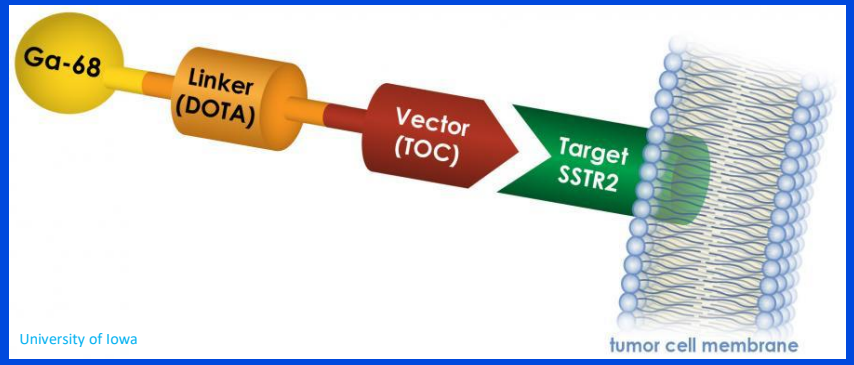
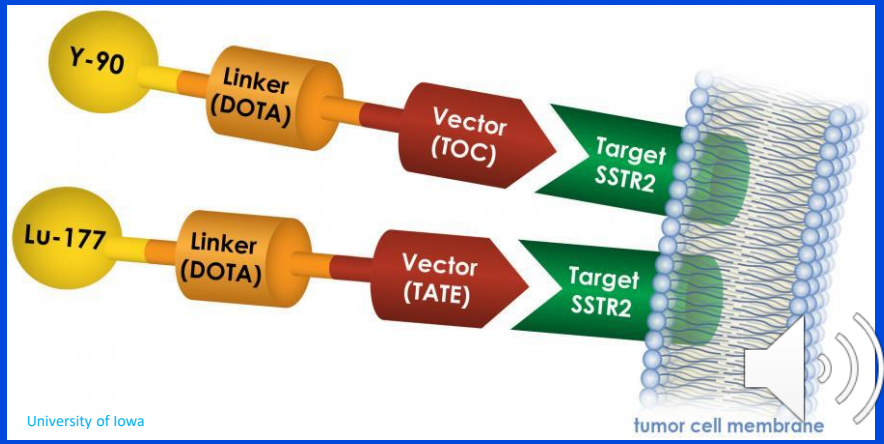
Introduction to Theranostics

Michael M. Graham, PhD, MD

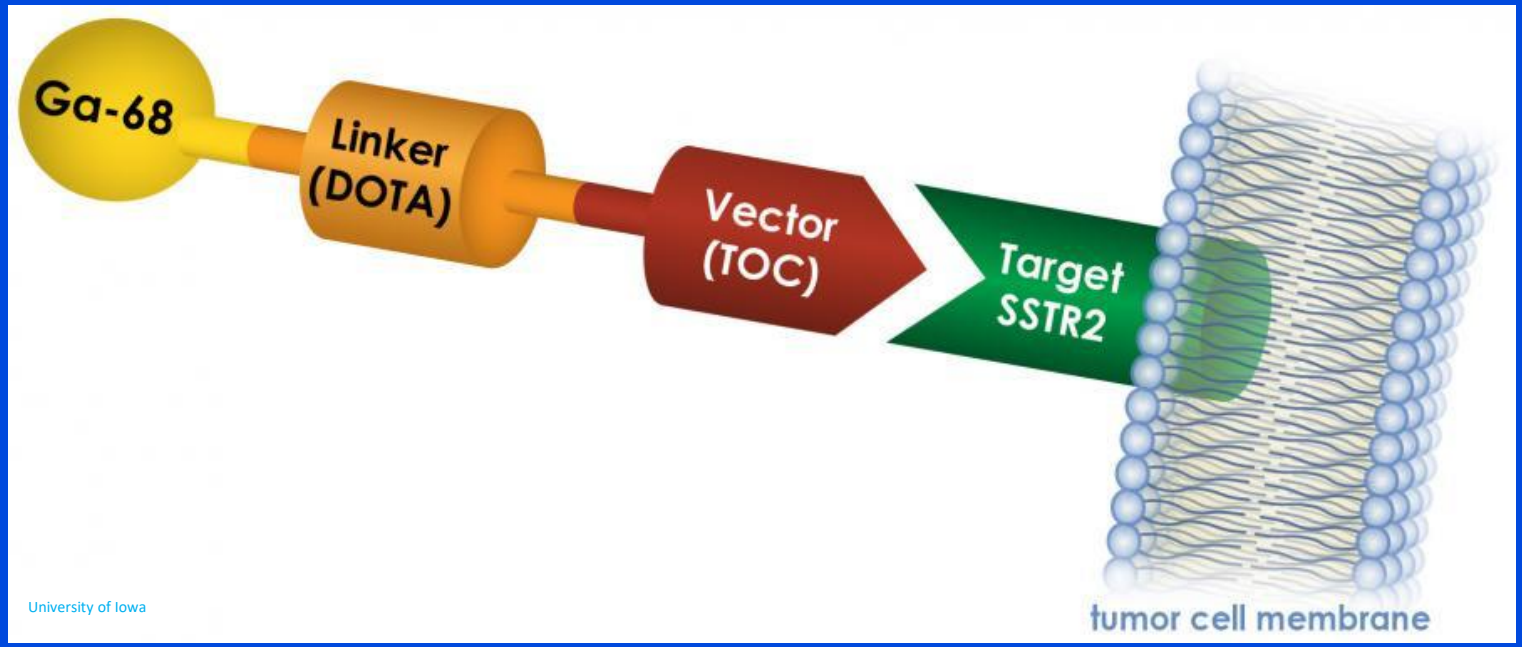
University of Iowa





Theranostics

Theranostics is a combination of the terms therapeutics and diagnostics. Theranostics is the term used to describe the combination of using one radioactive drug to identify (diagnose) and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.



Diagnostic Radiopharmaceutical

Theranostics

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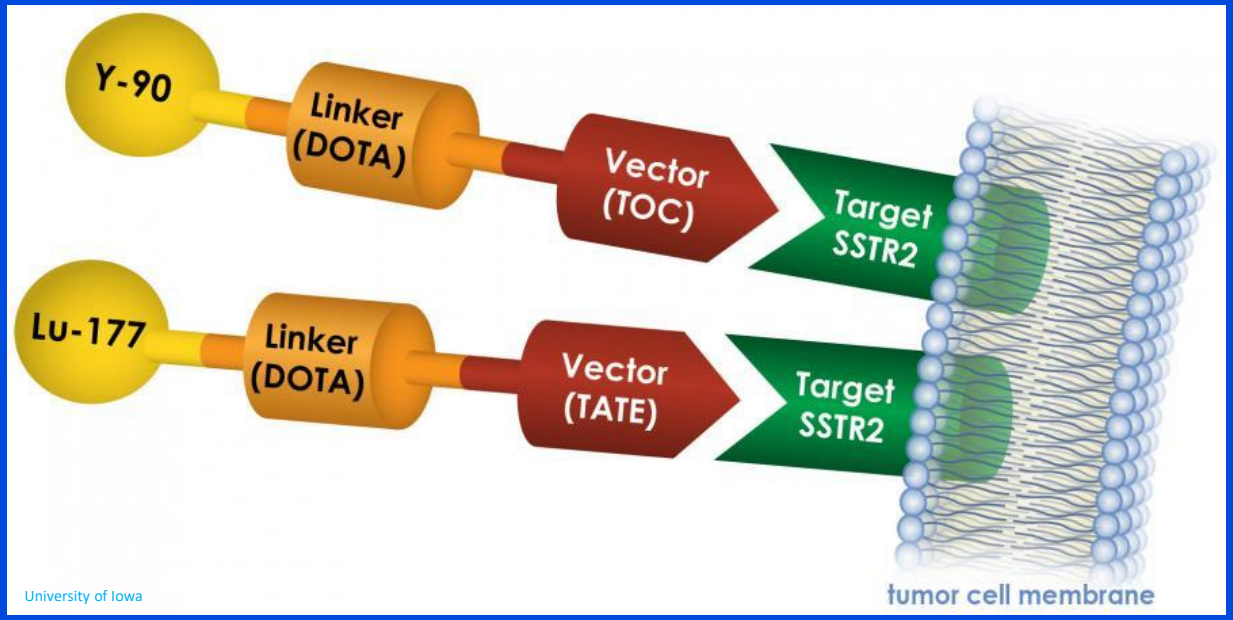

Therapeutic Radiopharmaceutical

Theranostic Combinations

Imaging	Therapy	Disease
• I-131	• I-131	• Thyroid Cancer • Graves Disease
• Ga-68 DOTATATE • Ga-68 DOTATOC	• Lu-177 DOTATATE • Y-90 DOTATATE	• Neuroendocrine tumors • Neuroendocrine tumors
• Ga-68 PSMA11 • F-18 PSMA • Tc-99m PSMA	• Lu-177 PSMA617 • Ac-225 PSMA • Th-227 PSMA	• Prostate Cancer
• Ga-68 FAPI	• Lu-177 FAPI	• Tumor associated fibroblasts
• Pb-203 MCH	• Pb-212 MCH	• Melanoma

FDA -approved **In Clinical Trial**

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FDA -approved **In Clinical Trial**

Table 1. Current diagnostic PSMA ligand

Isotope	Target	Imaging agent
^{89}Zr		
	Monoclonal antibody	^{89}Zr-DFO-7E11
	Monoclonal antibody	^{89}Zr-DFO-J591
	Antibody fragment	^{89}Zr-Cys-Db
^{64}Cu		
	Monoclonal antibody	^{64}Cu-DOTA-3/A12
	Monoclonal antibody	^{64}Cu-DOTA-3/F11
	Monoclonal antibody	^{64}Cu-DOTA-3/E7
^{111}In		
	Antibody fragment	^{111}In-JVZ007-cys
^{99m}Tc		
	Antibody fragment	^{99m}Tc-J591Cdia
	Small molecule inhibitor	^{99m}Tc-MIP-1404
	Small molecule inhibitor	^{99m}Tc-MIP-1405
	Small molecule inhibitor	^{99m}Tc-DUPA
^{68}Ga		
	Antibody fragment	^{68}Ga-THP-scFv
	Small molecule inhibitor	^{68}Ga-rhPSMA
	Small molecule inhibitor	^{68}Ga-THP-PSMA
	Small molecule inhibitor	^{68}Ga-PSMA-11
	Small molecule inhibitor	^{68}Ga-PSMA-I&T
^{18}F		
	Small molecule inhibitor	^{18}F-SFB
	Small molecule inhibitor	^{18}F-CTT-1298
	Small molecule inhibitor	^{18}F-CTT-1057
	Small molecule inhibitor	^{18}F-DCFBC
	Small molecule inhibitor	^{18}F-DCFPyL
	Small molecule inhibitor	^{18}F-YC-88
	Small molecule inhibitor	^{18}F-PSMA-1007
	Small molecule inhibitor	^{18}F-rhPSMA-7.3
	Small molecule inhibitor	^{18}F-FSU-880

Tateishi U. Prostate-specific membrane antigen (PSMA)–ligand positron emission tomography and radioligand therapy (RLT) of prostate cancer Jpn J Clin Oncol. 2020;50(4):349-356.

Table 3. Clinical use of PSMA ligands (Oct 2019)

18F-PSMA ligands		Organization or company	Clinical phase
1	^{18}F-DCFPyL	Progenics Pharmaceuticals	Phase 3
2	^{18}F-PSMA-1007	ABX	Clinical study
3	^{18}F-CTT1057	Novartis (AAA)	Phase 1
4	^{18}F-rhPSMA-7.3	Blue Earth Diagnostics	Phase 1
5	^{18}F-FSU-880	Kyoto University	Phase 2
^{68} Ga-PSMA ligands		Organization or company	Clinical phase
1	^{68}Ga-PSMA-11	Telix Pharmaceuticals	Phase 3
2	^{68}Ga-PSMA-617	Novartis (Endocyte)	Clinical study
3	^{68}Ga-PSMA-I&T	Technical University of Munich	Clinical study
PSMA ligands for RLT		Organization or company	Clinical phase
1	^{177}Lu-PSMA-617	Novartis (Endocyte)	Phase 3
2	^{225}Ac-PSMA-617	Novartis (Endocyte)	Phase 1
3	^{177}Lu-TX591	Telix Pharmaceuticals	Phase 2
4	^{177}Lu-PSMA-R2	Novartis (AAA)	Phase 1/2
5	^{227}Th-PSMA-TTC	Bayer	Phase 1

Tateishi U. Prostate-specific membrane antigen (PSMA)–ligand positron emission tomography and radioligand therapy (RLT) of prostate cancer Jpn J Clin Oncol. 2020;50(4):349-356.

