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DIP. STRUTT. AZ. DIAGNOSTICA PER IMMAGINI E DI RADIOLOGIA INTERVENTISTICA
U.O.C. MEDICINA NUCLEARE
Dir. Prof. Diego Cecchin
(E-mail: diego.cecchin@unipd.it)

Theranostics potential in clinical practice

Prof. Diego Cecchin

Thanks To Prof. Ceciclia Giron and Dr. Monica Santimaria !

1

PREMISES

2

European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:519
https://doi.org/10.1007/s00259-018-4204-z

LETTER TO THE EDITOR

Why should we be concerned about a "g"?

Savvas Frangos[1] · John R. Buscombe[2]

Received: 18 October 2018 / Accepted: 23 October 2018 / Published online: 6 November 2018

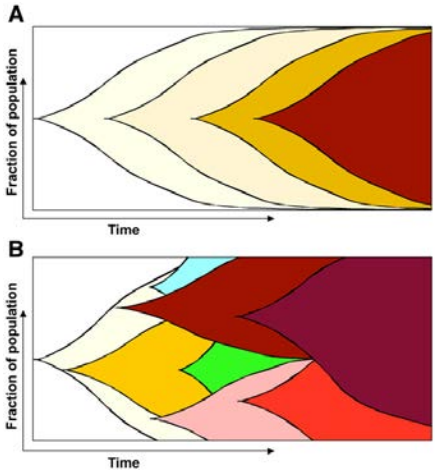
Theragnostics is the better term ! In theranostics the second part of the word "nostics" refer more to the disease than diagnostics

TERANOSTIC or TERAGNOSTIC

*…Dia**gnostic** (Imaging) and **Thera**py with the same radiopharmaceutical…*

3

Is tumor heterogeneity in cancer a problem?



Traditional, linear model of clonal succession

Multi-clonal model of tumor progression

Tumor heterogeneity: Causes and consequences
Andriy Marusyk, Kornelia Polyak *
Biochimica et Biophysica Acta 1805 (2010) 105–117

4

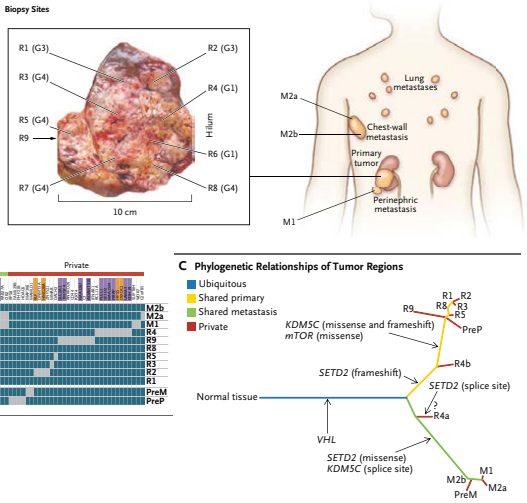
Intratumor heterogeneity fosters tumor evolution/adaptation and hinders personalized-medicine strategies that depend on results from single tumor-biopsy samples


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

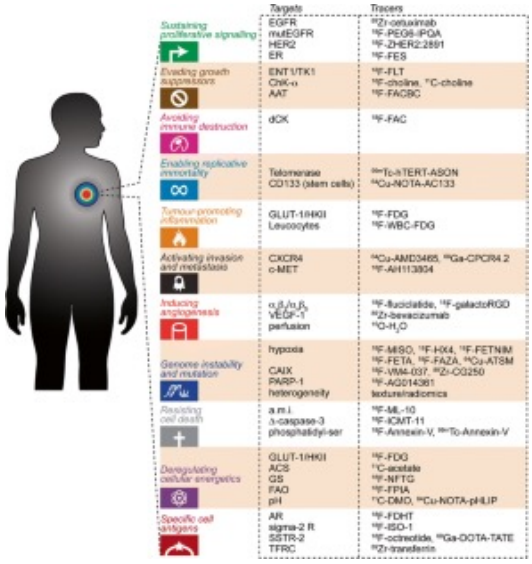


- Genomic analysis from single tumor-biopsy underestimates the mutational burden of heterogeneous tumors
- A single tumor-biopsy reveals a minority of genetic aberrations
- Such spatially diverse somatic mutations alter pathway activity suggesting the need of multiregional analyses to predict the therapeutic outcome"

So heterogeneity in space and time !!!

5

Intratumor heterogeneity: an opportunity for radiopharmaceuticals

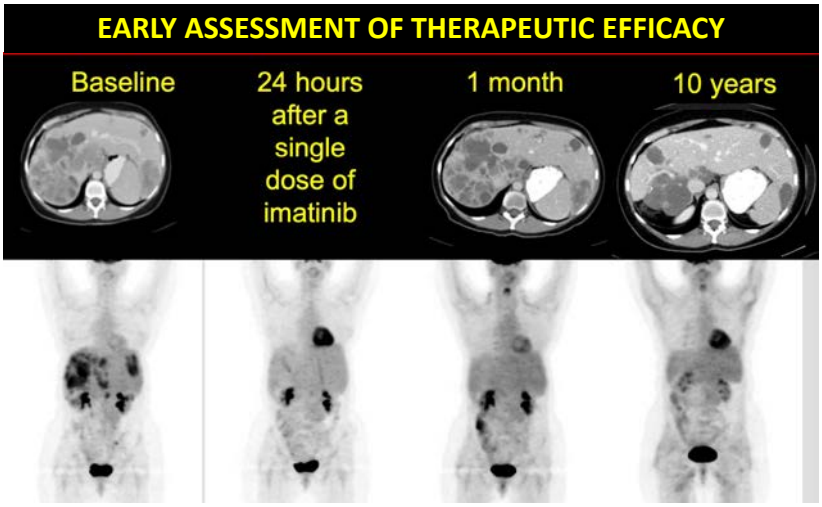


Imaging of Hallmarks of Cancer Biology: a real time visualization of intratumor "biomarkers" with radiopharmaceuticals

Alam IS et al., Eur J Nucl Med Mol Imaging, 2015
Van den Abbeele AD, Theranostics Consensus Conference 2018

6

Molecular Imaging as a pharmacodynamic biomarker



Metabolic response precedes anatomic response

Clinical benefit is obtained regardless of tumor shrinkage

Van den Abbeele AD, Ertuk M. PET Clin. 2008;3(1):77-87.

7

Modern Medicine: where are we?

PERSONALIZED MEDICINE

*a term used for the treatment focusing on the patients based on their **individual clinical characterization**, considering the diversity of symptoms, severity, and genetic traits.*

PRECISION MEDICINE

*an emerging approach for disease treatment and prevention that takes into account **individual variability in genes, environment, and lifestyle** among individuals.*

8

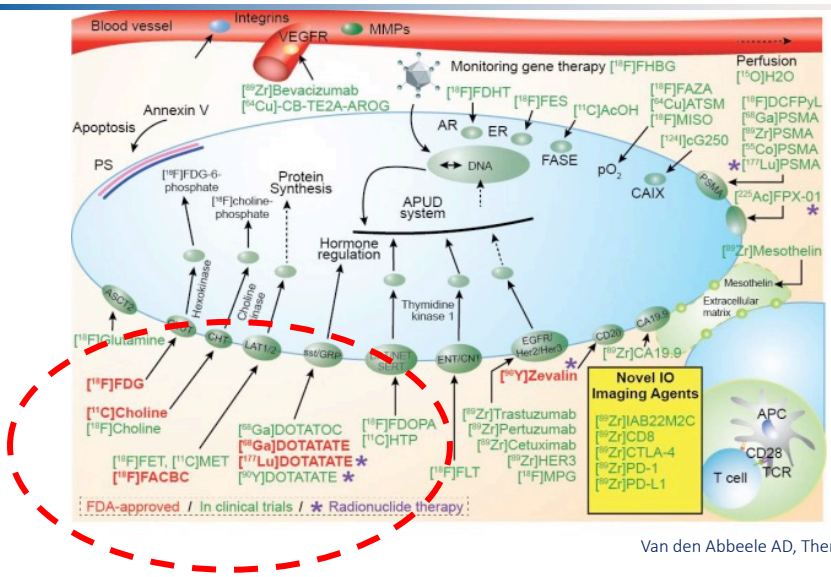
US Precision Medicine Initiative

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine — one that delivers the right treatment at the right time. In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable. Tonight, I'm launching a new ***Precision Medicine Initiative*** *to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."*

President Barack Obama, State of the Union Address, January 20, 2015

9

Molecular Imaging as a virtual biopsy of cancer biology hallmarks



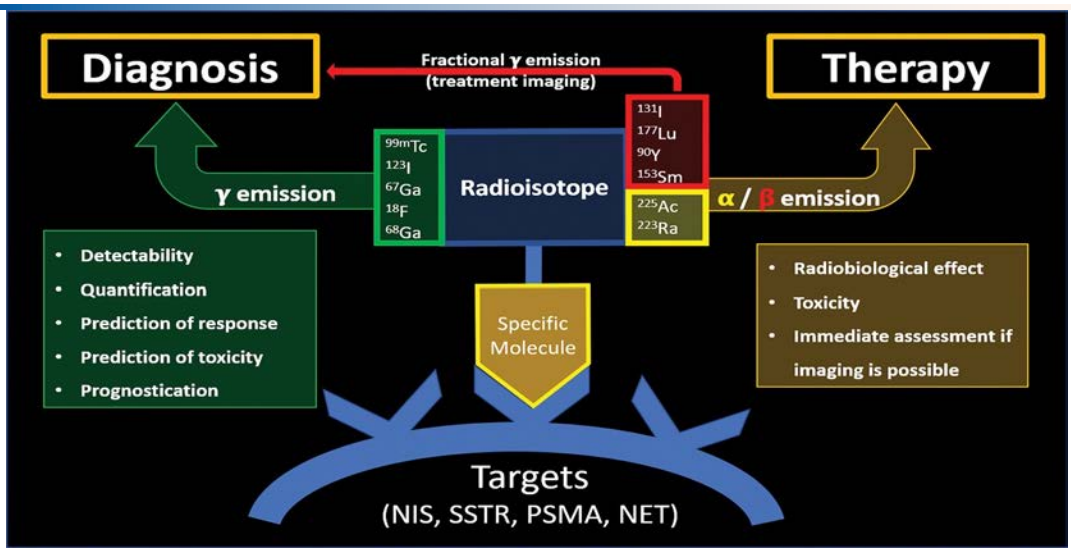
Van den Abbeele AD, Theranostics Consensus Conference 2018

10

SO .. WHAT IS TERAGNOSTIC ?

