Delivering on the Promise of Theranostics

A Pillar of Progress at IPO Porto

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CONFLICTS OF INTEREST STATEMENT

Presenter's Name: Gonçalo Ferreira

Compensated by Novartis for presentation services (speaker fees) and consulting.

Shareholder: Bristol Myers Squibb, Telix Pharmaceuticals, Fusion Pharma

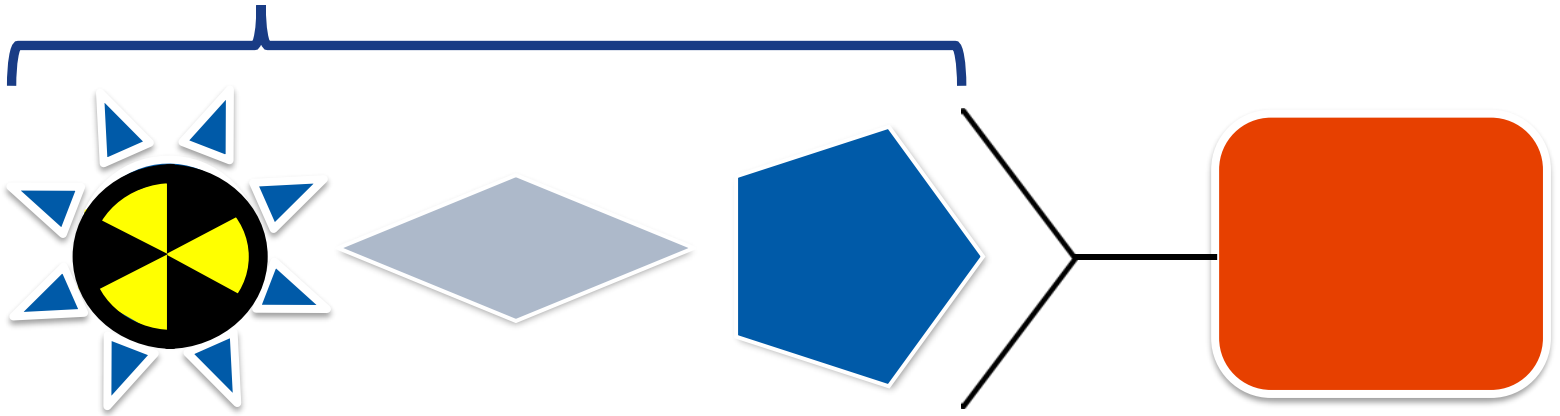
Professional affiliations: IPO Porto, Atrys, Unilabs

Recognizing the importance of transparency and ethics in all professional activities, conflicts of interest have been disclosed with the aim of ensuring the integrity and impartiality of this presentation. I am committed to providing objective, evidence-based, and quality information to the participants.

The opinions and recommendations expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the position of any other institution.

BASIS OF NUCLEAR MEDICINE

- **Radiopharmaceutical**



RADIONUCLIDE

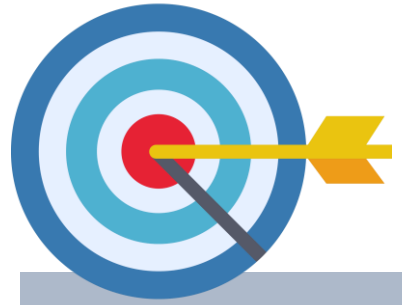
- ^{18}F
- ^{68}Ga
- ^{99}mTc
- ^{177}Lu
- ^{90}Y

LIGAND

- Antibodies
- Peptides
- Aminoacids

MOLECULAR TARGET

- Antigens
- Receptors
- Transporters



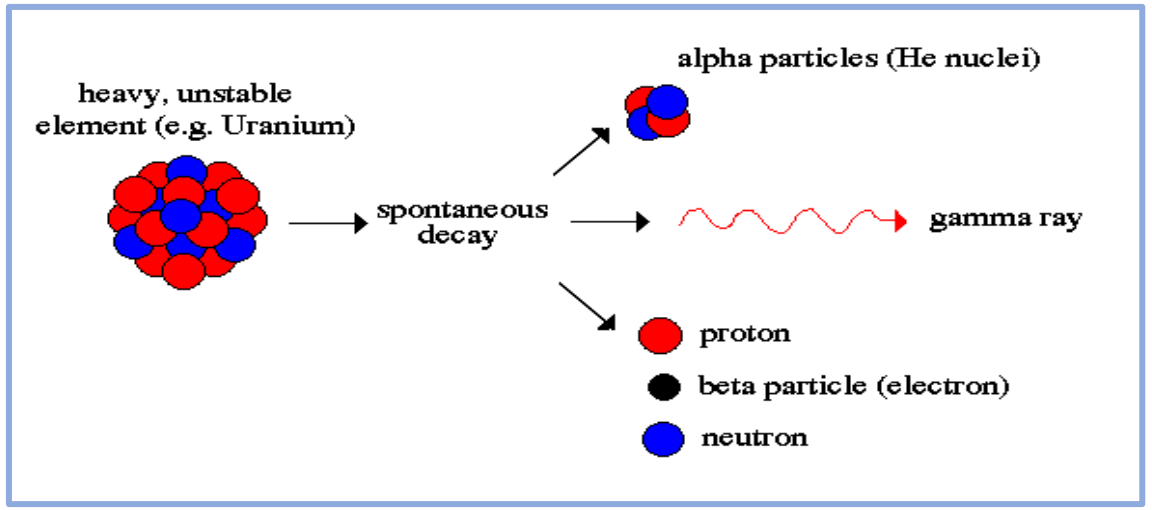
TRACER PRINCIPLE:

Radiopharmaceuticals are distributed, metabolized, and excreted based on their chemical structure, without having pharmacological action.

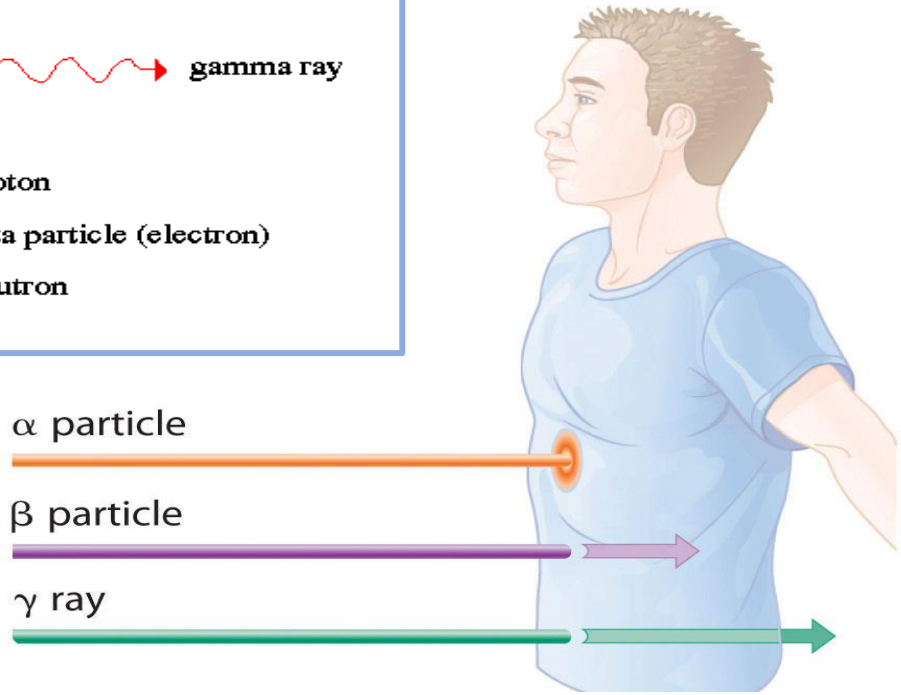
Nuclear Medicine The Requisites, 4th Ed, "Radiopharmaceuticals", chapter 1

BASIS OF NUCLEAR MEDICINE

- **Different types of radiation**



- Penetration $\gamma > \beta > \alpha$
- Ionization $\alpha > \beta > \gamma$

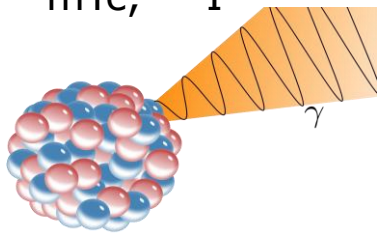


Principles of General Chemistry, "Nuclear Chemistry", chapter 20
Accessed on 03/07/2023 at https://2012books.lardbucket.org/books/principles-of-general-chemistry-v1.0/

BASIS OF NUCLEAR MEDICINE

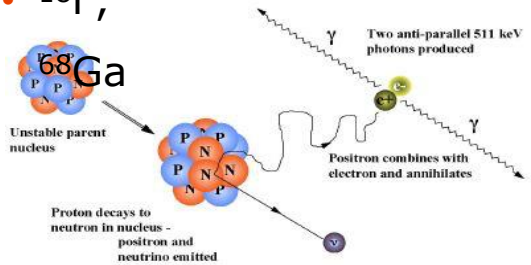
- **Radiopharmaceuticals for Diagnosis and Therapy**

