SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova

Istituto in tecnologie avanzate e modelli assistenziali in oncologia
Istituto di Ricovero e Cura a Carattere Scientifico

La terapia radiorecettoriale quando e come: efficacia e tossicità

Angelina Filice

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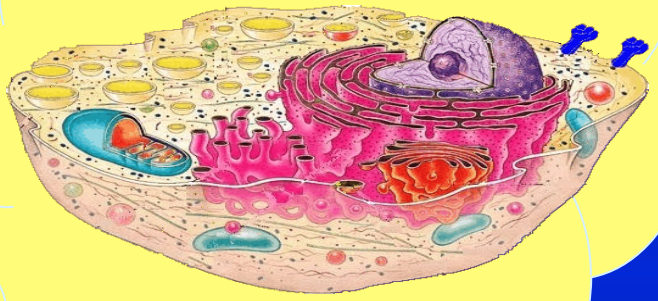
Imaging medico-nucleare=Imaging molecolare

Le immagini sono espressione delle caratteristiche biochimiche e metaboliche dei tessuti

Peptidi

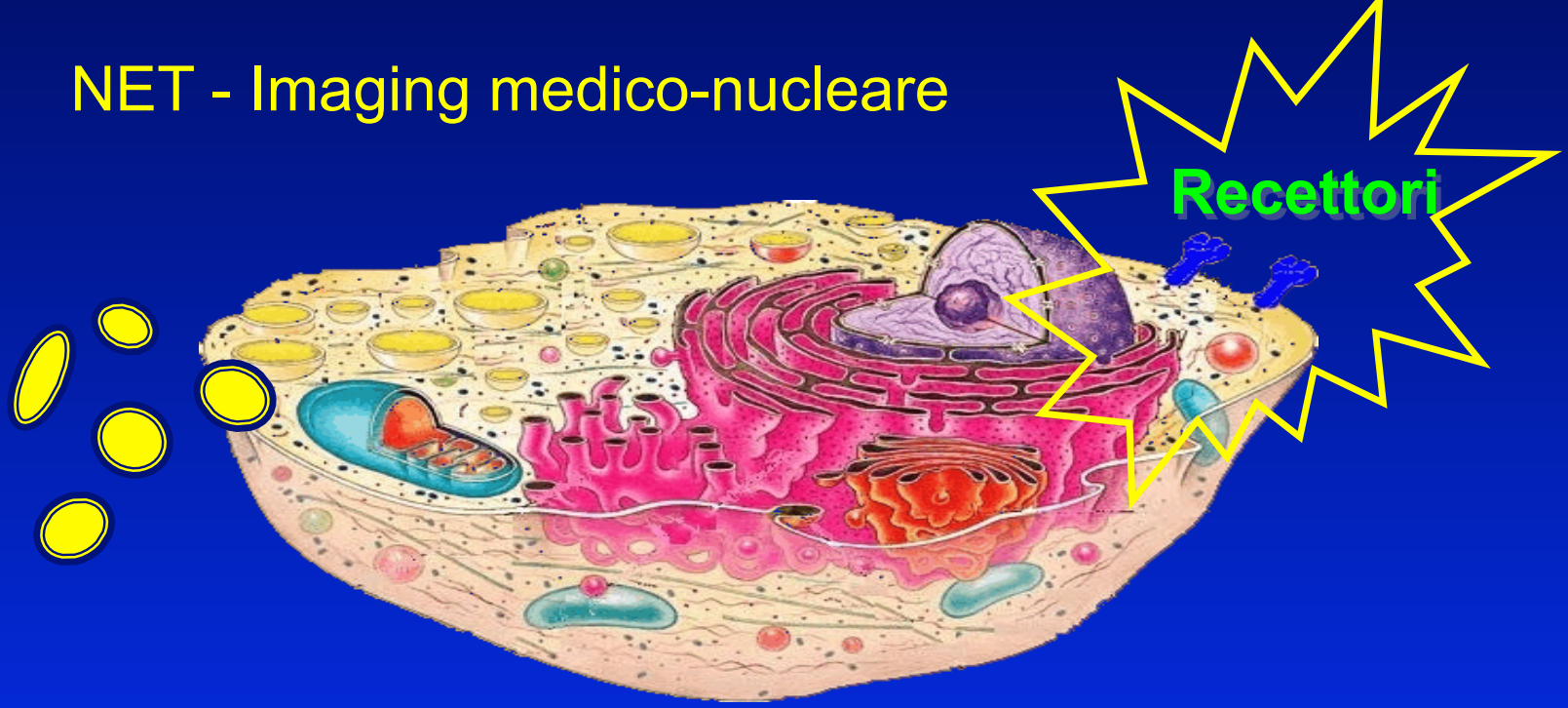
Recettori

Ormoni



Neurotrasmettitori

NET - Imaging medico-nucleare



Recettori per Peptidi Espressi Preferenzialmente dai Tumori GEP

- **Somatostatina (5 sotto-tipi)**
- **Bombesina (3 sotto-tipi)**
- **Colecistochinina (2 sotto-tipi)**
- **VIP (2 sotto-tipi)**
- **Glucagone (1 principale)**

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%

Imaging medico-nucleare

Presupposti fisiopatogici

Bersaglio:

neoplasie neuroendocrine che esprimono recettori per la somatostatina

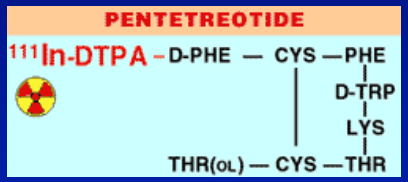
Analoghi della somatostatina

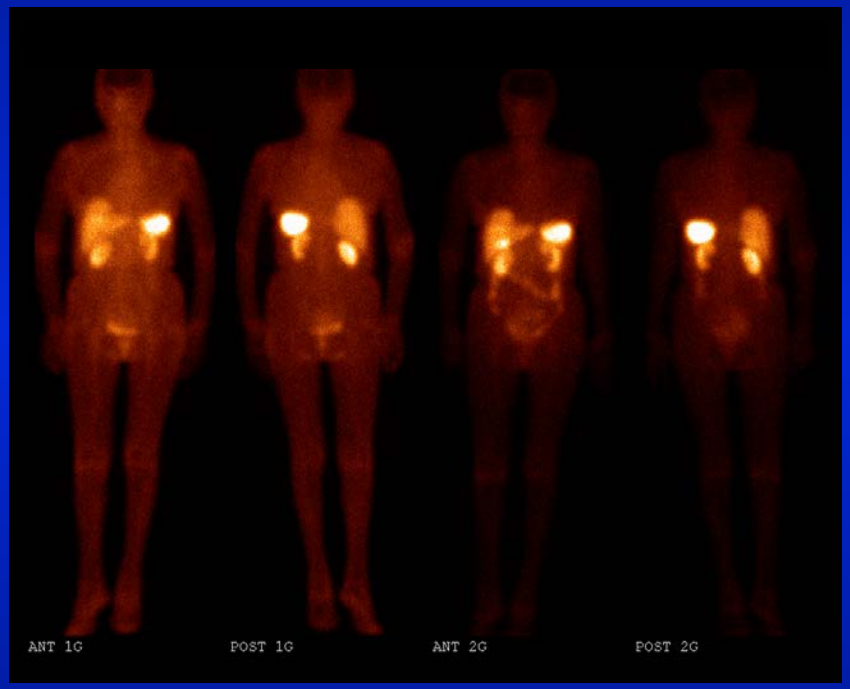
Metodiche

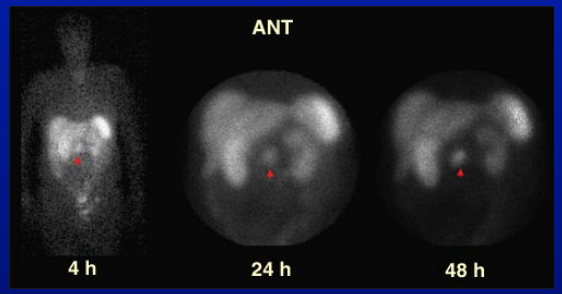
Scintigrafia, SPECT, SPECT/CT con
- ^{111}**In-Octreoscan**

PET/CT con
- ^{68}**Ga-DOTATOC**
- ^{68}**Ga-DOTANOC**
- ^{68}**Ga-DOTATATE**

Pentetreotide (Octreoscan)

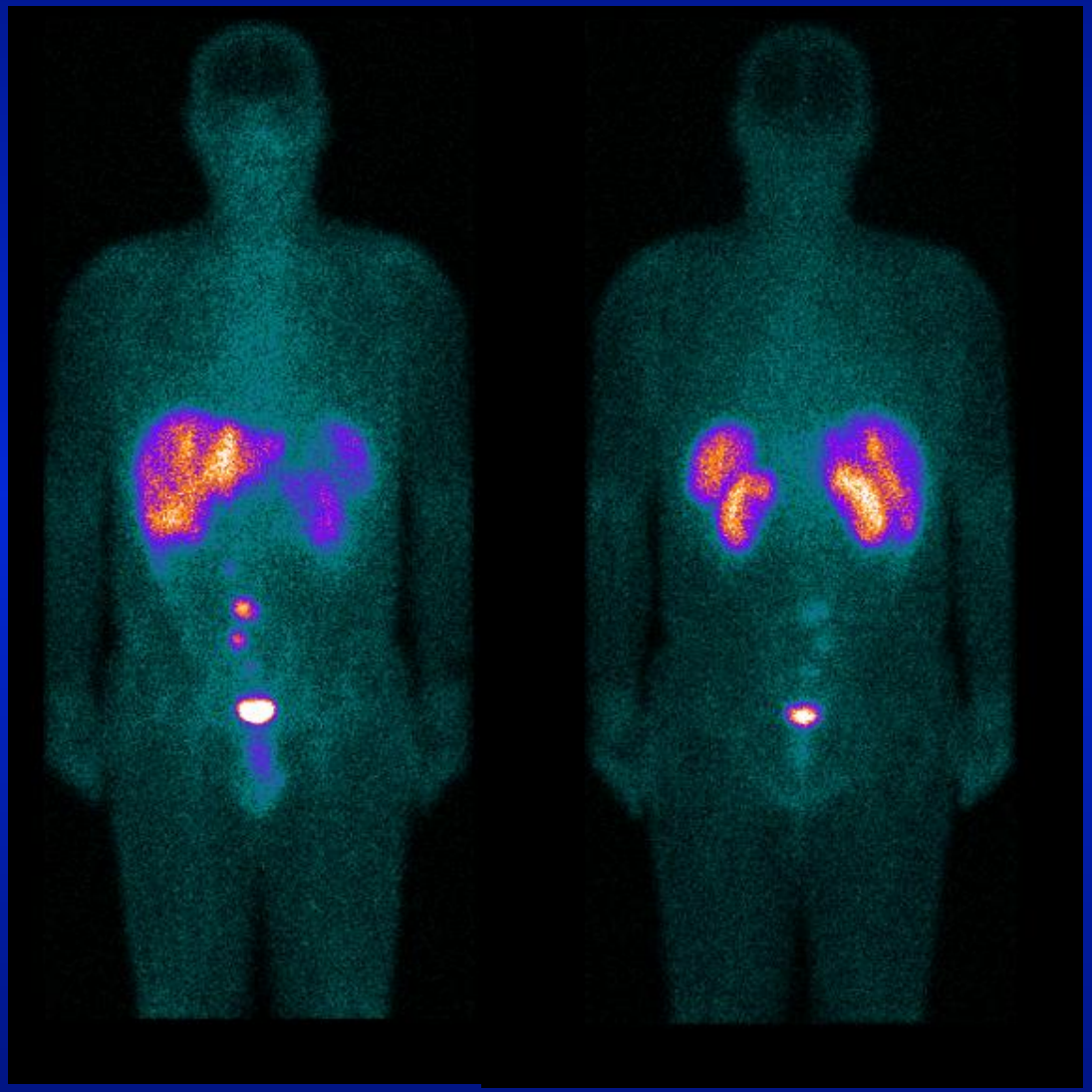






- Acquisizioni: 4 ore, 24 ora (48 ora)
- Risoluzione spaziale > 1,5 cm
- Elevato uptake fegato, milza e reni
- Attività tardiva (aspecificità intestinale?)

