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MEDICIS-Promed Summer School - Pavia

Treatment Planning in Nuclear Medicine

Prof. Dr. Christophe Deroose
Nuclear Medicine - University Hospitals Leuven (UZ Leuven)
Department of Imaging & Pathology – KU Leuven
Leuven Cancer Institute (LKI)
Leuven, Belgium

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Overview

- Nuclear medicine treatment: radionuclide therapy (RNT)
- Therapeutic radioisotopes and radiopharmaceuticals
- Dosimetry
- Currently used RNT and planning aspects
  - $Na^{131}I$ for thyroid disease
  - ^{131}I-MIBG
  - Peptide receptor radionuclide therapy (PRRT)
  - ^{177}Lu-PSMA (Prostate specific membrane antigen)
  - Radium-223 for bone metastases
  - Selective internal radiation therapy (SIRT)
- Conclusions

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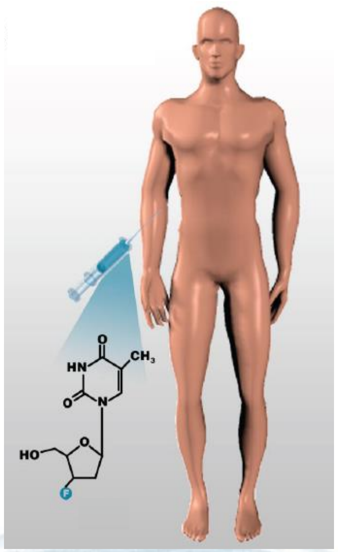
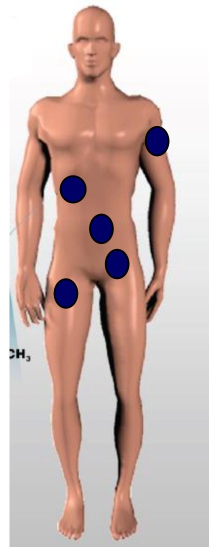
Nuclear medicine treatment: Radionuclide Therapy (RNT)



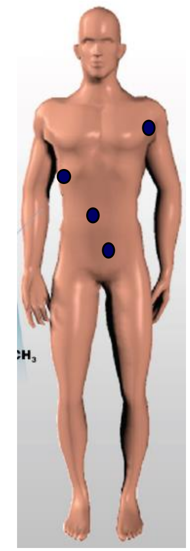
Radiopharmaceutical administration

ΔTime



Radiopharmaceutical binds to molecular target and accumulates in the tissue

ΔTime



Particulate emission leads to local cellular destruction

Theranostics: at the heart of nuclear medicine treatments

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On the 31st March 1941, Saul Hertz performed the first treatment of hyperthyroidism by a mixture of iodine-131 and iodine-130 isotopes, in Mass. General Hospital

Theranostics: what's in a name?

Different words, same concept

- Theranostics
- Theragnostics
- Diapeutics

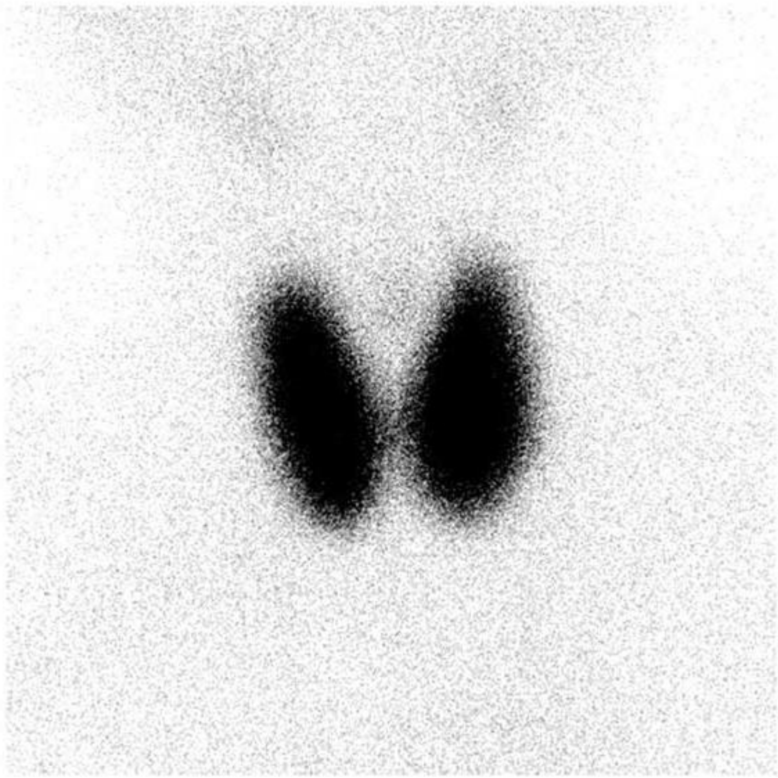
Definition

- Wiktionary: "A form of diagnostic testing employed for selecting targeted therapy"
- "Set of molecules used for both diagnostic and therapeutic medical purposes".

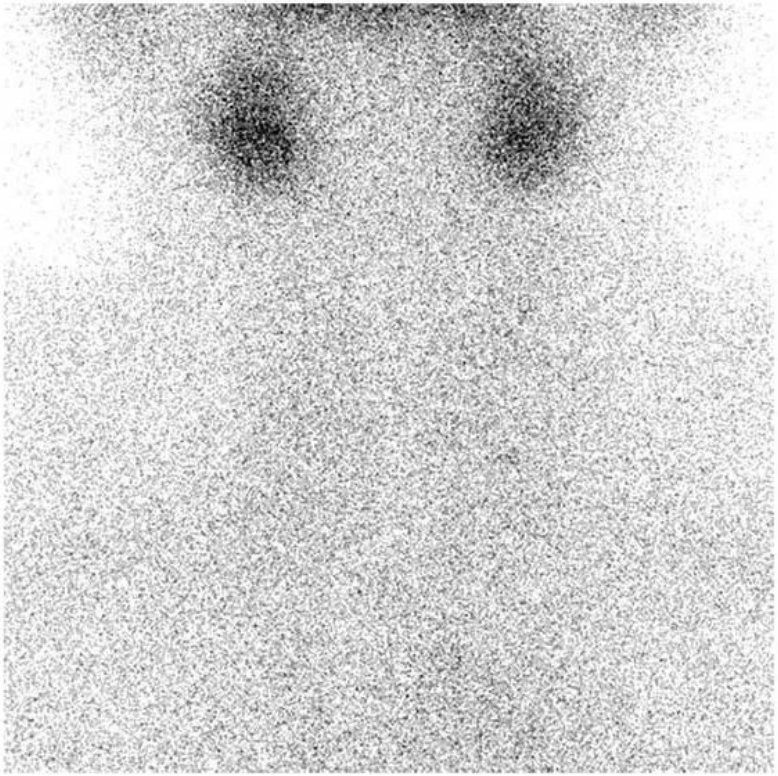
Key features

- Diagnostic test allows to predict the efficacy or toxicity of the corresponding treatment
- Allows to inidividualize a treatment for a given patient
- In its most extreme form, the same vector molecule or even the exact same chemical entity is used for both a diagnostic and therapeutic purpose

Imaging the thyroid gland in hyperthyroidism

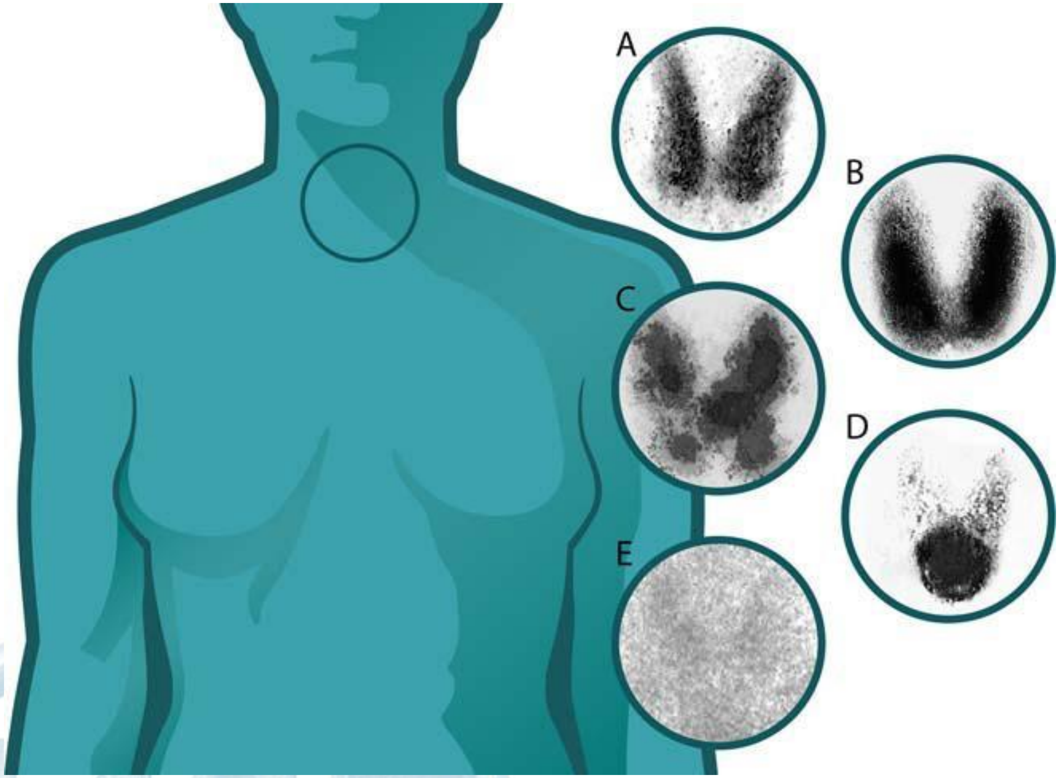


Graves' disease



Thyroiditis

Treatment of the thyroid with iodine-131



A: Normal

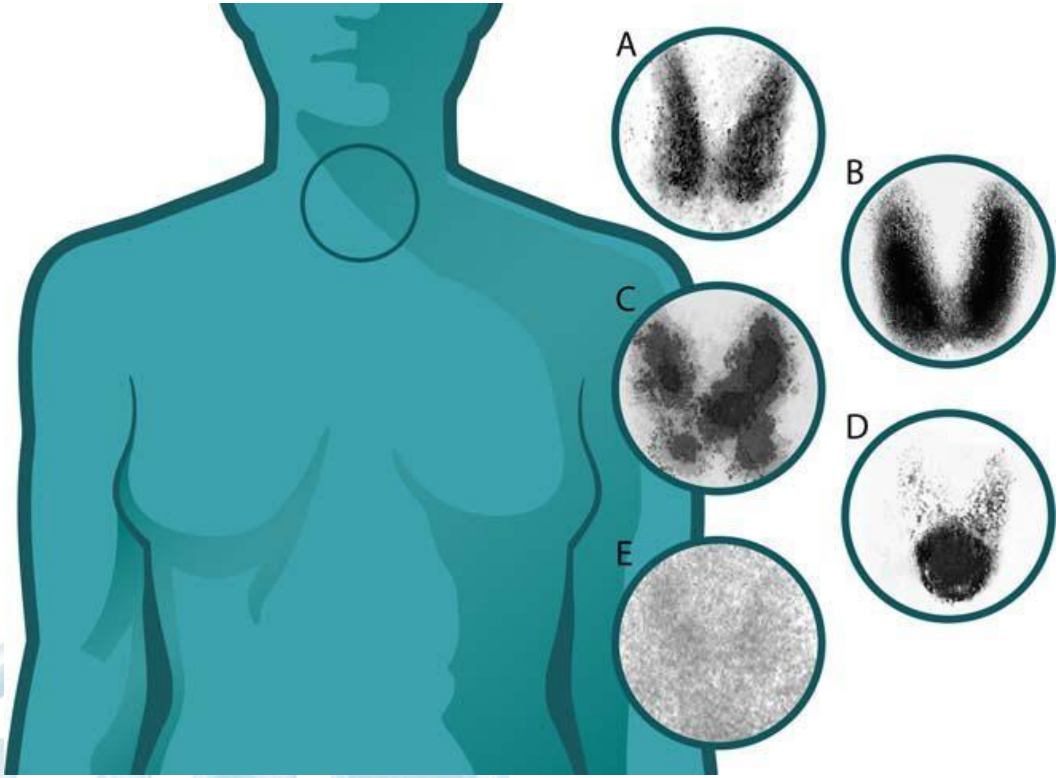
B: Graves

C: Toxic multinodular goiter

D: Autonomous Nodule

E: Thyroiditis

Treatment of the thyroid with iodine-131



~~A: Normal~~

B: Graves

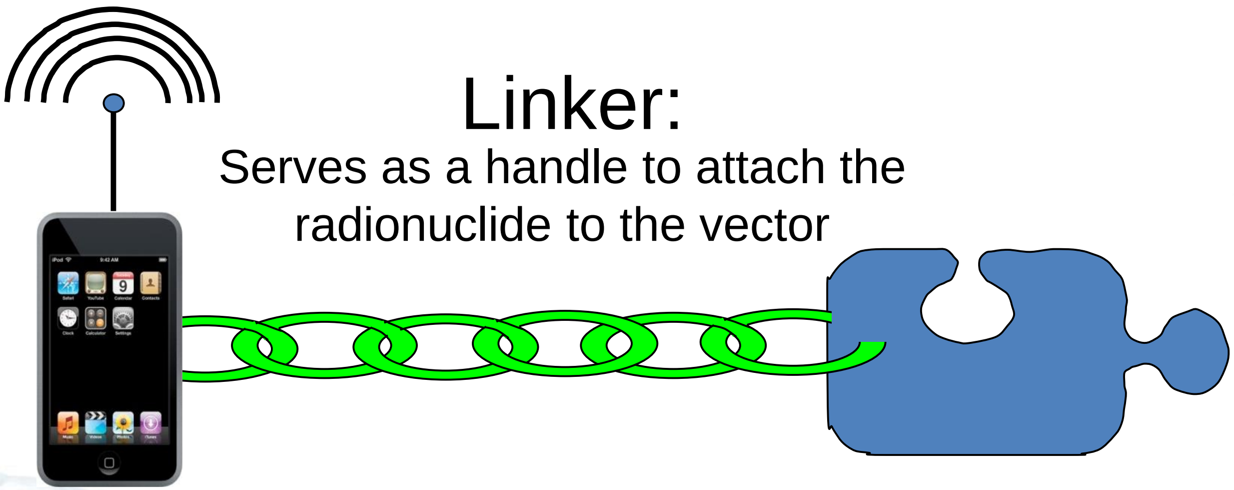
C: Toxic multinodular goiter

D: Autonomous Nodule

~~E: Thyroiditis~~

Radiopharmaceutical: diagnostic

For molecular imaging (diagnosis)



Linker:

Serves as a handle to attach the radionuclide to the vector

Radionuclide:

Emits radiation upon decay. The radiation can be detected by the nuclear medicine cameras

Vector:

Is responsible for a specific interaction with the target (receptor, transporter, enzyme,…)

Diagnostic use: imaging

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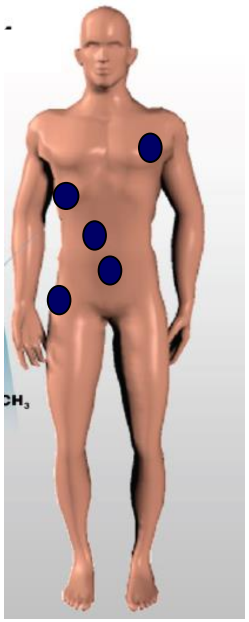
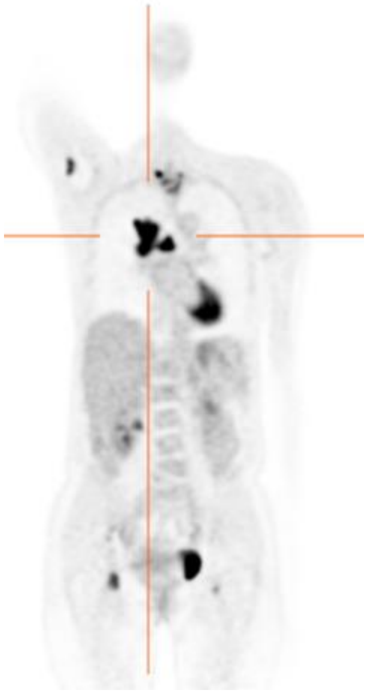
Injection radiofarmaceutical

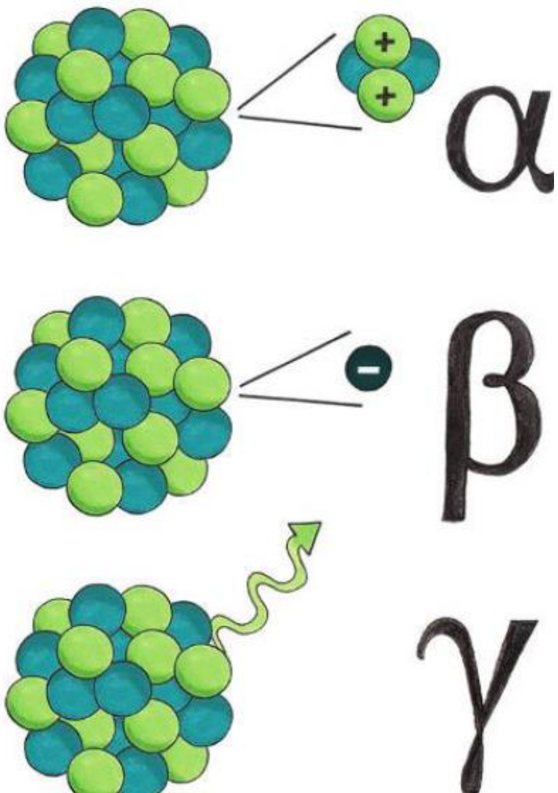
ΔTime

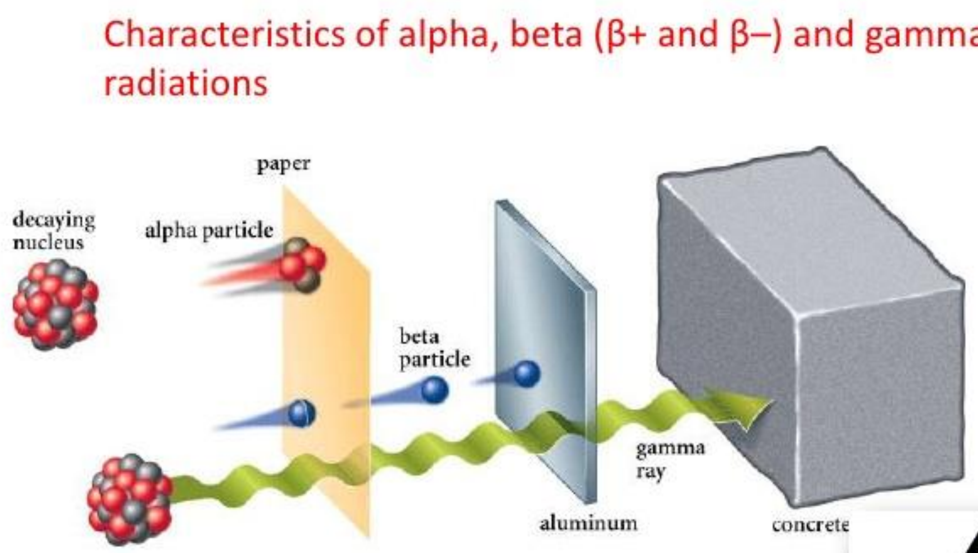


Accumulation radiofarmaceutical in cancer cells



Limited penetration power of α et β-particles: allows therapeutic applications



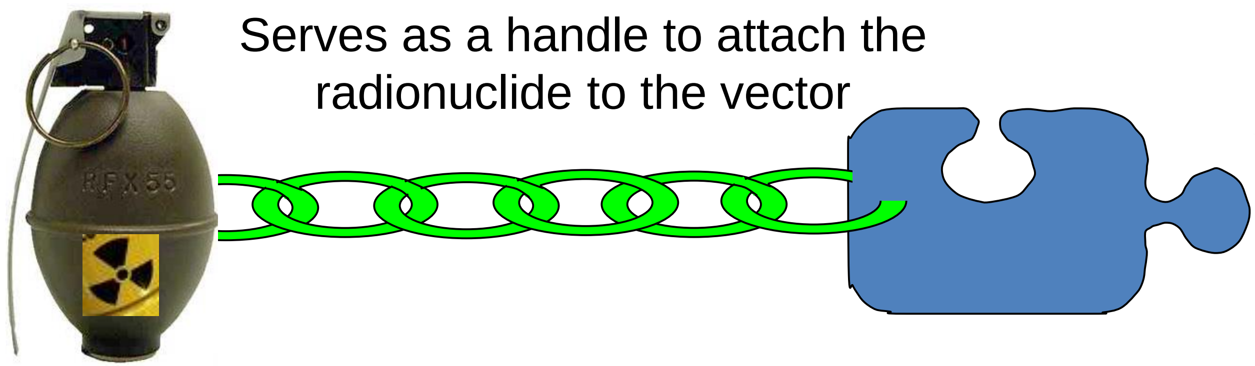


Radiopharmaceutical: therapeutic

For therapy

Linker:

Serves as a handle to attach the radionuclide to the vector



Radionuclide:

Upon decay emits particulate radiation for destruction of the tissue target cells

Vector:

Is responsible for a specific interaction with the target (receptor, transporter, enzyme,…)

Specific features of the radionuclide: example from PRRT

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- Most documented: ^{111}In - ^{90}Y – ^{177}Lu
- Differ in:
  - emitted particles
  - energy of particles
  - tissue penetration

Radionuclides	Emitted particle	Energy of particles	Max tissue penetration	Half life
Indium-111	Auger elektron γ-radiation	3 & 19 keV 171 & 245 keV	10 µm	2.8 days
Yttrium-90	β-radiation	935 keV	11 mm	2.7 days
Lutetium-177	β-radiation γ-radiation	130 keV 113 & 208 keV	2 mm	6.7 days
Bismuth-213	α-radiation β-radiation γ-radiation	8400 keV 435 & 198 keV 440 keV	0.080 mm	46 min

Large tumors

Small tumors

Large & small

Microscopic disease

The Oncological Treatment Triangle

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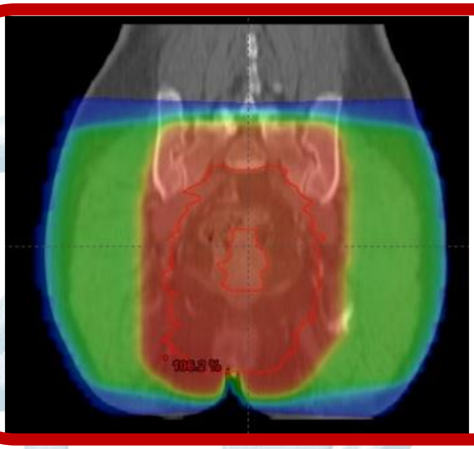
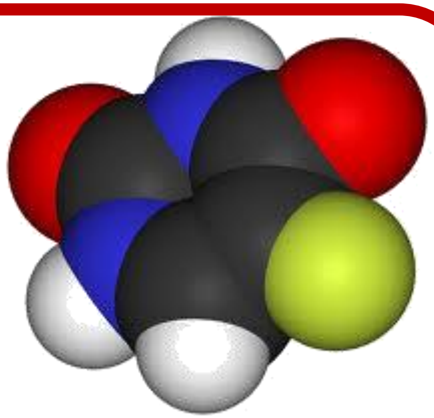
Surgery



Radionuclide therapy

RNT



External beam radiation therapy

Systemic treatment (chemo, hormono, targeted, immuno)

RNT compared to EBRT

RNT = EBRT

	RNT	EBRT
Ionising radiation tissue damage	**YES**	**YES**

RNT ≠ EBRT

	RNT	EBRT
Source in relation to patient	Internal	External
Source	Radiopharmaceutical	Accelator
Regulatory aspects	Drug + Radiation	Radiation
Prescription	Activity (Bq)	Dose (Gy)
Dose rate	Gy/hour – Gy/day	Gy/min
Potential to harm	Low	High

TechneScan® MAA LyoMAA. Mallincrodt Medical B.V., Petten, The Netherlands.
SIR-Spheres ® microspheres (Yttrium-90 miscrospheres), SSL-US-10, NOV 2014, Sirtex, North Sydney, Australia

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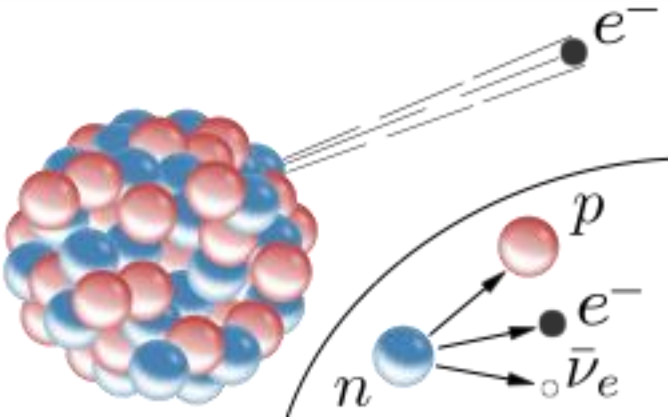
Beta-particle (β^-)



- 1 electron

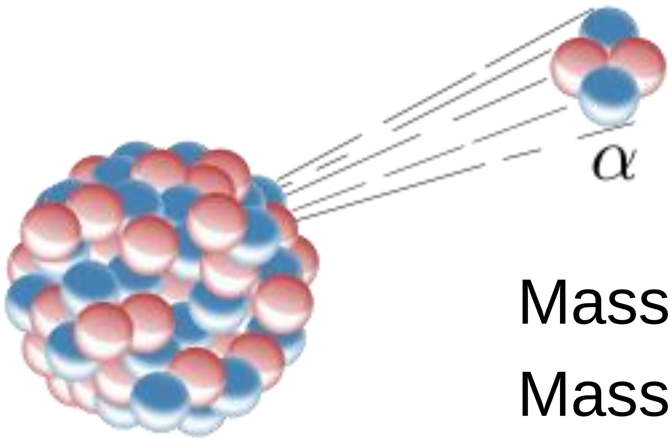
Mass:	9.109×10^{-31} kg	
Mass:	0.00055	u
Electric charge:	-1	e
Spin	1/2	
Kinetic Energy	continuous spectrum few keV – 10's MeV	
Speed	typically > 75% c	
Source	^{131}I, ^{90}Y, ^{177}Lu, ^{153}Sm, ^{89}Sr,…	

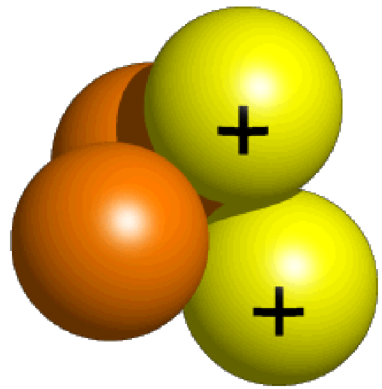
Particle emitted during β-decay by some radioactive atoms

http://en.wikipedia.org/wiki/Electron
http://en.wikipedia.org/wiki/Beta_particle
http://en.wikipedia.org/wiki/Beta_decay

Alpha-particle (α)