11

..So what is TERAGNOSTIC ?



Gomes Marin JF, et al. 2020;40(6):1715-1740.

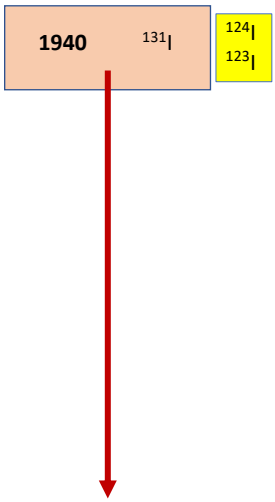
12

JNM The Journal of NUCLEAR MEDICINE

Driving the Future of Nuclear Medicine

Ken Herrmann, Patrick Veit-Haibach and Wolfgang A. Weber

J Nucl Med. 2019;60:1S-2S
Doi: 10.2967/jnumed.119.232264



~Twenty years ago	**PET/CT + SPET/CT**
~Seven years ago	**PET/MRI**
~Present	**Digital PET**
~Future	**New PET tracers, new theranostic compounds + Artificial intelligence and machine learning**

13

Neuroendocrine Tumors

- **72% gastrointestinal tract (particularly midgut and pancreas)**
- **25% broncopolmunary system**
- **~3% others: head and neck, prostate, others…**

- **Asymptomatic for years … late stages … metastatic or locally advanced**
- **Variable response to the same therapy**

Which Treatment ?

- **Anatomic location ?**
- **Local invasion of adjacent structures ?**
- **Tumor functionality ?**
- **Histologic tumor grading ?**
- **Staging ?**
- **SSTR status ?**

3 GRADES (WHO)
- **Cell proliferation**
- **Number of mitoses**
- **Expression of nuclear antigen Ki-67**

G1 (Ki-67 <2%)
G2 (Ki-67 3-20%)
G3 (Ki-67 >20%)

Poorly differentiated carcinomas (NECx, small and large cells)

14

Role of Nuclear Medicine in NETs ?

1. **Diagnosis**
2. **Staging and Restaging (superior to CT and MR)** →
3. **Planning PRRT (Peptide Receptor Radionuclide Therapy)**
4. **Response to treatment**
5. **Prognosis**

- N. Naswa, P. Sharma, A. Kumar, et al.Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single-center study Am J Roentgenol, 197 (2011), pp. 1221-1228
- D. Putzer, M. Gabriel, B. Henninger, et al.Bone metastases in patients with neuroendocrine tumor: ^{68}Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy J Nucl Med, 50 (2009), pp. 1214-1221
- M. Gabriel, C. Decristoforo, C. Kendler, et al.^{68}Gallium-DOTA-Tyr(3)-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography J Nucl Med, 48 (2007), pp. 508-518

Eur J Nucl Med Mol Imaging (2017) 44:1588–1601
DOI 10.1007/s00259-017-3728-y

GUIDELINES

Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F–DOPA

Murat Fani Bozkurt[1] · Irene Virgolini[2] · Sona Balogova[3,4] · Mohsen Beheshti[5,6] · Domenico Rubello[7] · Clemens Decristoforo[2] · Valentina Ambrosini[8] · Andreas Kjaer[9] · Roberto Delgado-Bolton[10] · Jolanta Kunikowska[11] · Wim J. G. Oyen[12] · Arturo Chiti[13] · Francesco Giammarile[14] · Stefano Fanti[8]

15

Eur J Nucl Med Mol Imaging (2016) 43:2072–2083
DOI 10.1007/s00259-016-3395-4

REVIEW ARTICLE

Current knowledge on the sensitivity of the ^{68}Ga-somatostatin receptor positron emission tomography and the SUV_{max} reference range for management of pancreatic neuroendocrine tumours

Irene Virgolini[1] · Michael Gabriel[1] · Alexander Kroiss[1] · Elisabeth von Guggenberg[1] · Rupert Prommegger[1] · Boris Warwitz[1] · Bernhard Nilica[1] · Ilanos Geraldo Roig[1] · Margarida Rodrigues[1] · Christian Uprimny[1]

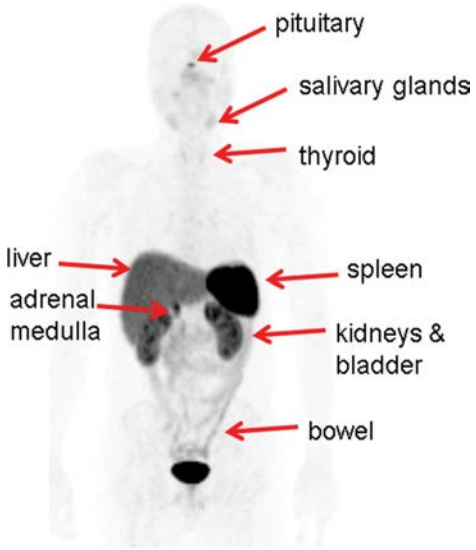
SSTR binding affinity of 68Ga-sstr-ligands

Peptide	sstr1	sstr2	sstr3	sstr4	sstr5
DOTATOC	>10,000	14 ± 2.6	880 ± 324	>1,000	393 ± 84
DOTATATE	>10,000	1.5 ± 0.4	>1,000	453 ± 176	547 ± 160
DOTALAN	>10,000	26 ± 3.4	771 ± 229	>10,000	73 ± 12
Ga-DOTATOC	>10,000	2.5 ± 0.5	613 ± 140	>1,000	73 ± 21
Ga-DOTATATE	>10,000	0.2 ± 0.04	>1,000	300 ± 140	377 ± 18
Ga-DOTANOC	>10,000	1.9 ± 0.4	40.0 ± 5.8	260 ± 74	7.2 ± 1.6
Y-DOTATOC	>10,000	11 ± 1.7	389 ± 135	>10,000	114 ± 29
Y-DOTATATE	>10,000	1.6 ± 0.4	>1,000	523 ± 239	187 ± 50
Y-DOTANOC	>1,000	3.3 ± 0.2	26 ± 1.9	>1,000	10.4 ± 1.6
Y-DOTALAN	>10,000	22.8 ± 4.9	290 ± 105	>10,000	16.3 ± 3.4

The table lists the values for the inhibitory constant (nmol/L) for sstr-binding peptides and their gallium and yttrium complexes. The IC_{50}-value indicates the concentration when 50 % of binding is inhibited

16

Physiologic uptake of 68Ga-DOTA-X in …



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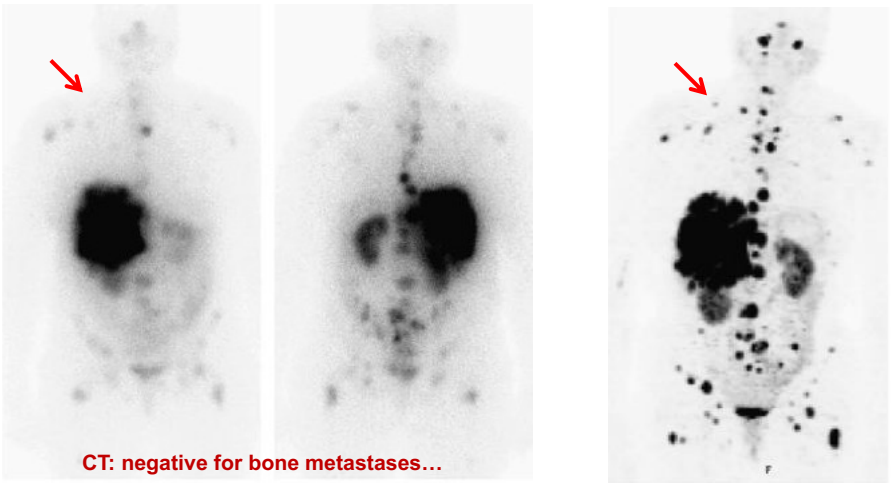
17

SPET (^{111}In-Pentetreotide) **PET (^{68}Ga-DOTATOC)**



CT: negative for bone metastases…

modified from Gabriel et al. (84 pz) - J Nucl Med. 2007 Apr;48(4):508-18.

	Sens	Spec	PPV	NPV
^{68}Ga-DOTATATE PET/CT	96% (86–100)	93% (77–99)	96% (86–100)	93% (77–99)
^{111}In-pentetreotide, all types	72% (58–75)	93% (77–99)	95% (82–99)	65% (48–94)

J Nucl Med 2016; 57:708–714

…So .. technological differences in SPET/PET systems matters !

