THERAPEUTICALLY USED RADIONUCLIDES AND RADIOPHARMACEUTICALS IN NUCLEAR MEDICINE

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Joint ICTP-IAEA Workshop on Radiation Protection in Diagnostic and Therapeutic Nuclear Medicine | (smr 4112)

Disclosures

Travel
- Nothing to declare

Research grant
- AAA/Novartis
- Oncobeta
- Life Molecular

Honorarium
- GE Healthcare
- Oncobeta

Advisory Board/Consultant
- GE Healthcare
- Novartis
- Lilly

Agenda

- current therapies and future developments
- most important radionuclides / pharmaceuticals
  - Beta Particles
    - Iodine-131
    - Lutetium-177
    - Yttrium-90
    - Samarium-153
    - Rhenium-188
  - Alpha Particles
    - Radium-223
    - Actinium-225
  - „New“ radionuclides / pharmaceuticals
    - Terbium-161

Note: Radiation protection issues are covered in the corresponding lecture on radiation protection.

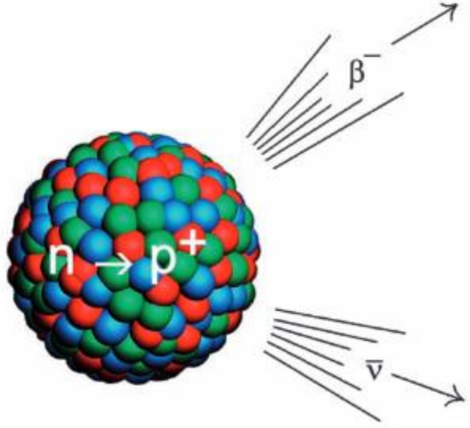
Current therapies and future developments

- use of ^{131}I for therapy of malignant and benign thyroid diseases still dominant
  - incidence of benign thyroid diseases is decreasing → partly due to better iodine supply
  - MIBG-therapy
- ^{177}Lu will be increasingly used
  - pharmaceuticals like DOTA-TATE and PSMA-617 will have an growing role in clinical arena
    - successful phase III-trials (NETTER-I, NETTER-II for NET and VISION for prostate cancer)
  - possibly the most widely used in the future
  - new therapeutic agents are on the horizon (i. e. FAPI, Bombesin (GRPr))
- medical devices, such as microspheres labeled with ^{90}Y are used in the treatment of hepatocellular carcinoma (HCC) and liver metastases
- alpha emitters will enter clinical arena
  - already estabslished → ^{223}Ra in the treatment of bone metastasis of prostate cancer
  - ^{225}Ac and ^{212}Pb labeled pharmaceutiacls will be used more frequently in future
- New beta emitters
  - ^{161}Tb, ^{67}Cu, …

PHARMACEUTICALS LABELED WITH β^- - RADIONUCLIDEDS

Beta Particles – Interaction with matter

$n \rightarrow p^{+} + \boldsymbol{\beta}^{-} + \bar{\nu}$ → caused by neutron/proton (n/p) imbalance



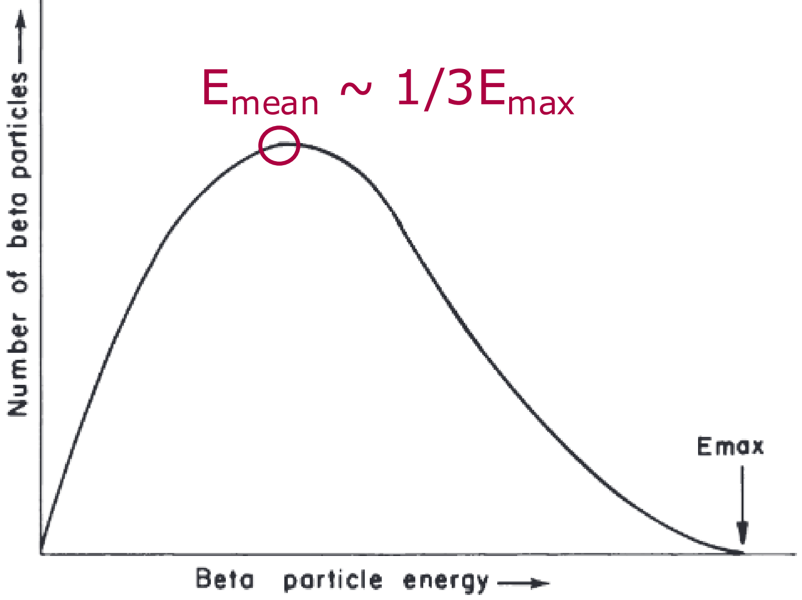
- occurs when n/p ratio is too high
- Neutron → Proton + Electron + Antineutrino
- Atomic number +1, mass number unchanged
- often accompanied by gamma emission

$^{131}_{53}I \rightarrow {}^{M}_{Z}X + {}^{0}_{-1}e$

M: 131 = M + 0, so M = 131
Z: 53 = Z - 1, so Z = 53 + 1 = 54

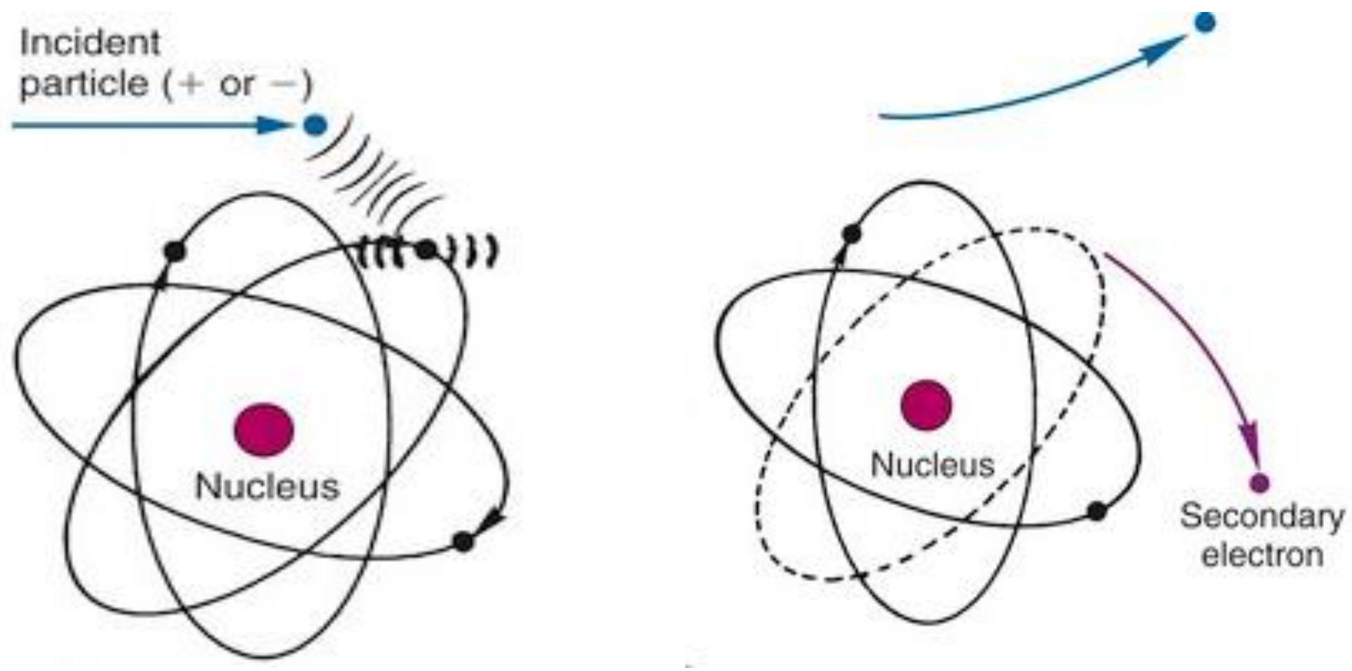
$$^{131}_{53}I \rightarrow {}^{131}_{54}Xe + {}^{0}_{-1}e + 0{,}97\ \text{MeV}$$

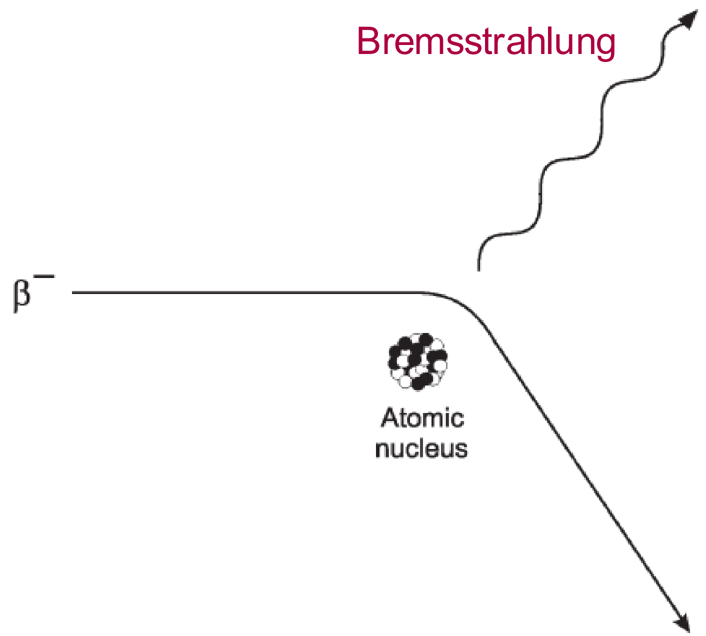
Continuous energy spectrum
Range: 0 → E_{max}, most ≈ ⅓ E_{max}



L'Annunziata Michael F. Radioactivity. Elsevier Science B.V. 2007

Beta Particles – Interaction with matter





Interaction with an orbital electron resulting in ionization. Less-close encounters may result in atomic excitation without ionization.

Bremsstrahlung: An electron is deflected by a nucleus and loses kinetic energy → emission of a photon of x-radiation

https://radiologykey.com/interaction-of-radiation-with-matter/
L'Annunziata Michael F. Radioactivity. Elsevier Science B.V. 2007

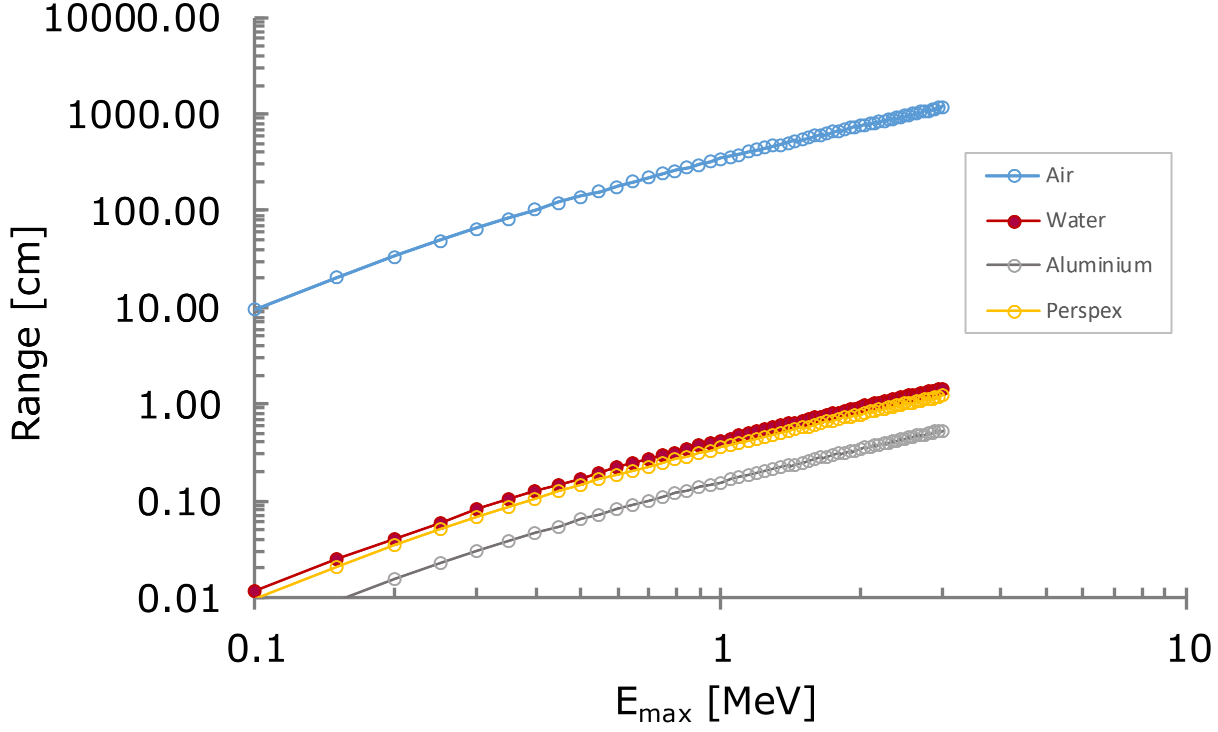
Beta Particles - Range in matter

$$r = \begin{cases} \frac{1}{\rho}(0{,}542 \cdot E_{max} - 0{,}133)\,; & E_{max} > 0{,}8\ \text{MeV} \\ \frac{1}{\rho} 0{,}407 \cdot E_{max}\,; & 0{,}15\ \text{MeV} < E_{max} < 0{,}8\ \text{MeV} \end{cases}$$

Glendenin et al. 1948

$$r = \frac{1}{\rho} \cdot 0{,}11 \cdot \left(\sqrt{1 + 22{,}4 \cdot {E_{max}}^2} - 1\right)\,; \quad 0 < E_{max} < 3\ \text{MeV}$$

Paul and Steinwedel. 1955

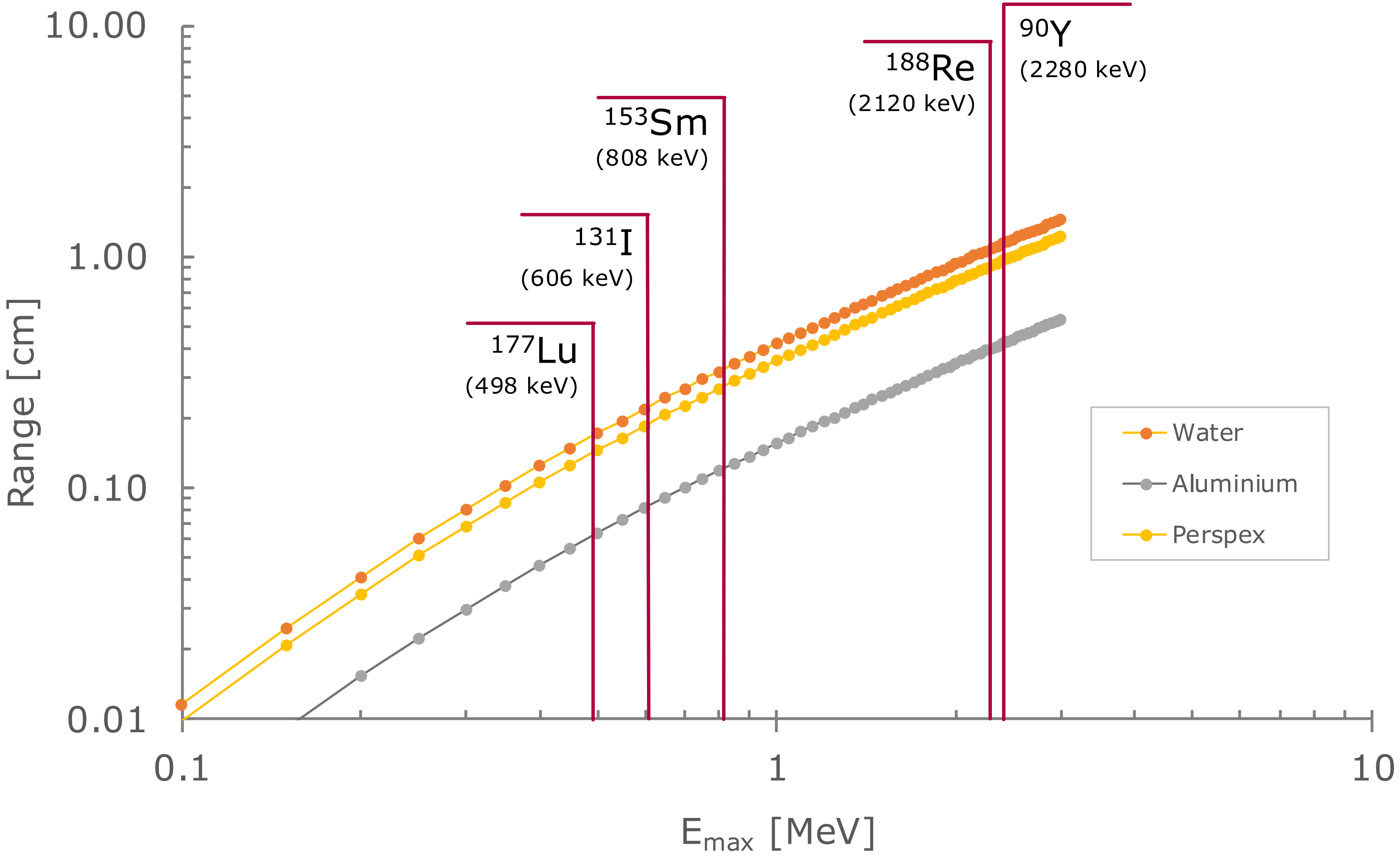


r: range in matter; [r] = cm

ρ: density of matter; $[\rho] = \text{g/cm}^3$

https://mirdsoft.org/products/MIRDspecs

Beta Particles - Range in matter, shielding



Shielding of beta particles
Rule of thumb

Thickness of absorber

$$D[\mathrm{cm}] \approx 0{,}5 \cdot E_{max}[\mathrm{MeV}]$$

Y_{90}: $0{,}5 \cdot 2{,}3\ MeV$

$D \approx \mathbf{1\ cm}$ **Perspex**

THERAPEUTIC PROCEDURES
RADIONUCLIDES

NM-Therapies - Mechanisms of Uptake

- Specific cellular active transporters
  - e. g. NIS for ^{131}I or norephrine transporters for [^{131}I]mIBG
- Selectivity for certain receptors or antigens (+/- internalization)
  - e. g. peptides, small molecules, antibodies
    PSMA- or DOTATATE-therapies
- Local deposition
  - e. g. SIRT (radiolebaled spheres) or RSO

NM-Therapies - Administration Routes

Systemic

- Oral: Liquid of Solid (Capsule)
  - e. g. ^{131}I
- Intra-venous / (Intra-arterial)