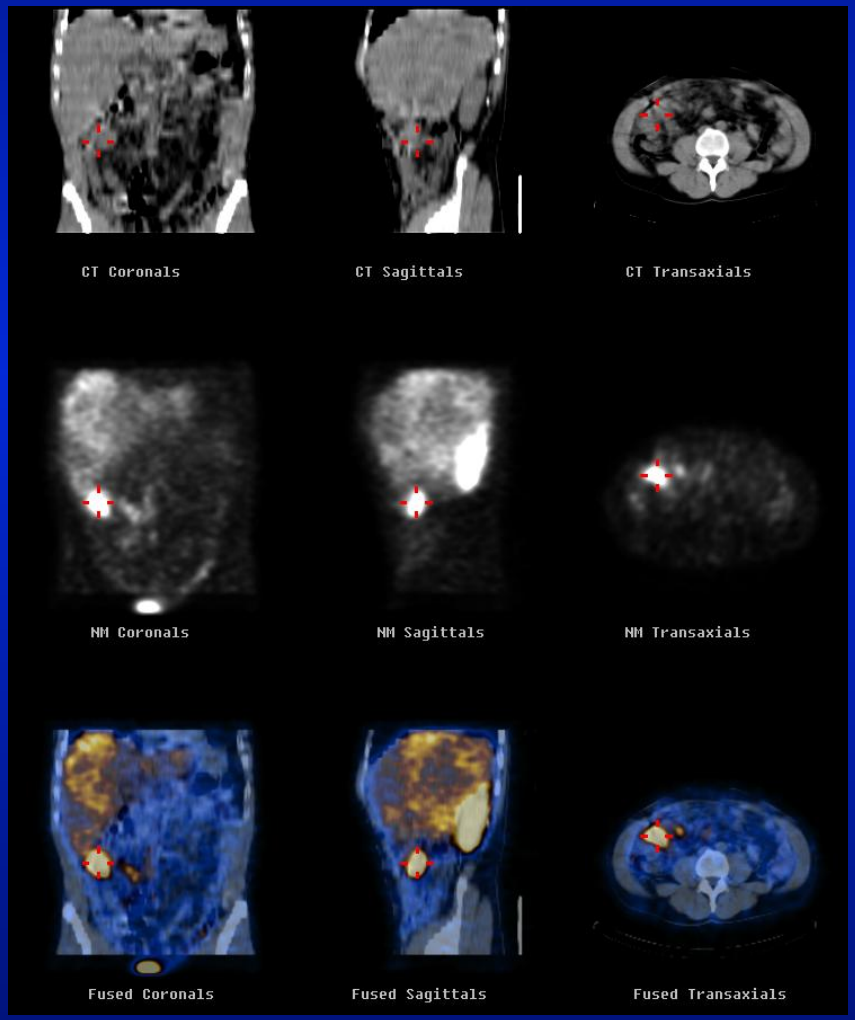
Scintigrafia con ^{111}In-Octreoscan

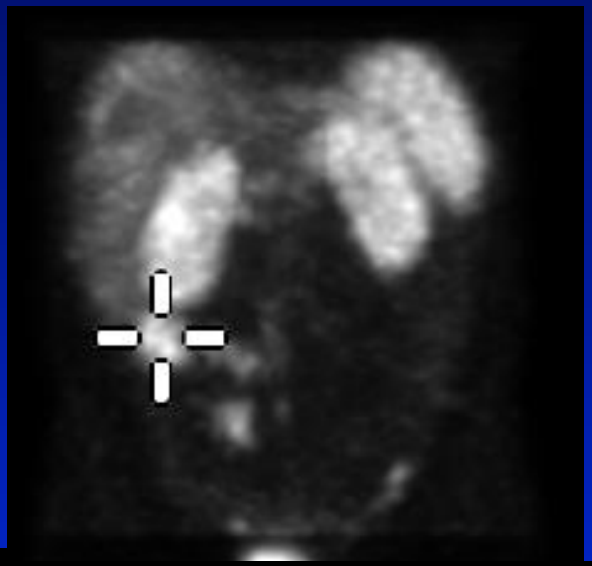


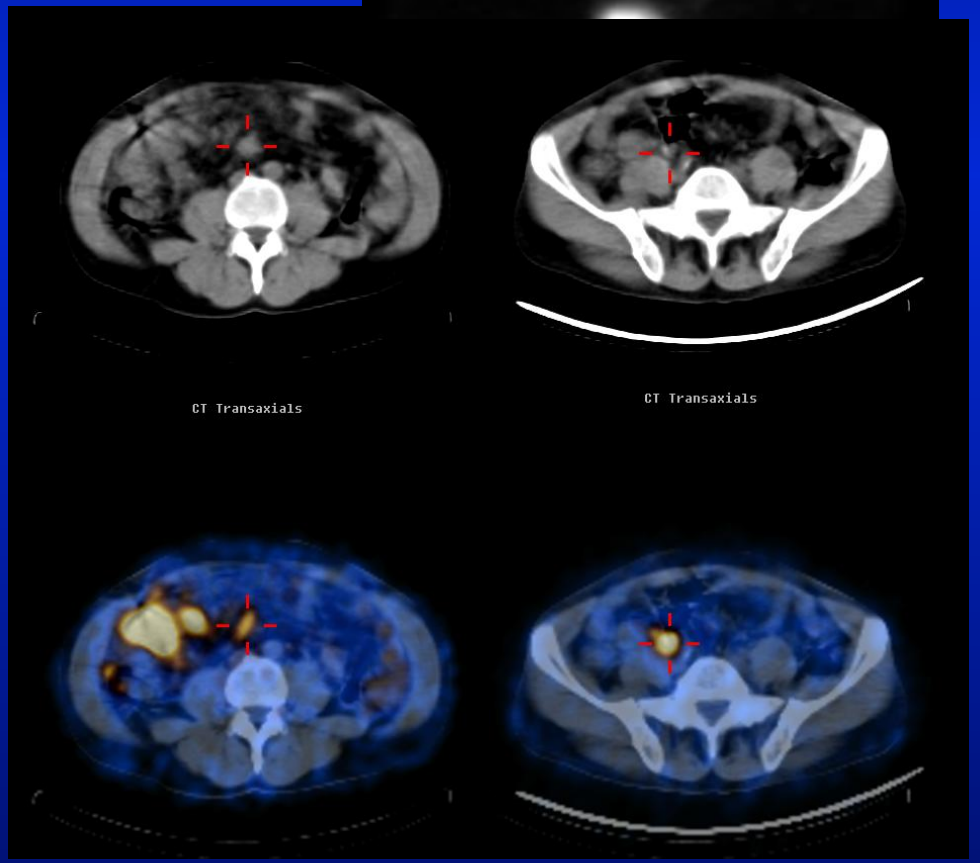
Carcinoide Ileale

Octreoscan®: SPECT/CT

Carcinoide Ileale



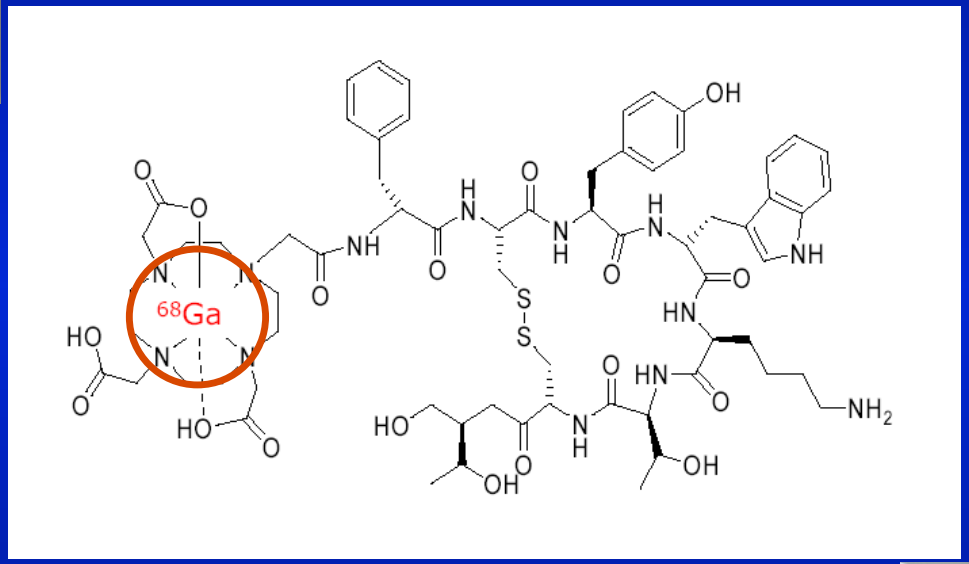


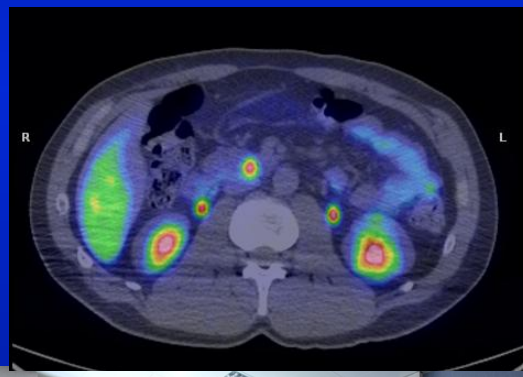


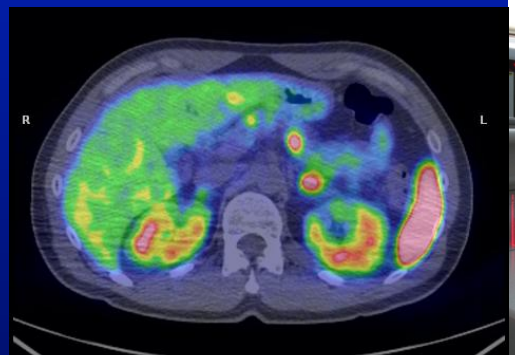
Prof. Giuliano Mariani - Pisa

^{68}Ga DOTATOC/TATE PET/CT

Generatore 68Ge/68Ga





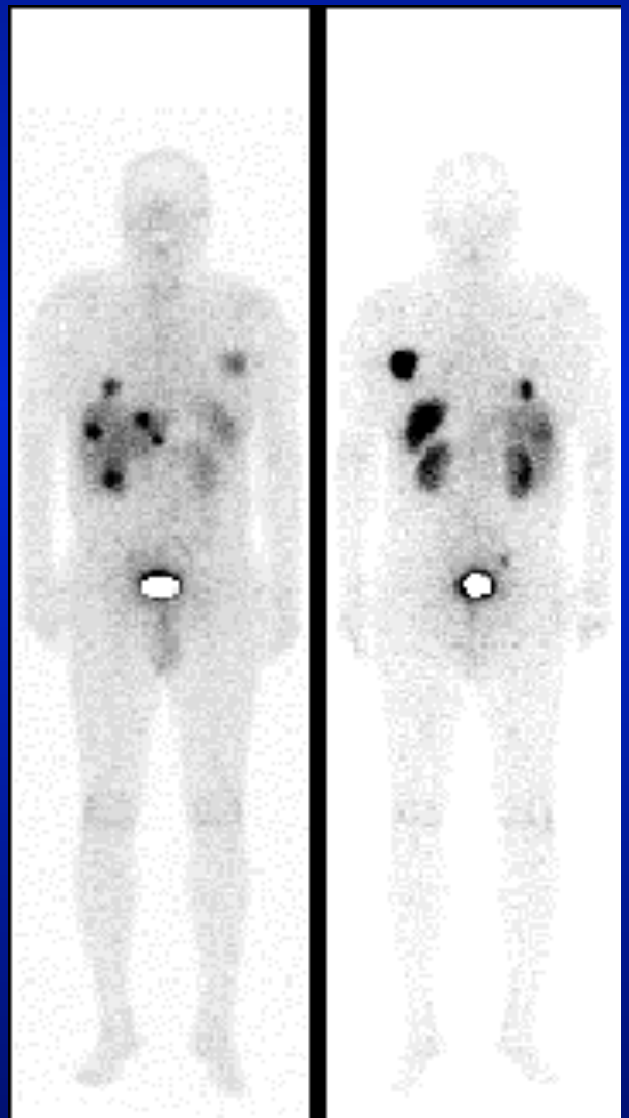


^{68}Ga-*DOTATOC*/*TATE* PET/CT

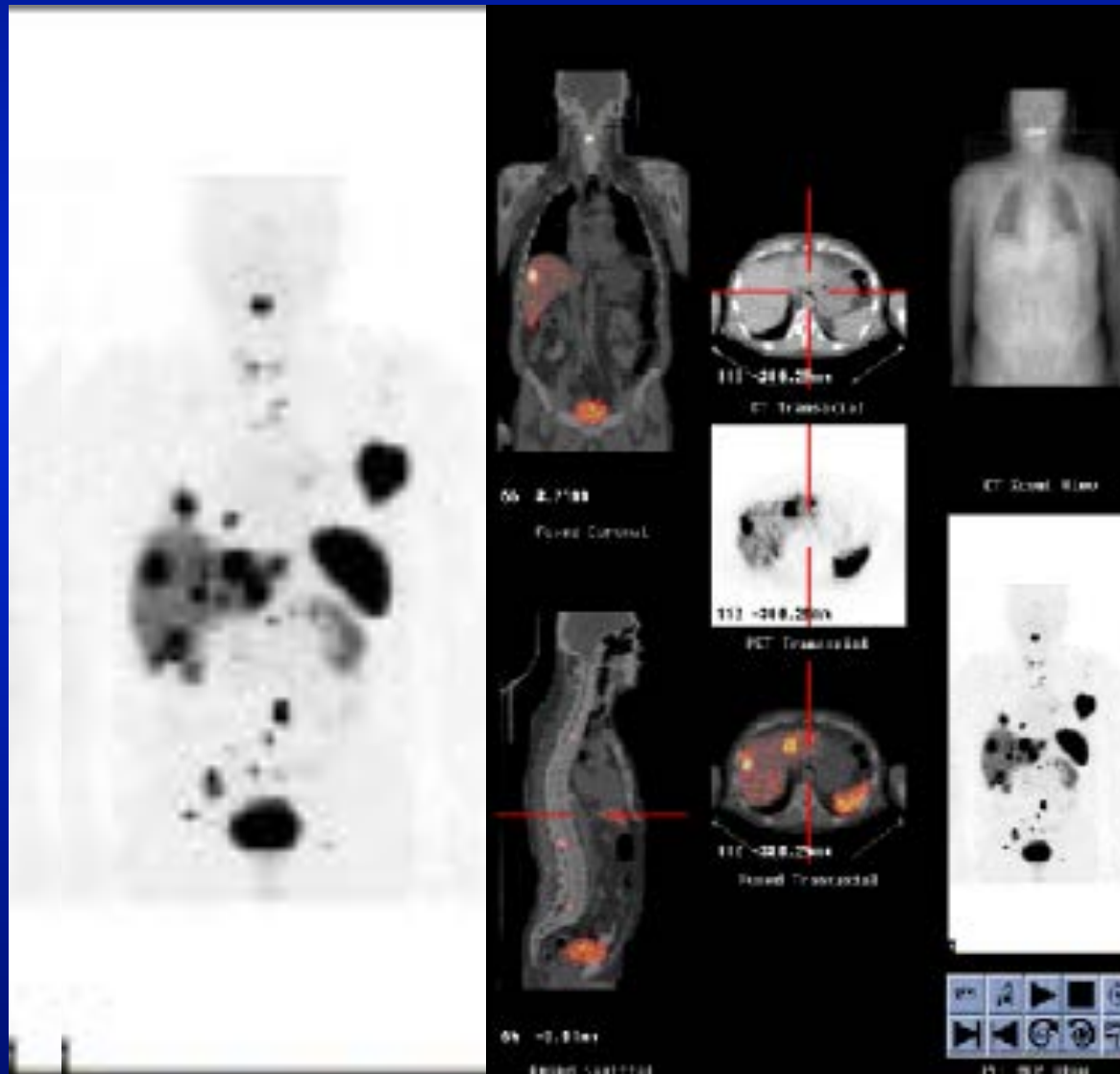
- Maggior affinità per SSTR2 e buona affinità per SSTR5 rispetto a octreoscan
- Miglior contrasto
- Migliore sensibilità ed accuratezza diagnostica (soprattutto su fegato ed addome)
- Potere di risoluzione spaziale: 5 mm
- Possibilità di correlazione diretta del dato funzionale con il dato morfologico