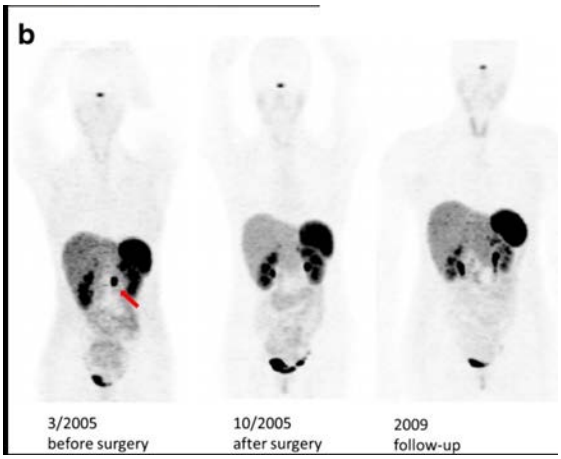
18

Eur J Nucl Med Mol Imaging (2016) 43:2072–2083
DOI 10.1007/s00259-016-3395-4

REVIEW ARTICLE

Current knowledge on the sensitivity of the ^{68}Ga-somatostatin receptor positron emission tomography and the SUV_{max} reference range for management of pancreatic neuroendocrine tumours

Irene Virgolini[1] · Michael Gabriel[1] · Alexander Kroiss[1] · Elisabeth von Guggenberg[1] · Rupert Prommegger[1] · Boris Warwitz[1] · Bernhard Nilica[1] · Ilanos Geraldo Roig[1] · Margarida Rodrigues[1] · Christian Uprimny[1]



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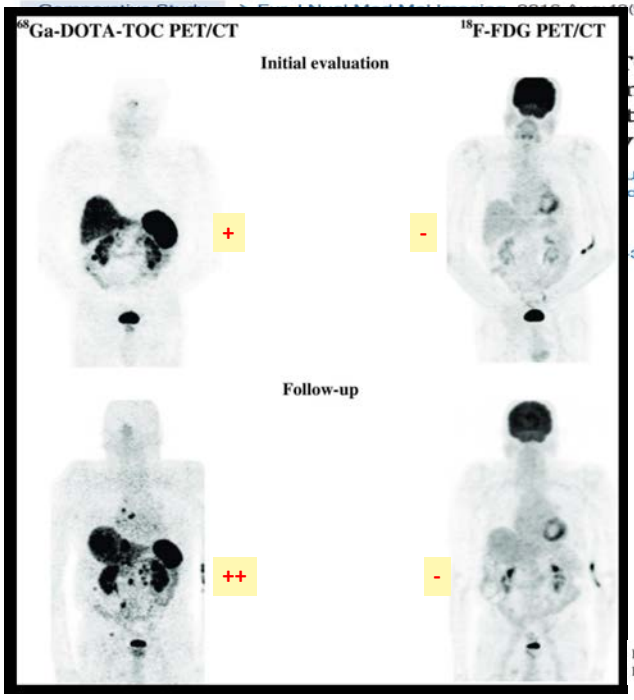


(9):1585-92.

OC and (18)F–
nts with
the first full
cycle

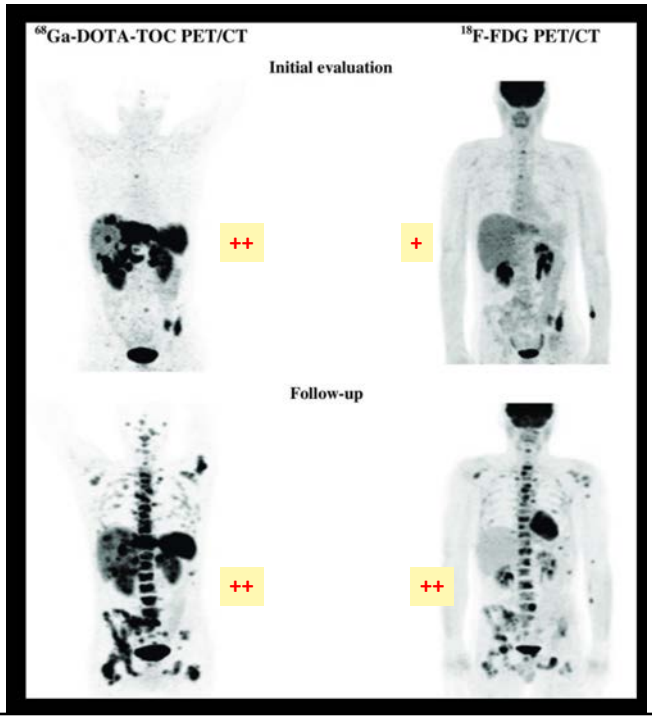
Uprimny [1],
do [1], Benjamin Henninger [2],

3328-2

GROUP 1:
[18F] FDG always negative

Eur J Nucl Med Mol Imaging (2016) 43:1585–1592
DOI 10.1007/s00259-016-3328-2

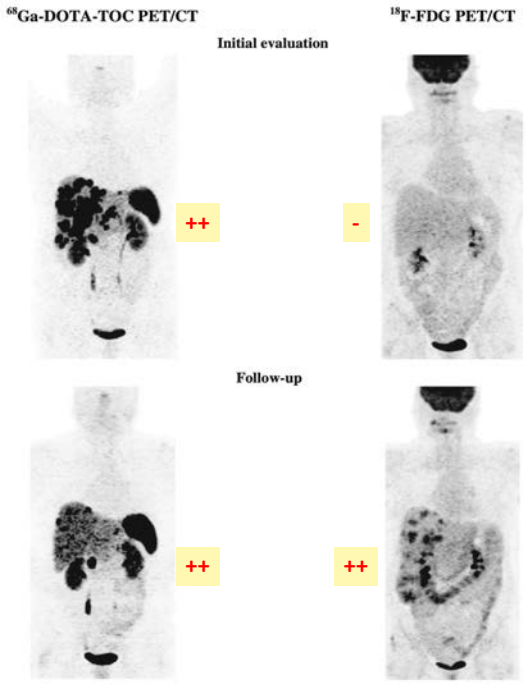
20



GROUP 2:
[18F]FDG always positive

Eur J Nucl Med Mol Imaging (2016) 43:1585–1592
DOI 10.1007/s00259-016-3328-2

21



GROUP 3:
[18F]FDG negative initially but positive during follow up

Eur J Nucl Med Mol Imaging (2016) 43:1585–1592
DOI 10.1007/s00259-016-3328-2

22

DUAL TRACER APPROACH (ALSO in FOLLOW UP) !
[68Ga]SSTR Imaging + [18F]FDG

Why a dual tracer approach ?

1) **High grade poorly differentiated NET could have a low expression of SSTR**
2) **High uptake of FDG correlates strongly with more aggressive tumor and higher risk of progression**
3) **SSTR expression could vary longitudinally**
4) **Also G1 and G2 NET could be [18F]FDG positive**

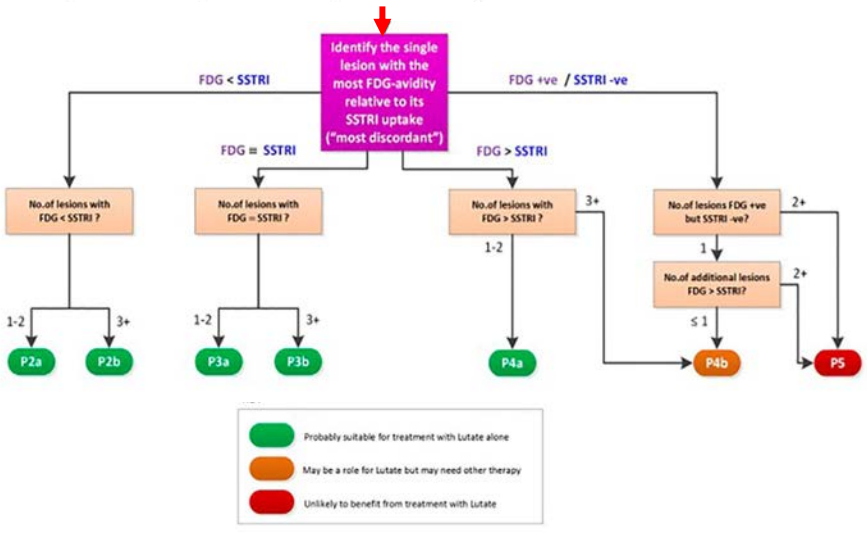
So when [68Ga]SSTR Imaging + [18F]FDG:
In high grade NET G2 and NET G3 (NECs) !
(G1, low grade G2 … ?)

23

Dual PET Imaging in Bronchial Neuroendocrine Neoplasms: The NETPET Score as a Prognostic Biomarker

J Nucl Med 2021; 62:1278–1284
DOI: 10.2967/jnumed.120.257659

David L. Chan[1,2], Gary A. Ulaner[3], David Pattison[4,5], David Wyld[5,6], Rahul Ladwa[5,6], Julian Kirchner[3], Bob T. Li[7], W. Victoria Lai[7], Nick Pavlakis[1,2], Paul J. Roach[8,9], and Dale L. Bailey[8,9,10]



24

A role for [18F]DOPA ?