Particle emitted during α-decay
by some radioactive atoms





2 neutrons
2 protons
= He Nucleus

Mass:	6.645×10^{-27} kg	
Mass:	4.0015	u
Electric charge:	2	e
Spin	0	
Kinetic Energy	typically 3-7 MeV	
Speed	≈ 5% speed of light (c)	

http://physics.nist.gov/cgi-bin/cuu/Value?mal

http://en.wikipedia.org/wiki/Alpha_particle

Ionisations of α-particles in air

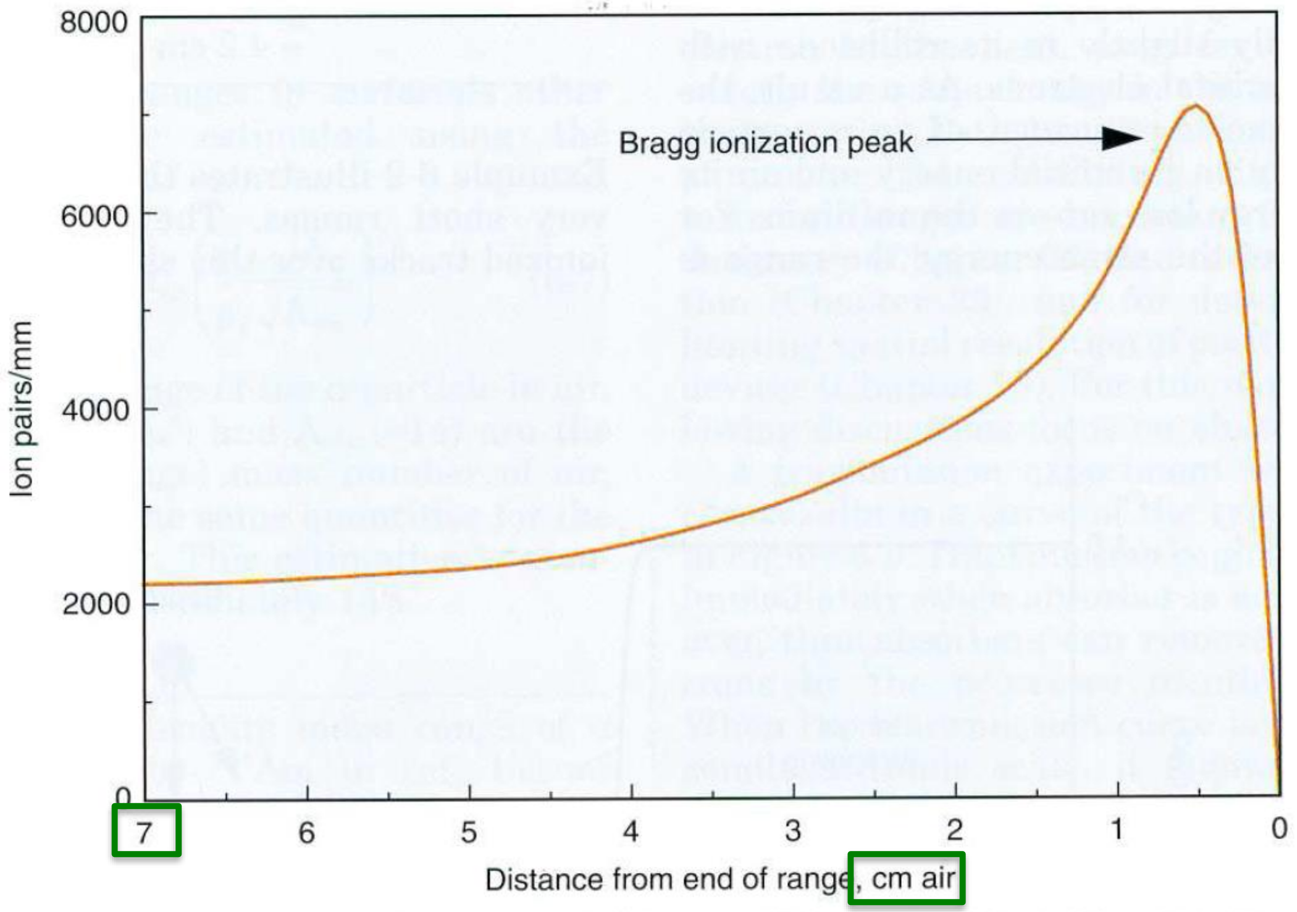
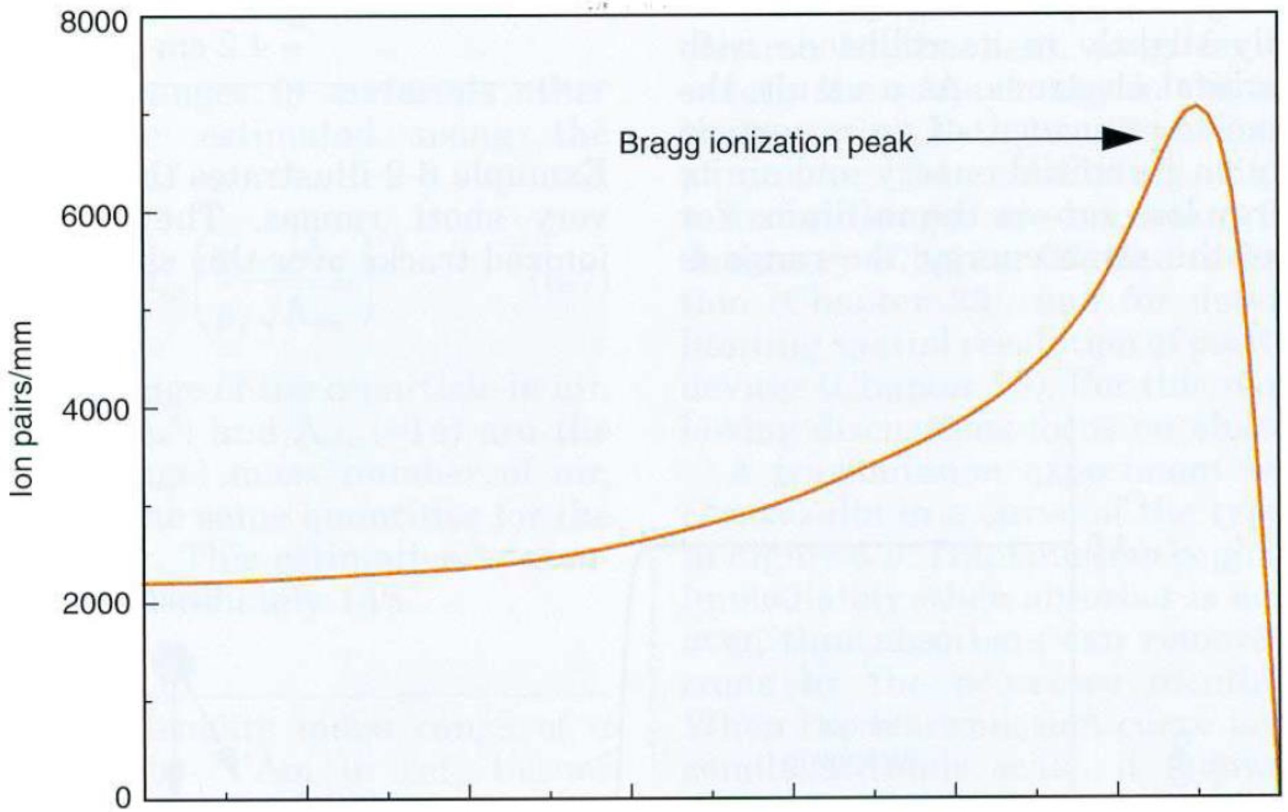


FIGURE 6-7 Specific ionization versus distance traveled for α particles in air. (*Adapted from Mladjenovic M:* Radioisotope and Radiation Physics. *New York, 1973, Academic Press, p 111.*)

Physics in Nuclear Medicine, Cherry, Sorenson et al, Elseviers Saunders, 4th edition, 2012

Ionisations of α-particles in water



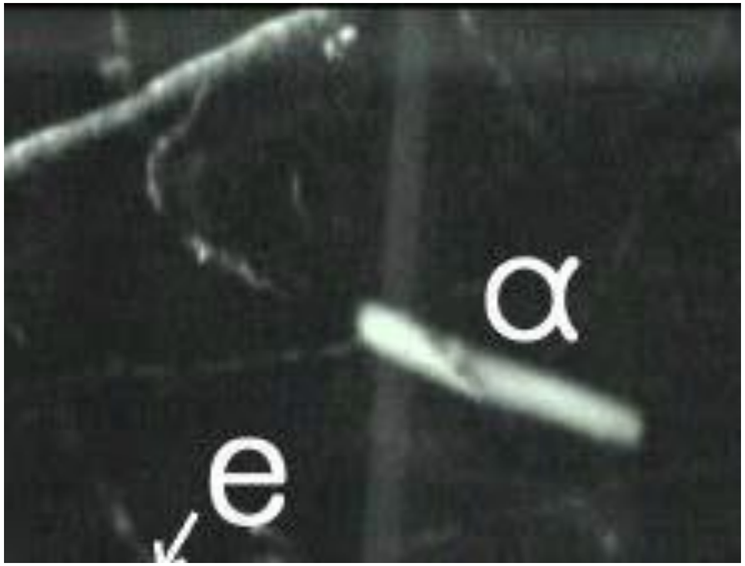
70 60 50 40 30 20 10 00

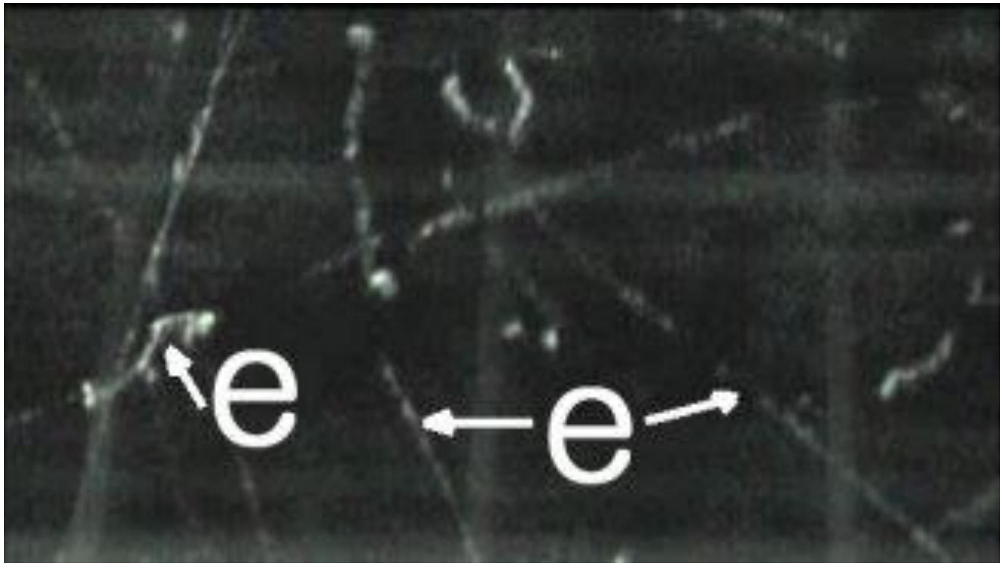
Distance from end of range, μ water

c M: Radio-

Adapted from Physics in Nuclear Medicine, Cherry, Sorenson et al, Elseviers Saunders, 4th edition, 2012

Difference in ionisations induced by α and β-particles



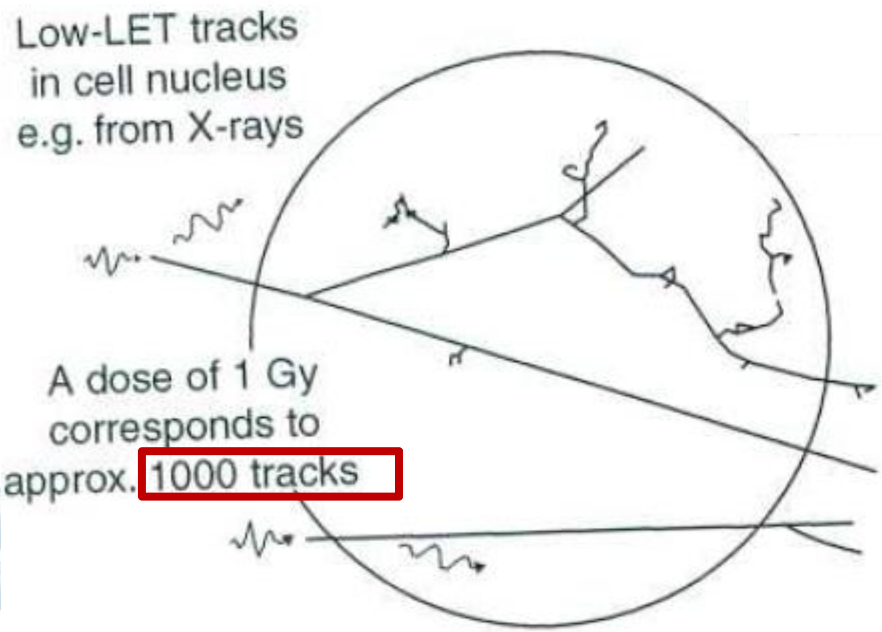


α	**β**
Short range (≈ microns)	Longer range (≈ millimeters)
Many ionisations	Less ionisations
⇒High linear energy transfer (LET)	⇒Low linear energy transfer (LET)
Irrepairable cell damage	Cell damage can be repaired

http://www.molecularimagingcenter.org/index.cfm?PageID=8892

Difference of particle track compared to mammalian nucleus

β



Basic Clinical Radiobiology, Joiner, van der Kogel, CRC press, 4th edition 2009

Radiopharmaceuticals used for the therapy of bone metastases

Isotope	Form	Decay	$T^{1/2}$	Particle Energy		γ-Energy		Soft-tissue range		Typical Activity
			(days)	Max (MeV)	Mean (MeV)	(keV)	(%)	Max (mm)	Mean (mm)	
^{32}P	^{32}P-orthophosphate	β	14.3	1.7	0.70	na		8.5	3	5-10 mCi i.v. 10-12mCi p.o.
^{89}Sr	$^{89}SrCl_2$	β	50.5	1.46	0.58	909	0.01%	7.0	2.4	4 mCi i.v. 40-60 µCi/kg i.v.
^{153}Sm	^{153}Sm-EDTMP	β	1.9	0.81	0.23	103	28%	3.4	0.6	1 mCi/kg i.v.
^{186}Re	^{186}Re-HEDP	β	3.7	1.07	0.35	137	9%	3.7	1.1	35 mCi i.v.
^{117m}Sn	^{117m}Sn-DTPA	Conv e^-	13.6	0.15	≈0.13	159			0.2-0.3	0.05-0.27 mCi/kg i.v.
^{223}Ra	$^{223}RaCl_2$	α	11.4	5.98	5.64	154 269 351 (<^{211}Bi)	6% 14% 13%		0.05-0.08	1.4 µCi/kg i.v.

Adapted from Nuclear Medicine Therapy, Aktolun, Goldsmith, Springer, 2013

Radiopharmaceuticals used for the therapy of bone metastases - normalised

Isotope	Form	Decay	$T^{1/2}$	Particle Energy		γ-Energy		Soft-tissue range		Typical Activity
			(days)	Max	Mean	(keV)	(% des)	Max	Mean	IV
^{32}P	^{32}P-orthophosphate	β	125%	28%	12%	na		131	46	74
^{89}Sr	$^{89}SrCl_2$	β	443%	24%	10%	909	0.01%	108	37	37
^{153}Sm	^{153}Sm-EDTMP	β	17%	14%	4%	103	28%	52	9	740
^{186}Re	^{186}Re-HEDP	β	32%	18%	6%	137	9%	57	17	345
^{117m}Sn	^{117m}Sn-DTPA	Conv e^-	119%	3%	2%	159			4	118
^{223}Ra	$^{223}RaCl_2$	α	100%	100%	100%	154 269 351 (<^{211}Bi)	6% 14% 13%		1	1

Adapted from Nuclear Medicine Therapy, Aktolun, Goldsmith, Springer, 2013

Examples of therapeutic radionuclides

- Strontium-89 (β) — Previous routine clinical use

- Iodine-131 (β-γ)
- Radium-223 (α)
- Yttrium-90 ("pure" β)
- Lutetium-177 (β-γ)
- Samarium-153 (β-γ)

} Current routine clinical use

- Holmium-166 (β-γ) — Extensive experimental human data

- Thorium-227 (α) — In developement

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Internal Dosimetry: definition

- Dosimetry = calculation of the (absorbed) dose within matter (tissue) caused by (in)direct ionising radiation from a certain amount of (radio)activity.
- Dosimetry : activity (Bq) → absorbed dose (Gy)

Unit of internal dosimetry

- Rad: energy deposited per unit mass (any material, any radiation)
- Kerma (kinetic energy released in matter)
  - Sum of initial kinetic energies of all charged particles liberated by uncharged ionizing radiation per unit mass
- Rad ~ Kerma
- SI Unit: Gray (Gy)
  - 1 Gy ≡ 1 J/kg absorber
  - 4186 Joules to heat a kilogram of water 1°Celsius
  - 1 Gy heats 1 kg water by 1/4186 °C (~0.0002°C)

Radiation weighting factors

Table 14.1. Radiation weighting factors.

Type and energy range		Radiation weighting factors, W_r
Photons, all energies		1
Electrons, muons, all energies		1
Neutrons, energy	<10 keV	5
	10 keV to 100 keV	10
	>100 keV to 2 MeV	20
	>2 MeV to 20 MeV	10
	>20 MeV	5
Protons, other than recoil protons, energy >2 MeV		5
Alpha particles, fission fragments, heavy nuclei		20

Adapted with permission from ICRP Publication 60: *1990 Recommendations of the International Commission on Radiological Protection*. New York: Pergamon Press; 1991.

What factors determine dose?

- Administered activity (sometimes called "Dose" or "Dosis")
- Physical half-life
- Fractional abundance of radiation from the radionuclide
- Biodistribution within the body and its evolution over time
- Fraction of energy released from the source organ absorbed in the target organ:
  - Shape
  - Composition
  - Location

  } of the target

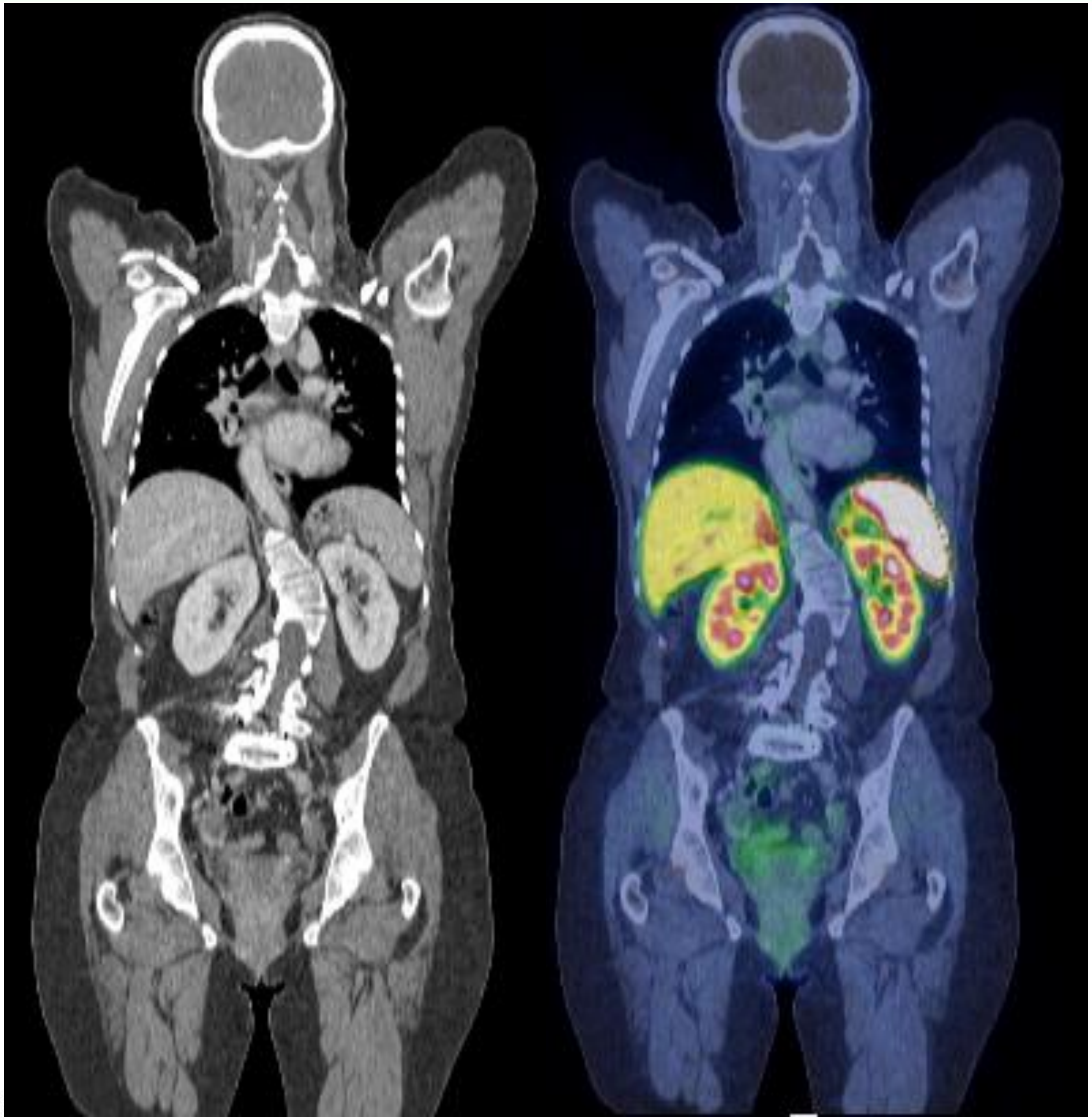
Green: measured dose calibrator

Dark green: constant

Red: unknown, biological variation

Purple: unknown, biological variation


Left

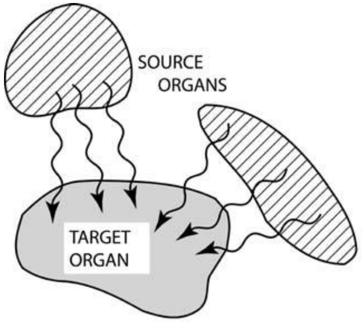


Liver

Spleen

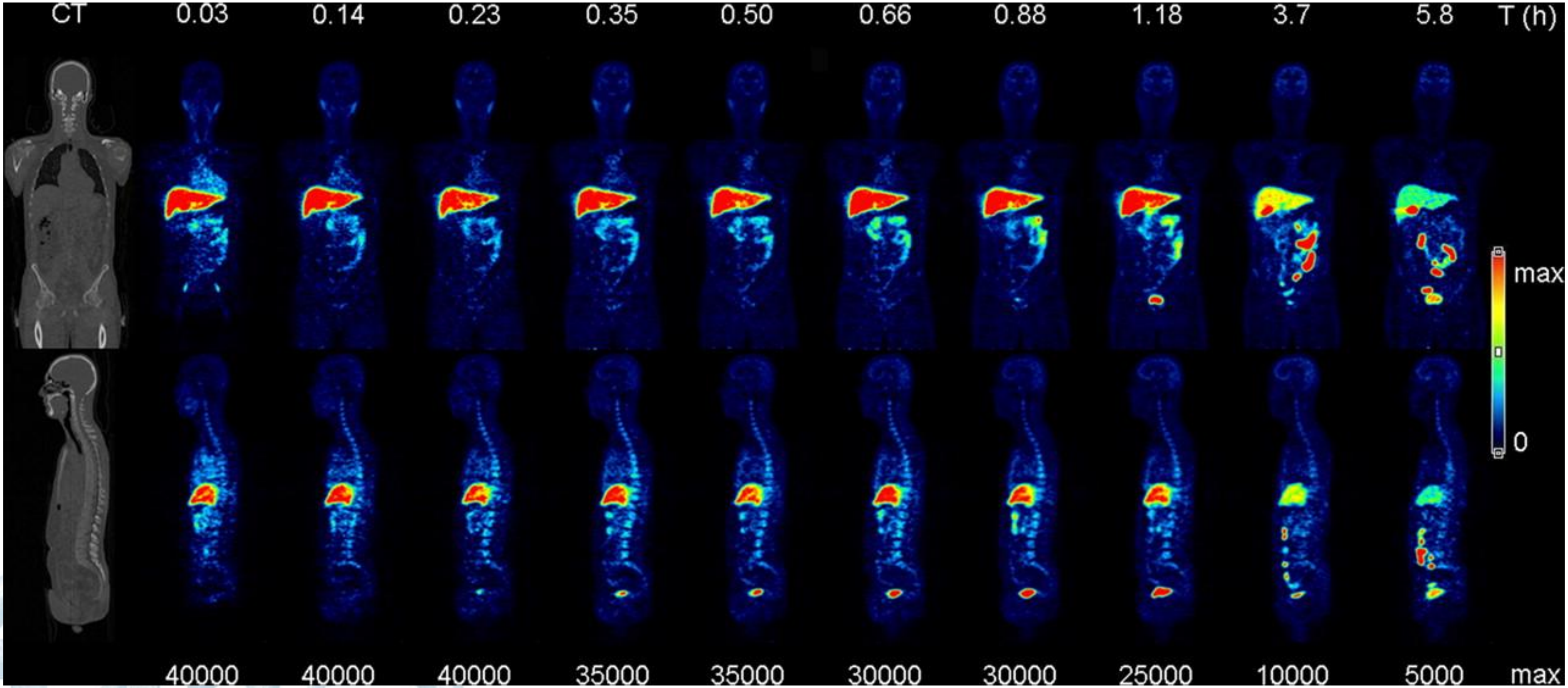
Kidneys

All relevant organs



(a)

Biodistribution: serial imaging

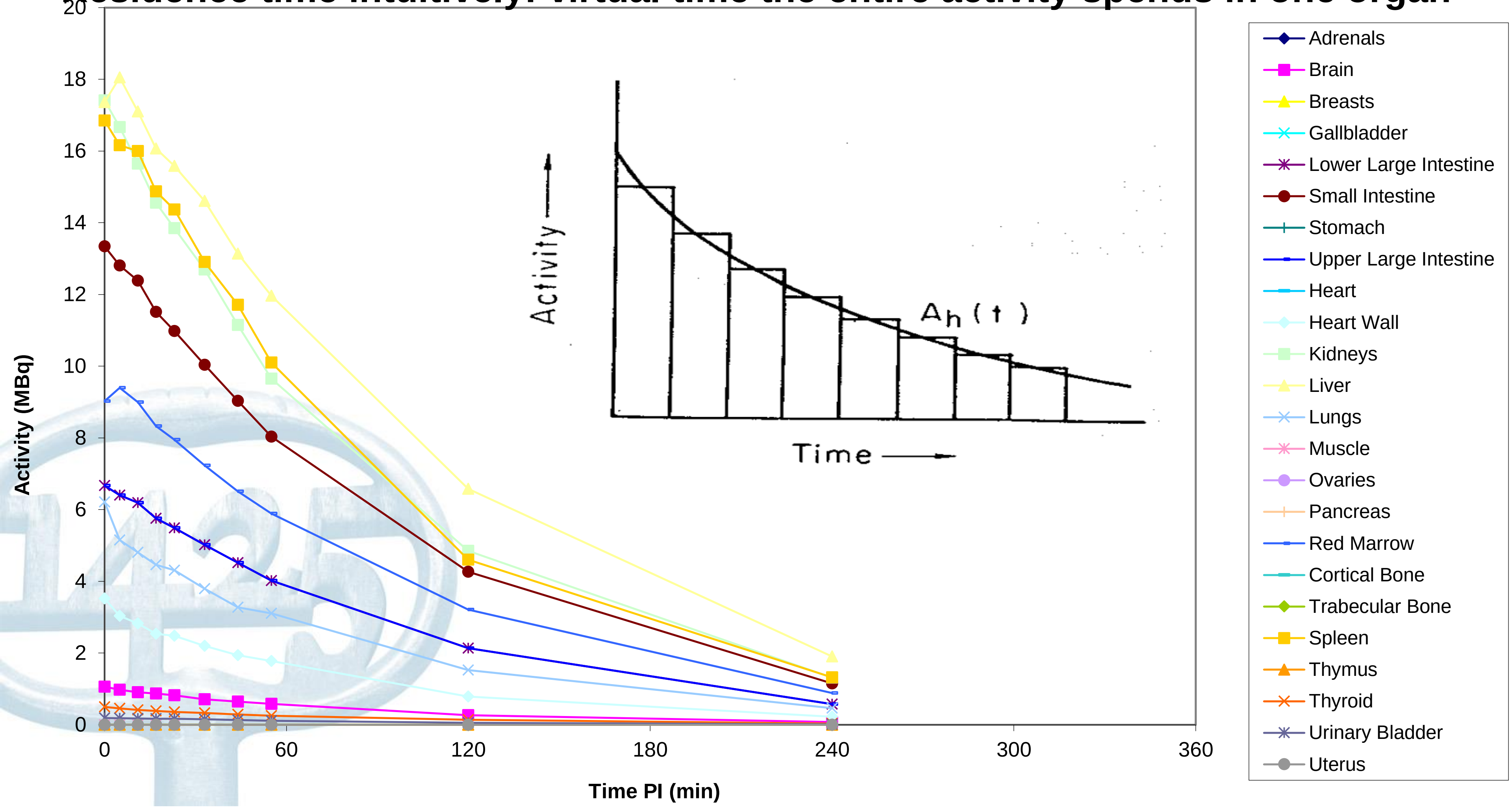


Biodistribution: time activity curve

Integral (Bq.hrs)

