Radionuclide Production:
The Clinical Perspective

PRISMAP School on radionuclide production - Leuven
27-31 MAY 2024

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Disclosures

C. Deroose is / has been a consultant for: Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo

Travel fees: GE Healthcare, Sirtex

Nuclear Medicine & Radioactivity

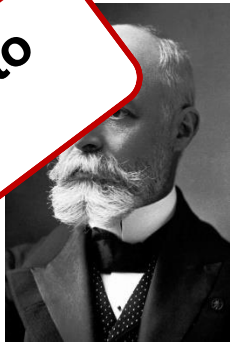
Nuclear medicine: branch of medicine using radioactive drugs for

- Diagnostic use
- Therapeutic use

Radioactivity:

- Discovered by Henri Bequerel in 1896 – 125
- Marie Sklodowska-Curie discovered po 8
- George De Hevesy: Nobel prize Che 3 for development of radioactive trace emical process, e.g. animal metaboli ars ago
- Saul Hertz:
  - First Graves patie with radioiodine in 1941 > 80 years ago
  - Followed s ent of thyroid carcinoma patients

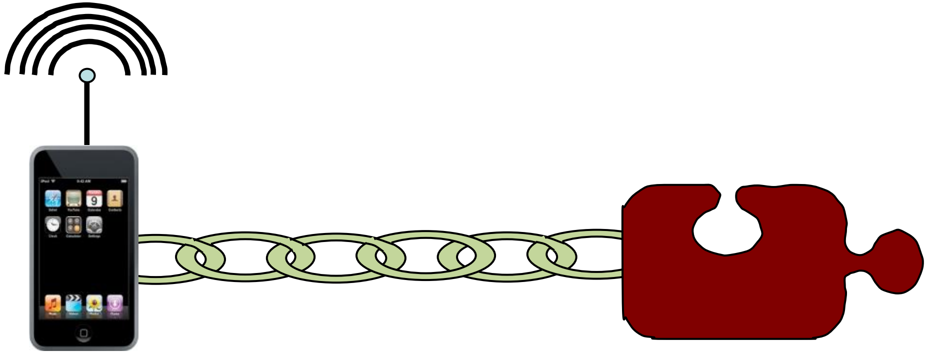
Don't we have all the radionuclides we want to use at our disposal by now?



Hertz S, Roberts A., J Am Med A 946 May 11;131:81-6. PMID: 21025609
Seidlin SM et al., J Am Med Assoc. 1946 Dec 7;132(14):838-47. PMID: 20274882

Diagnostic Radiopharmaceutical

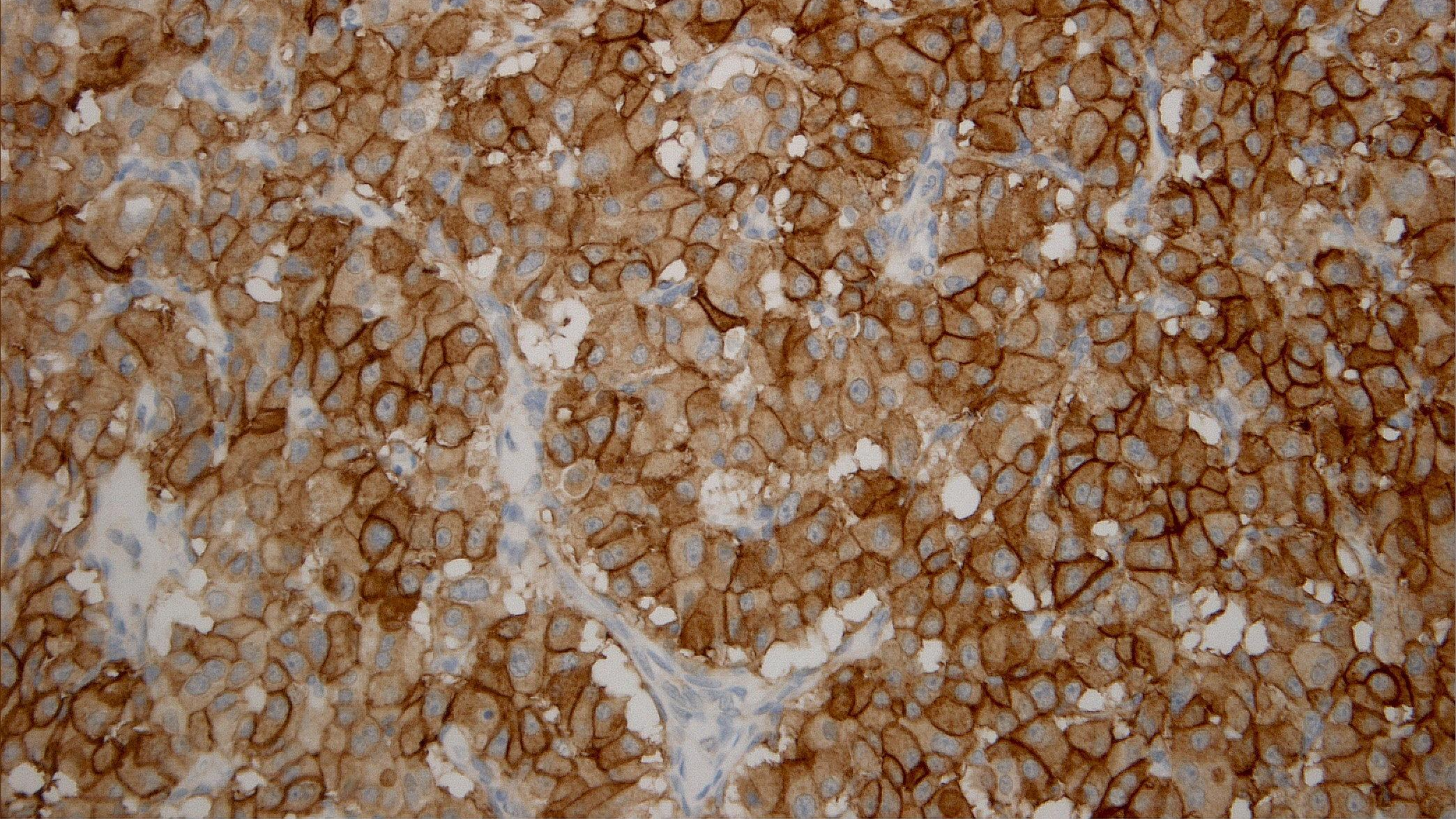
For molecular imaging



Radionuclide	Linker	Vector molecule
Upon decay emits externally **detectable** radiation upon decay	Attaches radionuclide to the vector	Is responsible for a specific molecular interaction with the target (receptor, transporter, enzyme,…)

Advantages of Molecular Imaging

- Very high sensitivity for molecular target
- Unique disease characterization: detecting pathogenic molecules
- Detect cancer cells without morphological alterations
- Discrimination between benign and malignant tissue
- Whole body imaging → staging, restaging
- Can be repeated as often needed/relevant
- Early and accurate detection of therapy response @ molecular level
- Prognostic & Predictive marker

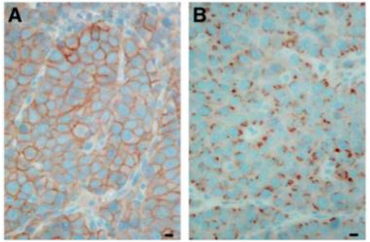


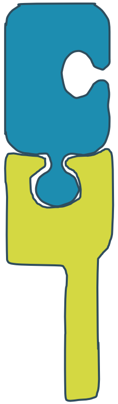
Somatostatin Receptor (SSTR)

- Seven transmembrane G-coupled receptor
- Five human subtypes:

  SSTR1, SSTR 2 (2A & 2B),

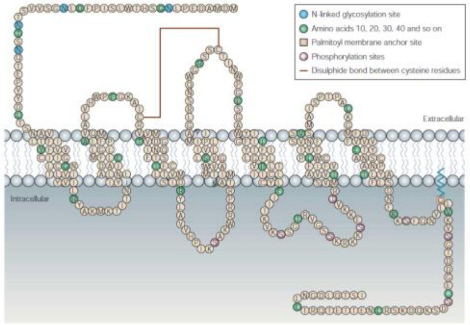
  SSTR3, SSTR4, SSTR5
- Function
  - ↓ Secretions
    - Endocrine
    - Exocrine
  - ↓ Cell growth
  - ↑ Apoptosis
- Internalise upon agonist binding / recycle

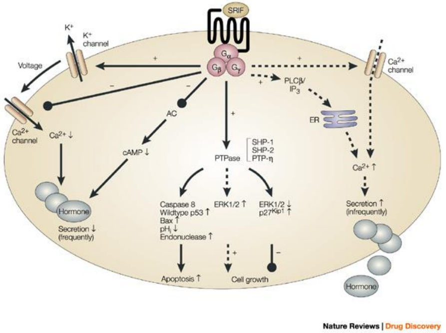




Vector

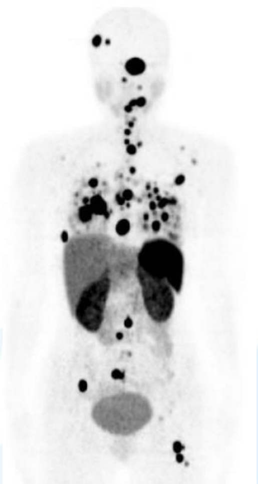
Receptor

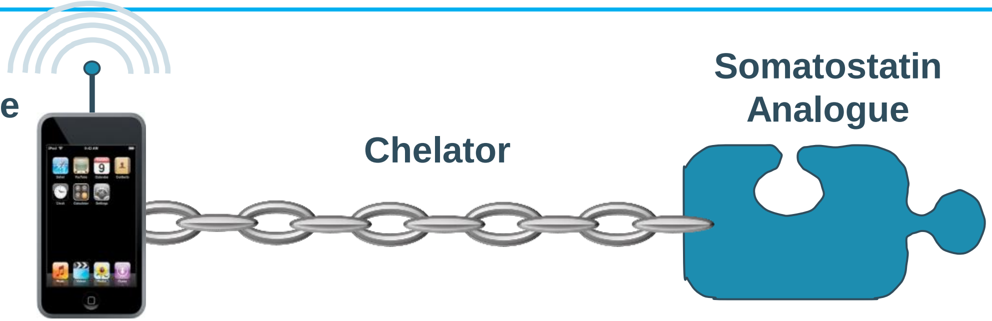




Weckbecker et al. Nat Rev Drug Discov. 2003;2(12):999-107. PMID: 14654798
Waser et al. J Nucl Med. 2009;50(6):936-41. PMID: 19443580.