Eur J Nucl Med Mol Imaging (2017) 44:1588–1601
DOI 10.1007/s00259-017-3728-y

GUIDELINES

Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F–DOPA

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1) Low/variable SSTR expression (neuroectodermal tumours)

2) Catecholamine metabolic pathway

- **Medullary thyroid carcinoma**
- **Jejuno-ilial NEN (midgut)**
- **Neuroblastoma**
- **Pheochromocytoma**
- **Abdominal paraganglioma**

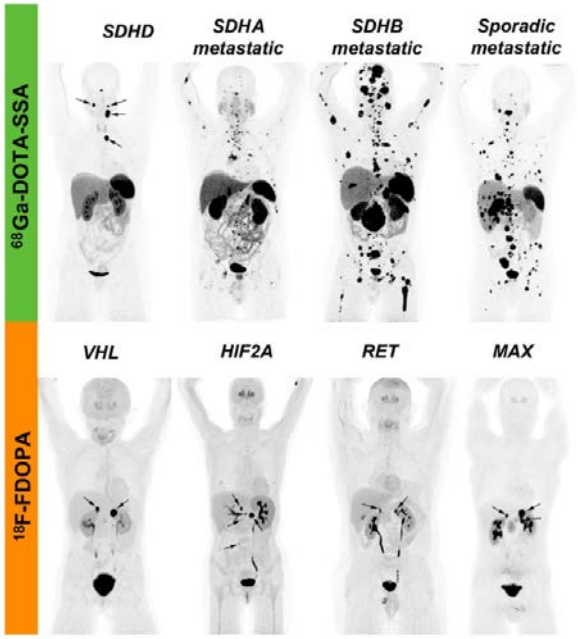
25

Endocrine-Related Cancer | D Taïeb *et al.* | Theranostics of pheochromocytoma and paraganglioma | 26:11 | R627–R656

REVIEW

Molecular ima pheochromoc era of genomi subgroups

David Taïeb[1,*], Abhishek Jha[2,*], G



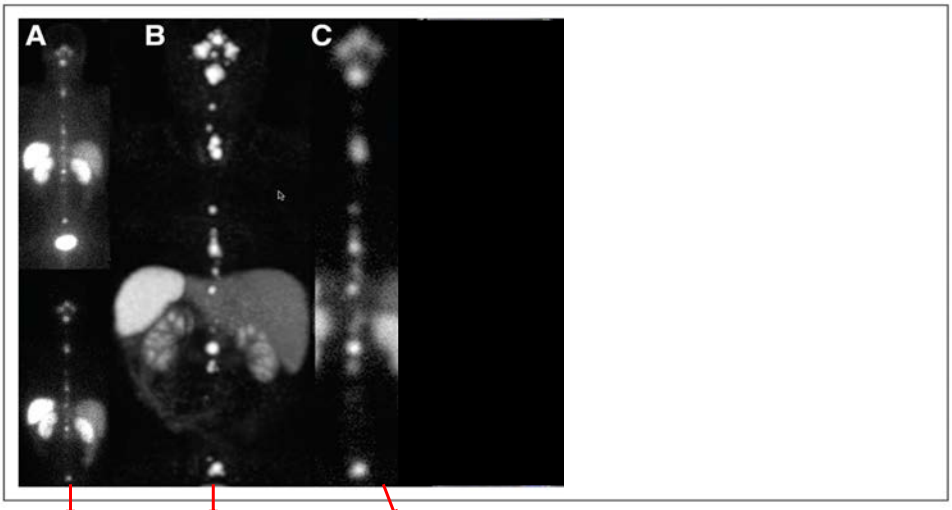
+ FDG

26

VOLUME 29 · NUMBER 7 · MARCH 1 2011
JOURNAL OF CLINICAL ONCOLOGY
DIAGNOSIS IN ONCOLOGY

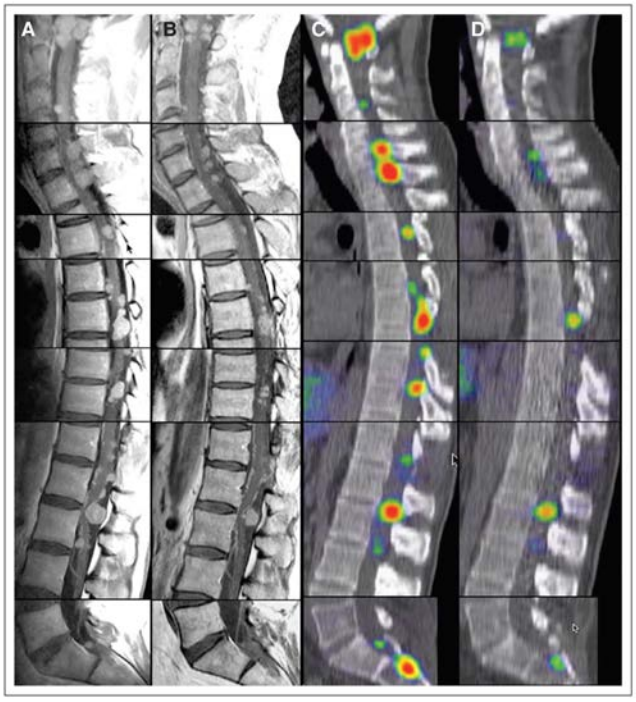
Peptide Receptor Radionuclide Therapy in a Case of Multiple Spinal Canal and Cranial Paragangliomas

Cecchin D. et al



^{111}In-Octreo. ^{68}Ga-DOTA. [^{177}Lu-DOTA0,Tyr3]-Octreotate + *SDHB* immunohistochemistry

27



28

TERAGNOSTICS: NET INDICATIONS

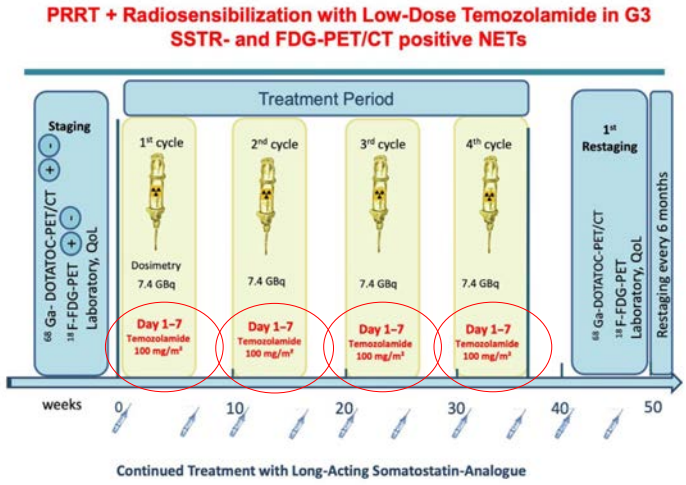
- **Usually after failing first line medical therapy (es cold compounds)**
- **Well differentiated or moderately differentiated NET (Grade 1 or Grade 2 WHO)**

- **Ongoing multicenter studies on G3 (NECs)**

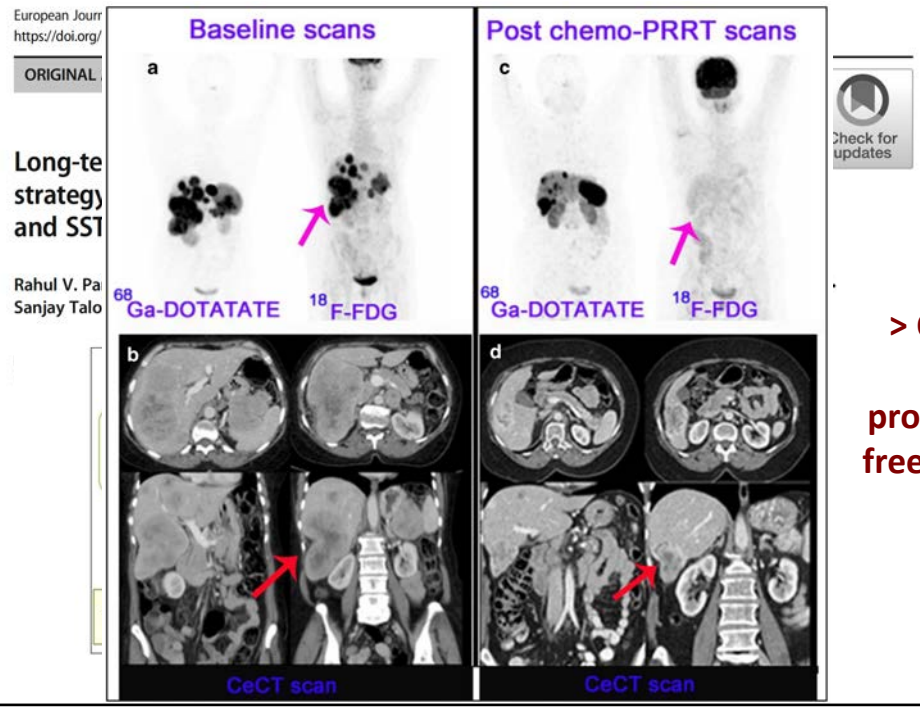
Theragnostics in Neuroendocrine Tumors

Margarida Rodrigues, MD*, Hanna Svirydenka, MD, Irene Virgolini, MD

PRRT could be considered: Ki-67 <=55% (G3) (Thang et al.)