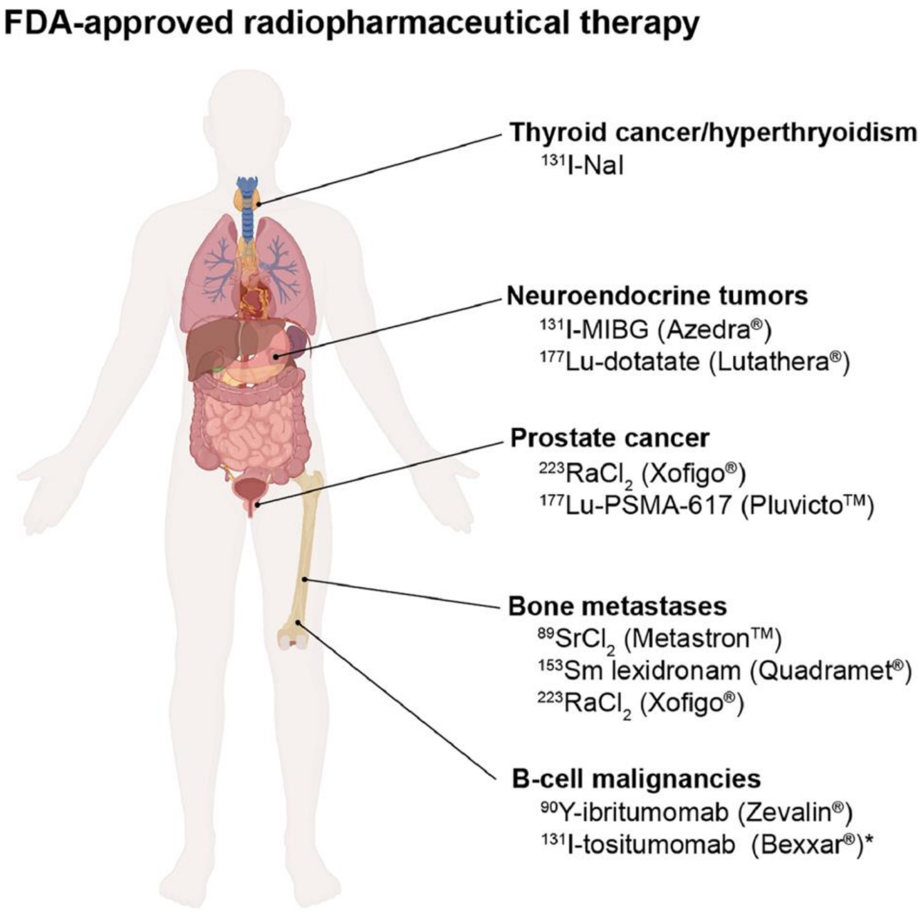
Locoregional

- Intra-arterial: hepatic radioembolization (SIRT)
- Intra-cavitary: intraperitoneal/intratumoral
- Intra-articular: radiosinoviortesis
- Cutaneous application

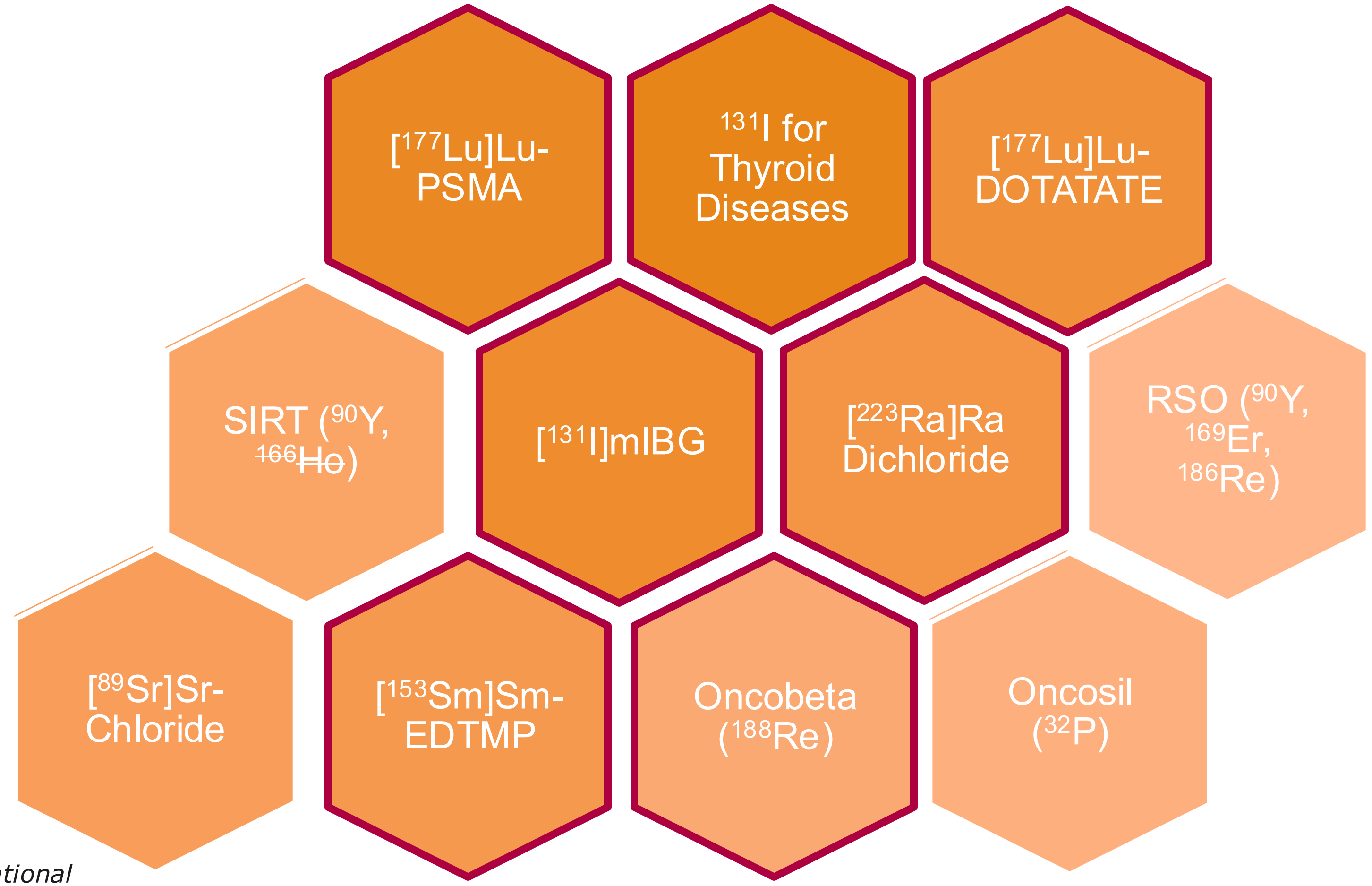
NM-Therapies - Radionuclides

Radio-nuclide	Type	Energy [MeV]	Gamma Energy used for Imaging [keV]	Half Live [d]
^{131}I	β^-	0,61; Mean: 0,2	364	8,0
^{177}Lu		0,5; Mean: 0,1	113; 208	6,6
^{90}Y		2.3; Mean 0,9	Bremsstrahlung	2,7
~~^{166}Ho~~		1,8; Mean:	81	1,1
^{188}Re		2,1; Mean: 0,8	155	0,7
^{153}Sm		0,8; Mean: 0,2	103	1,9
^{89}Sr		1,5; Mean: 0,6	Bremsstrahlung	50,6
^{32}P		1,7 ; Mean: 0,7		14,3
^{223}Ra	α	5…7,5	82	11,4
^{225}Ac	α	5,8 … 8,4	441	10
^{169}Er	β^-	0.4; Mean: 1,0	Bremsstrahlung	9,4
^{186}Re		1,1; Mean: 0,4	137	3,7

THERAPEUTIC PROCEDURES



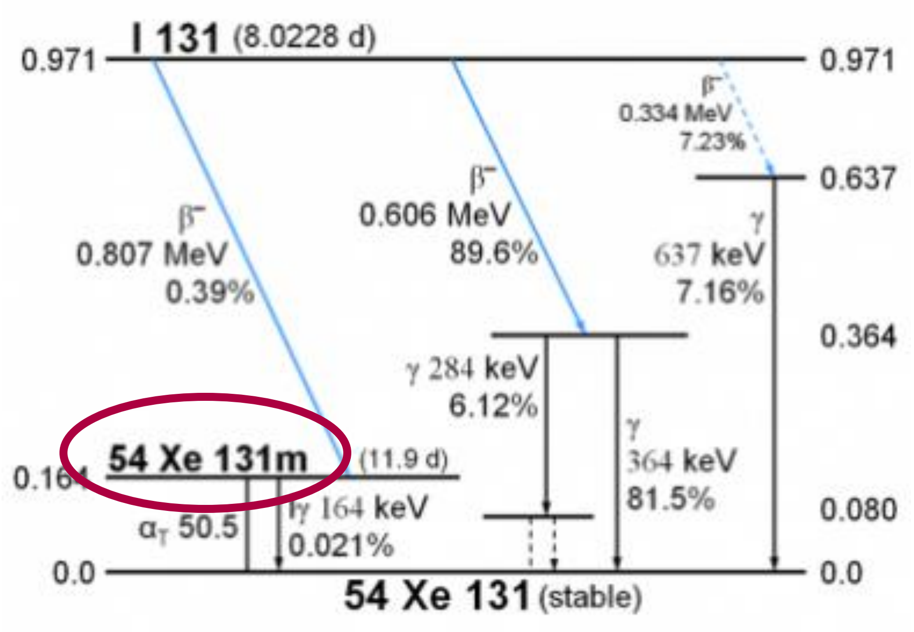
NM therapy practices in Europe



Salerno, Kilian E et al. "A Primer on Radiopharmaceutical Therapy." *International journal of radiation oncology, biology, physics* vol. 115,1 (2023): 48-59.

IODINE-131

Iodine-131 Physical Half-Life: 8.05 d



PHYSICAL DATA

Gamma
364 keV (82% abundance)
637 keV (7% abundance)

Beta
192 keV (89% abundance / average)
606 keV (89% abundance)

Maximum Beta Range in Water: 2 mm
Maximum Beta Range in Air: ~165 cm

SHIELDING

Betas and electrons (complete)
3,3 mm of plastic

Gamma and X-rays
HVL (Lead): 2 mm
TVL (Lead): 11 mm

INTERNAL EXPOSURE FOR STAFF

Critical Organ: Thyroid

Effective Doses per Unit intake (Sv/Bq)
Ingestion: 2.2E-8
$ALI_{ingestion}$ ~ 1 MBq

Inhalation: 1.1E-8
$ALIi_{nhalation}$ ~ 2 MBq

Delacroix et al. RADIONUCLIDE AND RADIATION PROTECTION DATA HANDBOOK 2002

^{131}I-Therapies for treatment of thyroid diseases

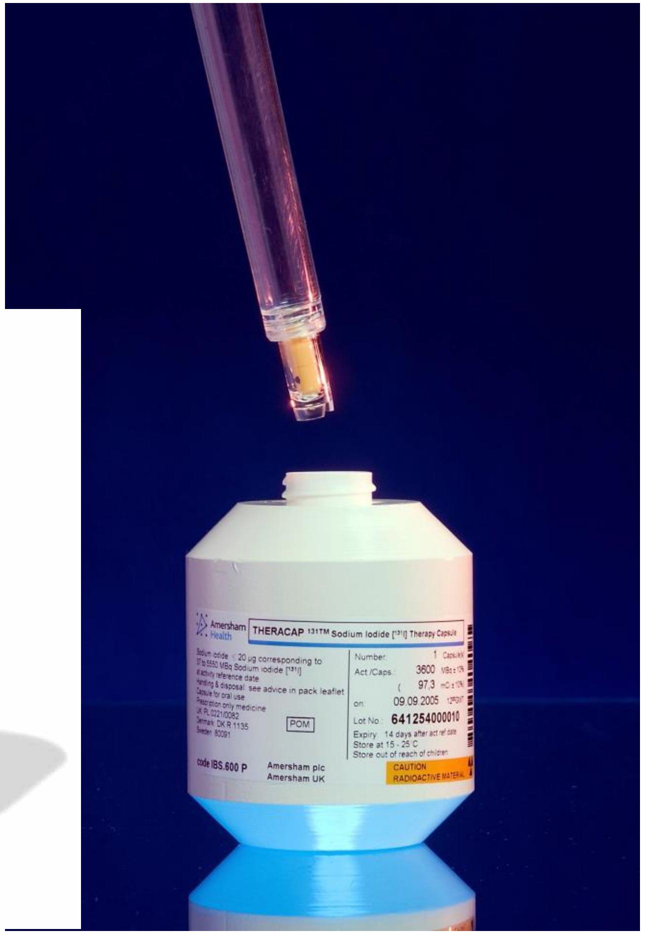
- **Common Use**: Radioiodine therapy is widely used across Europe for treating hyperthyroidism (like Graves' disease) and differentiated thyroid cancers (such as papillary and follicular thyroid cancer)

- **Guidelines and Standards**: Treatment follows guidelines set by organizations like the EANM and national societies and health bodies to ensure effectiveness, and standardized dosing protocols
  → fixed activities vs dosimetry

- **Hospitalization Rules**: Some European countries require hospital stays after therapy depending on the dose administered, while others allow outpatient treatment if radiation exposure to others remains below legal limits

- **Access and Availability**: Access to radioiodine therapy is generally good across Europe, but waiting times and availability can vary significantly between countries and even between regions within a country
  → however, availability needs to be watched: very recently, closure of production facility in Germany

Iodine-131 – Capsules - Treatment of thyroid diseases



Iodine-131 – mIBG therapy

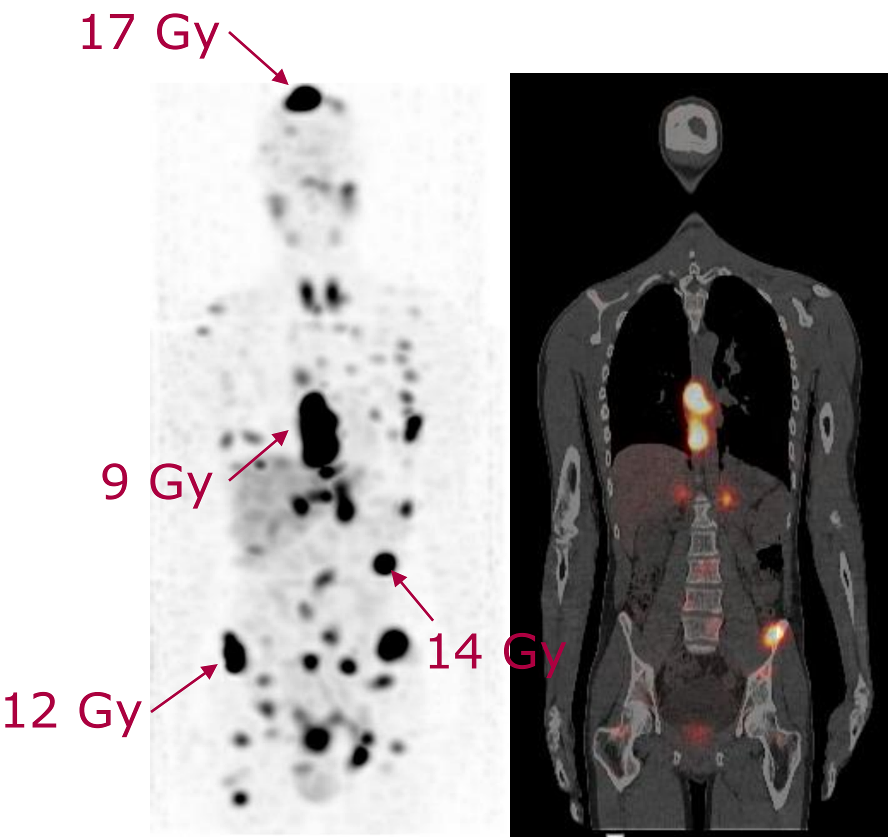
Meta-iodobenzylguanidine, or Iobenguane

Indication: Treatment of

- phaeochromocytoma
- paraganglioma
- carcinoid tumour
- Stage III or IV neuroblastoma
- Metastatic or recurrent medullary thyroid cancer

- usual single-administered activities range between 3.7 and 11 GBq, may be modified for medical reasons

♂ 17 y, met. Neuroblastoma
4,2 GBq I-131-mIBG
Intratherapeutic Dosiemtry



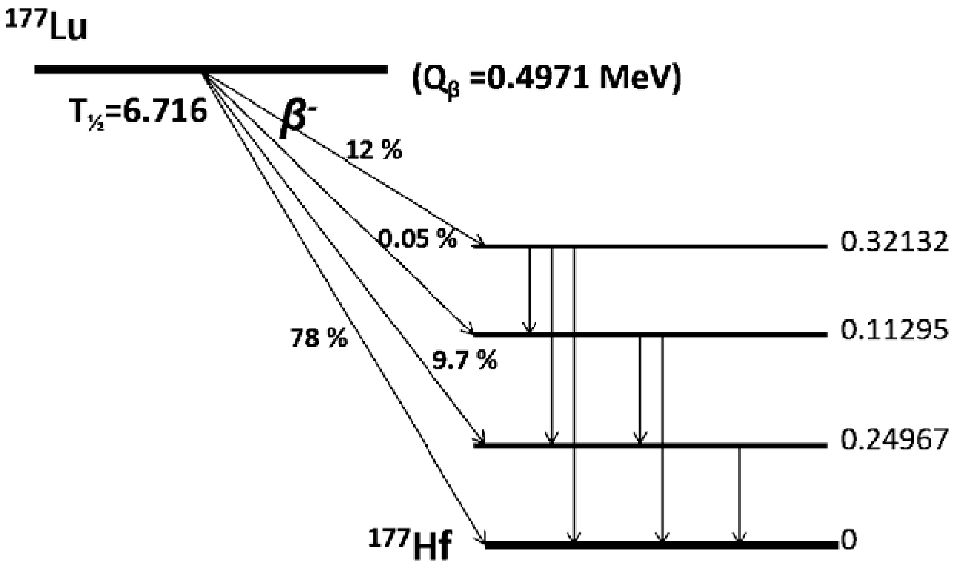
Iodine-131 – Take home

- Iodine-131 is a useful as a therapeutic agent, due to emission of beta particles
  - used for I-131-tretament of thyroid diseases (malign and benign)
  - ^{131}I-mIBG-therapy of neuroendocrine tumors
- gamma rays are also emitted → useful for imaging, need to be considered in radiation protection
- at environmental temperature, Iodine is a gas
  → even when it is in solution or embedded in a capsule, it is volatile and it is released in air
- Iodine capsules are solid radioactive source, but not a sealed source !
- In the decay of ^{131}I, radioactive ^{131m}Xe (T1/2 = 11.9 d) is produced in little amount (~ 1 %)
- In addition to any consideration on shielding and prevention of surface contamination, Iodine-131 should ALWAYS be manipulated within a vented hood

LUTETIUM-177

Lutetium-177

Physical Half-Life: 6.7 d



PHYSICAL DATA

Gamma
113 keV (6% abundance)
208 keV (11% abundance)

Beta
Betas: 490 keV (79% abundance/max)
160 keV (average)

Maximum Beta Range in Water: 1,4 mm
Maximum Beta Range in Air: ~140 cm

SHIELDING

Betas and electrons (complete)
1,5 mm of plastic

Gamma and X-rays
HVL (Lead): 0,6 mm
TVL (Lead): 2,1 mm

INTERNAL EXPOSURE FOR STAFF

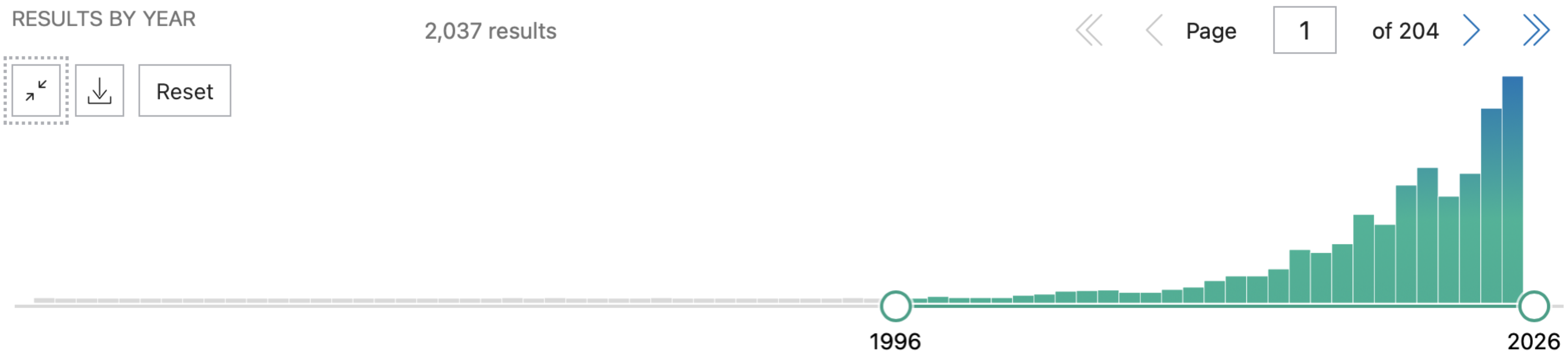
Critical Organ: Lower Large Intestine (ingestion)
Lung (inhalation)

Effective Doses per Unit intake (Sv/Bq)
Ingestion: 6,43E-9
$ALI_{ingestion}$ ~ 3 MBq

Inhalation: 3,33E-9
$ALIi_{nhalation}$ ~ 6 MBq

http://www.hpschapters.org/northcarolina/NSDS/177LuPDF.pdf

Use of Lutetium-177



Pubmed.org
Keywords: Lutetium-177 OR Lu-177

Why Lutetium-177 ?