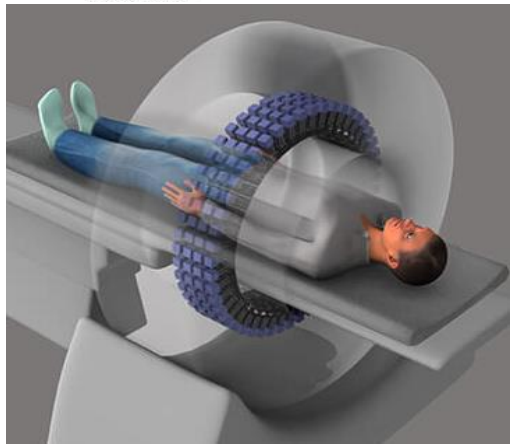
- ^{99}mTc, ^{123}I



SCINTIGRAPHY / SPECT

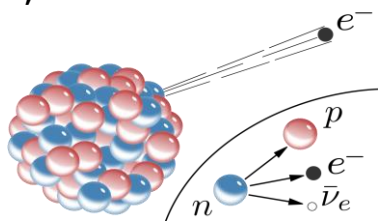
- ^{18}F, ^{68}Ga





PET

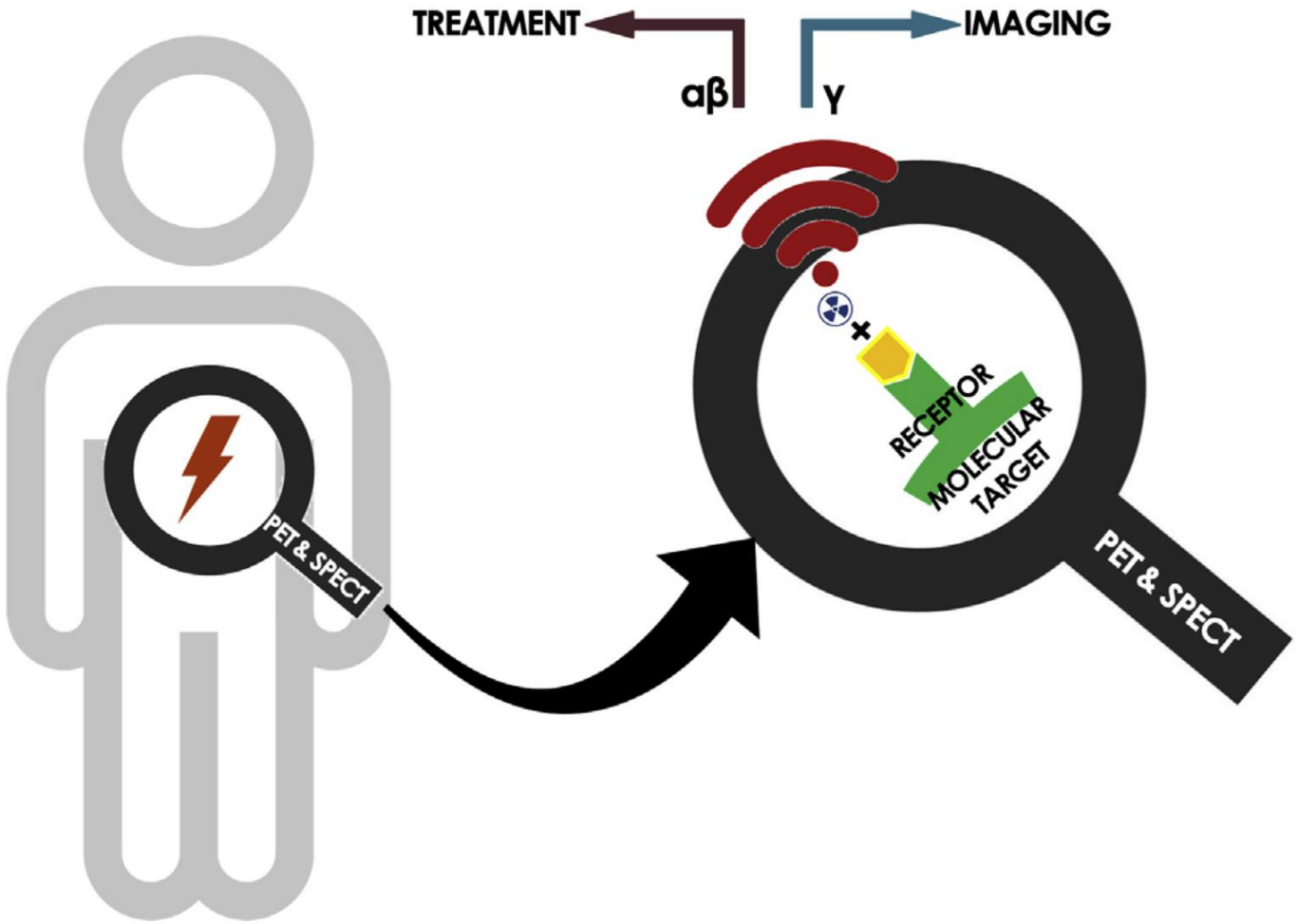
- ^{131}I, ^{177}Lu



RADIONUCLIDE THERAPY

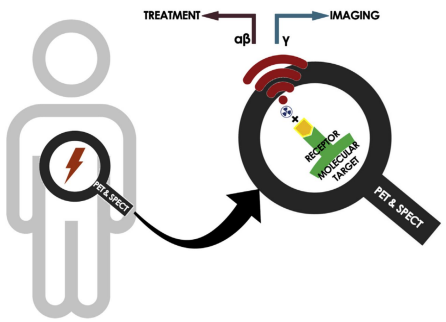
Nuclear Medicine The Requisites, 4th Ed, “Radiopharmaceuticals”, chapter 1, "Radiation Detection and Instrumentation", chapter 5

RADIOTHERANOSTICS



PET Clin . 2021 Jul;16(3):313-326.

RADIOTHERANOSTICS



^{68}Ga-DOTA-NOC

- **β$^+$ Emitter**
- **Chelating Agent**
- **Somatostatin Analog** → affinity for **ssrt2, ssrt3 e ssrt5**

PET scan

Imaging

^{177}Lu-DOTA-TATE

- **γ e β$^-$ Emitter**
- **Somatostatin Analog** → affinity for **ssrt2**

Post-therapy Scintigraphy

Therapy

THERANOSTICS: WE TREAT WHAT WE SEE

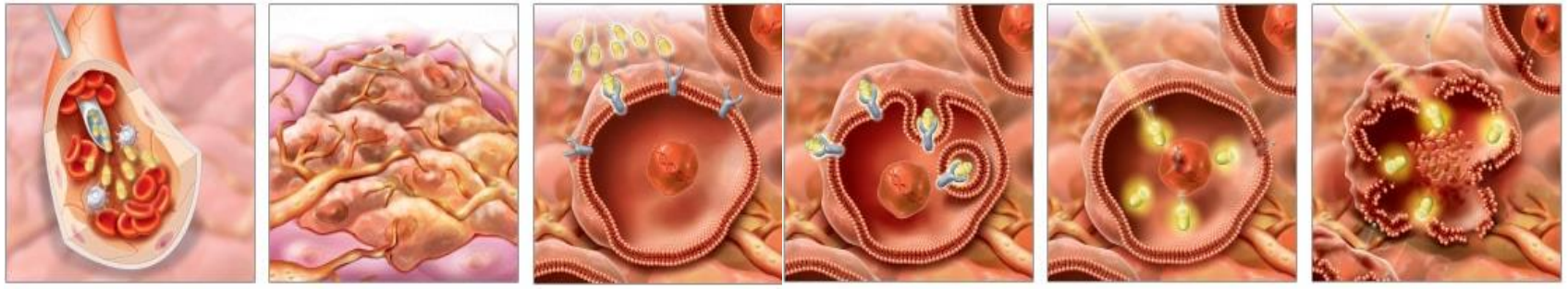
TRANSLATION TO ONCOLOGY

Birth of Clinical Nuclear Medicine

- 1941: 1st treatment with radioiodine (Saul Hertz)
- 1950: 1st thyroid scintigraphy with radioiodine (Benedict Cassem)

Evolution of Nuclear Medicine

- Development of molecular imaging techniques and new radiopharmaceuticals specific for the diagnosis and treatment of oncological pathologies (e.g., prostate cancer, neuroendocrine tumors, bone metastases).



PRRT, Advanced Accelerator Applications, accessed on 03/07/2023 at https://euhcp.lutathera.com/about-lutathera/

MERITS

- High uptake in tumor lesions.
- Low toxicity in normal tissues.
- Impact on symptom relief and Quality of Life (QoL).

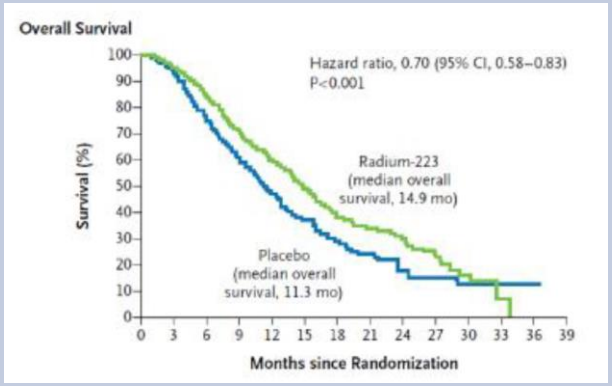
PET Clin . 2021 Jul;16(3):313-326.
Radiology . 2018 Feb;286(2):388-400.

THERANOSTICS IN THE ERA OF EVIDENCE-BASED MEDICINE

Clinical trials demonstrating the efficacy of therapies with radionuclides

ALSYMPCA (2013)

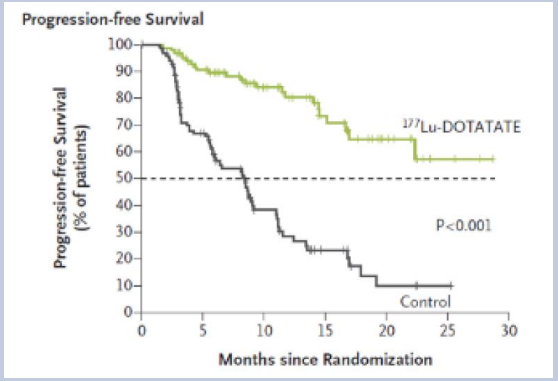
- **Ra-223:** improvement in overall survival in patients with mCRPC



N Engl J Med . 2013 Jul 18;369(3):213-23.

NETTER-1 (2017)

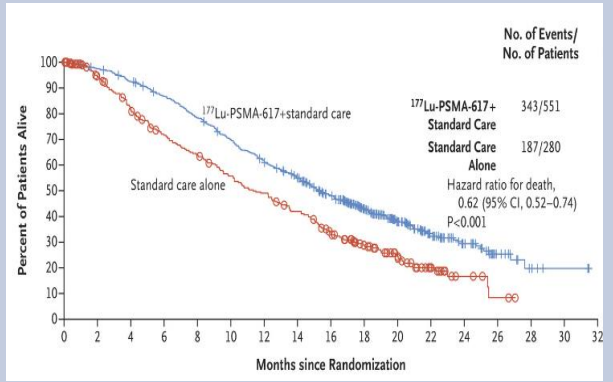
- **^{177}Lu-DOTATATE:** improvement in progression-free survival in NETs



N Engl J Med . 2017 Jan 12;376(2):125-135

VISION (2021)

- **^{177}Lu-PSMA:** Improvement in PFS and OS in patients with mCRPC



N Engl J Med . 2021 Sep 16;385(12):1091-1103.

THERANOSTIC PAIRS IN CLINICAL PRACTICE

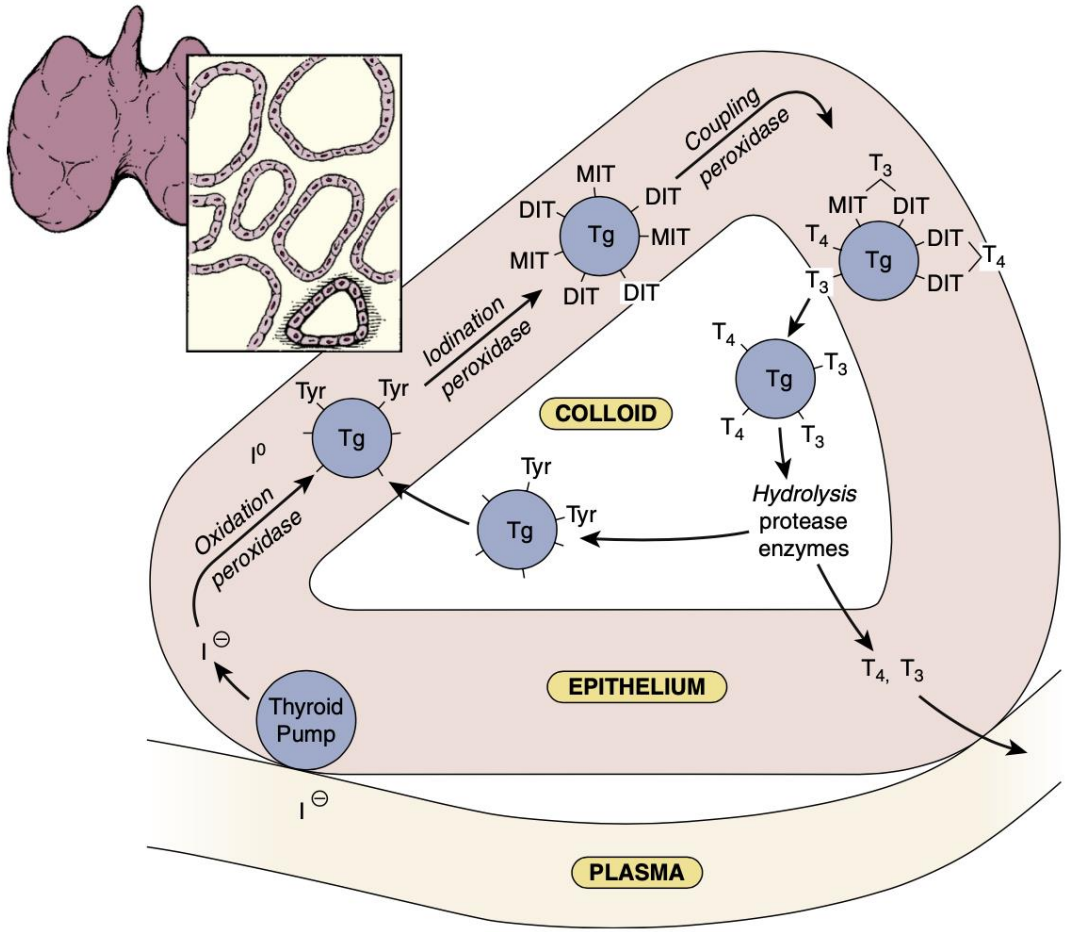
Table 1
Examples of nuclear medicine theranostics pairs commonly used in clinical routines worldwide