Diagnostic SSTR radiopharmaceuticals





Radionuclide	Chelator	Somatostatin Analogue
Indium-111 (^{111}In)	DTPA	Octreotide (OC)
Technetium-99m (^{99m}Tc)	DOTA	Tyr^{3}-octreotide (TOC)
Gallium-68 (^{68}Ga)	NOTA	Tyr^{3}-octreotate (TATE)
Fluorine-18 (^{18}F)	HYNIC	Naph-octreotide (NOC)
Copper-64 (^{64}Cu)		

Diagnostic Combinations

- ^{111}In-DTPA-octreotide (pentetreotide) (**Octreoscan®**) — **Scintigraphy / SPECT**
- ^{68}Ga-DOTA,Tyr^{3}-octreotide (^{68}Ga-DOTA**TOC**)
- ^{68}Ga-DOTA,Tyr^{3}-octreotate (^{68}Ga-DOTA**TATE**)
- ^{68}Ga-DOTA, [Phe^{1}-1-Nal^{3}]-octreotide (^{68}Ga-DOTA**NOC**)
- ^{64}Cu-DOTA, Tyr^{3}-octreotate (^{64}Cu-DOTAT**ATE**)
- Al^{18}F-NOTA-Octreotide (Al^{18}F-**OC**)

} **PET**

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Benefit of ^{68}Ga PET over ^{111}In SRS

Author	Year	n	^{68}Ga-Peptide	Level (Patient /lesion)	Sensitivity ^{111}In-pentetreotide	Sensitivity ^{68}Ga-peptide	Δ Sens
Gabriel	2007	84	-TOC	Patient	52.0%	97.0%	45.0%
Buchmann	2007	27	-TOC	Region	66.0%	100.0%	34.0%
Srirajaskanthan	2010	51	-TATE	Lesion	11.9%	74.3%	**62.4%**
Van Binnebeek	2016	53	-TOC	Lesion	60.0%	99.9%	39.9%
Deppen	2016	78	-TATE	Patient	72.0%	96.0%	**24.0%**
Sadowski	2016	131	-TATE	Lesion	30.9%	95.1%	64.2%
Morgat*	2016	19	-TOC	Lesion	20.0%	76.0%	56.0%
TOTAL		**443**		**Range**	**12-72%**	**74-100%**	**24-64%**

Gabriel, 2007, J Nucl Med; 48(4):508-18; **Buchmann**, 2007, Eur J Nucl Med Mol Imaging;34(10):1617-26; **Srirajaskanthan**, 2010, J Nucl Med; 51:875-82; **Van Binnebeek**...Deroose, 2016 Eur Radiol; 26(3):900-9; **Deppen**, 2016, J Nucl Med; 57: 708-14; **Sadowski**, 2016, J Clin Oncol; 34(6): 588-96; **Morgat**, 2016, Eur J Nucl Med Mol Imaging; 43:1258-66

Pauwels et al., Deroose, 2018, Am J Nucl Med Mol Imaging; 2018;8(5):311-331

Benefit of ^{68}Ga PET over ^{111}In SRS

Author	Year	n	^{68}Ga-Peptide	Level (Patient /lesion)	Sensitivity ^{111}In-pentet[illegible]	[illegible]nsitivity [illegible]Ga-peptide	Δ Sens
Gabriel	2007	84	-TOC	Patient	[illegible]	97.0%	45.0%
Buchmann	2007	27	-TOC	Region	[illegible]	100.0%	34.0%
Srirajaskanthan	2010	51	-TATE	L[illegible]	[illegible]11.9%	74.3%	**62.4%**
Van Binnebeek	2016	53	-TOC	[illegible]	60.0%	99.9%	39.9%
Deppen	2016	78	[illegible]	[illegible]ent	72.0%	96.0%	**24.0%**
Sadowski	2016	13[illegible]	[illegible]	Lesion	30.9%	95.1%	64.2%
Morgat*	2016	[illegible]	[illegible]OC	Lesion	20.0%	76.0%	56.0%
TOTAL				**Range**	**12-72%**	**74-100%**	**24-64%**

^{68}Ga-SSA PET detects ~double amount of lesions as ^{111}In-pentetreotide scintigraphy

Gabriel, 2007, J Nucl Med; 48[illegible]mann, 2007, Eur J Nucl Med Mol Imaging;34(10):1617-26; **Srirajaskanthan**, 2010, J Nucl Med; 51:875-82; **Van Binnebeek**...Deroose, 2016 Eur [illegible]):900-9; **Deppen**, 2016, J Nucl Med; 57: 708-14; **Sadowski**, 2016, J Clin Oncol; 34(6): 588-96; **Morgat**, 2016, Eur J Nucl Med Mol Imaging; 43:1258-6[illegible]

Pauwels et al., Deroose, 2018, Am J Nucl Med Mol Imaging; 2018;8(5):311-331

Comparison of ^{68}Ga-DOTATATE PET/CT vs. ^{111}In-pentetreotide SPECT: largest series on record

VOLUME 34 · NUMBER 6 · FEBRUARY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Comparison ^{111}In-Pentetreotide, ^{68}Ga-DOTATATE, CT (n=**131**)

- Sensitivity:
  - ^{68}Ga-DOTATATE 95.1%
  - ^{111}In-Pentetreotide SPEC/CT 30.9%
  - CT 45.3%
- ^{68}Ga-DOTATATE PET/CT induced **change in management** in **43** of 131 patients (**32.8%**)
- In patients with **carcinoid symptoms** and negative biochemical testing:
  - ^{68}Ga-DOTATATE PET/CT: positive in **65.2%**
  - **40%** of these were anatomic imaging and ^{111}In-pentetreotide SPECT/CT **negative**

Sadowski, 2016, J Clin Oncol; 34(6): 588-96

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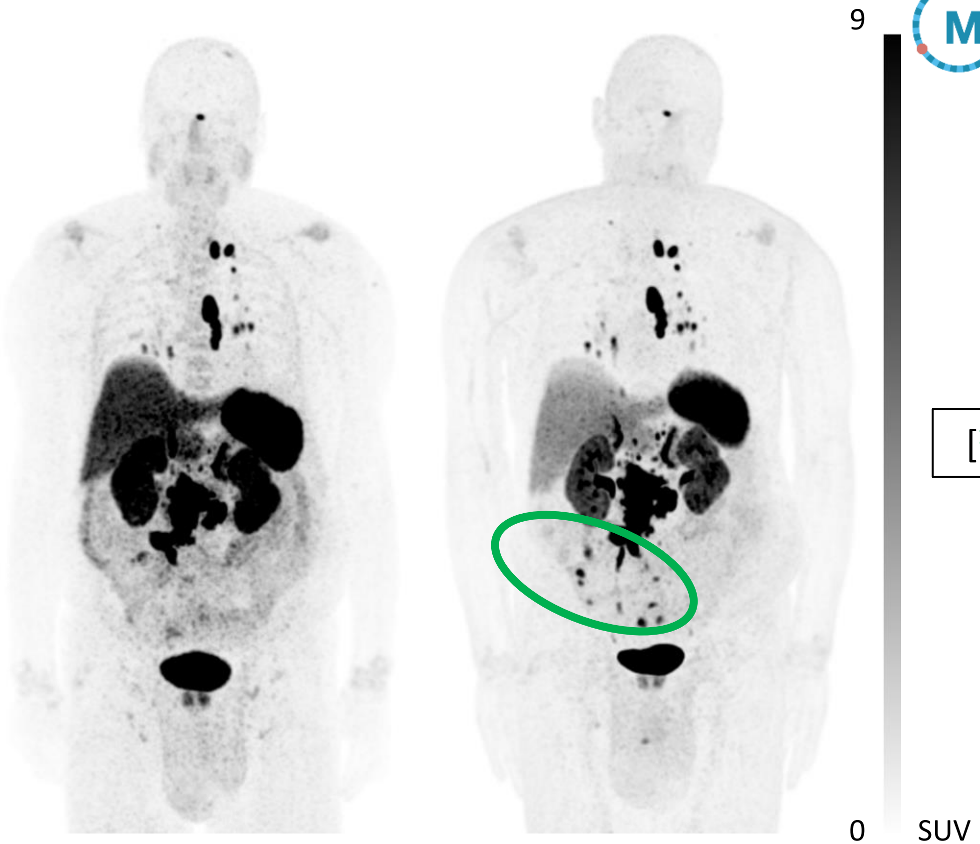
SAMEN GRENZEN VERLEGGEN

[^{18}F]AlF-NOTA-Octreotide: example

KU LEUVEN

MIRaCLe MOLECULAR IMAGING RESEARCH AND CLINIC LEUVEN

[^{68}Ga]Ga-DOTATATE

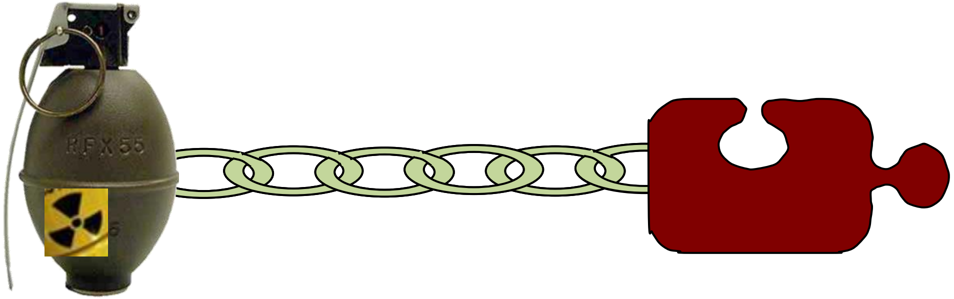


[^{18}F]AlF-OC

Pauwels E, ..., Deroose CM. *J Nucl Med*. 2022 doi: 10.2967/jnumed.122.264563. PMID: 36265911.