Gallium-68

$T_{1/2}$ = 68 min

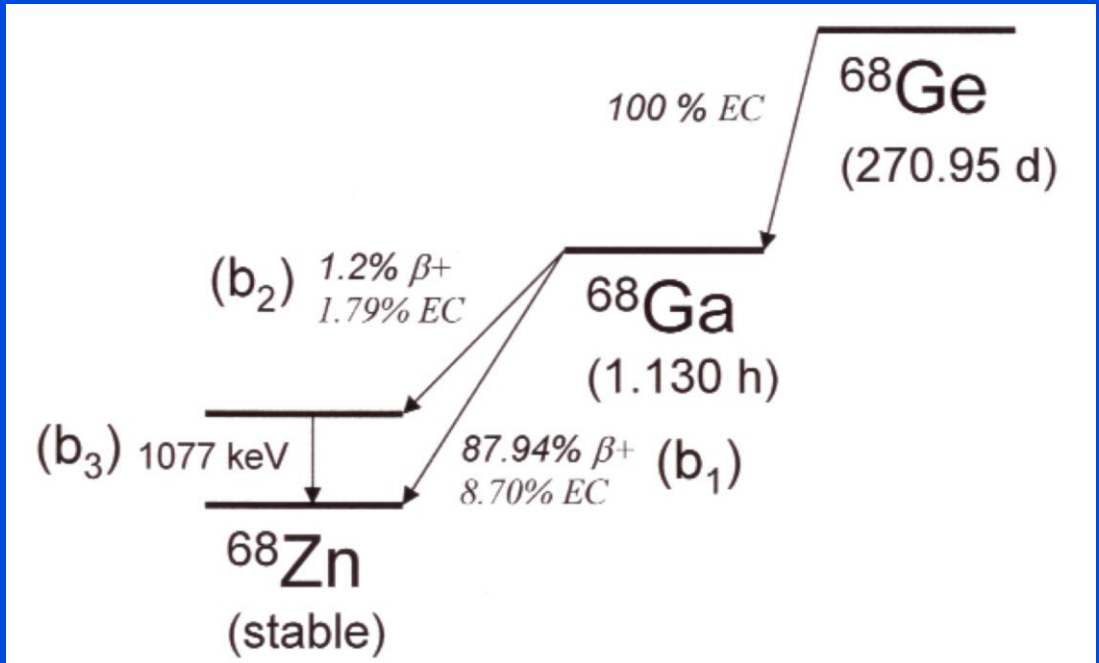


Fig. 1. Simplified decay scheme for ^{68}Ge-^{68}Ga. Data were taken from the DDEP data evaluation [4]. The branching probabilities b_1, b_2, and b_3 refer to the two positron emission and gamma emission probabilities, respectively.

Used with DOTATATE, PSMA, FAPI

Zimmerman BE, Cessna JT, Fitzgerald R. Standardization of ^{68}Ge/^{68}Ga Using Three Liquid Scintillation Counting Based Methods. J. Res. Natl. Inst. Stand. Technol. 113, 265-280 (2008)

Lutetium-177

$T_{1/2}$ = 6.7 d

Production: Neutron activation

$E_{\beta(max)}$ = 497 keV (78.6 %), 384 keV (9.1 %), 176 keV (12.2 %)

E_{γ} = 113 keV (6.6 %), 208 keV (11 %)]

The mean penetration range of β^- particles emitted by ^{177}Lu in soft tissue is 670 µm

Used with DOTATATE, PSMA, FAPI

Yttrium-90

$T_{1/2}$ = 64.6 h

Production: decay from Sr-90

$E_{\beta(max)}$ = 2.28 MeV (99.98 %)

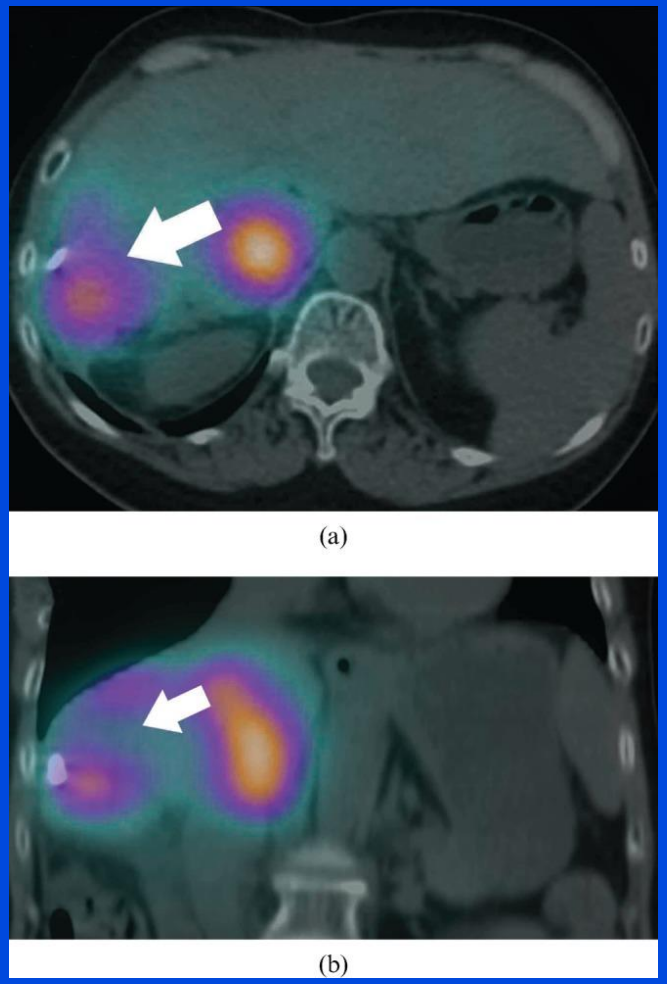
E_{γ} = 1.76 MeV (0.017 %)

The mean penetration range of β^- particles emitted by ^{90}Y in soft tissue is 2.5 mm

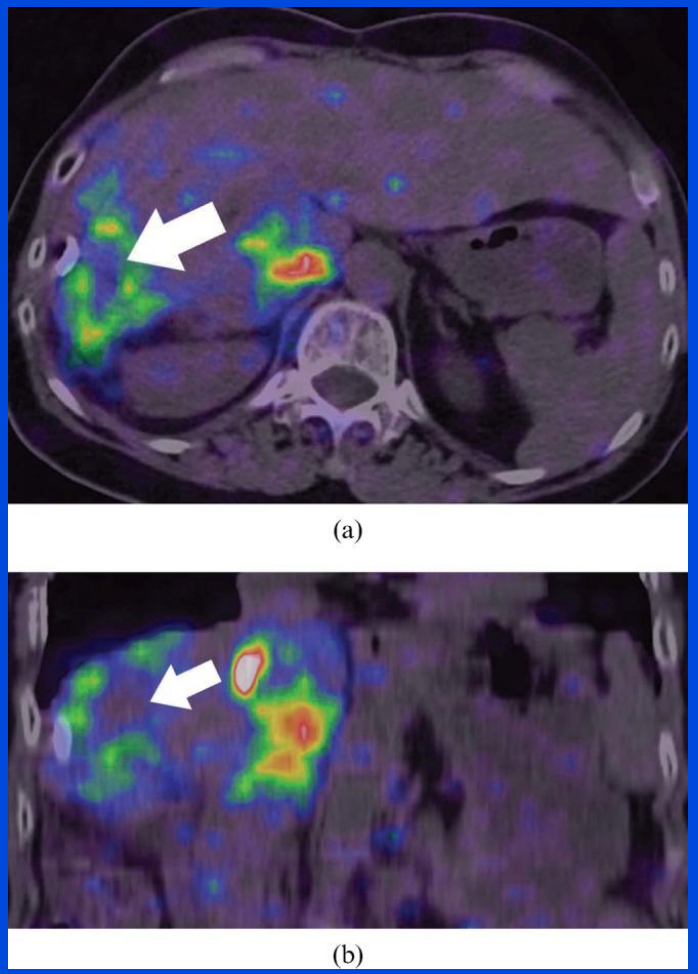
Positron emission = 32 ppm

Used with DOTATOC

Imaging following intra-arterial administration of ^{90}Y resin microspheres



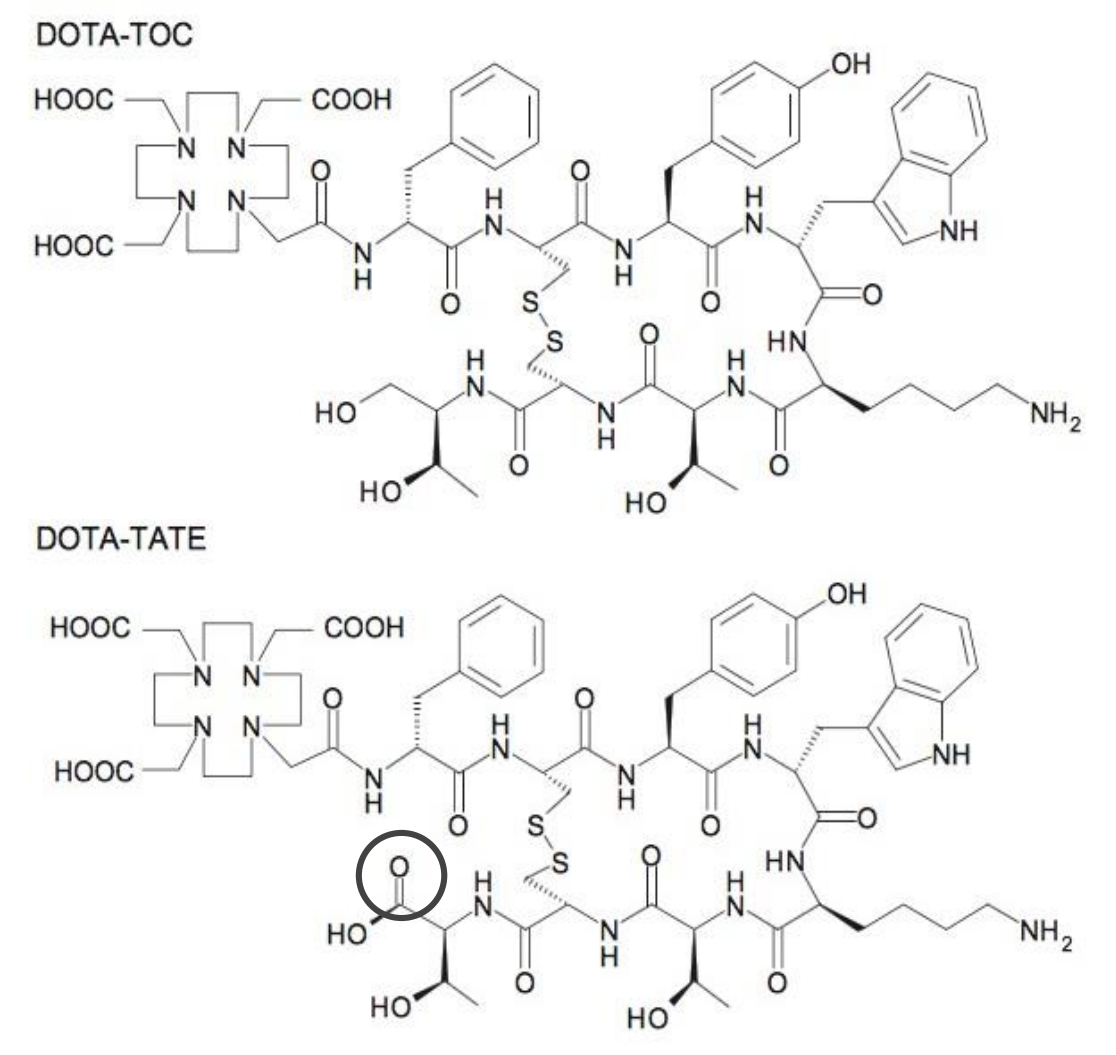
Bremsstrahlung SPECT/CT



PET-CT

Br J Radiol. 2012 Jul; 85(1015): 1018–1019.

DOTATOC and DOTATATE

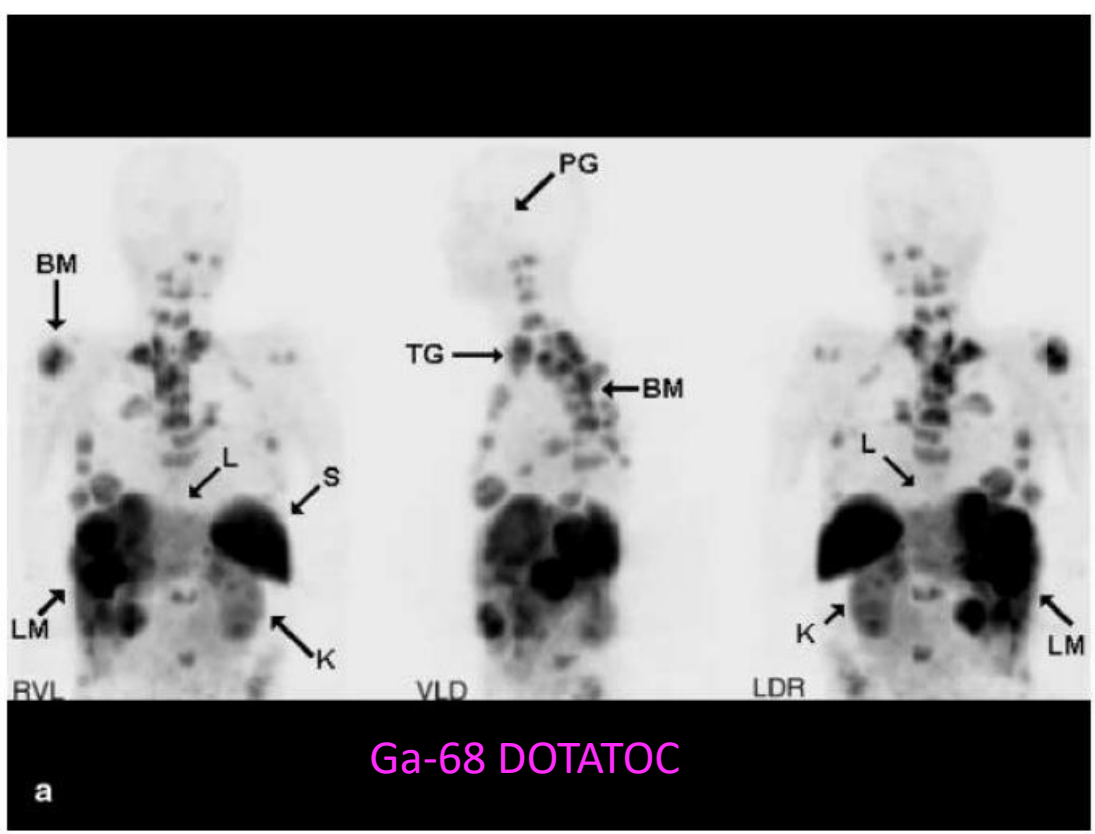


Approved 2019

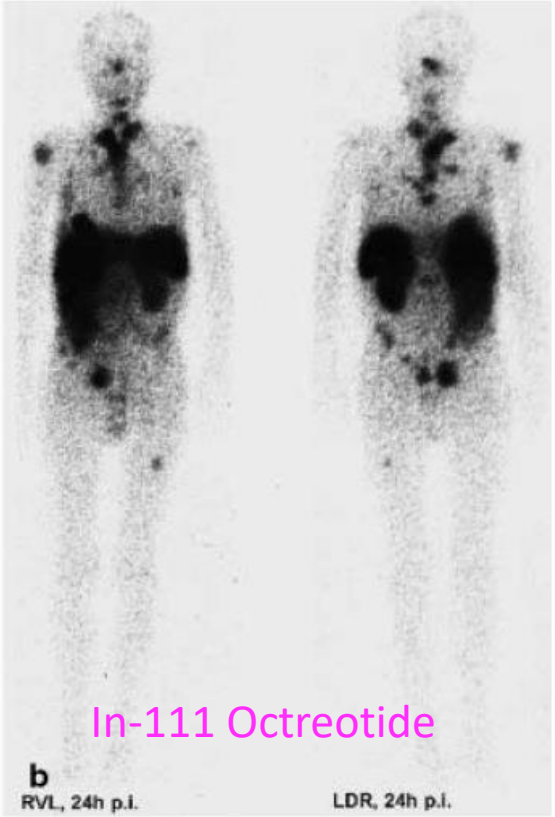
Approved 2016

The untapped potential of Gallium 68-PET: The next wave of ^{68}Ga-agents
D.L. Smith et al. / Applied Radiation and Isotopes 76 (2013) 14–23

Hofmann M, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand ^{68}Ga-DOTATOC: preliminary data. Eur J Nucl Med. 2001 v28:1751-7.