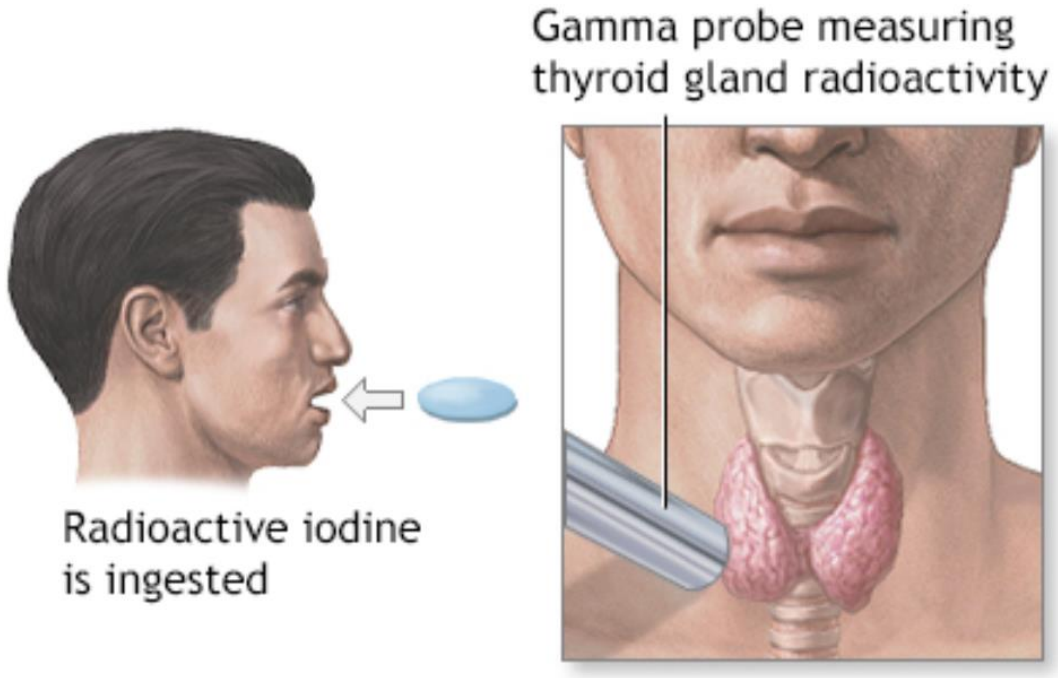
Molecular Target	Diseases	Diagnostic	Therapy
Sodium/iodide symporter	Hyperthyroidism Differentiated thyroid cancer	^{123}I (NaI) ^{99m}Tc-pertechnetate	^{131}I (NaI)
Norepinephrine transporter	Neuroblastoma Pheochromocytoma Paraganglioma Medullary thyroid cancer	^{123}I-mIBG	^{131}I-mIBG
Hydroxyapatite in bones	Prostate cancer	^{99m}Tc-MDP ^{18}F-NaF	^{223}Ra
Somatostatin receptors	Neuroendocrine tumors	^{68}Ga-DOTA-peptides ^{99m}Tc/^{111}In-octreotate	^{177}Lu/^{90}Y-octreotate
PSMA	Prostate cancer	^{68}Ga/^{18}F-PSMA	^{177}Lu/^{225}Ac-PSMA
Hepatic microvasculature	Hepatocellular carcinoma Cholangiocarcinoma Liver metastases	^{99m}Tc-MAA	^{90}Y-microspheres
CD20 (B-lymphocyte antigen, expressed on the surface of B cells)	Non-Hodgkin lymphoma	Anti-CD20 immunohistochemistry	^{131}I/^{90}Y-anti-CD20

PET Clin . 2021 Jul;16(3):313-326.

RADIOIODINE

Iodine metabolism in the thyroid follicular cell





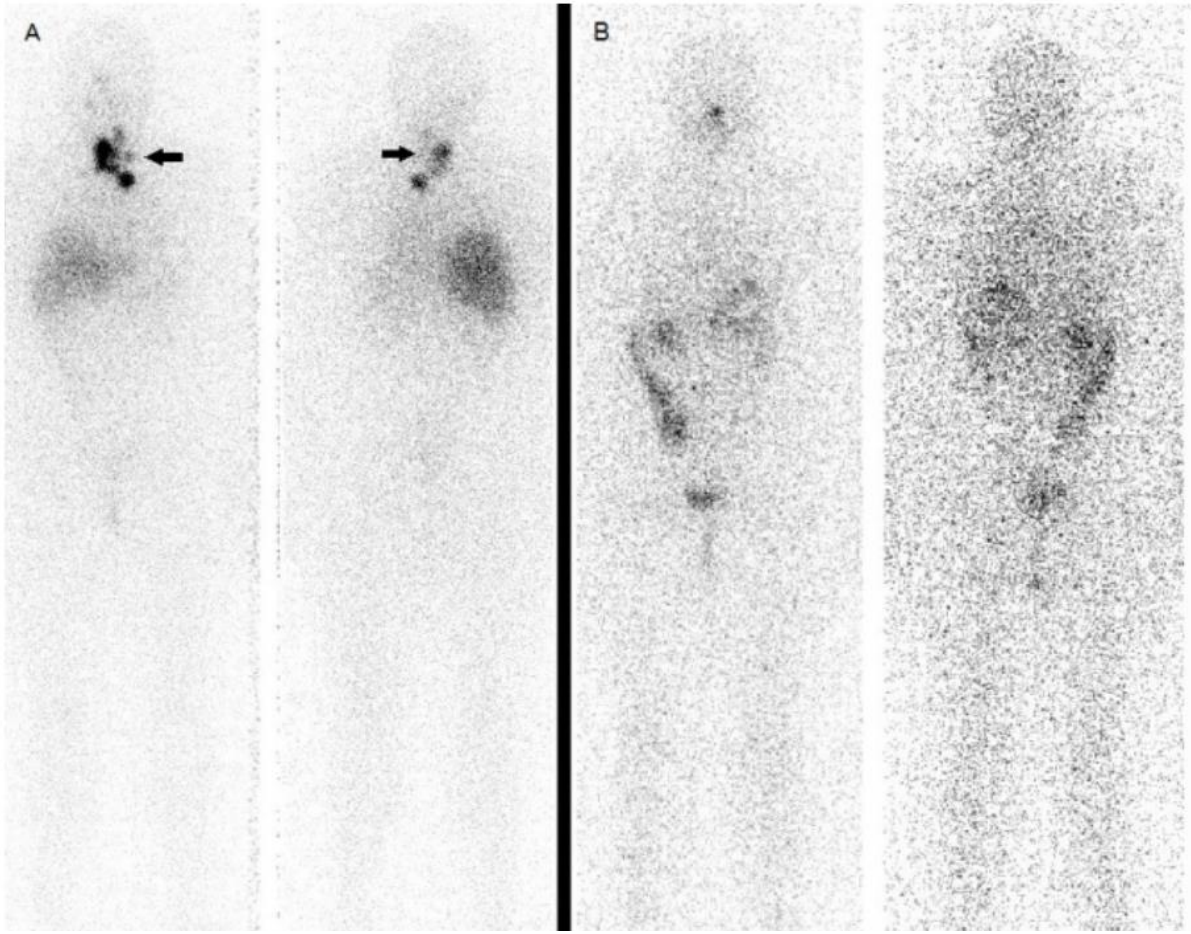
Nuclear Medicine The Requisites, 4th Ed, "Endocrine System", chapter 8

RADIOIODINE

In differentiated thyroid carcinoma

Hx

- ♀, 42y, papillary thyroid carcinoma, underwent total thyroidectomy (pT2N1b).
- Ajuvant/ ablation therapy with radioiodine (^{131}I, 3700 MBq).
- After 8 months, there was observed a scintigraphic absence of pathological uptakes and normalization of Tg values (20 → 0.2 ng/mL).



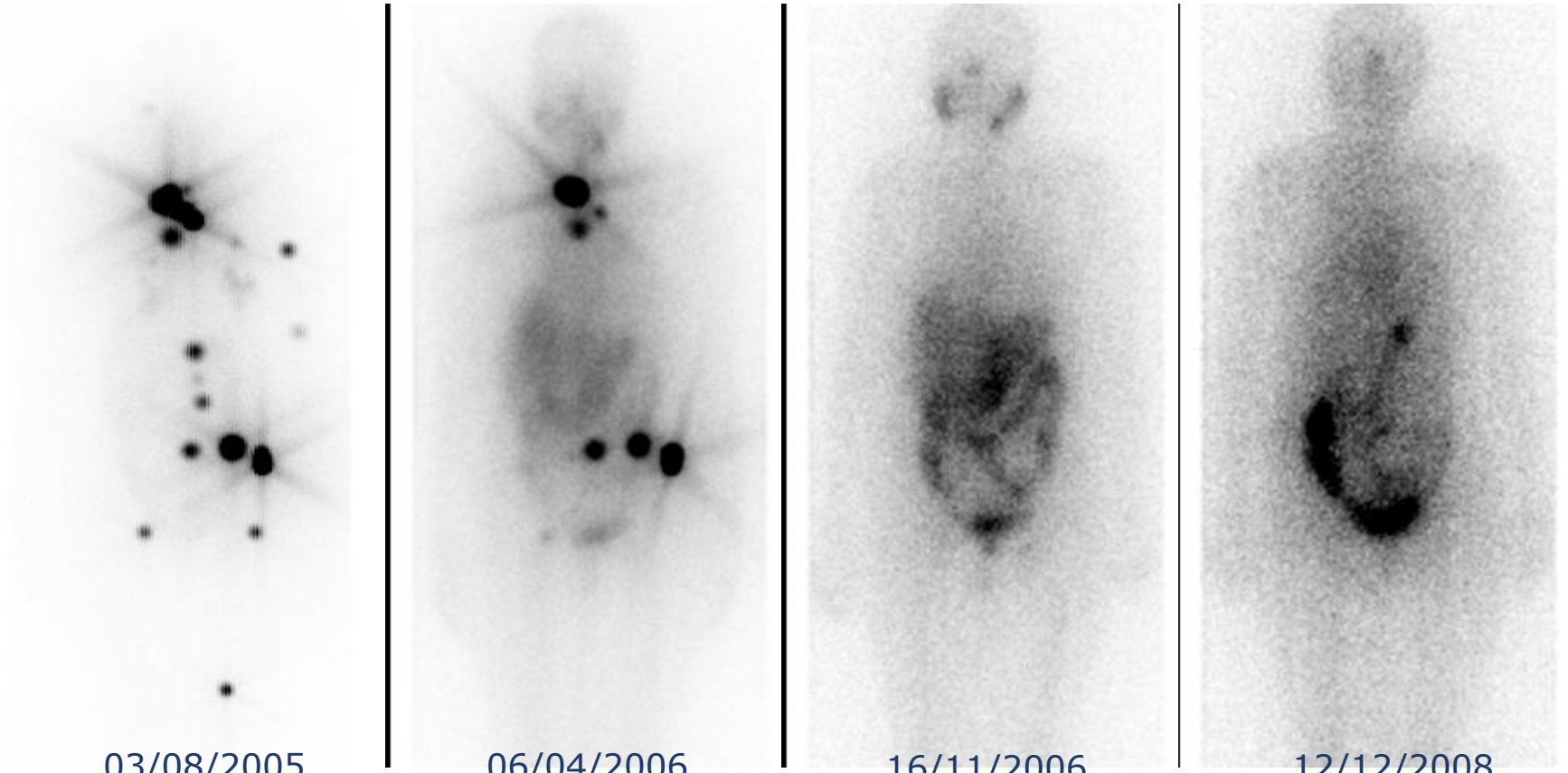
Expert Rev Med Devices . 2020 Apr;17(4):331-343.