Residence time: integral divided injected Activity (A_0) (hrs)

Residence time intuitively: virtual time the entire activity spends in one organ



S-value

- Conversion factor between activity in one part of the body and dose in an other part of the body
- S-value
  - Fysical characteristics of the radionuclide
    - Type of desintegration (X-rays, gamma, beta, …)
    - Desintegration probability
    - Energy per desintegration
  - Absorbed fraction of the emitted energy
    - Attenuation of the medium
    - Scatter
    - Morphology
  - Mass of the target organ
  - Conversion constant

$$\text{dose rate} \propto (\text{activity}) \overbrace{\frac{\left(\dfrac{\text{energy}}{\text{transition}}\right)}{\text{mass}} \; \frac{\text{energy absorbed in a target}}{\text{energy emitted from a source}}}^{\text{S-value}}$$

Emitted Energy per transition

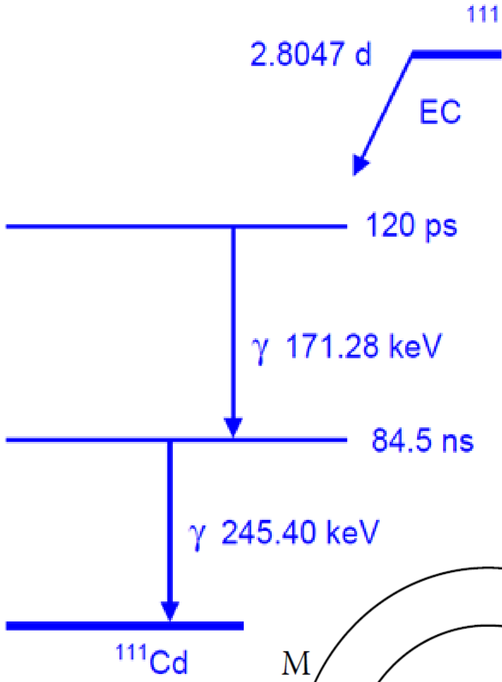
TABLE 3. Nuclear Data for ^{111}In

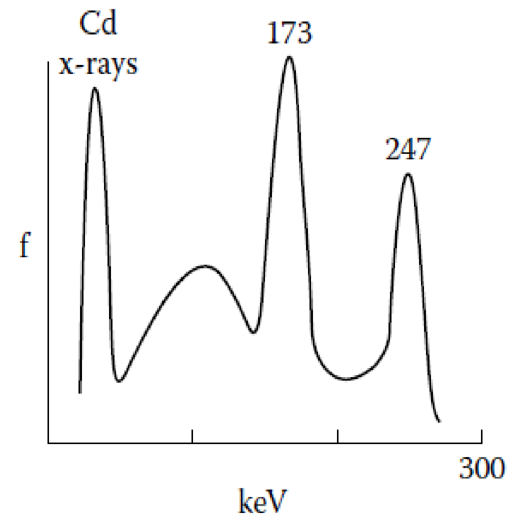
Principal radiation	E_i (keV)*	n_i	Equilibrium dose constant, Δ_i (rad g μCi^{-1} h^{-1})	Equilibrium dose constant, Δ_i (Gy kg Bq^{-1} s^{-1})
Auger electron	2.7	0.98	5.68E−03	4.27E−16
	19.3	0.156	6.41E−03	4.82E−16
Conversion electron	144.6	0.078	2.40E−02	1.80E−15
	167.3	0.0106	3.78E−03	2.84E−16
	170.5	0.00203	7.37E−04	5.54E−17
	171.2	0.000424	1.55E−04	1.16E−17
	218.7	0.0493	2.30E−02	1.73E−15
	241.4	0.00785	4.04E−03	3.03E−16
	244.6	0.00151	7.87E−04	5.91E−17
	245.3	0.000301	1.57E−04	1.18E−17
x-ray	3.1	0.069	4.60E−04	3.46E−17
	23	0.235	1.15E−02	8.64E−16
	23.2	0.443	2.19E−02	1.64E−15
	26.1	0.145	8.06E−03	6.06E−16
γ	171.3	0.902	3.29E−01	2.47E−14
	245.4	0.94	4.91E−01	3.69E−14

*Average electron energies.

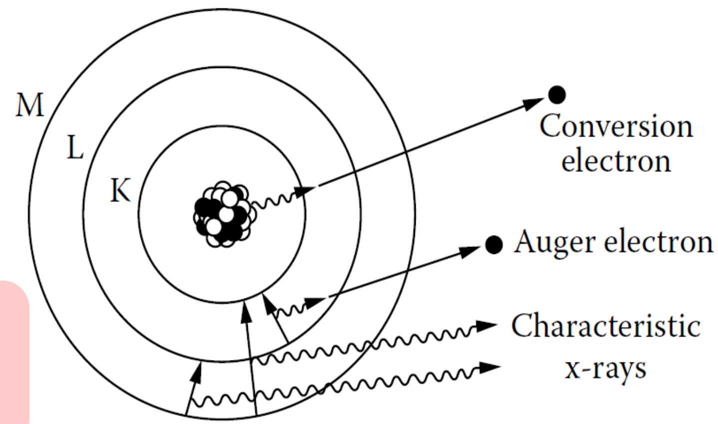
E_i = mean energy per particle or photon; n_i = mean number of particles or photons per nuclear transition; Δ_i = mean energy emitted per nuclear transition.

^{111}In has the following properties: physical half-life, 67.3 h; decay constant, 0.0103 h^{-1}; and decay mode, electron capture.





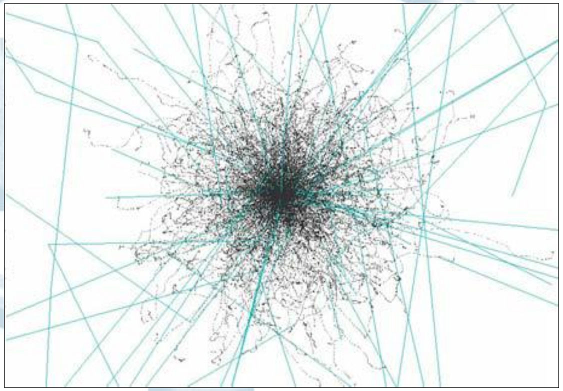
$$\frac{\text{energy}}{\text{transition}}$$

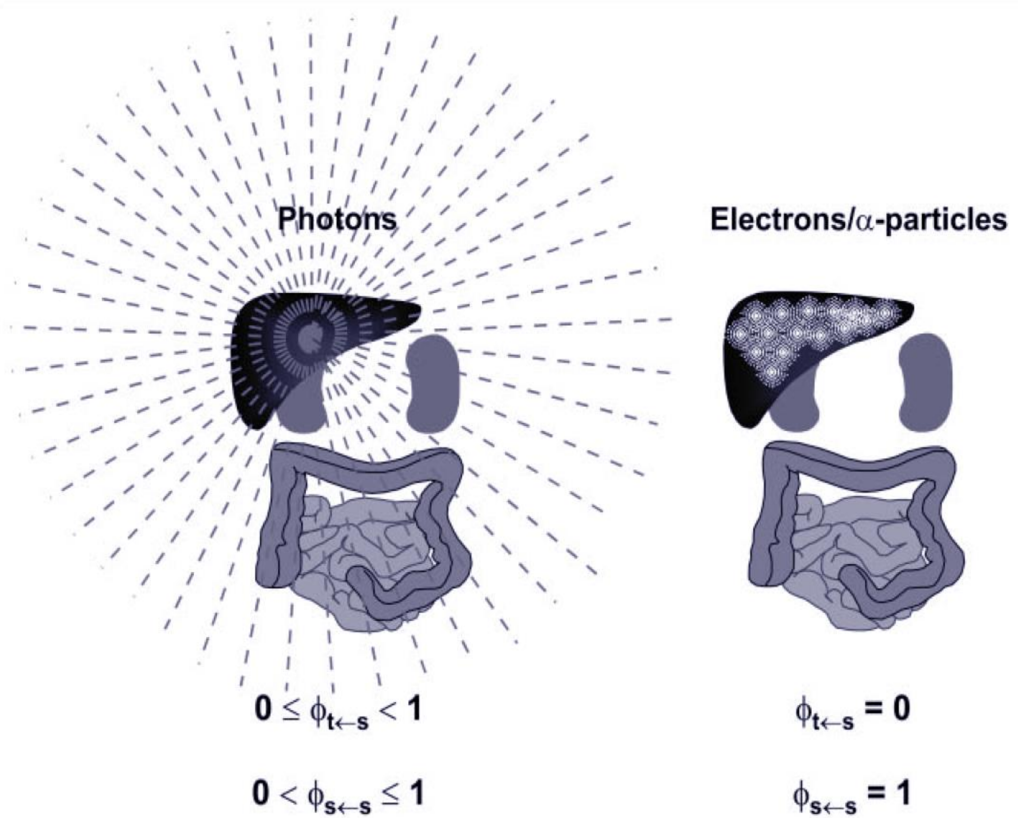


Absorbed fraction

- Fraction of the energy emitted in the source which is absorbed by the target tissue
- Determined by Monte Carlo simulations
- Depends on
  - type radiation
  - energy
- Particular case: α and β:
  - Source → Source ~1
  - Source → Target ~0

$$\frac{\textit{energy absorbed in a target}}{\textit{energy emitted from a source}}$$





Specific absorbed fraction

- SAF (unit: kg^{-1})
- Determined based on phantoms
- More or less realistic compared to normal human

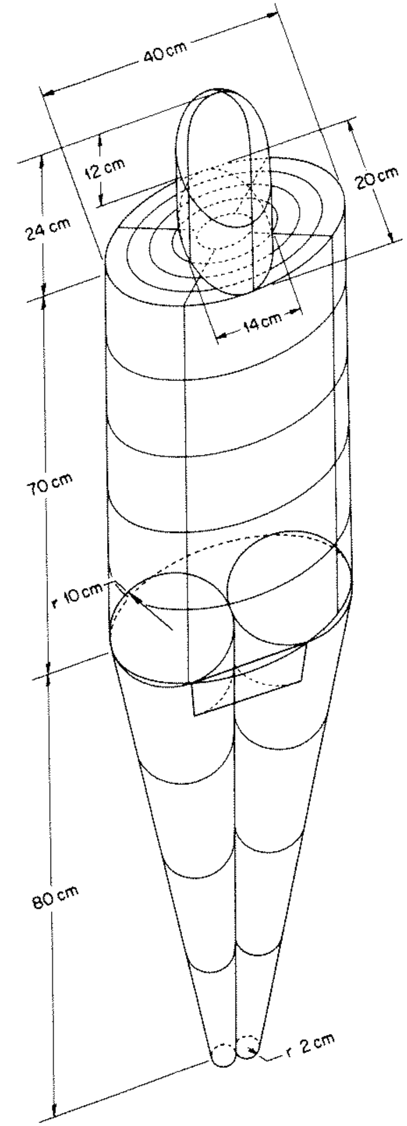
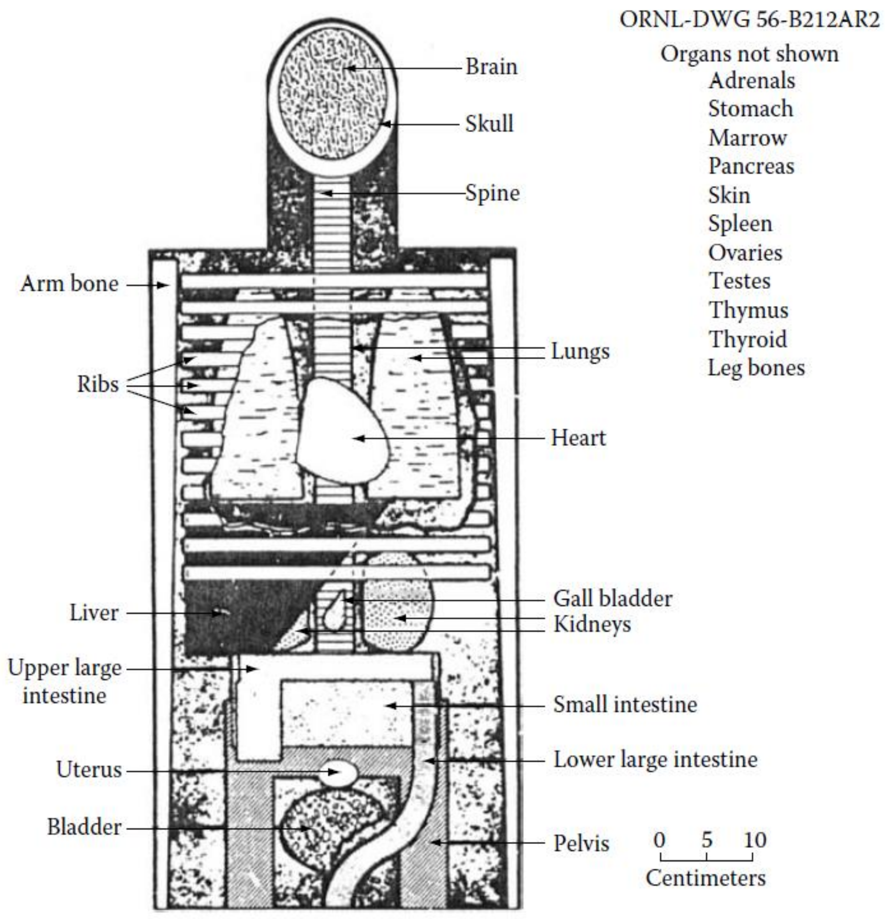
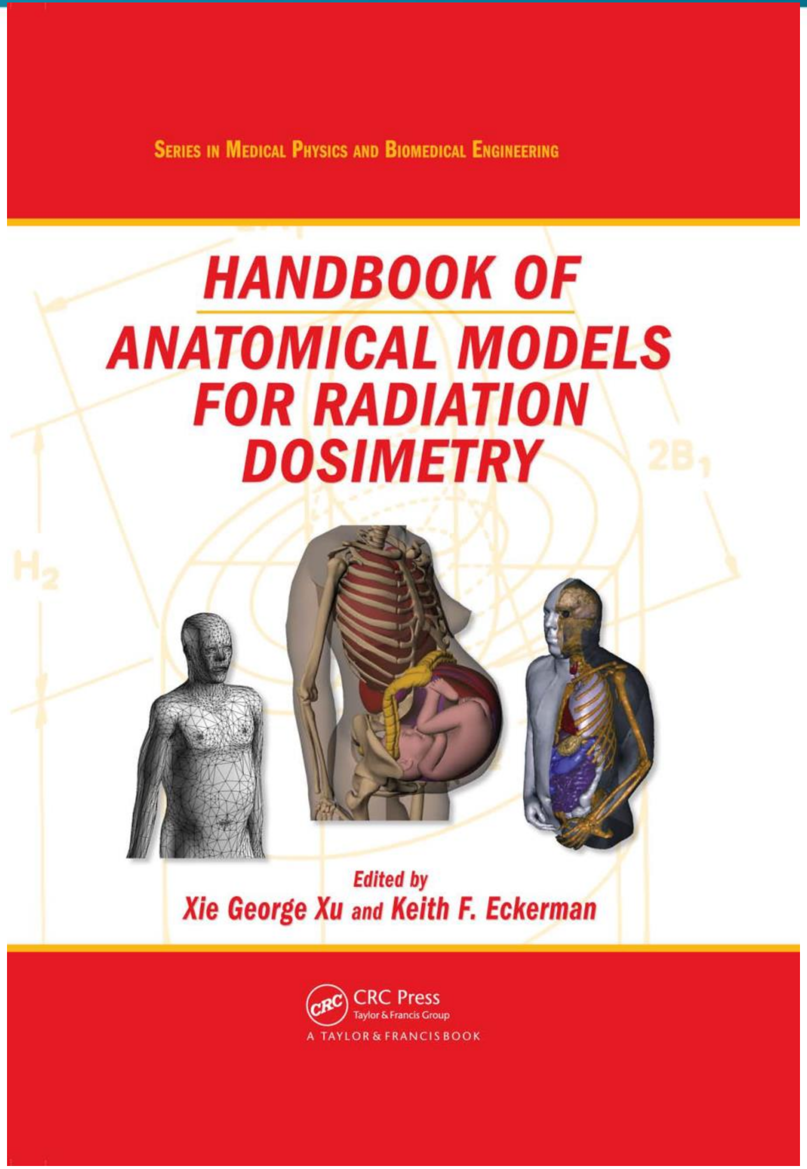


FIG. B-1. Exterior of the adult phantom.

Evolution regarding phantoms





Example of internal dosimetry result: ^{111}In-Octreotide (Octreoscan®)

impact the real

•Constipation (l
significant rep
cl ce)

•Splenecto
with

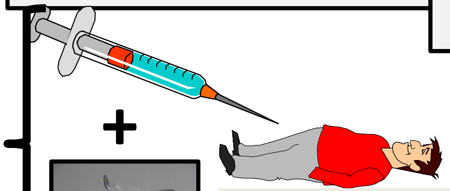
2.9.4. Absorbed doses: ^{111}In labelled-octreotide

^{111}In 2.83 days

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	5.8E−02	7.5E−02	1.2E−01	1.7E−01	3.0E−01
Bladder	2.0E−01	2.5E−01	3.1E−01	4.6E−01	8.2E−01
Bone surfaces	2.7E−02	3.4E−02	5.0E−02	7.6E−02	1.5E−01
Brain	9.6E−03	1.2E−02	2.0E−02	3.3E−02	5.8E−02
Breast	1.2E−02	1.5E−02	2.3E−02	3.7E−02	6.8E−02
Gall bladder	5.2E−02	6.3E−02	9.2E−02	1.4E−01	2.2E−01
GI-tract					
Stomach	4.3E−02	5.0E−02	7.8E−02	1.1E−01	1.8E−01
SI	2.9E−02	3.8E−02	5.9E−02	9.1E−02	1.6E−01
Colon	2.9E−02	3.6E−02	5.5E−02	8.9E−02	1.5E−02
(ULI	3.0E−02	3.7E−02	5.8E−02	9.4E−02	1.6E−01)
(LLI	2.7E−02	3.4E−02	5.0E−02	7.6E−02	1.3E−01)
Heart	2.5E−02	3.2E−02	4.9E−02	7.1E−02	1.3E−01
Kidneys	4.1E−01	4.9E−01	6.7E−01	9.6E−01	1.6E+00
Liver	1.0E−01	1.3E−01	2.0E−01	2.7E−01	4.8E−01
Lungs	2.3E−02	3.0E−02	4.4E−02	6.8E−02	1.2E−01
Muscles	2.0E−02	2.6E−02	3.8E−02	5.7E−02	1.1E−01
Oesophagus	1.4E−02	1.9E−02	2.8E−02	4.4E−02	7.8E−02
Ovaries	2.7E−02	3.5E−02	5.1E−02	8.1E−02	1.4E−01
Pancreas	7.2E−02	8.8E−02	1.3E−01	2.0E−01	3.2E−01
Red marrow	2.2E−02	2.7E−02	3.9E−02	5.3E−02	8.7E−02
Skin	1.1E−02	1.3E−02	2.1E−02	3.3E−02	6.2E−02
Spleen	5.7E−01	7.9E−01	1.2E+00	1.8E+00	3.1E+00
Testes	1.7E−02	2.3E−02	3.5E−02	5.5E−02	1.0E−01
Thymus	1.4E−02	1.9E−02	2.8E−02	4.4E−02	7.8E−02
Thyroid	7.6E−02	1.2E−01	1.8E−01	3.7E−01	6.9E−01
Uterus	3.9E−02	4.9E−02	7.1E−02	1.1E−01	1.9E−01
Remaining organs	2.3E−02	2.8E−02	4.2E−02	6.3E−02	1.1E−01
Effective dose (mSv/MBq)	**5.4E−02**	**7.1E−02**	**1.0E−01**	**1.6E−01**	**2.8E−01**

Clinical Therapeutic Dosimetry
^{90}Y-DOTATOC PRRT DOSIMETRY PROTOCOL

185MBq ^{111}In-pentetreotide



+

BLOOD SAMPLES

15 min | 4 h | 24 h | 48 h

PLANAR IMAGING

1

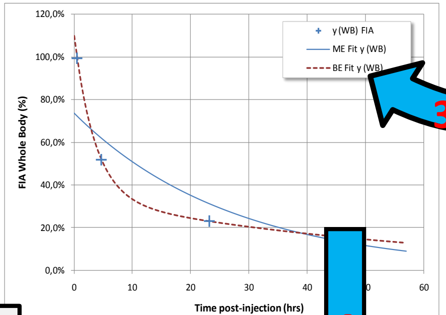
15 min | 4 h | 24 h | 48 h

GEOMETRIC MEAN COUNTS

2

FRACTION OF INJECTED ACTIVITY

3



4

Bi-exponential (BE) fit		
Fit: a exp(b x) + c exp(d x)		
a	0,75850	FIA
b	-0,27910	1/hours
c	0,33940	FIA
d	-0,01708	1/hours
Residence time	22,58886	hours
Pearson:	1,0000	

*Baechler et al, Med Phys 2008

KIDNEY VOLUMES

OLINDA

5

Target Organ	Total (mGy/MBq)	Total (mGy)	Total after 4 administration (Gy)
Adrenals	0,135	428	[illegible]
Brain	0,135	428	[illegible]
Breasts	0,135	428	[illegible]
Gallbladder Wall	0,135	428	1,71
LLI Wall	0,135	428	1,71
Small Intestine	0,135	428	1,71
Stomach Wall	0,135	428	1,71
ULI Wall	0,135	428	1,71
Heart Wall	0,135	428	1,71
Kidneys	2,22	7031	28,13
Liver	2,23	7063	28,25
Lungs	0,135	428	1,71
Muscle	0,135	428	1,71
Ovaries	0,135	428	1,71
Pancreas	0,135	428	1,71
Red Marrow	0,101	320	1,28
Osteogenic Cells	0,237	751	3,00
Skin	0,135	428	1,71

ABSORBED DOSE

6

Kidney dosimetry

Fractions of administration:	4	
Absorbed dose after 1 administration:	7031	mGy
Absorbed dose after 4 administration(s):	28125	mGy
Alfa-Beta ratio:	2600	mGy
Repair half-time:	2,8	hrs
Repair rate constant µ:	0,248	1/hrs
	Right	Left
Contribution to total kidney activity :	100%	100%

Lea-Catcheside factor:	G	0,07950	
Relative effectiveness:	RE	1,21500	
Biological effective dose after 1 administration:	BED(1)	8,5	Gy
Biological effective dose after 4 administration(s):	BED(4)	34,2	Gy

$$BED = D_i \times (1 + (G \times D_i)/(\alpha/\beta))^*$$

BIOLOGICAL EFFECTIVE DOSE

Overview

- Nuclear medicine treatment: radionuclide therapy (RNT)
- Therapeutic radioisotopes and radiopharmaceuticals
- Dosimetry
- **Currently used RNT and planning aspects**
  - **$Na^{131}I$ for thyroid disease**
  - ^{131}I-MIBG
  - Peptide receptor radionuclide therapy (PRRT)
  - ^{177}Lu-PSMA (Prostate specific membrane antigen)
  - Radium-223 for bone metastases
  - Selective internal radiation therapy (SIRT)
- Conclusions

SODIUM-IODIDE SYMPORTER TARGETING:

$^{123}I^{-}$

$^{131}I^{-}$

Treatment planning Na^{131}I therapy (Thyroid)

- Limit iodide exposure
  - No contrast enhanced CT in 6 previous weeks
  - Avoid iodide rich food (seasalt, seaweed, vitamins)
- Benign thyroid disease:
  - Empiric: standard activity is prescribed e.g. 37 to 555 MBq
  - "Dosimetric method":
    - Volume is taken into account
    - Uptake and retetion is taken into account (with $123I^{-}$ scintigraphy)
- Malignant thyroid disease
  - Thyroidectomy!
  - Activate the sodium-iodide symporter (NIS):
    - Hormone withdrawal
    - Recombinant Thyroid Stimulating Hormone (THS)

Overview

- Nuclear medicine treatment: radionuclide therapy (RNT)
- Therapeutic radioisotopes and radiopharmaceuticals
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- **Currently used RNT and planning aspects**
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  - **^{131}I-MIBG**
  - Peptide receptor radionuclide therapy (PRRT)
  - ^{177}Lu-PSMA (Prostate specific membrane antigen)
  - Radium-223 for bone metastases
  - Selective internal radiation therapy (SIRT)
- Conclusions

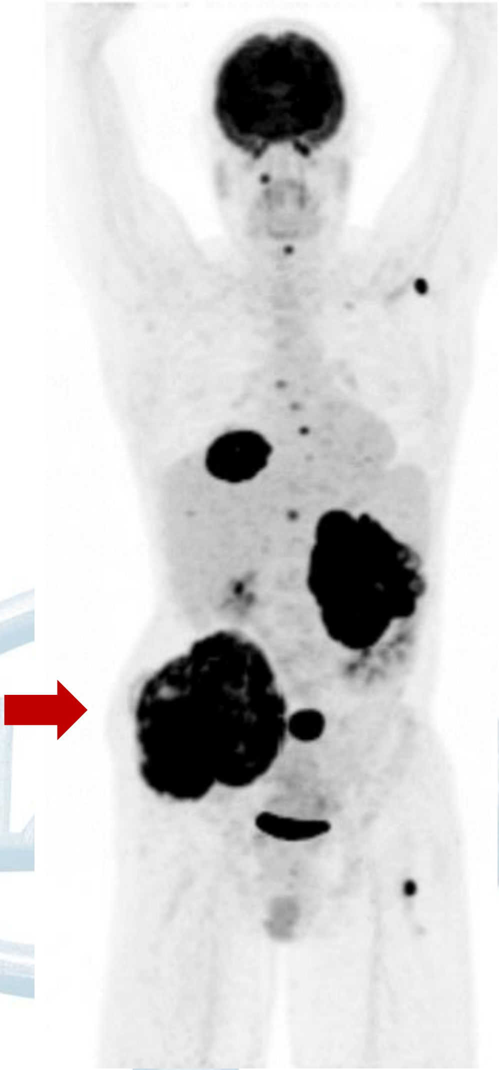
NOREPINEPHRINE TRANSPORTER TARGETING:

^{123}I-MIBG

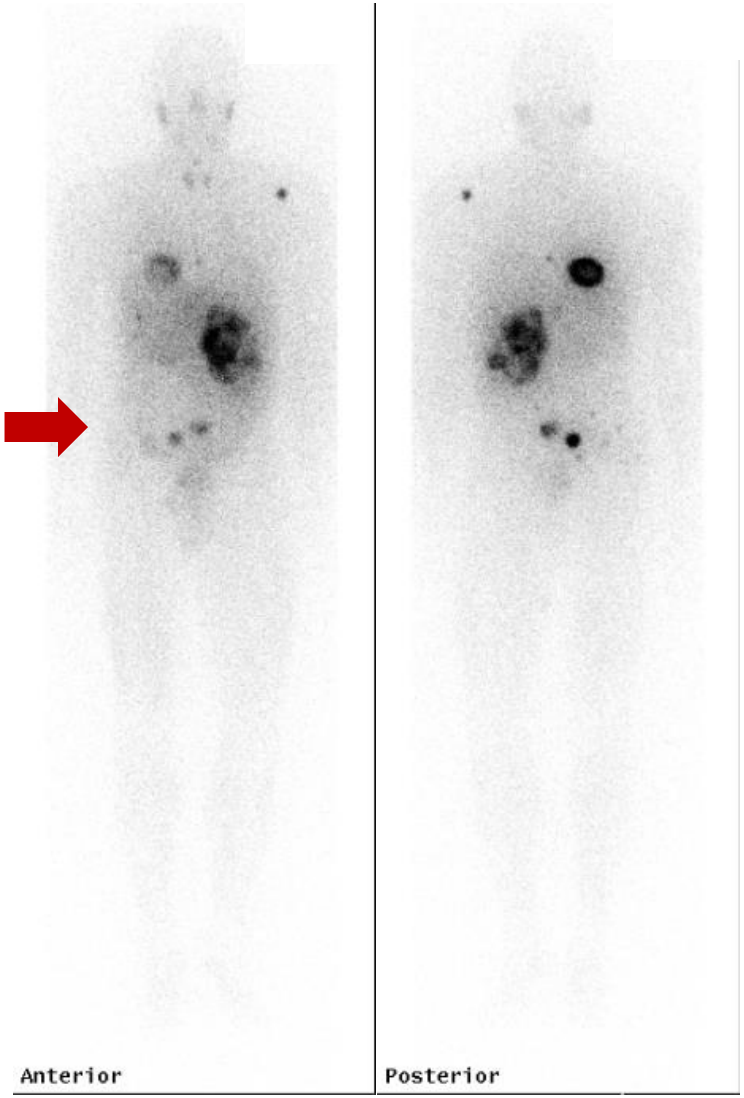
^{131}I-MIBG

Case: 34 year old man - paraganglioma

^{18}F-FDG

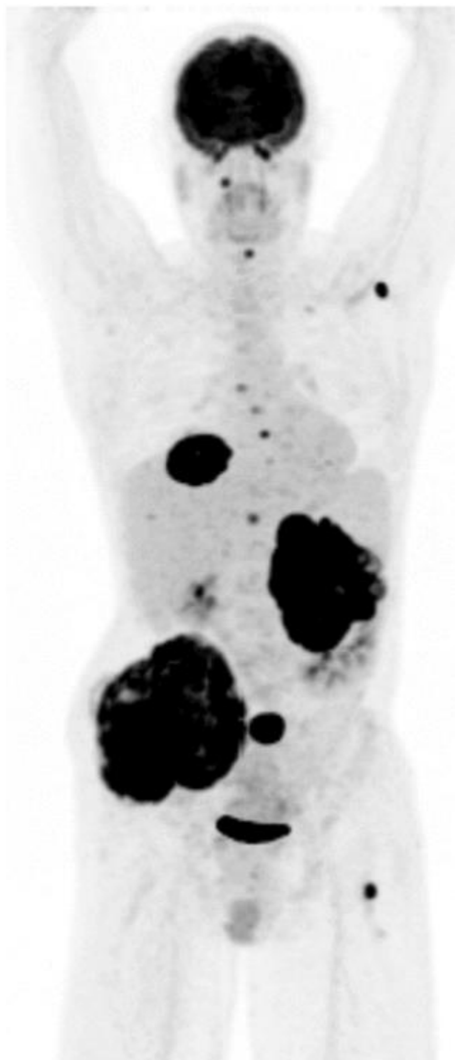


^{123}I-MIBG

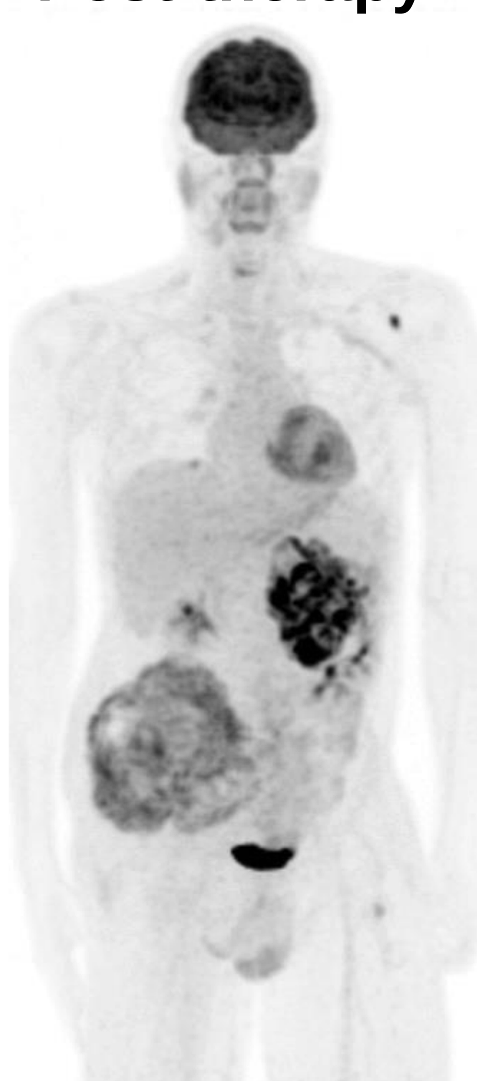


Case: status post chemo and EBRT

Baseline



Post-therapy



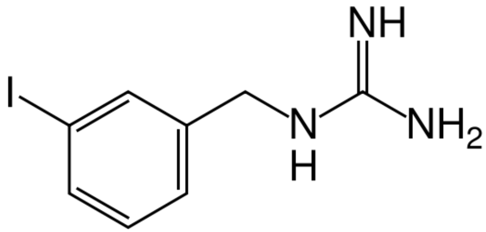
Partial metabolic reponse

Plan: ^{131}I-MIBG

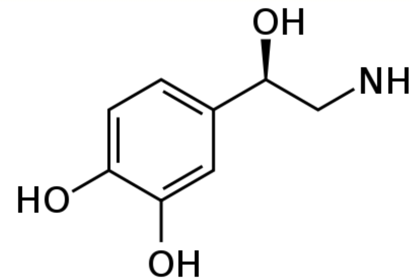
But: paraneoplastic thrombocytopenia: ~~^{131}I-MIBG~~

Sympatomimetics: MIBG/MFBG

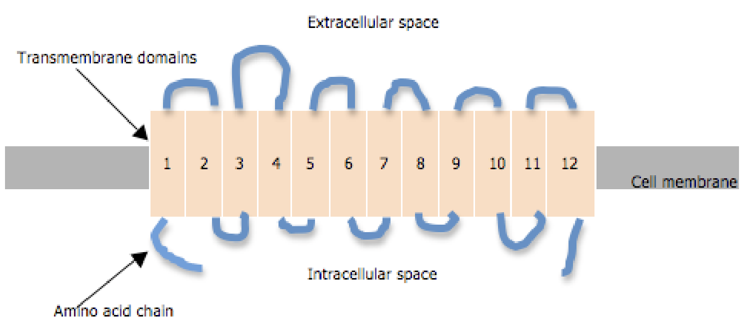
MIBG



Norepinephrine



- Metaiodobenzylguanidine (mIBG or MIBG)
- Can be labeled with
  - Iodine-123: ^{123}I-MIBG
  - Iodine-131: ^{131}I-MIBG
  - Fluorine-18: ^{18}F-MFBG
- Substrate for the human norepinephrine transporter (hNET or SLC6A2)



Wiseman GA, 2009, J Nucl Med; 50:1448-54.

Radiopharmaceuticals for Neuro-endocrine Tumors: Radiolabelled Catecholamines

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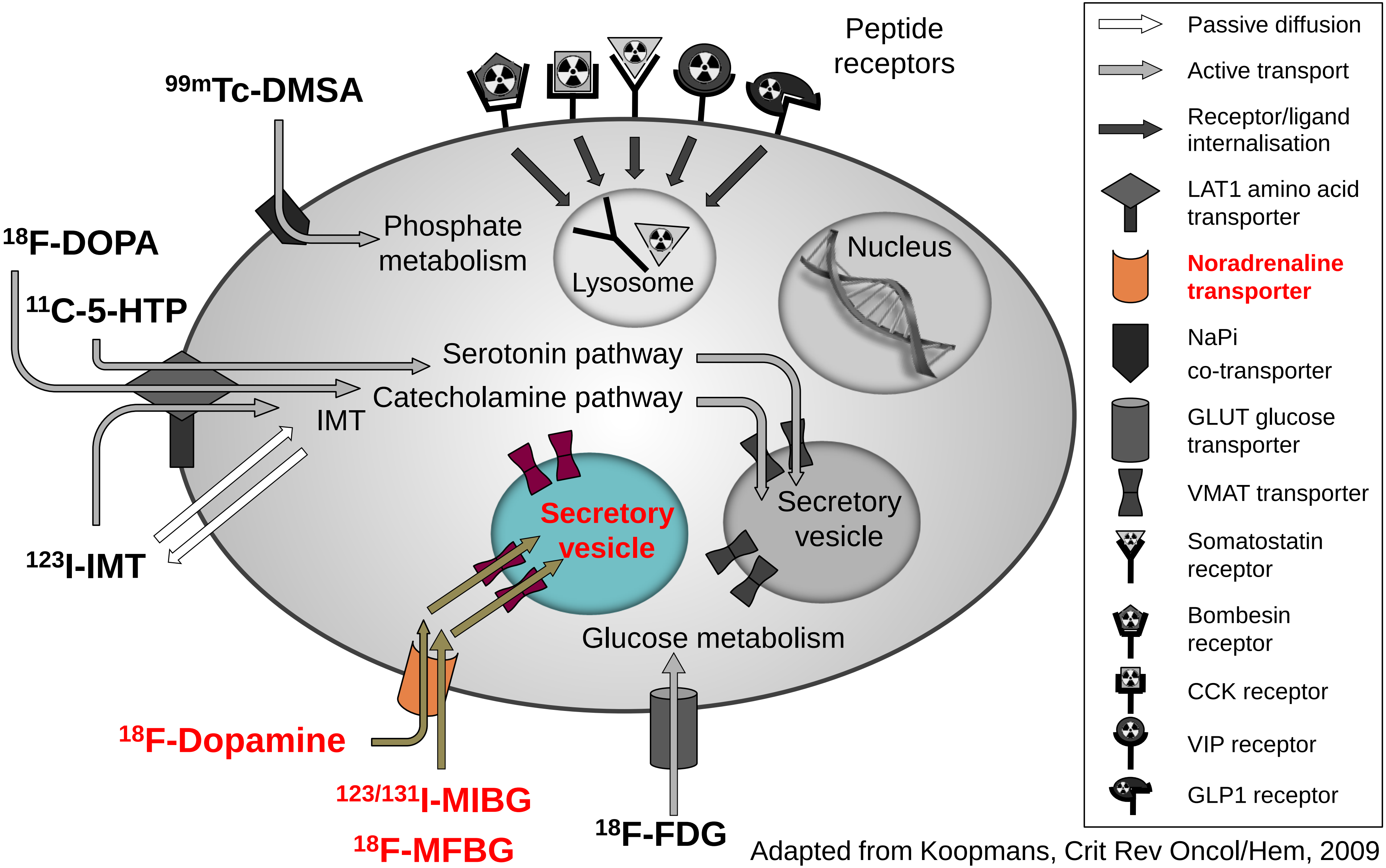
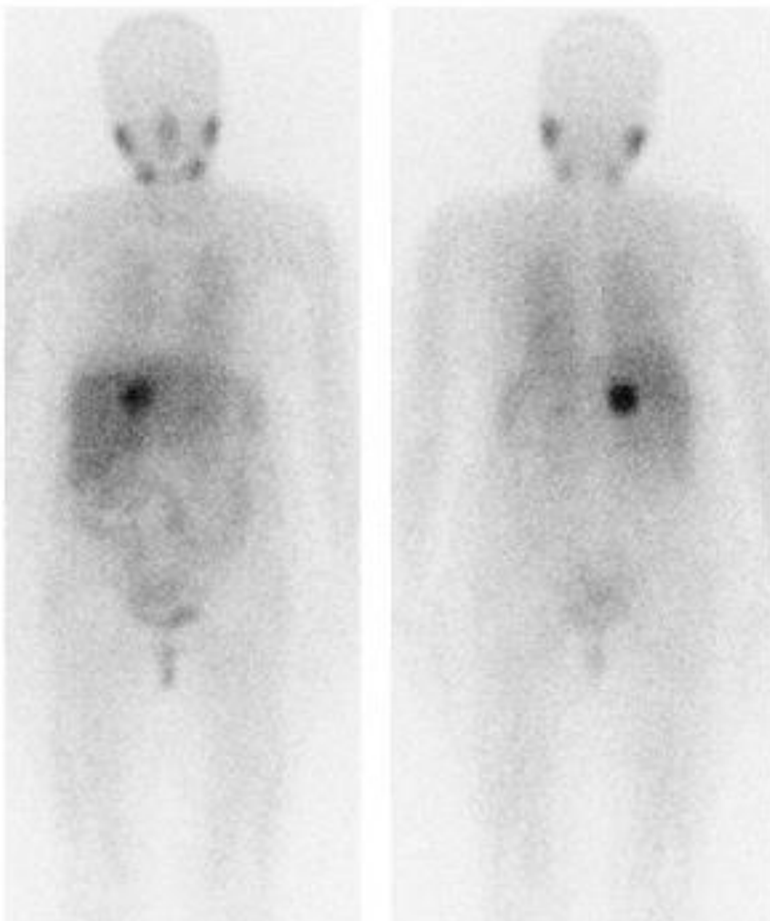


Adapted from Koopmans, Crit Rev Oncol/Hem, 2009

^{123}I-MIBG scintigraphy

Patient 1

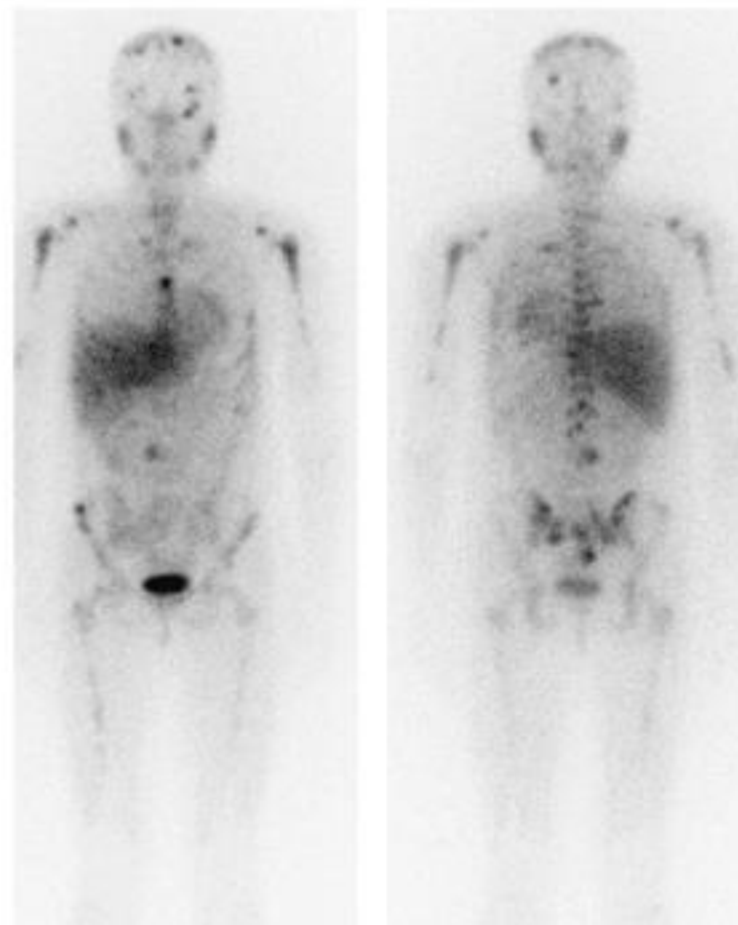


Phaechromocytoma

Solitary location

R/ Surgery

Patient 2



Paraganglioma

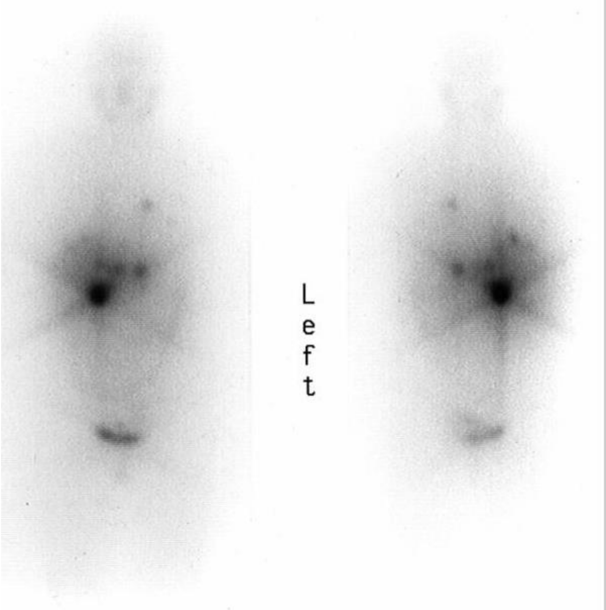
Diffuse bone metastases

R/ **^{131}I-MIBG**

Wiseman GA, 2009, J Nucl Med; 50:1448-54.

131I-MIBG therapy

- Efficient therapy of neural crest tumors
  – Phaechromocytoma
  – Paraganglioma
  – Neuroblastoma
- Overall response rates around 30% in refractory or recurrent diseases
- Combined with
  – Chemotherapy (e.g. topotecan)
  – Radiosensitizers
  – Autologous stem cell transplant
- Most efficient nonsurgical therapeutic modality
- Antisecretory effect with powerful palliation of symptomatic disease (response rate: 75%-90%)



Post therapy ^{131}I-MIBG sctinigraphy

Grünwald, 2010, Semin Nucl Med; 40:153-63 – PMID: 20113683

Ezzidin S, 2012, Radiat Oncol; doi: 10.1186/1748-717X-7-8 – PMID: 22277577

Treatment planning ^{131}I-MIBG Therapy

- Theranostic imaging
- Avoidance of medication that can block the Norepinephrin transporter (hNET)
- Administration of KI (Potassium Iodide) to block uptake of free $^{131}I^{-}$ by the thyroid gland ("saturation")

- Activity: fixed or per kg

- In dosimetry based strategy:
  - 2 treatments 2 days apart
  - Myeloablative dose of 4Gy whole body dose
  - Dosimetry after first course, compute dose
  - Administer activity that will lead to cumulative 4Gy WB dose in second treatment

Overview

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  - **Peptide receptor radionuclide therapy (PRRT)**
  - ^{177}Lu-PSMA (Prostate specific membrane antigen)
  - Radium-223 for bone metastases
  - Selective internal radiation therapy (SIRT)
- Conclusions

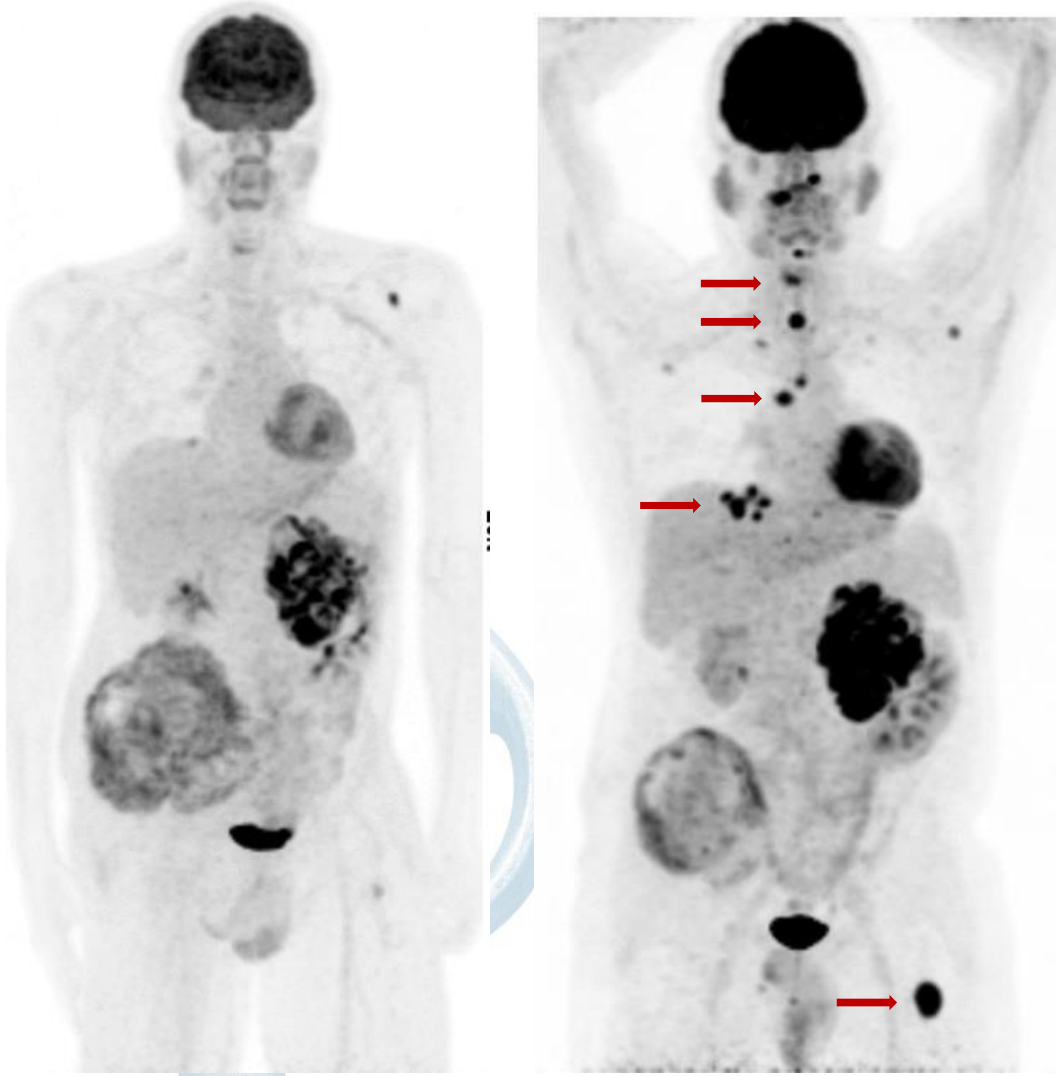
SOMATOSTATIN RECEPTOR TARGETING:
^{68}Ga-DOTATATE
^{177}Lu-DOTATATE