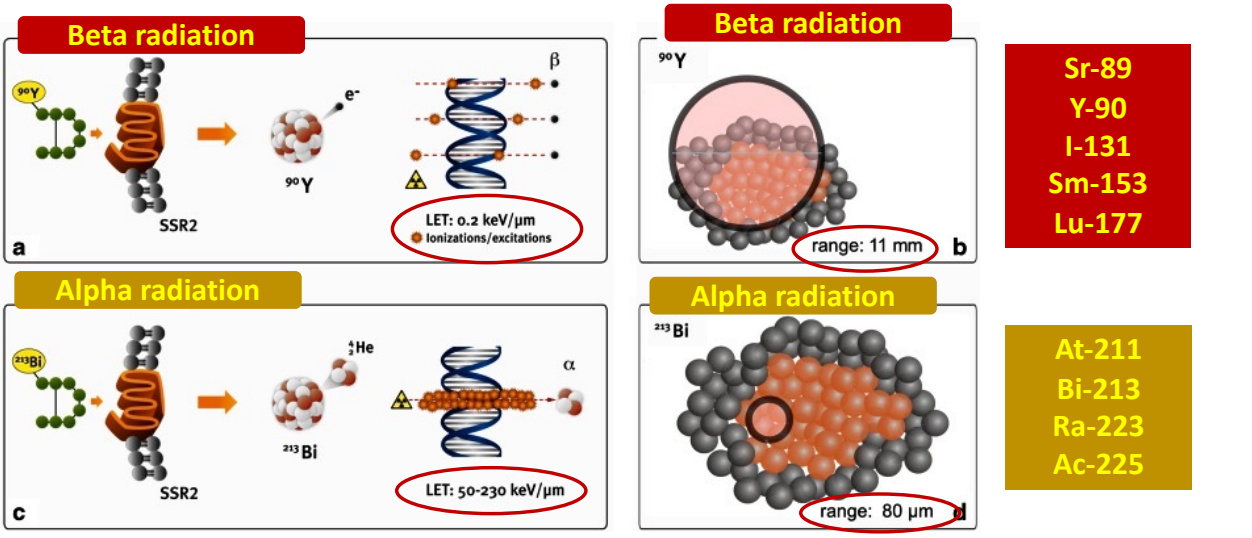
29



> Overall and progression free survival

30

Beta or Alpha radiation (?) …leads to DNA damage in radionuclide therapy



Sr-89
Y-90
I-131
Sm-153
Lu-177

At-211
Bi-213
Ra-223
Ac-225

Kratochwil C, et al. Eur J Nucl Med Mol Imaging. 2014 Nov;41(11):2106-19.

31

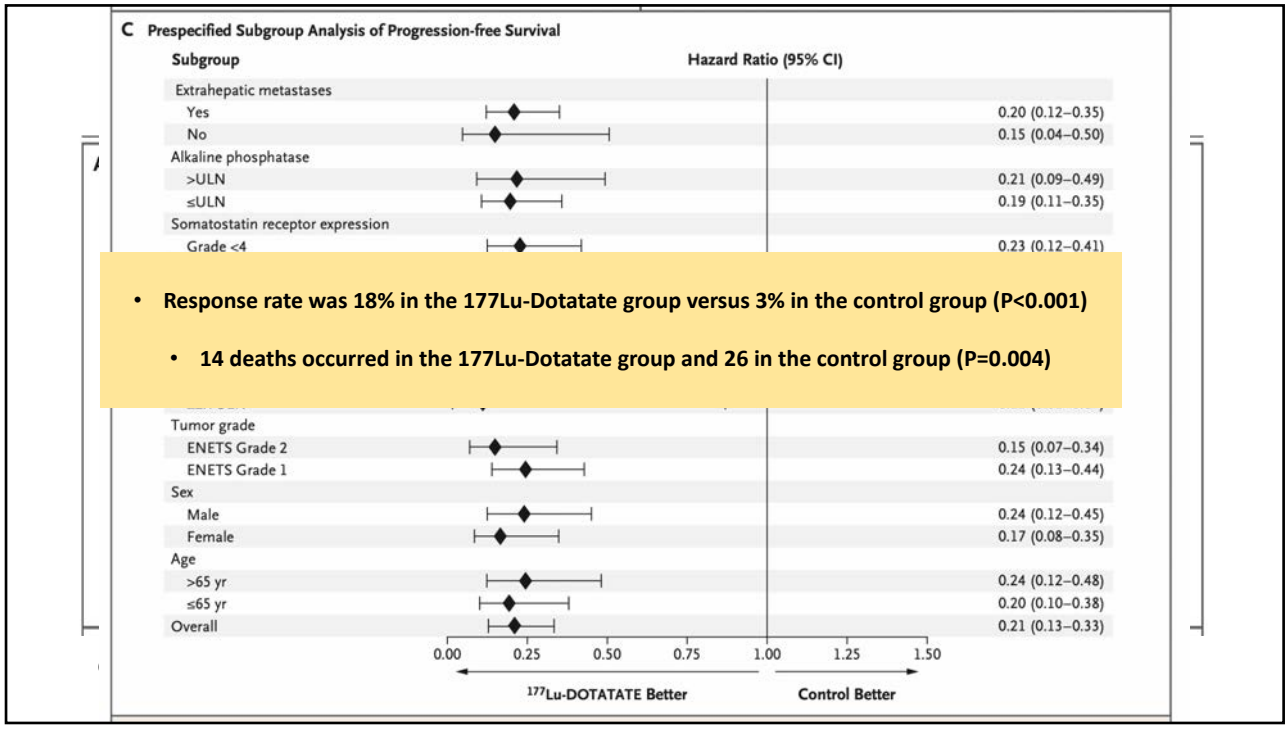
TERAGNOSTICS: NET

^{90}Y-DOTA-TOC/TATE	^{177}Lu-DOTA-TOC/TATE
(beta range ~12 mm)	(beta range ~2 mm) More favorable kidney Tox.
2.7-4.4 GBq every 6-12 weeks	5.5-7.4 GBq every 6-12 weeks
2-4 cycles	3-5 cycles

A number of protocols including:

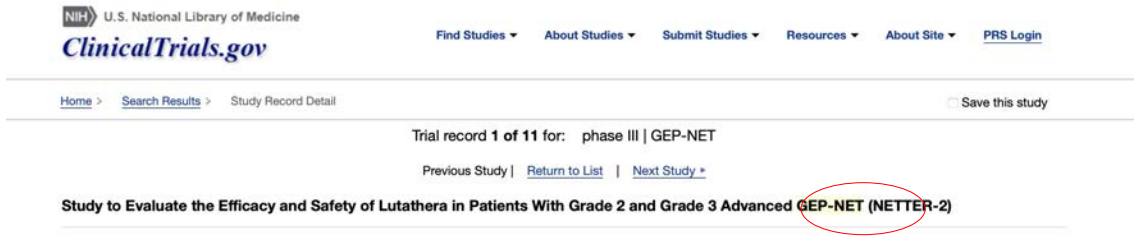
- **Combination of ^{90}Y-DOTA-TOC/TATE and ^{177}Lu-DOTA-TOC/TATE**
- **Cold somatostatin analogs between cycles (at least 4 weeks apart from radioactive cycle)**
- **A number of radiosensitizing chemotherapy combinations**

32



- **Response rate was 18% in the 177Lu-Dotatate group versus 3% in the control group (P<0.001)**
  - **14 deaths occurred in the 177Lu-Dotatate group and 26 in the control group (P=0.004)**

33



The aim of NETTER-2 is to determine if Lutathera in combination with long-acting octreotide prolongs PFS in GEP-NET patients with high proliferation rate tumors (G2 and G3), when given as **a first line treatment** compared to treatment with high dose (60 mg) long-acting octreotide. Somatostatin analog (SSA) naive patients are eligible, as well as patients previously treated with SSAs in the absence of progression

. **ONGOING ….**

34

TERAGNOSTICS: NET -TOXICITY

Nephrotoxicity:

- **Any CTCAE (Common terminology Criteria for Adverse Events): 34.6 (Bodei); 30.4% (Rodriguez)**
- **GRADE 3-4: 1.5% (Bodei on 807 patients); 1/102 (Rodriguez)**

…renal radiation could be reduced by coinfusion of aminoacid during PRRT..

Very, very Few cases of leukopenia, thrombopenia or hematotoxicity !