- commercially available
- favourable physical properties
  - medium energy β^-emitter ($E_{\beta max}$ = 0.497 MeV)
  - half-life of 6.7 days
  - co-emission of low energy gammas (E_γ = 113 and 208 keV
- favorable radiochemistry
  - forms very stable complexes with DOTA and similar chelators
  - compatible with well-established targeting vectors
- clinical success (treatment of NET and PCa)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

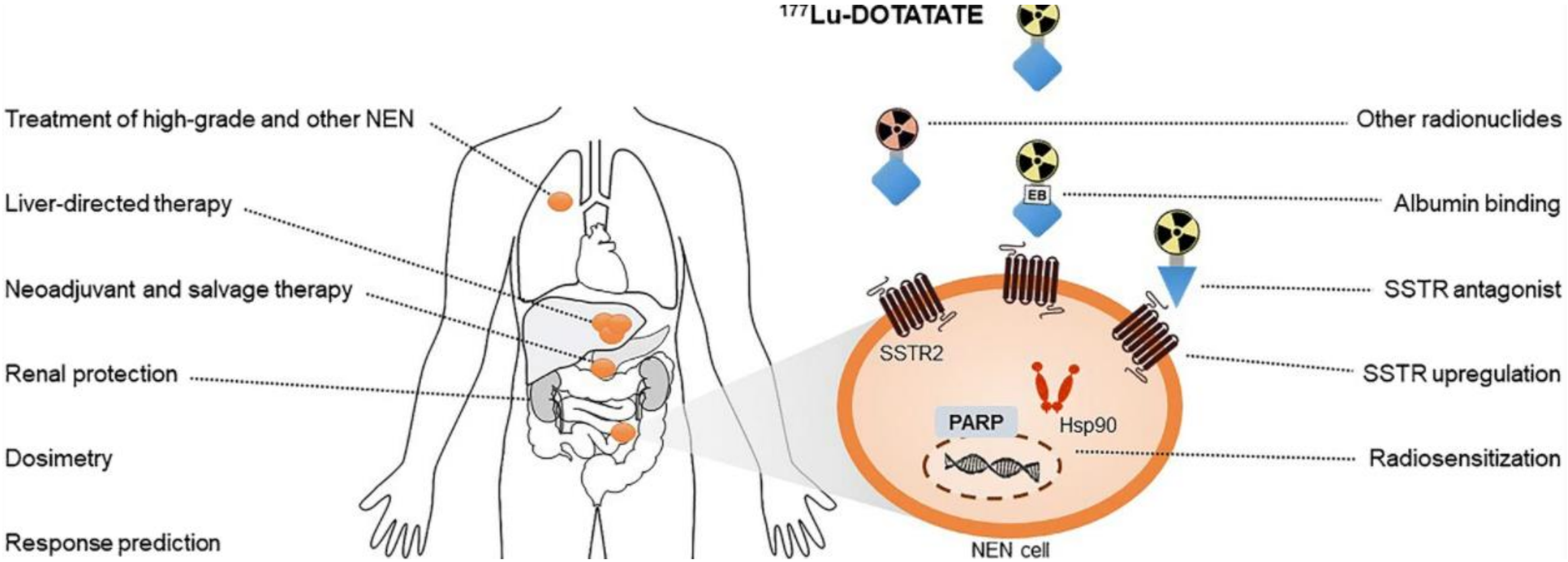
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

[^{177}Lu]Lu-DOTA-TOC / DOTA-TATE-therapy - Treatment option for neuroenodicrine tumors

- Neuroendocrine tumors (NET) are a relatively rare disease – incidence ~ 0,2 / 100.000
- most of the NET are diagnosed at advanced stages
- if local treatment isn’t possible, systemic therapies are needed (chemo, immunotherapy, somatostatin analogues, …)
- PRRT – Peptide receptor radionuclide therapy, a second or third-line therapy for treatment of NET



Taal BG, Visser O. Neuroendocrinology. 2004;80 Suppl 1:3-7.
Minczeles, N et al. Curr Oncol Rep 23, 46 (2021)

[^{177}Lu]Lu-DOTA-TOC / DOTA-TATE-therapy - Treatment option for neuroenodicrine tumors

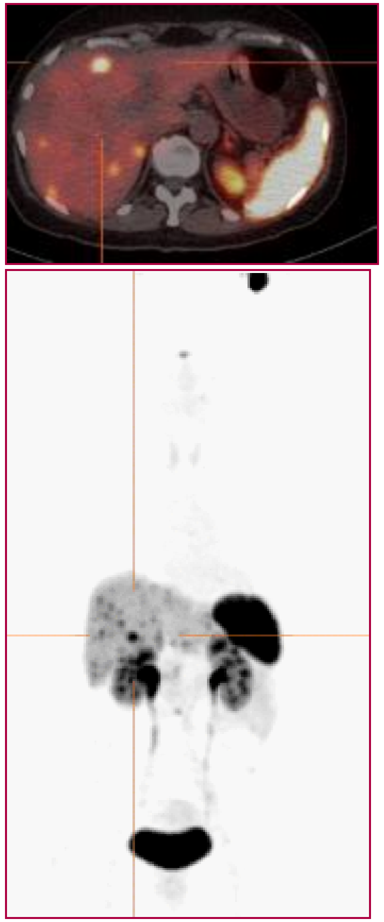
- Therapy has been developed and optimized mainly in the Netherlands (Rotterdam group), Italy, Sweden and Germany
- NETTER-I- Phase III-trial → major breakthrough
  - showed significant improvements in progression free survival and response rate
  - approved by FDA, EMA for GEP-NET–> [^{177}Lu]Lu-DOTA-TATE (Lutathera®)

- Lutathera® treatment:
  - 4 cycles with 6-10 weeks intervals
  - 7.4 GBq prescribed activity (depending on kidney function) infused in 30 min
  - infusion of amino acids for renal protection

Strosberg J et al. N Engl J Med 2017; 376:125-135

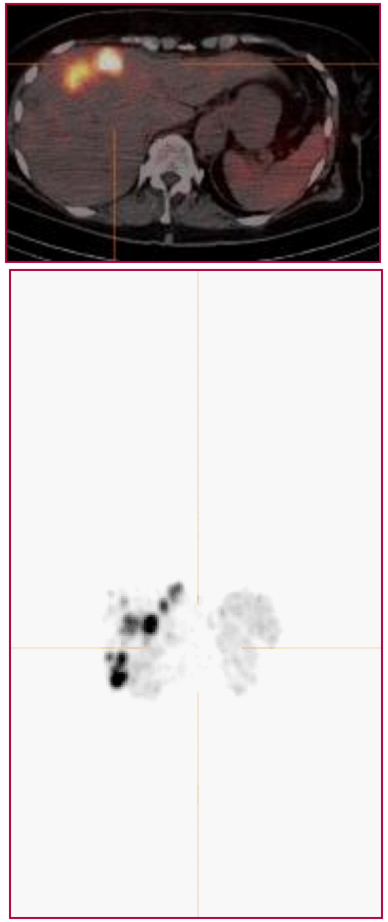
Example – patient with small intestine carcinoid

06/2015
[^{68}Ga]Ga-DOTA-TATE
PET/CT



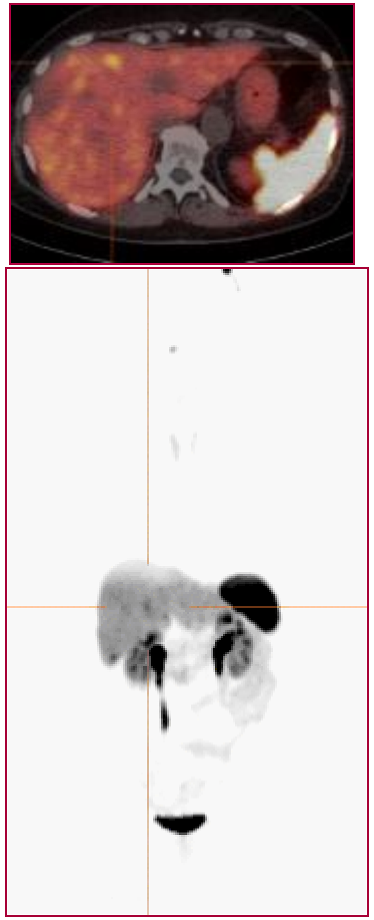
11/2017
[^{68}Ga]Ga-DOTA-TATE
PET/CT

11/2017
[^{177}Lu]Lu-DOTA-TATE
SPECT/CT



3 more cycles of
[^{177}Lu]Lu-DOTA-TATE

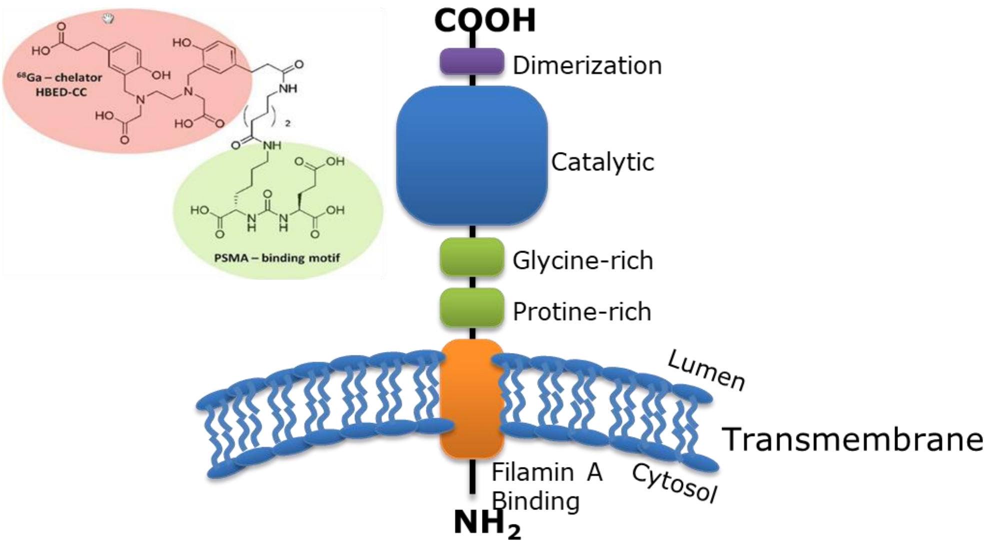
11/2018
[^{68}Ga]Ga-DOTA-TATE
PET/CT



therapie with sandostatin

[^{177}Lu]Lu-PSMA-617-therapy – treatment of prostate cancer

- Prostate cancer is the most common cancer and the third leading cause of cancer death among men in Europe.
- Androgen deprivation is the mainstay of advanced PC treatment; despite initial responses, almost all patients progress to CRPC/mCRPC
- For treatment of mCRPC a number of systemic therapies are available
- For radiotherapy, predominantly lutetium-177 labeled peptides targeting PSMA are used
- early clinical studies on the use of [^{177}Lu]Lu-PSMA therapy have yielded promising results
- **VISION-trial, phase III-study**
  - 831 of 1179 screened patients were randomized
  - 6 x 7.4 GBq/cycle with 6-8 weeks interval

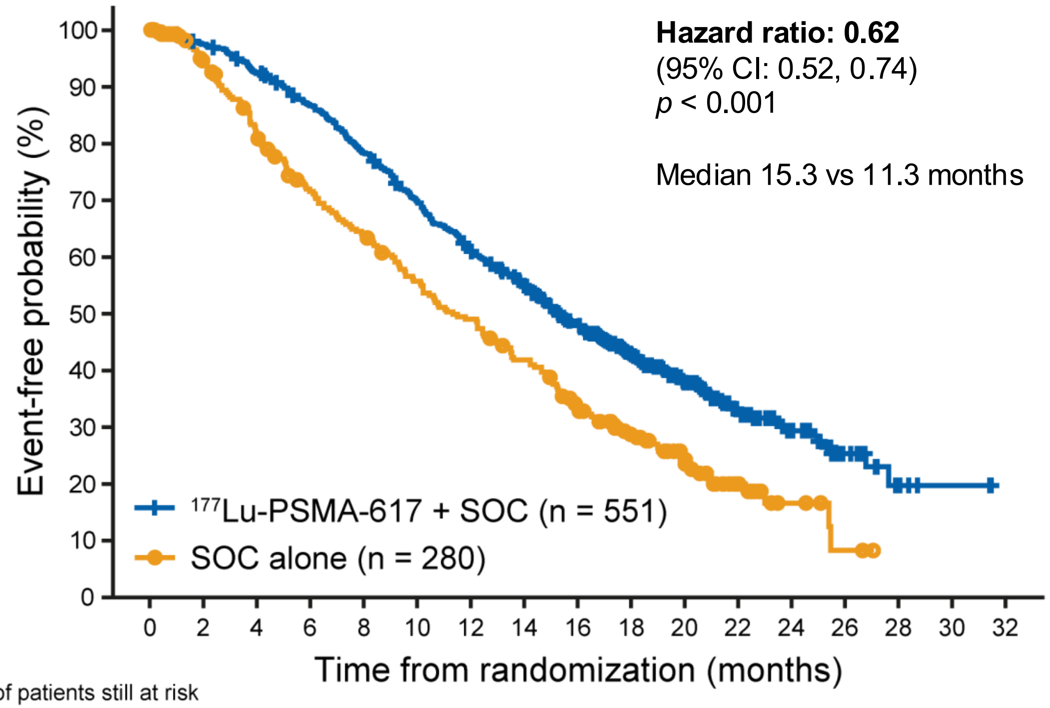


Eder et al., Bioconjugate Chem 2012

Alternate primary endpoints

^{177}Lu-PSMA-617 prolonged overall survival

All randomized patients (N = 831)

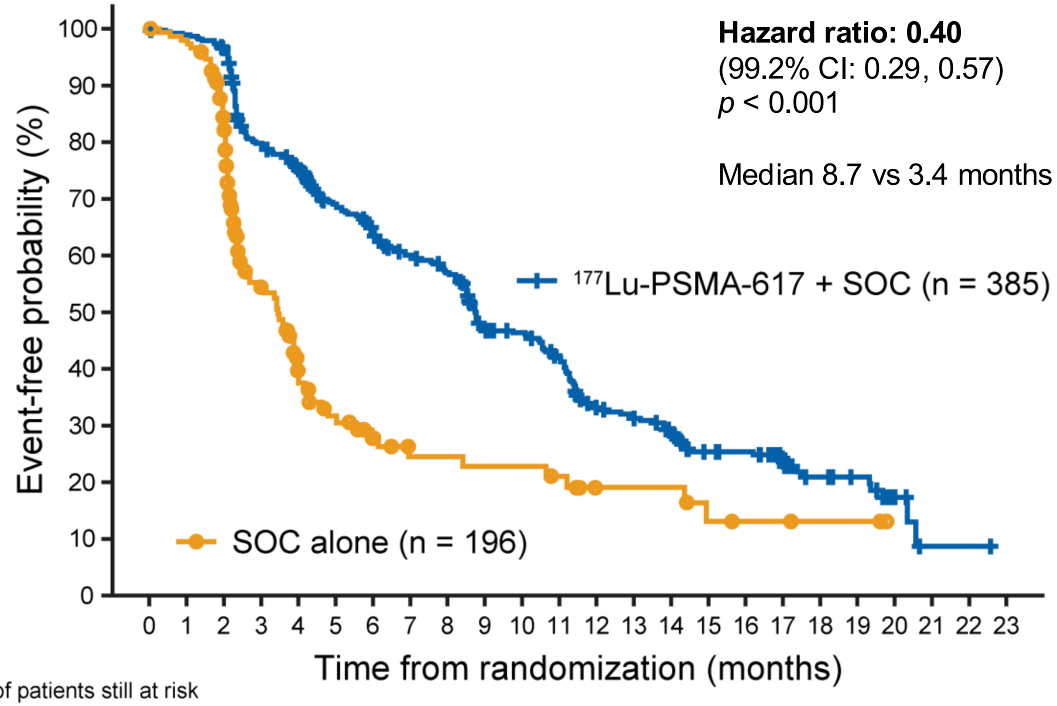


Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

^{177}Lu-PSMA-617 improved rPFS

rPFS analysis set (n = 581)



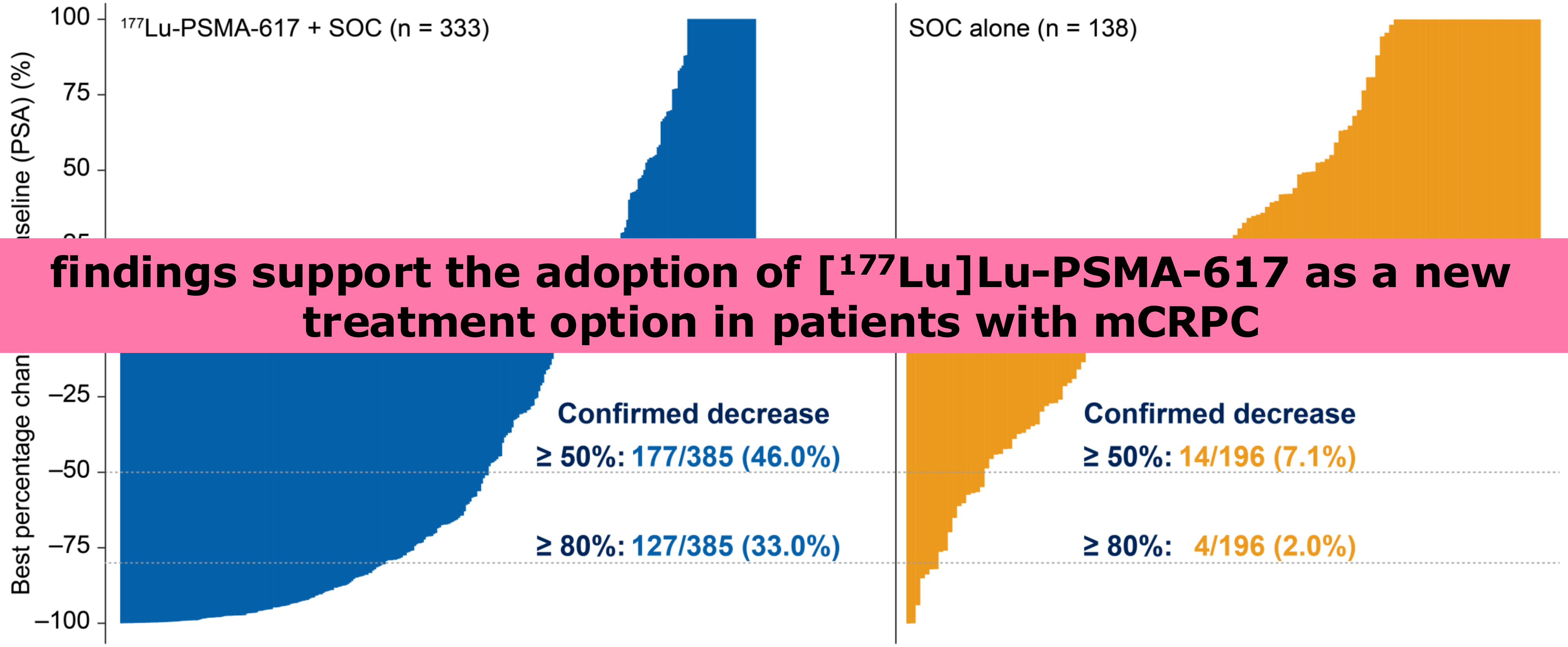
Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SOC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