RADIOIODINE

In differentiated thyroid carcinoma

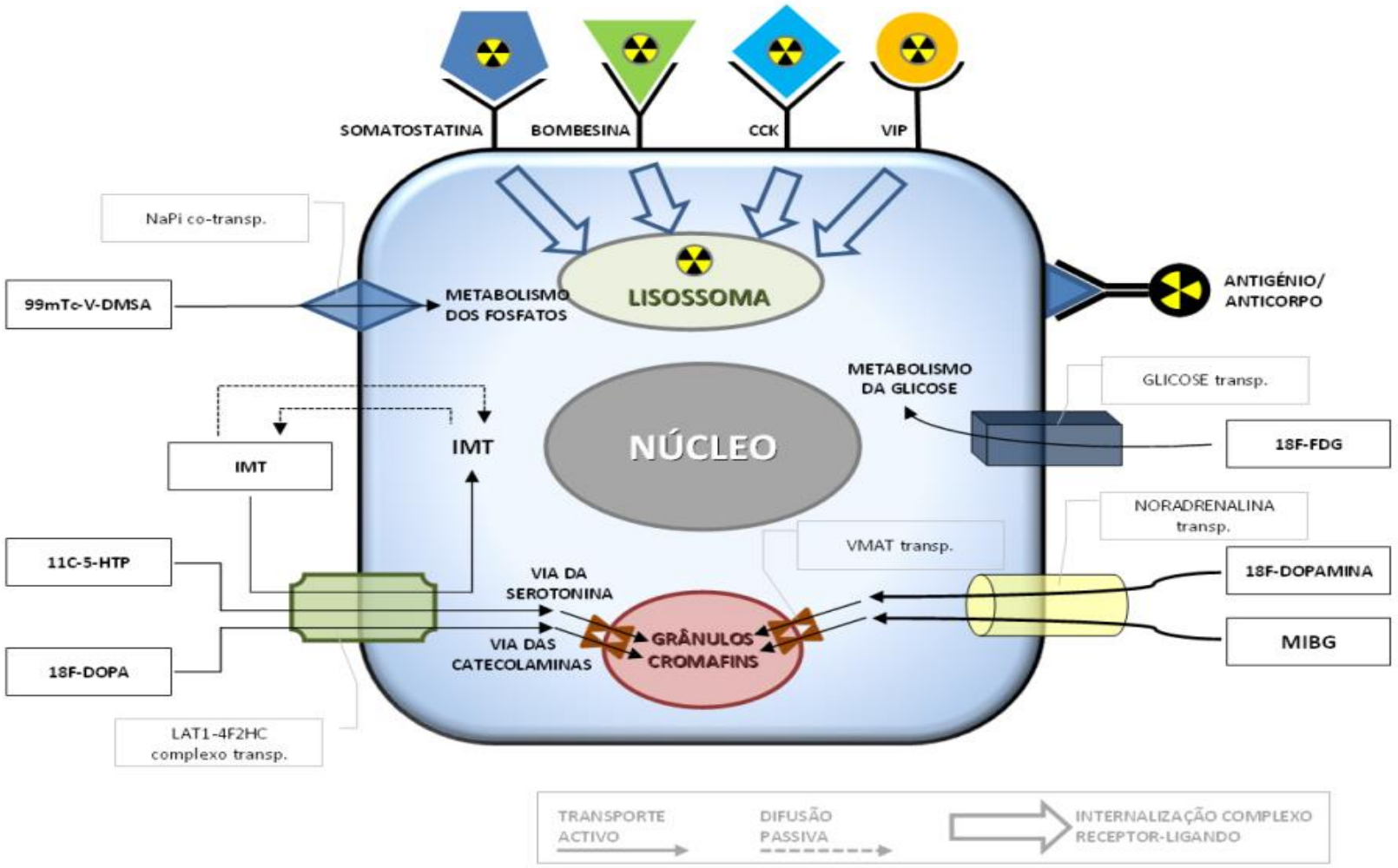
Hx

♀, 59y, FTC
Multiple bone metastasis at diagnosis



03/08/2005	06/04/2006	16/11/2006	12/12/2008
^{131}I 4440 MBq	**+ 131I 6660 MBq**	**+ 131I 7400 MBq**	**= ^{131}I Scintigraphy**
Tg = 253	**Tg = 108,3**	**Tg = 6,7**	**Tg = 3,6**

NETs: PARADIGM IN NUCLEAR MEDICINE

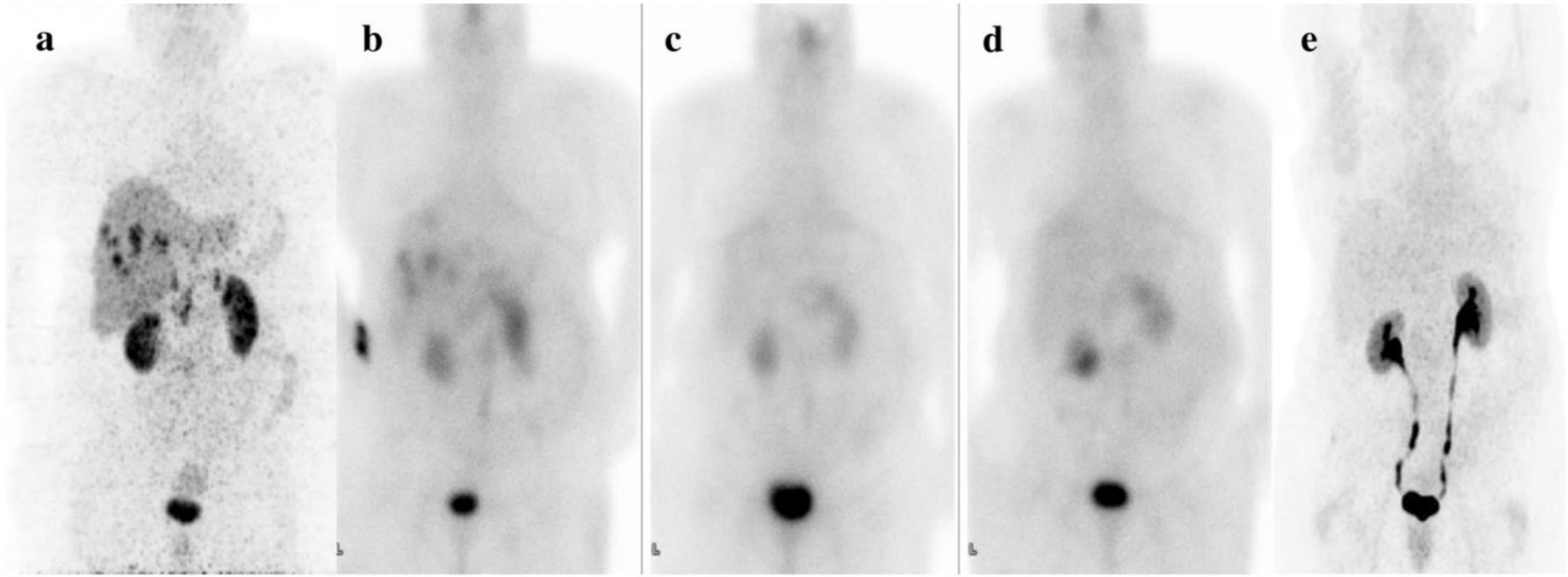


PRRT IN NETs

Clinical case – Malignant Insulinoma

Hx

Female, 55 years old, malignant insulinoma. Normalization of plasma glucose values after the first cycle of 177Lu-DOTATATE. Outstanding response to PRRT.

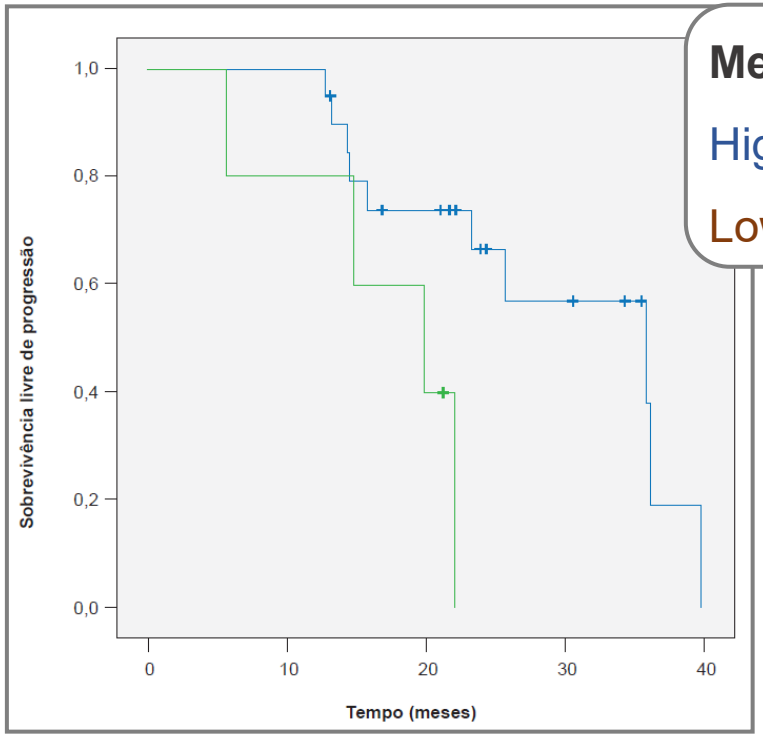


J Endocrinol Invest . 2019 Mar;42(3):249-260.

PRRT IN NETs - IPO PORTO

Initial experience (GEP-NETs)

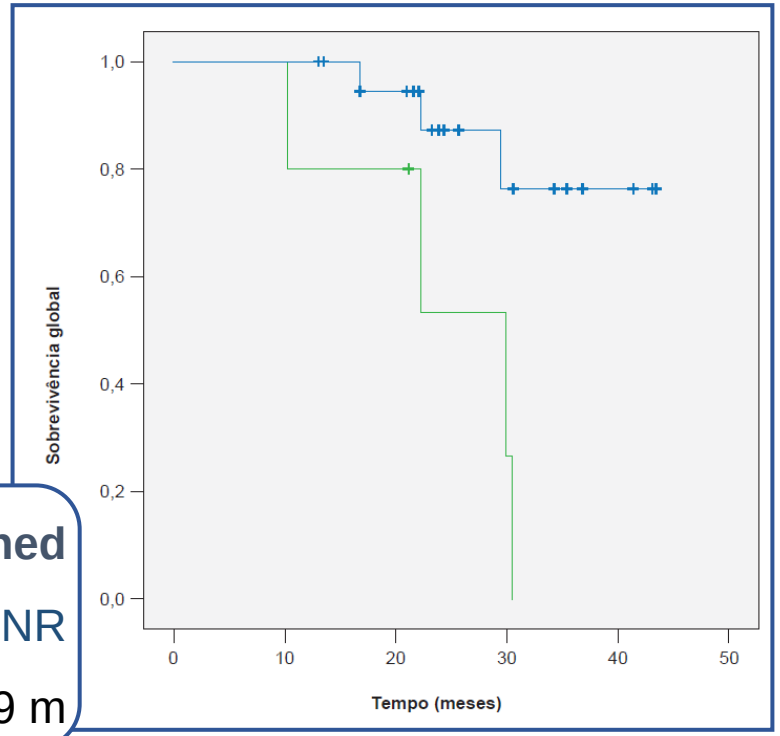
- 25 patients with GEP NETs
- 3 cycles of ^{177}Lu-DOTATATE (5.55 GBq/cycle)
- Median follow-up time 25.6 m