Case: 1½ years later: progression

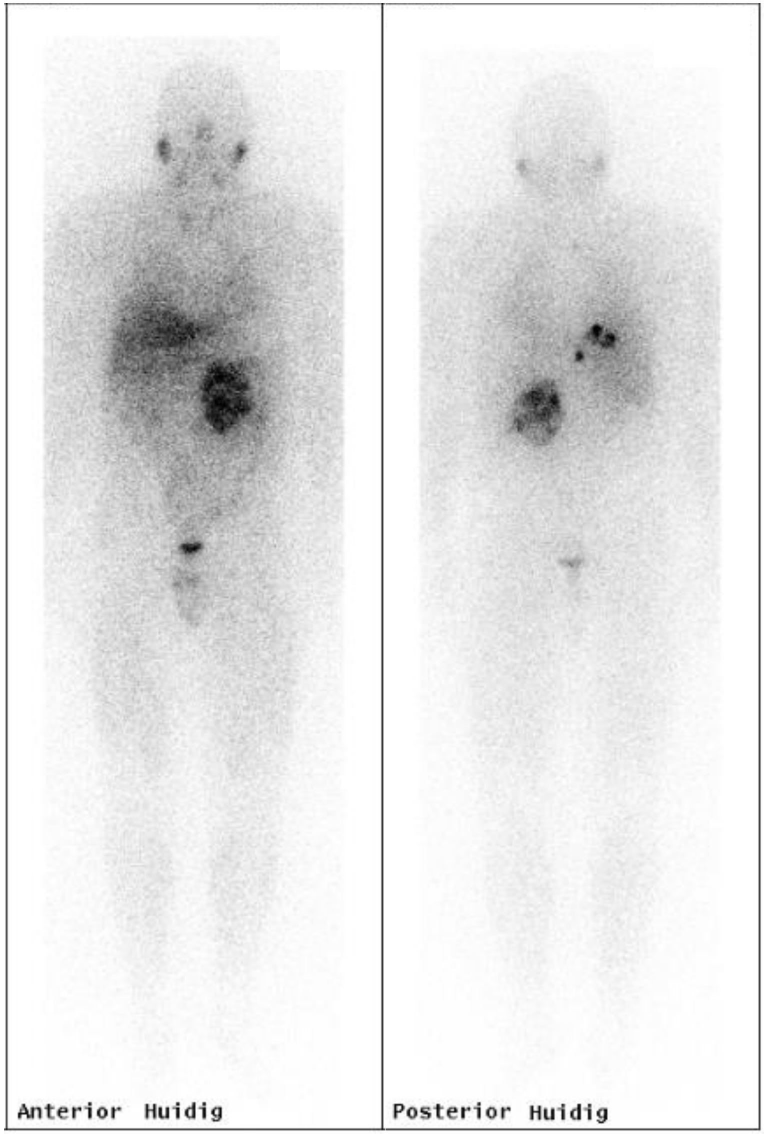
^{18}F-FDG

Post Chemo-RT

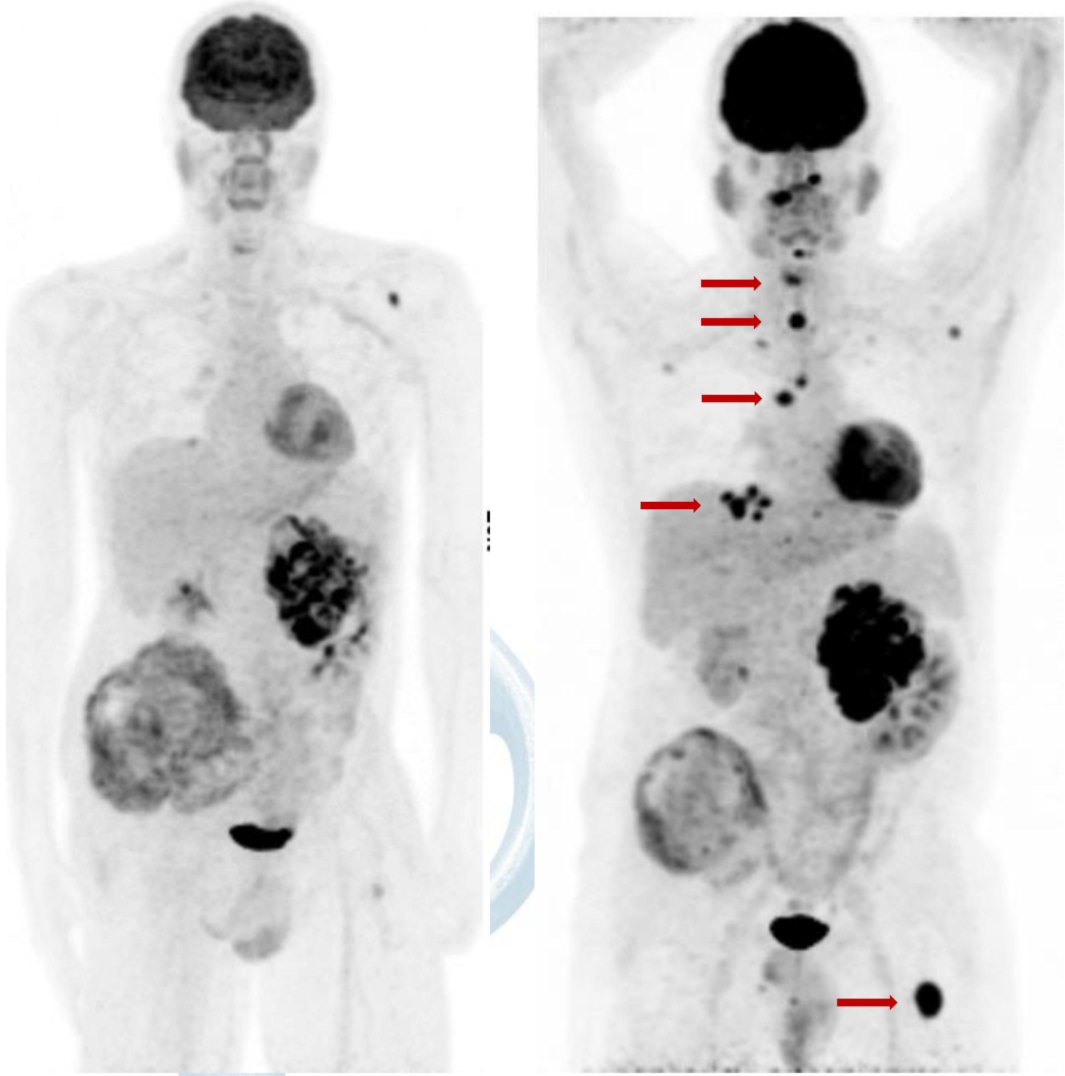
New scan

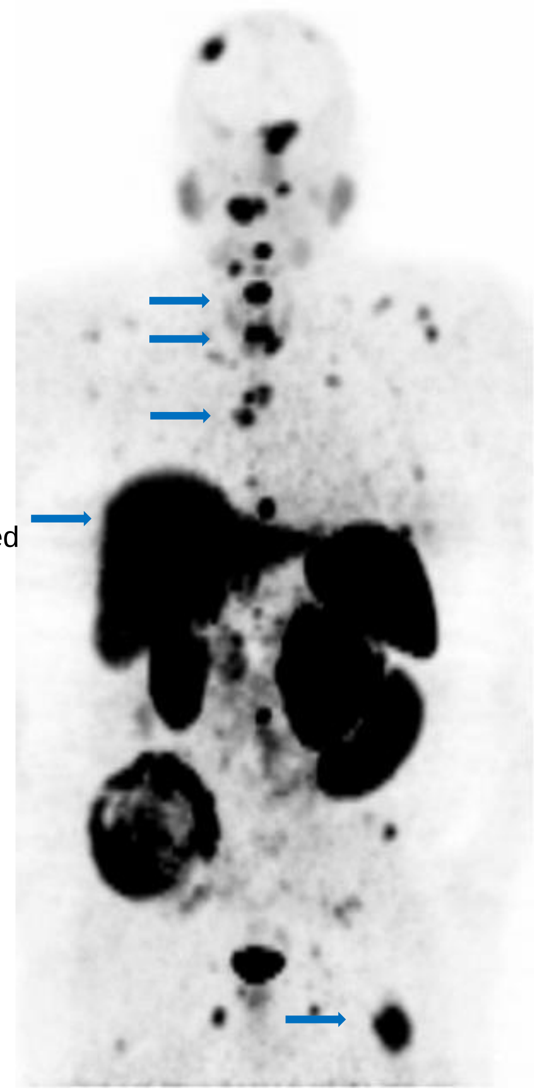


^{123}I-MIBG



Case: 1½ years later: progression





Case: 1½ years later: PRRT

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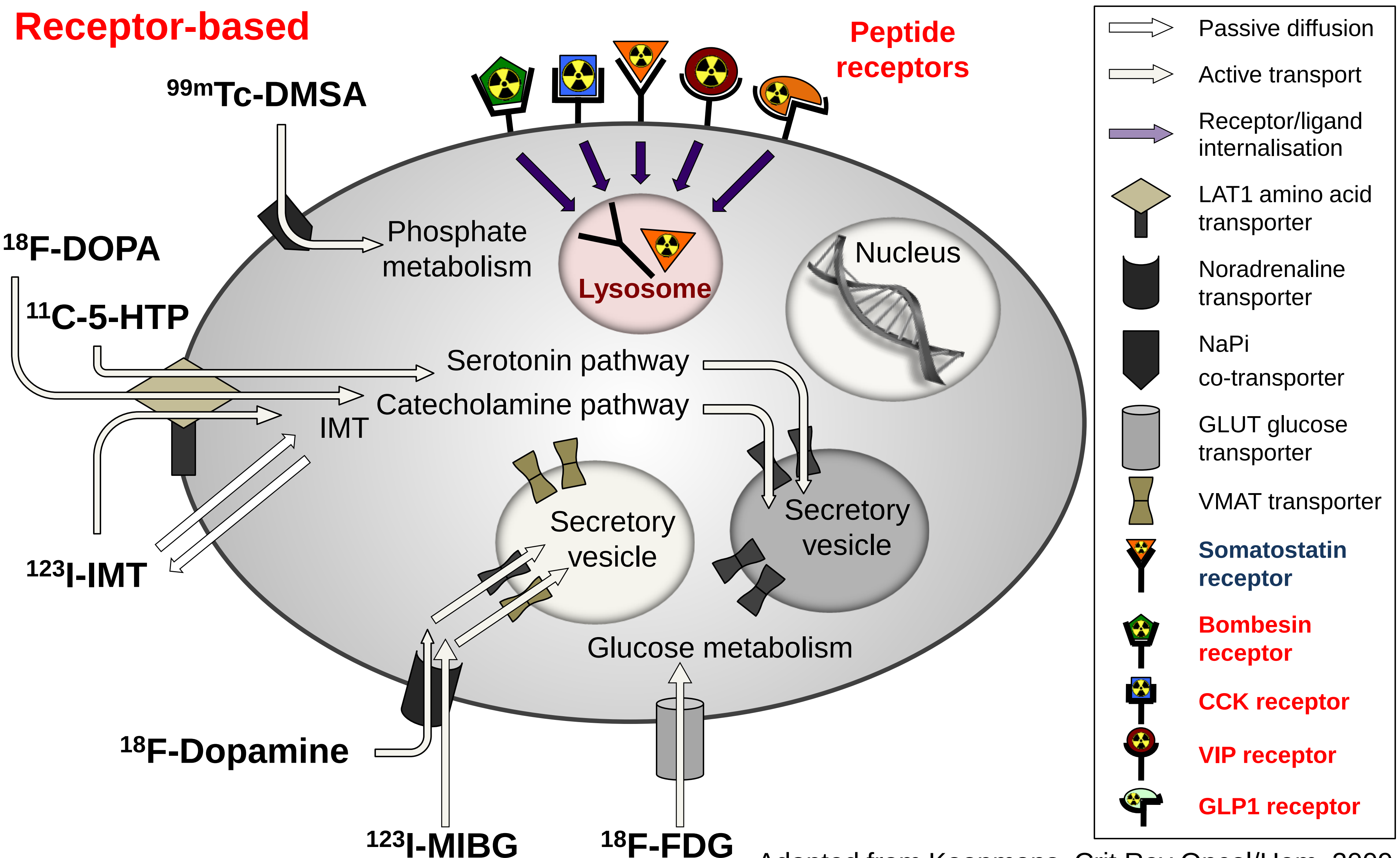
^{18}F-FDG

New scan

^{68}Ga-DOTATATE

^{177}Lu-DOTATATE

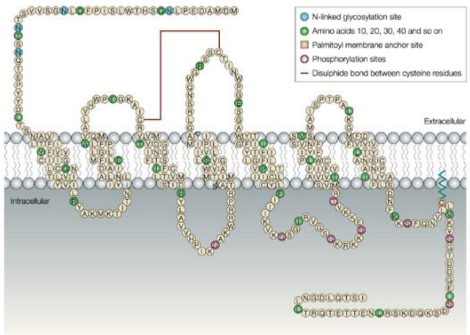
Peptide Receptors

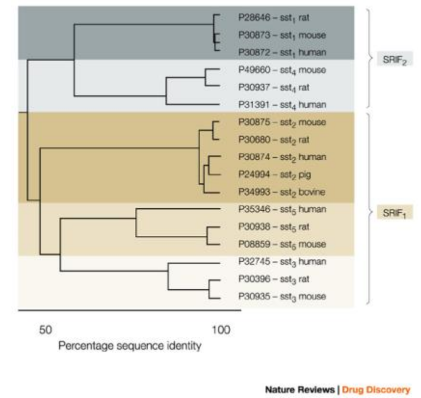


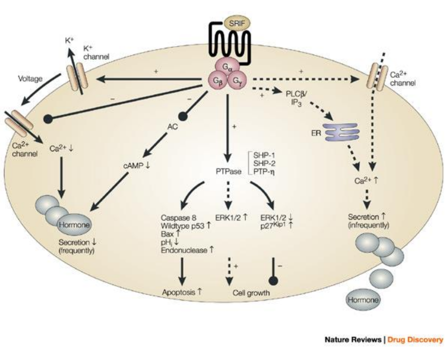
Adapted from Koopmans, Crit Rev Oncol/Hem, 2009

Somatostatin Receptor (SSTR)

- Seven transmembrane G-coupled receptor
- Six human subtypes
  - SSTR1
  - SSTR2 (2A & 2B)
  - SSTR3
  - SSTR4
  - SSTR5
- Function
  - ↓ secretions
    - Endocrine
    - Exocrine
  - ↓ Cell growth
  - ↑ Apoptosis
- Internalise upon agonist binding / recycle





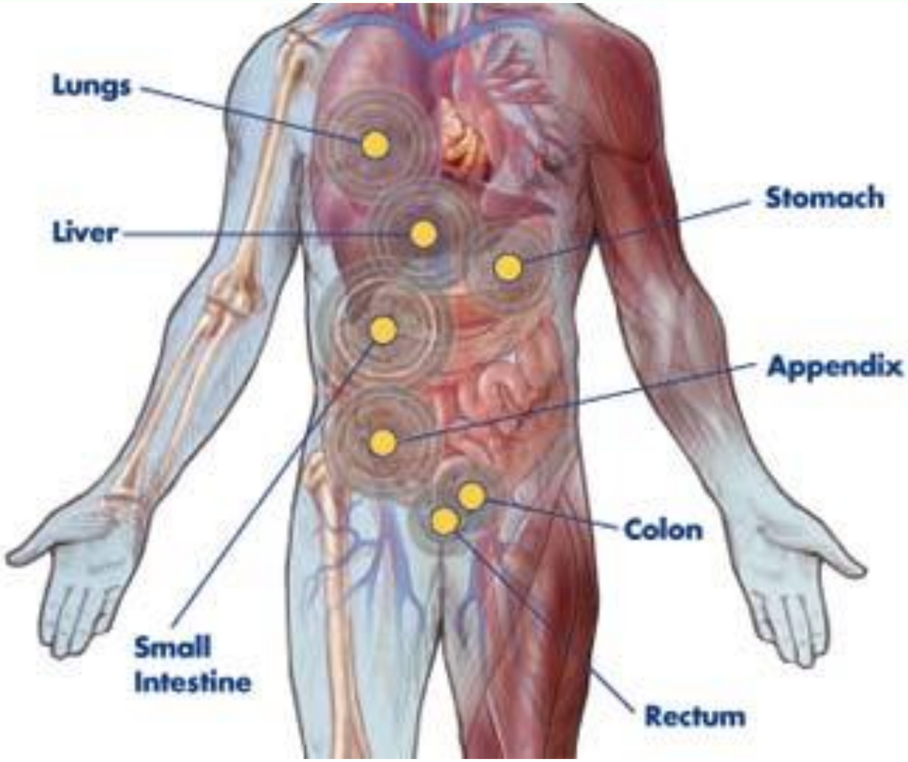


Weckbecker, 2003, Nat Rev Drug Disc

Neuro-endocrine Tumors (NET’s)

CHARACTERISTICS:

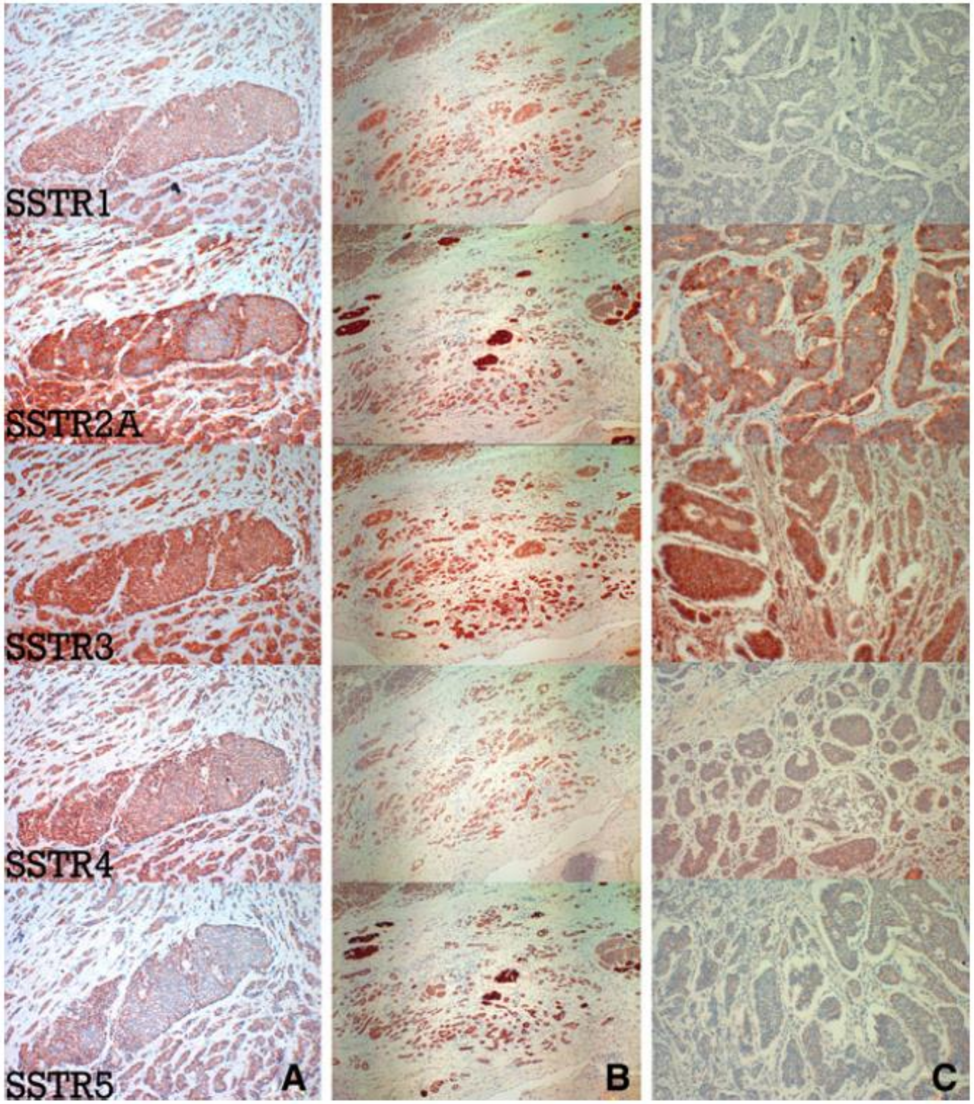
- Arise from neuroendocrine cells
- Slow growing and rare
- Young patients
- Heterogenic group of tumors with specific features
- Can secrete hormones,
  - e.g. serotonin -> carcinoid syndrome



DIAGNOSIS:

- Clinical: complaints
  - Mechanical
  - Hormonal
- Tumormakers in blood and urine
- Imaging: US, CT, MRI, Octreoscan, 68Ga-DOTATOC PET/CT
- Pathology

Overexpression of SSTR subtypes on NET



48%

86%

87%

50%

46%

- cytoplasmic staining
  - SSTR1
  - SSTR3
  - SSTR5
- membrane bound
  - SSTR2A

LN M+ NET ileum NET pancreas

Kaemmerer, EJNM&MI, 2011

Diagnostic agents for SSR

Radionuclide + Chelator + Somatostatin analogue

Radionuclide	Chelator	Somatostatin analogue
^{111}Indium	DTPA	Octreotide
^{99m}Technetium	DOTA	Tyr^{3}-octreotide (TOC)
^{68}Gallium	NOTA	Tyr^{3}-octreotate (TATE)
^{18}Fluorine	HYNIC	Naph-octreotide (NOC)

DIAGNOSTIC COMBINATIONS:

- ^{111}In-DTPA-octreotide (Octreoscan®) — SPECT
- ^{68}Ga-DOTA,Tyr^{3}-octreotide (^{68}Ga-DOTATOC) — PET
- ^{68}Ga-DOTA,Tyr^{3}-octreotate (^{68}Ga-DOTATATE) — PET
- ^{68}Ga-DOTA, [Phe^{1}-1-Nal^{3}]-octreotide) (^{68}Ga-DOTANOC) — PET

SSR imaging: very sensitive and specific technique for NET detection

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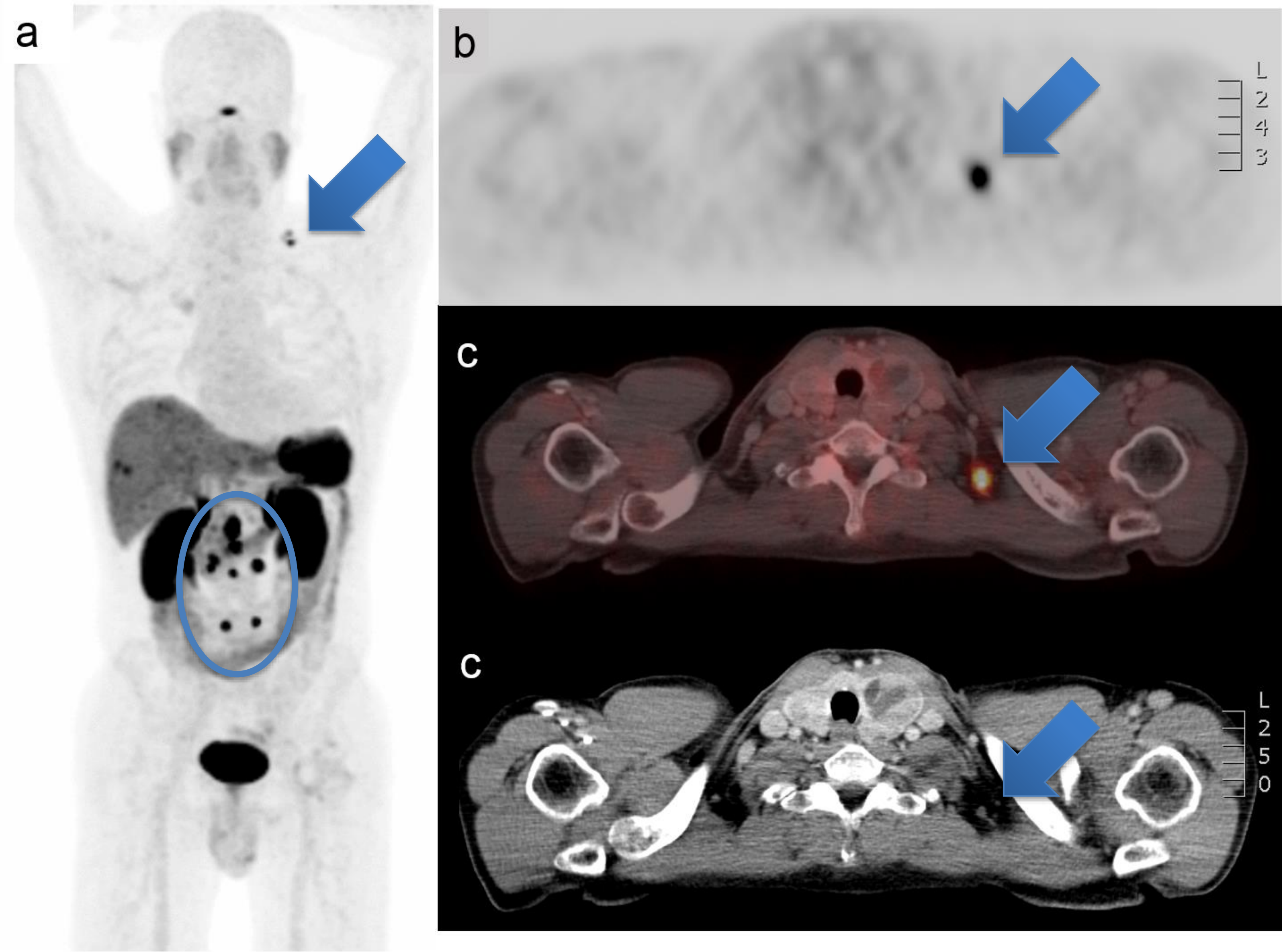


Comparison of ^{68}Ga-DOTATATE PET/CT vs. ^{111}In-pentetreotide SPECT: largest series on record

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

Comparison of ^{68}Ga-DOTA-peptide PET vs. ^{111}In-pentetreotide

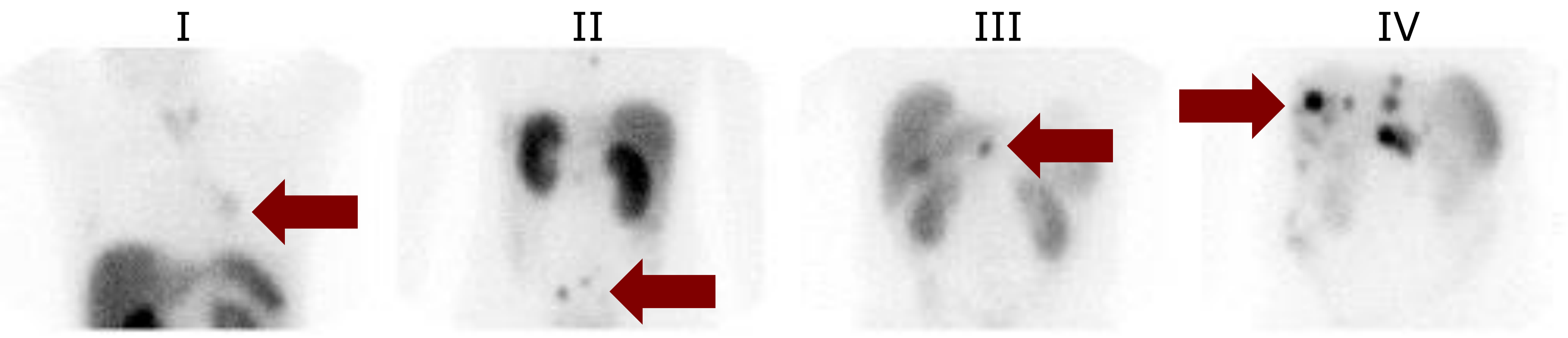
Author	Year	n	^{68}Ga-Peptide	Level (Patient /lesion)	Sensitivity ^{111}In-pentetreotide	Sensitivity ^{68}Ga-peptide	Δ Sens
Gabriel	2007	84	-TOC	Patient	52.0%	97.0%	45.0%
Buchmann	2007	27	-TOC	Region	66.0%	100.0%	34.0%
Srirajaskanthan	2010	51	-TATE	Lesion	11.9%	74.3%	**62.4%**
Van Binnebeek	2016	53	-TOC	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%
TOTAL		**424**		**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

Semi-quantitative determination of SSR expression with ^{111}In-pentetreotide

Krenning scale

Visual comparison of uptake in tumor versus normal organs



< Liver **= Liver** **> Liver** **Most intense**

Krenning ER et al., Somatostatin receptor scintigraphy. In: Nuclear medicine annual. 1995:1-5

Theranostic concept: Therapeutic agents for Peptide Receptor **Radionuclide** Therapy (PR**R**T)

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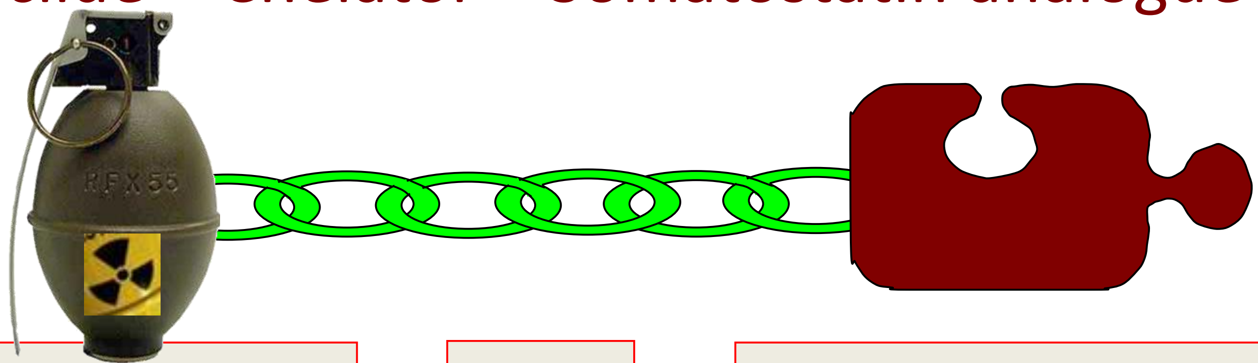
Radionuclide + Chelator + Somatostatin analogue