Sartor, O.; de Bono, J.; Chi, K.N.; Fizazi, K.; Herrmann, K.; Rahbar, K.; Tagawa, S.T.; Nordquist, L.T.; Vaishampayan, N.; El-Haddad, G.; et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med* **2021**

Secondary endpoint: PSA responses

PSA responses favoured the ^{177}Lu-PSMA-617 arm among evaluable patients



findings support the adoption of [^{177}Lu]Lu-PSMA-617 as a new treatment option in patients with mCRPC

Sartor, O et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med* **2021**

mCRPC: [^{177}Lu]Lu-PSMA-617 therapy

Summary for Lutetium-177

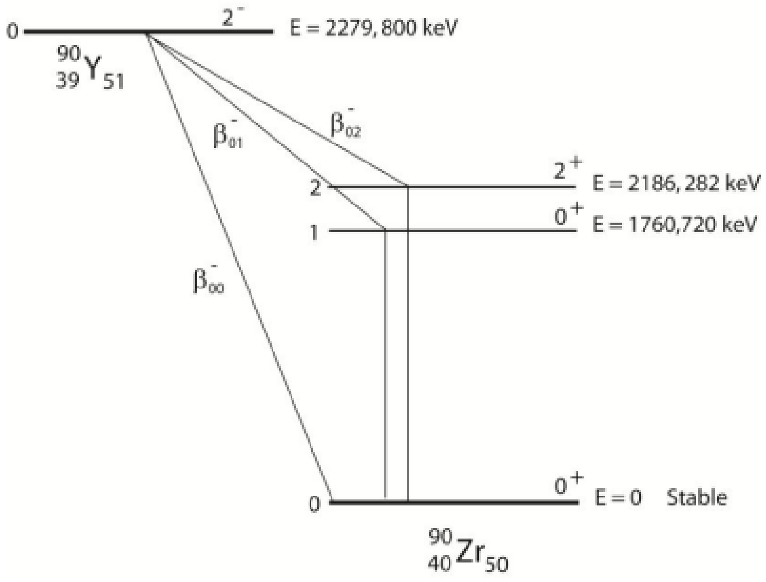
- energy emitted by beta radiation is lower compared to iodine-131
- nevertheless, therapeutic activities used can be signifcant, e.g 7400 MBq !
- ^{177}Lu emits a gamma dose per unit of acivity lower even to ^{99m}Tc
- widely used in treatment of NET and prostate cancer
- an increased use of Lutetium-177 will be seen in future

→ see lecture on non-I-131-therapies

YTTRIUM-90

Yttrium-90

Physical Half-Life: 2.7 d



PHYSICAL DATA

Positron
0.015 % abundance → 511 keV

Beta
2284 keV (99% abundance / maximum)

Maximum Beta Range in Water: 10,7 mm
Maximum Beta Range in Air: ~ 870 cm

SHIELDING

Betas and electrons
9 mm of plastic

Gamma and X-rays
none

considerable Bremsstrahlung
(4E-03 µGy/h per 1 MBq @ 100 cm)

INTERNAL EXPOSURE FOR STAFF

Critical Organ: Lungs

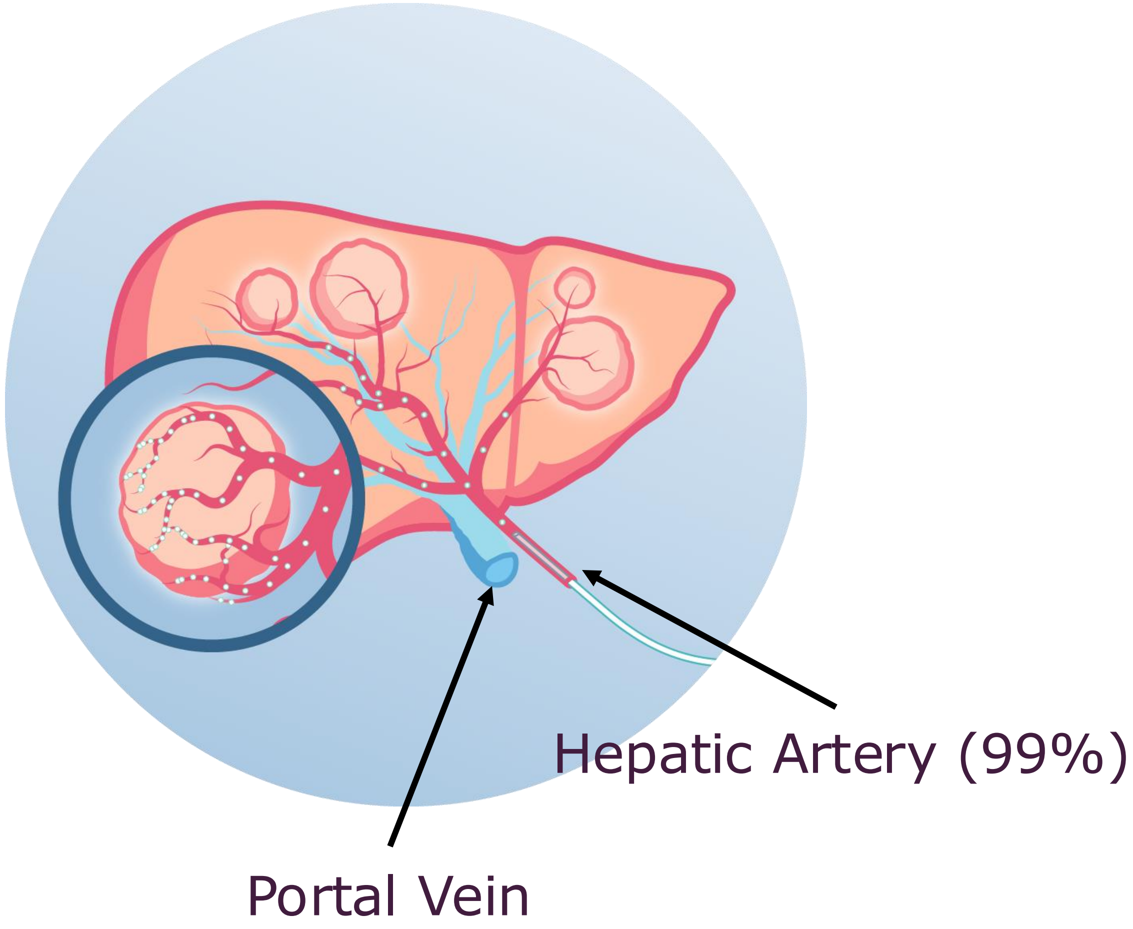
Effective Doses per Unit intake (Sv/Bq)
Ingestion: 2.7E-9
$ALI_{ingestion}$ ~ 7.4 MBq

Inhalation: 1.6E-9
$ALI_{inhalation}$ ~ 12 MBq

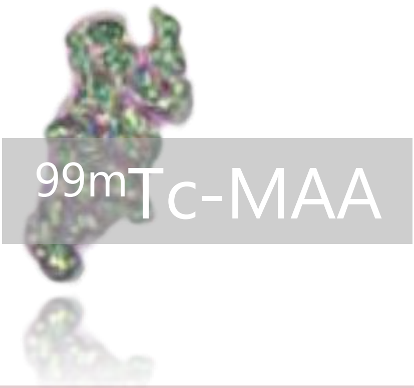
Delacroix et al. RADIONUCLIDE AND RADIATION PROTECTION DATA HANDBOOK 2002

Principles of Selective intra-arterial radiation therapy (SIRT)

- Option to treat patients with primary and secondary liver cancer
- majority of liver tumors receive blood supply by the hepatic artery
- Minimally invasive procedure
- Trans-femoral catheter access to hepatic artery and the tumour supplying vessels
- Radioactive microspheres to deliver radiation directly via the hepatic artery (catheter) to the site of the liver tumors



SIRT TREATMENT ALGORITHM WITH 90Y MICROSPHERES



Work-up
- Lung shunt assessment
- Intrahepatic distribution
- Extrahepatic deposition

SIRT Treatment

Dose Verification

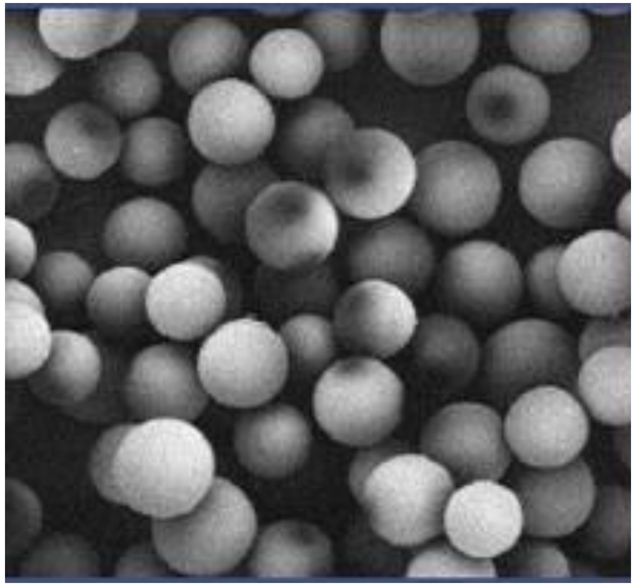
Treatment follow-up
(e.g. SPECT/CT PET/CT)

two Yttrium-90 based devices

- First of all, SIRT systems are approved as medical devices, not radiopharmaceuticals!

- Resin microspheres (SIR-Spheres®, Sirtex)
  - ^{90}Y is coated on the surface of the spheres
  - particle size: 20-60 µm; activity per particle: 50 Bq
  - about 20-40 million particles per administration
  - uniform dose biodistribution

- Glass microspheres (TheraSphere®, Boston Scientific)
  - ^{90}Y is produce by neutron activation inside the glass matrix (^{89}Y is an integral constituent of the glass)
  - particle size: 20-30 µm; activity per particle: 2500 Bq
  - about 1.2 to 8 million particles per administration
  - less embolic effect on microvessels
  - potential influence of gravity on biodistribution



Practical implementation of the SIRT

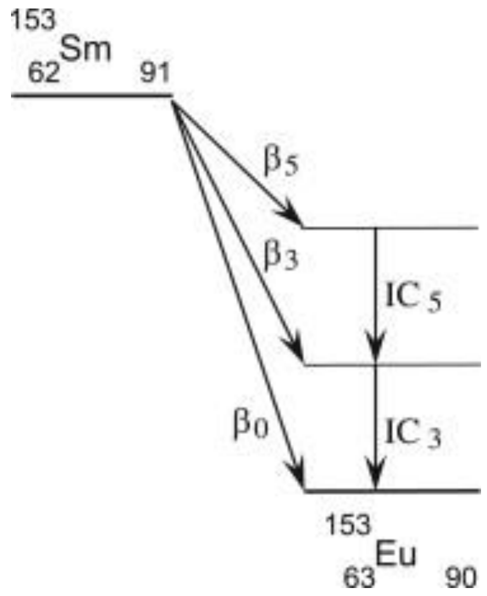
sterile
(radiologist)

non-sterile
(nuclear medicie physician)

Practical implementation of the SIRT

SAMARIUM-153

SAMARIUM-153 Physical Half-Life: 1.95 d



PHYSICAL DATA

Gamma
41 keV (49% abundance)
103 keV (28% abundance)

Beta
634 keV (35% abundance)
703 keV (44% abundance)

Maximum Beta Range in Water: 3 mm
Maximum Beta Range in Air: ~260 cm

SHIELDING

Betas and electrons
2.4 mm of plastic

Gamma and X-rays
HVL (Lead): <1 mm
TVL (Lead): <1 mm

INTERNAL EXPOSURE FOR STAFF

Critical Organ: lower large intestine

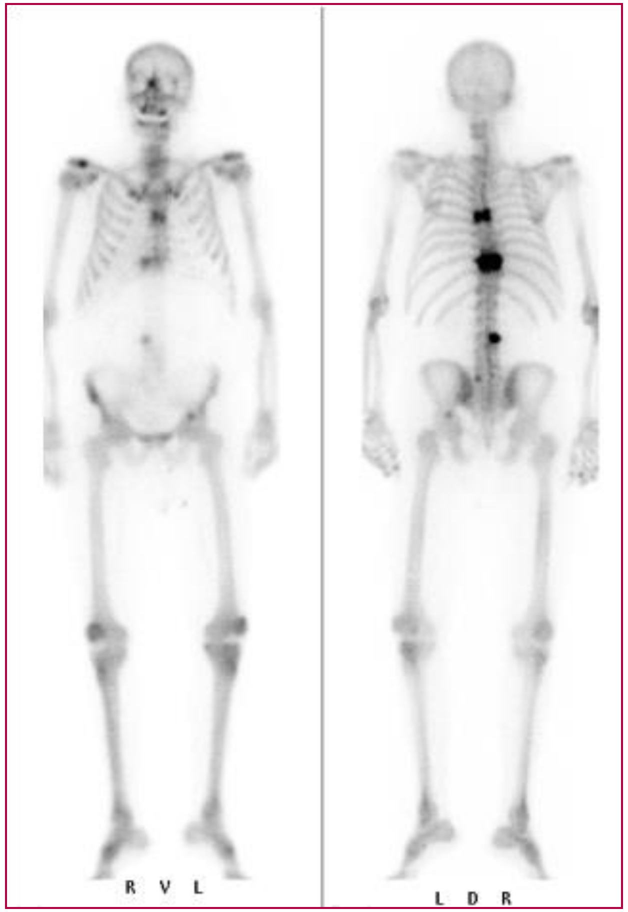
Effective Doses per Unit intake (Sv/Bq)
Ingestion: 7.4E-10
$ALI_{ingestion}$ ~ 27 MBq

Inhalation: 6.8E-10
$ALIi_{nhalation}$ ~ 29 MBq

SAMARIUM-153-EDTMP THERAPY

- limitations of other therapies
  - analgetics
  - bisphosphonates
  - chemotherapy
  - hormonal therapy and external beam radiotherapy
- bone-seeking radiopharmaceuticals have an important role in palliation of pain from bone metastases
- $[^{153}Sm]Sm$-EDTMP is indicated for the treatment of bone pain in patients with multiple, painful skeletal osteoblastic metastases that uptake technetium-labeled bisphosphonates (^{99m}Tc).
- typical activity administered (according to Quadramet spc) is 37 MBq/kg

Bone Scan
730 MBq $[^{99m}Tc]Tc$-DPD



3500 MBq $[^{153}Sm]Sm$-EDTMP

RHENIUM-188

Rhenium -188

$^{188}W/^{188}Re$-Generator

PHYSICAL DATA

Half Life
17,0 hours

Gamma
155 keV (15% abundance)

Beta
Betas: 2,12 keV (72% abundance/max)
784 keV (average)

Maximum Beta Range in Water: ~ 1 cm
Mean Beta Range in Water: ~ 0,3 cm
Maximum Beta Range in Air: ~ 820 cm

SHIELDING

Betas and electrons (complete)
8,3 mm of plastic

Gamma and X-rays
HVL (Lead): 3 mm
TVL (Lead): 23 mm

EXPOSURE (SKIN DOSE)

$$\Gamma_{\beta,H_{Haut}} = 1{,}8 \frac{\mu Sv}{h \cdot Bq \cdot cm^2}$$

Uniform Distribution: 2,32 mSv/h
(1 kBq/cm²)

Droplet: 1,35 mSv/h
(1 kBq)

Radionuclide and Radiation Protection Data Handbook

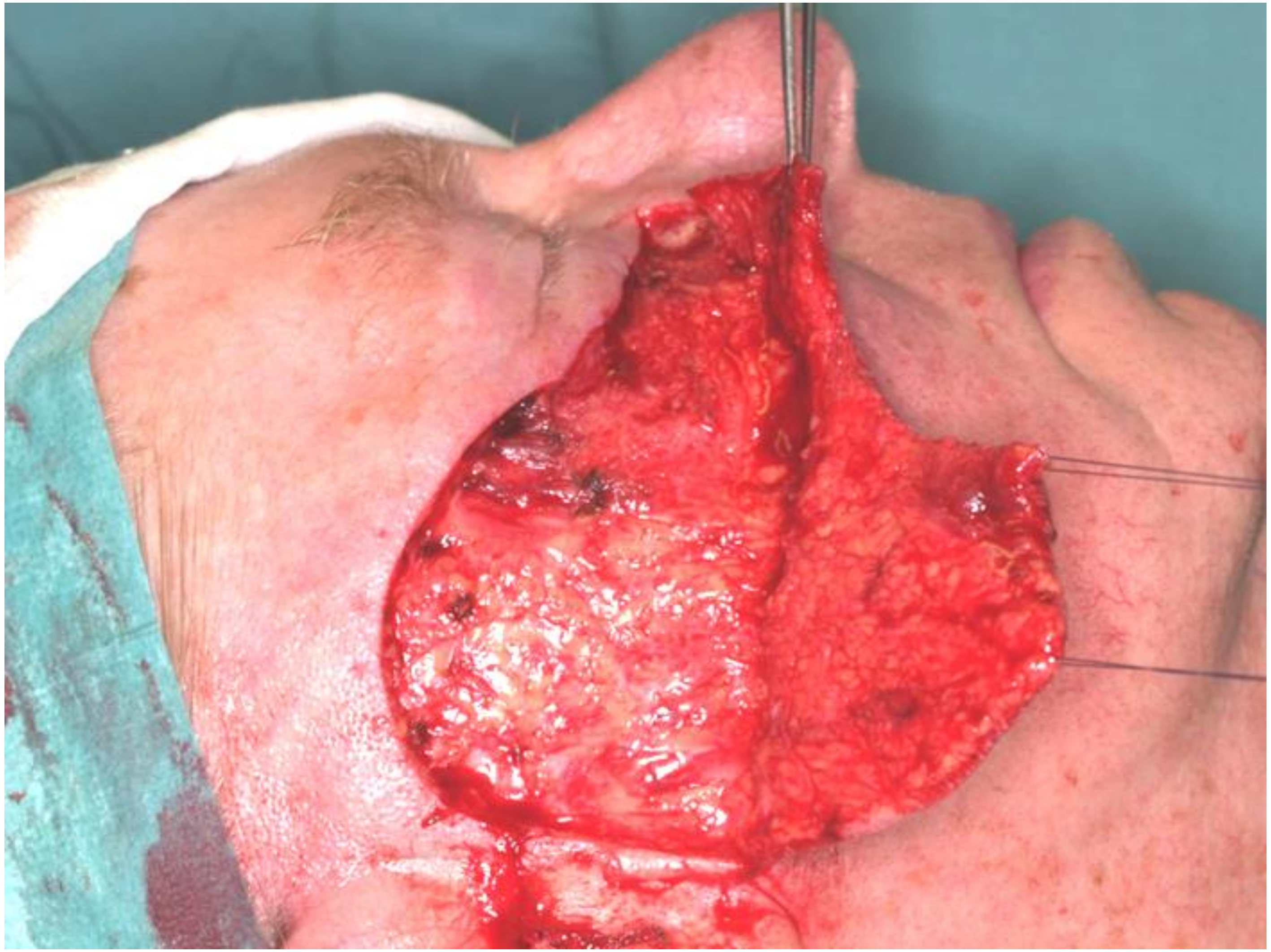
TREATMENT OF BCC - RHENIUM-SCT®

Oncobeta – Treatment of Non-Melanoma Skin Cancer

Most common tumour in humans (lifetime risk > 30%)