Median PFS 25.6 months

High SSTr expression: 35,7 m

Low/ heterogeneous SSTr: 19.6m



Median OS not reached

High SSTr expression: NR

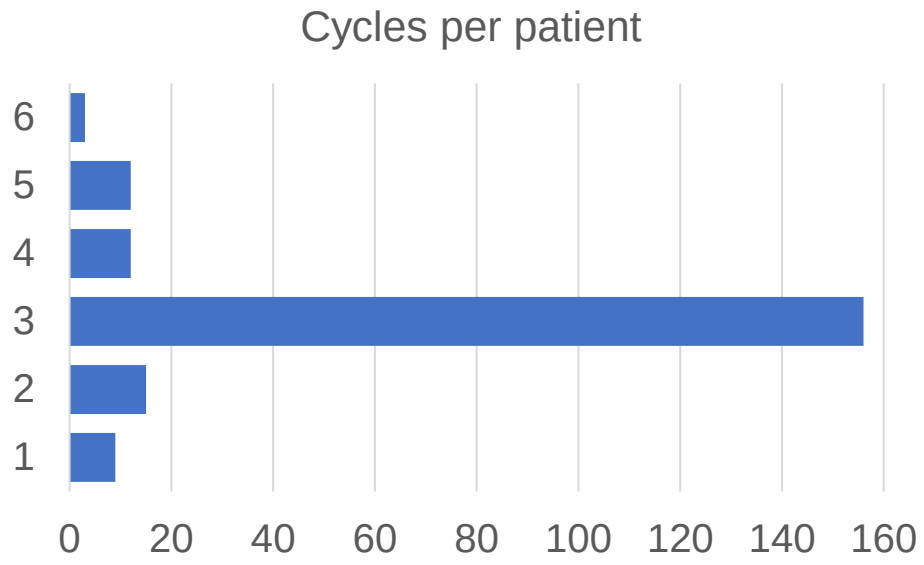
Low/ heterogeneous SSTr: 29,9 m

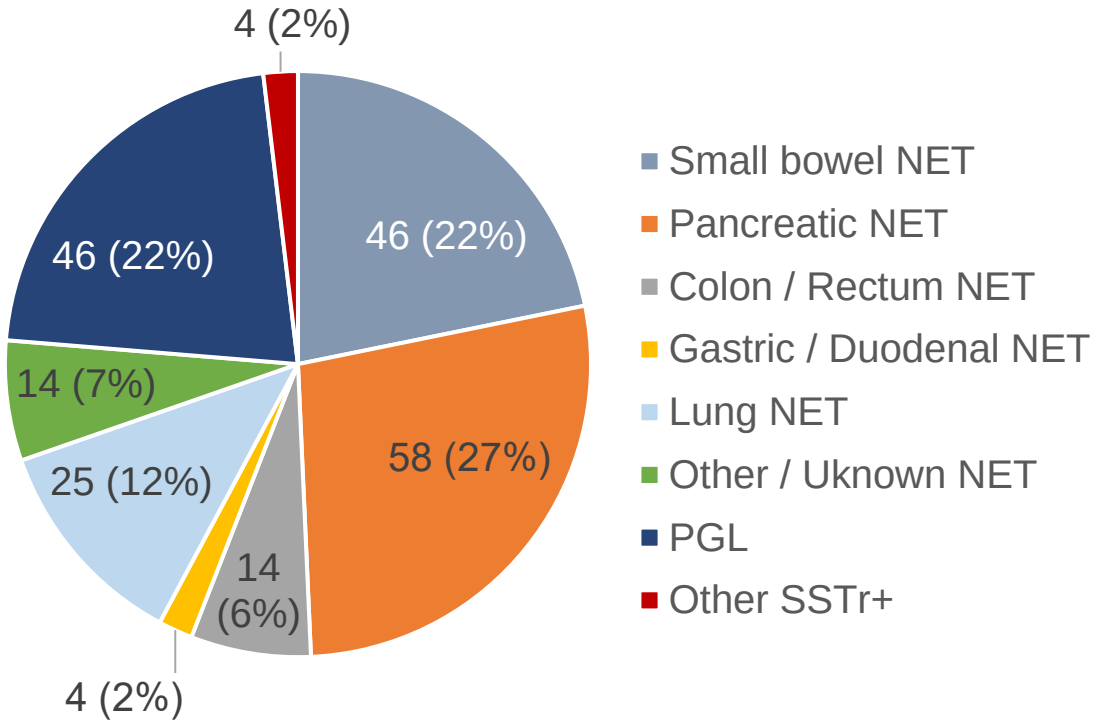
Sampaio IL et al. Acta Med Port. 2016 Nov;29(11):726-733.

PRRT - IPO PORTO AT THE END OF 2020

Ongoing Experience

- 211 patients treated
- 656 administered cycles (4.8-7.4 GBq
- 24 patients re-treated





PRRT IN NETs - IPO PORTO

Ongoing Experience

Series	MIDGUT NET			PANCREAS NET			LUNG NET		
	N	PFS	OS	N	PFS	OS	N	PFS	OS
IPO Porto	37	24 m (19-36.8)	NR	31	25.6 m (16.7 – 34.5)	NR	20	19.2 m (13.9-24.4)	50.1 m (estimated)
ERASMUS[1]	181	30 m	60 m	133	30 m	71 m	23	20 m	52 m
Bad Berka[2]	315	22 m	69 m	384	20 m	44 m	75	11 m	40 m

1 Brabander T et al. Clin Cancer Res. 2017 Aug 15;23(16):4617-4624
2 Richard P. Baum et al. Oncotarget . 2018 Feb 15;9(24):16932-16950

PRRT IN mPCC/PGL

Clinical case

54y female patient with sporadic JGT paraganglioma, recurring after surgery

Disease remains stable after ~9y
Improvement in bone pain

PRRT IN mPCC/PGL – IPO PORTO

Ongoing Experience

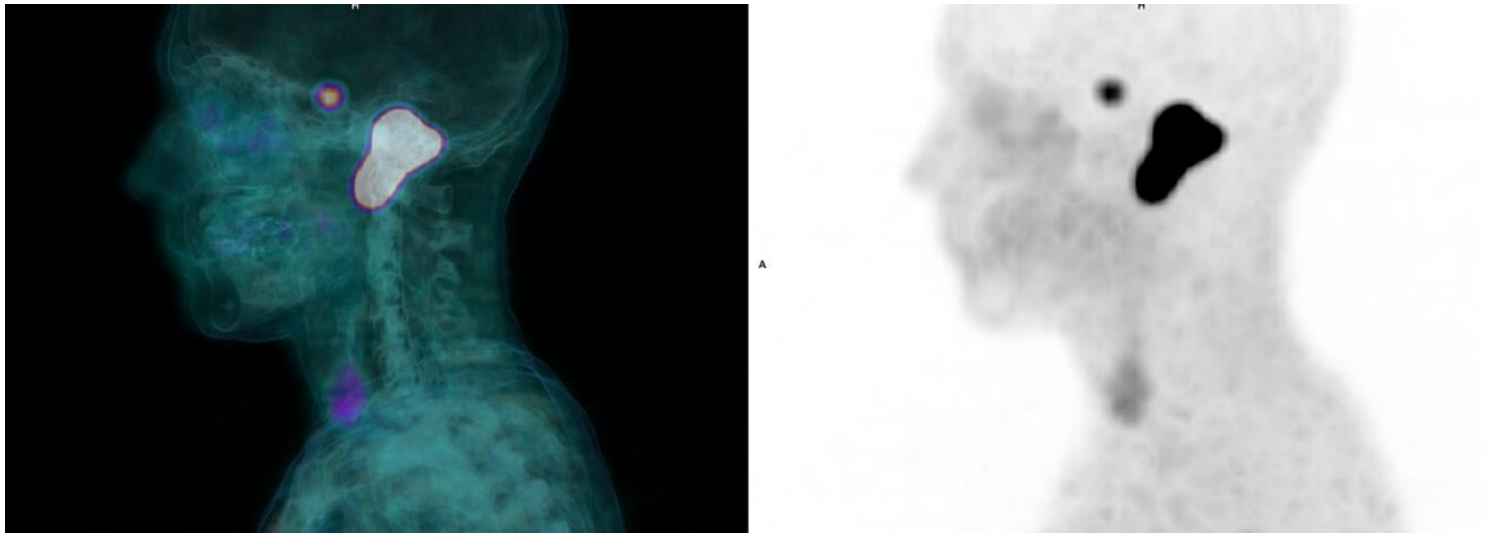
Series	Materials / Methods		Outcomes		
	N	Therapy Regimen	DCR	PFS	OS
IPO Porto	11	PRRT (^{177}Lu-DOTATATE)	60%	24.6 m	NR
ERASMUS[1]	17	PRRT (^{177}Lu-DOTATATE)	85%	13 m	23 m
Uppsala[2]	22	PRRT (^{177}Lu-DOTATATE)	100%	21.6 m	49.6 m
Peter MacCallum[3]	20	PRRT (^{177}Lu-DOTATATE) + ChT	86%	39 m	NR

1. Zandee W. et al.Eur J Endocrinol. 2019 Jul;181(1):45-53.
2. Vyakaranam AR et al. Cancers (Basel). 2019 Jun 28;11(7):909.
3. Kong G. et al. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3278-3287.

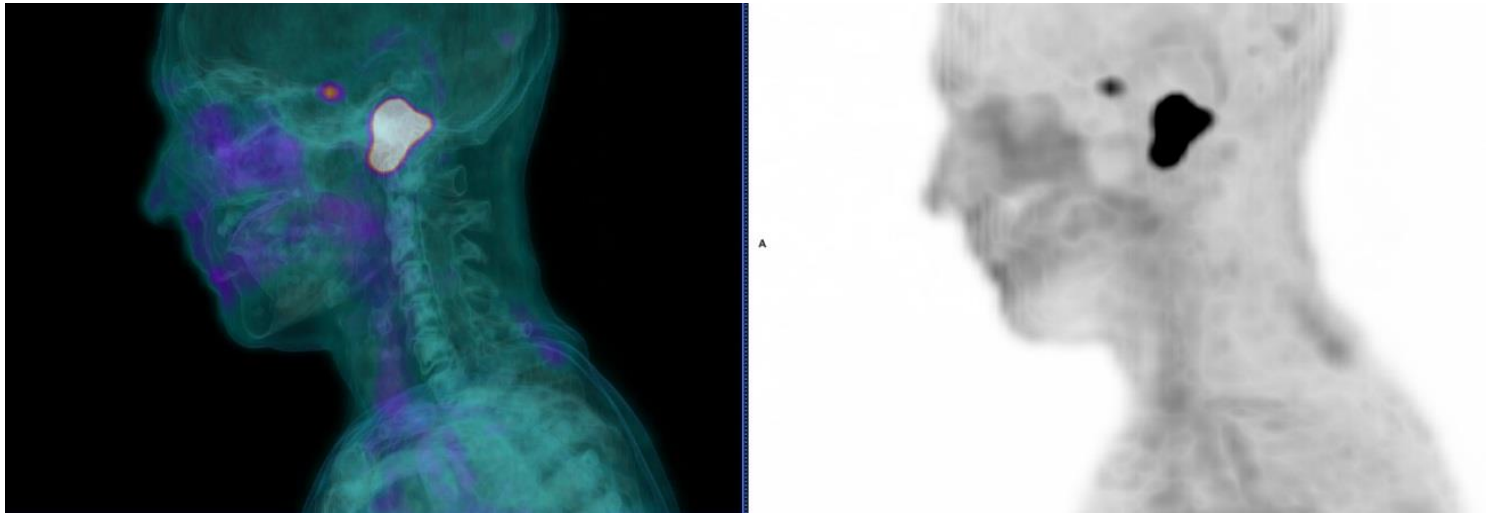
PRRT IN HNPGLs – IPO PORTO

Clinical Case

PRE PRRT



POST PRRT (5y)



PRRT IN HNPGLs – IPO PORTO

Ongoing Experience

Results of peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in patients with head and neck paragangliomas

Ferreira G, Sampaio IL, Violante L, Pinto A, Estevão R, Duarte H

- 33 patients with inoperable HNPGL consecutively treated with PRRNT (2011-2016).
- Followed for 11.2 - 69.3 m (median 34.6, IQR 37.4).
- Molecular response in 15 (45.5%) patients
- The majority (87.9%) of patients remained stable according to RECIST 1.1
- Baseline SUVpeak optimal threshold of 30.55 was found to predict molecular response fairly (AUC 0.759, p=0.011) and clinical response well (AUC 0.826, p=0.008)
- No grade 3/4 haematological or renal toxicity