Radiopharmaceutical

For radionuclide therapy



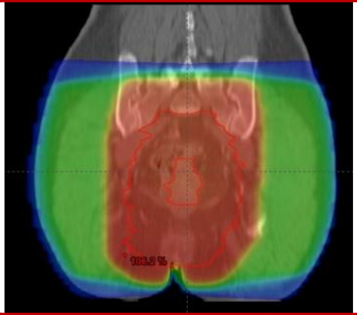
Radionuclide	Linker	Vector molecule
Upon decay emits particulate radiation for **destruction** of the tissue target cells	Attaches radionuclide to the vector	Is responsible for a specific molecular interaction with the target (receptor, transporter, enzyme,…)

RNT: Systemic Radiation Treatment

Cancer Treatment Triangle

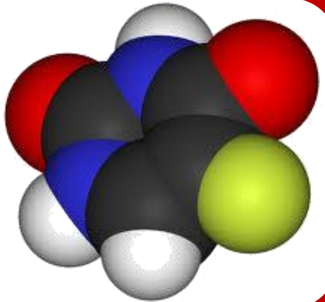
Surgery

Systemic Radiation Treatment



Radionuclide therapy

RNT



External beam radiation therapy

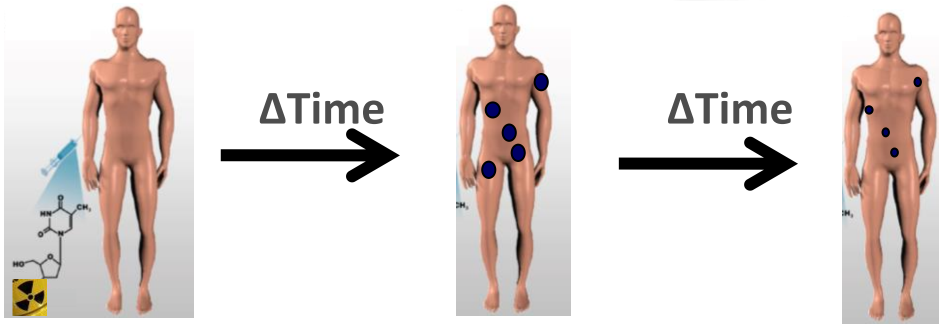
Systemic treatment (chemo, hormono, targeted, immuno)

Aims of the radionuclide

- Functional evaluation without imaging
  - e.g. ^{51}Cr-EDTA assay
- Perioperative dections with/without imaging:
  - sentinel node imaging and detection
  - radioguideded surgery, e.g. PSMA-ligands.
- Imaging:
  - SPECT(/CT)
  - PET(/CT)(/MRI)
- Therapy
  - "adjuvant"
  - therapy of macroscopic disease
  - with/or without need for post-therapy imaging

Gamma-counter

Gamma/beta probe



Properties of the radionuclide

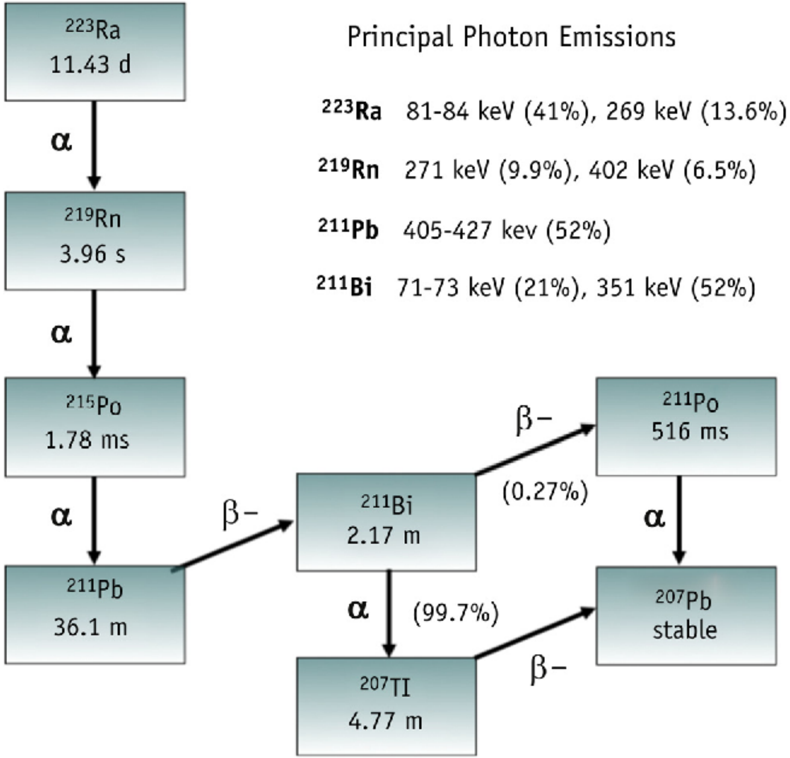
- Physical properties:
  - Emission type
  - Energy => range in tissue
  - Half-life: Ideal half-life depends on kinetics of vector molecule
- Chemical properties:
  - Covalent bonds? Stabile?
  - Chelation-only?
  - Reaction conditions for radiolabeling?
- Logistics:
  - Availability
  - Quantity
  - Purity of radionuclide, e.g. long-lived contaminants
  - Periodicity
  - Cost

Physical Properties

Emission Type

- α/β⁻: Clinically validated for therapy
- β⁺: Clinically validated for PET
- γ: clinically validated for gamma-camera
- Auger e⁻ : studied for therapy

- Combined emitters:
  - β⁻/ β⁺ (e.g. ^{90}Y)
  - β⁻/ γ emitters (e.g. ^{177}Lu)
  - α often combined w. β⁻/ γ decay cascades (e.g. ^{223}Ra)



Humm JL, et al. Int J Radiat Oncol Biol Phys. 2015;91(5):898-906. PMID: 25832684

Physical Properties

Emission Type

- α/β^-: Clinically validated for therapy
- β^+: Clinically validated for PET
- γ: clinically validated for gamma-camera
- Auger e^- : studied for therapy
- Combined emitters:
  - β^-/ β^+ (e.g. ^{90}Y)
  - β^-/ γ emitters (e.g. ^{177}Lu)
  - α often combined w. β^-/ γ Decay cascades (e.g. ^{223}Ra)

Energy / Range

- Branching ratio
- Energy per emission
- High impact on effects
- γ:
  - Low energy: high absorption
  - High energy: septal penetration, low detection yield
- α: MeV range, 100 µ
- β^-: 100s keV, range, ~1-10 mm
- β^+: ^{18}F: E_{max}: 0.635 MeV
  - ^{68}Ga: E_{max}: 1.92 MeV

Half-life

- Short:
  - ^{82}Rb: 76.4 s – generator
  - ^{15}O: 122.2 s – cyclotron
- Moderate:
  - ^{68}Ga: 1.13 hrs – generator
  - ^{18}F: 1.83 hrs – cyclotron
  - ^{99m}Tc: 6.01 hrs – generator
- Long:
  - ^{64}Cu: 0.53 days
  - ^{111}In: 2.83 days
  - ^{89}Zr: 3.27 days
- Very long:
  - ^{177}Lu: 6.73 days
  - ^{223}Ra: 11.4 days
  - ^{51}Cr: 27.7 days

Physical Properties – $T_{1/2}$

Short

No incorporation in radiopharmaceutical

- Dependent on intrinsic properties: $H_2{}^{15}O$ (perfusion), ^{82}Rb potassium analogue (uptake ~perfusion)
- Low radiation burden

Long

Allows incorporation in radiopharmaceuticals & QC

- For molecules with slow targeting kinetics, e.g. MoAbs
- Allows distribution
- Higher radiation burden

Moderate

Allows incorporation in radiopharmaceutical & quality control

- Suitable for molecules with rapid to intermediate targeting kinetics
- Distribution: feasible or no

Very long

- Cfr long
- Provides high radiation burden to target (for RNT)
- Long shelf life and low activity procedure (high counting time).

Half-life

- Short:
  - ^{82}Rb: 76.4 s – generator
  - ^{15}O: 122.2 s – cyclotron
- Moderate:
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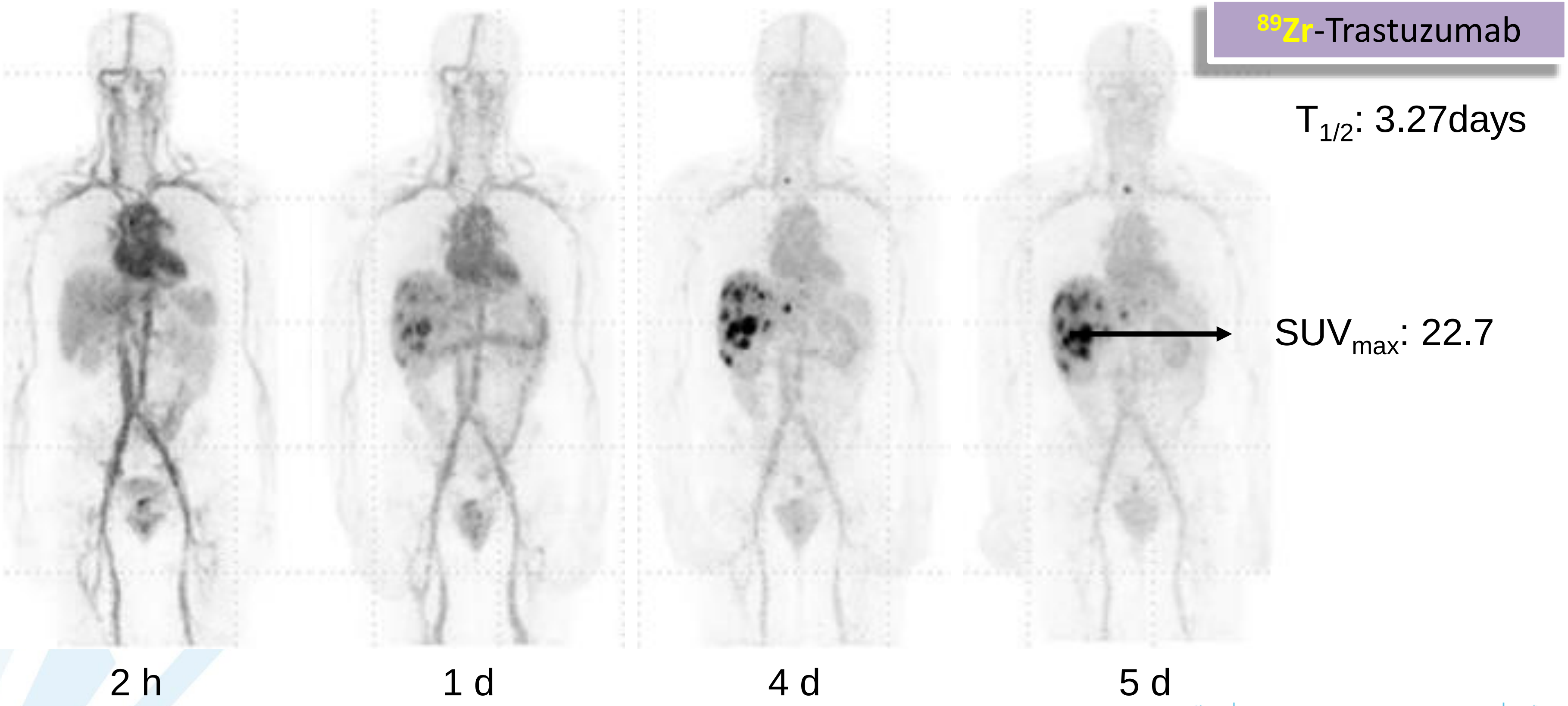
Importance of vector kinetic adapted half-life: Her-2 PET