© J. Tietze (Dermatology, UMR)

Source: J. Tietze (Dermatology, UMR)

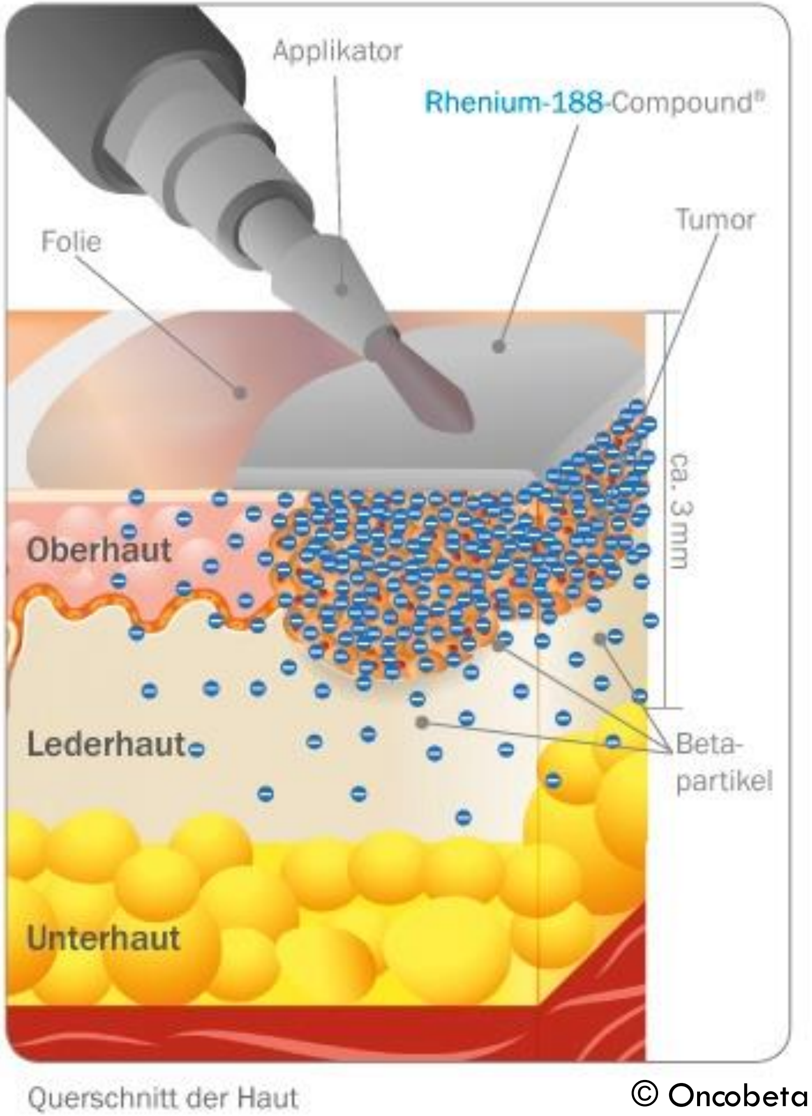


Source: J. Tietze (Dermatology, UMR)

Quelle: J. Tietze (Dermatologie, UMR)

Rhenium-SCT® - mechanism of action

- Local irradiation of the tissue surface using Re-188 → brachytherapy
- Therapeutic penetration depth of beta-emitting Re-188 is approx. 2-3 mm
- Beta particles cause damage to the first layers of skin and trigger a local immune response
- Required Activity is dervice lesion specific (depending on lesion area and depth) → Dosimetry



Rhenium-SCT® - Components of the treatment set

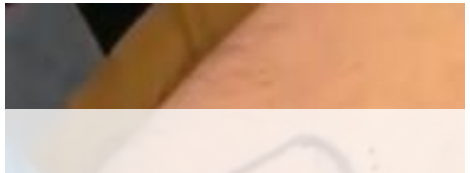
Quelle: Oncobeta

Rhenium-SCT® - Treatment Procedure

1

Mark the area to be treated (Target Area)

2



3

4

5

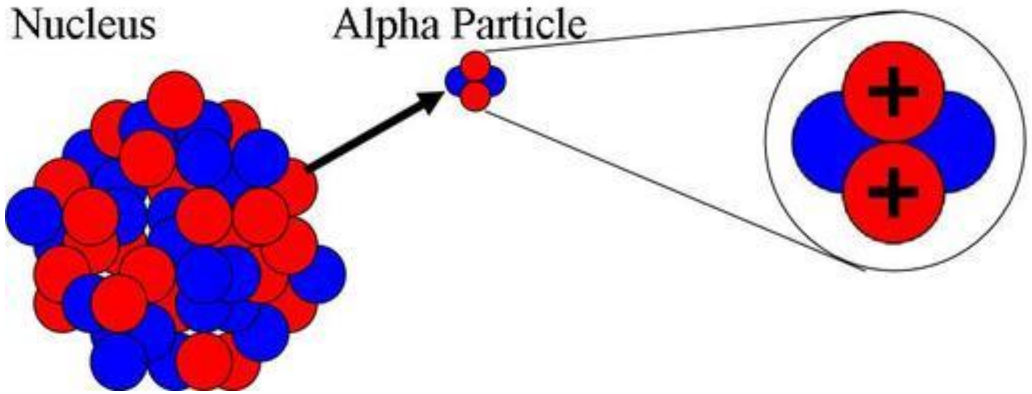
Remove foil with activity after lesion/dose specific treatment time

pretherapeutic

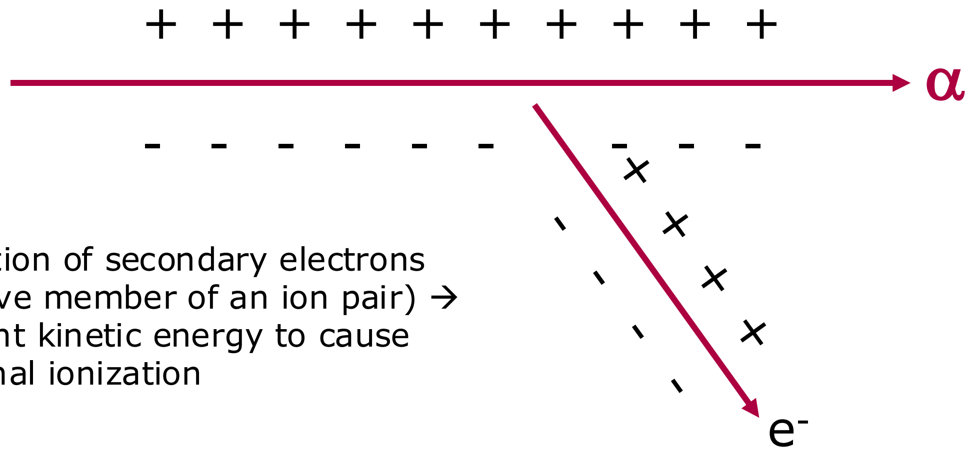
posttherapeutic (1.5 y)

ALPHA-EMITTER

Alpha Particles – Interaction with matter

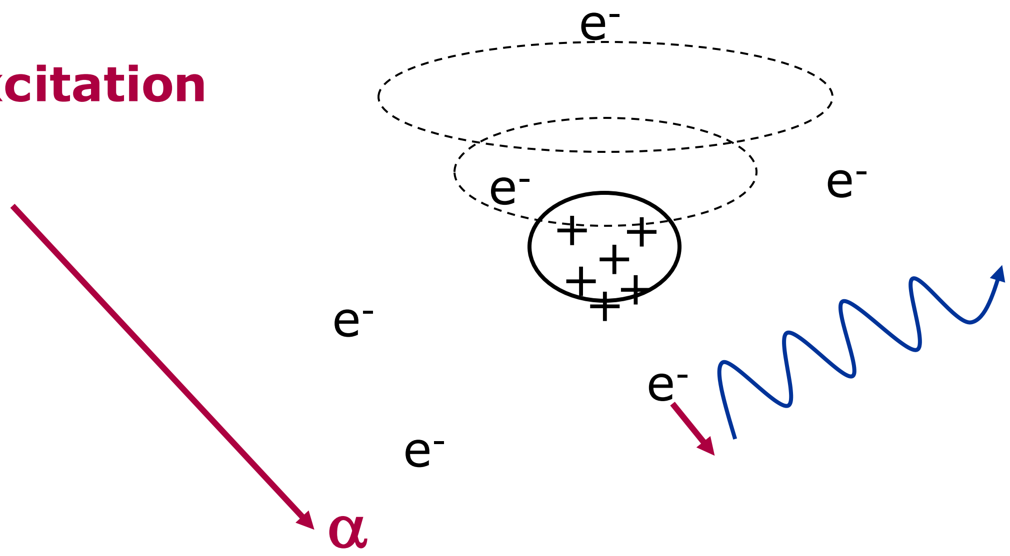


Ionization



generation of secondary electrons (negative member of an ion pair) → sufficient kinetic energy to cause additional ionization

Excitation



types of interactions

- Ionization
- Excitation

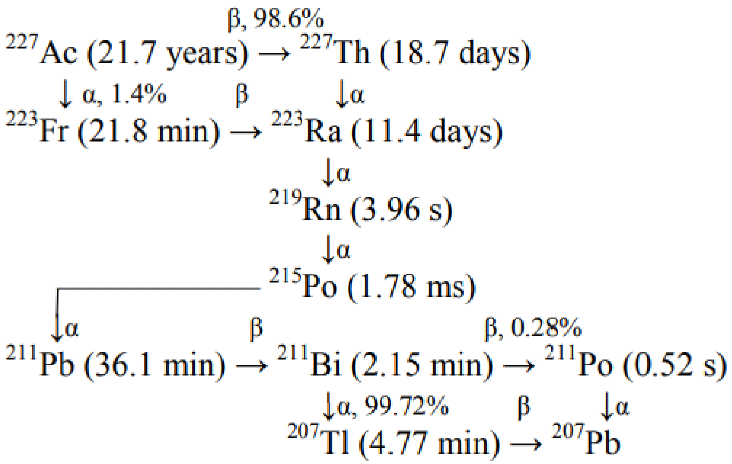
https://physicsopenlab.org/2016/02/11/alpha-%CE%B1-radioactivity/
L'Annunziata Michael F. Radioactivity. Elsevier Science B.V. 2007

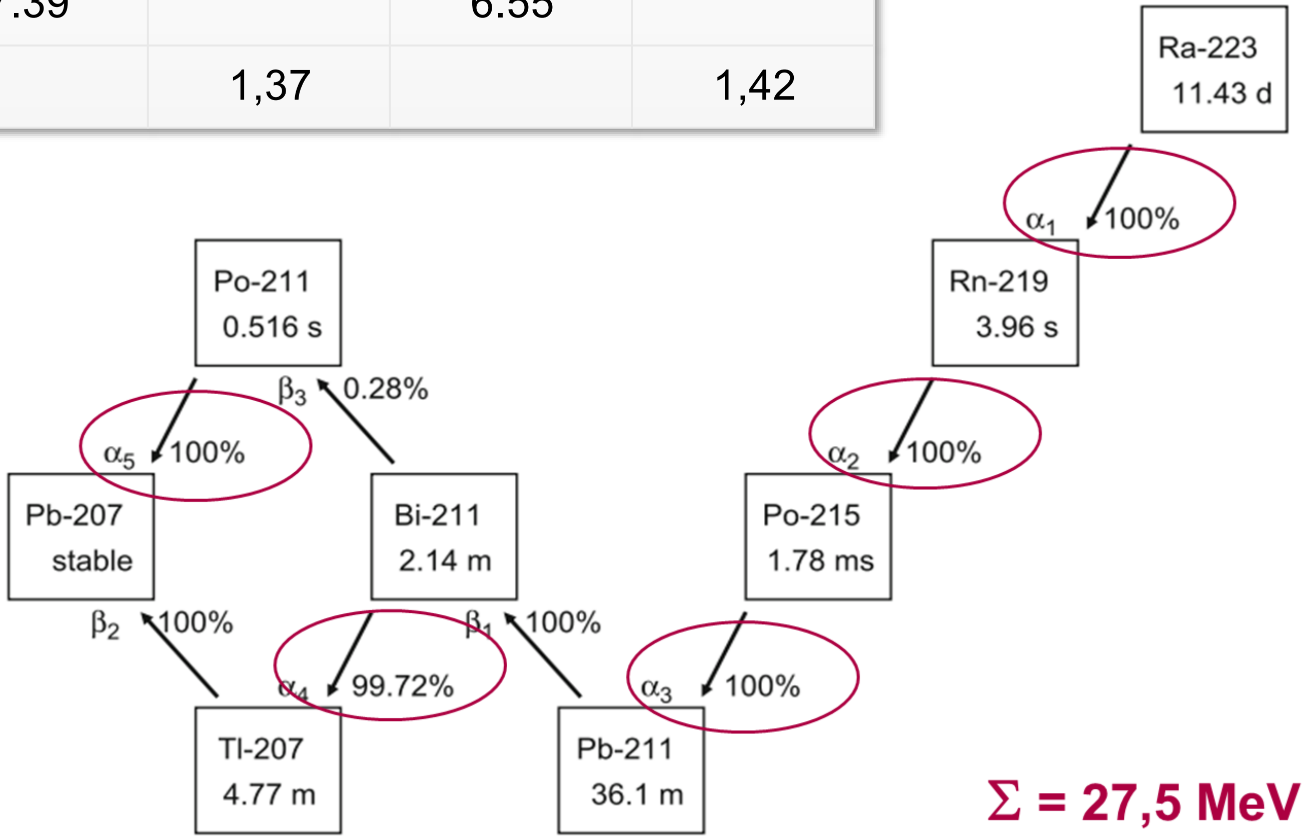
RADIUM-223

Radium-223

Parameter	^{223}Ra	^{219}Rn	^{215}Po	^{211}Pb	^{211}Bi	^{207}Tl
$t_{1/2}$	**11,43 d**	**3,96 s**	**1,78 ms**	36,1 min	**2,17 min**	4,77 min
α-energy (MeV)	5.64	6.75	7.39		6.55	
β-energy (MeV)				1,37		1,42

Ac-227 / Ra-223 generator

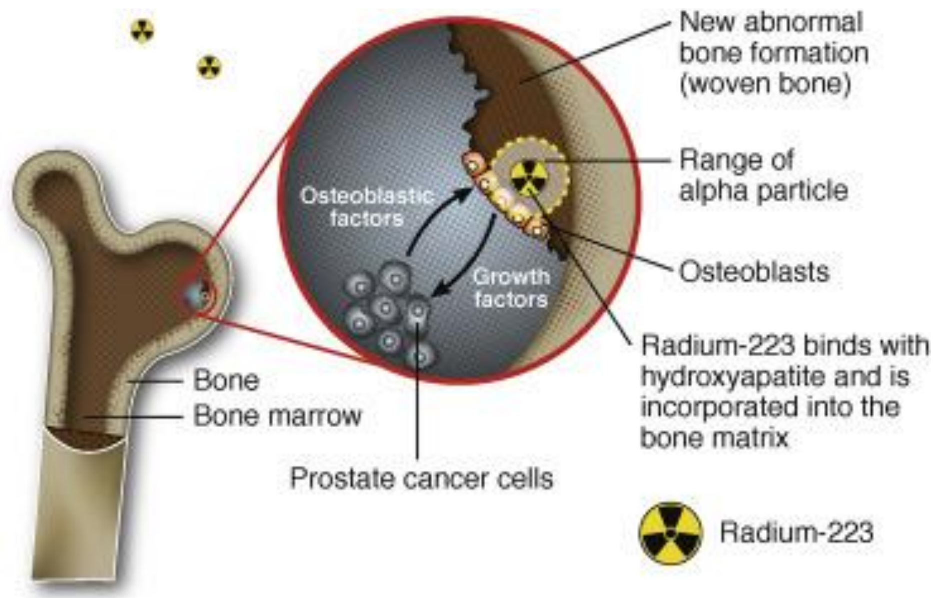




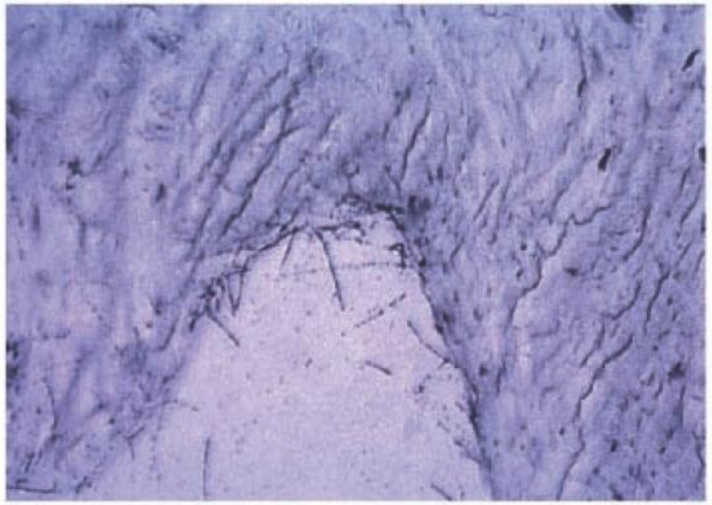
Σ = 27,5 MeV

Shishkin DN et al. Radiochemistry (53). 2011

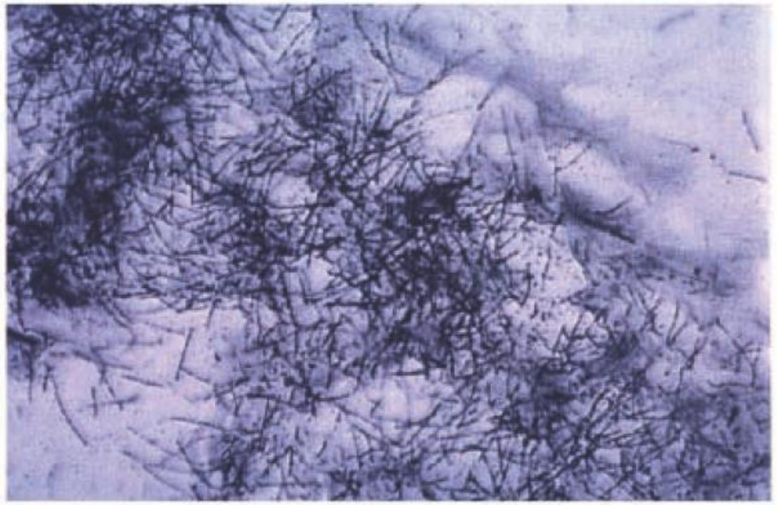
Ra-223-Dichlorid (Xofigo®)



Microautoradiography of the bone of a dog after injection ^{223}Ra



spongious bone



osteoblastic area

- energy fraction emitted as alpha particles is ~ 95 %, Σ=27.5 MeV
- fast biodistribution (~ 10 min until incorporation into bone)
- excretion is mainly with feces, ~ 5% via urine, no evidence for hepatobiliary excretion

Bruland, O. S. Clin Cancer Res 2006;12

Tai-Lung Cha, Journal of the Formosan Medical Association,Volume 116, Issue 11,2017,

Xofigo®

- intravenous administration; approved by EMA for the treatment of men with mCRPC and symptomatic bone mets without visceral mets
- applied activity: 50 kBq per kg bodyweight and cacle