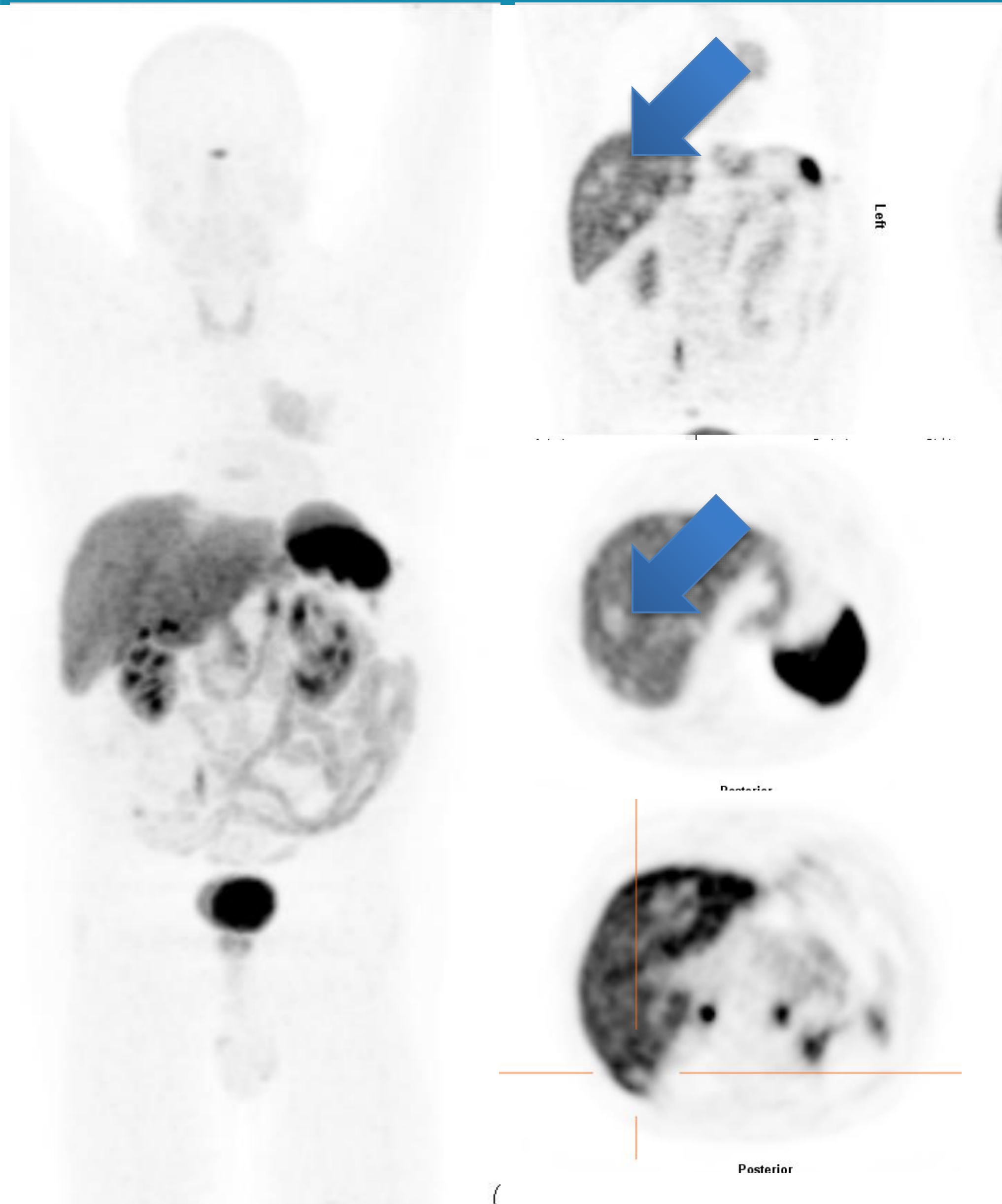


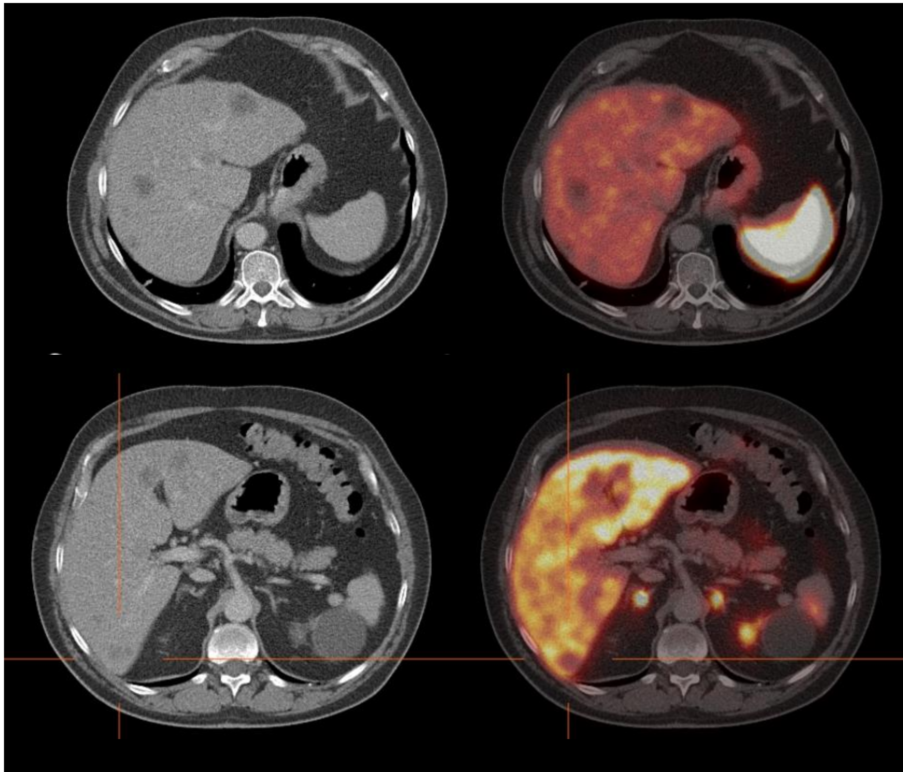
Radionuclide	Chelator	Somatostatin analogue
^{111}Indium	DTPA	Octreotide
^{90}Yttrium	DOTA	Tyr^{3}-octreotide (TOC)
^{177}Lutetium	NOTA	Lanreotide
^{213}Bismuth		Tyr^{3}-octreotate (TATE)

THERAPEUTIC COMBINATIONS:

1st generation	• ^{111}In-DTPA-octreotide	(Octreoscan®)
2nd generation	• ^{90}Y-DOTA, Tyr^{3}-octreotide	(^{90}Y-DOTATOC)
3rd generation	• ^{177}Lu-DOTA,Tyr^{3}-octreotate	(**^{177}Lu-DOTATATE**)
4th generation	• ^{213}Bi-DOTA, Tyr^{3}-octreotide	(^{213}Bi-DOTATOC)

Absence of SSR expression – no candidate for PRRT





High SSR expression: PRRT candidate

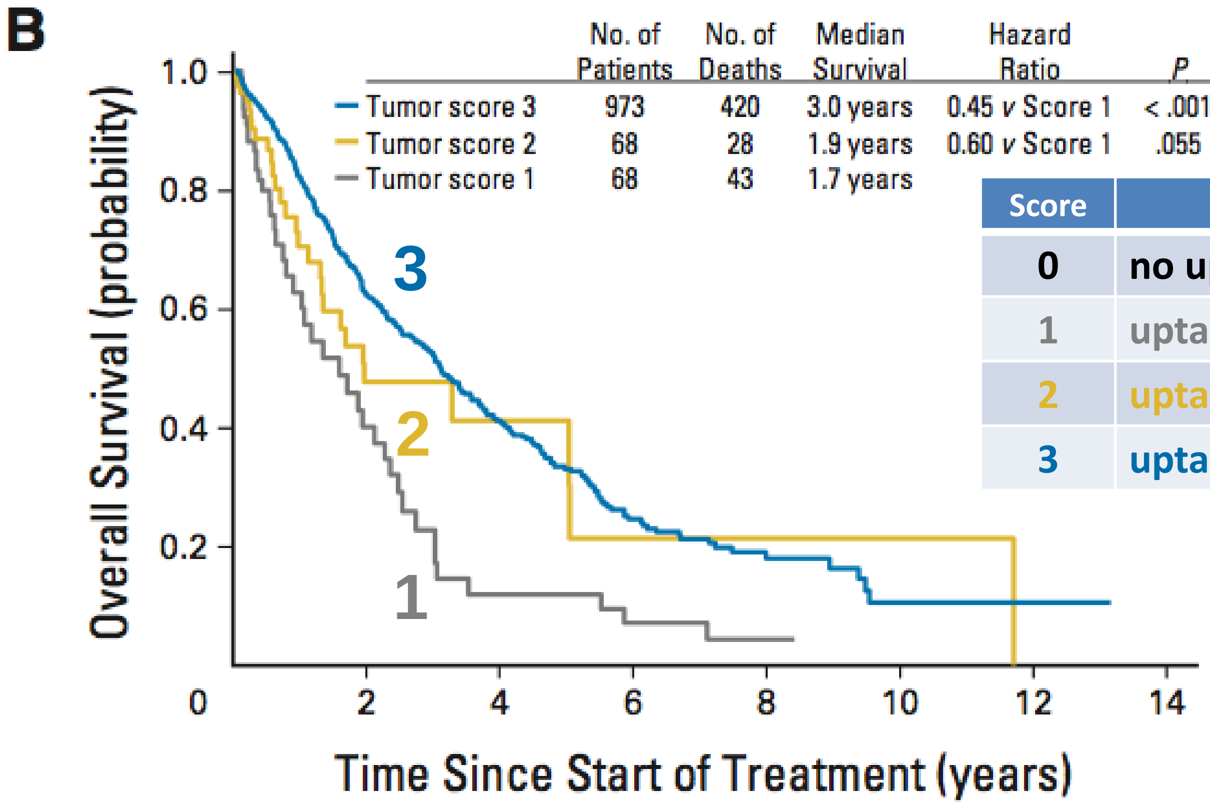
Normal biodistribution

Patient with multifocal disease

VOLUME 29 · NUMBER 17 · JUNE 10 2011
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

^{90}Y-DOTATOC (Basel experience; n=1109)

Overall survival as function of ^{111}In-pentetreotide binding



	No. of Patients	No. of Deaths	Median Survival	Hazard Ratio	P
Tumor score 3	973	420	3.0 years	0.45 v Score 1	< .001
Tumor score 2	68	28	1.9 years	0.60 v Score 1	.055
Tumor score 1	68	43	1.7 years		

No. at risk

Total	1,109	381	172	66	27	5	1	0
Score 3	973	344	155	58	23	3	1	0
Score 2	68	19	11	4	3	2	0	0
Score 1	68	18	6	4	1	0	0	0

Score	Hottest tumor
0	no uptake
1	uptake < liver uptake
2	uptake = liver uptake
3	uptake > than liver uptake

Imhof, JCO, 2011, 29(17):2416-23

Randomised Controlled Trial NETTER-1

Metastatic NET (midgut)

- RECIST progression on fixed dose SSA
- Ki67 <20% (Gr 1/2)
- **SRS + all lesions**
- Adequate GFR, blood, liver
- No prior PRRT

Stratification

- Fixed dose SSA: <6 months vs >6 months
- **SRS uptake score**

229

1 → **116**

PRRT ^{177}Lu-DOTATATE
4 x 7.4GBq; interval 8±1w
30 mg Octreotide LAR/4w

1 → **113**

60 mg Octreotide LAR/4w

1^{ary} end: PFS

2^{ary} end: ORR, TTP, OS, DoR, PFS_2

NETTER-1: **primary endpoint PFS**

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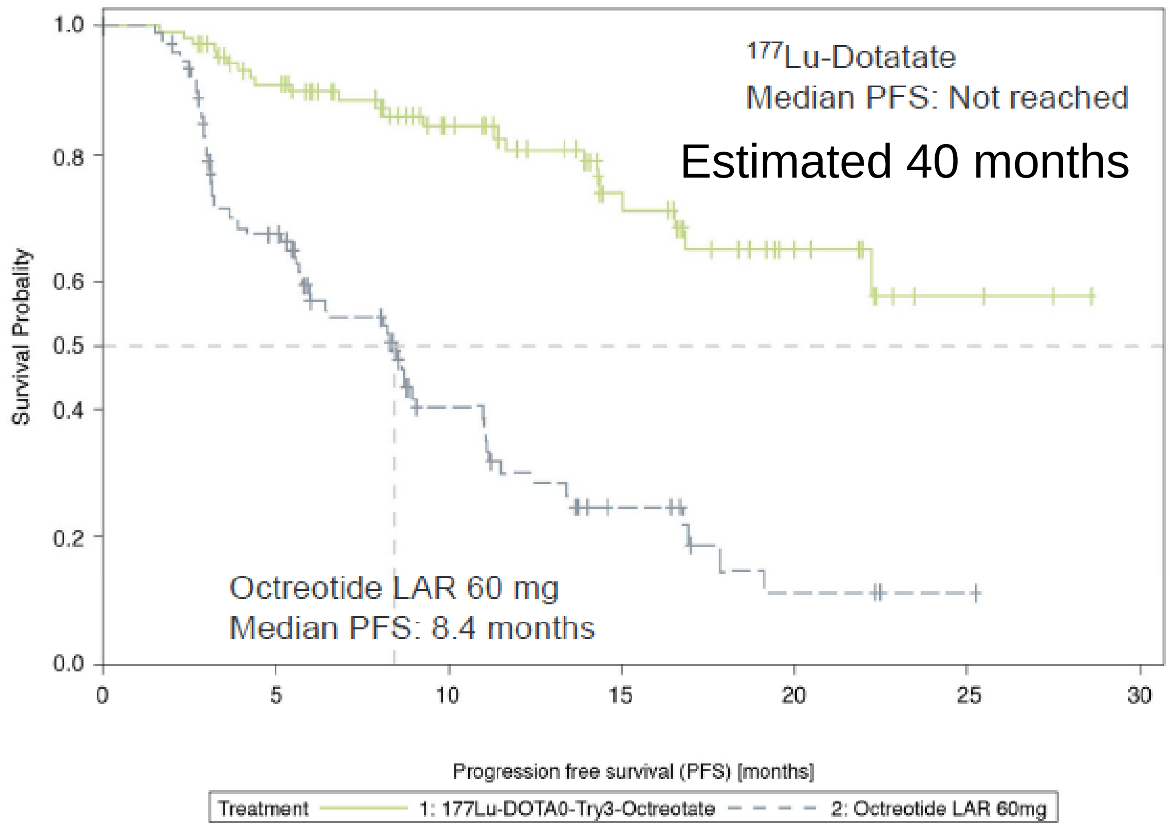
Progression-Free Survival

N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001

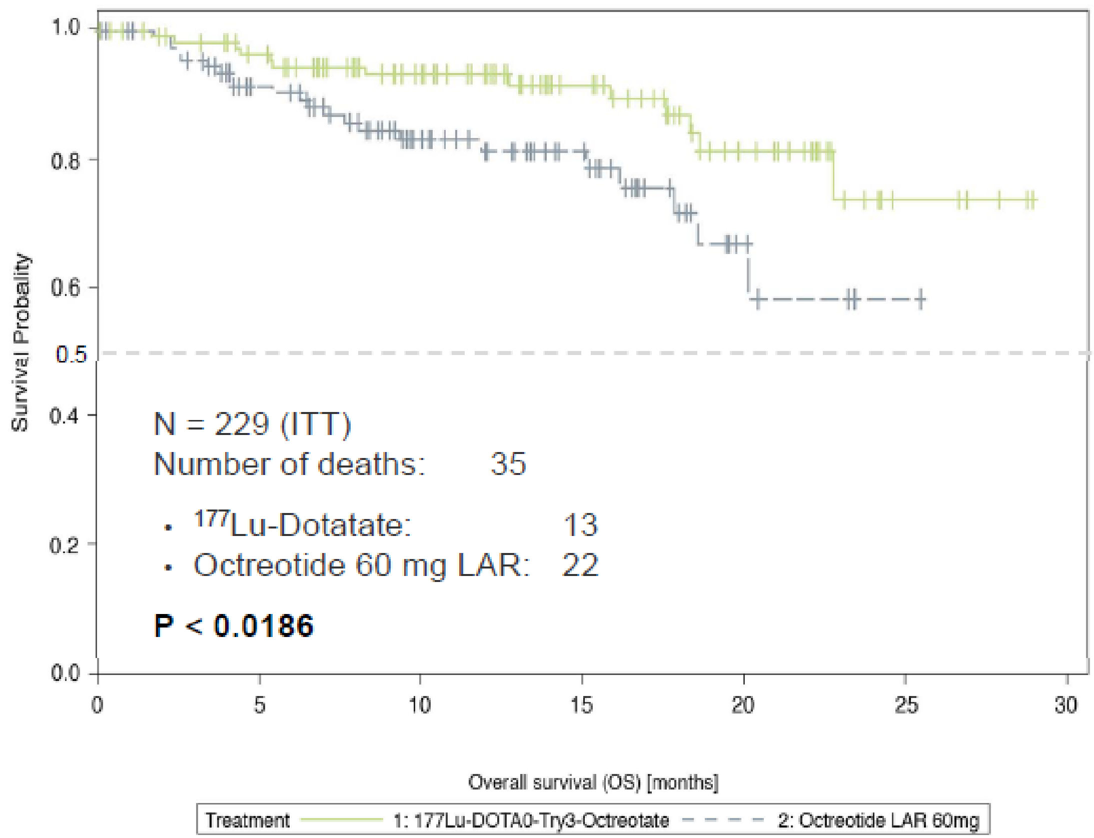


All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

NETTER-1: secondary endpoint OS

Overall Survival (interim analysis)



Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

NETTER-1: Historical Landmark Trial

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Validation of the concept that directing beta-emitters to tumorcells can prolong overall survival in metastatic cancer patients.

Treatment planning PRRT

- Pre-therapy work-up
  - Determine kidney function
  - Determine hematological function (blood draw)
  - Theranostic imaging
  - Optional: Pre-therapeutic dosimetry (e.g. for yttrium-90 treatment)
- Pre-administration
  - Stop cold somatostatin analogues:
    - >24 hours for short acting
    - >6 weeks for long acting
  - Amino-acid infusion (blocks kidney retention)
  - Anti-emetics (block emetic effect of amino acids)
  - Hydration
- Post-therapy
  - Lutetium-based dosimetry (prepare for next cycle)

Overview

- Nuclear medicine treatment: radionuclide therapy (RNT)
- Therapeutic radioisotopes and radiopharmaceuticals
- Dosimetry
- **Currently used RNT and planning aspects**
  - $Na^{131}I$ for thyroid disease
  - ^{131}I-MIBG
  - Peptide receptor radionuclide therapy (PRRT)
  - **^{177}Lu-PSMA (Prostate specific membrane antigen)**
  - Radium-223 for bone metastases
  - Selective internal radiation therapy (SIRT)
- Conclusions

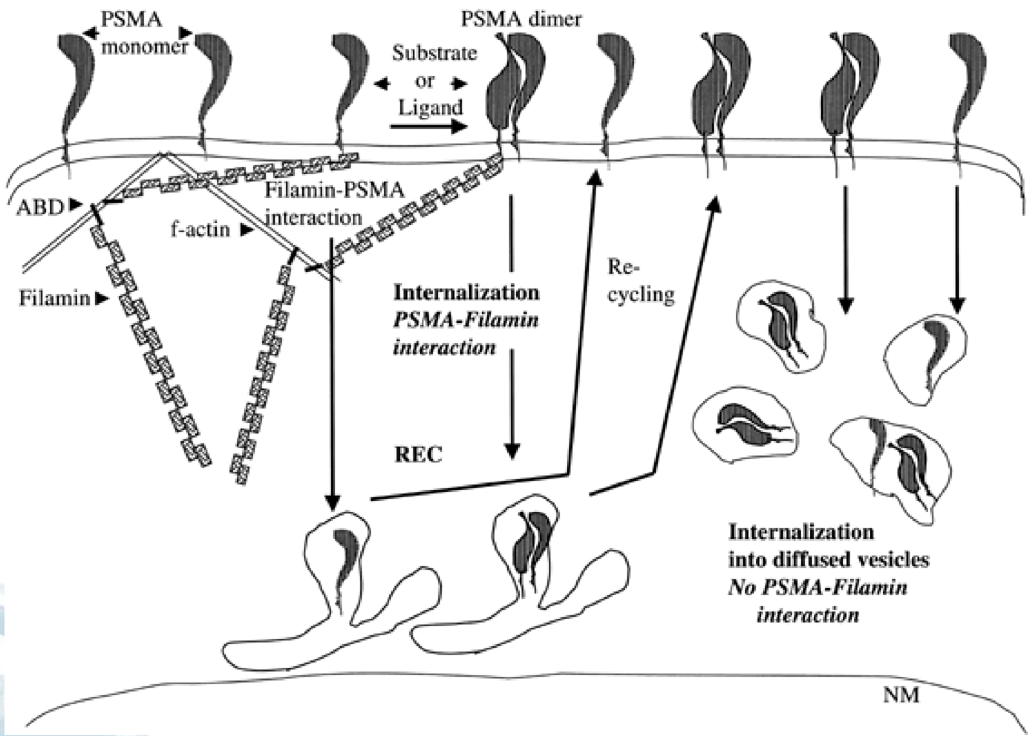
PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA) TARGETING: ^{68}Ga-HBED-CC (aka ^{68}Ga-PSMA) ^{177}Lu-PSMA

Prostate-specific membrane antigen (**PSMA**) (≠ PSA!)

- Type II transmembrane protein
- Over-expressed in Prostate carcinoma
- Including androgen-independent, advanced and metastatic disease
- Overexpressed in bladder carcinoma , schwannoma, and in the tumor neovasculature of many solid tumors
- Membrane bound receptor
- Binds ligands as a dimer before internalization through clathrin-coated pits
- PSMA-bound ligands are internalized within the cell
  - either retained in lysosomal compartments along with the degrading PSMA receptor
  - may be released to distribute within the cell

Mease et al., 2013 Curr Top Med Chem 13(8): 951-62

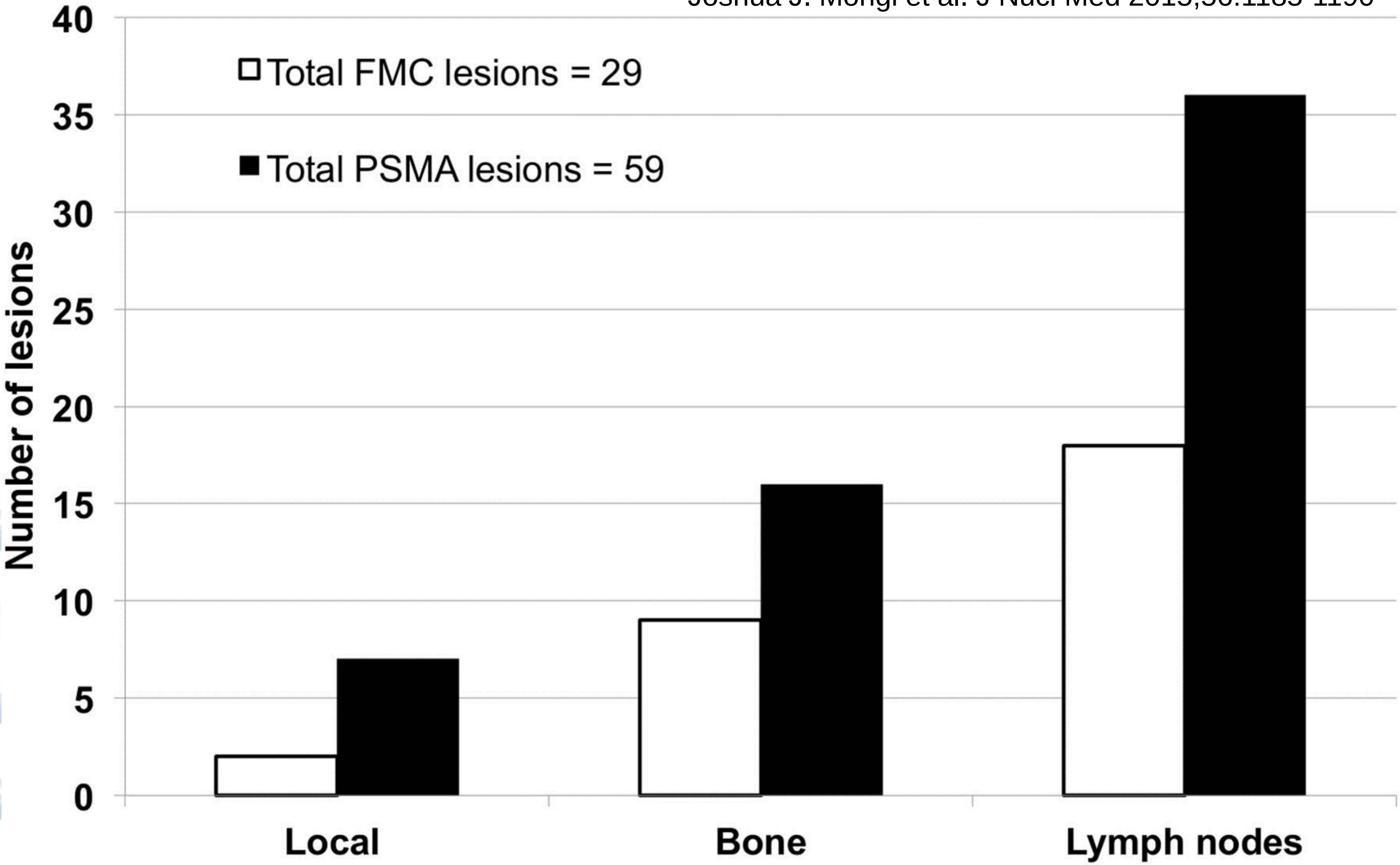
PSMA Regulation in prostate cancer



Ghosh and Heston, Journal of Cellular Biochemistry
Volume 91, Issue 3, pages 528-539, 7 OCT 2003 DOI: 10.1002/jcb.10661
http://onlinelibrary.wiley.com/doi/10.1002/jcb.10661/full#fig4

Number of lesions per site

Joshua J. Morigi et al. J Nucl Med 2015;56:1185-1190



^{68}Ga-PSMA PET/CT: detection of lesions missed by other techniques

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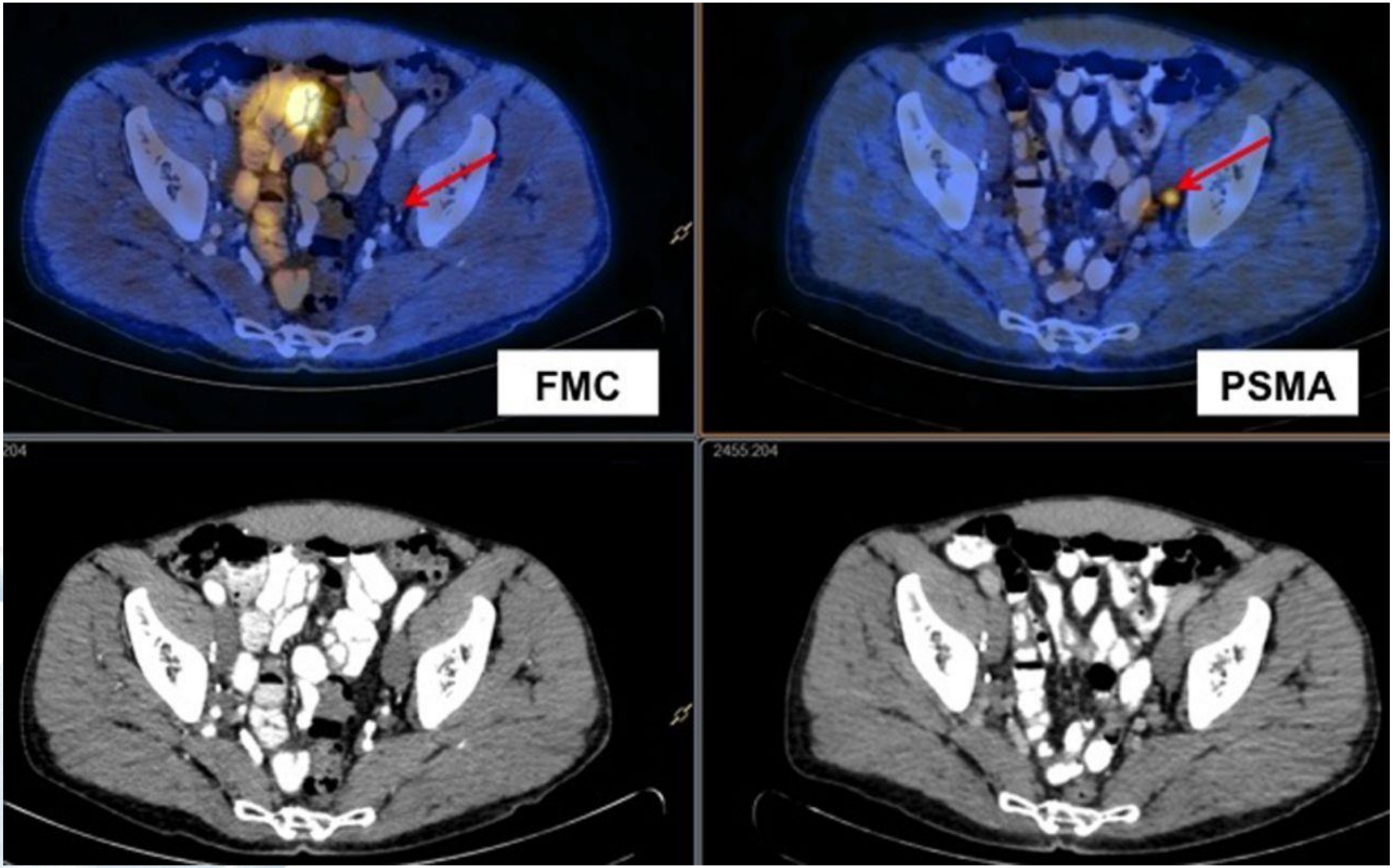
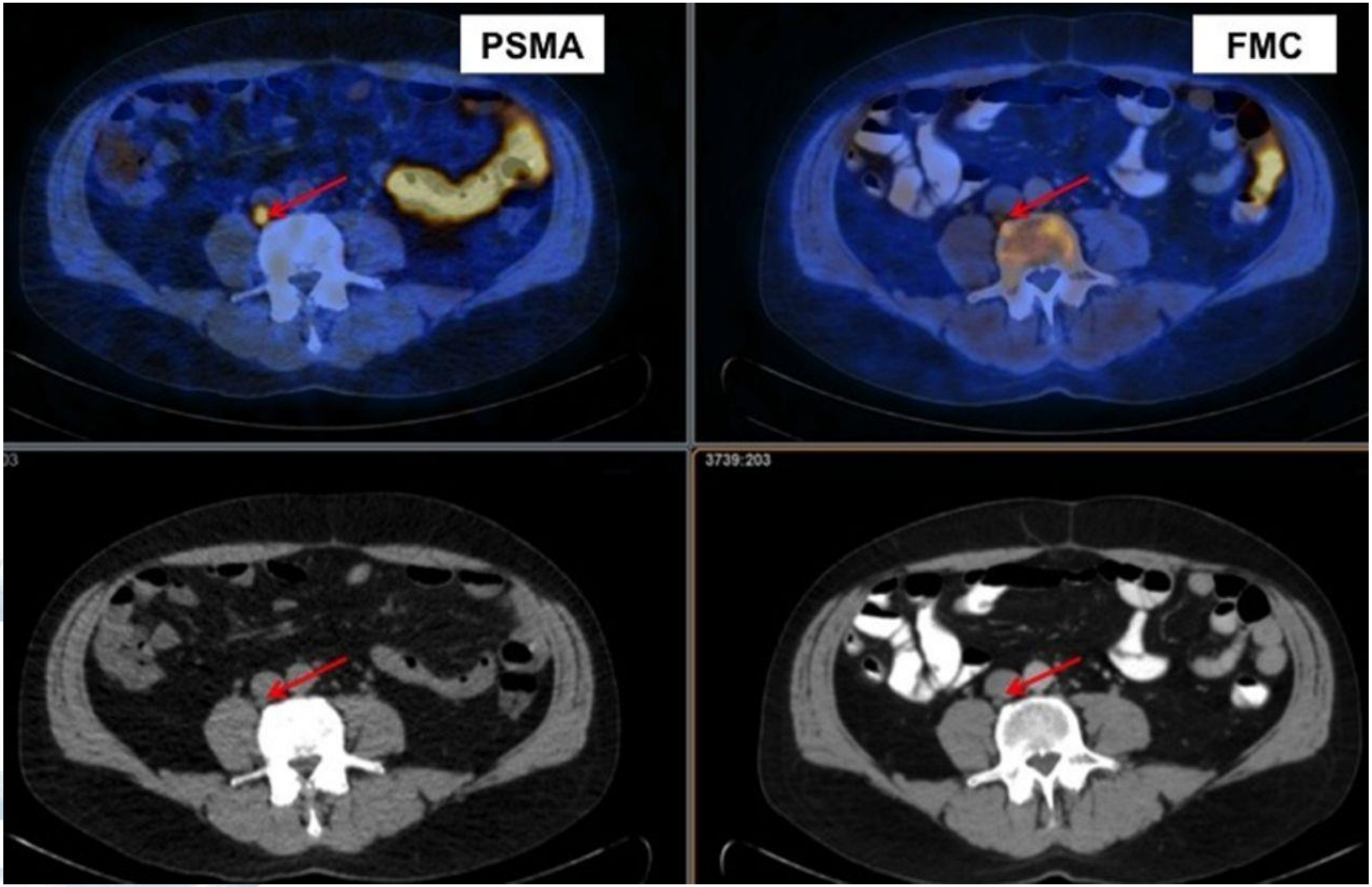