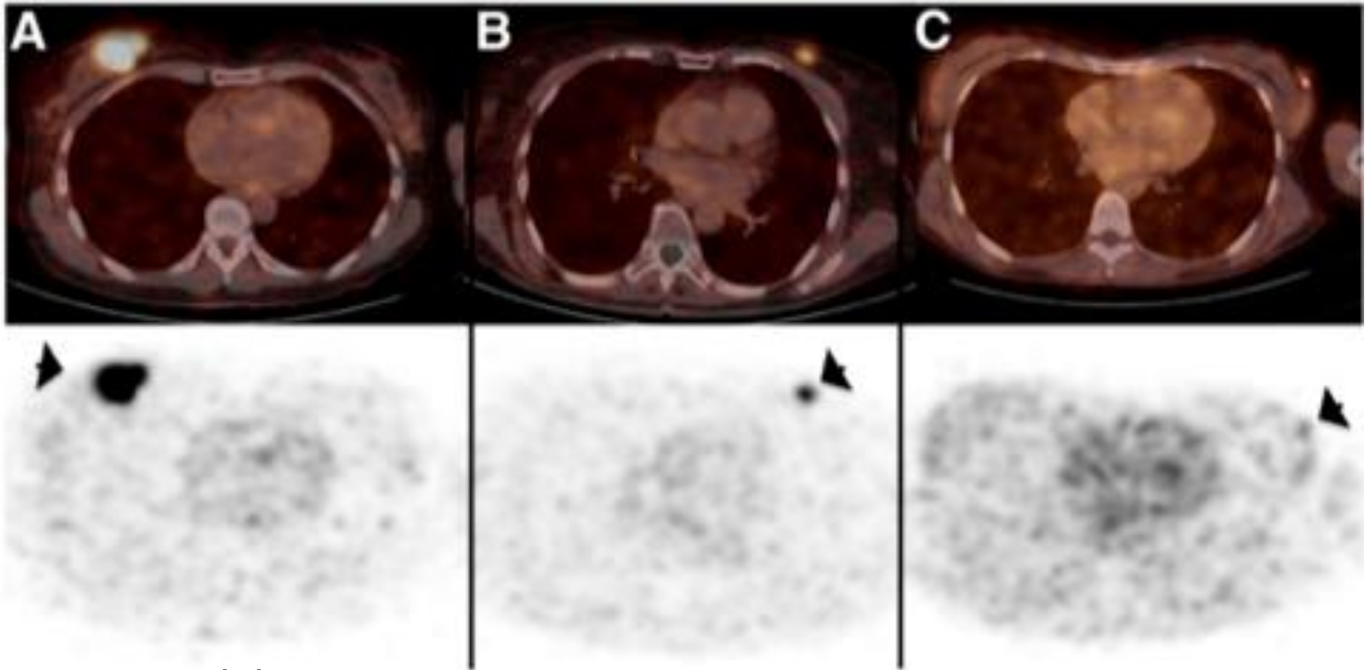
O'Donoghue JA,et al. J Nucl Med. 2018 Jan;59(1):161-166. PMID: 28637800

Importance of adapted half-life: Her-2 PET

^{68}Ga-HER2-Nanobody

90 min PI

$T_{1/2}$: 68 min



High

Moderate

Low

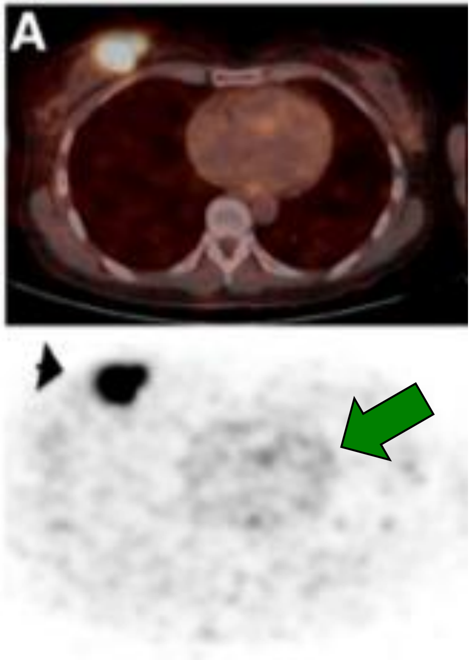
Keyaerts M, et al. J Nucl Med. 2016 Jan;57(1):27-33. PMID: 26449837

Importance of adapted half-life: Her-2 PET

^{89}Zr-Trastuzumab

120 min PI

High Bloodpool



^{68}Ga-HER2-Nanobody

90 min PI

Low Bloodpool

Keyaerts M, et al. J Nucl Med. 2016 Jan;57(1):27-33. PMID: 26449837
O'Donoghue JA,et al. J Nucl Med. 2018 Jan;59(1):161-166. PMID: 28637800

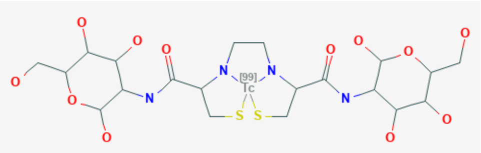
Chemical Properties

Covalent bonds

- Allows direct incorporation into the vector molecule
- Stable bond is necessary
- Limited impact on the biological behaviour: affinity, substrate recognition
- e.g.
  - Carbon-11
  - Halogens (^{18}F, $^{123/124/131}$Iodine)
  - Astatin-211
  - ^{99m}Tc Carbonyl

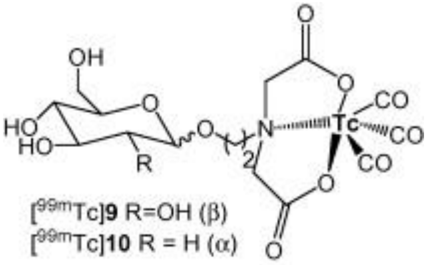
Chelation chemistry

- Radiometals
- No direct bonds
- Chelators necessary
- Changes biological properties (e.g. glucose, BBB)
- Varying yields, chelation time, conditions, stability
- e.g. ^{111}In, ^{177}Lu, ^{90}Y, ^{51}Cr
- ^{99m}Tc – no good glucose analogue



Reaction conditions

- Simple kit preparations vs. more complex
- Harsh reaction conditions
- (↑T°, low pH, organic solvents,…)
- Compatible with biomolecules or not

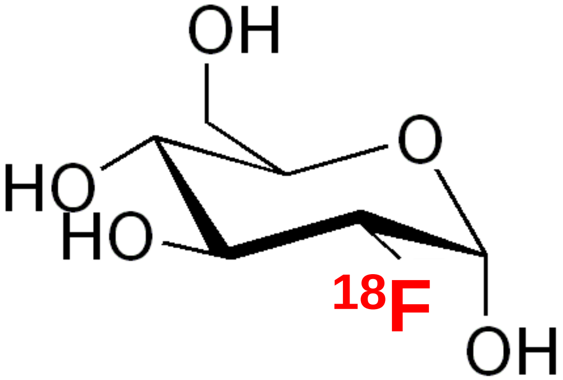


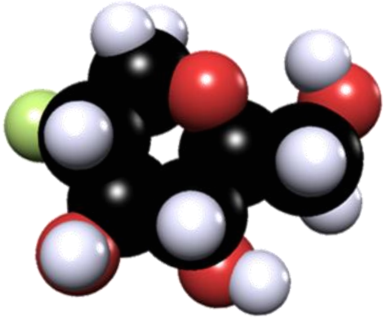
Leung K. 2009. MICAD PMID: 20641546;
Dapueto R, et al. Bioorg Med Chem Lett. 2011;21(23):7102-6. PMID: 22014828

Chemical Properties

Direct

- Covalent bonds allow direct incorporation into the vector molecule
- Stable bond is necessary
- Limited impact on the biological behaviour: affinity, substrate recognition
- e.g.
    - Carbon-11
    - Halogens (^{18}F, $^{123/124/131}$Iodine)
    - Astatin-211
    - ^{99m}Tc-Carbonyl





Fluorine-18 labels maintains:

- Substrate for GLUT transporters
- Substrate for hexokinase

$\Rightarrow$ Metabolic trapping

Fluorine-18 labels disrupts:

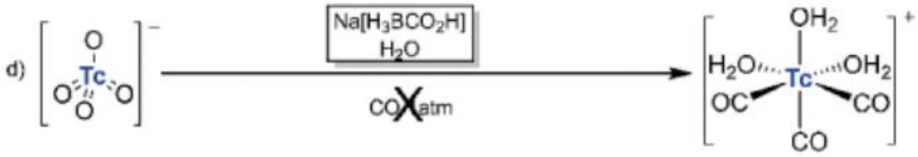
- Substrate for SGLT $\Rightarrow$ renal excretion

Chemical Properties

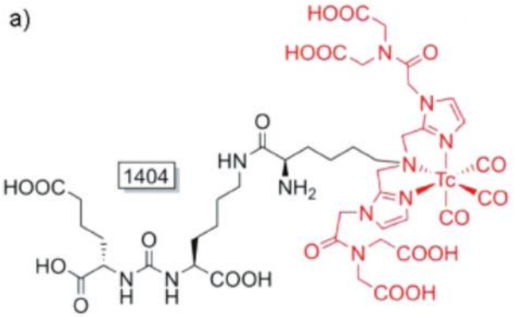
Direct

- Covalent bonds allow direct incorporation into the vector molecule
- Stable bond is necessary
- Limited impact on the biological behaviour: affinity, substrate recognition
- E.g.
  - Carbon-11
  - Halogens (^{18}F, $^{123/124/131}$Iodine)
  - Astatin-211
  - ^{99m}Tc Carbonyl