Tumore neuroendocrino del tratto gastroenteropancreatico metastatico

111In-Octreoscan



^{68}Ga-Dotatoc PET/CT



^{68}Ga-*DOTATOC/TATE* PET/CT
INDICAZIONI

- Localizzazione
- Stadiazione

- **Selezione dei pazienti per terapia radiorecettoriale**

- Ristadiazione
- Follow-up

^{68}Ga-DOTANOC PET/CT Clinical Impact in Patients with Neuroendocrine Tumors

J Nucl Med 2010; 51:669–673

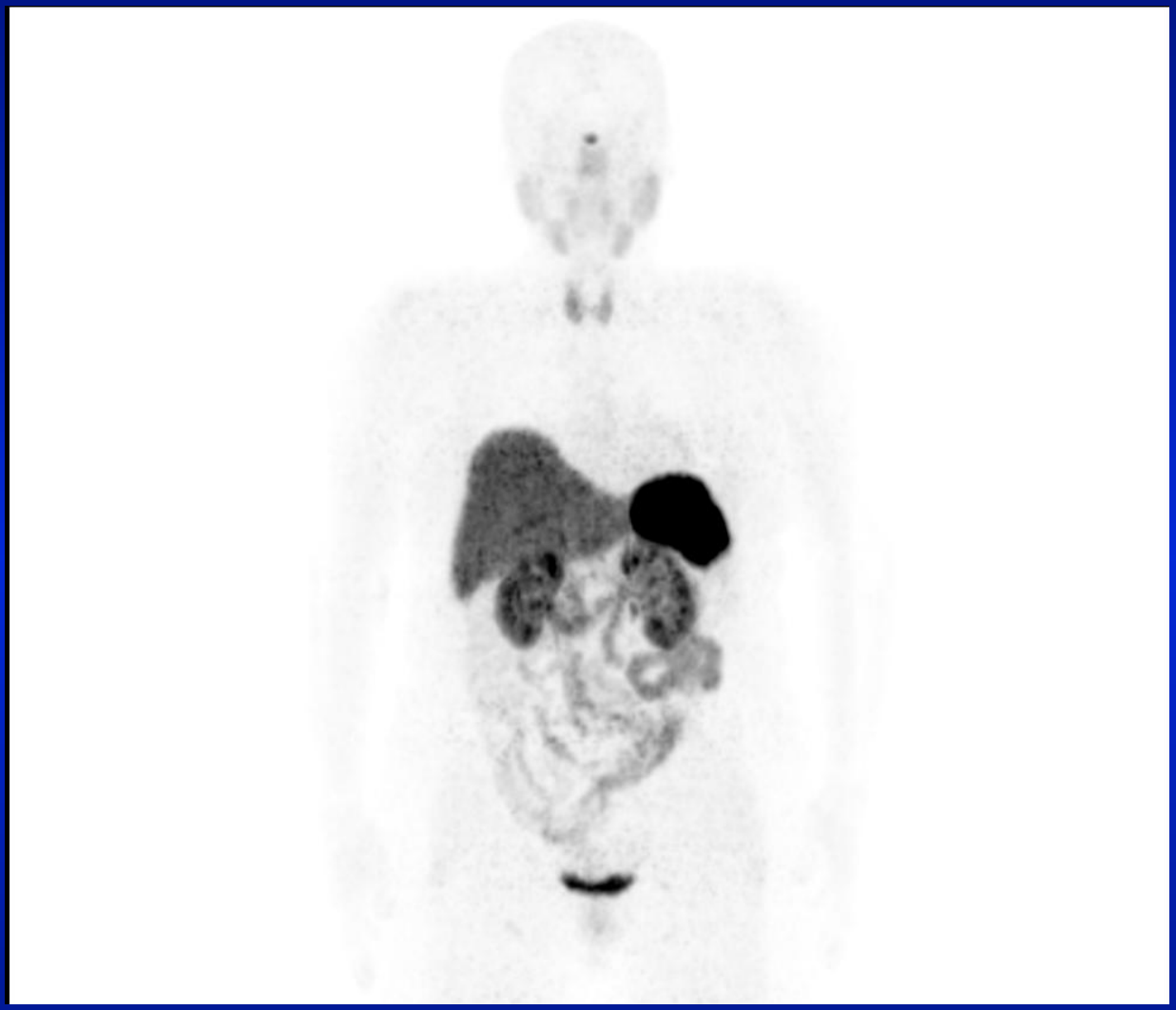
Valentina Ambrosini[1], Davide Campana[2], Lisa Bodei[3], Cristina Nanni[1], Paolo Castellucci[1], Vincenzo Allegri[1], Gian Carlo Montini[1], Paola Tomassetti[2], Giovanni Paganelli[3], and Stefano Fanti[1]

[1]Department of Nuclear Medicine, Azienda Ospedaliero-Universitaria di Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy; [2]Department of Internal Medicine, Azienda Ospedaliero-Universitaria di Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy; and [3]Division of Nuclear Medicine, European Institute of Oncology, Milano, Italy

TABLE 3. Overall Impact of PET on Clinical Management

Impact	*n*
SSA medical therapy started or continued	3/4
SSA medical therapy prevented	2
PRRT started or continued	26*/1
PRRT prevented	0
Radiotherapy started	1
Surgery initiated	6*
Surgery prevented	6
Indication for further diagnostic procedure	1
Indication for liver transplantation	1
Total	51*

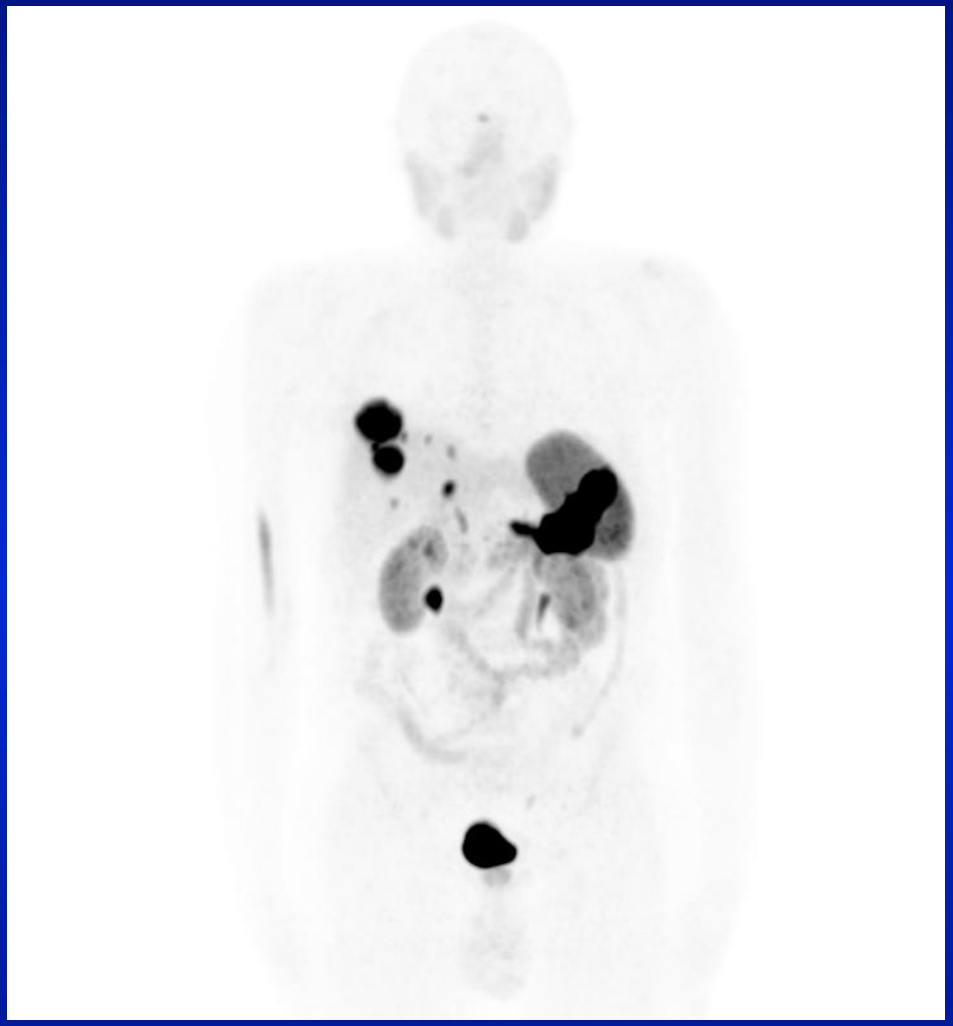
^{68}Ga-DOTATATE PET/CT

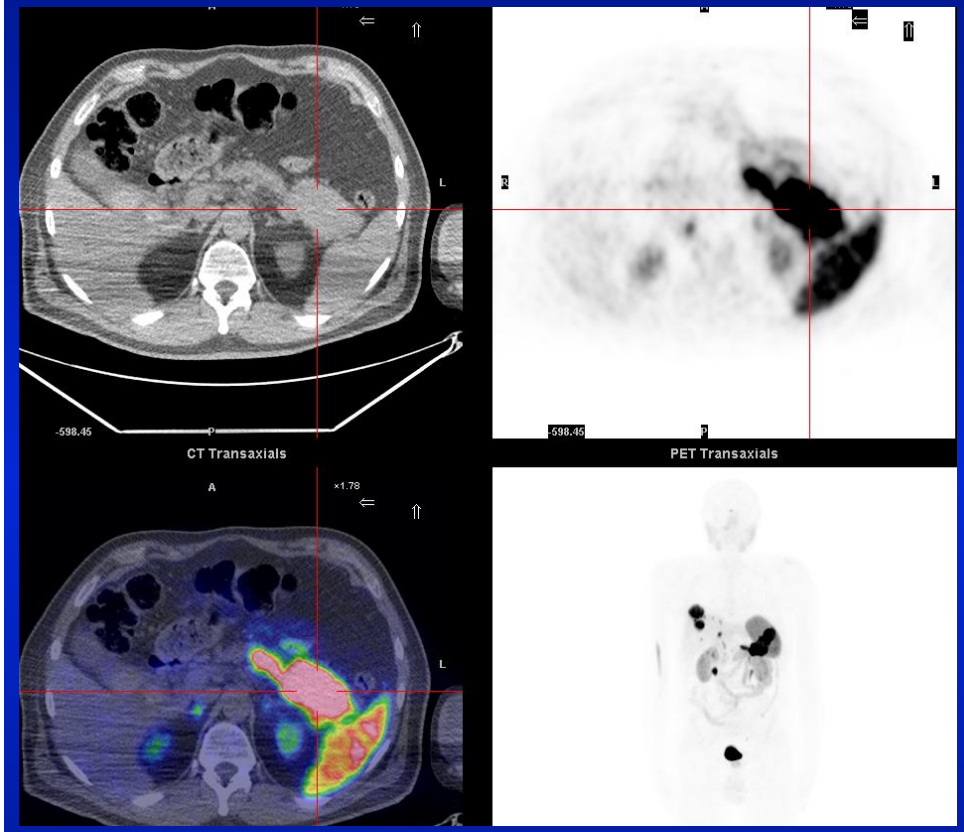


F
59 aa

Sospetto insulinoma in paziente con
frequenti crisi ipoglicemiche

^{68}Ga-DOTATATE PET/CT

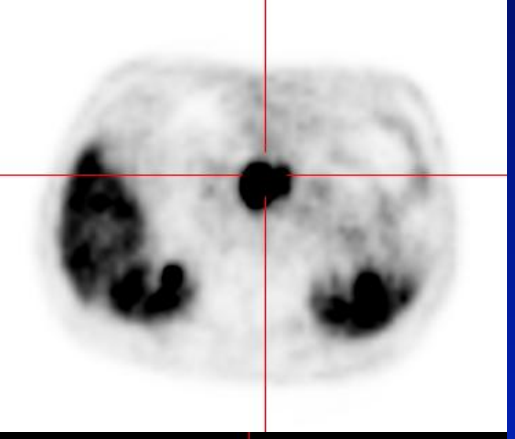


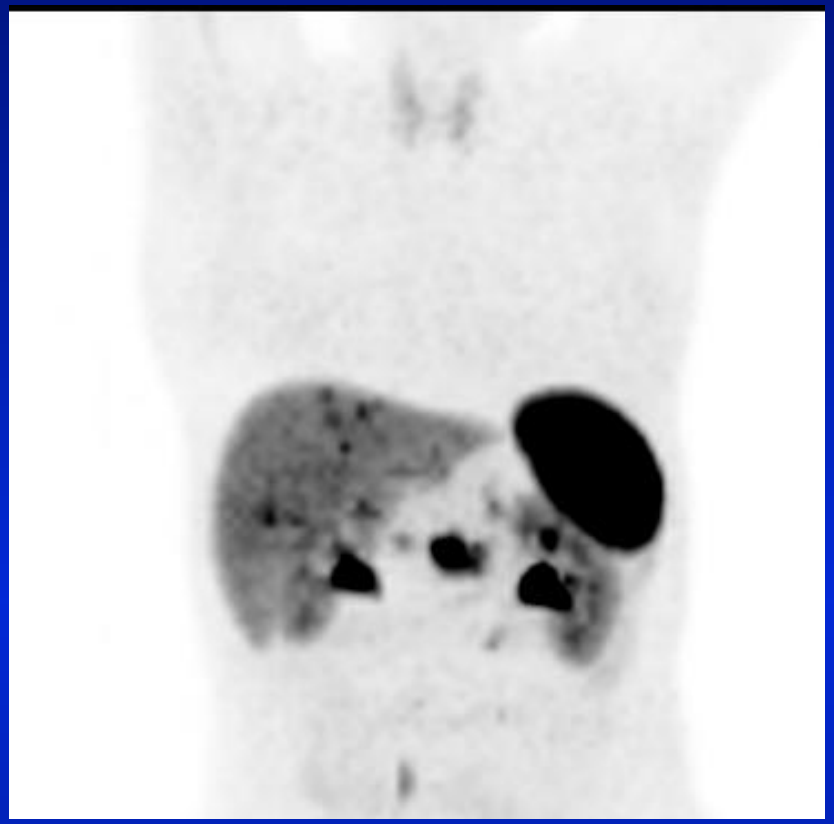


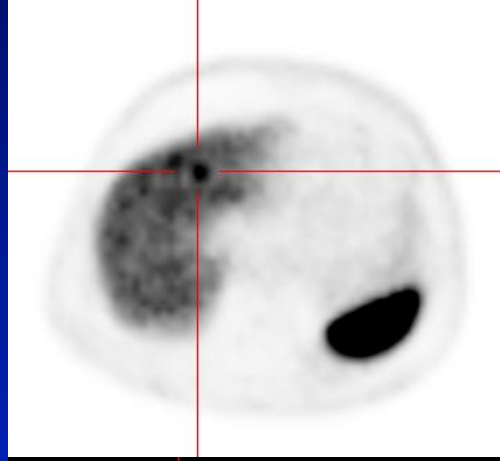
M
67 aa

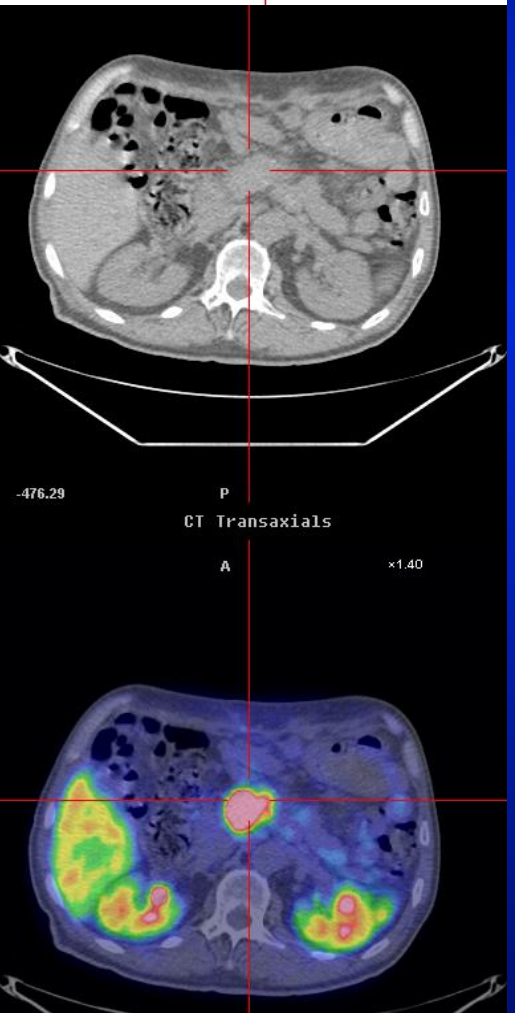
Riscontro occasionale in corso di esame ecotomografico addominale (per calcolosi della colecisti) di metastasi epatiche da ca neuroendocrino del corpo-coda del pancreas.