35

Curr. Treat. Options in Oncol. (2022) 23:703–720
DOI 10.1007/s11864-022-00967-z

Neuroendocrine Cancers (M Cives, Section Editor)

New PET Radiotracers for the Imaging of Neuroendocrine Neoplasms

36

Table 1. Emerging radiopharmaceuticals and their targets

Radiotracer	Targets	Advantages	Theranostic	
SSTR agonists				
[18F]F-AlF-NOTA-octreotide	SSTR expression	- NET - High TBR	No	
[18F]F-SiFAlin-TATE	SSTR expression	- NET - Favourable tumour-to-liver and tumour-to-spleen ratios	No	
[64Cu]Cu-SARTATE	SSTR expression	- High tumour-to-liver ratio - Possibility of diagnostic studies and for prospective dosimetry for [67Cu]Cu-PRRT	Yes, [67Cu]Cu-SARTATE	1
SSTR antagonists (NODAGA-JR11; DOTA-JR11)	SSTR expression	- Compared to analogues: recognise a higher number of SSTR-binding sites, lower dissociation rate, higher TBR, not internalised	Yes, [177Lu]Lu-DOTA-JR11	2
Exendin	GLP-1R expression	- Insulinoma - High tumour-to-pancreas ratio	Yes, with the limit of high kidney uptake	
[18F]F-MFBG	Norepinephrine transporter expression	- Neuroblastoma or paraganglioma/pheochromocytoma - High TBR	No	
[68Ga]Ga-CXCR4	C-X-C motif chemokine receptor 4 expression	- Dedifferentiated NEN	Yes	3
[68Ga]Ga-PSMA	PSMA expression	- Highly vascularised lesions	Yes	4
[68Ga]Ga-FAPI	Fibroblast activation protein expression	- Preliminary data show uptake in NEN - Favourable biodistribution	Yes	5

Legend: *SSTR*, somatostatin receptor; *TBR*, tumour-to-background ratio; *GLP-1R*, glucagon-like peptide-1 receptor; *PSMA*, a transmembrane protein with enzymatic function as folate hydrolase-carboxypeptidase

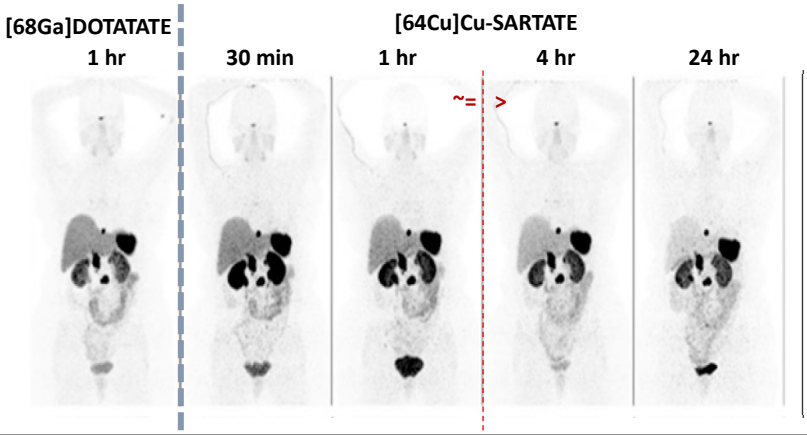
37

1 **[64Cu]Cu-SARTATE - [67Cu]Cu-SARTATE**

^{64}Cu-SARTATE PET Imaging of Patients with Neuroendocrine Tumors Demonstrates High Tumor Uptake and Retention, Potentially Allowing Prospective Dosimetry for Peptide Receptor Radionuclide Therapy

J Nucl Med 2019; 60:777–785
DOI: 10.2967/jnumed.118.217745

[64Cu]Cu-SARTATE= T1/2 : 12.7 hr (compared with 68Ga: 68 min ~ 1 hr)
Mean effective dose 0.0454 mSv/MBq (SARTATE) vs 0.023 mSv/MBq (DOTA)



1. **High late retention in tumor and clearance from liver (better lesion detection, improved sensitivity..)**
2. **Prospective dosimetry for 67Cu-sartate**
3. **T 1/2 would allow distribution to sites (as compared to 68Ga..)**
4. **Production by cyclotron**

38

2 SSTR ANTAGONISTS (NODAGA-JR11; DOTA-JR11) - [177Lu]Lu-DOTA-JR11

WHY ?
- Higher number of SSTR-bidings
- Are not internalized
- Could have lower dissociation rate

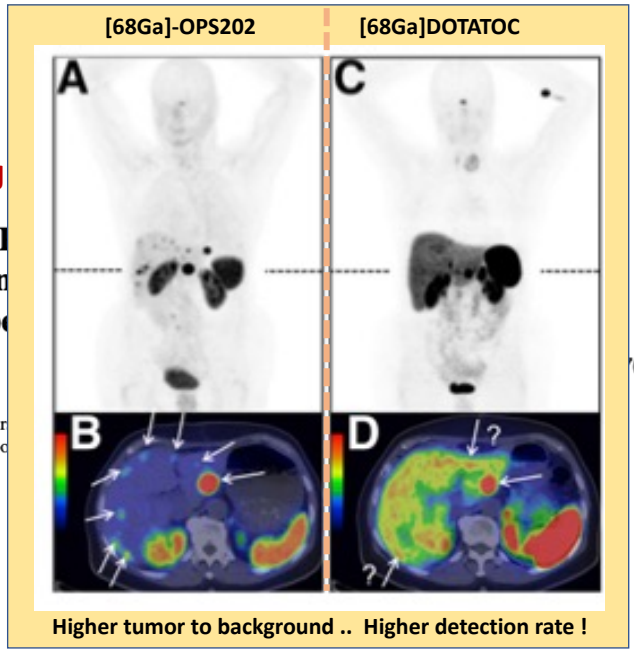
[68Ga]Ga-OPS202 (Nogada-J

Sensitivity Comparison of ^{68}Ga-OI PET/CT in Patients with Gastroen Neuroendocrine Tumors: A Prospe Imaging Study

Guillaume P. Nicolas[1,2], Nils Schreiter[3,4], Felix Kaul[1,2], John Uiter Tobias E. Erlanger[7], Richard Cathomas[8], Emanuel Christ[2,9], Melpo

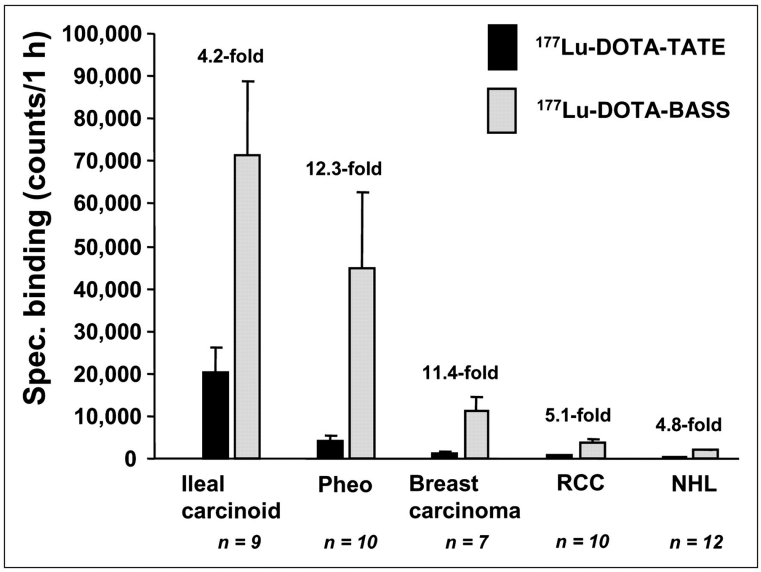
760

Mean effective dose:
0.024 mSv/MBq (Nogada)
0.023 mSv/MBq (DOTA)



Higher tumor to background .. Higher detection rate !

39



Agonist

Antagonist

Quantitation of in vitro receptor autoradiography experiments with various types of human cancers (ileal carcinoid, pheochromocytoma, breast carcinoma, renal cell carcinoma, and non-Hodgkin lymphoma) using 177Lu-DOTATATE and 177Lu-DOTA-BASS as radioligands. Renzo Cescato et al. J Nucl Med 2011;52:1886-1890

JNM The Journal of NUCLEAR MEDICINE

40

Somatostatin Receptor Imaging of Neuroendocrine Tumors: From Agonists to Antagonists

Invited perspective

Lisa Bodei[1] and Wolfgang A. Weber[2]

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 59 • No. 6 • June 2018

[1]Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; and [2]Department of Nuclear Medicine, Technical University of Munich, Munich, Germany

Markedly more LIVER metastases were detected:
Antagonists: 68Ga-NODAGA-JR11 94%
Agonist: 68Ga-DOTATOC 59%

Nicolas GP, Schreiter N, Kaul F, et al. Sensitivity comparison of 68Ga-OPS202 and 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: a prospective phase II imaging study. JNuclMed. 2018;59:915–921.

NB: "…a 50-mg peptide mass is identical to a pharmacologically active dose of octreotide (which has an affinity for sstr2 similar to that of NODAGA-JR11). In patients with hormone-secreting tumors treated with octreotide, injection of 68Ga-NODAGA-JR11 may antagonize the inhibitory effects of octreotide on hormone secretion." so .. "slow intravenous … for safety reasons"..

NB: "…68Ga-DOTATOC also binds to sstr5 and to a lesser extent sstr3, whereas 68Ga-NODAGA-JR11 is a pure sstr2 ligand. Differences in bio-distribution and tumor uptake may therefore reflect not only differences between their agonistic and antagonistic properties but also differences in the SSR binding profile"..