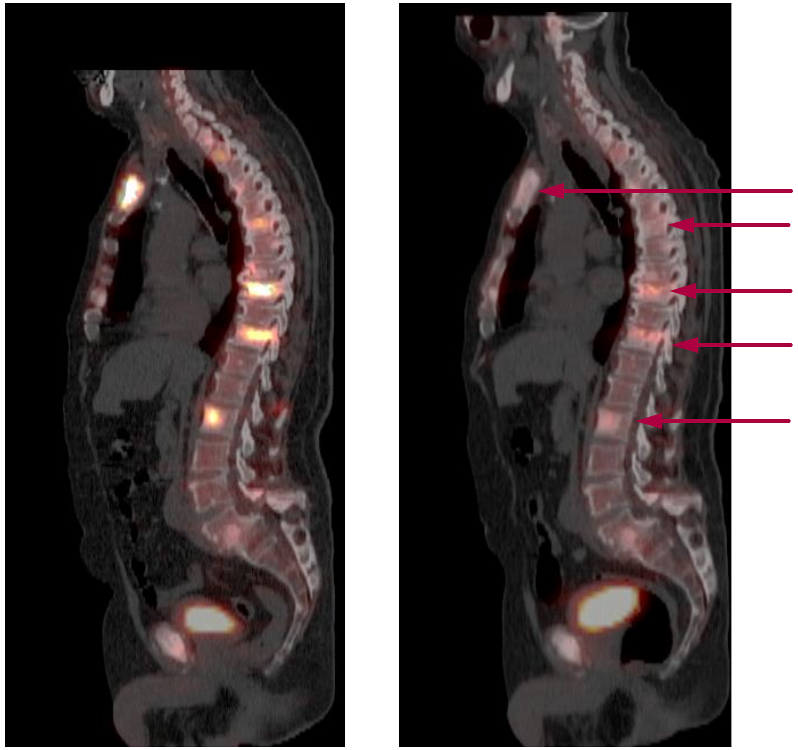
Patient Case

♂, 72 years
chemotherapy
osseous mets

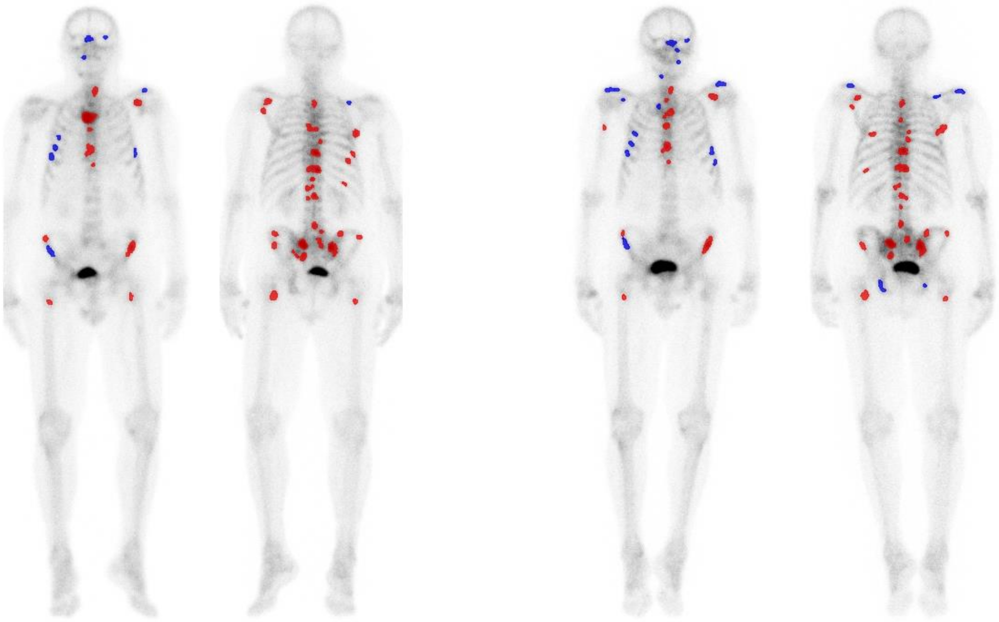
6 x 50 kBq/kg p.i. Xofigo®

Bone Scan
pre- and
postherpeutical

pretherapeutic **postherapeutic**



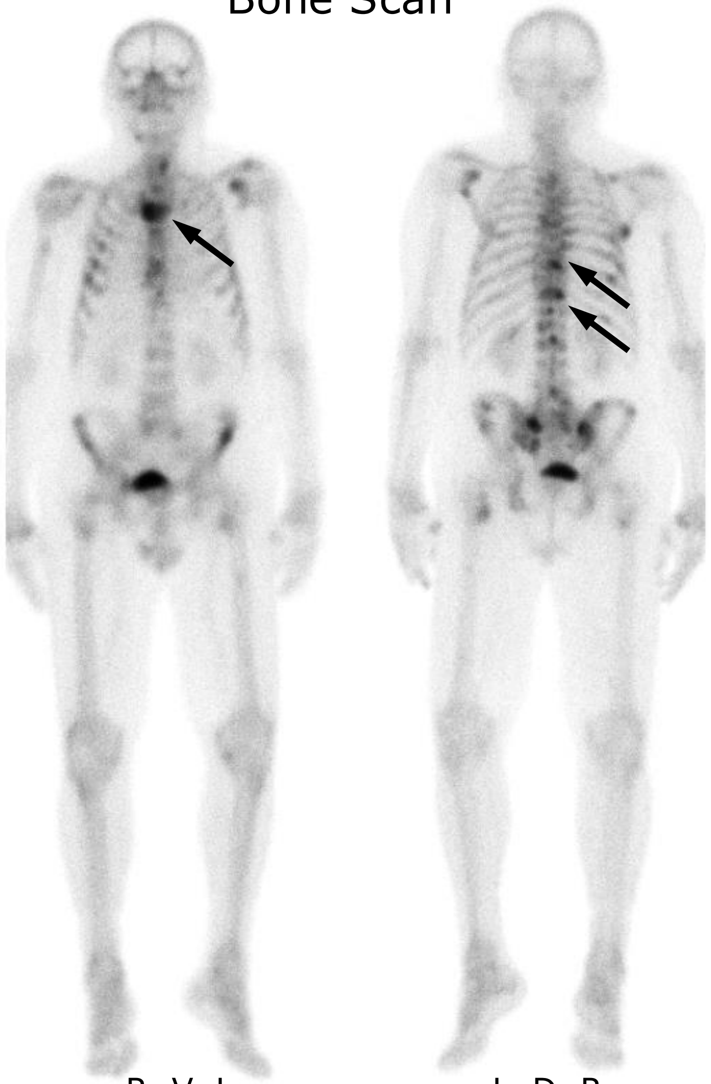
pretherapeutic **postherapeutic**

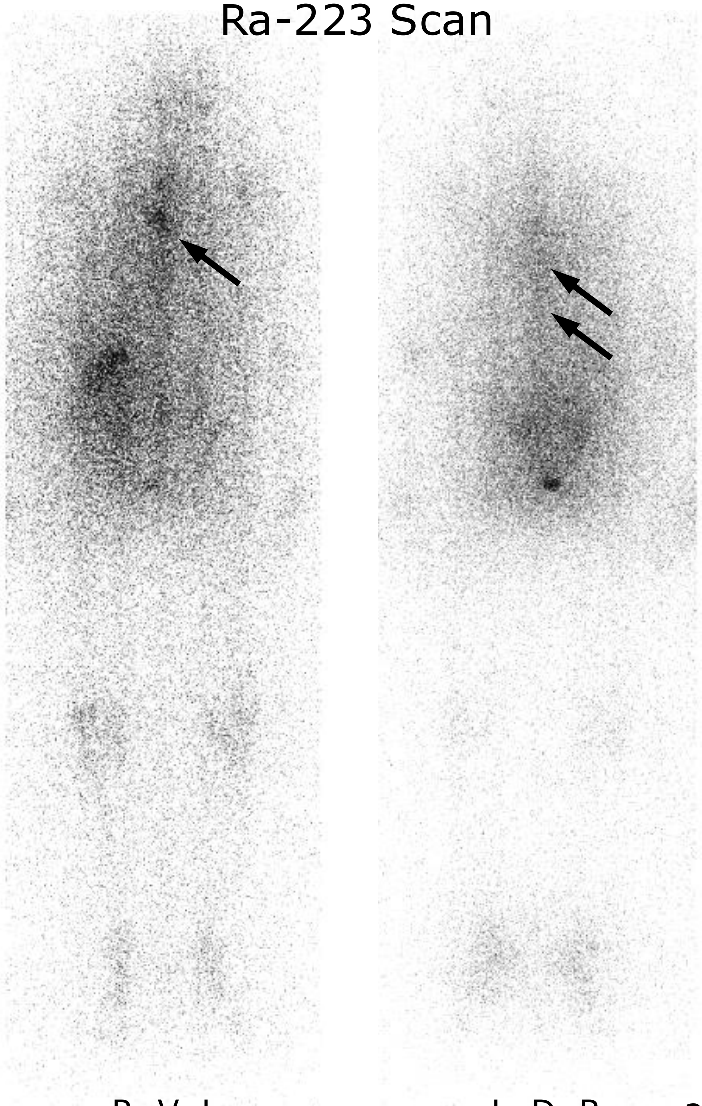


BSI [%] = 2,50

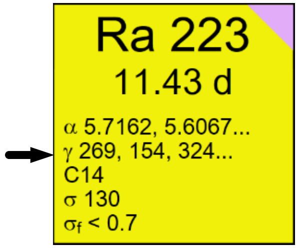
BSI [%] = 2,18

Intratherapeutic Imaging



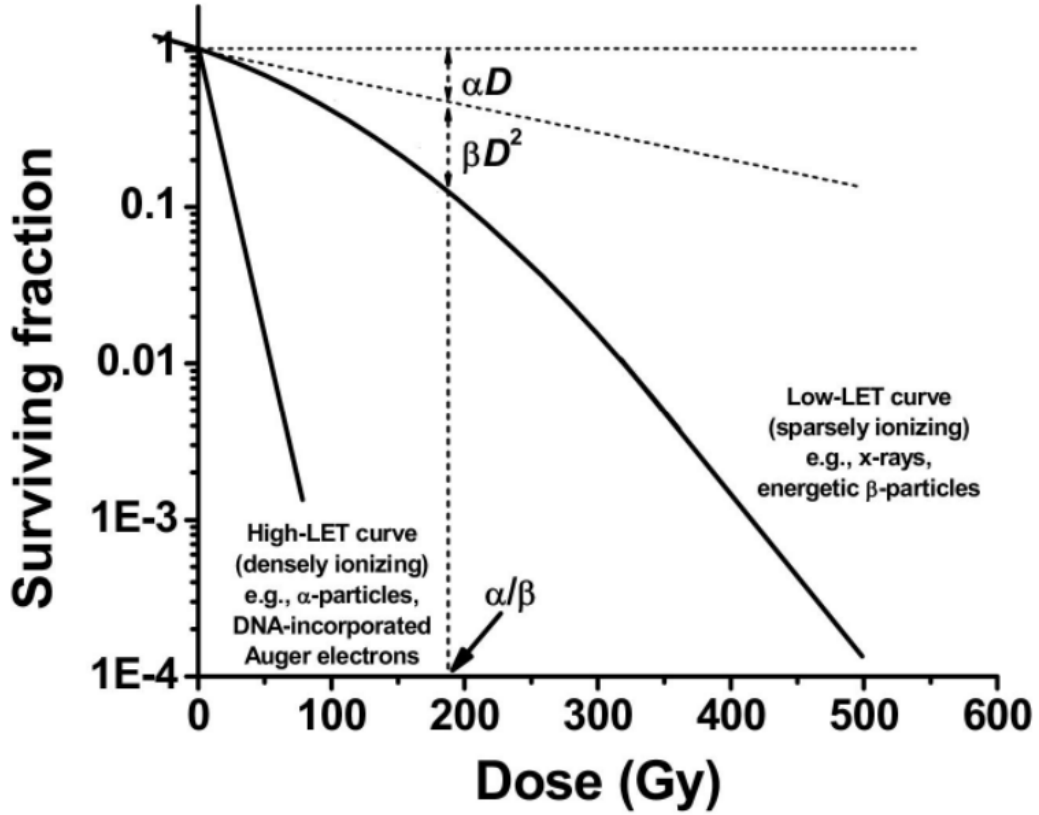


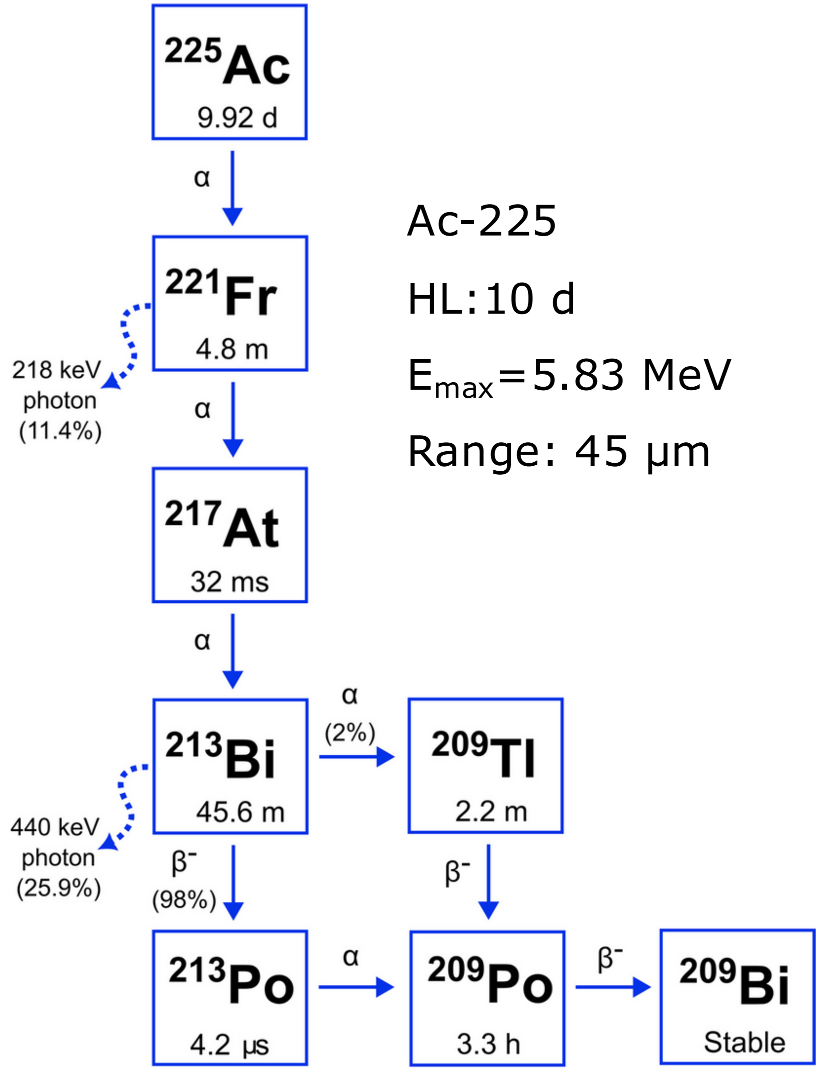
20 h p. i.



ACTINIUM-225

[^{225}Ac]Ac-PSMA-617- for treatment of mCRPC





Ac-225

HL:10 d

E_{max}=5.83 MeV

Range: 45 µm

Kassis, A.I. 2008. Therapeutic Radionuclides: Biophysical and Radiobiological Principles. Seminars in Nuclear Medicine 38, 358-366

[^{225}Ac]Ac-PSMA-617- therapy of mCRPC

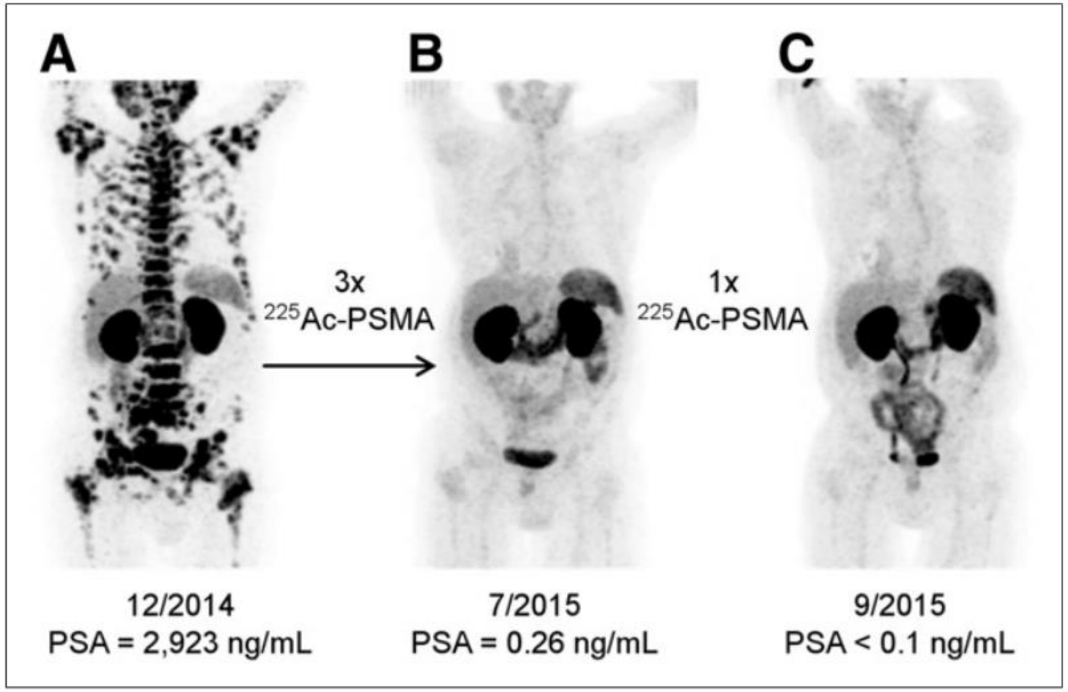


FIGURE 1. ^{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of ^{225}Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C).