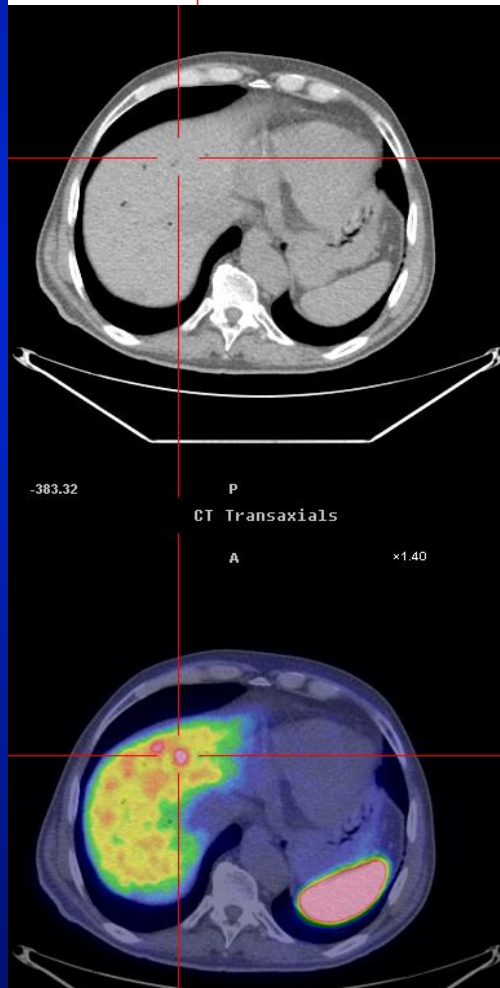
^{68}Ga-DOTATOC PET





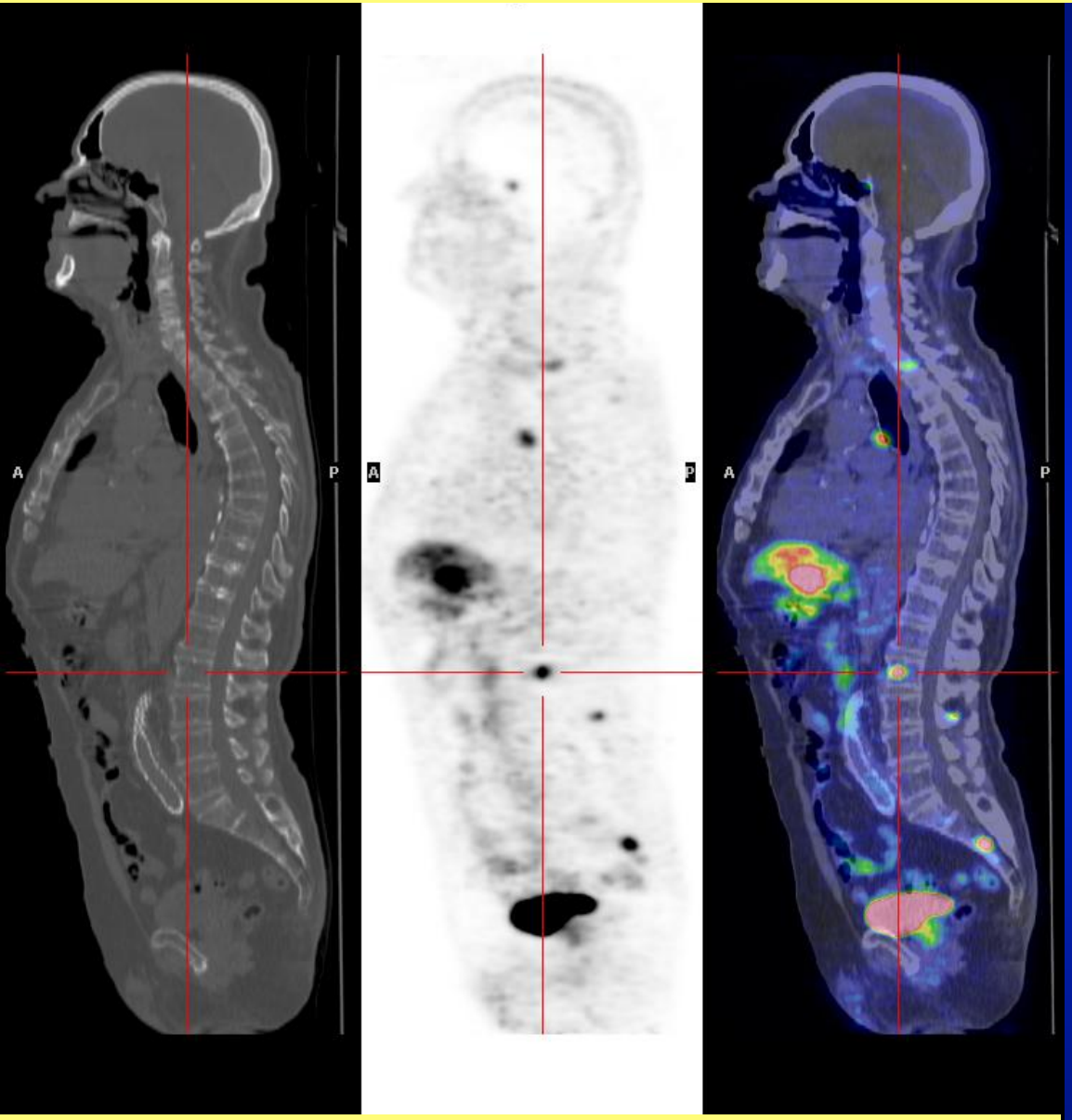


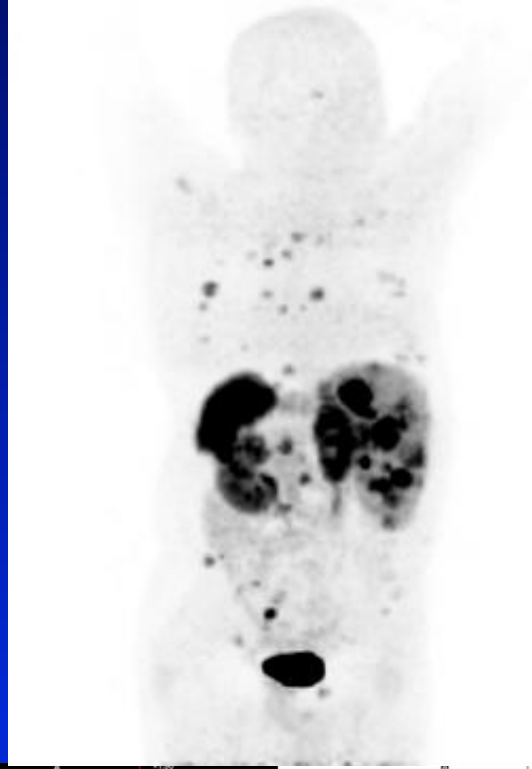


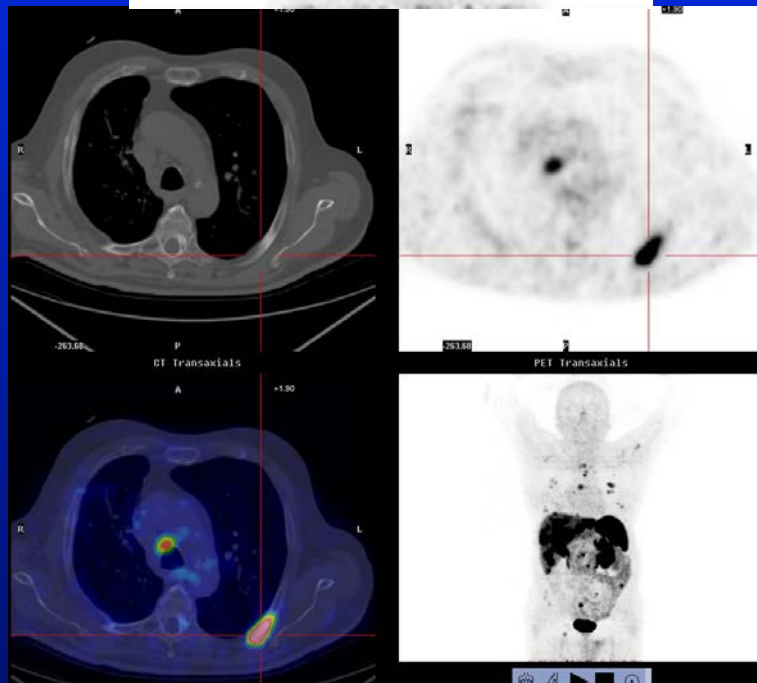


Carcinoma neuroendocrino del pancreas con metastasi epatiche

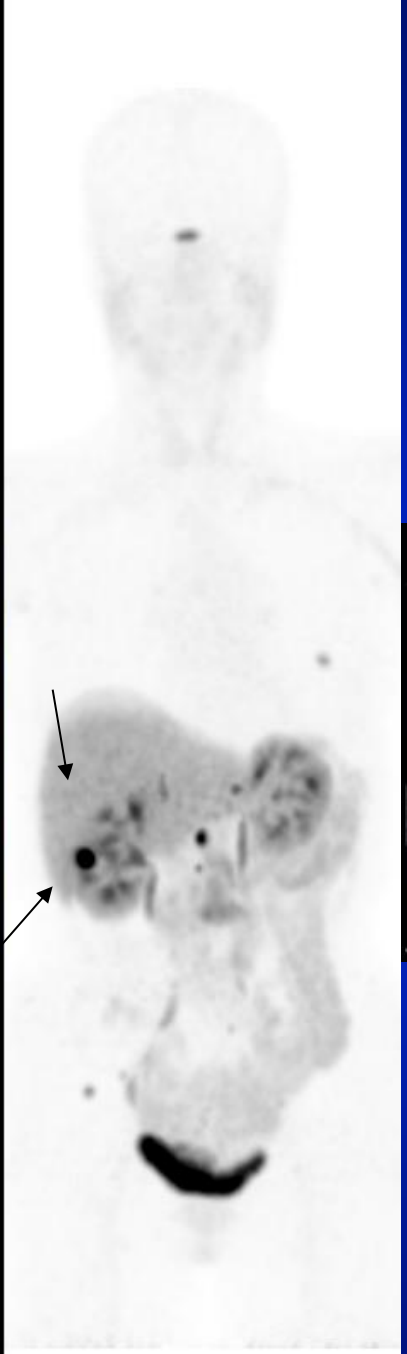
^{68}Ga-DOTATOC PET

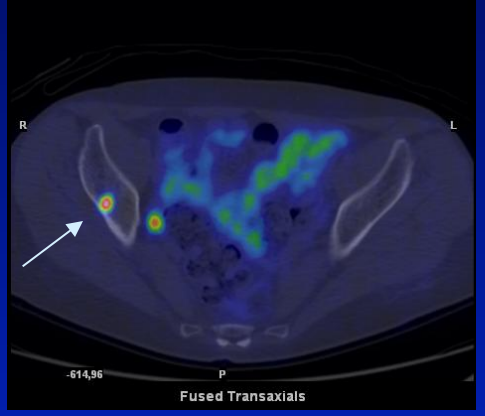


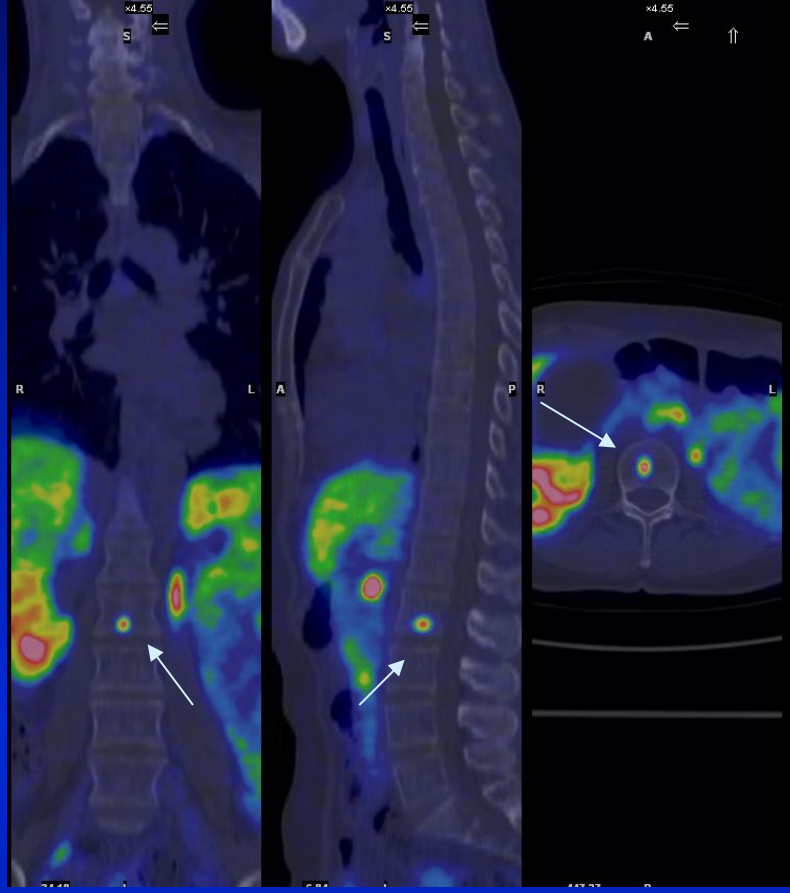


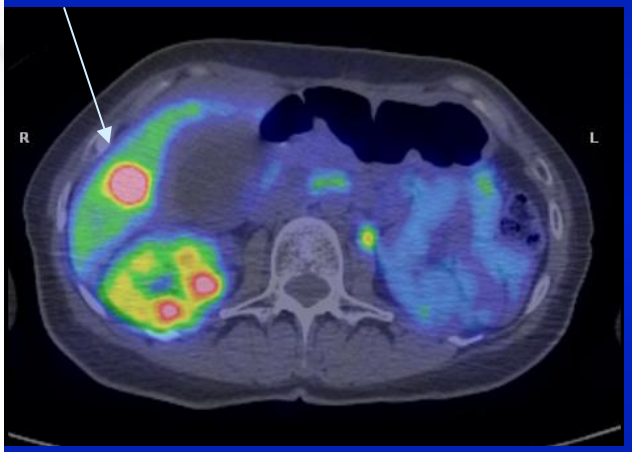


Metastasi multiple da carcinoma neuroendocrino intestinale

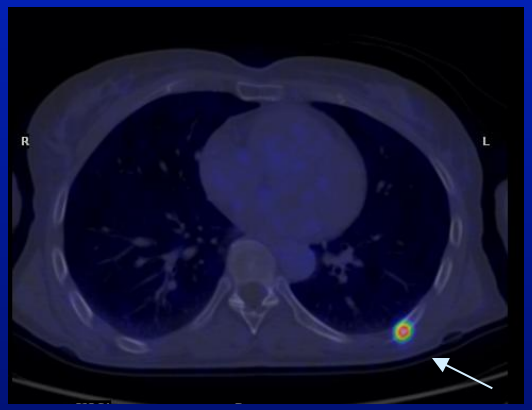


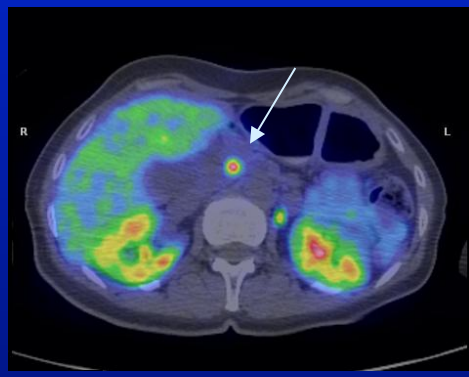






Localizzazioni secondarie multiple da carcinoma neuroendocrino del pancreas

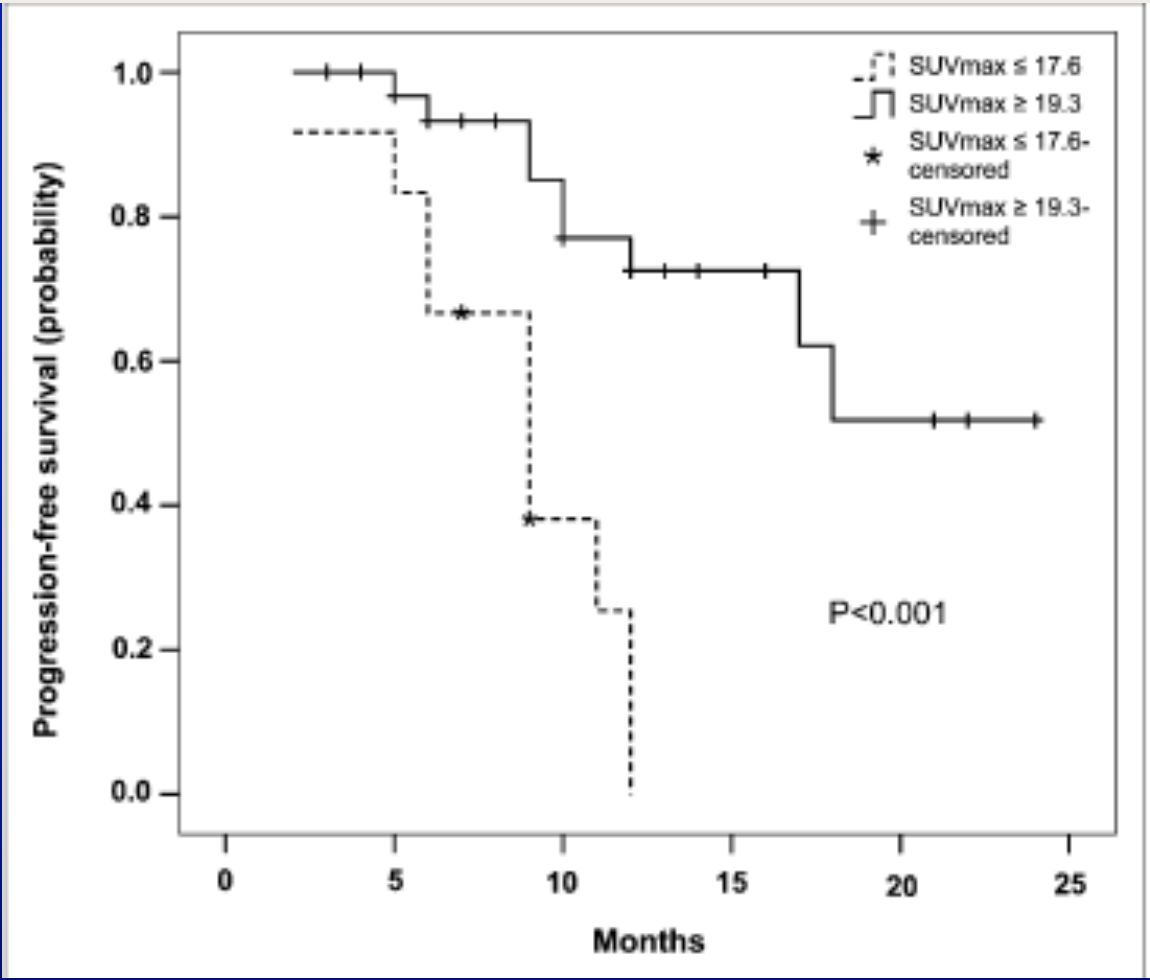




Standardized Uptake Values of ^{68}Ga-DOTANOC PET: A Promising Prognostic Tool in Neuroendocrine Tumors

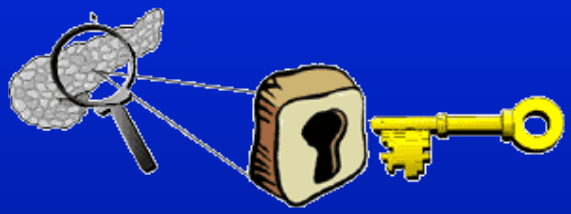
J Nucl Med 2010; 51:353–359