41

First-in-Humans Study of the SSTR Antagonist ^{177}Lu-DOTA-LM3 for Peptide Receptor Radionuclide Therapy in Patients with Metastatic Neuroendocrine Neoplasms: Dosimetry, Safety, and Efficacy

J Nucl Med 2021; 62:1571–1581
DOI: 10.2967/jnumed.120.258889

Richard P. Baum*[1,2], Jingjing Zhang*[1,3,4], Christiane Schuchardt[1], Dirk Müller[1], and Helmut Mäcke[5]

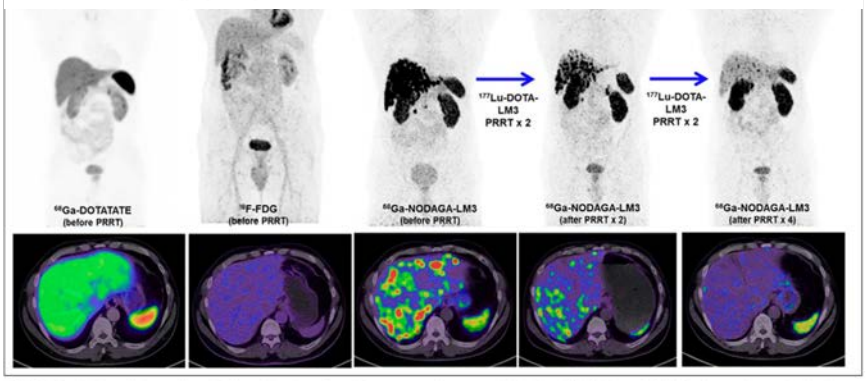


FIGURE 5. A 55-y-old man with well-differentiated, nonfunctioning metastatic pancreatic NEN and Ki-67 index of 13%. Patient underwent Whipple procedure, with histologically confirmed G2 pancreatic NEN. MRI had revealed multiple small-volume liver metastases. ^{68}Ga-DOTATATE PET/CT showed weakly ^{68}Ga-DOTATATE–avid small-volume lesions in liver and lymph nodes with extremely low uptake (leftmost image), which did not exhibit significant glucose hypermetabolism (second image from left). ^{68}Ga-NODAGA-LM3 PET/CT then showed disseminated bilobar liver metastases, demonstrating intense SSTR antagonist (LM3) uptake in liver and lymph node metastases (third image from left). Patient was treated with 4 cycles of ^{177}Lu-DOTA-LM3 PRRT, with cumulative administered radioactivity of 25.7 GBq. Restaging ^{68}Ga-NODAGA-LM3 PET/CT showed excellent response to ^{177}Lu-DOTA-LM3 PRRT, with partial remission of disease according to RECIST and EORTC criteria (rightmost image).

42

3

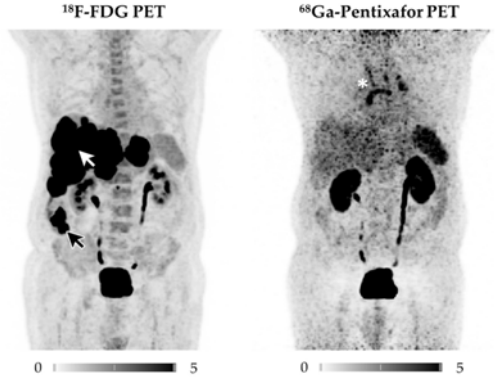
[68Ga]Pentixafor - [177Lu]Pentixather

Article

CXCR4-Directed PET/CT in Patients with Newly Diagnosed Neuroendocrine Carcinomas

Alexander Weich [1,2,†], Rudolf A. Werner [2,3,4,†], Andreas K. Buck [2,3], Philipp E. Hartrampf [3], Sebastian E. Serfling [3], Michael Scheurlen [1,2], Hans-Jürgen Wester [5], Alexander Meining [1,2], Stefan Kircher [6], Takahiro Higuchi [3,7,8], Martin G. Pomper [4], Steven P. Rowe [4], Constantin Lapa [2,3,9] and Malte Kircher [2,3,9,*]

Rationale: C-X-C motif chemochine receptor overexpressed in more aggressive and de-differentiated NENs



"…in poorly differentiated NEC … 68Ga-Pentixafor PET/CT is inferior to 18F-FDG PET/CT"

43

4

[68Ga]FAPI

Favorable biodistribution (high TBR): improved detection in brain, H&N, peritoneum, mesentery, omentum, skeleton

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:721–731
https://doi.org/10.1007/s00259-021-05488-9

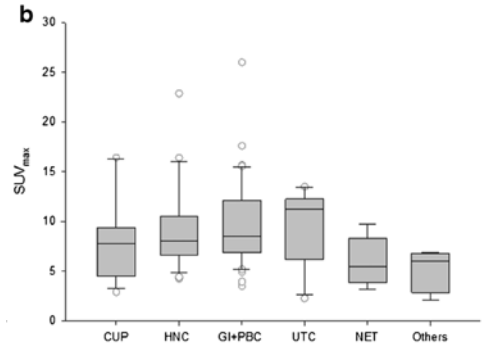
ORIGINAL ARTICLE

55 cases

FAP imaging in rare cancer entities—first clinical experience in a broad spectrum of malignancies

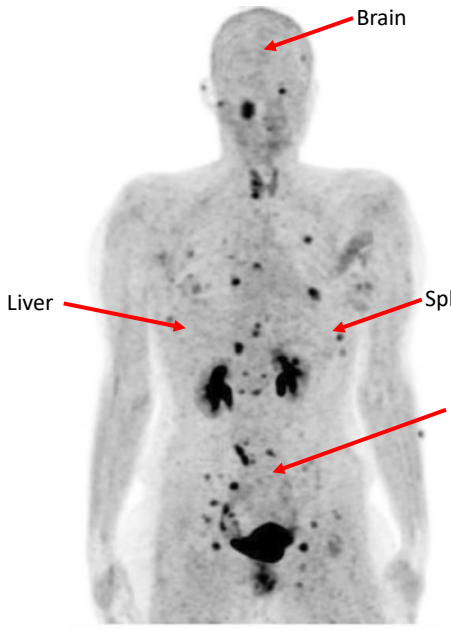
K. Dendl[1] · R. Finck[1] · F. L. Giesel[1,2,3] · C. Kratochwil[1] · T. Lindner[1] · W. Mier[1] · J. Cardinale[1] · C. Kesch[4] · M. Röhrich[1] · H. Rathke[1] · H. Gampp[5] · J. Ristau[2,6,7] · S. Adeberg[2,6,7] · D. Jäger[2] · J. Debus[2,6,7,8,9,10] · U. Haberkorn[1,11,12] · S. A. Koerber[2,6,7]

Received: 23 March 2021 / Accepted: 4 July 2021 / Published online: 3 August 2021



- CUP: Cancer of Unknown Primary (*n* = 10)
- HNC: head and neck cancer (*n* = 13)
- GI+PBC: gastrointestinal and biliary-pancreatic cancer (*n* = 17)
- UTC: urinary tract cancer (*n* = 4)
- **NET neuroendocrine tumors (*n* = 4)**
- Others (*n* = 7)

44



Favorable biodistribution (high TBR) due to low background in critical organs

Glomus cancer

Modified from "**European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:721–731"**

45

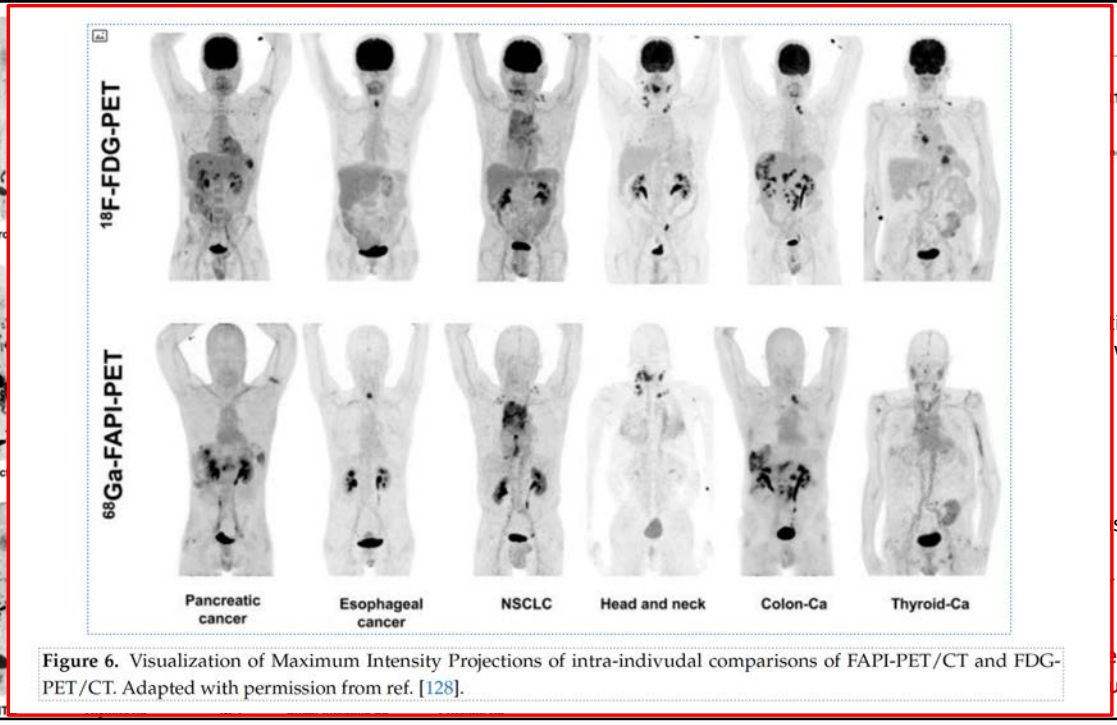


Figure 6. Visualization of Maximum Intensity Projections of intra-indivudal comparisons of FAPI-PET/CT and FDG-PET/CT. Adapted with permission from ref. [128].

46

5 [68Ga]PSMA - [177Lu]PSMA in MTC? Inoperable Paraganglioma ?