JNM The Journal of NUCLEAR MEDICINE

Joshua J. Morigi et al. J Nucl Med 2015;56:1185-1190

^{68}Ga-PSMA PET/CT: detection of lesions missed by other techniques

KU LEUVEN



JNM The Journal of NUCLEAR MEDICINE

Joshua J. Morigi et al. J Nucl Med 2015;56:1185-1190

PSMA: Theranostic target

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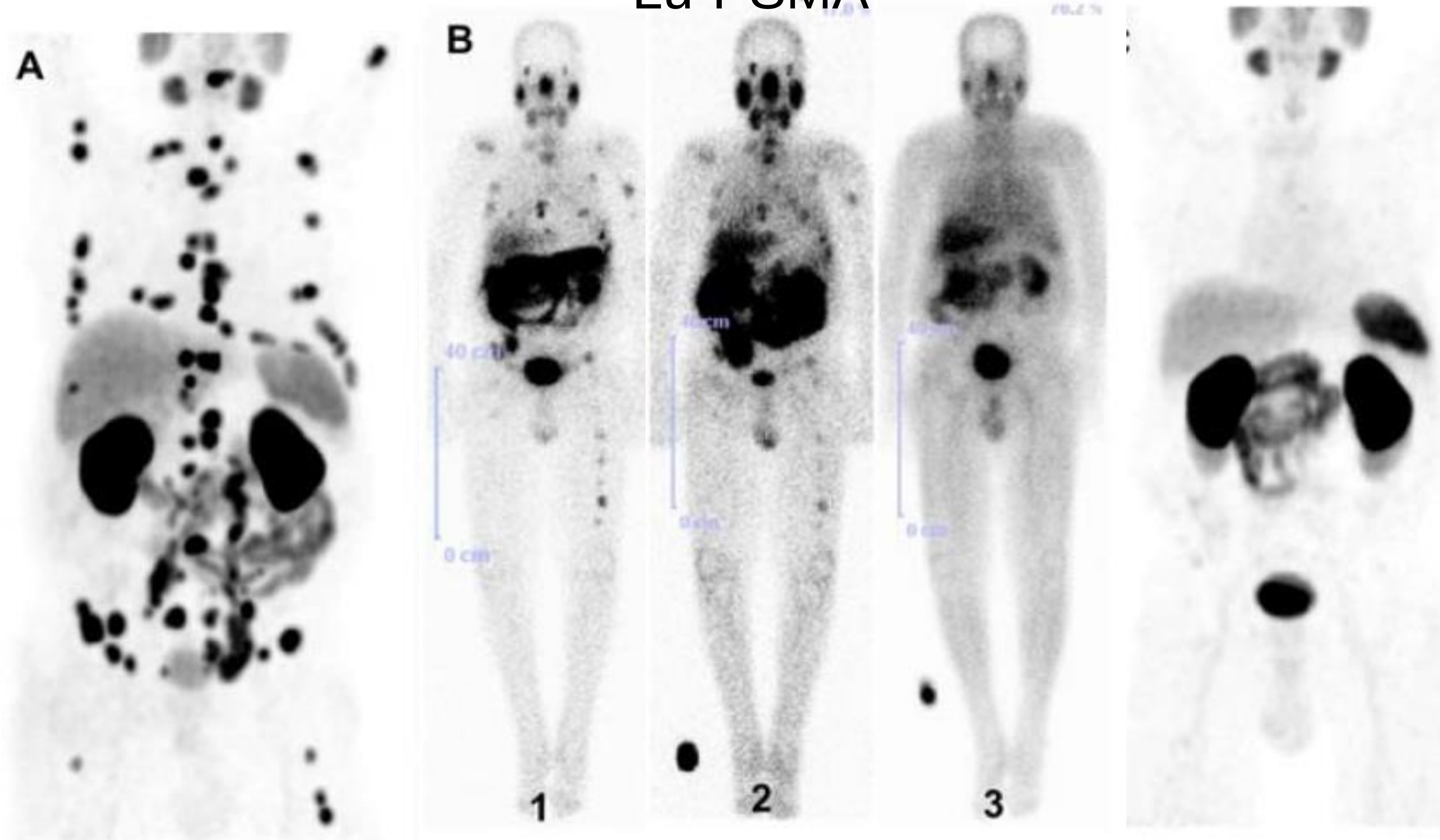
PSMA: theranostic target (^{177}Lu-PSMA)

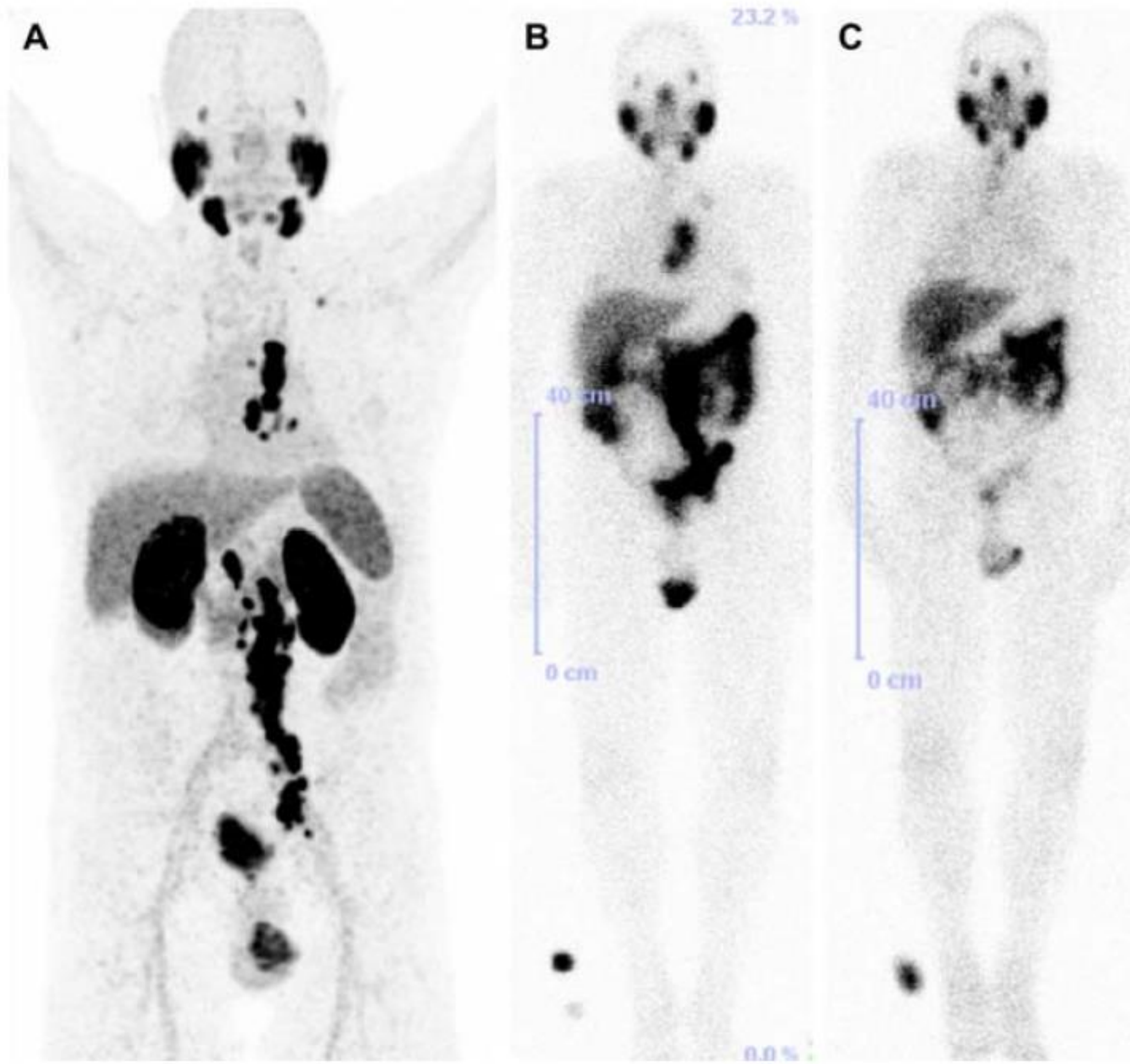
PSMA PET 1 ^{177}Lu-PSMA **PSMA PET 2**



^{177}Lu-PSMA 1 ^{177}Lu-PSMA 3

Baum et al. J Nucl Med 2016; 57(7):1006-13

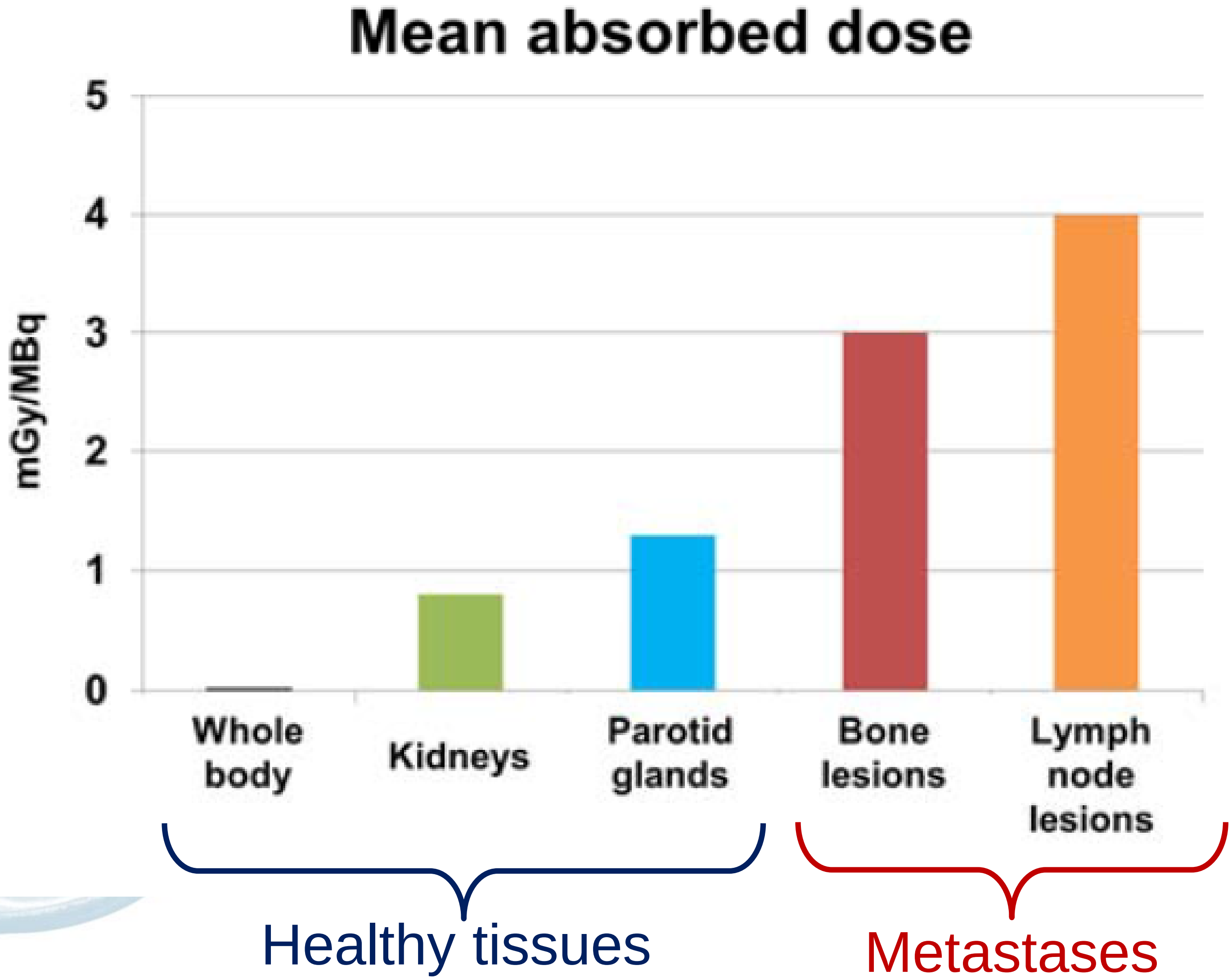
PSMA: theranostic target (^{177}Lu-PSMA)



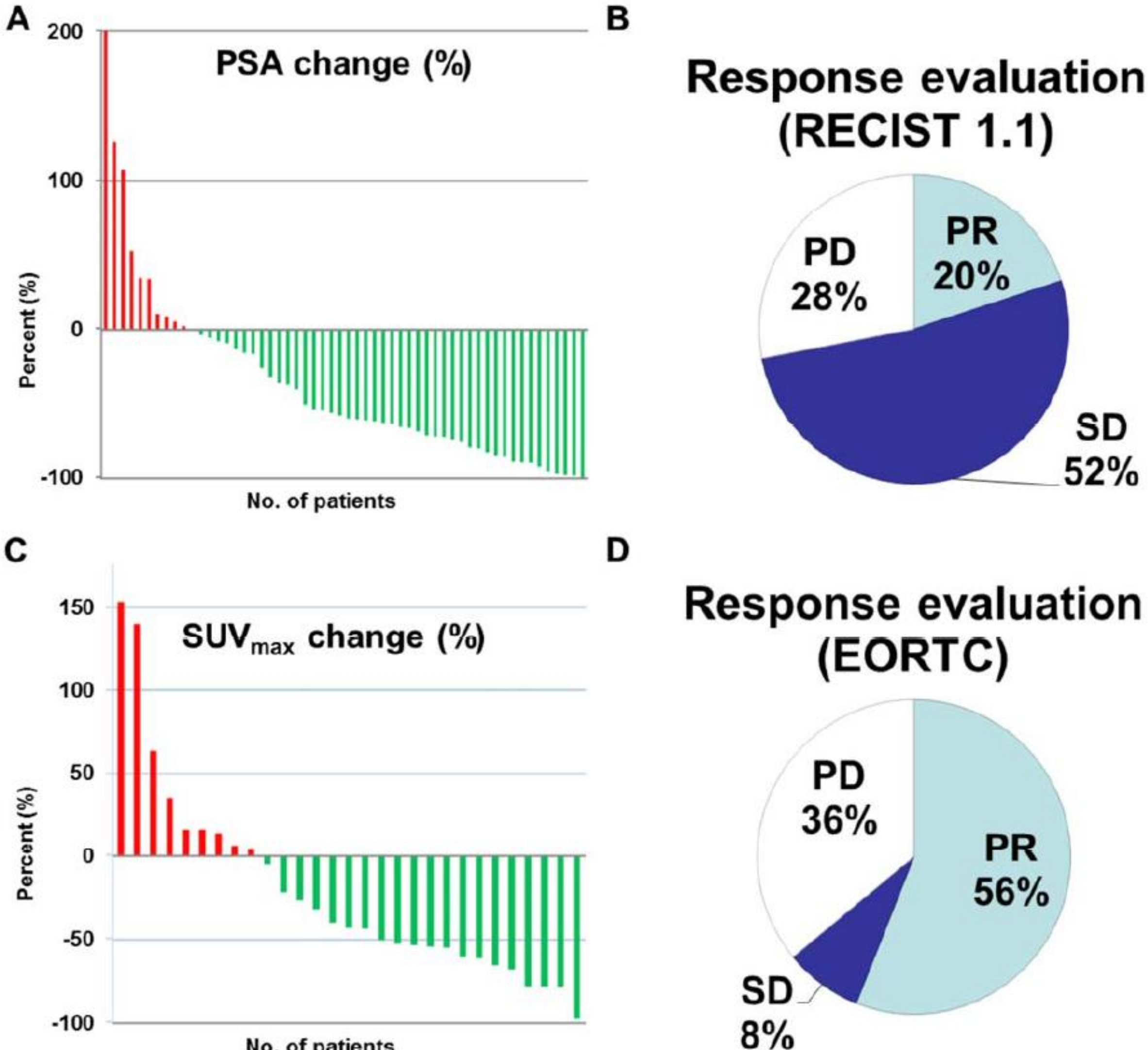
Baum et al. J Nucl Med 2016; epub; PMID: 26795286

Absorbed dose to tissues

Baum et al. J Nucl Med 2016; 57(7):1006-13

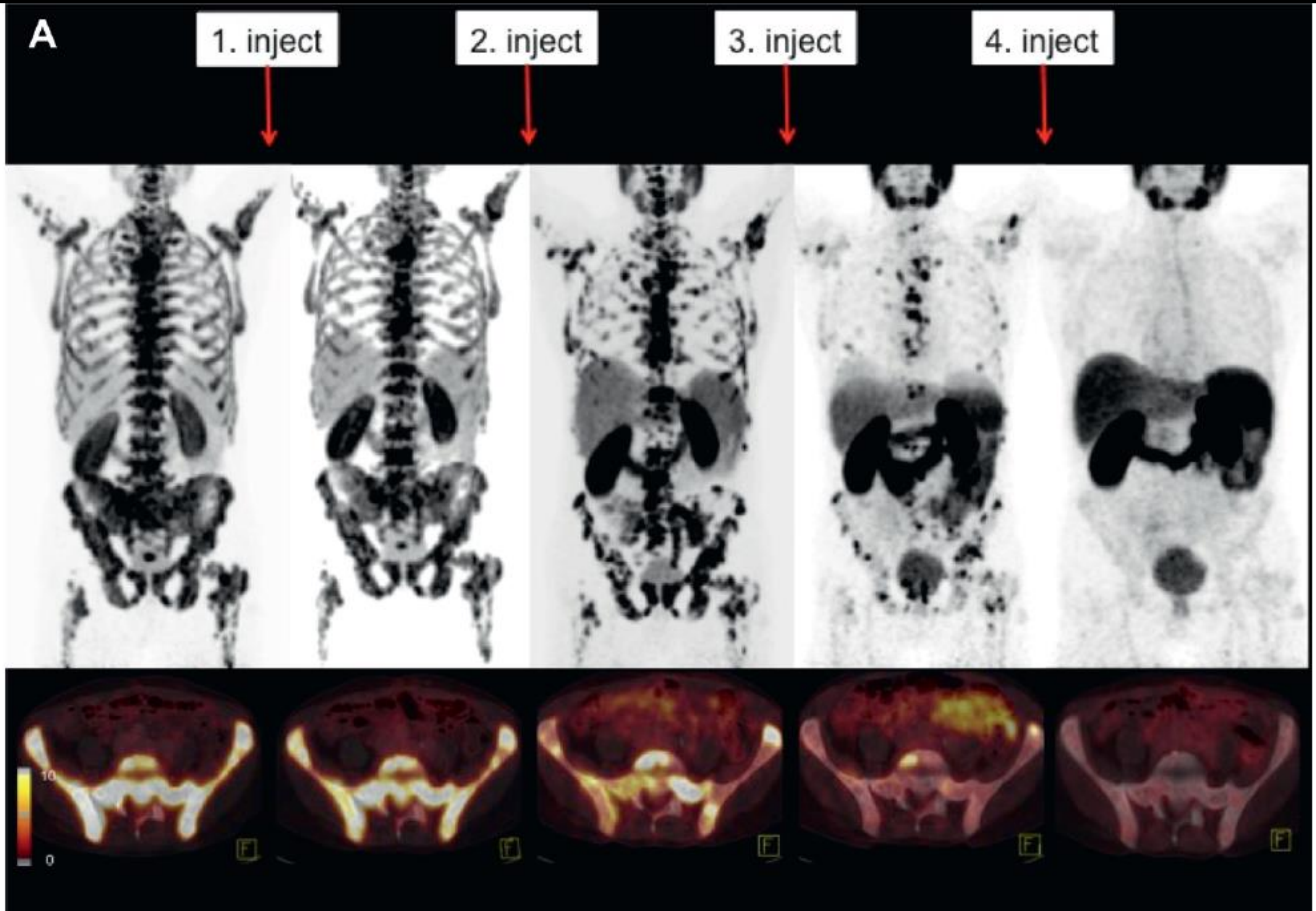


Response evaluation



Baum et al. J Nucl Med 2016; 57(7):1006-13

Dramatic response in superscan patient



Heck et al. J Urol 2016; epud PMID 26964917

SNMMI 2015 Image of the year

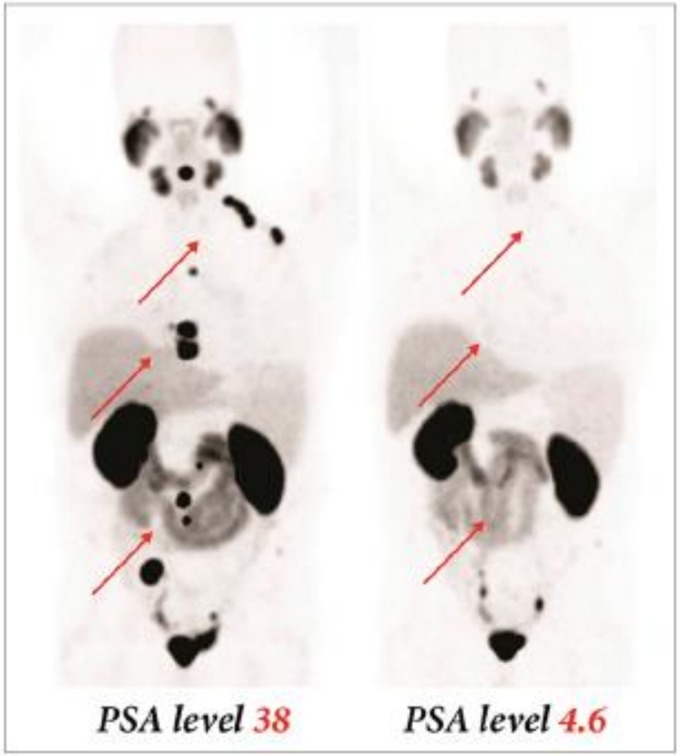
SNMMI 2015 Image of the Year

At the final session of the SNMMI Annual Meeting on June 8, society leaders announced the award of the 2015 Image of the Year to a group working under Matthias Eder, PhD, from the German Cancer Research Center (Heidelberg, Germany) for images acquired with an agent that can be labeled with ^{68}Ga for imaging for treatment stratification and with ^{177}Lu for therapy in prostate cancer. PSMA-617 is a prostate-specific membrane antigen inhibitor that targets prostate cancer cell surfaces at both local and metastatic sites. Their podium presentation was titled "PSMA-617—a novel theranostic PSMA inhibitor for both diagnosis and endoradiotherapy of prostate cancer."

"We feel very honored to receive this prestigious award as it is the result of the excellent work of many people," said Eder. "I would like to thank all the team members who contributed to this work." This team included the first author of the presentation, Martina Benesova, PhD.

The same group, in partnership with researchers at Heidelberg University Hospital under Uwe Haberkorn, MD, have already used ^{177}Lu-PSMA-617 to treat patients with advanced prostate cancer. After treatment, >50% of patients experienced sharp drops in prostate-specific antigen (PSA) levels. In addition, PET/CT imaging confirmed that metastases had shrunk and were no longer detectable. "The results were so promising that we plan to go ahead with a clinical trial as soon as possible to examine whether PSMA-617 is superior to other therapy methods," said Haberkorn in a press release from the researchers' institutions.