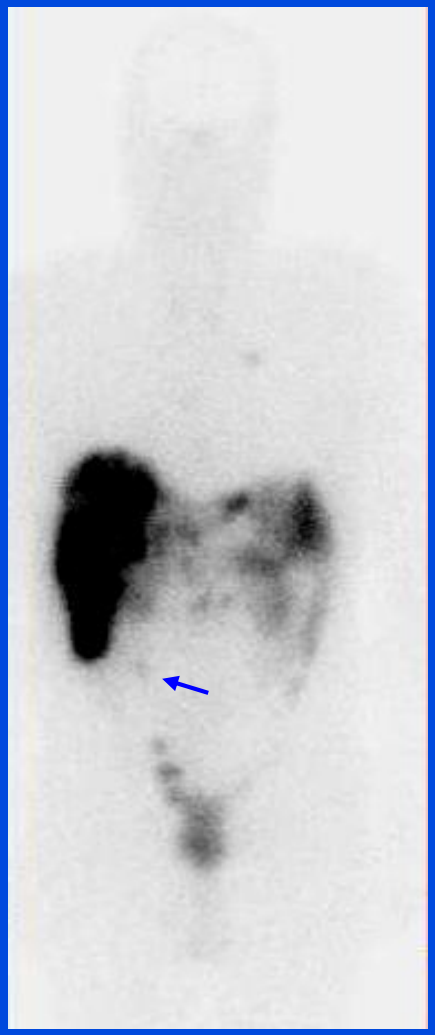


Ga-68 DOTATOC

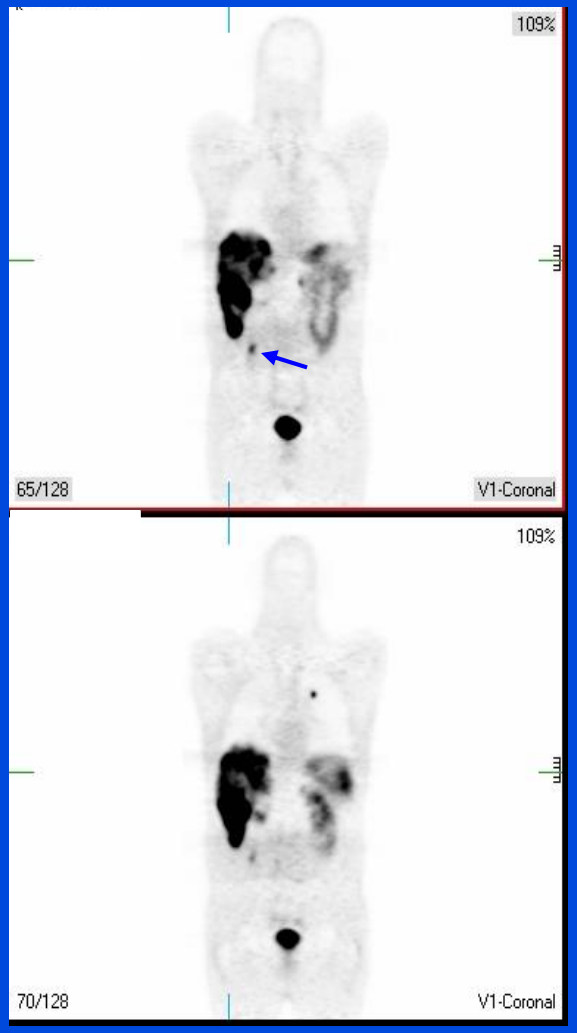


In-111 Octreotide

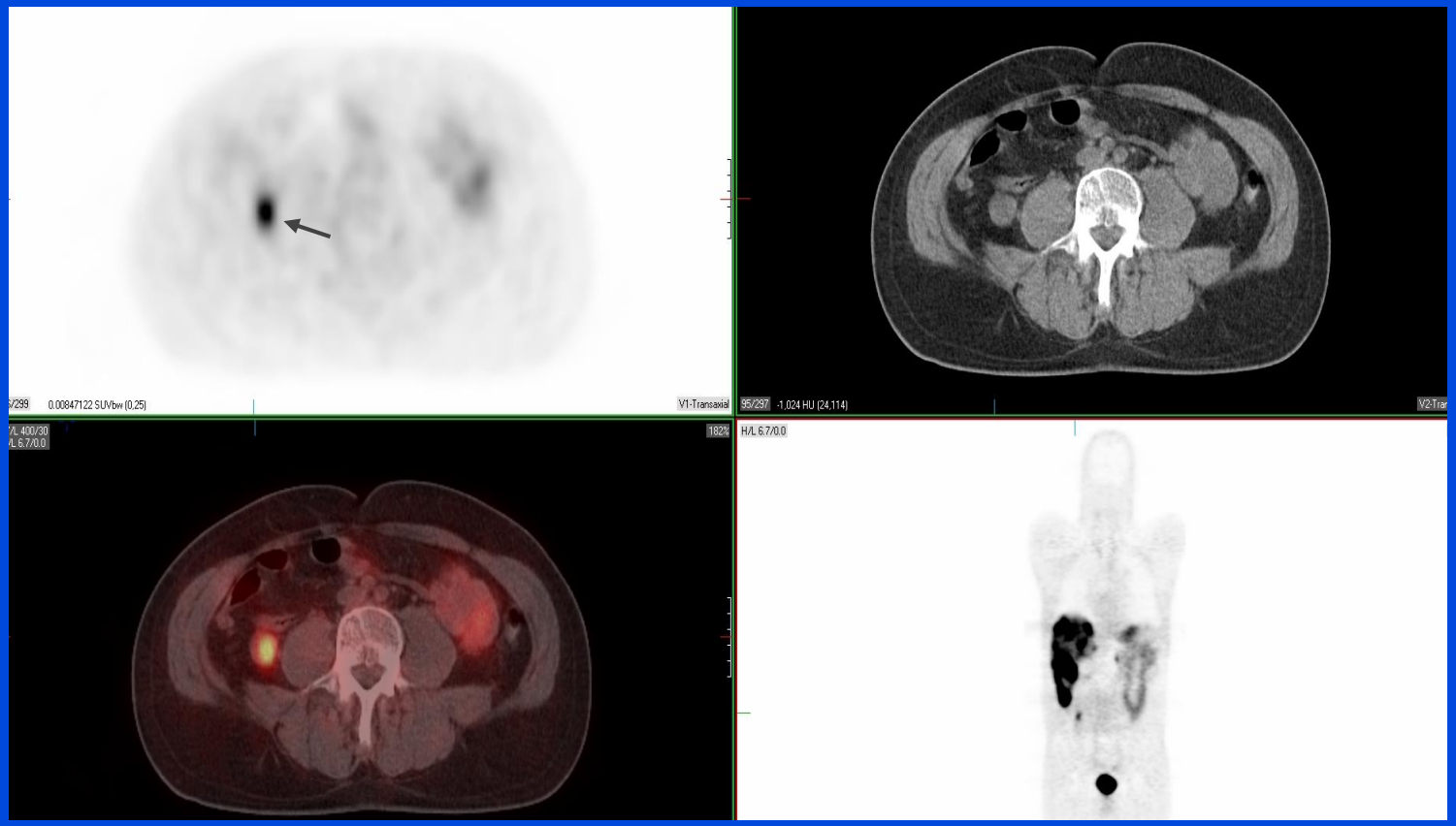
67 year old with episodic flushing, loose stools, documented liver mets, elevated chromogranin A. Primary NET site not established.



In-111 Octreotide



Ga-68 DOTATOC



Ga-68 DOTATOC

Ga-68 DOTATATE

Lu-177 DOTATATE (Approved 2018)

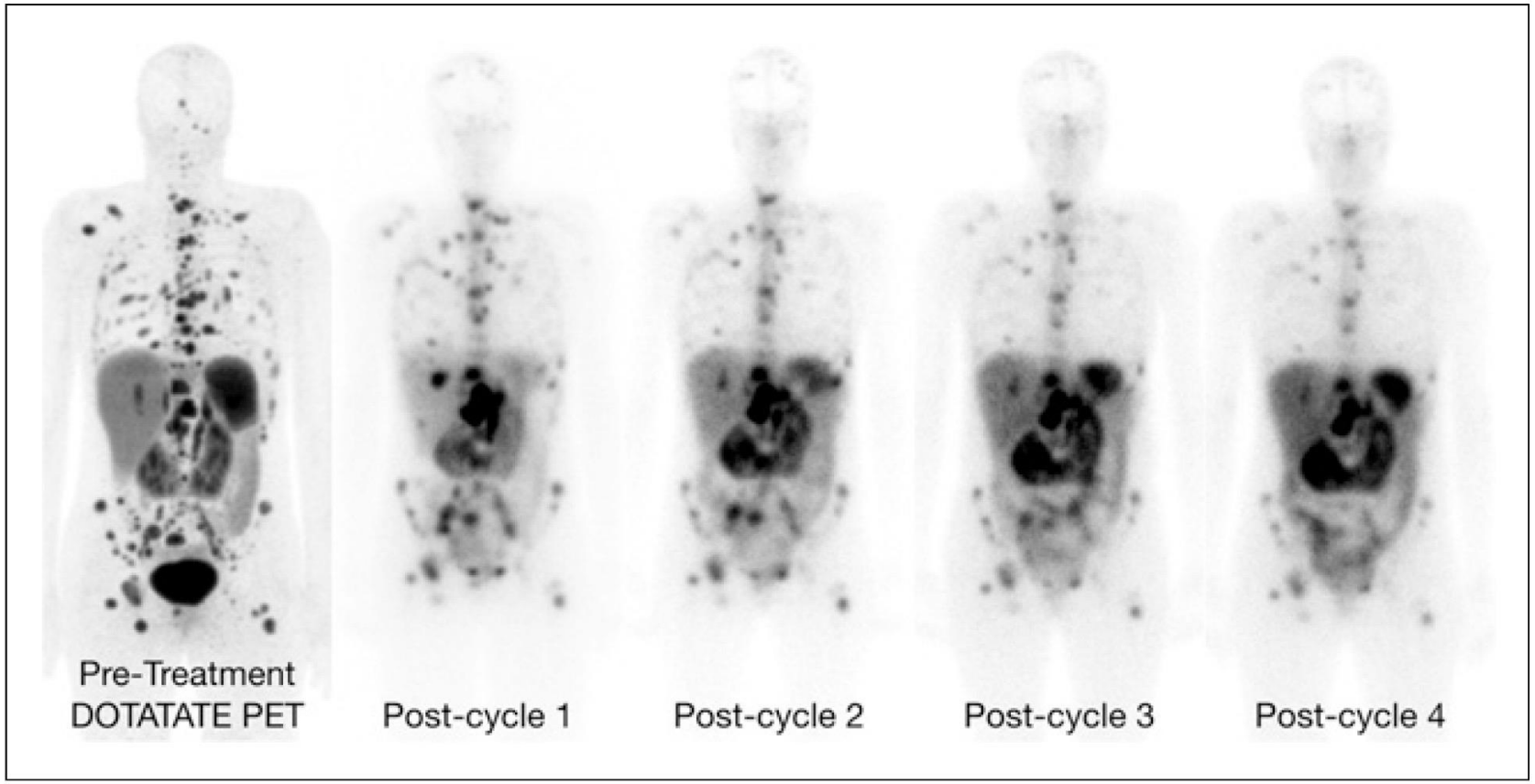
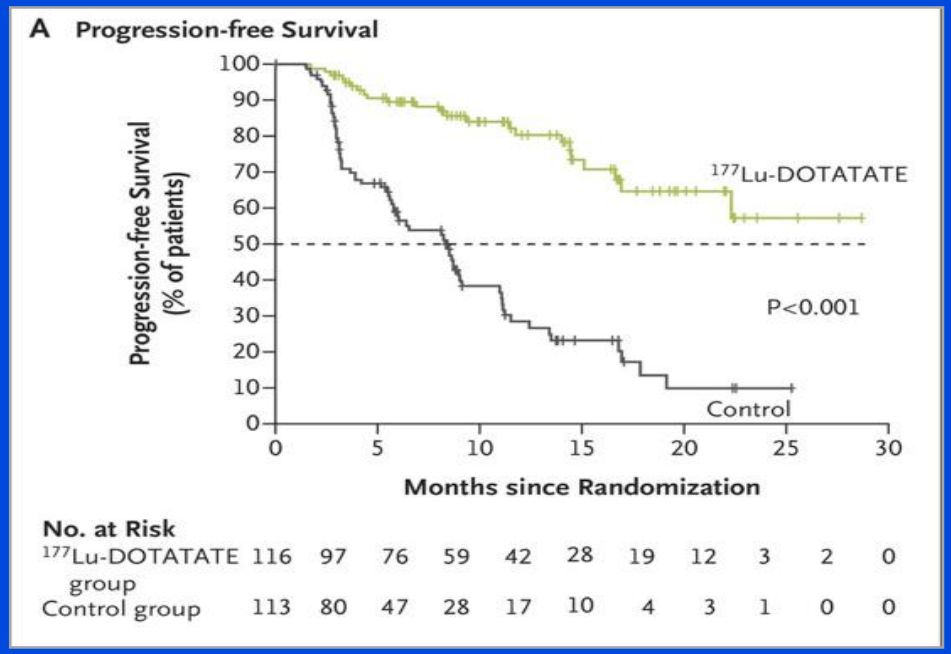
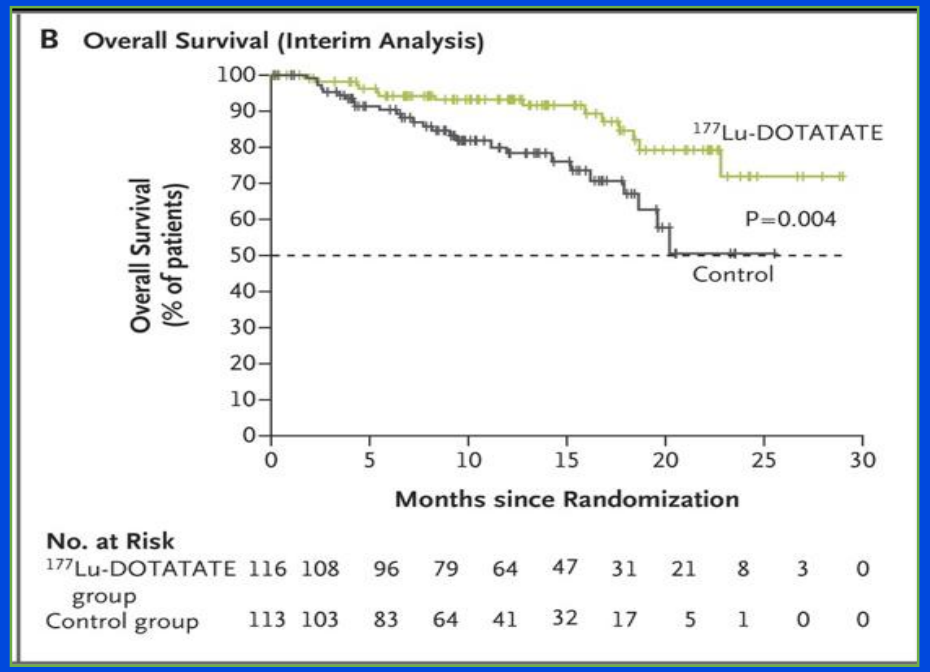


