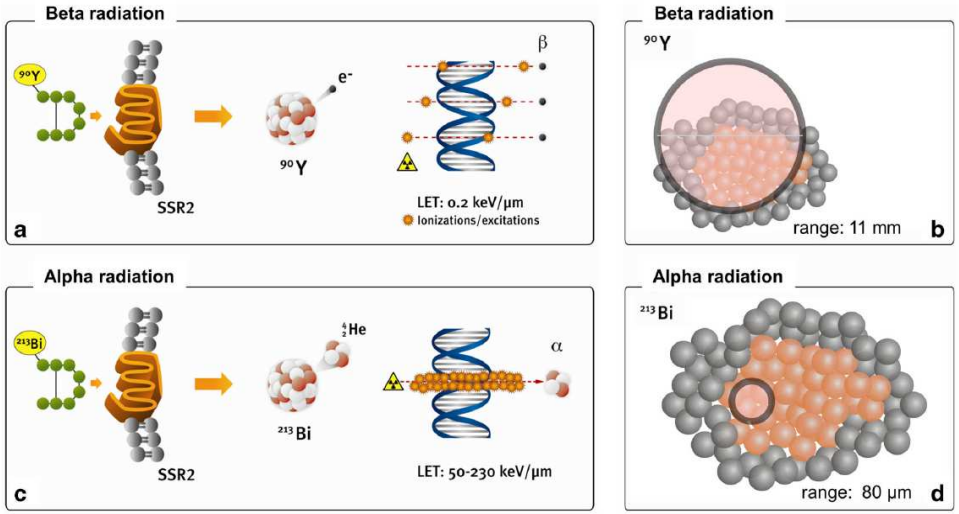
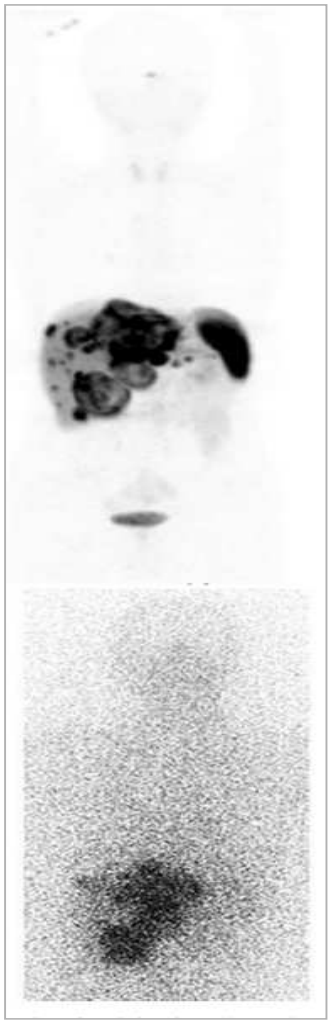


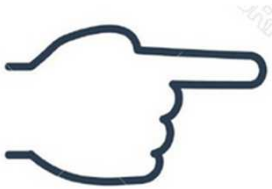
Fig. 1 Comparison of alpha and beta emitters. **a**, **c** After binding of the radionuclide-labelled octreotide analogue DOTATOC to the somatostatin receptor subtype-2 (*SSR2*), which is overexpressed in NETs, the emitted alpha particle causes high-density ionization effects, resulting mainly in double-strand DNA breaks. In contrast, the beta particles emitted by established radiopharmaceuticals mainly cause repairable single-strand DNA damage. **b**, **d** The tissue range of alpha emitters (about 80 µm) is approximately two cell diameters. The mean tissue range of the beta emitter ^{90}Y (3 mm) is approximately 75 cell diameters. Thus, alpha emitters result in less "cross-fire" radiation to surrounding normal tissue



CONCLUSIONI

Le Terapie Medico Nucleari:

- ❑ **sono efficaci e sicure (ma anche potenzialmente pericolose)**
- ❑ **devono essere proposte in ambito multidisciplinare**
- ❑ **la loro collocazione nei piani di cura può essere ottimizzata**
- ❑ **attualmente la loro standardizzazione non è completamente perseguibile**
- ❑ **di contro devono essere erogate in modo personalizzato**



"standardizzazione della personalizzazione del trattamento"

«In un contesto normativo europeo che verosimilmente limiterà gli studi spontanei di nuovi radiofarmaci, sarà necessario sviluppare un dialogo scientifico con l'Industria, pur mantenendo sempre l'autonomia decisionale dell'atto medico a garanzia della salute del paziente»


Grazie per l’attenzione