Davide Campana[1], Valentina Ambrosini[2], Raffaele Pezzilli[1], Stefano Fanti[2], Antonio Maria Morselli Labate[1], Donatella Santini[3], Claudio Ceccarelli[3], Francesca Nori[1], Roberto Franchi[2], Roberto Corinaldesi[1], and Paola Tomassetti[1]

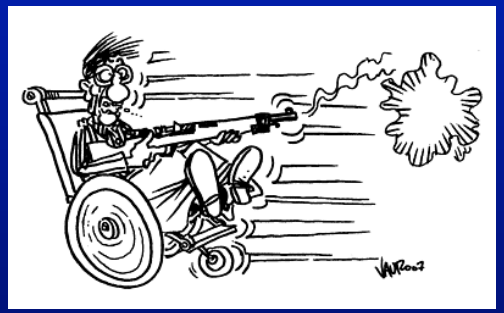


Dalla Diagnosi al Trattamento

Diagnosi
^{68}Ga



DOTA-TOC/TATE



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

Terapia Radiorecettoriale
Radiofarmaci

[^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide (^{90}Y-**DOTATOC**)

[^{177}Lu-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide (^{177}Lu-**DOTATOC**)
Alta affinità SSTR 2 e bassa affinità per SSTR3 e SSTR 5

[^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotate (^{90}Y-**DOTATATE**)

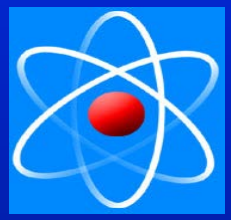
[^{177}Lu-DOTA]-D-Phe^{1}-Tyr^{3}-octreotate (^{177}Lu-**DOTATATE**)

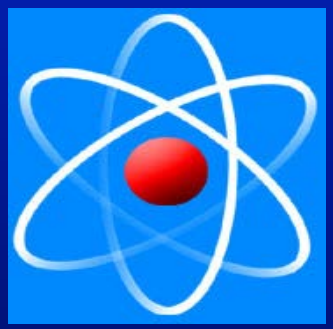
Affinità per SSTR 2 maggiore rispetto al DOTATOC.
No affinità per SSTR 3 e SSTR 5

Physics properties (LET)