Review

PSMA-Targeting Positron Emission Agents for Imaging Solid Tumors Other Than Non-Prostate Carcinoma: A Systematic Review

Int. J. Mol. Sci. **2019**, *20*, 4886; doi:10.3390/ijms20194886

Christophe Van de Wiele [1,2,*], Mike Sathekge [3], Bart de Spiegeleer [4], Pieter Jan de Jonghe [1], Laurence Beels [1] and Alex Maes [1,5]

"prostate-specific membrane antigen (PSMA) has been shown… to also be over-expressed in the tumor neovasculature of a wide variety of solid tumors other than prostate carcinoma":

- Renal Carcinoma
- Breast Carcinoma
- Differentiated Thyroid carcinoma
- Lung adenocarcinoma
- Hepatocellular Carcinoma
- ecc

About NENs ?:

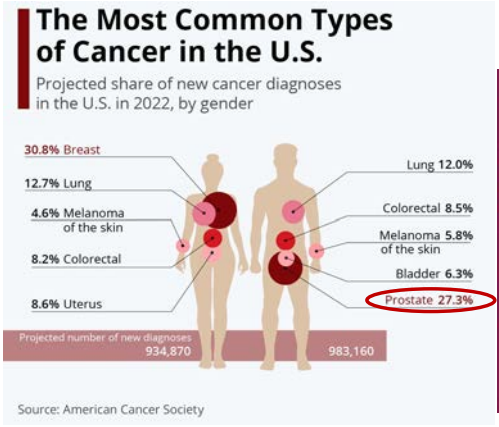
- **2 cases of pancreas (NENs histologically proven)**
- **2 cases of Medullary Thyroid Carcinoma (MTC) -> [177Lu]PSMA ?**
- **2 cases of paraganglioma**
- **1 pheocromocytoma**

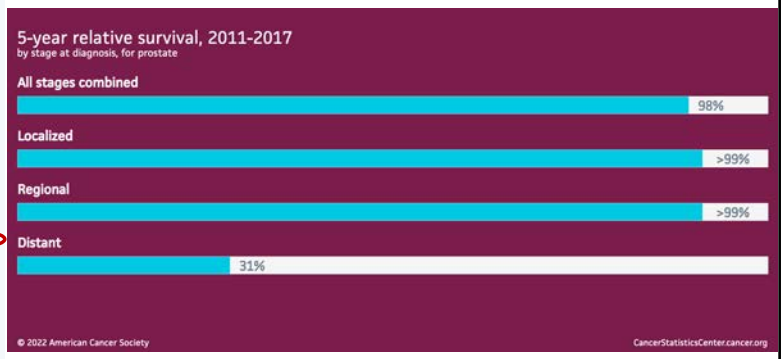
47

MOVING FROM NET .. TO PROSTATE

48

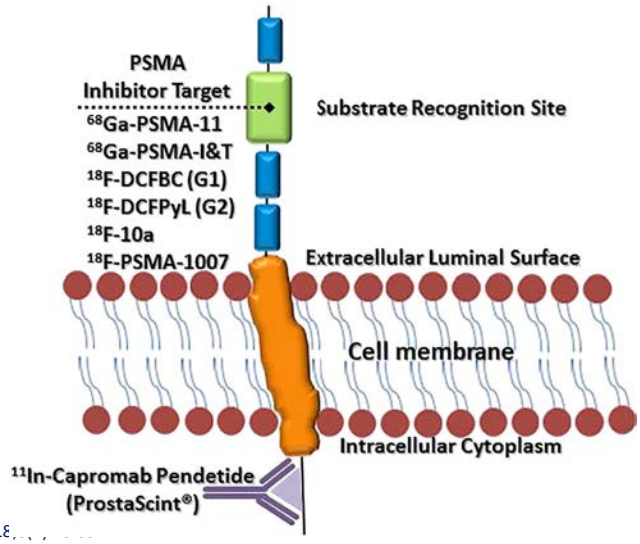
PROSTATE CANCER





49

THERANOSTICS: RDPH for Prostate-specific Membrane Antigen (PSMA) Imaging



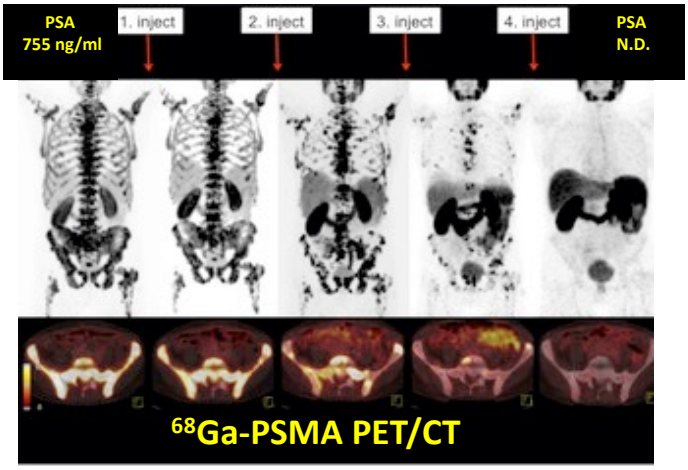
Evans JD, et al. Pract Radiat Oncol. 2018[illegible]
Heck MM, et al. J Urol. 2016;196(2):382-391.

50

THERANOSTICS of Prostate Cancer: ^{68}Ga-PSMA-PET/^{177}Lu-PSMA

Radionuclide Therapy:

4 cycles of ^{177}Lu-PSMA determined complete remission and fading of multiple bone metastasis



1st line treatment: docetaxel

2nd line treatment: abiraterone

3rd line treatment: enzalutamide

4th line treatment: $^{223}RaCl_2$

5th line treatment: ^{177}Lu-PSMA

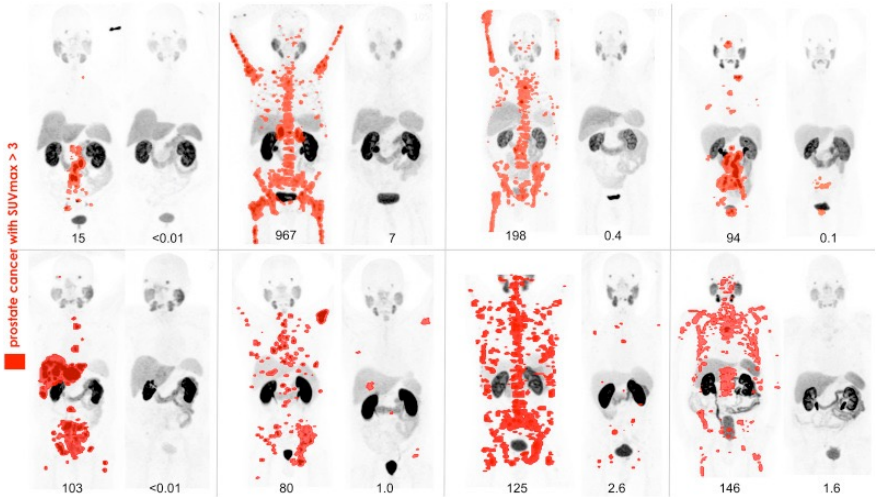
Complete remission ongoing 13 months

Evans JD, et al. Pract Radiat Oncol. 2018;8(1):28-39
Heck MM, et al. J Urol. 2016;196(2):382-391.

51

Theranostics of Prostate Cancer: ^{68}Ga-PSMA-PET/^{177}Lu-PSMA

- ✓ [^{68}Ga]Ga-PSMA-PET images at baseline and 3 months after [^{177}Lu]Lu-PSMA treatment with PSA decline of ≥98%
- ✓ Lesions with standardized uptake value (SUV) are highlighted in red.
- ✓ PSA values (ng/mL) with PSA decline of ≥98% are indicated below images.

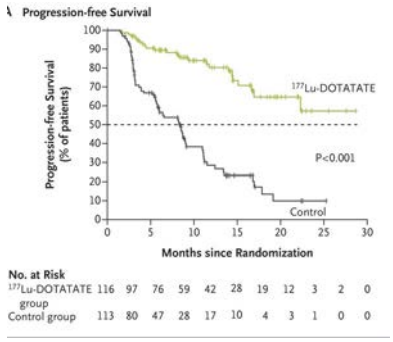


52

THERANOSTICS: efficacy of radionuclide therapy

NETTER-1 Trial:

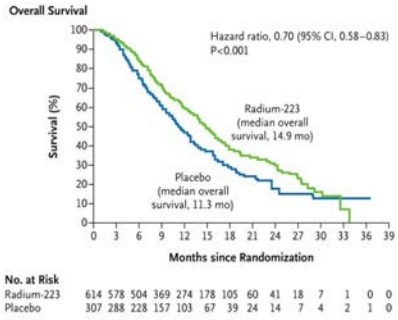
Lu-177 DOTATATE improves progression free survival in GEP neuroendocrine tumors



Strosberg J, et al. 2017. N Engl J Med; 376:125.

ALSYMPCA Trial:

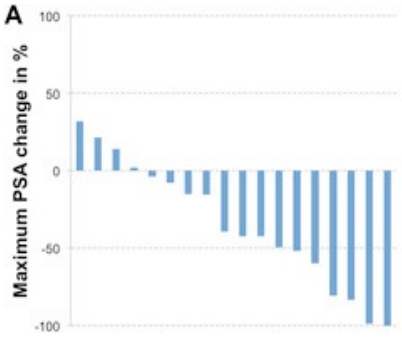
Ra-223 improves survival in castrate-resistant prostate cancer



Parker CC, et al. 2013. N Engl J Med;369:213.

VISION Trial:

Lu-177 PSMA-617 for metastatic castrate resistant prostate cancer



Heck MM, et al. 2016. J Urol.196:382.

53

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- Dr.ssa Bodanza Valentina
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- Prof. Liviana da Dalt
- Prof. Gianni Bisogno
- Prof.ssa Silvia Carraro
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- Equipe Sedazione pediatrica **! etc !**

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Orizzonte degli eventi...

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54