FIGURE 4. Whole-body images acquired after administration of ^{177}Lu-DOTATATE in different therapy cycles. (200 mCi (7.4 GBq) per dose)

Hope TA, et al. NANETS/SNMMI Procedure Standard for Somatostatin Receptor–Based Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE. J Nucl Med 2019; 60:937–943

NETTER 1 Prospective Randomized Clinical Trial
(Peptide Receptor Radiotherapy (PRRT) vs Conventional Therapy)



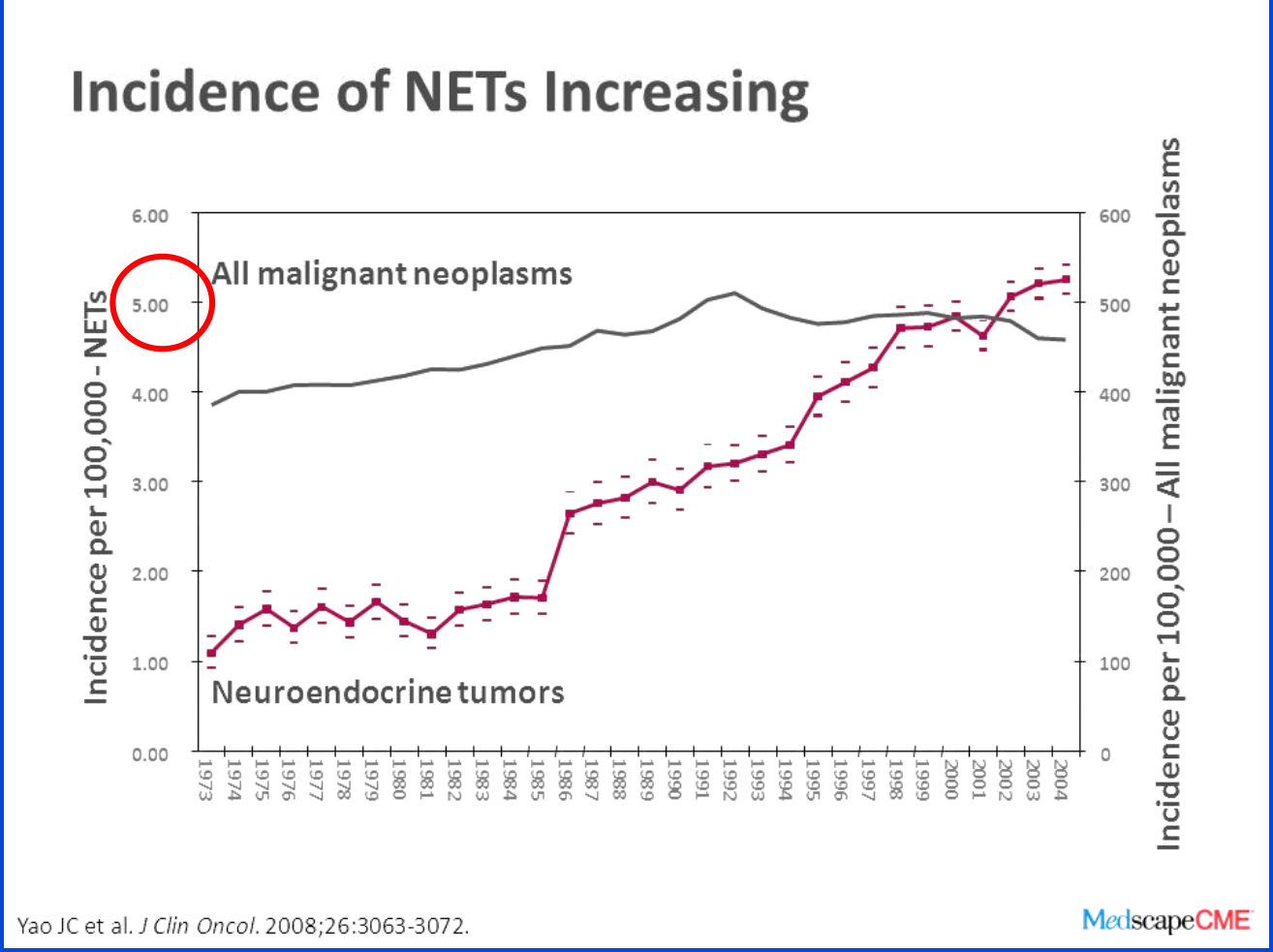


116 patients treated with Lu-177 DOTATATE plus low dose long-acting octreotide
113 patient treated with high dose long-acting octreotide

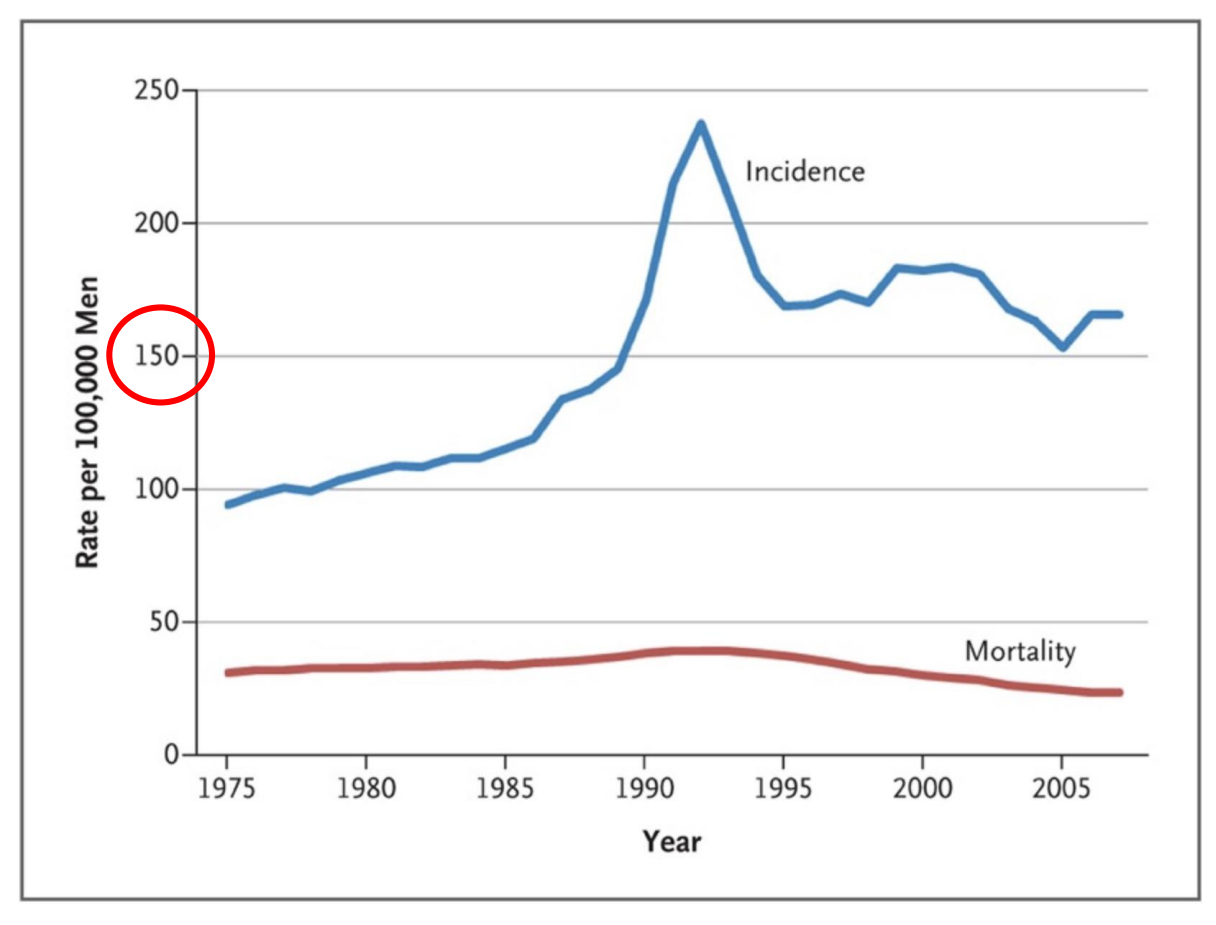
41 centers in 8 countries were involved

Strosberg J. et al. Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors N Engl J Med 2017;376:125-35.