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

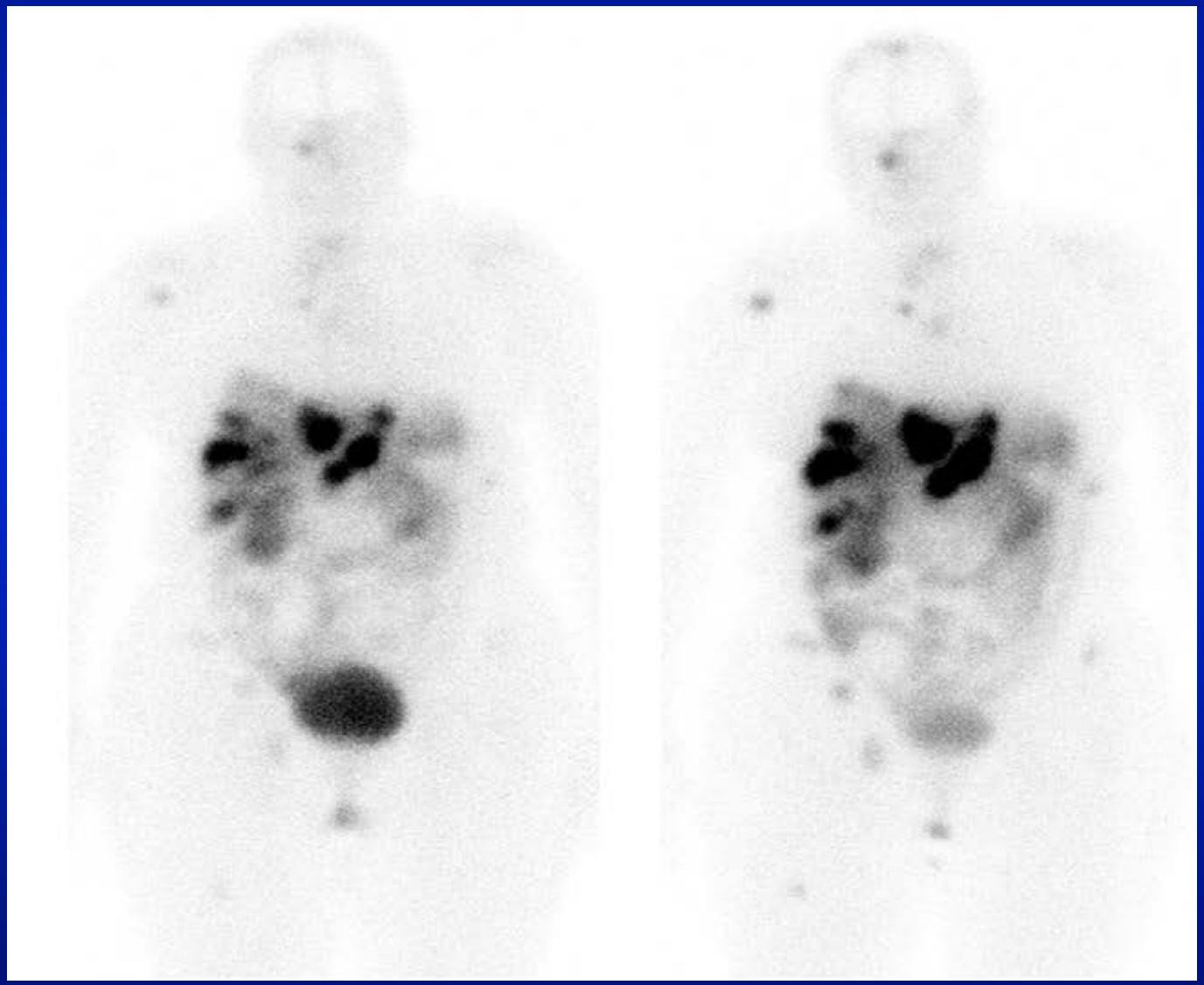
mean range in body tissue

^{177}Lu   → 0.23-1,7mm

^{90}Y   → 3,9-11 mm

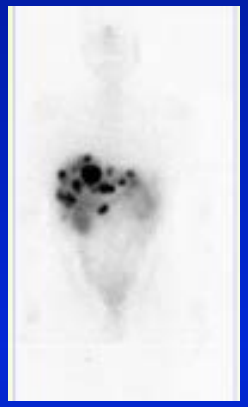
Semin Nucl Med 40:78-88 © 2010

177Lu-DOTATOC 24 h 177Lu-DOTATATE



Dosimetria personalizzata in PRRT

Direttamente con ^{177}Lu-DOTATOC/TATE in corso di terapia

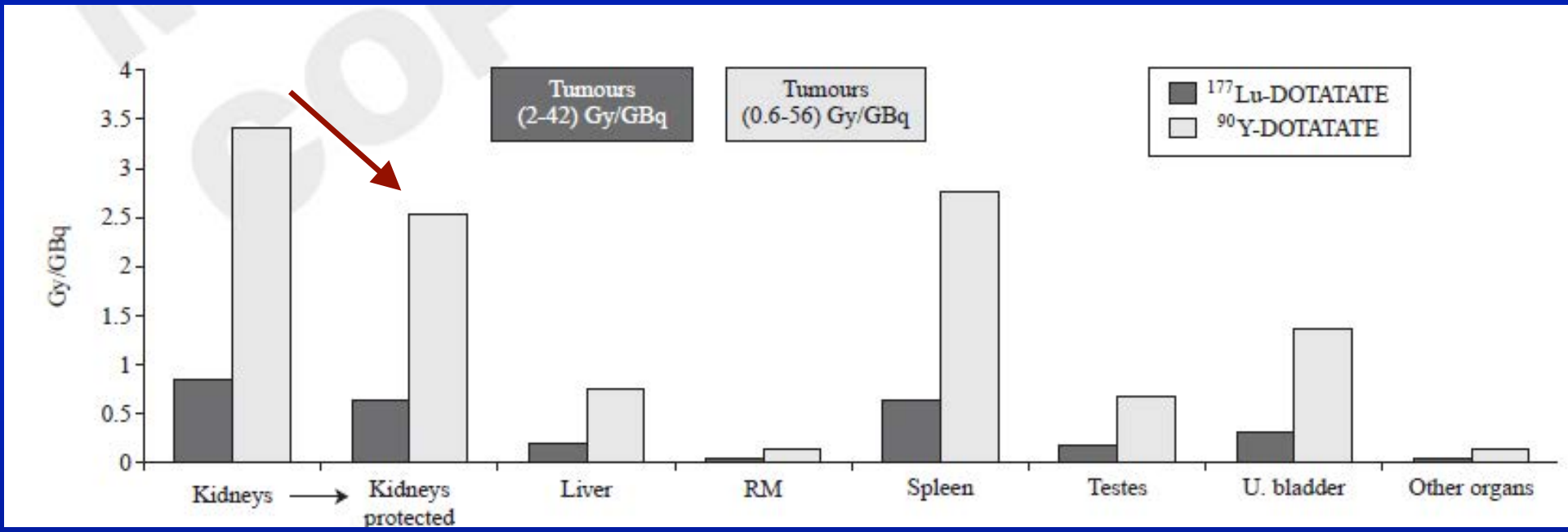


isotopi β/γ

Imaging Planare e/o SPECT-CT

Sandstrom M et al. Eur J Nucl Med Mol Imaging 2010 / Cremonesi M et al QJ Nucl Med Mol Imaging 2010

Organs and tumour doses estimates for ^{90}Y / ^{177}Lu-DOTATOC



Estimates of tumour and OAR doses per unit activity in patient undergoing PRRT trial

Cremonesi M et al QJ Nucl Med Mol Imaging 2010

Terapia Radiorecettoriale
Radiofarmaci

- **^{90}Y-DOTATOC**

  50-70 mCi (1850-2590 MBq)/ciclo

- **^{177}Lu-DOTATATE**

  100-150 mCi (3700-5550 MBq)/ciclo

Dosi ed isotopi radioattivi somministrati: criteri di valutazione

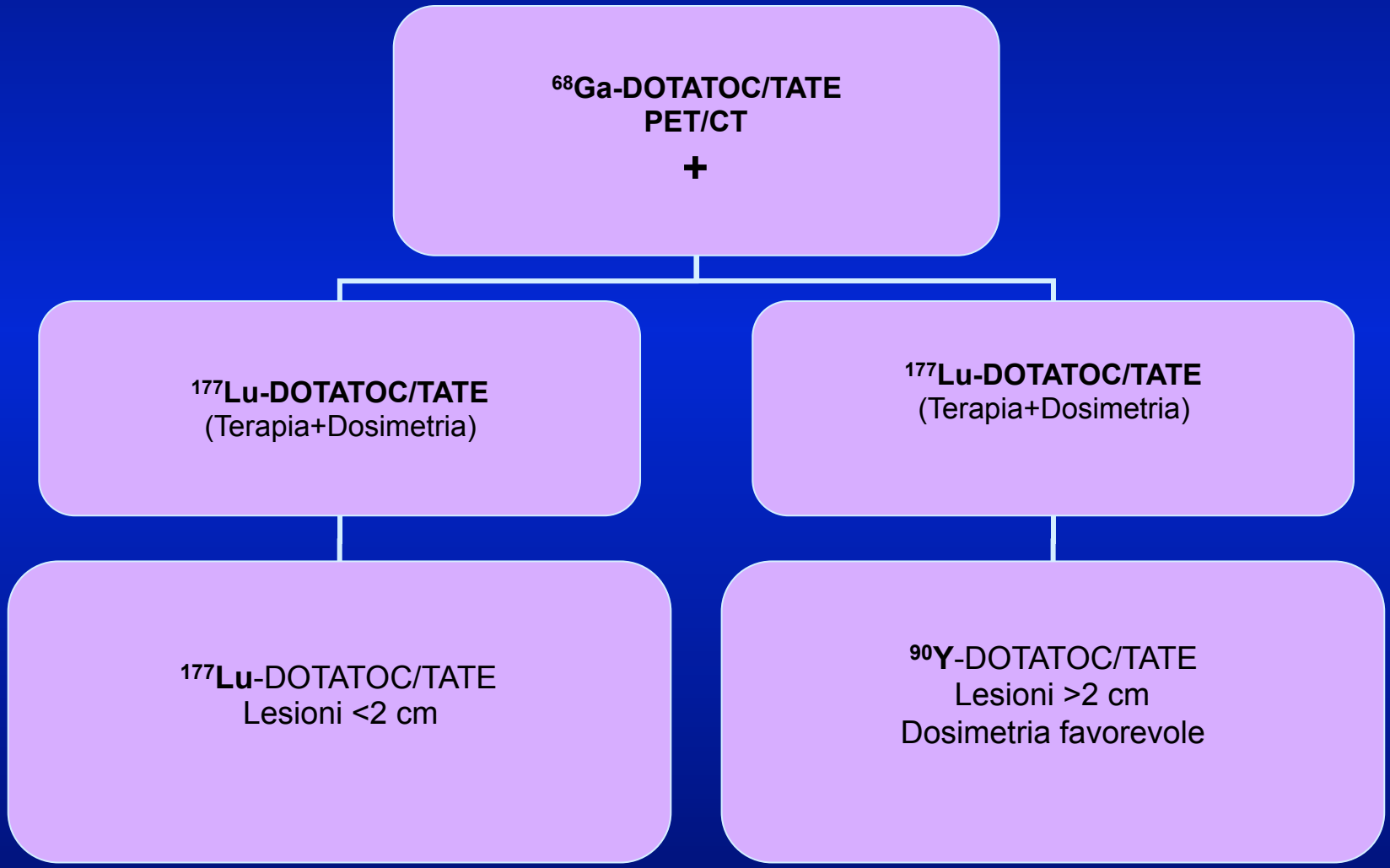
- Esami di laboratorio della fase iniziale di selezione del Paziente (Criteri di Inclusione: Creatinina <1.5; Hb >10; Leucociti >2.5; Piastrine >100; Bilirubina <2.5)

- Fattori di Rischio
  - **Ipertensione Arteriosa**
  - **Diabete**
  - Precedenti trattamenti chemio/radioterapici
  - Idronefrosi/altre condizioni patologiche a carico del rene
- Valutazione dosimetrica
- Dimensioni delle lesioni

Dosi ed isotopi radioattivi somministrati: criteri di valutazione

	177Lu	90Y
Esami di laboratorio della fase iniziale di selezione del Paziente	fuori range	nei range
Fattori di Rischio	presenti	assenti
Dimensioni delle lesioni	< 2 cm	> 2 cm
Valutazione dosimetrica	> 4Gy/GBq con 90Y	< 4Gy/GBq Rene (oar)

Terapia Radiorecettoriale
Algoritmo di Reggio Emilia



Terapia Radiorecettoriale

Procedura di Reggio Emilia

Esami ematologici

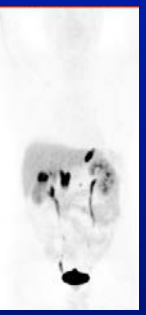
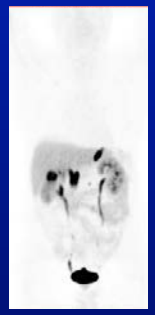
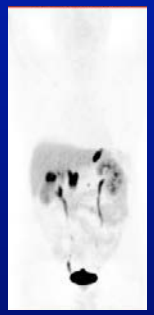




Follow up

0 2 4 6 8 12 20

mesi


Peptide Receptor Radionuclide Therapy in Patients With Gastroenteropancreatic Neuroendocrine Tumors

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Casper H.J. van Eijck, MD, PhD,‡ Boen L. Kam, MD,* Martijn van Essen, MD,*
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Semin Nucl Med 40:78-88 © 2010

Table 1 Tumor Responses in Patients With GEPNETs, Treated With Different Radiolabeled Somatostatin Analogues

			Tumor Response					
Center (Reference)	Ligand	No of Patient	CR	PR	MR	SD	PD	CR + PR
Rotterdam[5]	[^{111}In-DTPA^0]octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0%
New Orleans[7]	[^{111}In-DTPA^0]octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8%
Basel[8,9]	[^{90}Y-DOTA^0,Tyr^3]octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24%
Basel[10]	(^{90}Y-DOTA^0,Tyr^3)octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33%
Milan[11]	(^{90}Y-DOTA^0,Tyr^3)octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29%
Rotterdam[12]	[^{90}Y-DOTA^0,Tyr3]octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9%
Rotterdam[13]	[^{177}Lu-DOTA^0,Tyr3]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29%

Adapted from Kwekkeboom DJ et al.[6]

Semin Nucl Med 40:78-88 © 2010

Table 3 Results of Recent Chemotherapy Reports Compared With [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate

Regimen	Tumor Types	No of Patient	PR/CR (%)	Median PFS (mo)	Median OS (Mo)	Study (yr)
STZ + Doxorubicin	PNET	16	6	NA	NA	Cheng and Saltz[41]
Dacarbazine	Carc	56	16	NA	20	Bukowski et al[37]
Dacarbazine	Carc	7	14	NA	NA	Ritzel et al[38]
FU + IF-A	Carc/PNET	24	21	8	23	Andreyev et al[39]
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt et al[40]
Paclixatel	Carc/PNET	24	4	3	18	Ansell et al[42]
STZ + FU + Doxorubicin	PNET	84	39	18	37	Kouvaraki et al[47]
Doxorubicin + FU	Carc	85	13	5	16	Sun et al[48]
STZ + FU	Carc	78	15	5	24	Sun et al[48]
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux et al[49]
Oxaliplatin + Capecitabine	Well differentiated NET	27	30	NA	40	Bajetta et al[50]
Temozolomide	Carc/PNET	36	14	NA	16	Ekeblad et al[51]
^{177}Lu-octreotate	Carc/PNET	310	30	32	46	Kwekkeboom et al[13]

STZ, streptozotocin; FU, 5-fluorouracil; IF-A, interferon-alpha; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available. (Adapted from Kwekkeboom DJ et al.[13])

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

Therapeutic Response

Table 4 Best therapeutic response after the last administration of ^{177}Lu-DOTATATE

Primary tumour	Response						
	CR	PR	SD		PD	CR+PR	Total no. of pts.
	No. of pts.	No. of pts.	MR no. of pts.	SD no. of pts.	No. of pts.	No. of pts.	
Appendix	0	0	0	1	0	0	1
Bronchial	0	2	2	1	0	2	5
Duodenum	1	1	0	0	1	2	3
Ileum	0	2	6	7	4	2	19
Meninges	0	0	0	1	0	0	1
Pancreas	0	8	1	2	3	8	14
Paraganglia	0	0	2	1	0	0	3
Sigma-rectum	0	1	0	0	1	1	2
Unknown	0	0	2	1	0	0	3
Total	1 (2%)	14 (27%)	13 (26%)	14 (27%)	9 (18%)	15 (29%)	51

CR complete response, *PR* partial response, *MR* minimal response, *SD* stable disease, *PD* progressive disease

Eur J Nucl Med Mol Imaging (2011) 38:2125–2135

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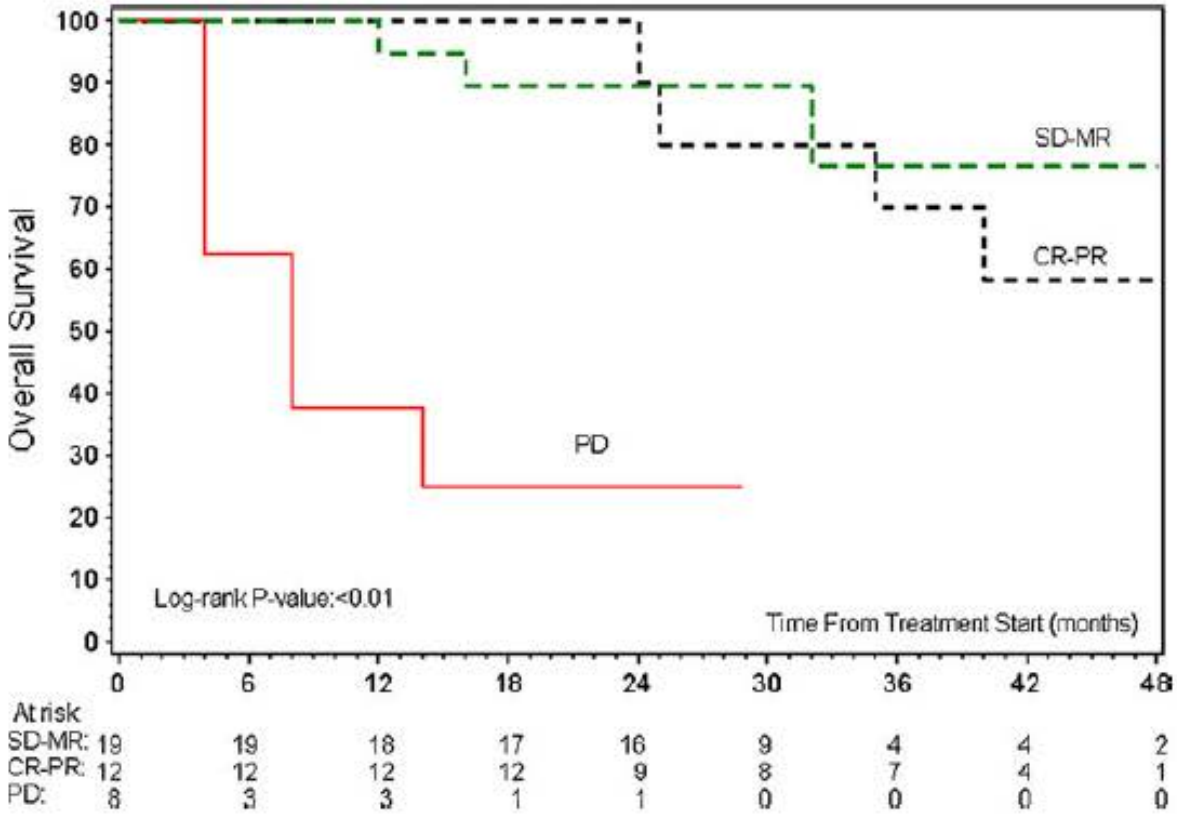