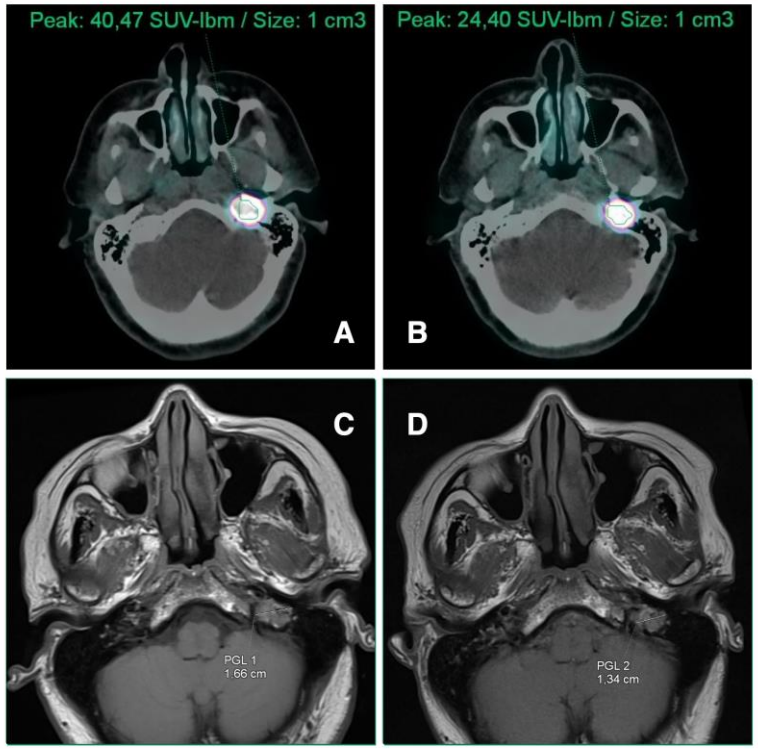
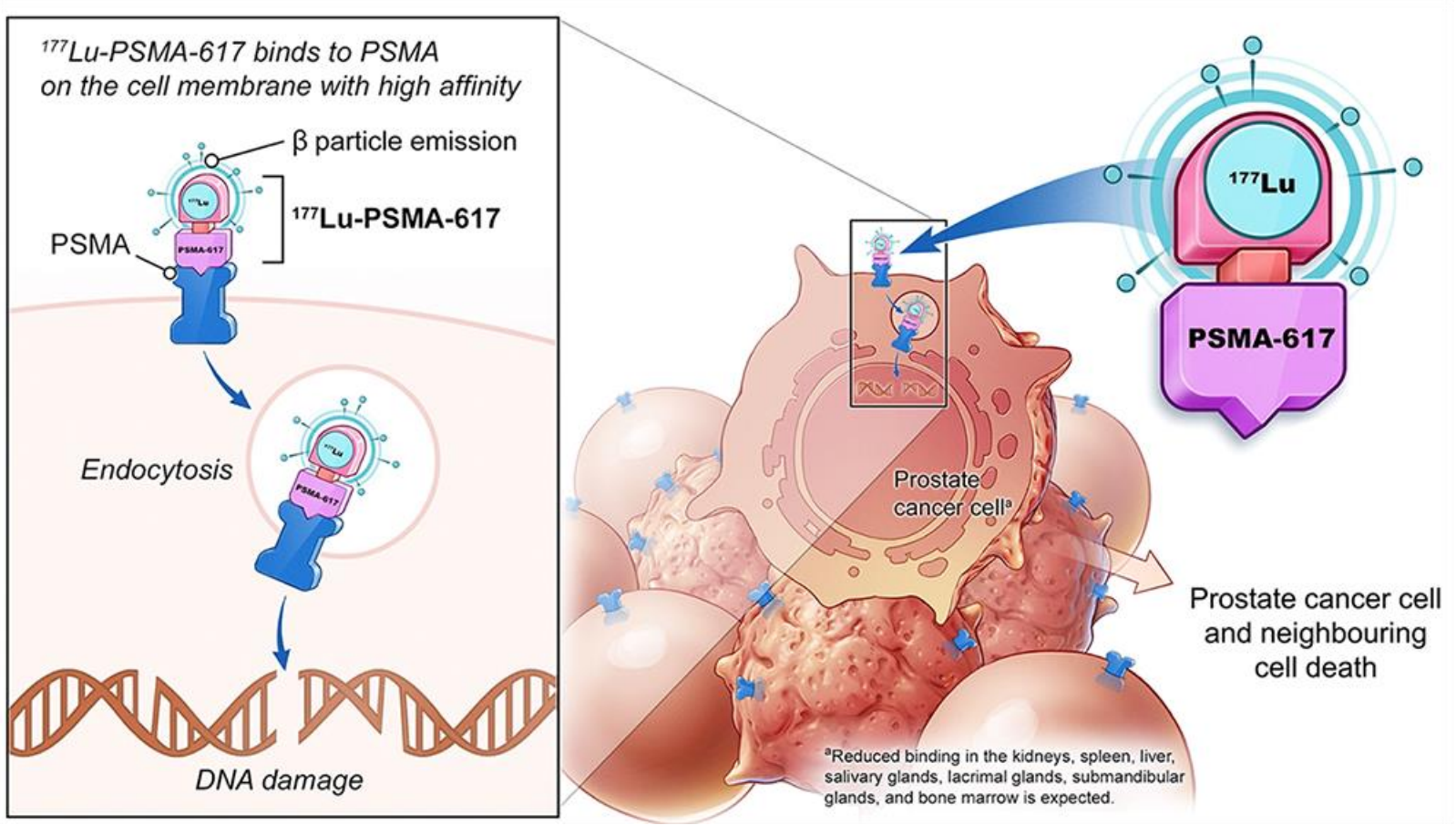


Figure 1: A patient showing partial molecular response on ^{68}Ga-DOTANOC PET/CT (ΔSUV_{peak}= -39.7%) and minimal response according to MRI (Δsize= -19.3%). This patient reported improvement of tinnitus after PRRNT. A, B: PET/CT before and after PRRNT, respectively; C, D: MRI (T1w) before and after PRRNT, respectively.

PSMA IMAGING AND THERAPY

RLT with ^{177}Lu-PSMA in mCR Prostate Cancer



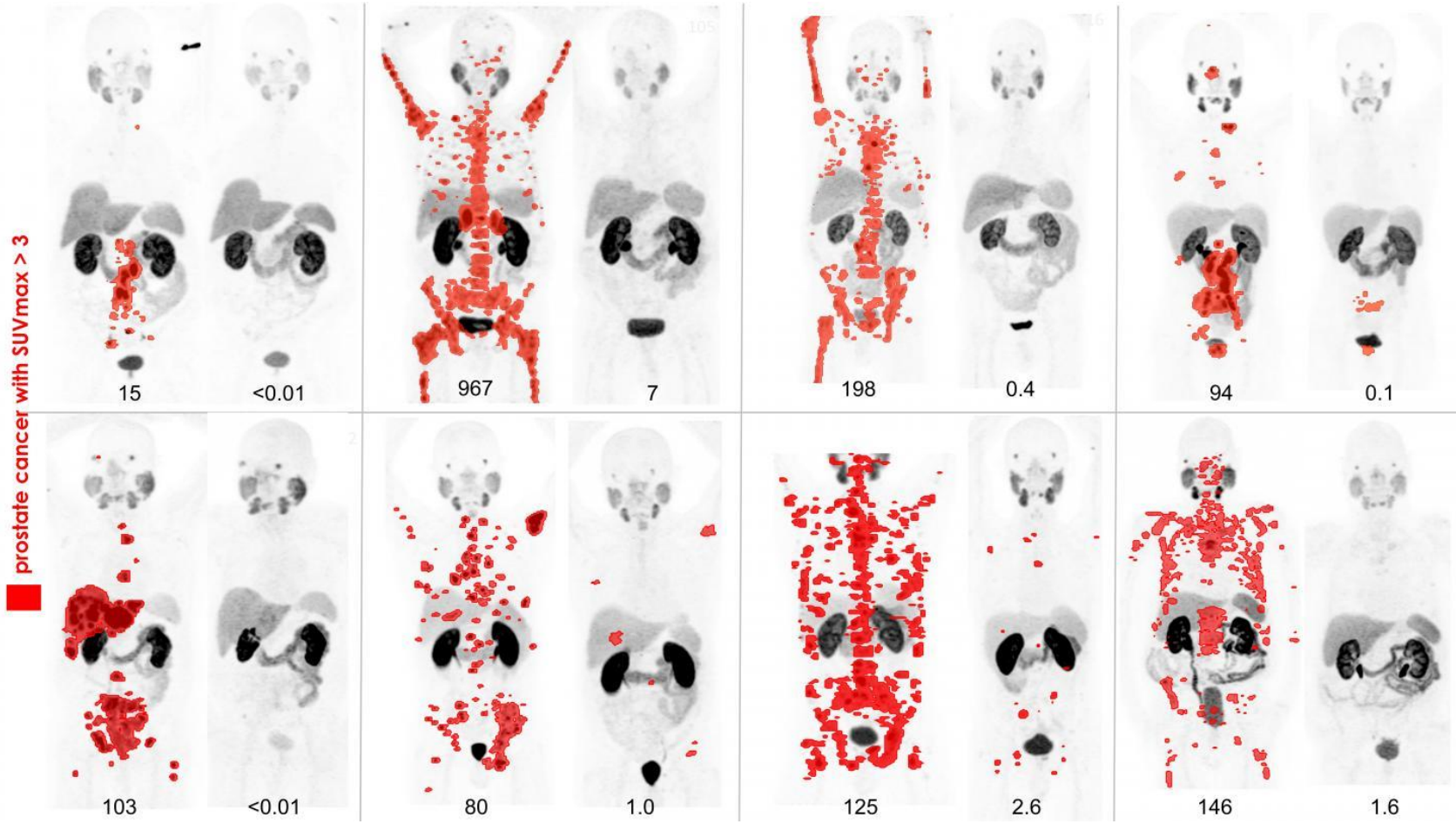
Accessed on 01/11/2023, at https://www.urotoday.com/conference-highlights/asco-2021/asco-2021-prostate-cancer/130016-asco-2021-vision.html

PSMA IMAGING AND THERAPY

RLT with ^{177}Lu-PSMA in mCR Prostate Cancer

SNMMI 2018 IMAGE OF THE YEAR

PET imaging before and after ^{177}Lu-PSMA617 therapy for metastatic CR prostate cancer.



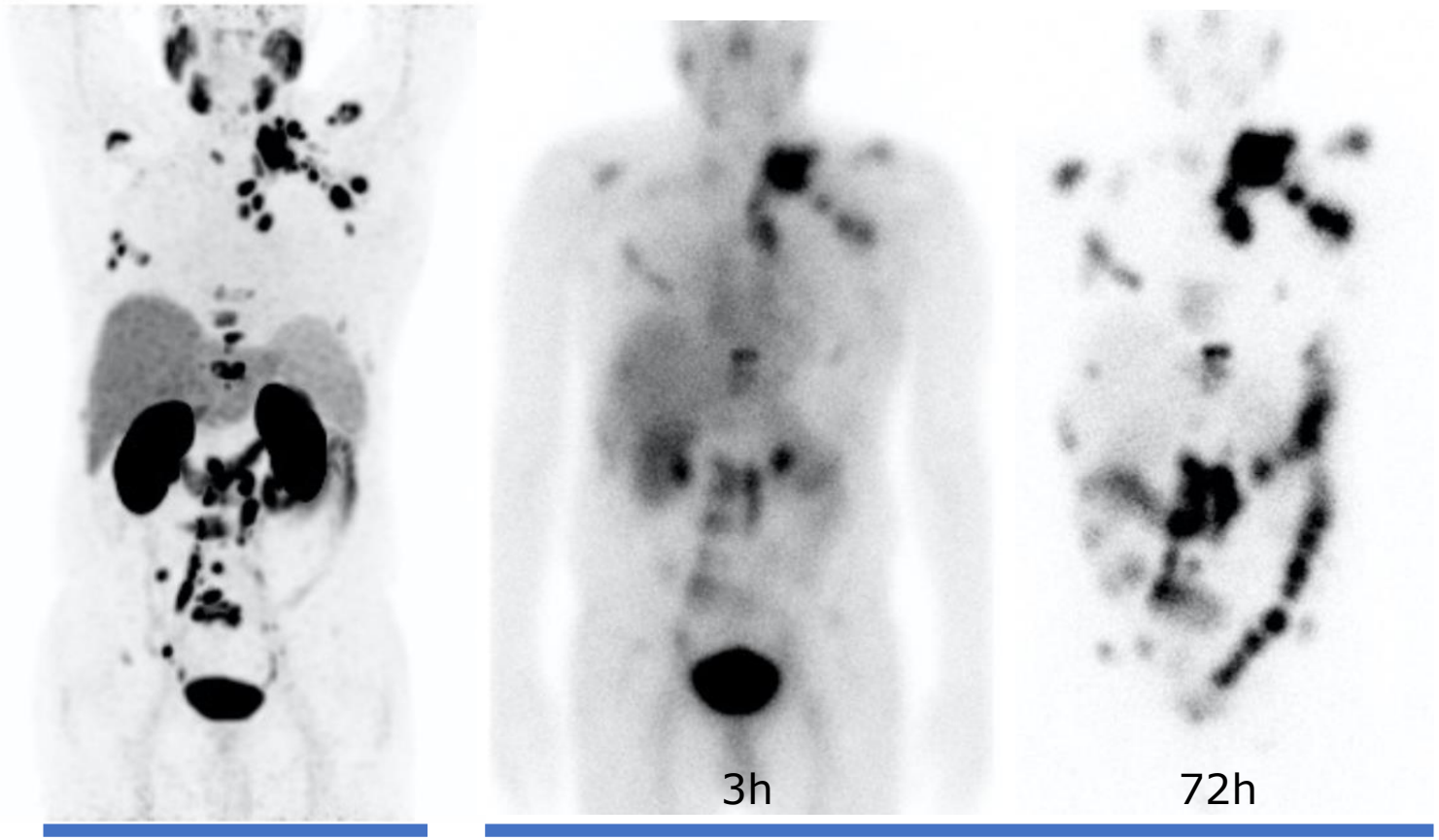
Journal of Nuclear Medicine August 2018, 59 (8) 9N-10N