Neuroendocrine tumors

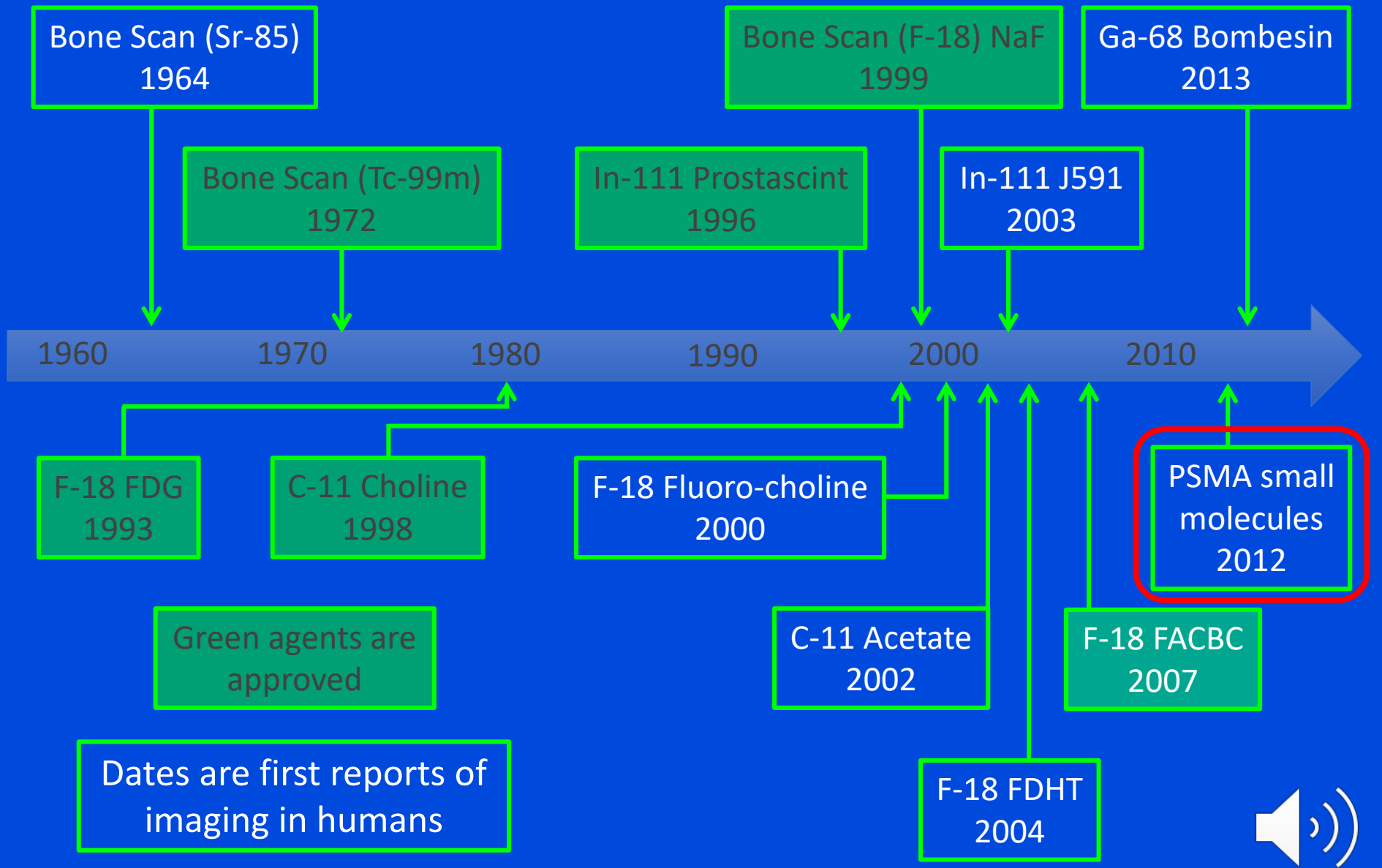


Prostate Cancer

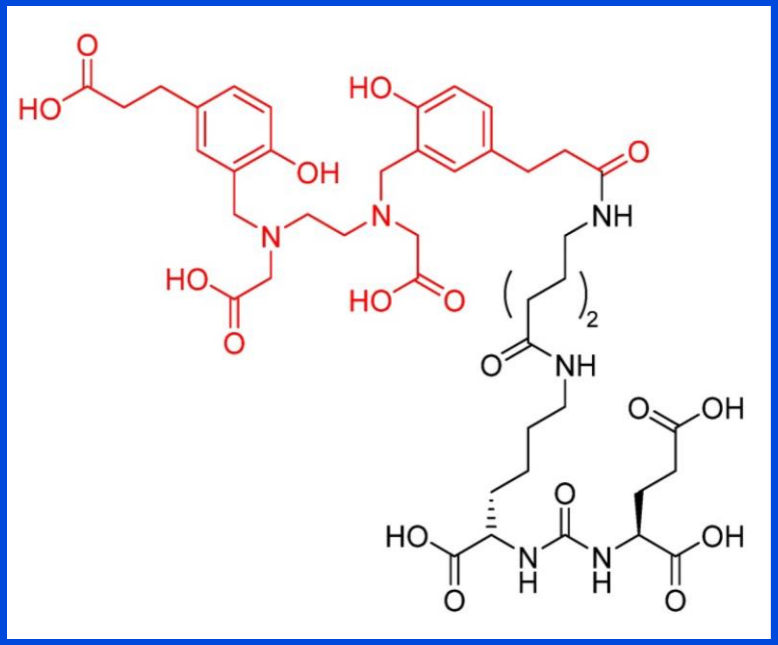


Hoffman RM. Screening for Prostate Cancer. N Engl J Med 2011; 365:2013-2019

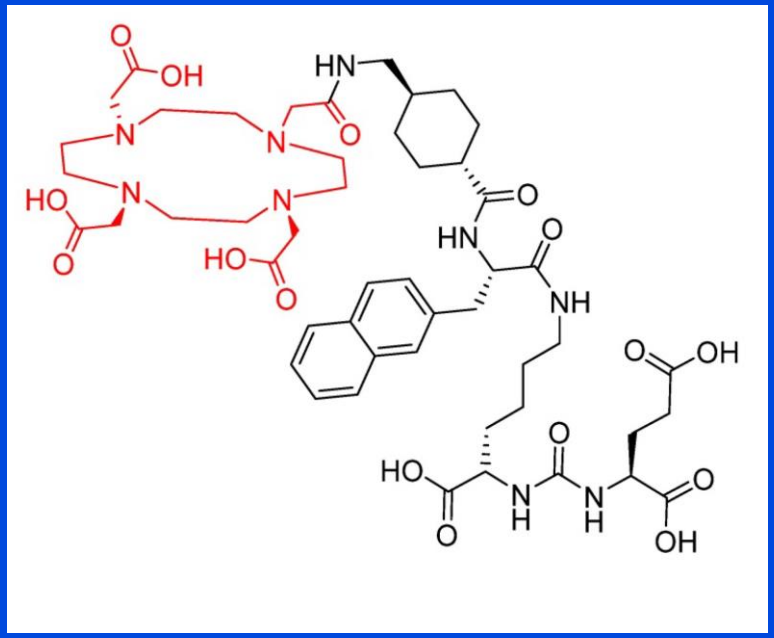
Radiotracers for Prostate Cancer



Most widely studied Prostate-Specific Membrane Antigen (PSMA) Radiopharmaceuticals



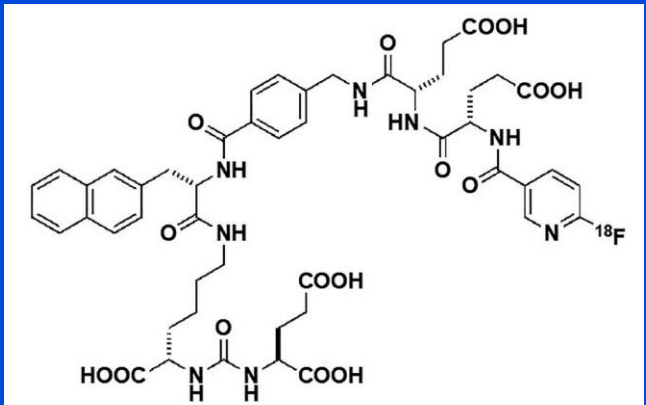
Ga-68 PSMA-11



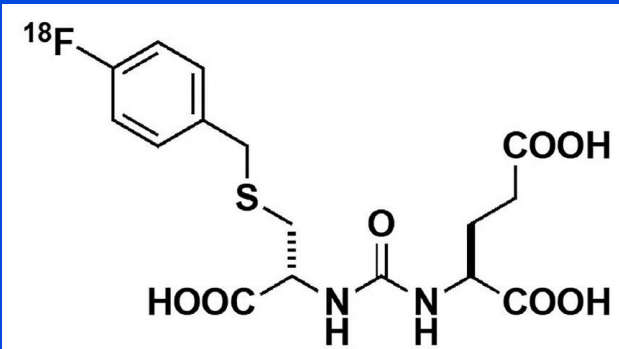
Lu-177 PSMA-617

Eppard E, et al. Clinical Translation and First In-Human Use of ^{44}Sc-PSMA-617 for PET Imaging of Metastasized Castrate-Resistant Prostate Cancer. Theranostics. 2017 Sep 26;7(18):4359-4369.

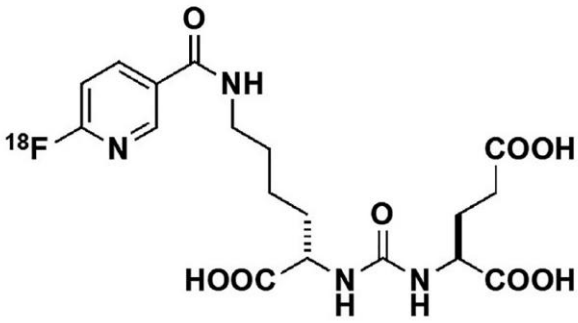
F-18 PSMA Targeted Radiopharmaceuticals



^{18}F-PSMA-1007



^{18}F-DCFBC



^{18}F-DCFPyL

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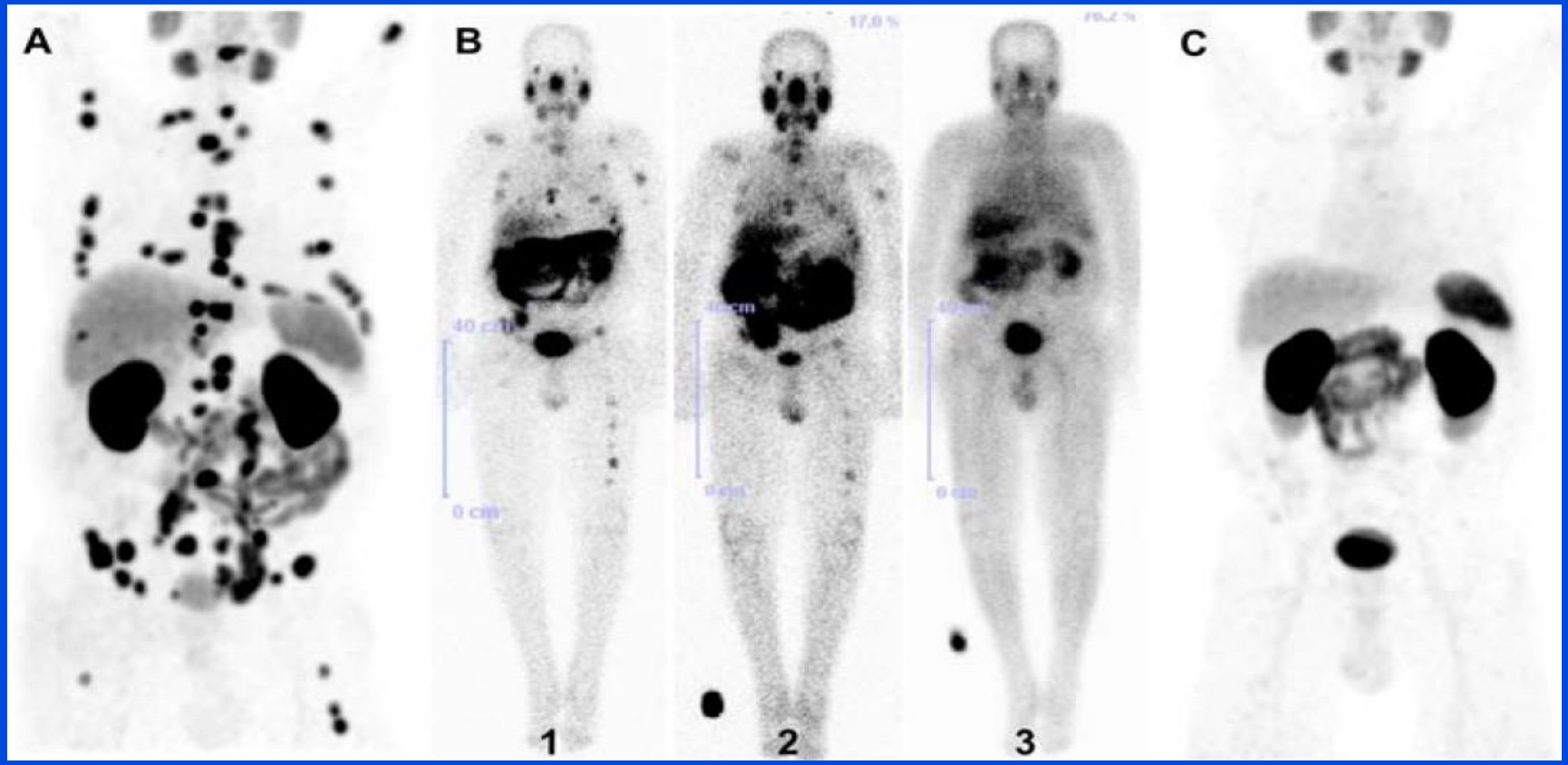
^{177}Lu-PSMA 617



^{68}Ga-PSMA

^{177}Lu-PSMA cycles

^{68}Ga-PSMA

Baum RP, et al. ^{177}Lu-PSMA Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. J Nucl Med. 2016 Jul;57(7):1006-13.

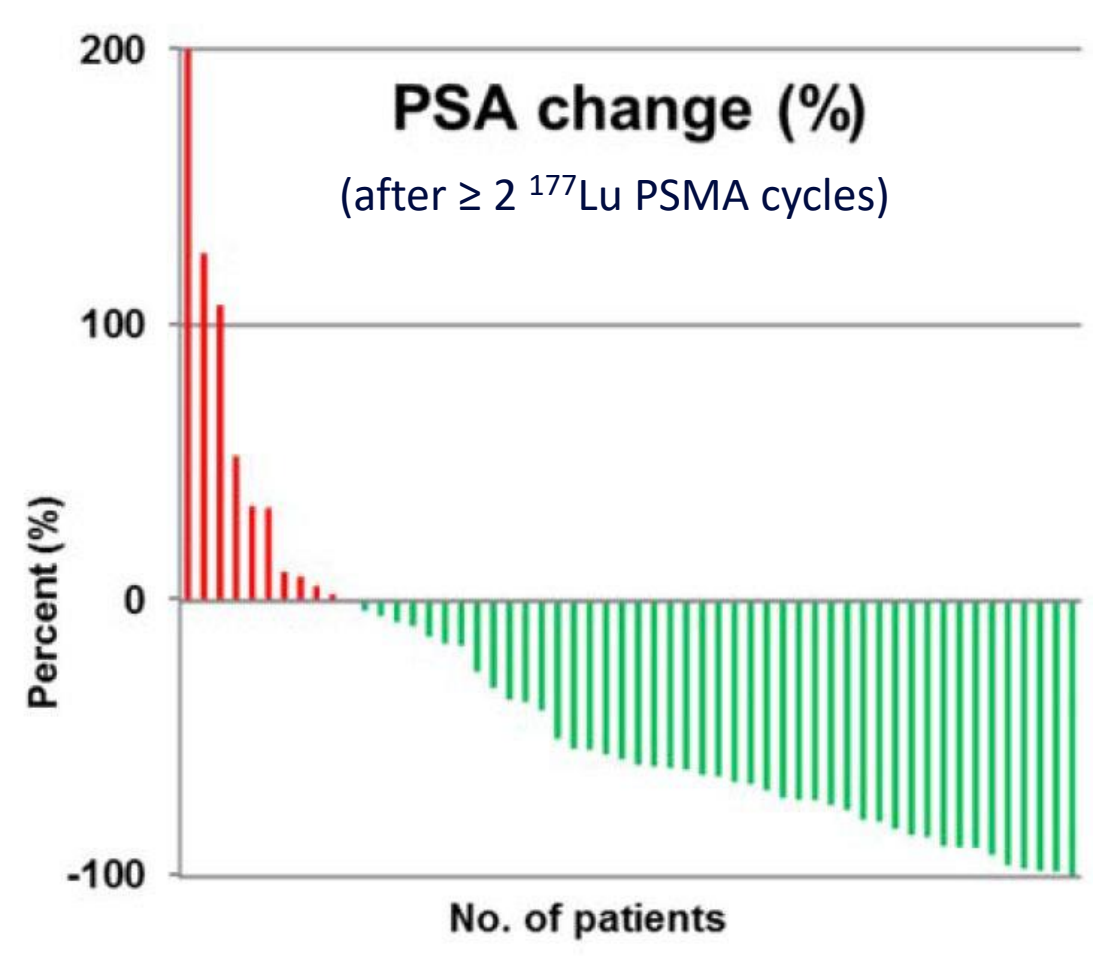
^{177}Lu T½ = 6.7 d

γ = 113 & 210 keV

β_{mean} = 149 keV

^{177}Lu-PSMA 617 (Germany)

N=25



Baum RP, et al. Lutetium-177 PSMA Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. J Nucl Med. 2016 Jul;57(7):1006-13.