Fig. 5 Overall survival in progressing patients at baseline. From a prognostic point of view, stabilizations and objective responses showed the same survival probability

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

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Eur J Nucl Med Mol Imaging (2011) 38:2125–2135

Table 5 Factors significantly associated with overall survival

Factor	Total no. of pts.	Death	Survival rate at 36 months	Median survival (months)	*p* value
			Treatment outcome		
CR/PR/MR	28	4	86.0%	–	<0.001
SD	14	3	65.0%	–	
PD	9	7	22.5%	12	
			Tumour involvement		
Extensive	18	10	43.7%	21.5	<0.001
Moderate	25	4	75.5%	–	
Limited	8	0	100%	–	
			Previous chemotherapy		
No	40	8	76.2%	–	0.01
Yes	11	6	36.4%	22	
			Presence of bone metastases		
No	40	9	75.3%	–	0.053
Yes	11	5	27.3%	34	

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

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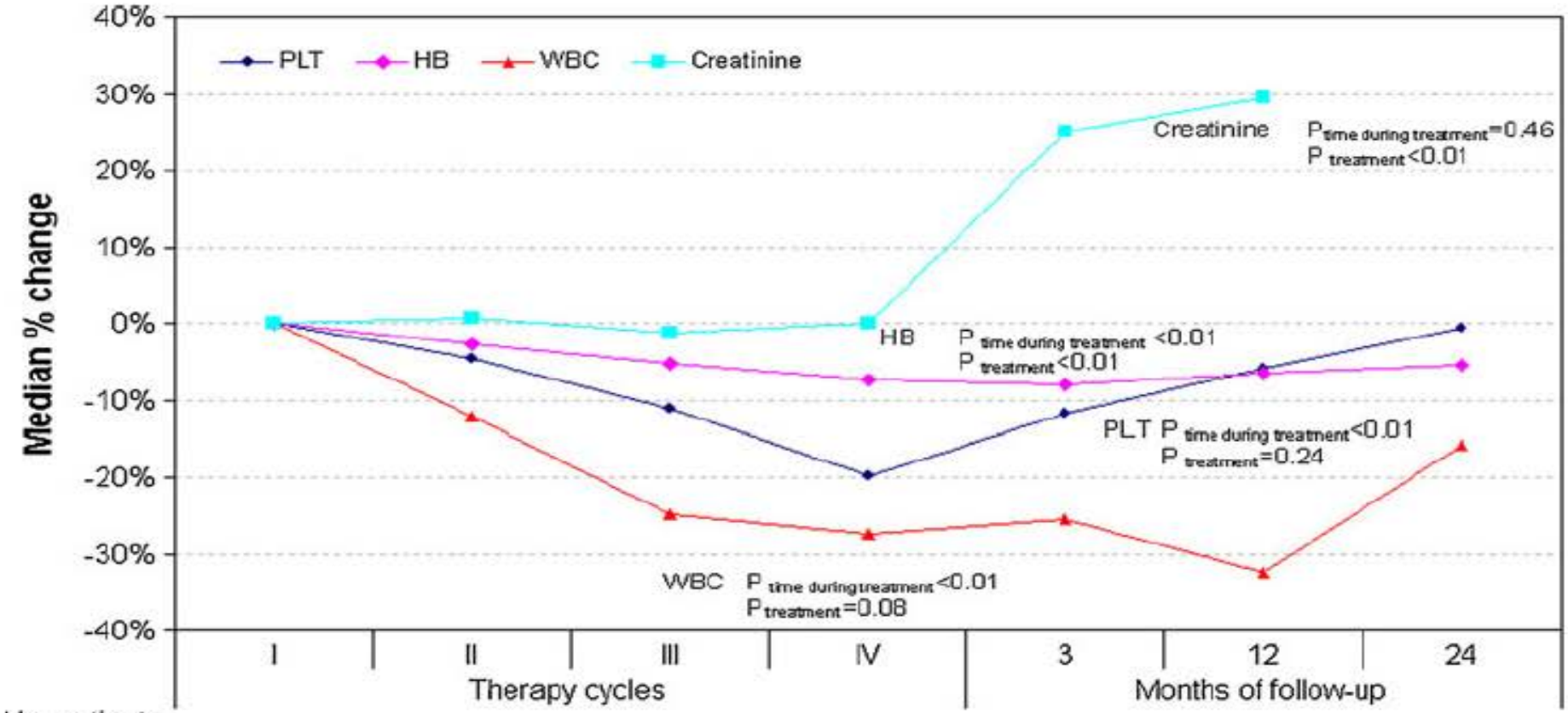
Haematological and renal toxicity

Eur J Nucl Med Mol Imaging (2011) 38:2125–2135



No. patients							
CR	51	50	49	45	41	25	7
HB	51	51	51	46	29	9	9
PLT	51	51	51	46	46	8	8
WBC	51	51	49	46	46	29	9

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-endocrinology

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Treatment with the Radiolabelled Somatostatin Analog ^{177}Lu-DOTATATE for Advanced Pancreatic Neuroendocrine Tumors

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Manuela Monti[b] Oriana Nanni[b] Anna Sarnelli[c] Lisa Bodei[d]
Lucia Garaboldi[d] Mirco Bartolomei[e] Giovanni Paganelli[d]

Table 3. Toxicity

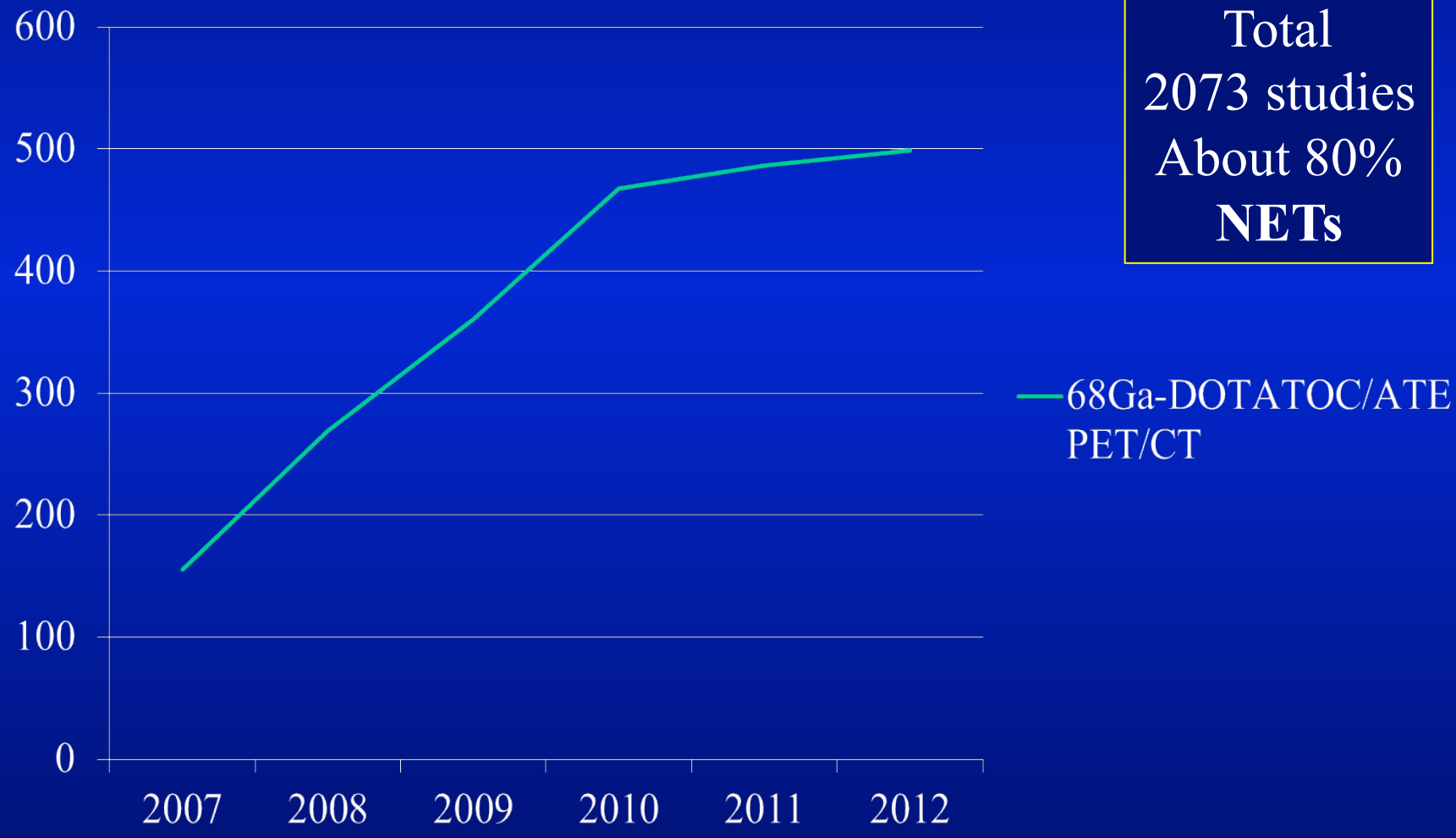
	Total population			FD group			RD group		
	G1	G2	G3	G1	G2	G3	G1	G2	G3
WBC	7 (13)	3 (6)	0	3 (11.5)	3 (11.5)	0	4 (15)	0	0
PLT	8 (15)	1 (2)	0	3 (12)	0	0	5 (19)	1 (4)	0
Hb	15 (29)	2 (4)	0	9 (35)	0	0	6 (23)	2 (8)	0
Creatinine	3 (6)	1 (2)	1 (2)	0	0	0	3 (11)	1 (4)	1 (4)

Values are n (%).

Terapia Radiorecettoriale
Casistica di Reggio Nell'Emilia

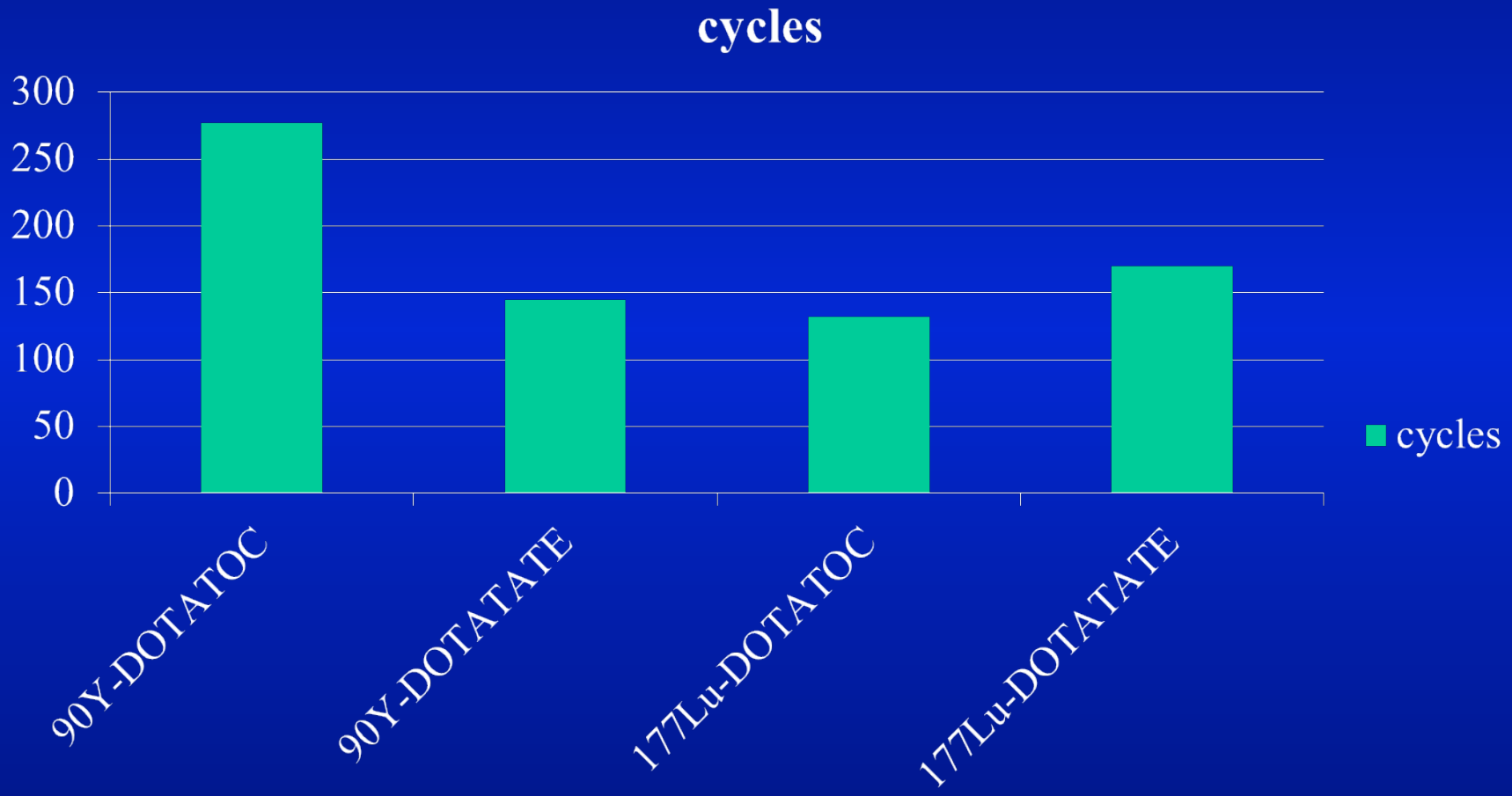
68Ga-DOTATOC/ATE PET/CT Experience of Reggio Emilia

January 2007 – August 2012



Total
2073 studies
About 80%
NETs

90Y/177Lu-DOTATOC/ATE
Experience of Reggio Emilia
January 2007 – August 2012



191 patients

724 cycles of treatment

Clinical Study

Radiolabeled Somatostatin Analogues Therapy in Advanced Neuroendocrine Tumors: A Single Centre Experience

A. Filice,[1] A. Fraternali,[1] A. Frasoldati,[2] M. Asti,[1] E. Grassi,[3] L. Massi,[1] M. Sollini,[1,4] A. Froio,[1] P. A. Erba,[1,4] and A. Versari[1]

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Journal of Oncology

59 patients

Clinical Study

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A. Filice,[1] A. Fraternali,[1] A. Frasoldati,[2] M. Asti,[1] E. Grassi,[3] L. Massi,[1] M. Sollini,[1,4] A. Froio,[1] P. A. Erba,[1,4] and A. Versari[1]

Journal of Oncology 2012

TABLE 5: Results of treatment responses tabulated on the basis of primary tumor site.