PSMA IMAGING AND THERAPY

First patient treated with ^{177}Lu-PSMA at IPO PORTO

Hx

- Male, 77 years
- mCRPC progressing after: LHRHa, bicalutamide, abiraterone, docetaxel (with rechallange) and cabazitaxel.
- PSMA PET shows intense uptake in known metastatic lesions



PET/CT
(08/09/23)

Post-therapy scintigraphy
(27/11/23)

LIMITATIONS OF THE THERANOSTIC MODEL

- Imperfect patient selection due to limitations in the sensitivity and specificity of diagnostic tools
- Controversial criteria for assessing response in morphological and molecular imaging procedures
- Difficulty in delivering radiation exclusively to target lesions, avoiding adjacent tissues
- Challenges related to technology availability, financial sustainability, and regulatory approval

Expert Rev Med Devices . 2020 Apr;17(4):331-343.

NEW AGENTS / THERANOSTIC PAIRS

Radionuclides

Alfa emitters

- ^{213}Bi, ^{225}Ac, ^{212}Pb (NCT03466216)

Perfect pairs

- $^{64}Cu/^{67}Cu$ (NCT04438304)

Molecules

SSTr antagonists

- ^{177}Lu-DOTA-JR11 (NCT02592707)

PSMA

- PSMA-I&T (NCT04647526)
- PSMA-J591 (NCT04886986)

Molecular Targets

FAPI

- NCT05432193

Integrin $\alpha v\beta_6$

CA-IX

- NCT05563272

Therapeutic Target

PD-L1 PET

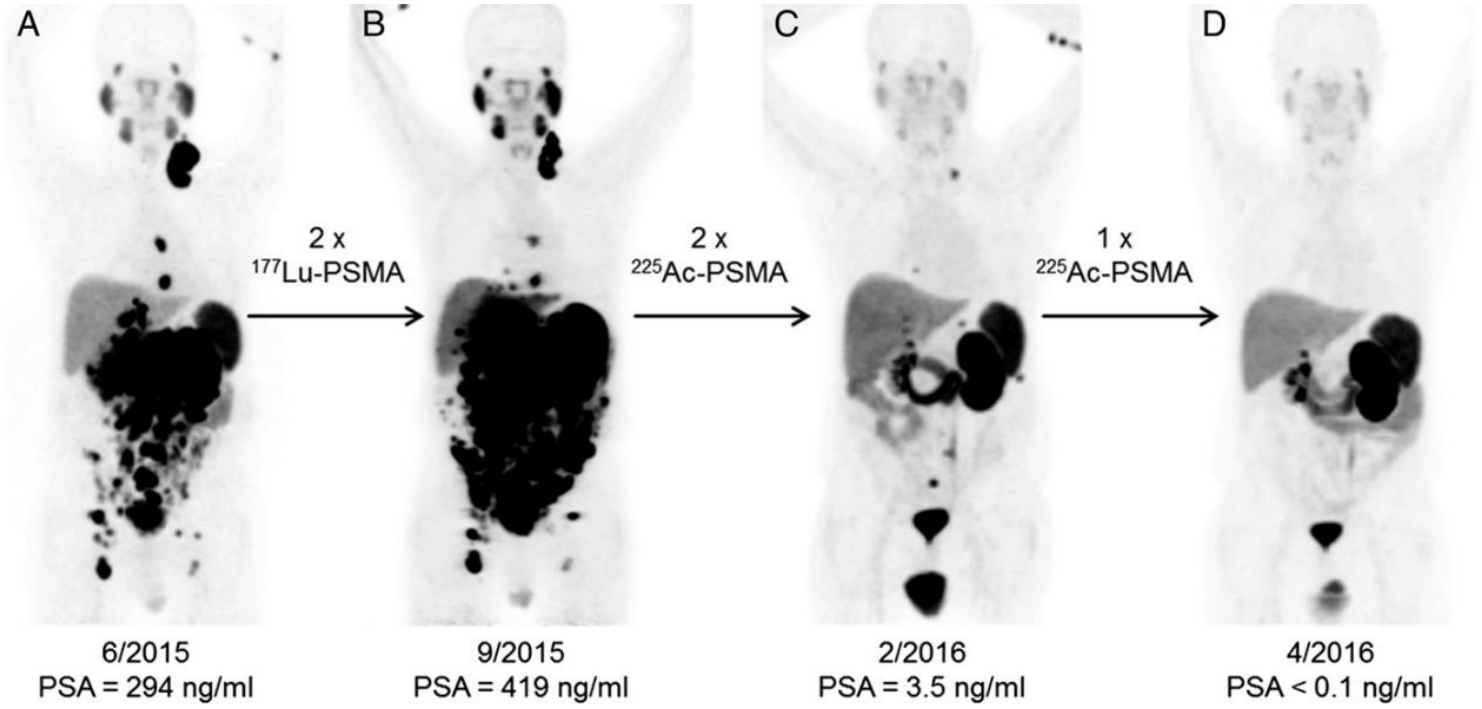
- NCT05533086

^{68}Ga-NOTA-Anti-HER2 PET

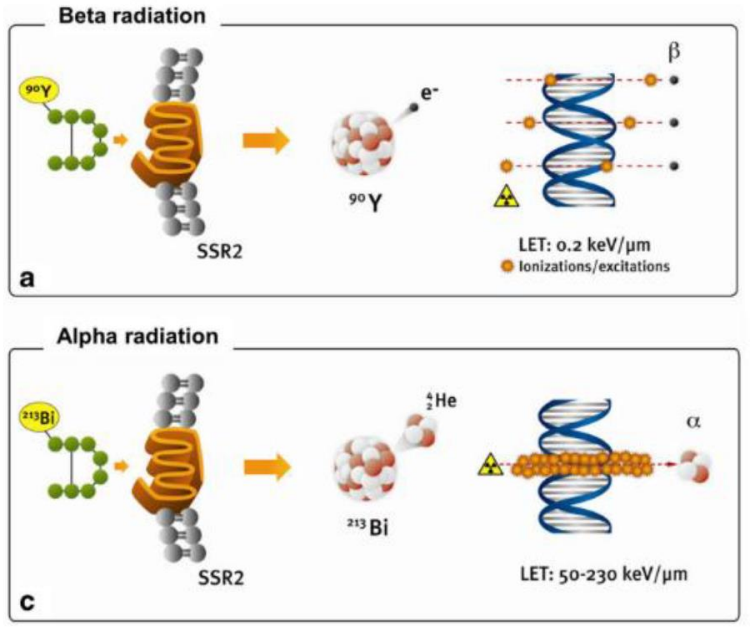
- NCT03924466

NEW AGENTS

^{225}Ac-PSMA in mCRPC after therapeutic failure with ^{177}Lu-PSMA



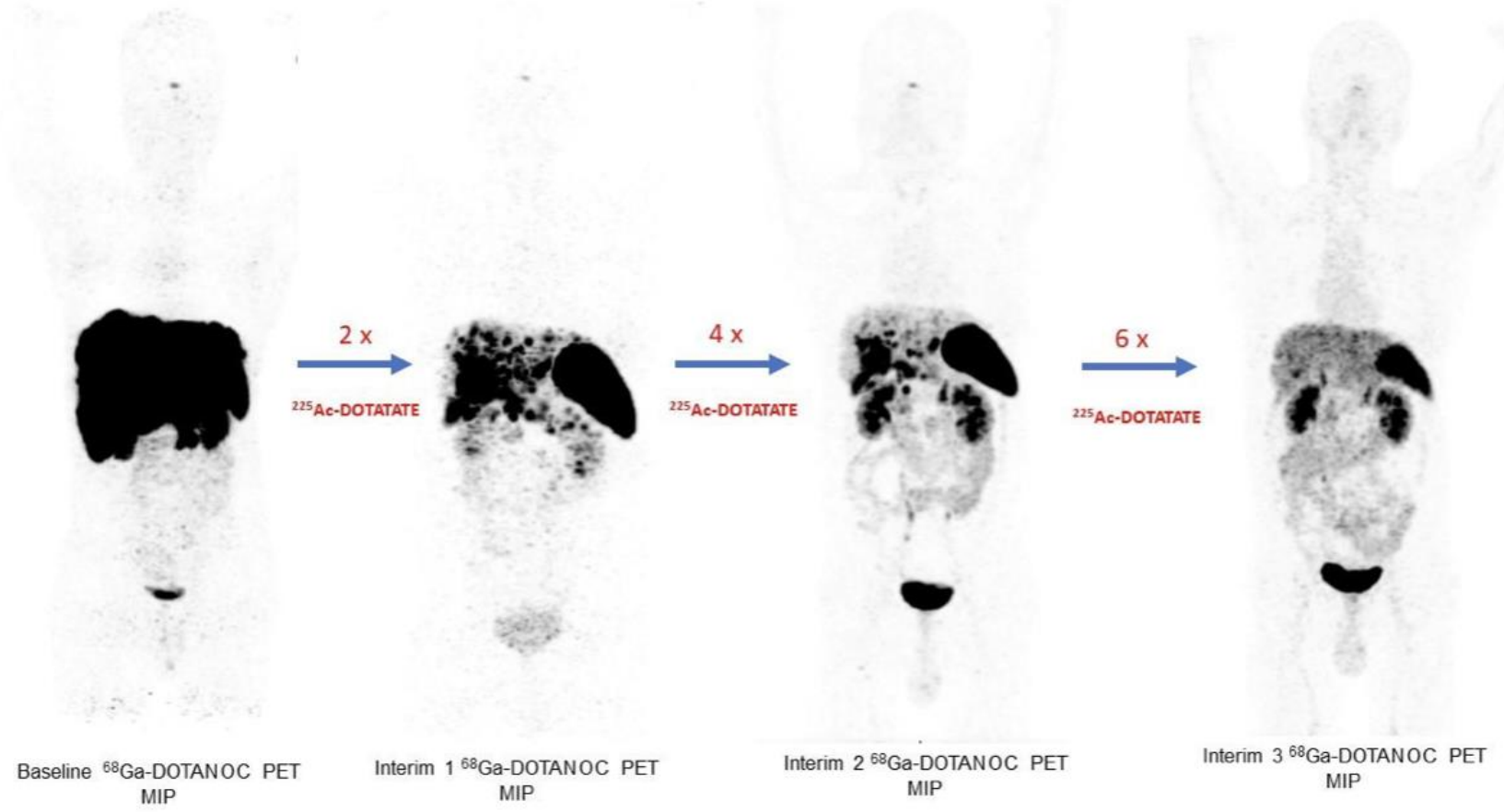
J Nucl Med . 2016 Dec;57(12):1941-1944.