^{177}Lu-PSMA 617 (Australia)

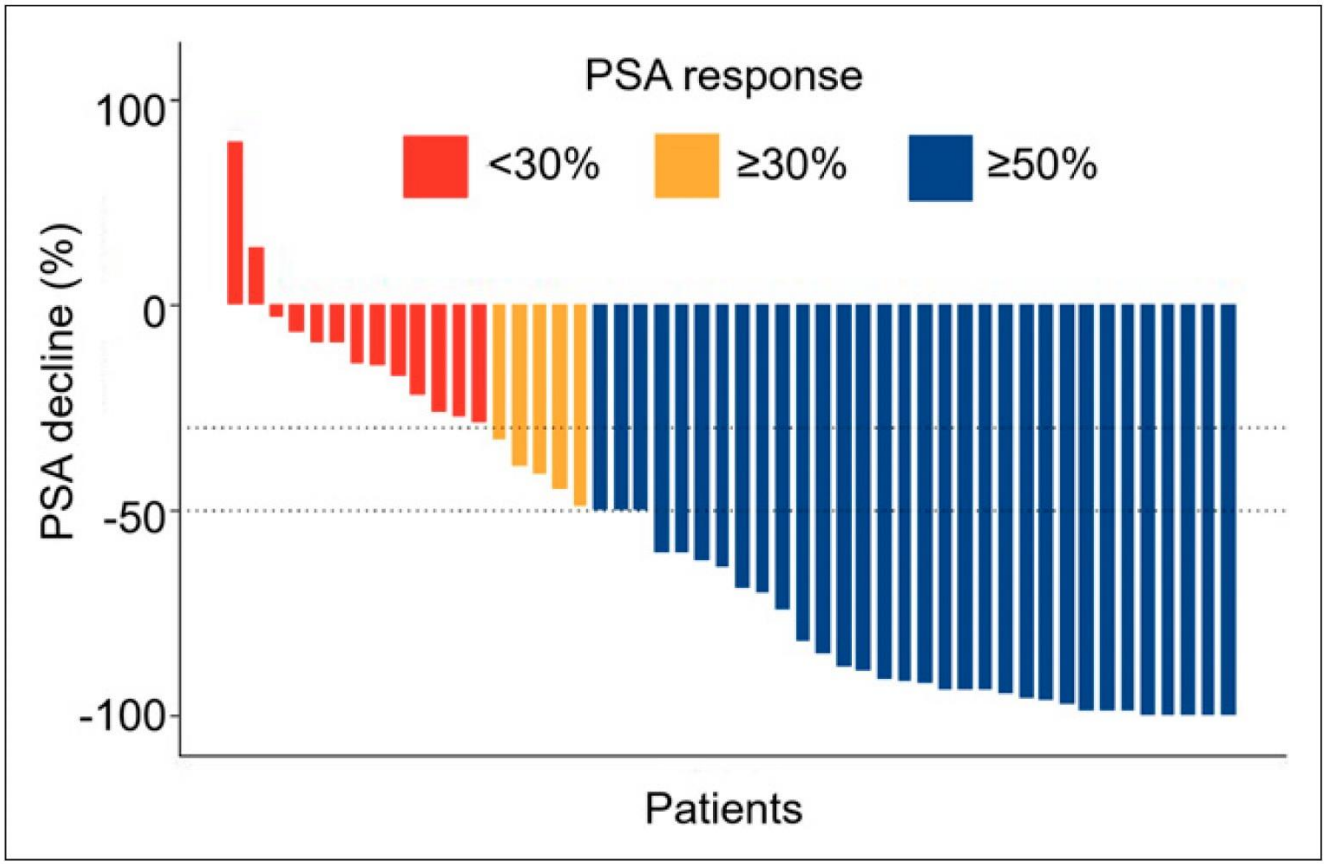
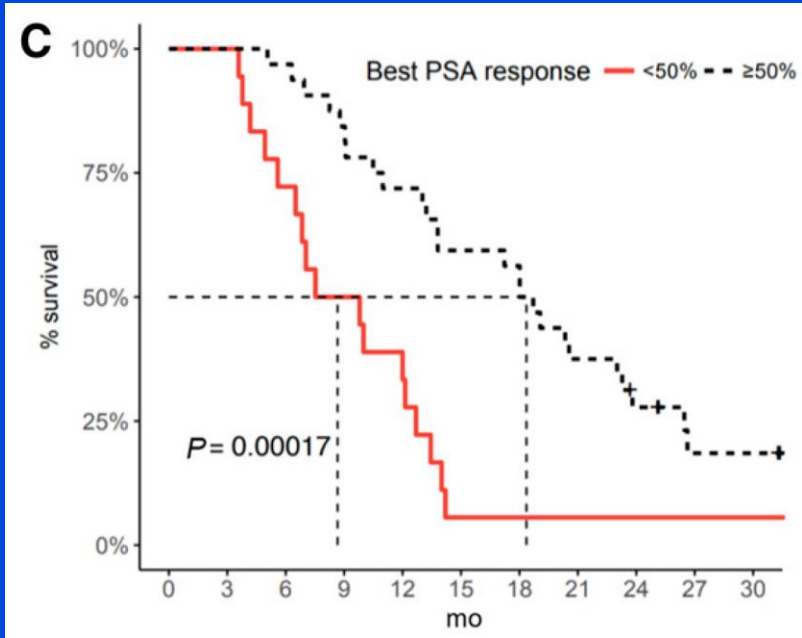


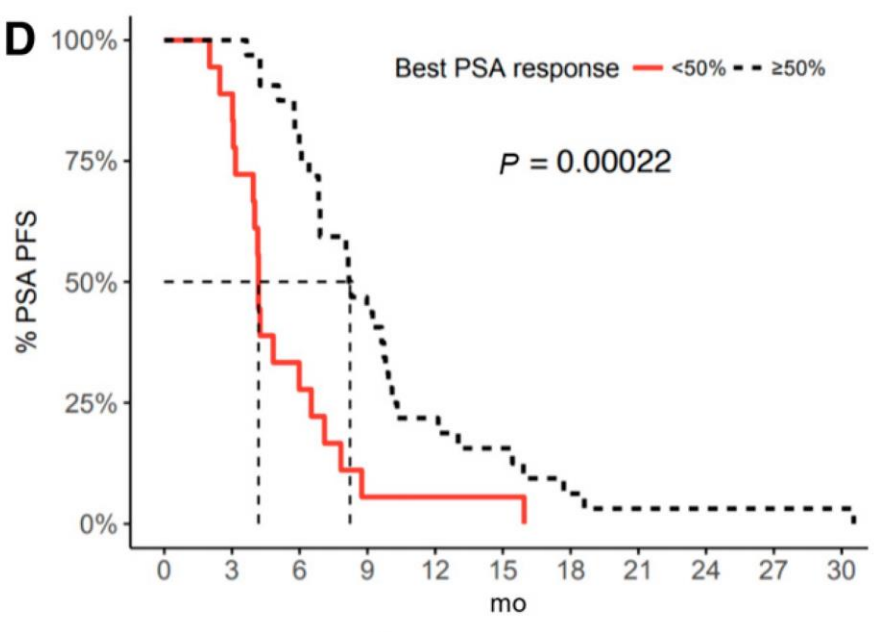
FIGURE 2. Waterfall plot of best PSA decline compared with baseline.

Violet J et al. Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of ^{177}Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer. J Nucl Med 2020; 61:857–865

Melbourne, Australia Group



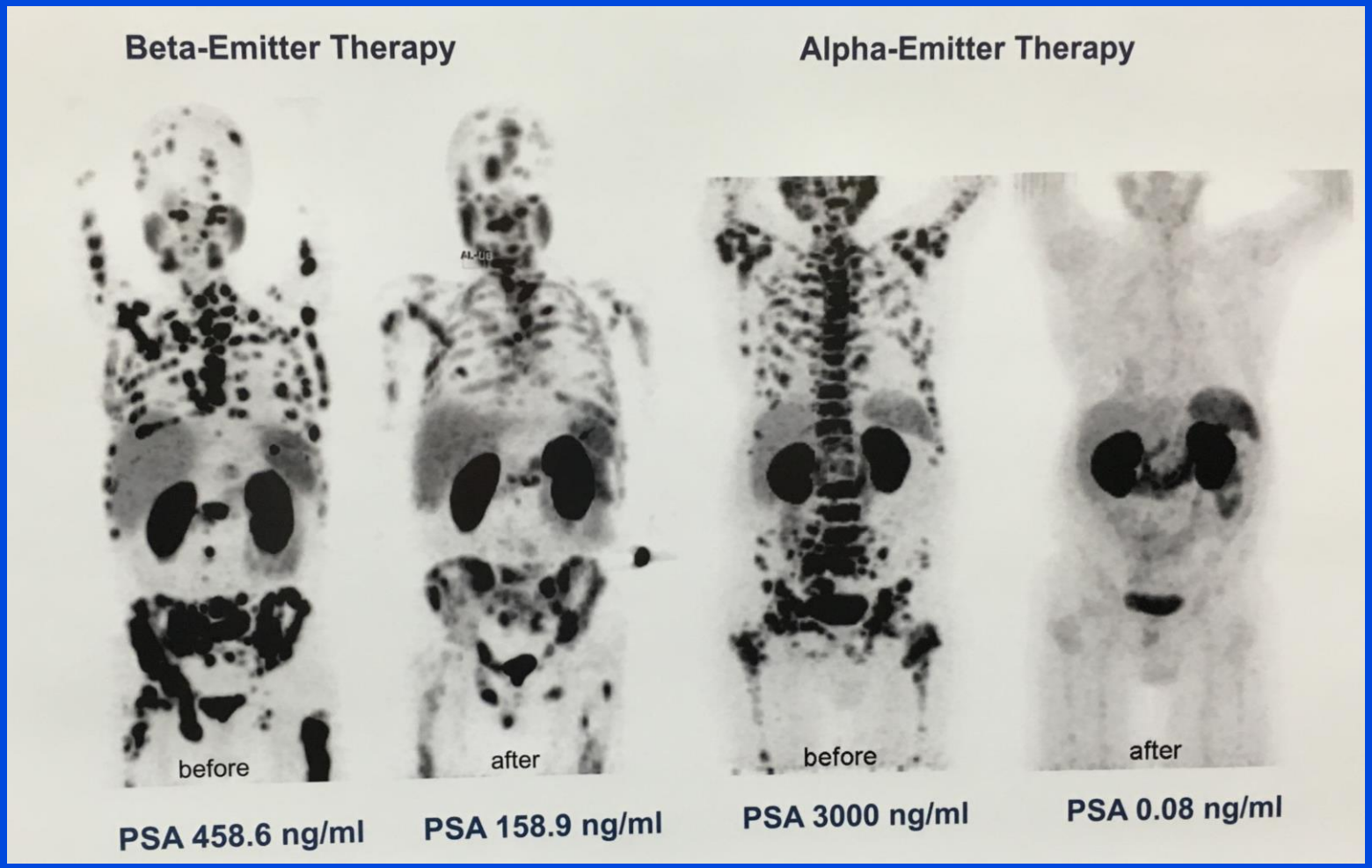
Overall Survival



Progression-free Survival

Violet J et al. Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of ^{177}Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer. J Nucl Med 2020; 61:857–865

^{177}Lu-PSMA ^{225}Ac-PSMA



Poster at SNMMI 2016 annual meeting

Ac-225-PSMA617 - a single center experience of 40 patients receiving PSMA-targeted Alpha therapy

C. Kratochwil[1], F. L. Giesel[1], F. Bruchertseifer[2], M. Rius[2], C. Apostolidis[2], U. Haberkorn[1], A. Morgenstern[2]

(1) Department of Nuclear Medicine, University of Heidelberg, Heidelberg, Germany
(2) Institute for Transuranium Elements, European Commission, Joint Research Centre, Karlsruhe, Germany