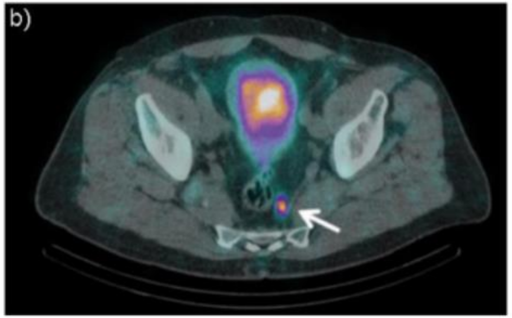
^{99m}Tc Cabonyl organometallic bond



[^{99m}Tc]MIP-1404 (PSMA ligand)



SPECT/CT



Alberto R. Chembiochem. 2020;21(19):2743-2749. PMID: 32875690

Logistics

Availability

- Generator
  - $^{99}Mo/^{99m}Tc$: 1 week
  - $^{82}Sr/^{82}Rb$: 6-8 weeks
  - $^{68}Ge/^{68}Ga$: 1 year
- On-site cyclotron production
- Industrial cyclotron production
- Reactor production
- Accelerator production

Periodicity

- Daily (^{18}F, ^{68}Ga,…)
- Weekly (^{99}Tc-generators, ^{90}Y, ^{131}I, ^{177}Lu ,…)
- Monthly - Trimester

Quantity

- Sufficient quantity for ^{99m}Tc, ^{90}Y, ^{131}I, ^{177}Lu
- ^{18}F: very high demand, might require additional cyclotron capacity
- ^{68}Ga: ↓ from 4 to 2/1 patients / elution ⇒ increase waiting list
- α- emitters:
  - ^{223}Ra: commecially available
  - Others: not GMP, not commercially available
  - Limited amounts, e.g. ^{225}Ac, ^{212}Pb

Cost

Δ {
^{99m}Tc: ~15/50€ / unit
^{18}F: incorporated in radiopharmaceutical; ~100-1000 €/unit
^{68}Ga: ~1500€/week
^{11}C: ~1000 €/unit
}

θ {
^{131}I: 100-775 €/unit
^{177}Lu: 2500 - ~20000 €/unit
}

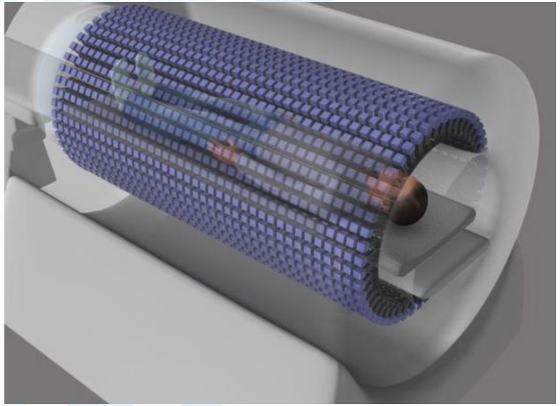
Radionuclidic purity

Most radionuclides OK
Long-lived contaminants:
^{177m}Lu ($T_{1/2}$: 160.4 d)
^{166m}Ho ($T_{1/2}$: 1200 Y)
^{152}Eu ($T_{1/2}$: 13.5 Y) (in ^{153}Sm)
⇒ serious waste problems

Diagnostic imaging: PET vs gamma camera

PET

- Intrinsically tomographic
- High spatial resolution (~4 mm)
- Quantitative (Bq/mL & SUV)
- High sensitivity (counts/Bq)
- Time of Flight
- Radionulides “of life” (^{11}C, ^{13}N, ^{15}O, ^{18}F)
- Ultrafast / ultra low doseimaging – LAFOV PET



20 min 18.75 s

SPECT

- From planar to tomographic set up, e.g. solid state based
- Lower spatial resolution (~10 mm)
- Can be quantitative (Bq/mL) – more elaborate quantitation
- Lower sensitivity (counts/Bq)
- Longer scanning for similar SNR
- Cheaper

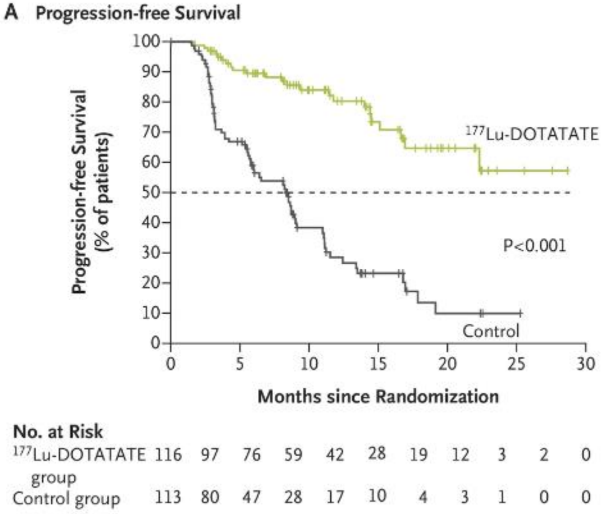
PET > SPECT

- PET > gamma camera in oncology, neurology, infectious disease
- Gamma camera OK for physiological imaging

Cherry SR et al. J Nucl Med. 2018;59(1):3-12. PMID: 28935835
Badawi RD et al. J Nucl Med. 2019;60(3):299-303. PMID: 30733314

Radionuclide Therapy anno 2024

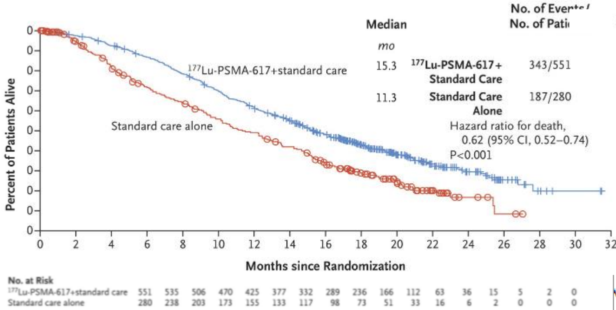
Progression-Free Survival



Control the growth of the disease

Strosberg, et al. N Engl J Med 2017; 376:125–35

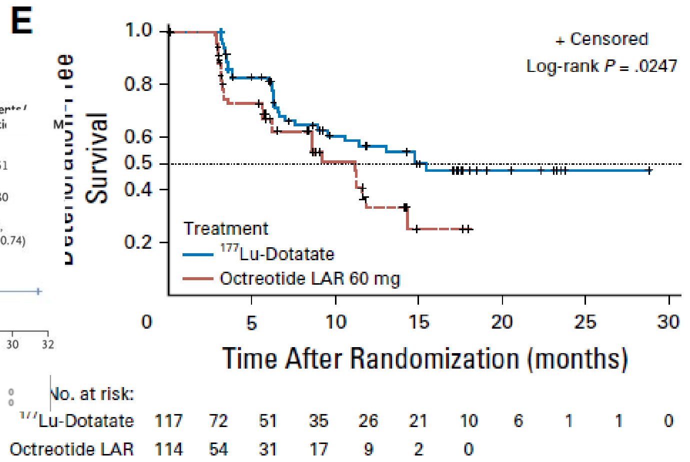
Overall Survival



Make patient **live longer**

Sartor O, et al. N Engl J Med. 2021;385(12):1091-1103

Quality of life: Pain

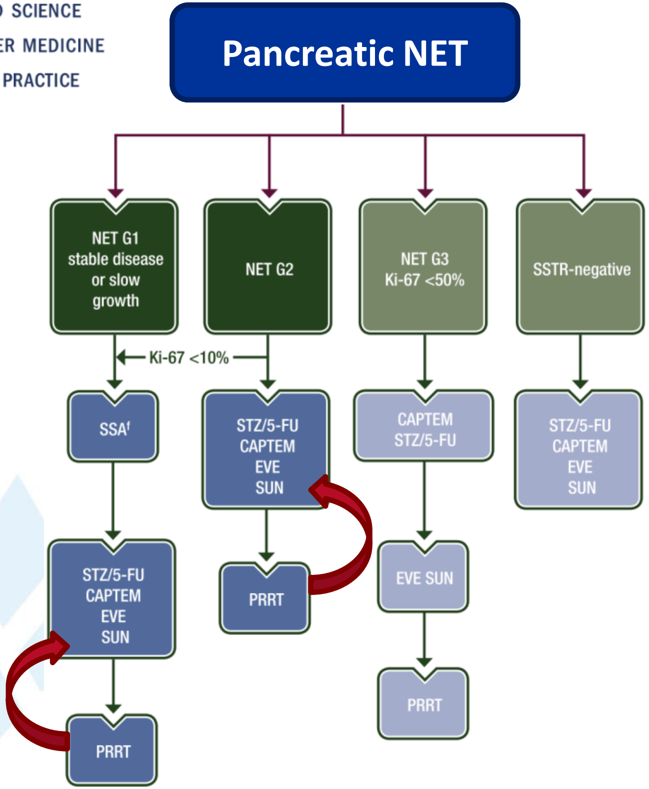


Make patient **live better**

Strosberg, et al. J Clin Oncol 2018; 36:2578–84.

RNT incorporated in authorative guidelines and moving up

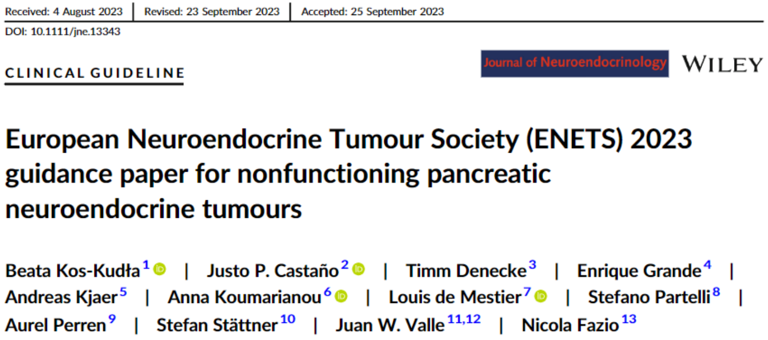
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



Oclurandom

Pavel M et al. Ann Oncol. 2020;31(7):844-860. PMID: 32272208

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY



PRRT may be considered **second-line treatment** in patients with **NF-Pan-NET** G1-G2 with a positive SST-PET/CT

(Level of evidence **2b**: Grade of recommendation **B**).