Eur J Nucl Med Mol Imaging . 2014 Nov;41(11):2106-19

NEW AGENTS

^{225}Ac-DOTATATE in NETs



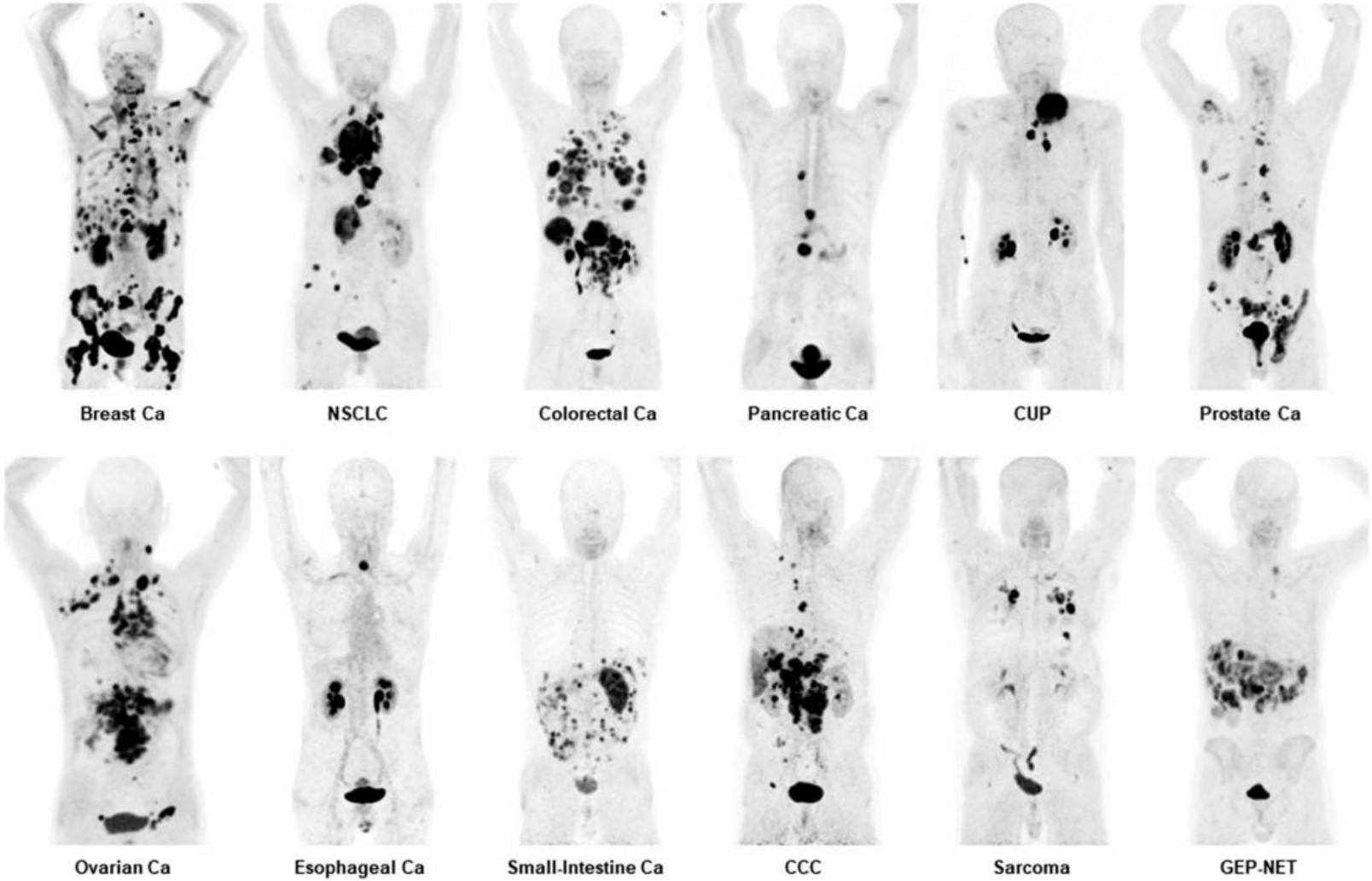
Ballal S et al. J Nucl Med . 2022 Jul 21:jnumed.122.264043.

NEW AGENTS

Fibroblast Activation Protein Inhibitor

SNMMI 2019 IMAGE OF THE YEAR

^{68}Ga-FAPI PET/CT in patients reflecting 12 different tumor entities



Journal of Nuclear Medicine August 2019, 60 (8) 8N-9N

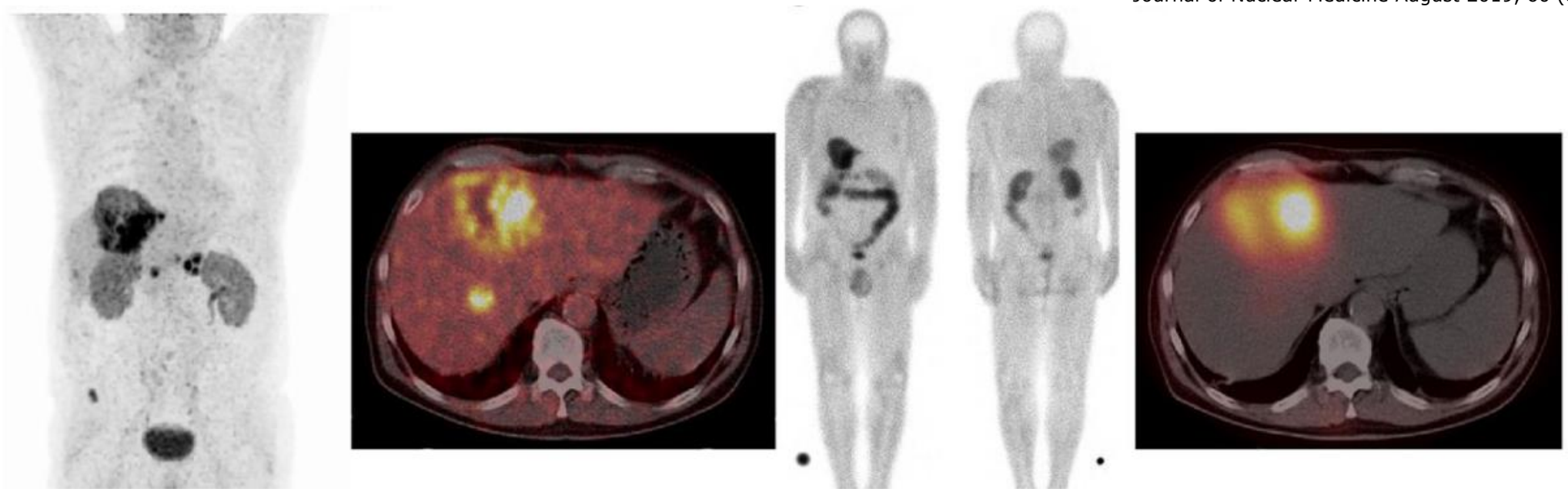
NEW AGENTS

Fibroblast Activation Protein Inhibitor

JNM 2022 ARTICLE OF THE YEAR

Feasibility, Biodistribution, and Preliminary Dosimetry in Peptide-Targeted Radionuclide Therapy of Diverse Adenocarcinomas Using ^{177}Lu-FAP-2286: First-in-Humans Results

Journal of Nuclear Medicine August 2019, 60 (8) 8N-9N



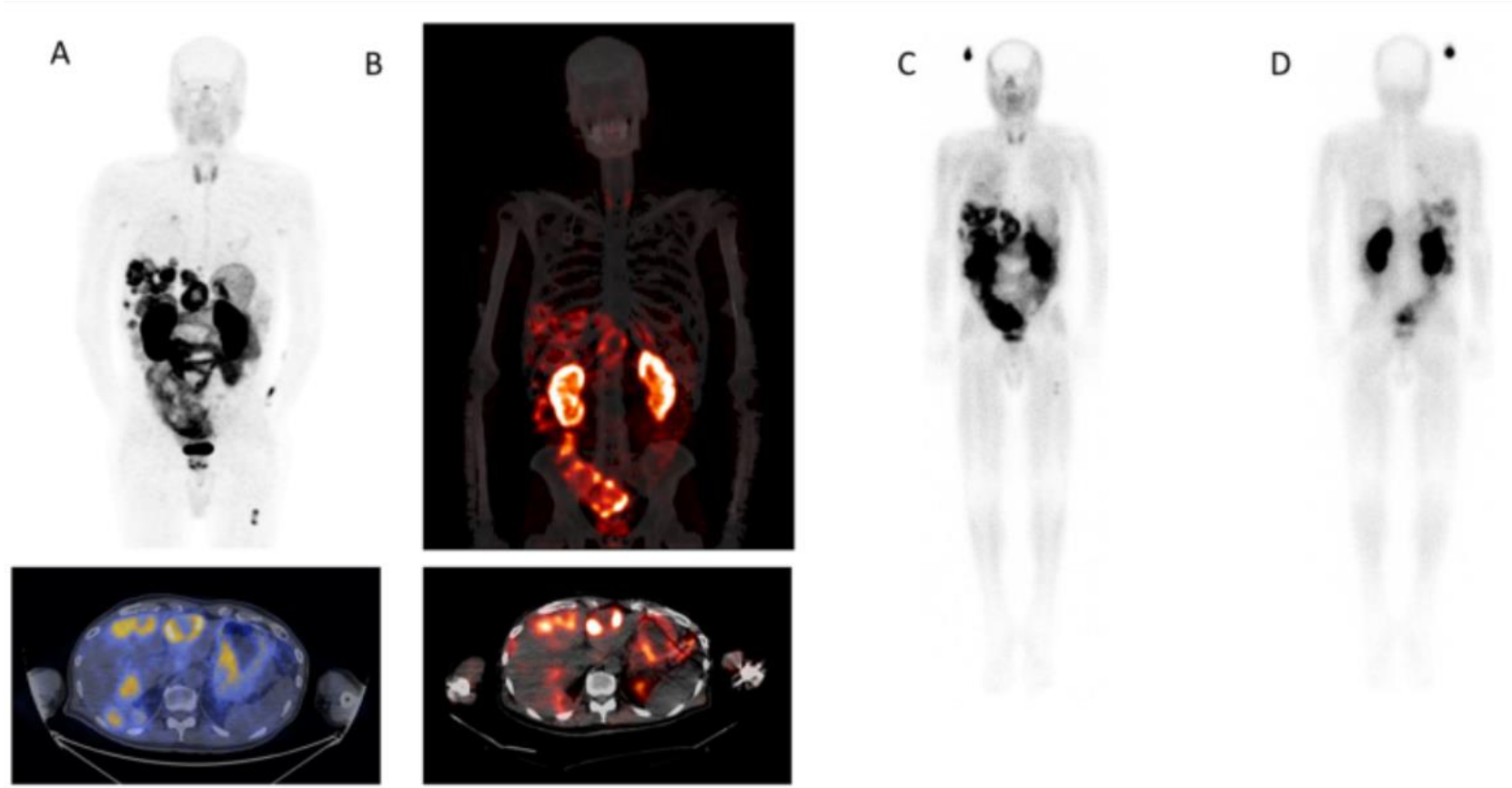
High uptake and **prolonged retention** of ^{177}Lu-FAPI-2286 in tumor lesions of various adenocarcinoma types. Prospective studies are needed.

NEW AGENTS

Integrin αvβ6-Targeting Radiotheranostic Peptides

SNMMI 2023 IMAGE OF THE YEAR

First-in-human evaluation of the theranostic pair ^{68}Ga-DOTA-5G / ^{177}Lu-DOTA-ABM-5G



Selected as the 'Image of the Year' by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) during its 2023 Annual Meeting.

CONCLUSION

THERANOSTICS - PRESENT

Theranostics already plays a crucial role in the field of Oncology

- Due to advances in molecular imaging and technological breakthroughs in therapeutic radioisotopes
- Transition to evidence-based medicine and industry support are driving the field of Nuclear Medicine and Theranostics.

Theranostic approaches have already demonstrated effectiveness, being approved and recommended in specific cancers.

THERANOSTICS - FUTURE

Recognition of imperfections in the theranostic model

- Challenges include diagnostic sensitivity and undesired affinity for healthy tissues (dosimetry potential)

Ongoing research is underway.

- Expanding the potential of the theranostic approach and revolutionizing cancer treatment

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