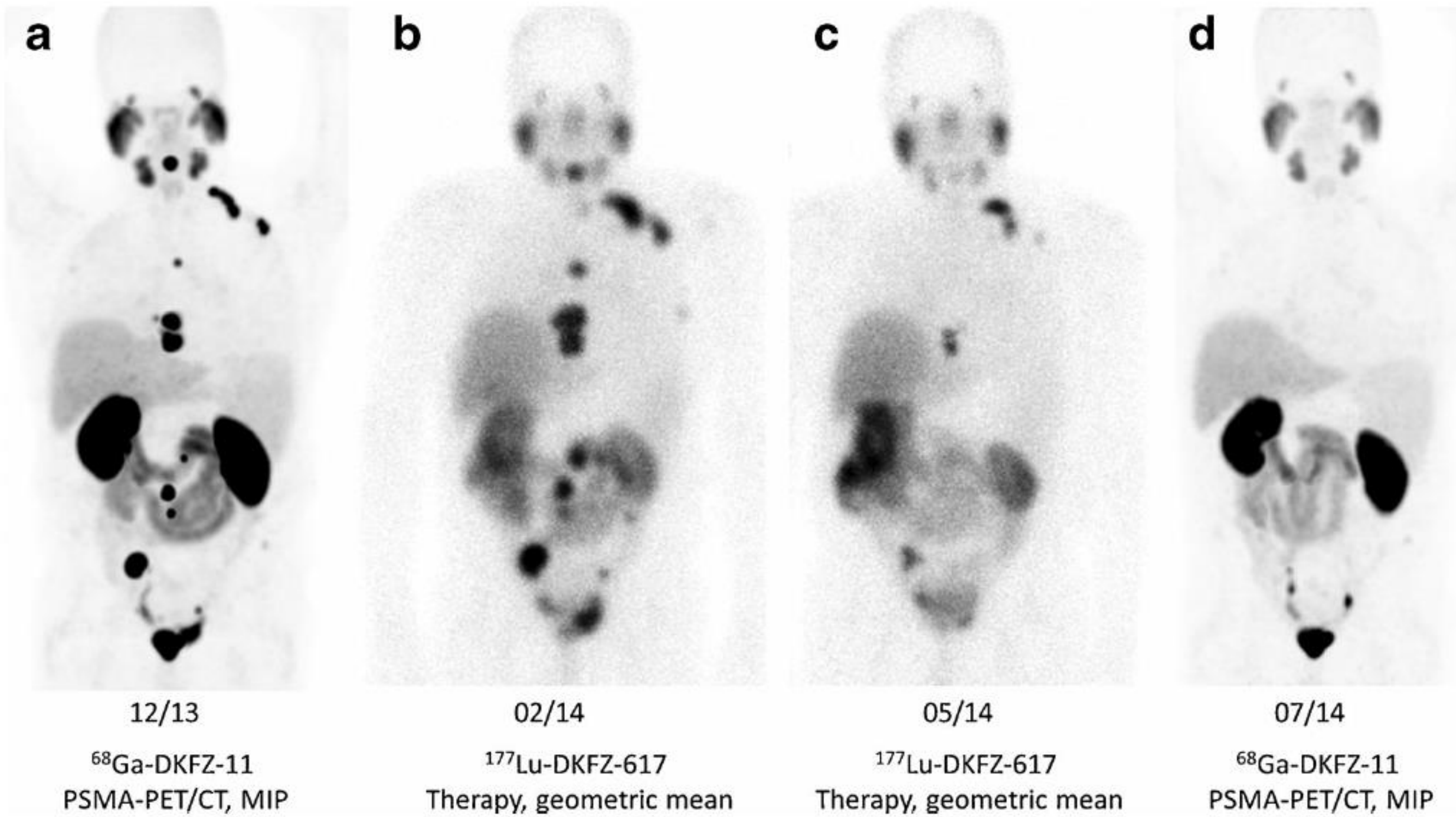
"Prostate cancer remains one of the main causes of cancer-related death among men worldwide," said Peter Herscovitch, 2014–2015 SNMMI president. "This new molecular imaging technology not only detects metastatic prostate cancer, but also can treat metastases noninvasively. It is the combined capability of diagnosis and therapy that makes this molecular theranostic so powerful."



Left: Baseline image of patient with widely metastasized prostate cancer before ^{177}Lu-PSMA-617 treatment (PSA = 38). Right: After treatment (PSA = 4.6).

Image of the Month January 2015

KATHOLIEKE UNIVERSITEIT LEUVEN



Eur J Nucl Med Mol Imaging (2015) 42:987–988

IMAGE OF THE MONTH

Kratochwil et al. Eur J J Nucl Med Mol Imaging 2015; 42:987-8

Great expectations….

KATHOLIEKE UNIVERSITEIT LEUVEN

Curr Radiopharm. 2016;9(1):6-7.

Lutetium-177 Labeled Therapeutics: ^{177}Lu-PSMA is Set to Redefine Prostate Cancer Treatment.

Pillai AM, Knapp FF Jr[1].

“Lutetium-177 Labeled Therapeutics: ^{177}Lu-PSMA is Set to Redefine Prostate Cancer Treatment”

Pillai AM & Knapp FF Jr

Current radiopharmaceuticals 2016:9(1):6-7

Treatment planning ^{177}Lu-PSMA

- Pre-therapy work-up
  - Determine kidney function
  - Determine hematological function (blood draw)
  - Theranostic imaging
- Pre-administration
  - Hydration
  - Apply cold packs to salivary glands
- Post-therapy
  - Lutetium-based dosimetry (prepare for next cycle)

Overview

- Nuclear medicine treatment: radionuclide therapy (RNT)
- Therapeutic radioisotopes and radiopharmaceuticals
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- **Currently used RNT and planning aspects**
  - $Na^{131}I$ for thyroid disease
  - ^{131}I-MIBG
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  - **Radium-223 for bone metastases**
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- Conclusions

The Diagnostic Vectormolecule can be Different from the Therapuetic

OSTEOID AND BONE METASTASES

^{99m}Tc-MDP / $^{18}F^-$

^{153}Sm-EDTMP / $^{223}RaCl_2$

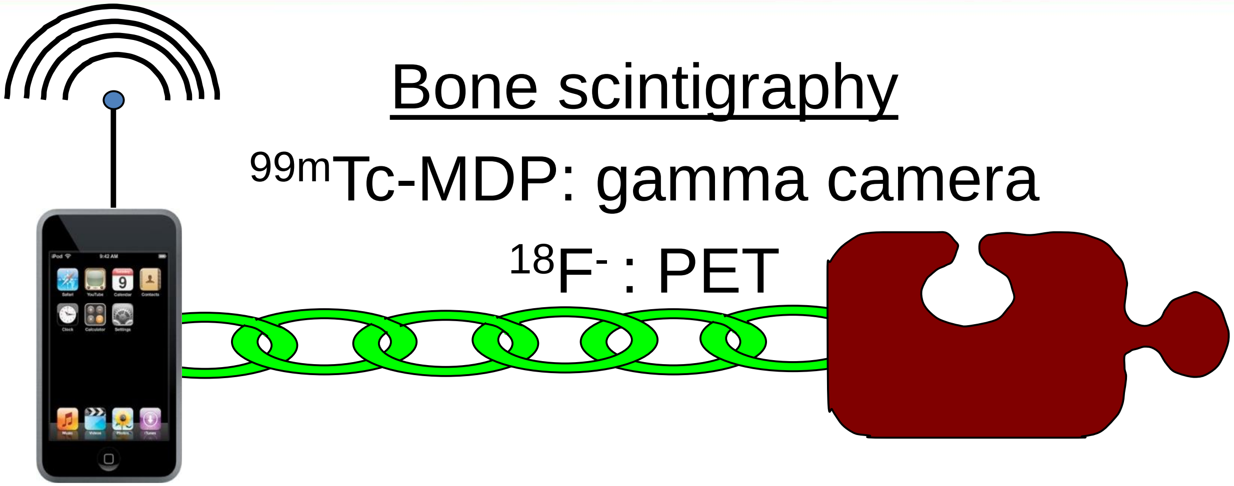
Bone turnover: theranostic duo's

IMAGE

<u>Bone scintigraphy</u>

^{99m}Tc-MDP: gamma camera

^{18}F^{-} : PET



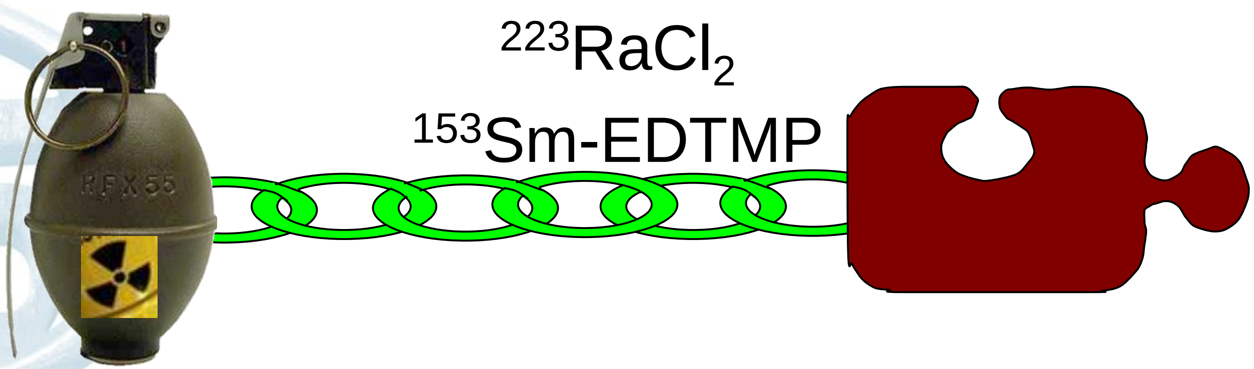
Radionuclide Linker Vector

THERAPY

<u>Bone radionuclide therapy</u>

^{223}RaCl$_2$

^{153}Sm-EDTMP



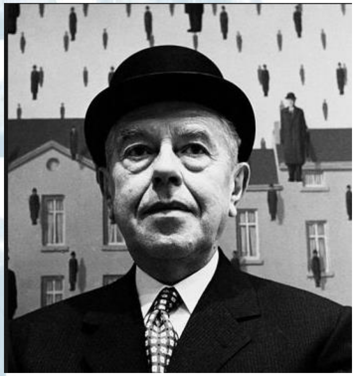
Radionuclide Linker Vector

“Ceci n’est pas un squelette”

“La Trahison des Images”

“The Treachery of Images”

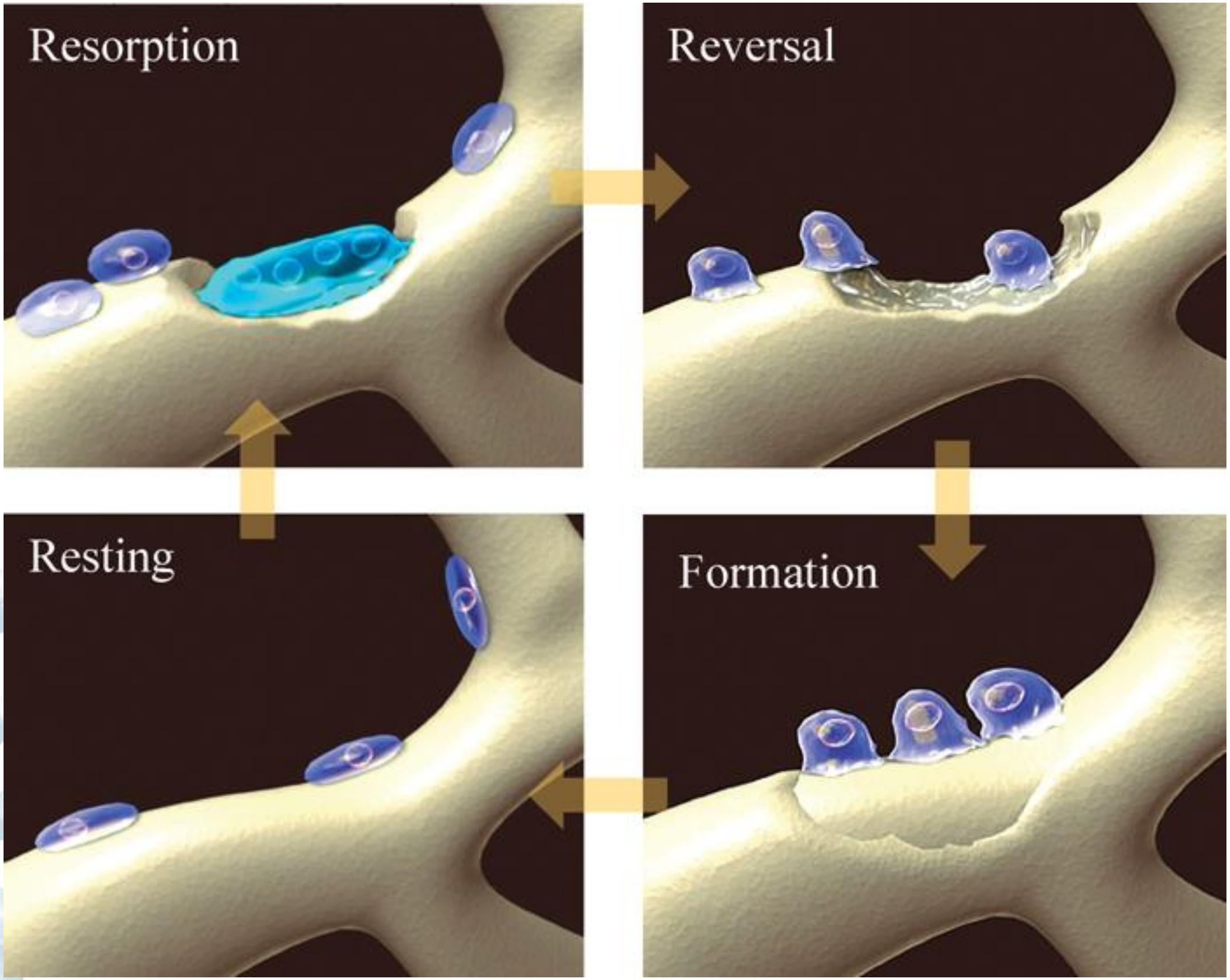
René Magritte, 1928-9



Bone scintigraphy

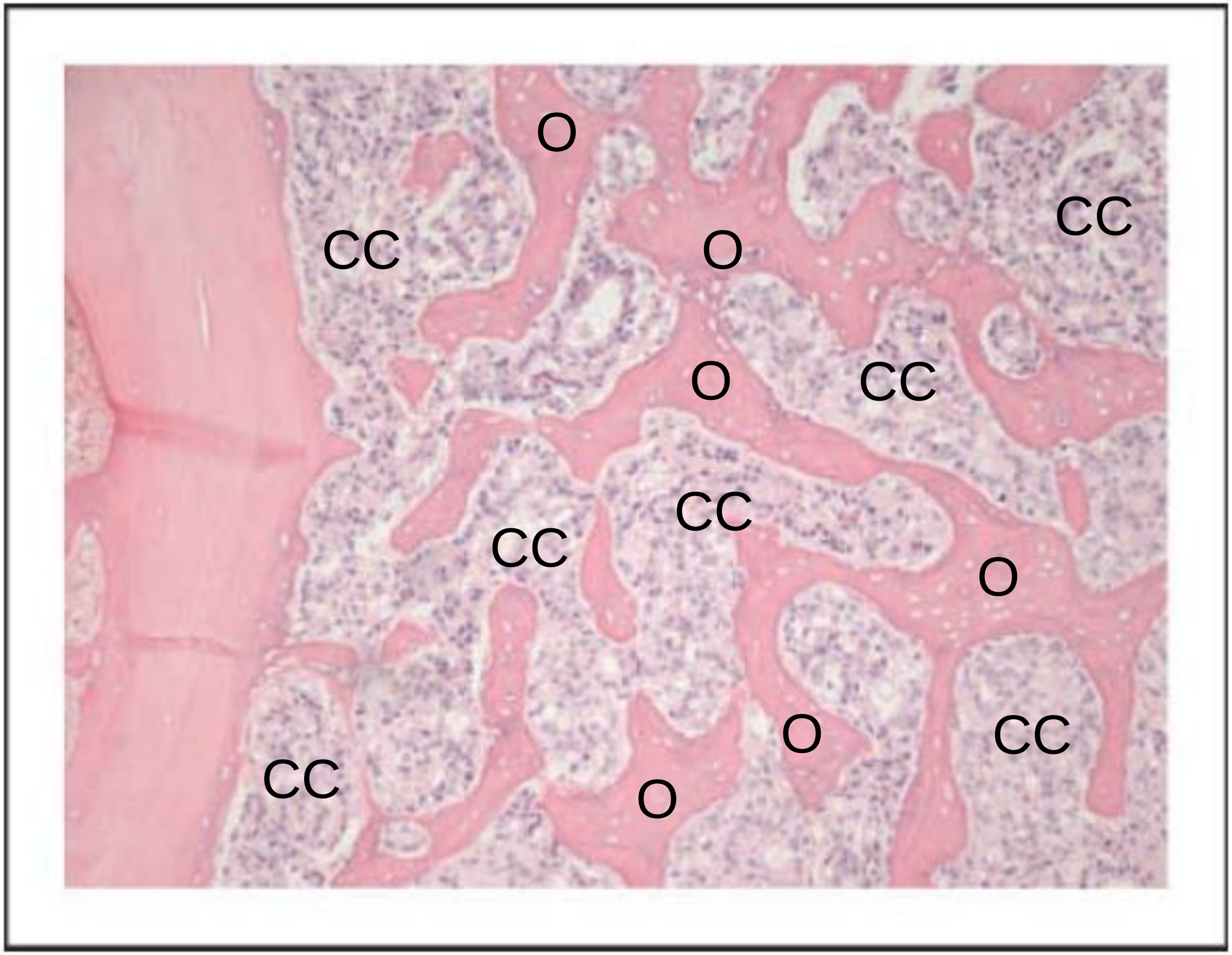
Bone **turnover**

Bone remodeling cycle



Coxon, Prostate Cancer Prostatic Dis, 2004

Theranostic target
Osteoid & hydroxyapatite



O: osteoid

CC: Cancer cells

Bruland, Clin Cancer Res, 2006

ALSYMPCA: Trial Design

CRPC

- ≥ 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 (50kBq/kg) + SOC**
6 inj @ 4w intervals

1 → **307**: **Placebo (Saline) + SOC**

1^{ary} end: OS

2^{ary} end: t↑ ALP, ALP resp, tSRE, t↑PSA

Parker, NEJM, 2013

Alsympca – Inclusion criteria

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Inclusion Criteria:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate
2. Known hormone refractory disease defined as:
   - Castrate serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L)
   - Bilateral orchiectomy or maintenance on androgen ablation therapy with LHRH agonist or polyestradiol phosphate throughout the study
   - Serum PSA progression defined as two consecutive increases in PSA over a previous reference value, each measurement at least 1 week apart
3. Serum PSA value > 5 ng/mL (µg/L)
4. Multiple skeletal metastases (≥ 2 hot spots) on bone scintigraphy within previous 12 weeks
5. No intention to use cytotoxic chemotherapy within the next 6 months
6. Either regular (not occasional) analgesic medication use for cancer related bone pain or treatment with EBRT for bone pain within previous 12 weeks
7. Age ≥ 18 years
8. ECOG Performance status (PS): 0-2
9. Life expectancy ≥ 6 months
10. Laboratory requirements:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x10^9/L
    c. Hemoglobin ≥ 10.0 g/dL (100 g/L; 6.2 mmol/L)
    d. Total bilirubin level ≤ 1.5 institutional upper limit of normal (ULN)
    e. ASAT and ALAT ≤ 2.5 ULN
    f. Creatinine ≤ 1.5 ULN
    g. Albumin >25 g/L
11. Willing and able to comply with the protocol, including follow-up visits and examinations
12. Must be fully informed about the study and signed the informed consent form

Parker, NEJM, 2013

Alsympca – Overall Survival (update)

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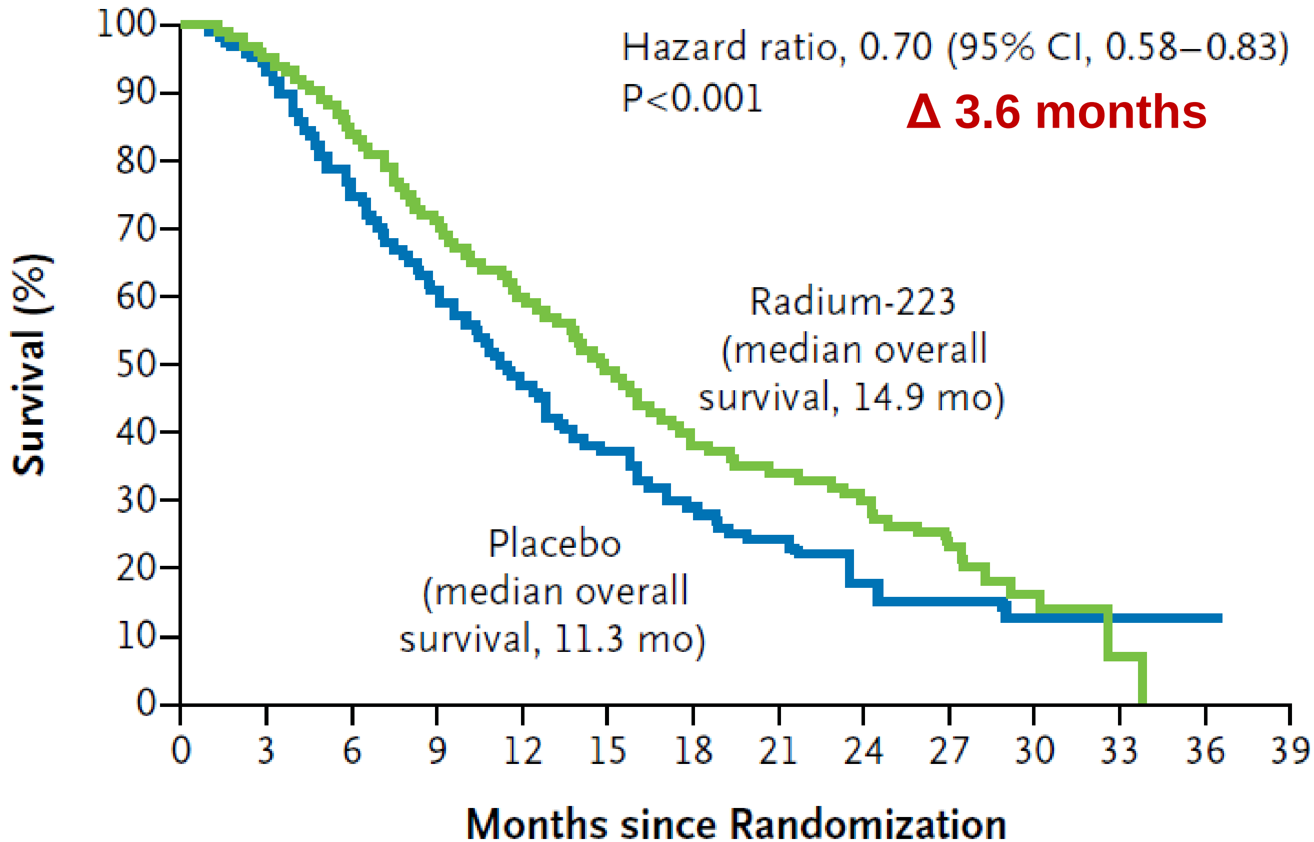
A Overall Survival



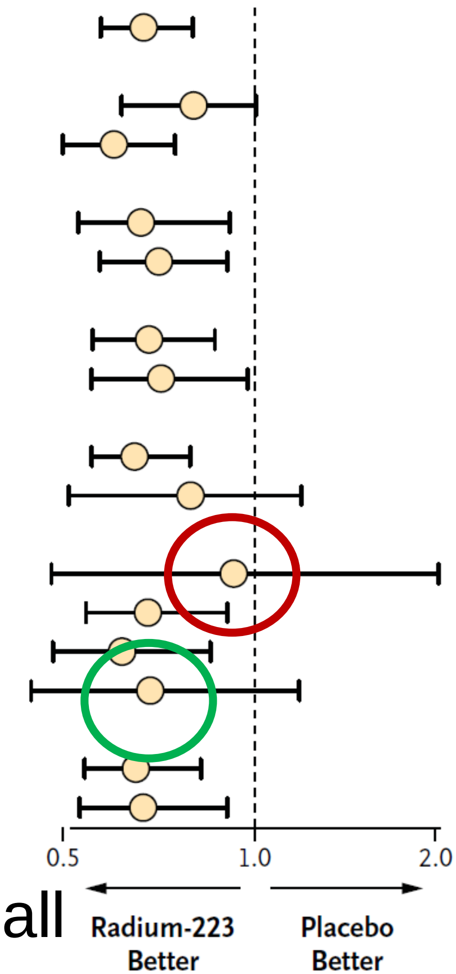
No. at Risk

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

Parker, NEJM, 2013

Alsympca – OS Subgroup Analysis

Subgroup	Radium-223 (no. of patients)	Placebo (no. of patients)	Radium-223 (median overall survival (mo))	Placebo (median overall survival (mo))	Hazard Ratio (95% CI)
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



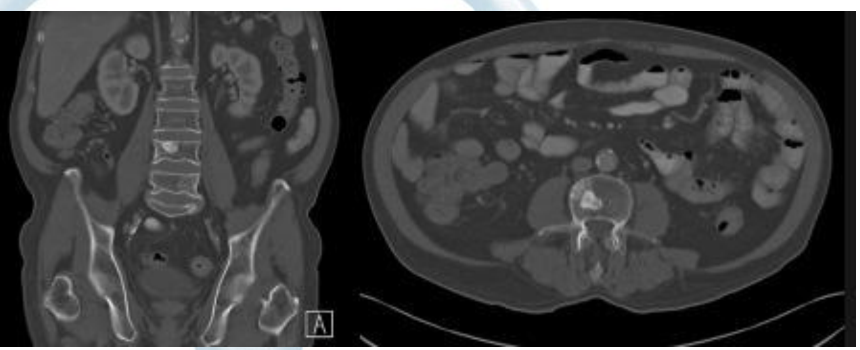
HR consistently favours* radium-223 in all subgroups, except 1-5 metastases group

*: but not always statistically significant due to lack of power

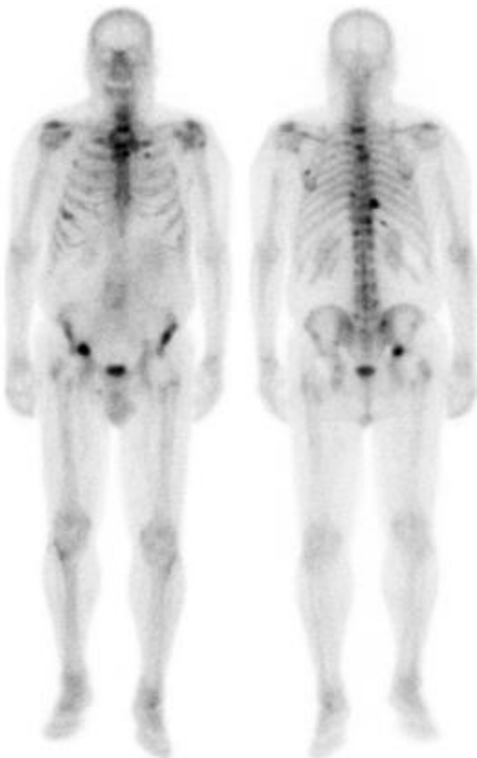
Parker, NEJM, 2013

Bone scans images prostate cancer metastases

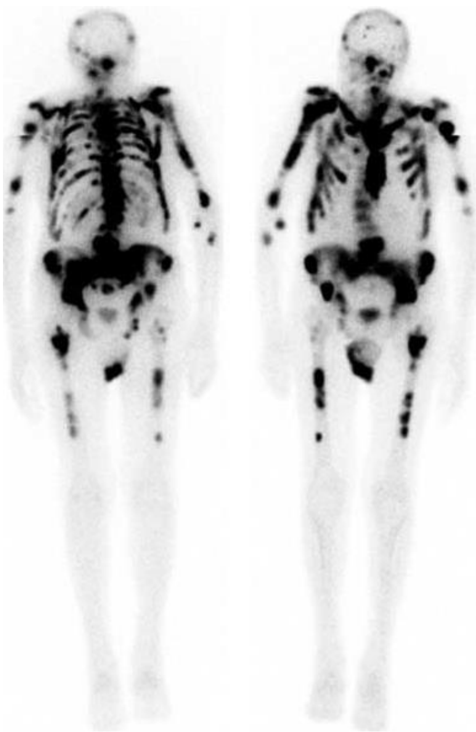
Solitary lesion



Multiple lesions



Diffuse lesions



Candidate for Ra-233

Treatment planning Radium-223

- 55 KBq/kg

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- **Conclusions**

Take Home Messages

- RNT is **DIFFERENT** from EBRT
- RNT is in most cases a **systemic radiation** treatment
- Imaging is currently used for many therapeutic radiopharmacauticals **(theranostic concept)**
- Preparation can range from **basic** antropemetric parameter collection to **full-blown** pre-therapeutic "dosimetry"
- **Post-therapy dosimetry** can be seen as the prepartion of the next treatment (cycle) and is full methodological development

Henry N. Wagner Jr

1927 - 2012

"Forefather of Nuclear Medicine"

"The future of nuclear medicine is PET….

…and Therapy"

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Questions?

Leuven City Hall