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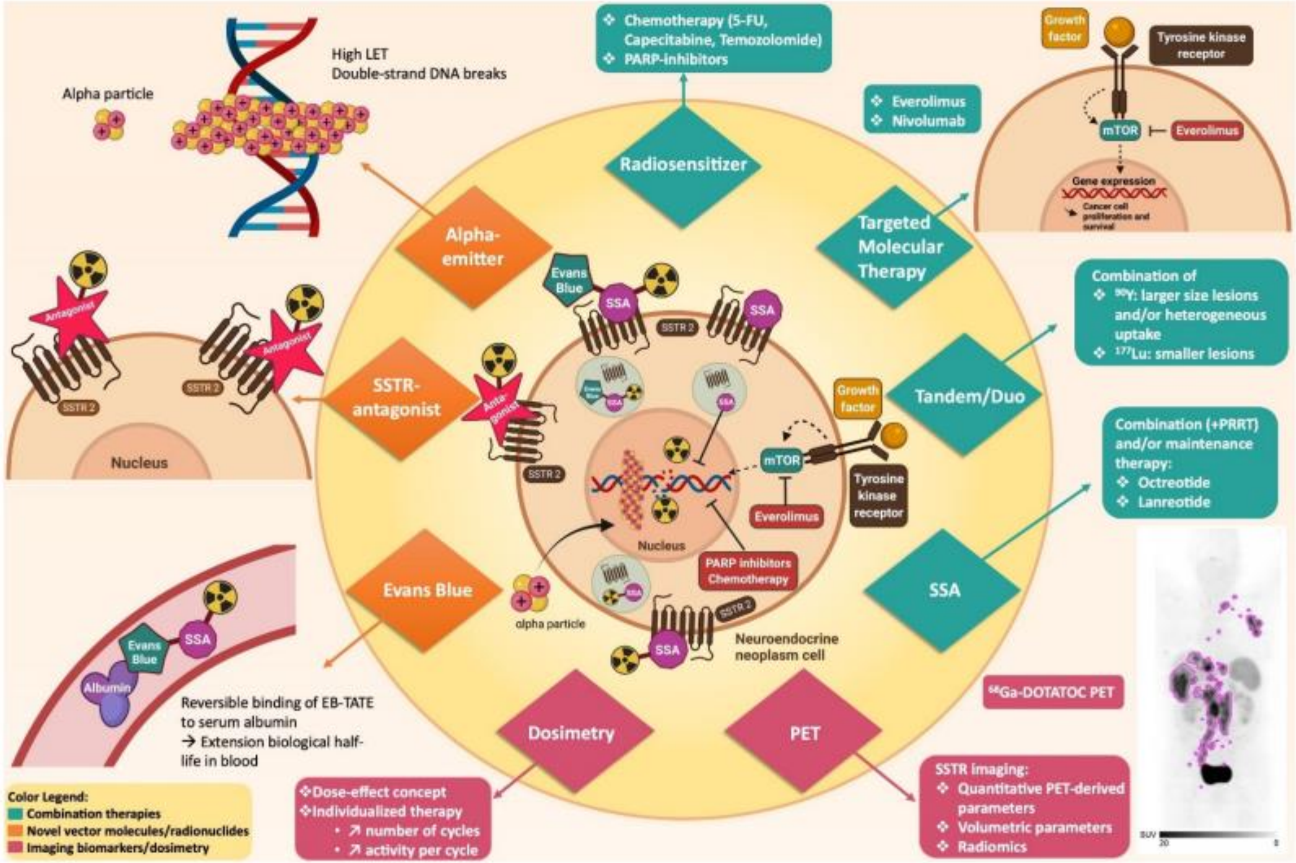
Reimbursement in Belgium

^{177}Lu-DOTATATE:

- Lutathera (AAA; Novartis). Since 1 SEP 2022 – GEP-NET; contains Lu-177m ($T_{1/2}$: 160 days)

- Magistral preparations. Since 1 JAN 2022
  UZ Leuven, I Jules Bordet, AZ Groeninge (Kortrijk)
  Contains no Lu-177m

Optimisation of PRRT



↑ SSTR expression (epigenitic modulators)

Ahmadi Bidakhvidi, …, Deroose Cancers (Basel). 2021;14(1):129. PMID: 35008293

Ongoing RCTs

Trial	Investigated	Endpoint/ number	Population
COMPETE NCT03049189	^{177}Lu-DOTATOC vs **Everolimus**	309 PFS	SSTR+, G1/2 (Ki-67≤ 20%) - GI: non-funct. - P: funct. and non-funct.
OCCLURANDOM NCT02230176	^{177}Lu-DOTATATE vs **Sunitinib**	80 PFS	SSTR+ **P**NET
COMPOSE NCT04919226	^{177}Lu-DOTATOC vs **CAPTEM or Everolimus or FOLFOX**	202 PFS	SSTR+ GEP-NET, G2/G3 (**Ki-67: 15 to 55%**)
NETTER-2 NCT03972488	^{177}Lu-DOTATATE + SSA vs **High dose SSA** (60mg Octreotide LAR q4)	222 PFS	SSTR+ GE**P**-NET, G2/G3 (**Ki-67: 10 to 55%**)
Lu-C-As NCT02736448	^{177}Lu-PRRT + **CAP** + SSA vs ^{177}Lu-PRRT + SSA	176 PFS	SSTR+ GEP-NET, G1/2/3 (**Ki-67≤50%; FDG+**)
CONTROL NETS NCT02358356	^{177}Lu-DOTATATE + **CAPTEM** vs ^{177}Lu-DOTATATE vs CAPTEM	75 G / 90 P PFS	SSTR+ Si/P-NET, G1/G2 Ki-67 ≤ 20%
DOBATOC NCT04917484	^{177}Lu-DOTATOC (4x 7.4 GBq) vs **Dosimetry-tailored** ^{177}Lu-DOTATOC (kidney)	100 PFS	NEN, SST+

$^{223}RaCl_2$ in Prostate Cancer: Alsympca

mCRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxel

Stratification
- Total ALP:
  - <220 U/L
  - ≥ 220 U/L
- Bisphosphonate use
- Prior docetaxel

921

2 → 614: **Radium-223 (55 kBq/kg) + SOC 6 inj @ 4w intervals**

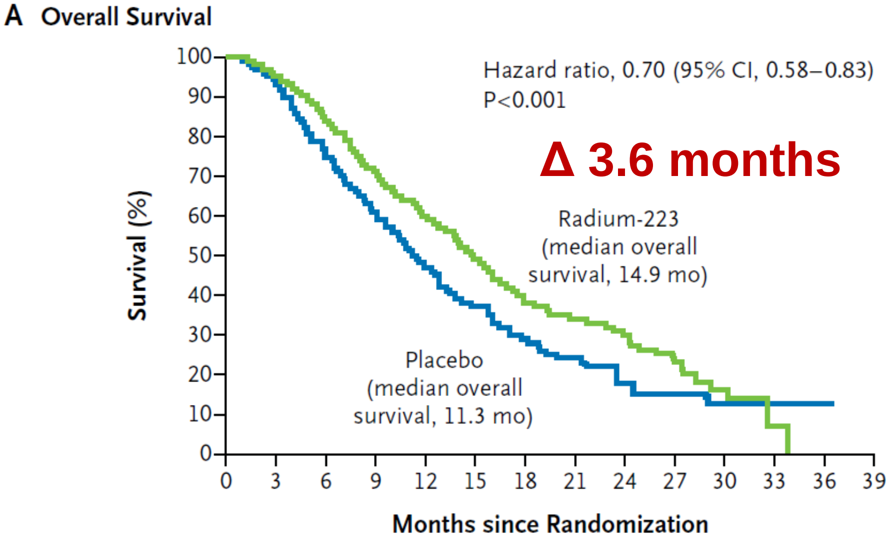
1 → 307: **Placebo (Saline) + SOC**

1ary end: OS

2ary end: t↑ ALP, ALP resp, tSRE, t↑PSA

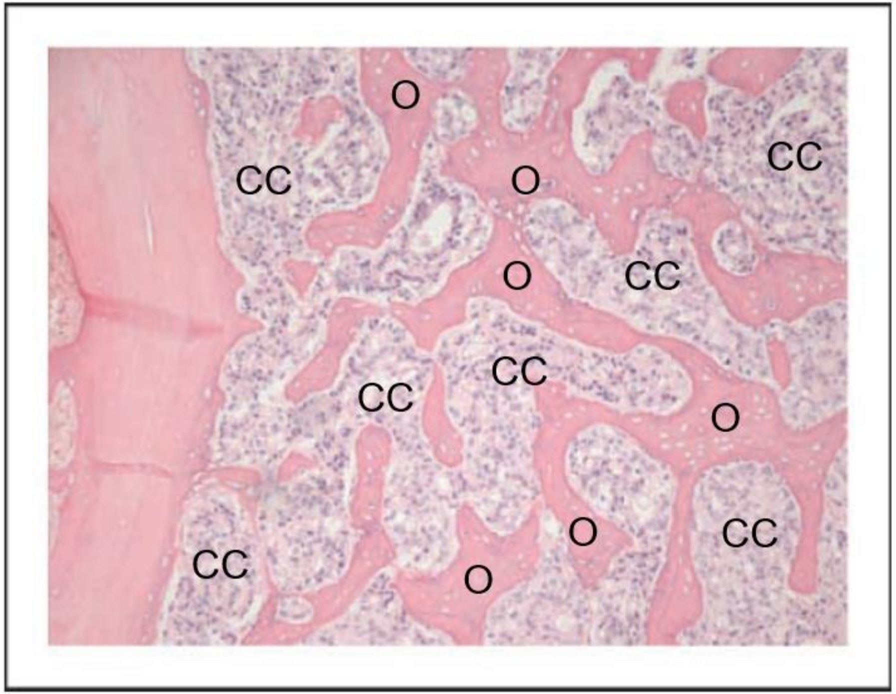
Parker C et al. N Engl J Med. 2013;369(3):213-23. PMID: 23863050.