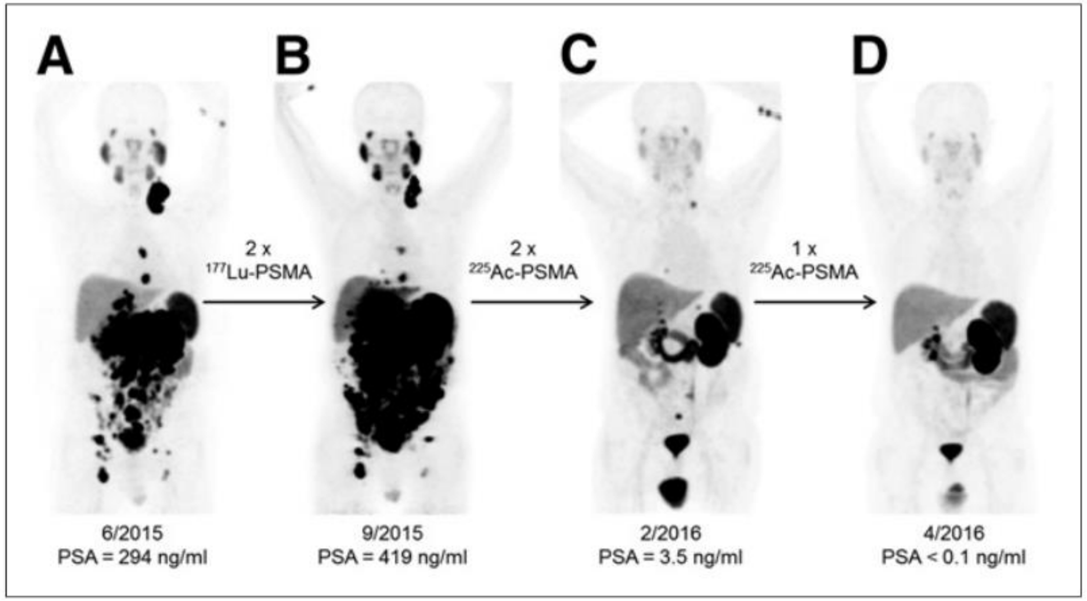
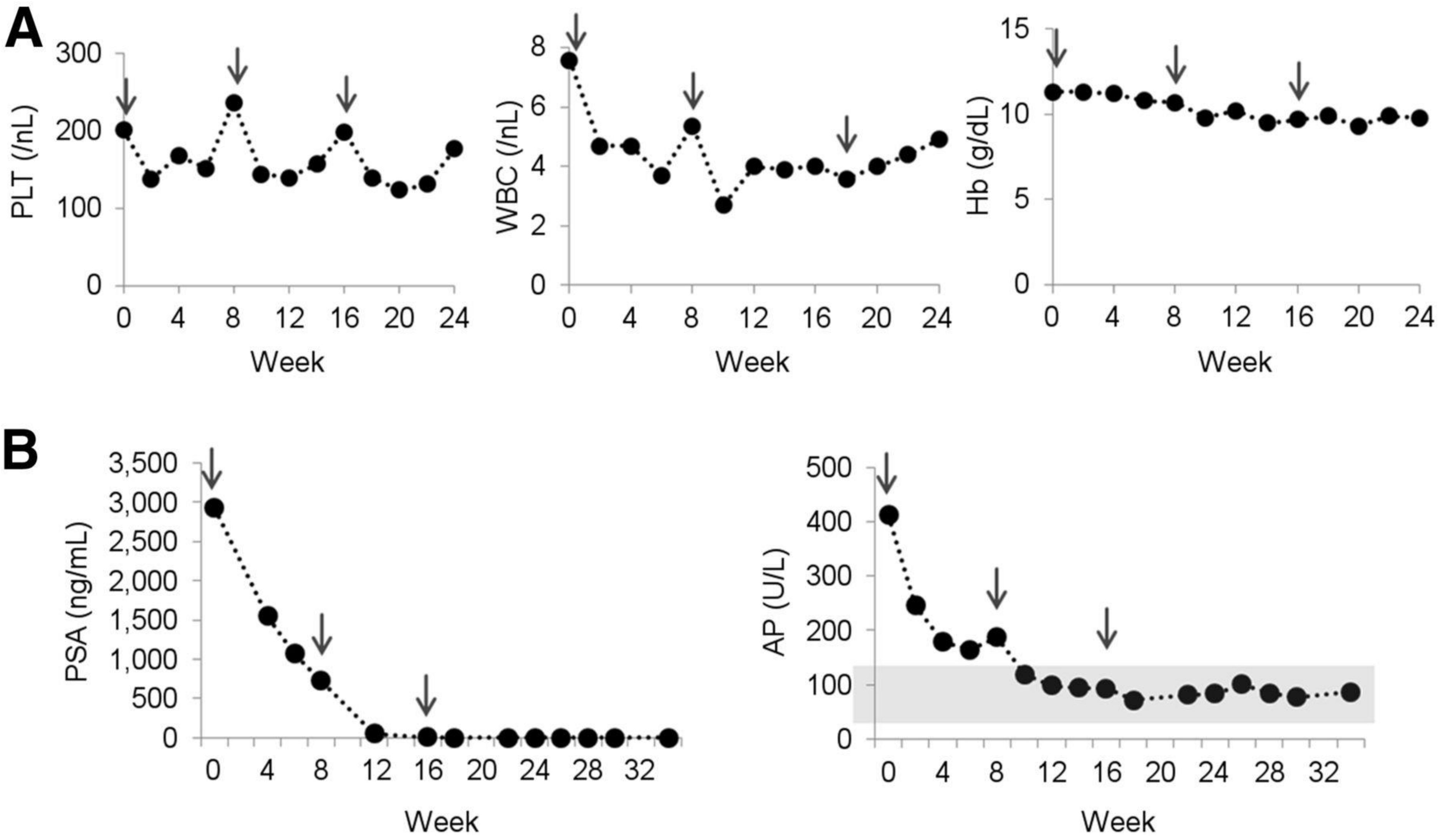


FIGURE 3. ^{68}Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting ^{177}Lu-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting ^{225}Ac-PSMA-617 presented impressive response.

Kratochwil et al. J Ncl Med , 2016 vol. 57 no. 12 1941-1944

[^{225}Ac]Ac-PSMA-617- therapy of mCRPC

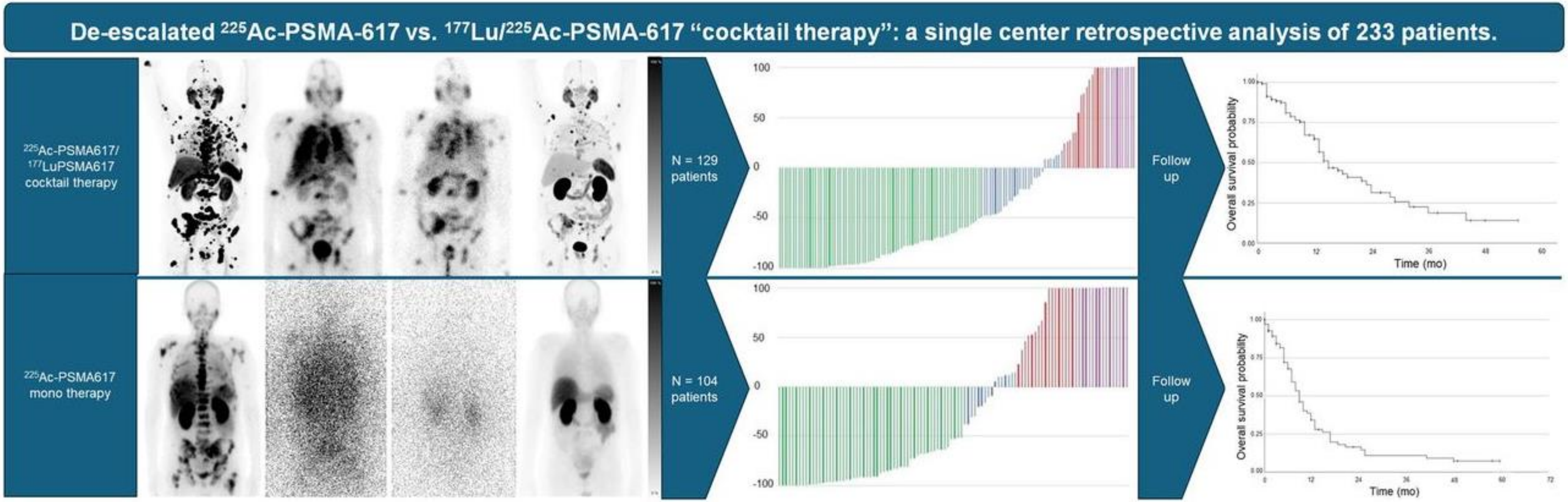


Laboratory test follow-up of patient A. Arrows indicate administration of treatment cycles.

Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

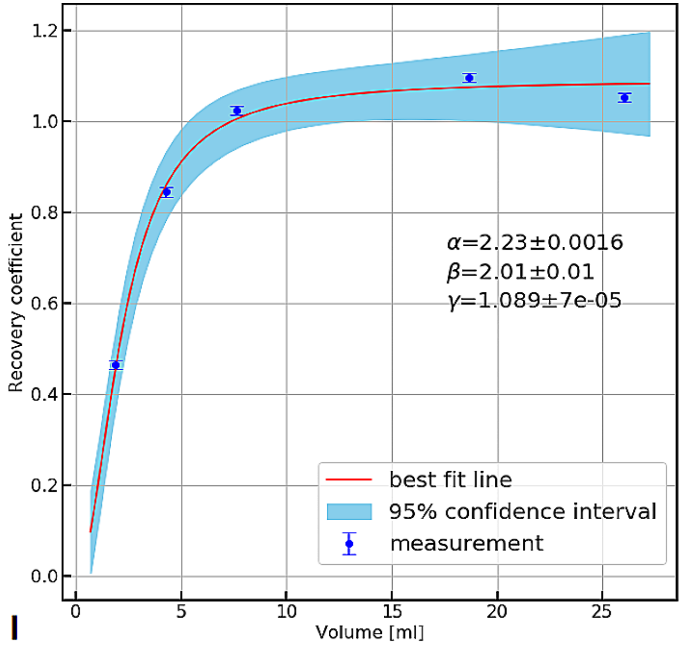
JNM The Journal of NUCLEAR MEDICINE

^{177}Lu/^{225}Ac-PSMA-617 Cocktail Therapy



Ac-225 – quant. SPECT-CT

Windows	Primary	Lower Scatter
II	217 keV, width 10%	5% width
III	444 keV, width 10%	5% width

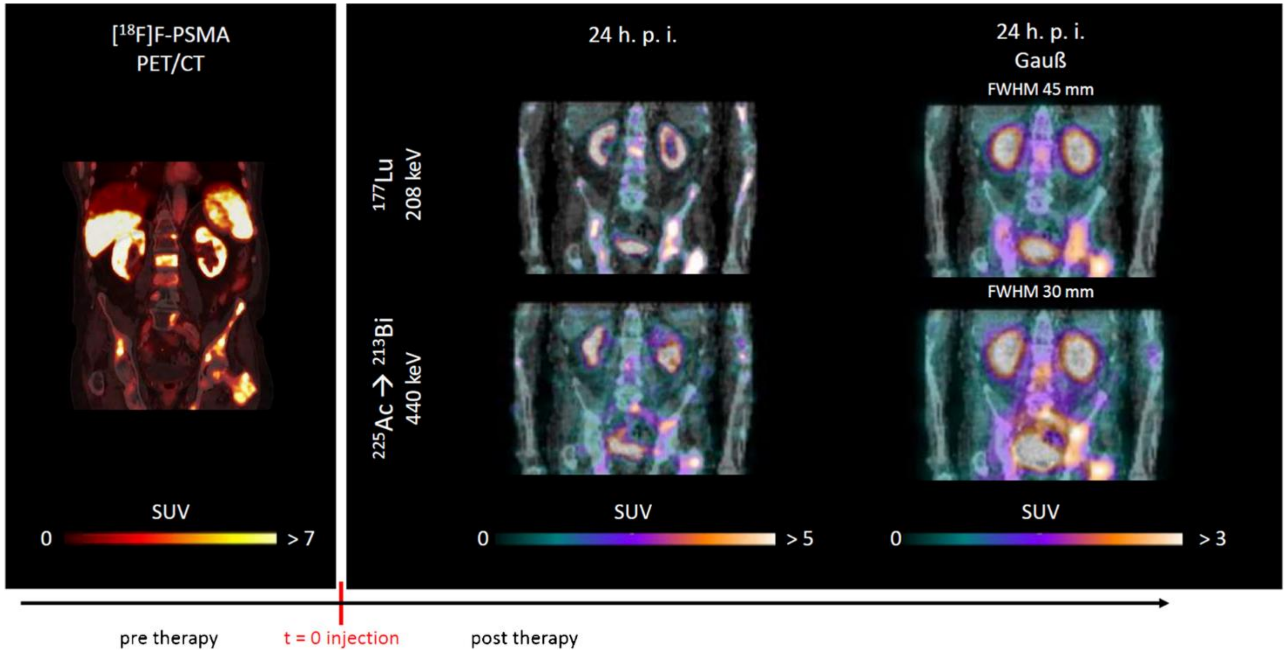


Tulik, M. et al. Quantitative SPECT/CT imaging of actinium-225 for targeted alpha therapy of glioblastomas. EJNMMI Phys 11, 41 (2024).

Combined ^{177}Lu/ ^{225}Ac imaging for dosimetry

^{177}Lu: 208 keV, 15% width
^{225}Ac: 440 kev, 20% width

Scan Time ~ 1h per bed position



Delker A et al. Biodistribution and dosimetry for combined [177Lu]Lu-PSMA-I&T/[225Ac]Ac-PSMA-I&T therapy using multi-isotope quantitative SPECT imaging. Eur J Nucl Med Mol Imaging. 2023;50(5):1280-1290.

$[^{225}Ac]$Ac-PSMA – Clinical Trials (selection)

- AcTION: A Phase I Study of $[^{225}Ac]$Ac-PSMA-617 in Men With PSMA-positive Prostate Cancer With or Without Prior $[^{177}Lu]$Lu-PSMA-617 Radioligand Therapy (NCT04597411)

- LUTACT: Comparison of ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617 (NCT07054346)

- PAnTHA: First-in-human Study of ^{225}Ac-PSMA-Trillium (BAY 3563254) in Participants With Advanced Metastatic Castration-resistant Prostate Cancer

- ^{225}Ac-J591 (nonoclonal antibody)
  - Phase I dose-escalation trial of ^{225}Ac-J591 in mCRPC patients (NCT03276572)
  - Pilot study of PSMA-targeted radionuclide therapy (TRT) re-treatment utilizing ^{225}Ac-J591 (NCT04576871)

- …

Production Routes of ^{225}Ac

- Limited availability constrains the more intensive use of ^{225}Ac

- route for ^{233}U decay is, at the moment, the only viable way to obtain ^{229}Th, the parent of ^{225}Ra and then of ^{225}Ac
  - concerns in the use of fissile ^{233}U (by-products and waste from its decay)
  - extensive purification is needed to get clinically relevant and pharma grade amounts of ^{225}Ac

- Alternative: Cyclotron production of ^{225}Ac by proton bombardment of ^{226}Ra

  → $^{226}Ra(p,2n)^{225}Ac$

Availability of ^{225}Ac

- Oak Ridge National Laboratory has been supplying 25 … 30 GBq per year of high-purity ^{225}Ac

- similar quantity is reported to be available from the Institute of Physics and Power Engineering, in Obninsk, Russia

- Institute for Transuranium Elements in Karlsruhe, Germany (ITU) maintains a smaller ^{229}Th source that is capable of producing 12 … 15 GBq of ^{225}Ac per year

- ITM, Eckert & Ziegler → new production facilities based on cyclotron production route

CURRENT AND FUTURE DEVELOPMENTS TO BE CONSIDERED

New Therapeutic Targets

Target	Full Name	Indications (Explored)	Radionuclides	Notes
FAPi	Fibroblast Activation Protein inhibitor	Many solid tumors (e.g., pancreatic, breast, lung, sarcoma)	^{177}Lu, ^{225}Ac, ^{90}Y	Targets tumor stroma (CAF-rich tumors); very high uptake and rapid clearance from non-tumor tissue.
GRPr	Gastrin-Releasing Peptide Receptor	Prostate cancer, breast cancer, small cell lung cancer	^{177}Lu, ^{90}Y	Mainly explored in prostate and breast cancers
CXCR4	C-X-C chemokine receptor type 4	Hematological malignancies (e.g., multiple myeloma, AML), some solid tumors	^{177}Lu, ^{90}Y	Important for aggressive and metastatic disease

Radionuclides used in Therapy + “new“

Radio-nuclide	Type	Energy [MeV]	Gamma Energy used for Imaging [keV]	Half Live [d]
^{131}I	β^-	0,61; Mean: 0,2	364	8,0
^{177}Lu		0,5; Mean: 0,1	113; 208	6,6
^{90}Y		2.3; Mean 0,9	Bremsstrahlung	2,7
^{166}Ho		1,8; Mean:	81	1,1
^{188}Re		2,1; Mean: 0,8	155	0,7
^{153}Sm		0,8; Mean: 0,2	103	1,9
^{89}Sr		1,5; Mean: 0,6	Bremsstrahlung	50,6
^{32}P		1,7 ; Mean: 0,7		14,3
^{223}Ra	α	5…7,5	82	11,4
^{225}Ac	α	**5,8 … 8,4**	**441**	**10**
^{169}Er	β^-	0.4; Mean: 1,0	Bremsstrahlung	9,4
^{186}Re		1,1; Mean: 0,4	137	3,7
^{211}At	α	5,8 … 7.5		0.29
^{161}Tb	β^-	**0,59 ;Mean: 0,15 (Auger Electrons)**	**49; 75**	**6,96**
^{212}Pb	β^-, α	0,57 ;Mean: 0,14 (α: 2,2; 6,2)	^{212}Bi: 230, 247	0,43
^{67}Cu	β^-	0,56 ;Mean: 0,14	93, 185	2,6

„NEW RADIONUCLIDE“ – TERBIUM-161

Targeted Radionuclide Therapy: ^{177}Lu & ^{161}Tb

- Lu-177: Standard β^- emitter with gamma photons
  → established clinical role
- Tb-161: Next-generation β^- emitter + conversion/Auger electrons
  → enhanced DNA-level damage potential
- Shared trait: Both chelate well with DOTA
  → same ligands can be used (DOTATATE, PSMA, etc.)