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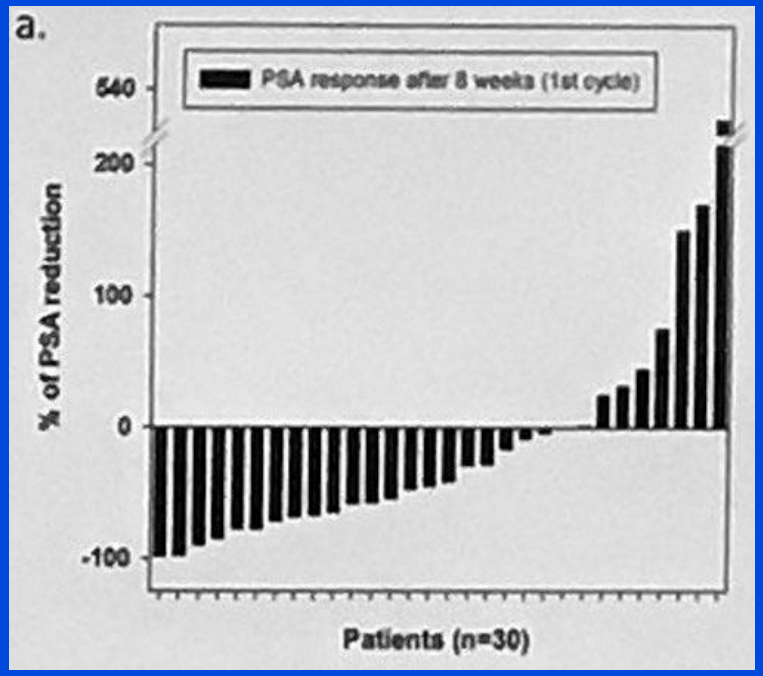
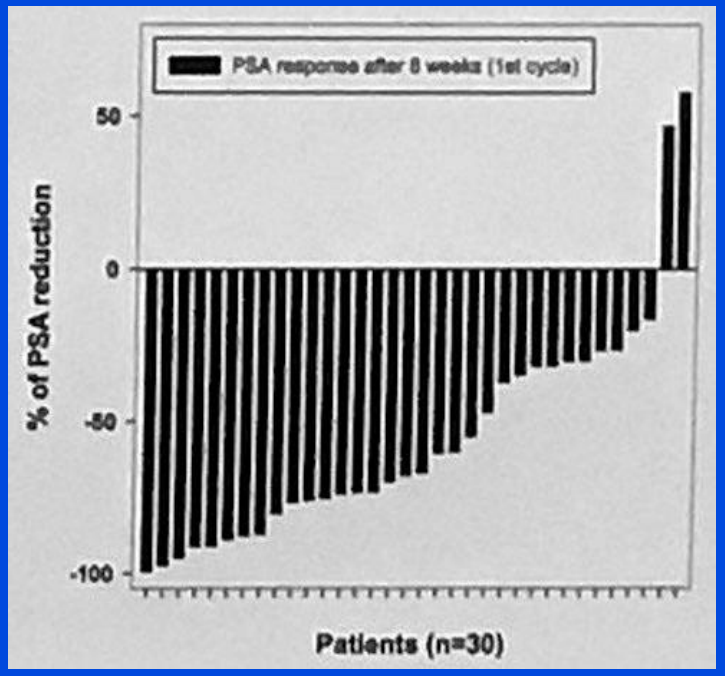




Poster at SNMMI 2016 annual meeting

^{177}Lu-PSMA

^{225}Ac-PSMA

Ac-225 PSMA

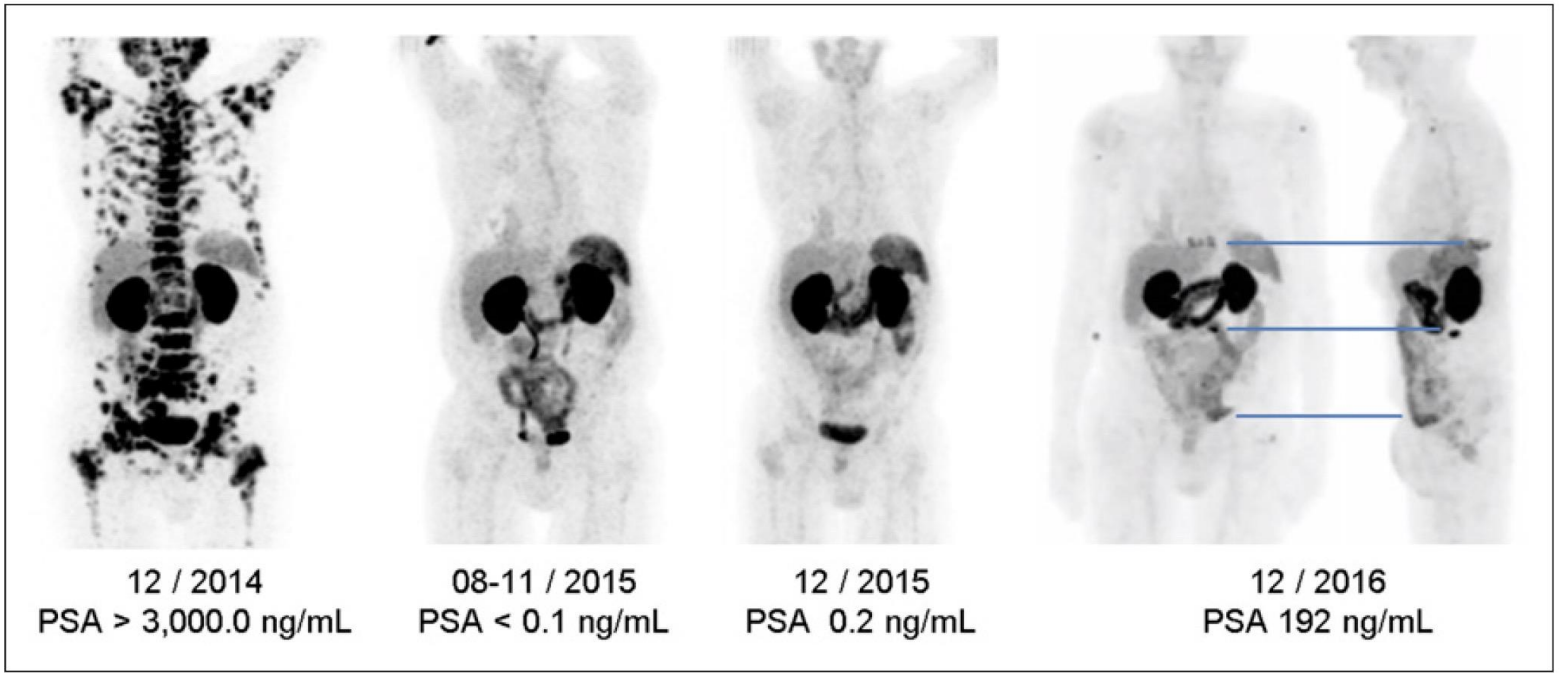


FIGURE 2. TTP vs. duration of clinical benefit. After favorable initial PSA and imaging response to complete remission, patient 14 had TTP of only 1 y (January to December 2015). However, duration of clinical benefit was more than 1 y longer: because of asymptomatic disease and slow growth velocity, treatment-free interval could be prolonged until April 2017. Whether patient will again respond to second series of ^{225}Ac-PSMA-617 is not yet known. (Images courtesy of Prof. Felix Mottaghy, Rheinisch-Westfälische Technische Hochschule Aachen.)

Kratochwil C, et al. Targeted a-Therapy of Metastatic Castration-Resistant Prostate Cancer with 225Ac-PSMA-617: Swimmer-Plot Analysis Suggests Efficacy Regarding Duration of Tumor Control. J Nucl Med 2018; 59:795–802

Ac-225 PSMA

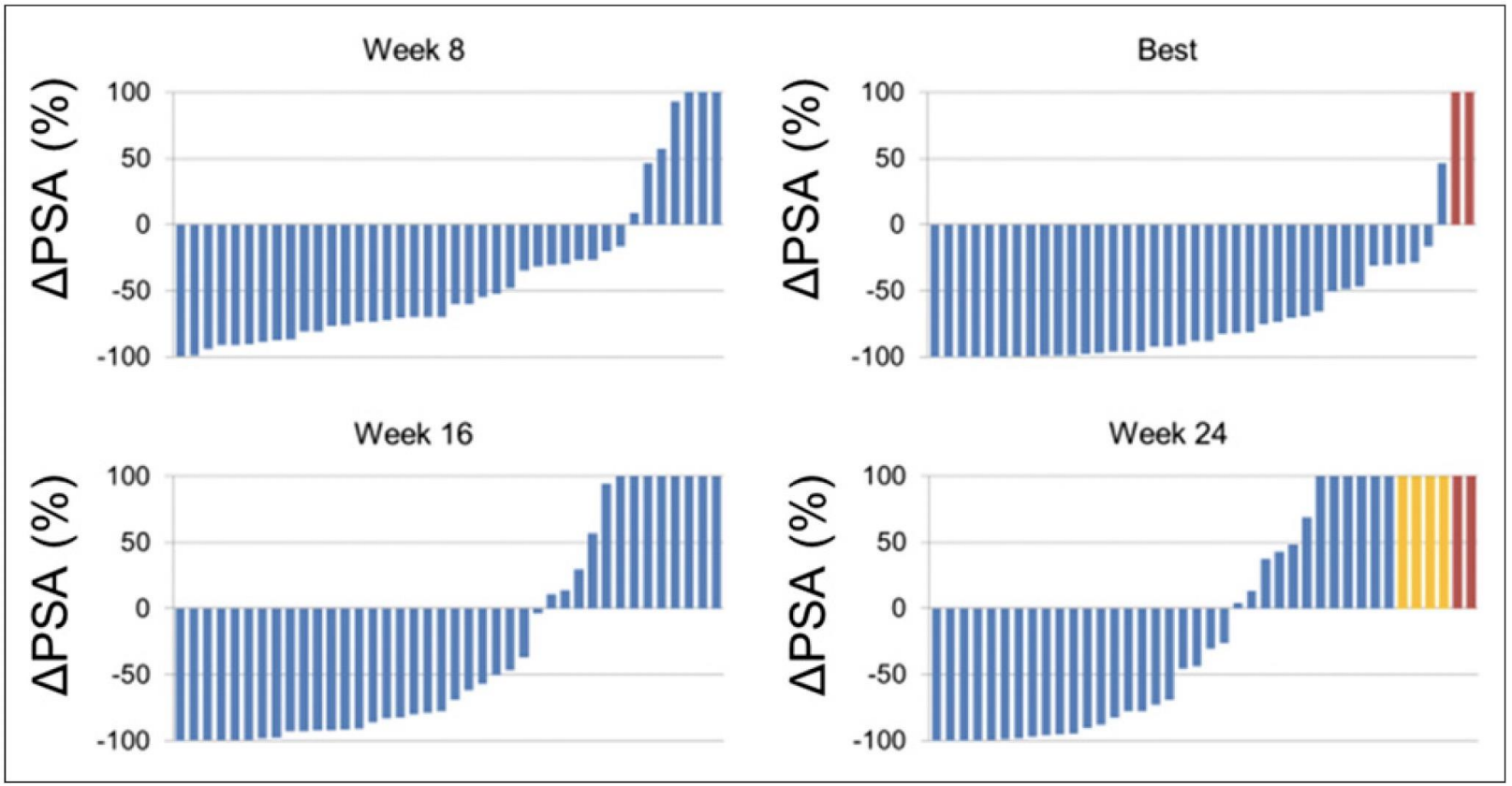


FIGURE 5. Waterfall graphs of PSA response. Patients who died before week 8 (red) or discontinued because of xerostomia (yellow) were classified as progression.

Kratochwil C, et al. Targeted a-Therapy of Metastatic Castration-Resistant Prostate Cancer with 225Ac-PSMA-617: Swimmer-Plot Analysis Suggests Efficacy Regarding Duration of Tumor Control. J Nucl Med 2018; 59:795–802

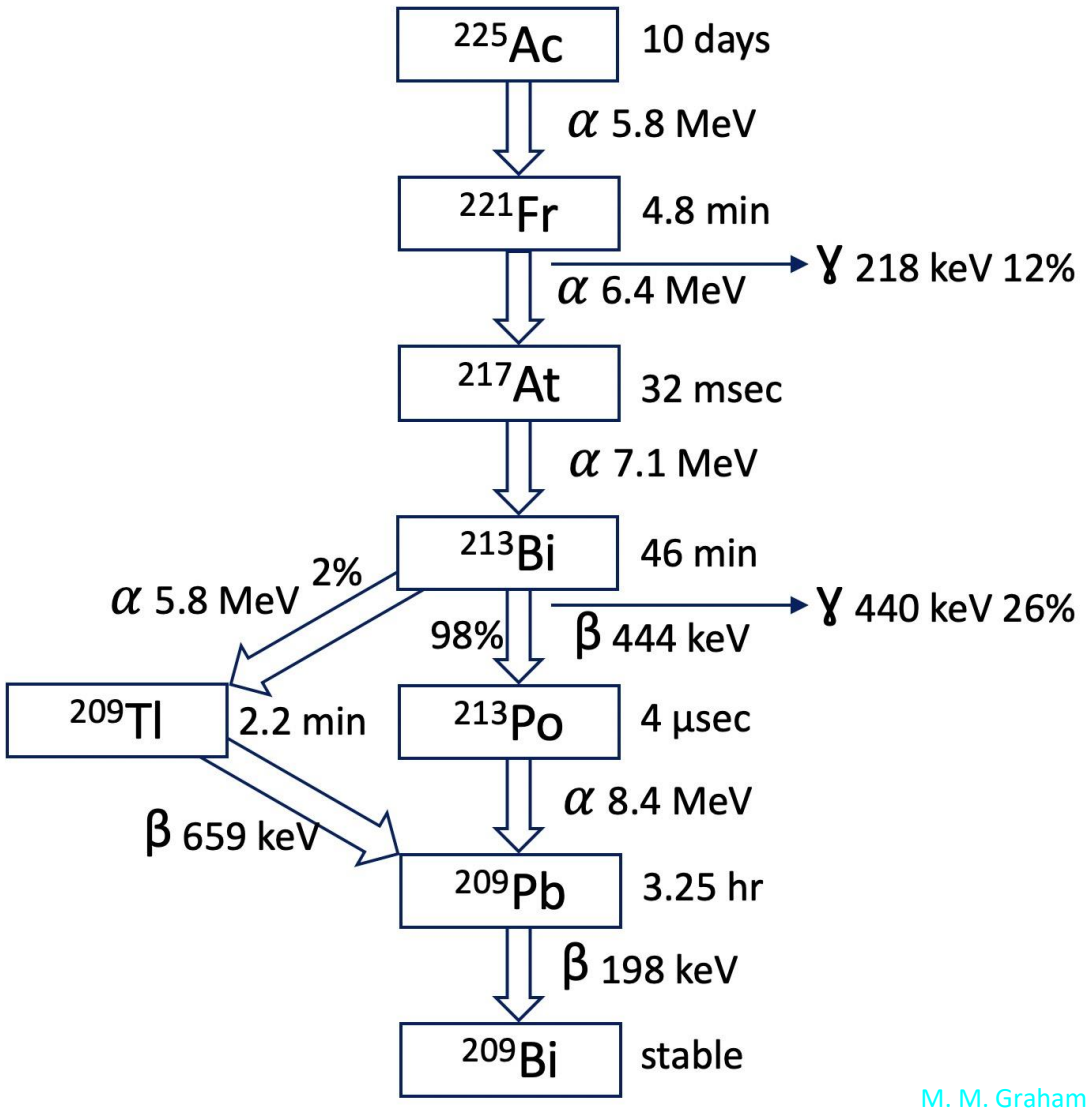
The Need for Dosimetry

"The high dose to kidney, bone marrow, and other nontarget tissues, as well as the large variability in biodistribution and tumor uptake among patients, should be addressed. Thus, precise and reliable dosimetry of normal organs and tumor with these agents is needed, and its achievement is challenging."