$^{223}RaCl_2$ in Prostate Cancer: ALSYMPCA



No. at Risk

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

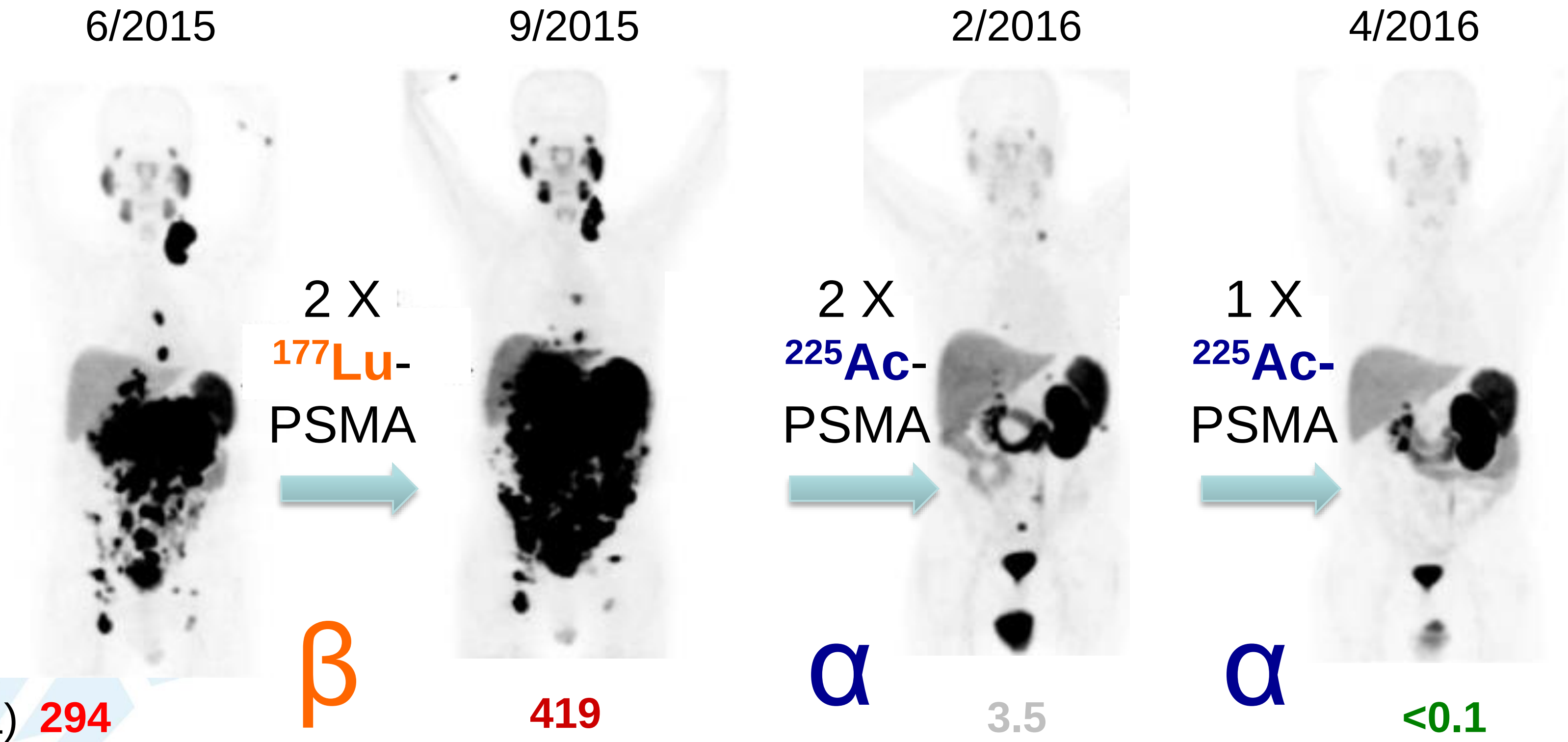


O: osteoid
CC: Cancer cells

Parker et al. N Engl J Med. 2013;369(3):213-23. PMID: 23863050
Bruland et al. Clin Cancer Res. 2006;12(20 Pt 2):6250s-6257s PMID: 17062709

The power of α-therapy

mCRPC



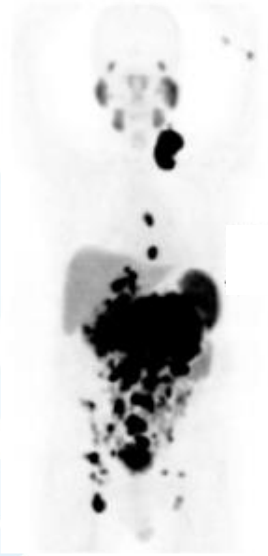
PSA (ng/mL) **294** **419** **3.5** **<0.1**

Kratochwil C, et al. J Nucl Med. 2016;57(12):1941-1944. PMID: 27390158

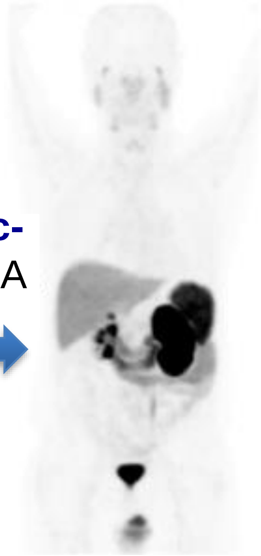
The power of α-therapy

^{68}Ga-PSMA PET

6/2015



4/2016



Total mass of actinium-225

8.9 **nano**gram

3 X

^{225}**Ac-**
PSMA

α

294
PSA (ng/mL)

<0.1

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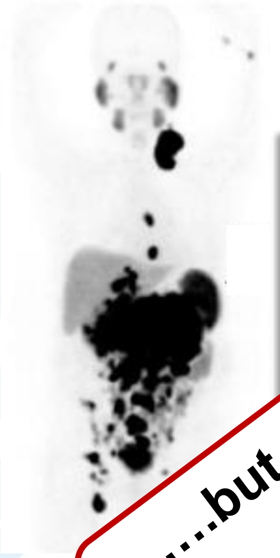
The power of α-therapy

^{68}Ga-PSMA PET

6/2015

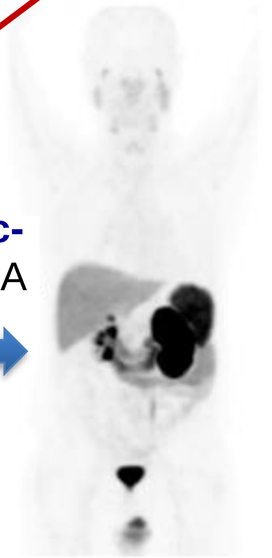


Total ...
a ... -225
nanogram

3 X
^{225}Ac-
PSMA

α

/2016



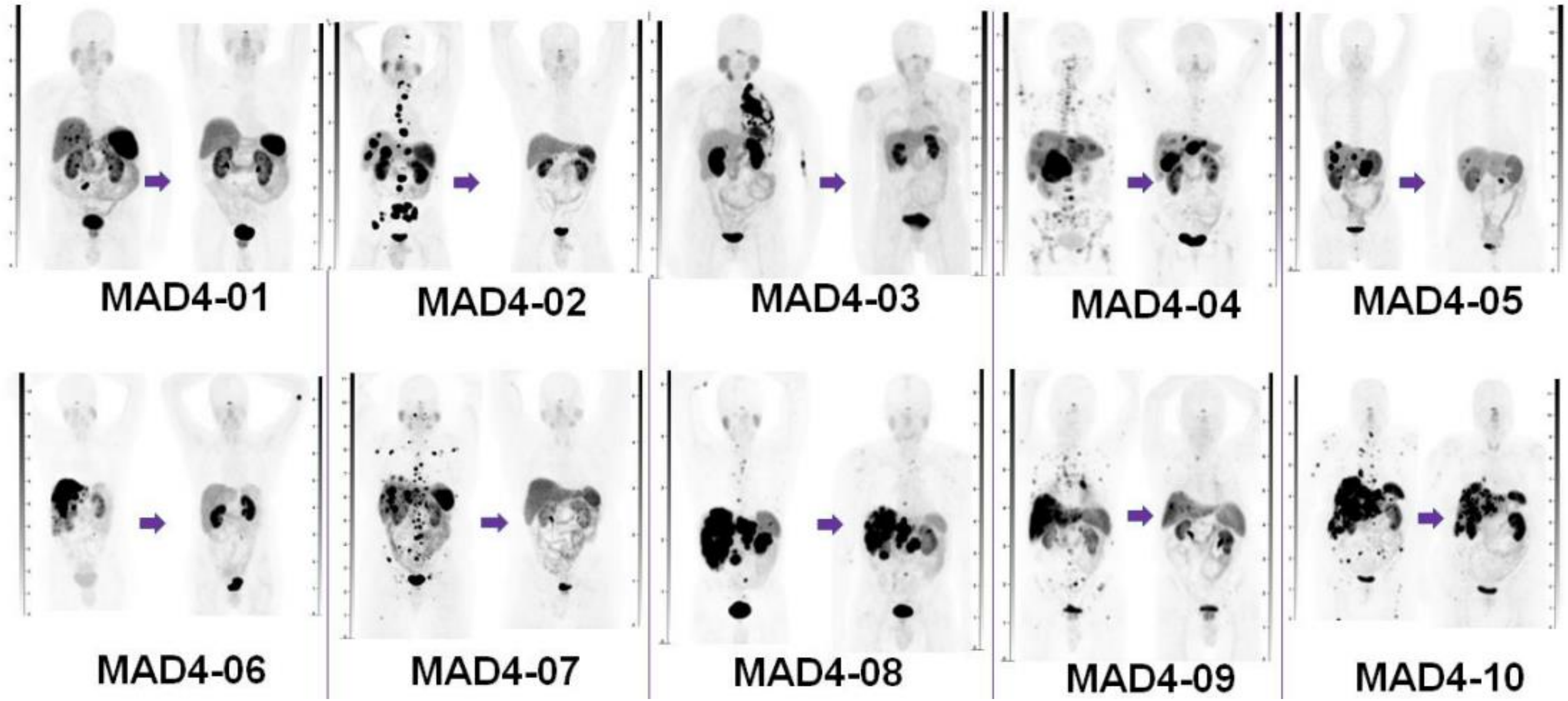
<0.1

PSA (... mL)

....but even 10 nanogram of ^{225}Ac is non-trivial to obtain

Tumor targeted α-emitters

^{212}Pb-DOTAMTATE (2.5 MBq/kg) – PRRT naïve NET patients – Phase I



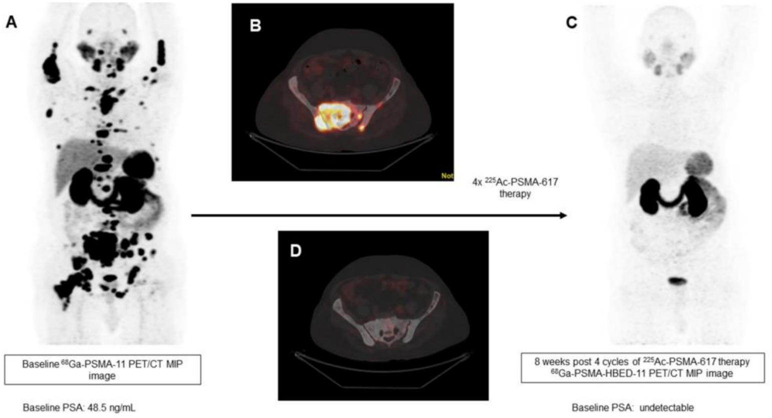
N=10
CR: 1
PR: 7
SD: 2
80% RR
100% DCR

Delpassand et al. J Nucl Med. 2022 PMID: 34992153.