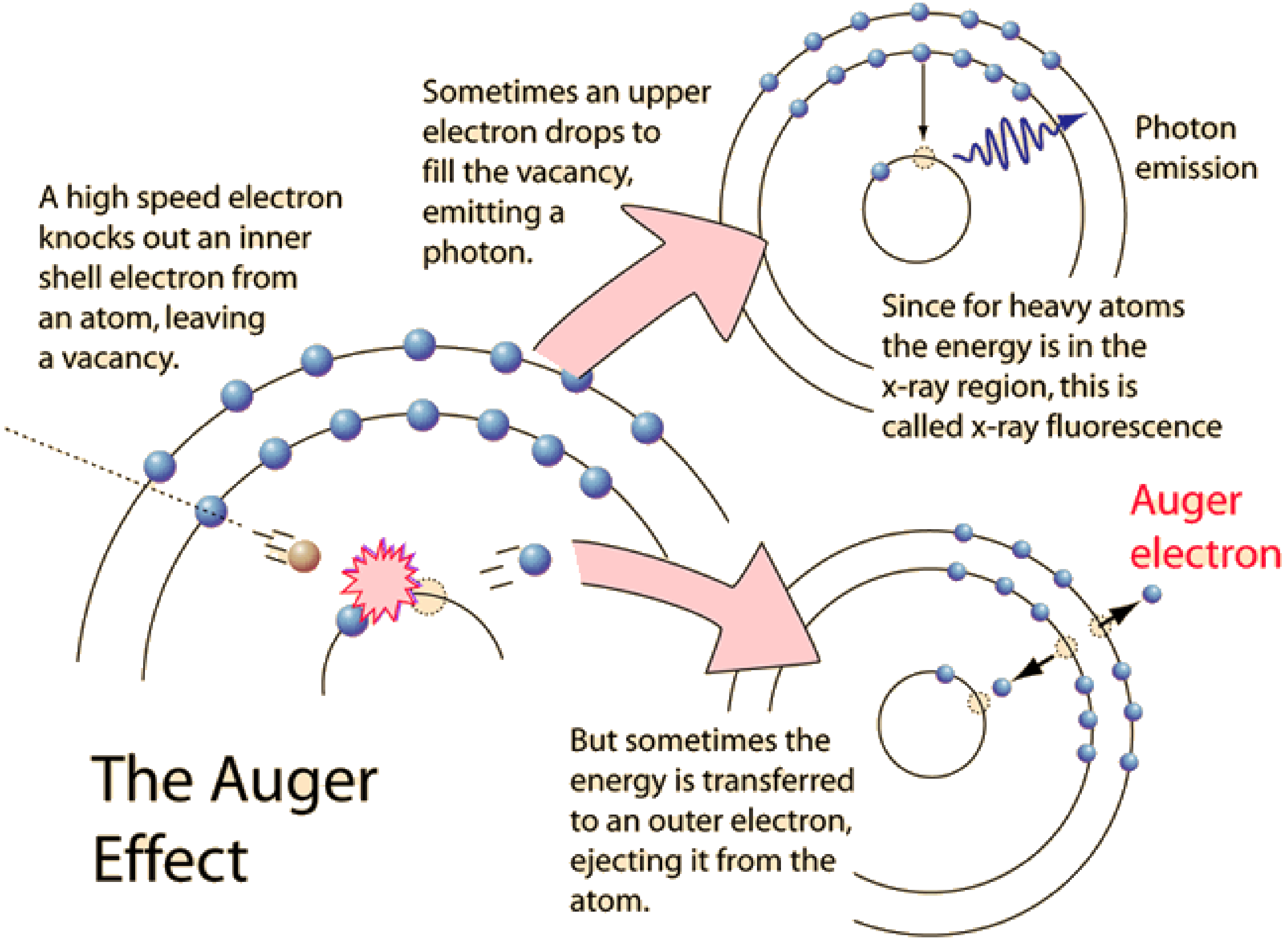
Auger Emitters – Precision Tools for Targeted Radiotherapy

Mechanism

- Radionuclide decays
  → inner-shell vacancy
- Cascade of Auger electron emissions
- Energy deposition localized around the atom
  → DNA damage if near nucleus

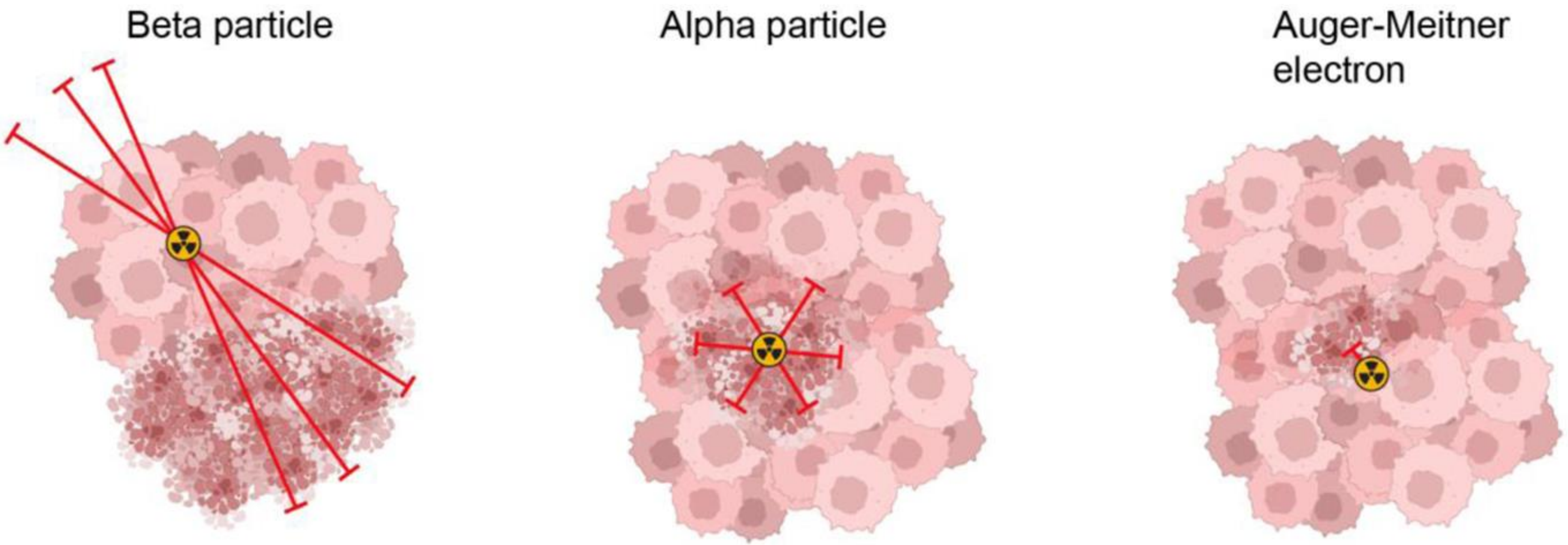
Physical Characteristics

Property	Typical Value
Energy	20 eV – 25 keV
Range in tissue	1 – 10 nm
LET	up to 30 keV/µm
Target scale	DNA / nucleus



http://hyperphysics.phy-astr.gsu.edu/hbase/Atomic/auger.html

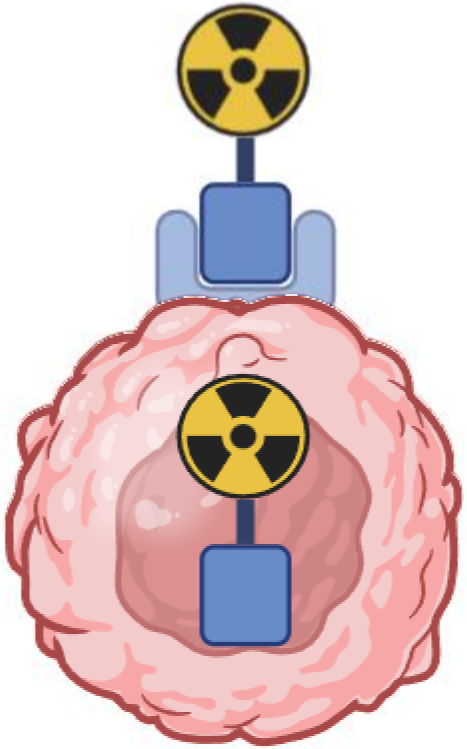
Therapeutic Radionuclides – A Question of Range



	Beta particle	Alpha particle	Auger-Meitner electron
Scale	tumors, tissues	< 10 cells	single cell
Range	0.1-10 mm	< 100 µm	< 1 µm
LET	<1 keV/µm	50 - 230 keV/µm	1 - 23 keV/µm
Example nuclides	^{177}Lu, ^{90}Y, ^{153}Sm, ^{131}I	^{223}Ra, ^{225}Ac, ^{212}Pb	^{123}I, ^{111}In
Example agents	[^{177}Lu]Lu-dotatate (Lutathera®) [^{177}Lu]Lu-PSMA-617 (Pluvicto™)	[^{223}Ra]RaCl$_2$(Xofigo®)	^{161}Tb - labelled pharmaceuticals

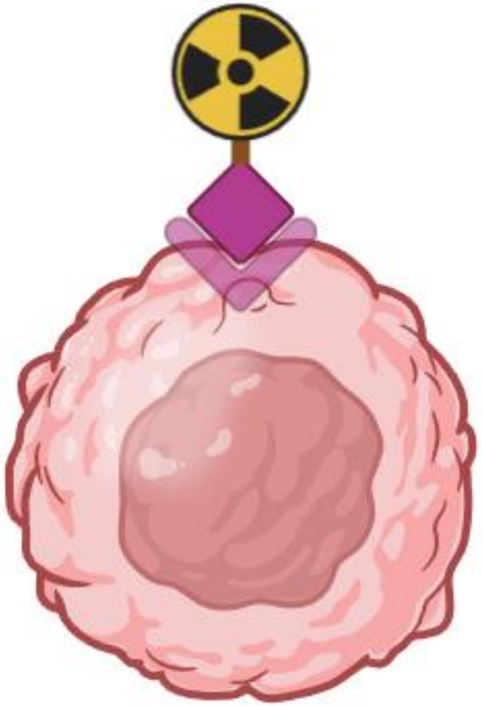
Salerno, Kilian E et al. "A Primer on Radiopharmaceutical Therapy." *International journal of radiation oncology, biology, physics* vol. 115,1 (2023): 48-59.

Therapeutic Radionuclides - Therapeutic Relevance - Localisation



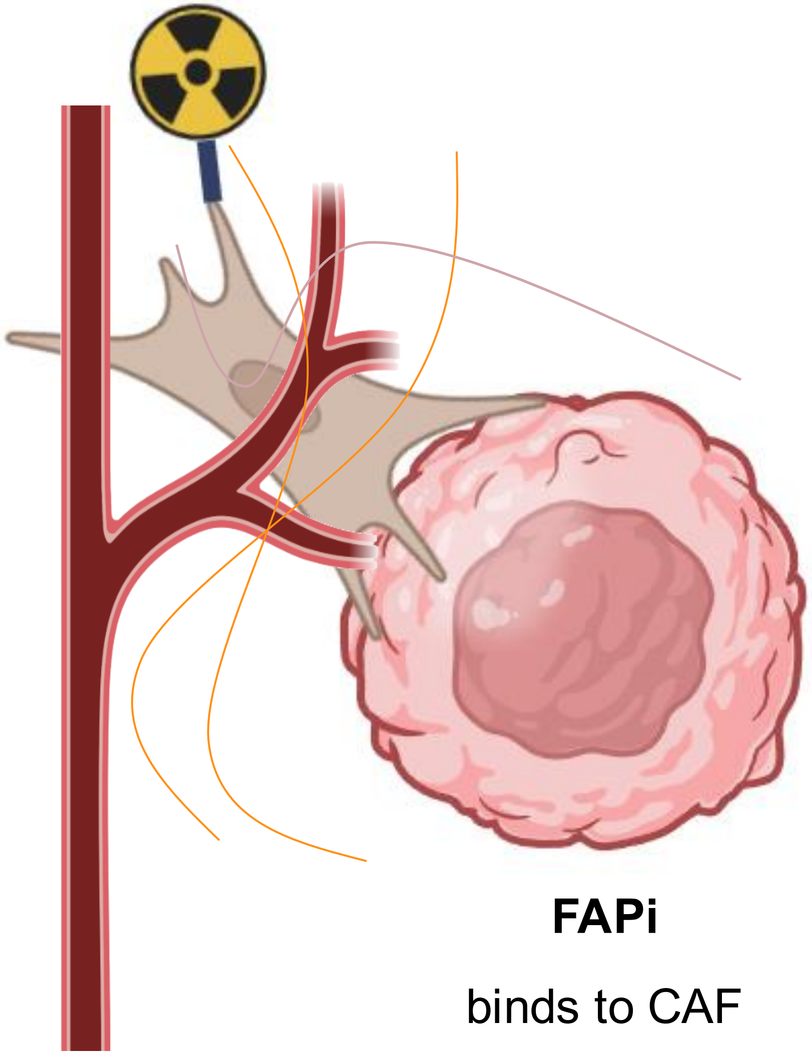
PSMA

Internalisation



GRPr

Antagonists/
Transmembrane Binding



FAPi

binds to CAF

Lu-177 vs Tb-161

Property	Lu-177	Tb-161	Key Takeaway
Half-life	~6.65 days	~6.89 days	Nearly identical → same logistics
β^- energy	Emax ~0.497 MeV (mean ~0.133 MeV)	Emax ~0.593 MeV (mean ~0.154 MeV)	Very similar tissue penetration (~1–2 mm)
Additional radiation	Minimal Auger/IC	High yield of conversion & Auger e^- (nm–μm range)	Extra DNA-level damage when ligand internalizes
Gamma emissions	113 keV (6.4%) 208 keV (11%)	49–103 keV (several low-energy γ lines)	Both allow SPECT imaging; Tb-161 lower energy
Chemistry	Lanthanide; stable DOTA chelation	Same; DOTA compatible	Ligands interchangeable (DOTATATE, PSMA, etc.)

Where They Are Used

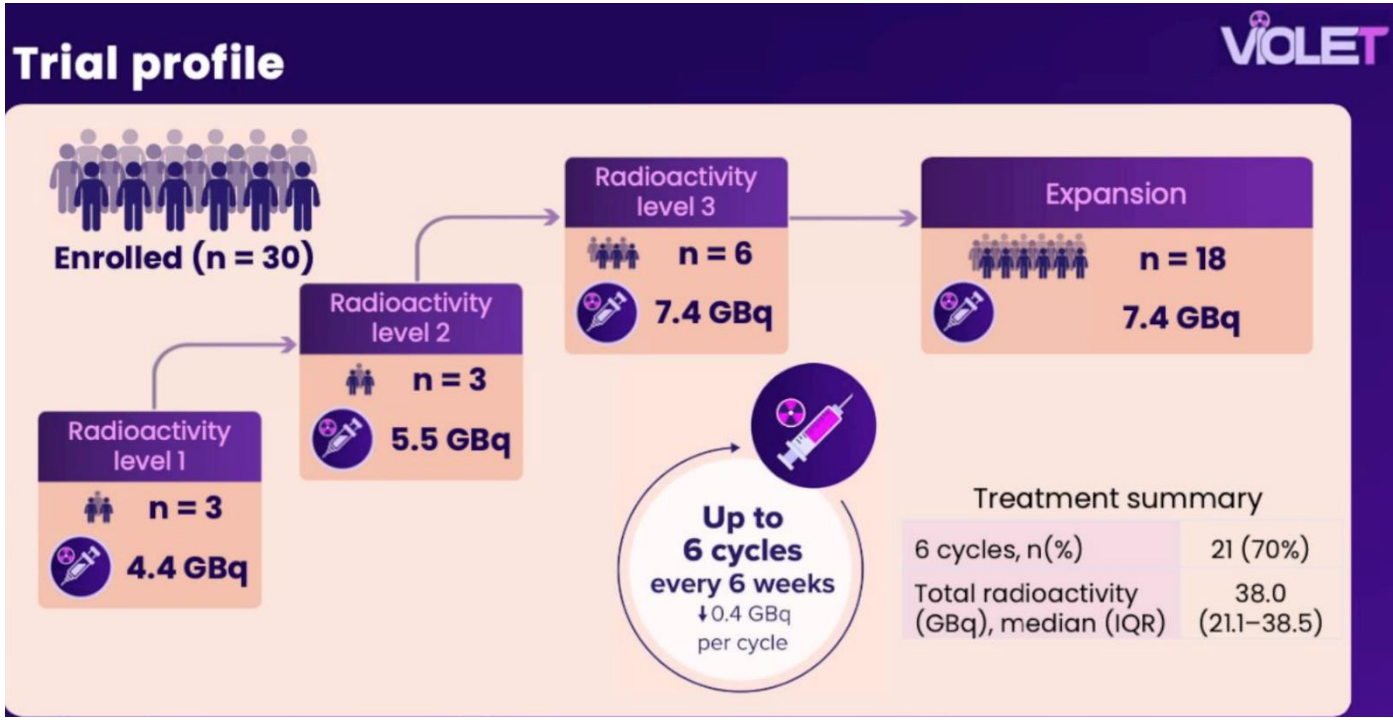
- Lu-177 Today
  - Approved:
    - Neuroendocrine tumors → Lu-177-DOTATATE (PRRT)
    - Prostate cancer (PSMA+ mCRPC) → Lu-177-PSMA-617 (Pluvicto)
  - Proven OS and PFS improvements in pivotal trials.

- Tb-161 Tomorrow
  - Still investigational, early trials in NETs and prostate cancer
  - Strong preclinical evidence of higher tumor kill, especially micro-metastases
  - First-in-human studies (PSMA-I&T) show feasibility and safety.

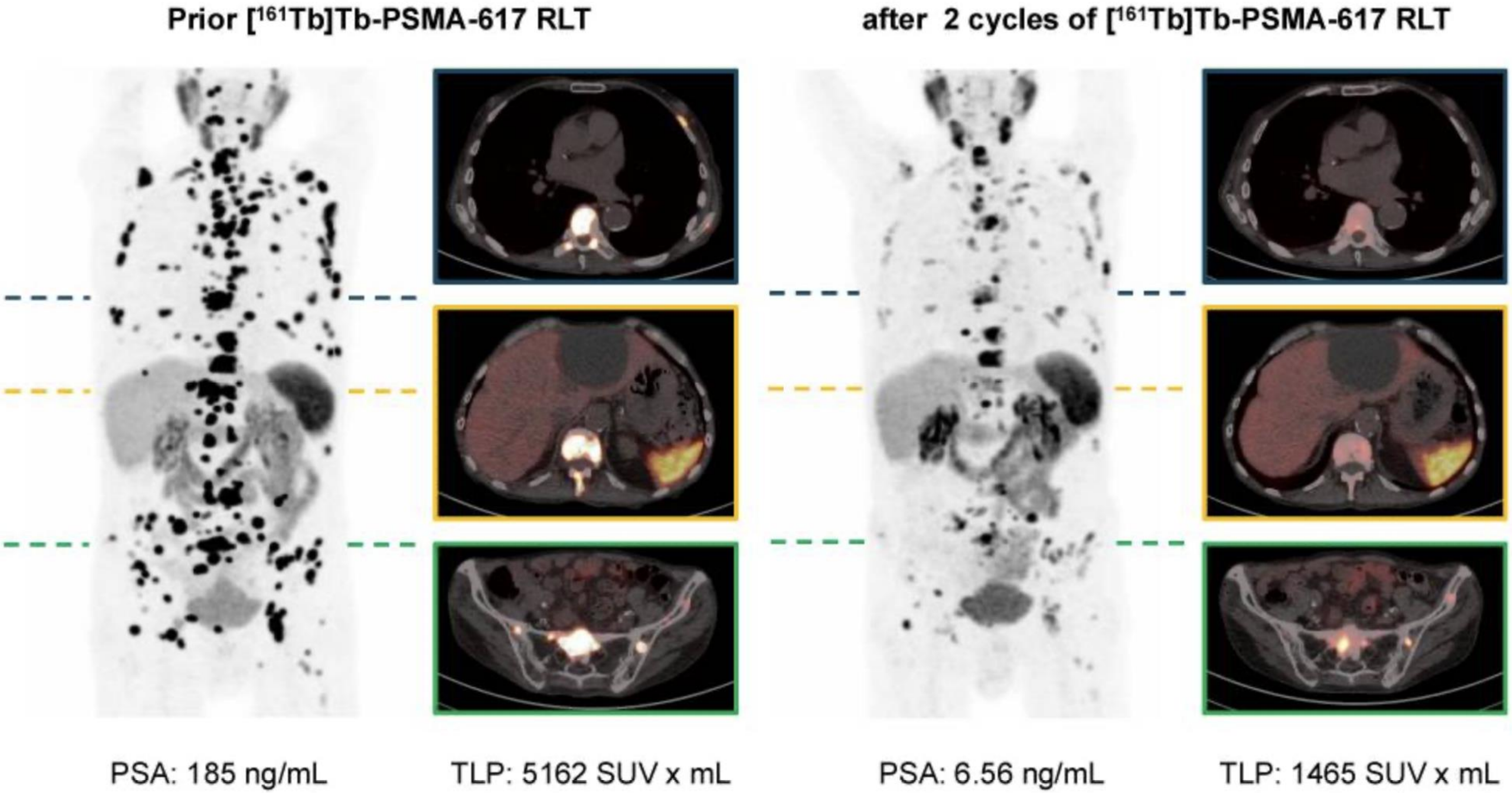
VIOLET trial

- VIOLET trial (led by P. Mac CC) uses [^{161}Tb]Tb-PSMA-I&T to treat patients with metastatic castration-resistant prostate cancer

- Initial results from the phase I/II study have shown great promise:
  - 70% of patients had their PSA levels decline by 50% or more
  - 40% of patients experienced an even more significant PSA decline of 90% or more
  - treatment was well-tolerated with low rates of side effects



Response



Rosar F et al. "Pilot experience of [^{161}Tb]Tb-PSMA-617 RLT in mCRPC patients after conventional PSMA RLT within a prospective registry." *Theranostics* vol. 15,17 9019-9028. 16 Aug. 2025, doi:10.7150/thno.115831

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Traditio et Innovatio

Universitätsmedizin Rostock




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