Dosimetry requires determination of (MBq - Hrs)/gm in tissue (quantitative imaging) and appropriate software

Cremonesi M et al. Dosimetry in Peptide Radionuclide Receptor Therapy: A Review
J Nucl Med 2006 v47 no. 9 1467-1475

Actinium - 225



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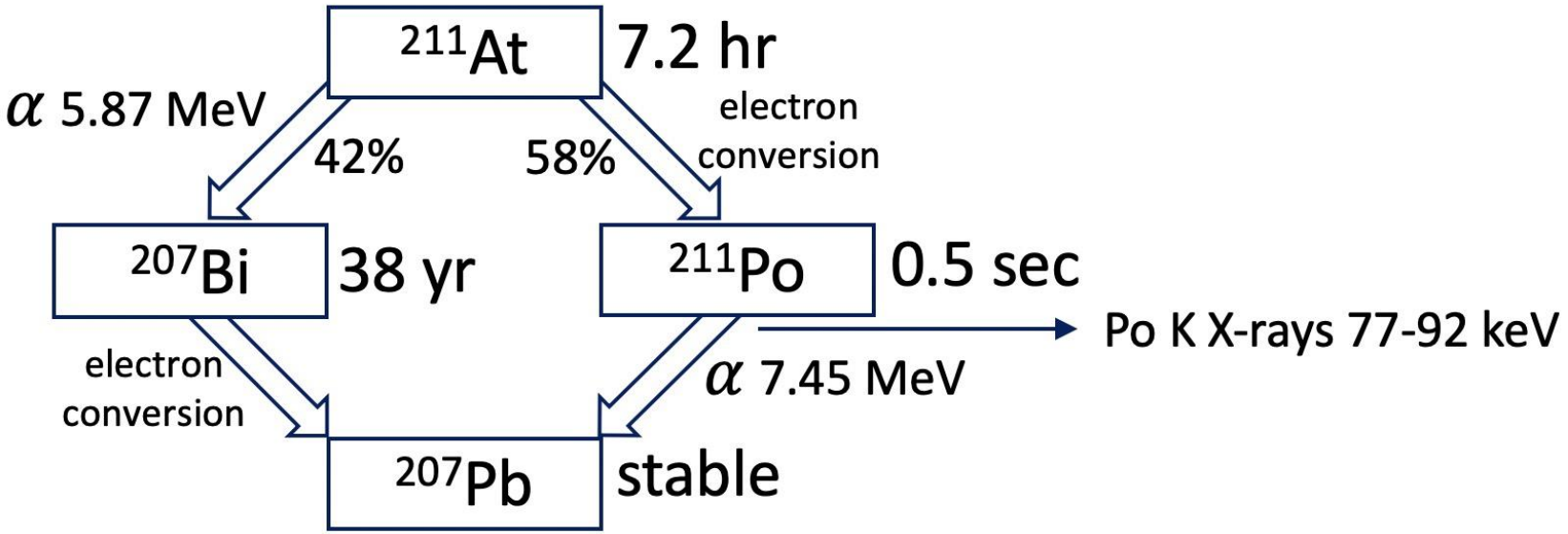
Other uncertainties in dosimetry arise from the unknown micro-distribution and the possible mobility of the daughter nuclides.

Astatine - 211



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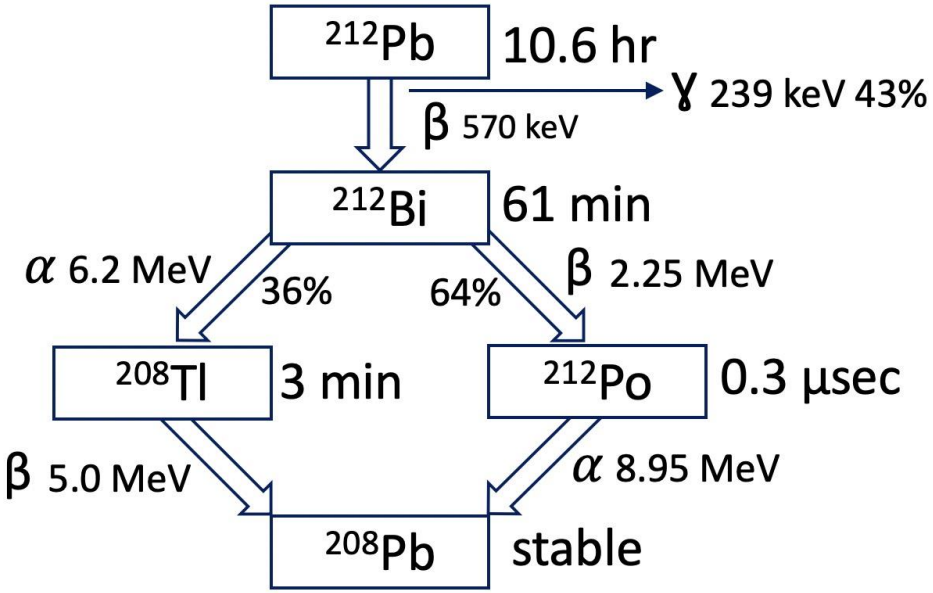
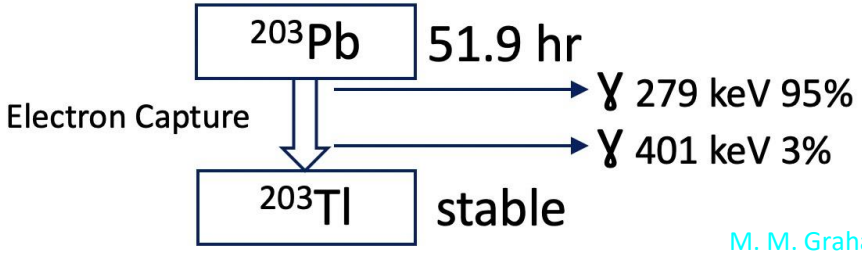
Lead – 212 and Lead - 203





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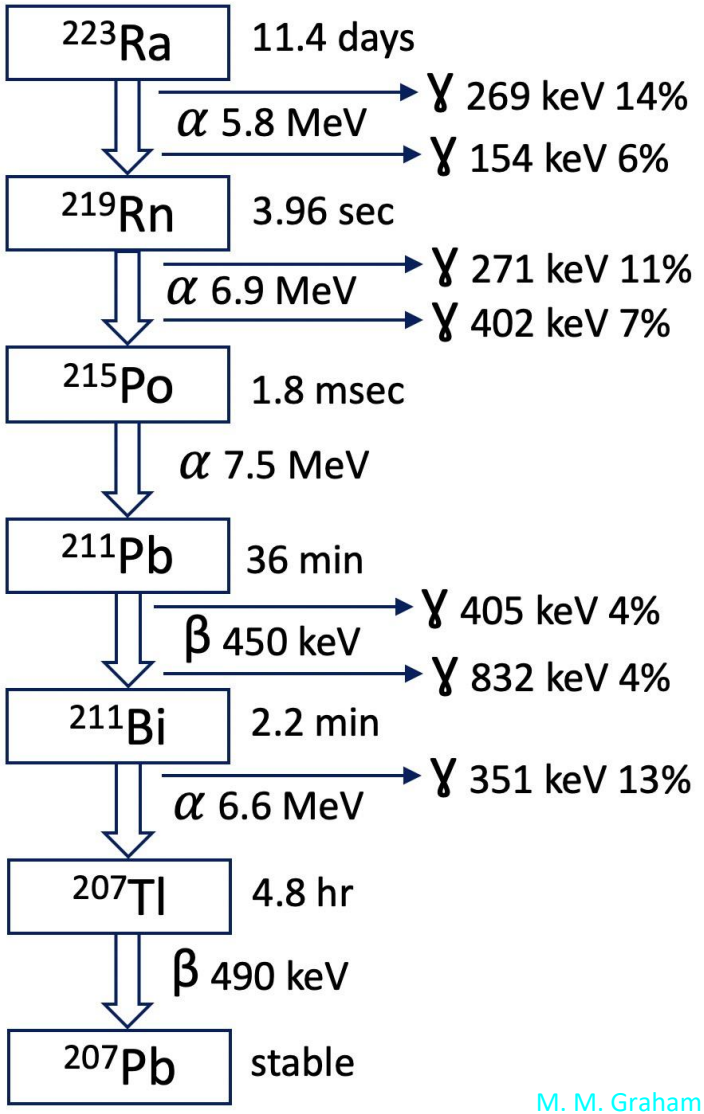
Radium - 223



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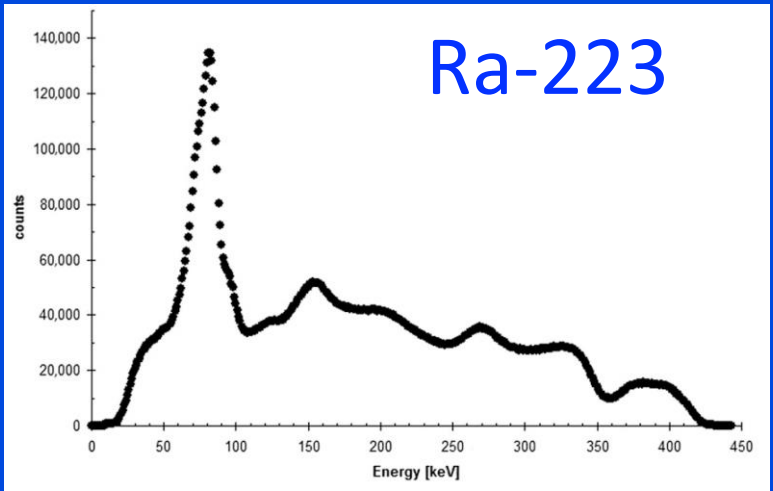
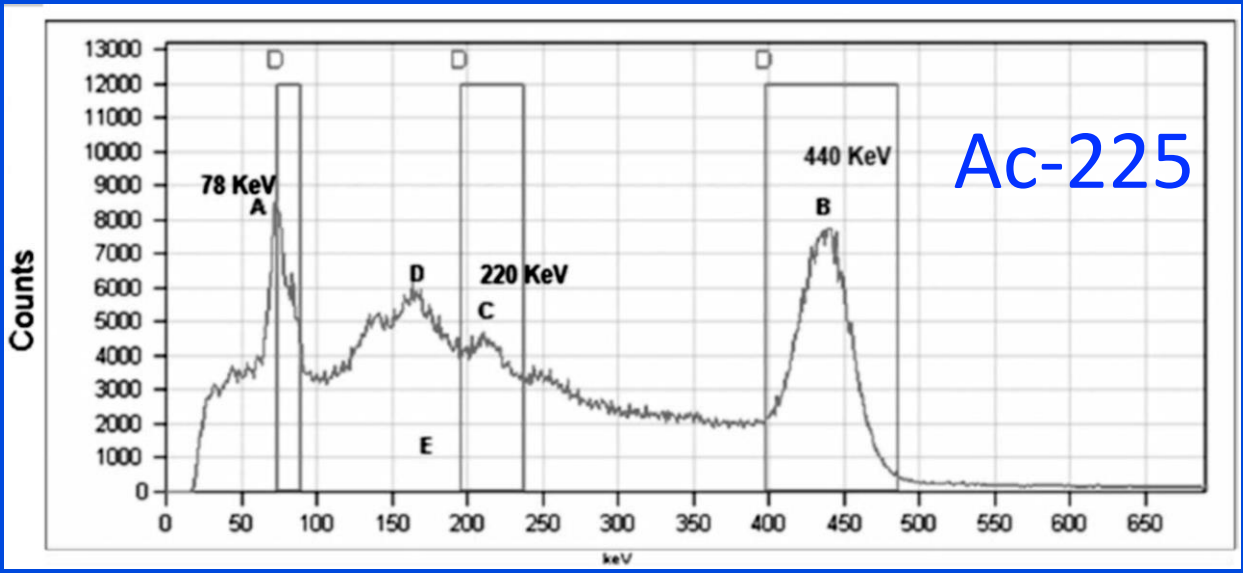
Alpha Emitters Gamma Spectra



Flux GD. Imaging and dosimetry for radium-223: the potential for personalized treatment. Br J Radiol 2017; 90: 20160748.



Usmani S, et al. ^{225}Ac Prostate-Specific Membrane Antigen Posttherapy α Imaging Comparing 2 and 3 Photo-peaks. Clin Nucl Med. 2019 May;44(5):401-403.

Current status

- Ga-68 and Lu-177 DOTATATE are currently approved in clinical use for treating neuroendocrine tumors
- Current approach is 200 mCi x 4 at monthly intervals
- Some patients get too much, many could get more

Near future

- Several PSMA agents are in clinical trial and will be approved in the next few years, including alpha-emitting agents

The challenge and opportunity

- Develop convenient, user-friendly methodology to provide
  - A-priori dosimetry to determine the appropriate 1st administered dose
  - Based of 1st dose dosimetry, determine appropriate next doses
  - Dosimetry for alpha-emitting radiopharmaceuticals

This needs to be developed for Lu-177 DOTATATE first, then for the prostate agents.

Theranostics

END