Tumor targeted α-emitters

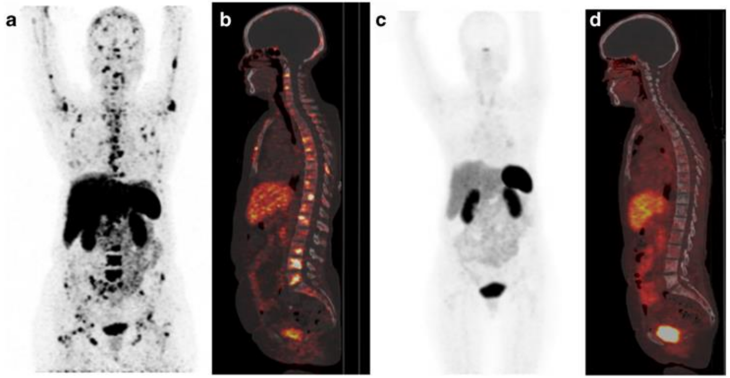
- α-emitters more potent:
  - Higher LET
  - More DSB
- Able to overcome resistance to β-RNT
  - ^{225}Ac-PSMA-617 (N=15)
    - CR:1/13; PR: 4/13; SD: 2/13 (ORR:38%)
  - ^{225}Ac-DOTATATE (N=32)
    - SD: 9/24; PR: 15/24 (ORR: 62%)
  - ^{212}Pb-DOTAM-TATE (N=11; NCT03466216)
    - ORR: 30%; CR: 1; PR: 2; SD: 7; PD:0
    - AE: 5 Grade 3/4; 3 SAE
- Much shorter energy deposition range
  - ⇒ Potential effect on microscopic disease
  - ⇒ Adjuvant and "pseudo"adjuvant potential

^{225}Ac-PSMA-617



Both ^{177}**Lu**-based RNT **refractory**

^{225}Ac-DOTATATE



Baseline ^{68}Ga-DOTANOC PET/CT MIP and sagittal Image

Post 2 cycles of ^{225}Ac-DOTATATE therapy, Interim ^{68}Ga-DOTANOC PET/CT MIP and sagittal image

Delpassand et al. ASCO 2022;
Ballal Eur J Nucl Med Mol Imaging. 2020;47(4):934-946. PMID: 31707430.
Yadav et al. Theranostics. 2020;10(20):9364-9377. PMID: 32802197.

^{225}Ac-DOTATATE

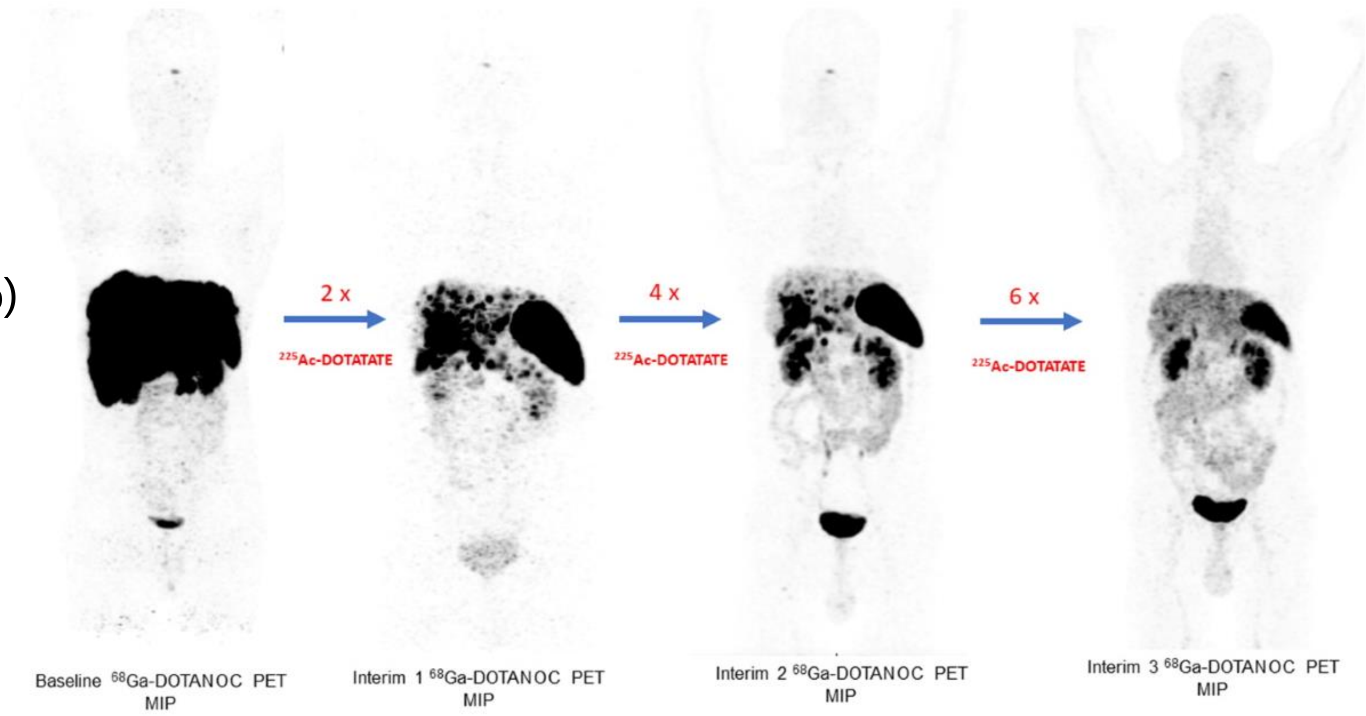
2022 SNMMI Henry N. Wagner, Jr., Abstract of the Year

Minimal toxicity

N=83
- 56 prior ^{177}Lu-DOTATATE (67%)
- 27 PRRT naïve (33%)

^{225}Ac-DOTATATE; q8

Response (RECIST)
CR: 2 (2.7%)
PR: 32 (43%)
SD: 25 (34%)
PD: 15 (20%)
DCR: 71%



Bal et al. SNMMI 2022, abstract 325

Need for novel α-emitters

- **^{223}Ra**:
  - Only α-emitters currently commercialised
  - Calcium-mimetic bone seeker
  - But major drawback**: no chelator** described
  - No vectorisation
- Other α-emitters
  - Not commercialised
  - Not GMP
  - Limited quantities

Review

Overview of the Most Promising Radionuclides for Targeted Alpha Therapy: The "Hopeful Eight"

Romain Eychenne [1,2,*], Michel Chérel [2], Férid Haddad [1,3], François Guérard [2] and Jean-François Gestin [2,*]

Actinium-225	Astatine-211	Bismuth-212	Bismuth-213
Lead-212	Radium-223	Terbium-149	Thorium-227
	Radium-224		

Eychenne R et al. Pharmaceutics. 2021;13(6):906. PMID: 34207408

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Eychenne R et al. Pharmaceutics. 2021;13(6):906. PMID: 34207408

Need for novel α-emitters

2021
Therapeutic Radionuclides

Ligtvoet, A., Scholten, C., Davé, A., King, R., Petrosova, L., Chiti, A., Goulart De Medeiros, M., Joerger, A.

JRC SCIENCE FOR POLICY REPORT

Study on sustainable and resilient supply of medical radioisotopes in the EU

European Commission

^{211}At	Very limited supply for medical use, experimental only, but small quantities. There are cyclotrons in Europe that could technically produce ^{211}At in the future. Short lifetime for foreign supply.
^{212}Pb	Experimental, currently limited supply for medical use. Short lifetime for foreign supply.
^{213}Bi	Relies on availability of ^{225}Ac, which has limited supply, currently reliant on US DOE.
^{223}Ra	No European supply disclosed (if available). Likely strong dependency on US. Only one pharmaceutical company has a radiopharmaceutical using ^{223}Ra on the market, which has supply secured for projected demand in next 10 years. This holds risk of monopolised supply of ^{223}Ra.
^{225}Ac	Very hard to obtain. Limited supply, currently largely reliant on US DOE. Other production routes need to be developed. When clinical trials successful, additional (European) sources are needed for clinical application.
^{227}Th	Experimental, not much produced yet. No European irradiation source identified but has potential to be scaled.

No “ideal” radionuclide – larger arsenal needed

- No single ideal radionuclide
- Depending on applications (e.g. PET / SPECT / Therapy) and vector molecules
- Trade-off between different properties
- Need to increase the range of possibilities
  - Alpha-therapy
  - Medium-lived PET radionuclides
  - Medium-lived, short range β^- emitter
  - Theranostic pairs or combos
    - ^{86}Y PET for dosimetry ^{90}Y
    - ^{149}Tb, ^{152}Tb, ^{155}Tb, and ^{161}Tb quartet

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Acknowledgements

Nuclear Medicine department & Radiopharmacy

moSAIC www.saic.be

Molecular small animal imaging center

RADIOPHARMACEUTICAL RESEARCH KU LEUVEN

Laboratory for Radiopharmaceutical Research

Prof. Guy Bormans

Prof. Frederik Cleeren

LEUVEN KANKERINSTITUUT LKI

fwo Research Foundation Flanders Opening new horizons

Kom op tegen Kanker

Stichting tegen Kanker

Thank you for your attention

Questions?