Site of primitive tumor	CR	PR	SD	PD
GI (19/59)	—	8/19 (42%)	9/19 (47%)	2/19 (11%)
Pancreas (16/19)	1/16 (6%)	5/16 (31%)	6/16 (38%)	4/16 (25%)
Lung (13/59)	—	8/13 (62%)	3/13 (23%)	2/13 (15%)
Unknown origin (11/59)	—	3/11 (27%)	6/11 (55%)	2/11 (18%)

TABLE 6: Results of treatment responses tabulated on the basis of the type of treatment.

Type of treatment	CR	PR	SD	PD
^{90}Y-PRRT (33/59)	1/33 (3%)	13/33 (40%)	11/33 (33%)	8/33 (24%)
^{177}Lu-PRRT (10/59)	—	2/10 (20%)	6/10 (60%)	2/10 (20%)
Both ^{90}Y-PRRT and ^{177}Lu-PRRT (16/59)	—	9/16 (56%)	7/16 (44%)	—

Effetti precoci:

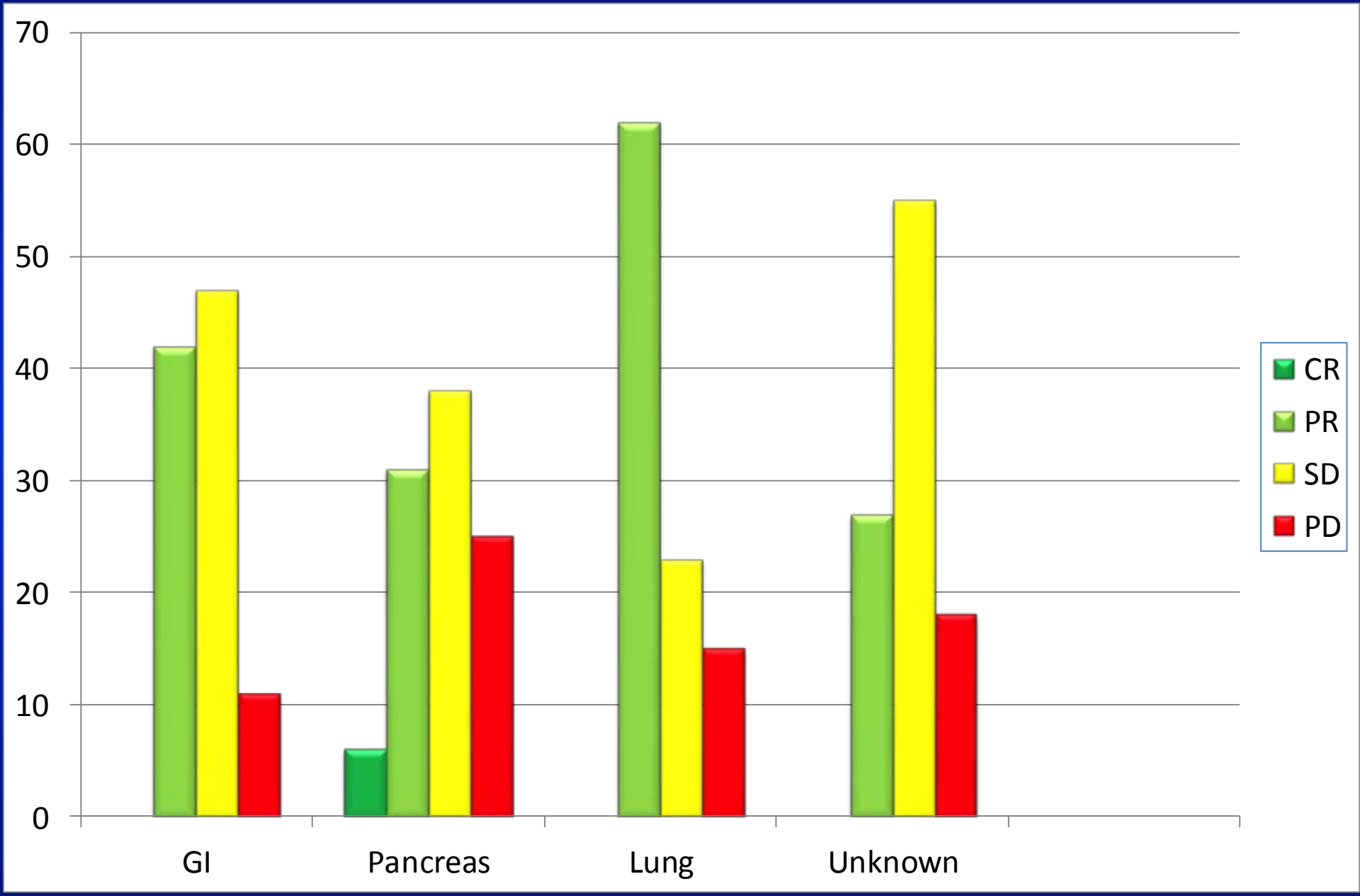
- Nausea
- Astenia
- Anoressia
- Aumento della sintomatologia algica

Effetti tardivi:

- Tossicità Ematologica (12/59)
- Tossicità Renale (3/59)

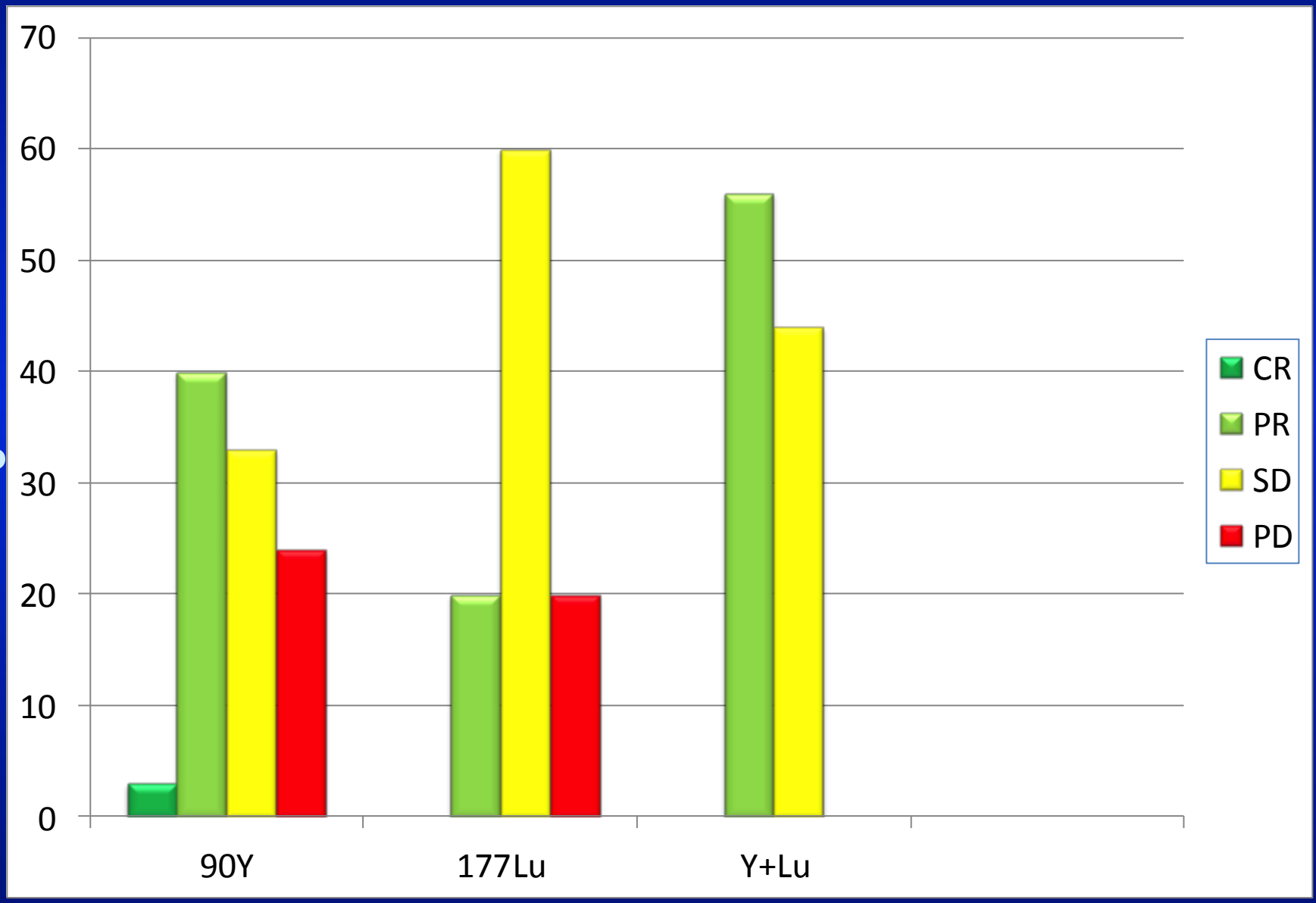
PRRT 59 pts

A. Filice et al J of Oncology 2012



PRRT 59 pts

A. Filice et al J of Oncology 2012



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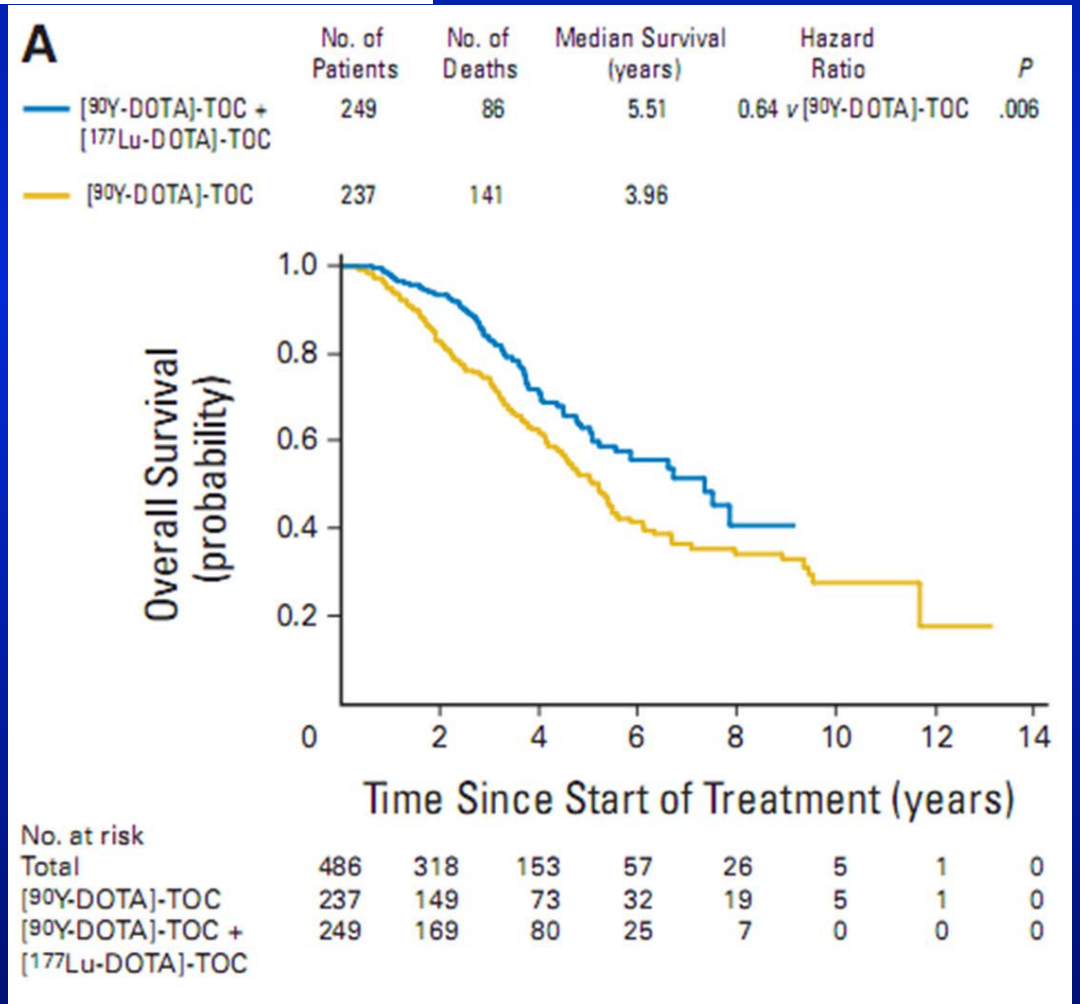
ORIGINAL REPORT

Cohort Study of Somatostatin-Based Radiopeptide Therapy With [^{90}Y-DOTA]-TOC Versus [^{90}Y-DOTA]-TOC Plus [^{177}Lu-DOTA]-TOC in Neuroendocrine Cancers

Linda Villard, Anna Romer, Nicolas Marincek, Philippe Brunner, Michael T. Koller, Christian Schindler, Quinn K.T. Ng, Helmut R. Mäcke, Jan Müller-Brand, Christoph Rochlitz, Matthias Briel, and Martin A. Walter



Eur J Nucl Med Mol Imaging (2014) 41:223–230
DOI 10.1007/s00259-013-2578-5

Treatment with tandem [^{90}Y]DOTA-TATE and [^{177}Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy

E. Seregni · M. Maccauro · C. Chiesa · L. Mariani · C. Pascali · V. Mazzaferro · F. De Braud · R. Buzzoni · M. Milione · A. Lorenzoni · A. Bogni · A. Coliva · S. Lo Vullo · E. Bombardieri

patients with NET refractory to conventional therapy. This approach induced an objective response in 43 % of patients with a time to progression of 25 months and a symptomatic response with an improvement in quality of life in the majority of patients.

The absence of kidney damage and the cumulative BED values below the toxicity limit in the majority of patients suggest the feasibility of increasing the number of tandem administrations of [^{90}Y]DOTA-TATE and [^{177}Lu]DOTA-TATE.

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