The Clinical Evolution of Alpha Particle Radiopharmaceutical Therapy: Focus on Actinium-225

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President: SNMMI

Disclosures

- Scientific Advisory board, consultant, stock options: Clarity Pharmaceuticals (Australia)
- Consulting/SAB: BMS, Jubilant Draximage
- Lecture fees: ITM
- Stockholder: Lantheus
- Research contracts: Actinium Pharmaceuticals, BMS, Siemens, White Rabbit AI, Bayer.
- Lu177 PSMA-617 and Ac225 labeled pharmaceuticals are not FDA approved

Outline of Lecture

Renaissance of Radiopharmaceutical Therapies and Theranostics

Randomized Trials of RPT

Why alpha particles? What are the choices?

Why Ac225? Ac225 characteristics-match T1/2 with carrier, what is the source of the Ac225? Daughters?

Literature on Ac225

Ongoing Clinical trials in Clinical Trials.Gov
Results to date
Imaging with Ac225

Issues: Supply of Ac225 How do we dose/image?
Moving Forward?

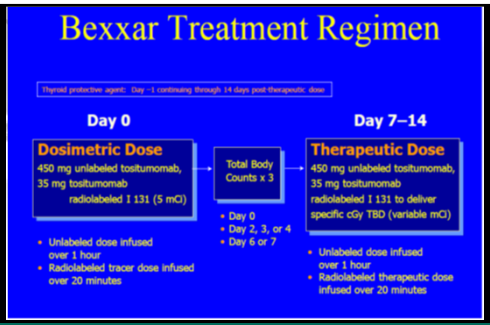
Theranostics

- Pairing a Diagnostic Test with a Therapeutic Procedure
- RadioTheranostics: Pairing a diagnostic radiopharmaceutical with a therapeutic Radiopharamceutical
- Diagnostic radiopharmaceutical: Establishes the presence of a target. Can inform on whether to treat, what dose to use to treat.
- Radiopharmaceutical therapeutic can be given as a fixed dose (s) or patient specific dose.
- Can be SPECT, PET, or no imaging of therapeutic agent.

I-131 anti CD-20 RIT: "Precision Therapeutic"

- Specific Targeting to an identifiable protein targeted identified in a specific patient (CD-20)
- Patient Specific Precision Radiation Dose calculated using a tracer dose of radiation
- I-131 for thyroid cancer has done this as well, esp. when given with the "Leeper" dosimetry scheme for high dose RIT

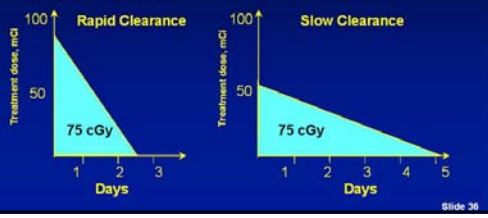
Bexxar Treatment Regimen



Effect of Clearance Rate on Radiation Exposure (mCi)

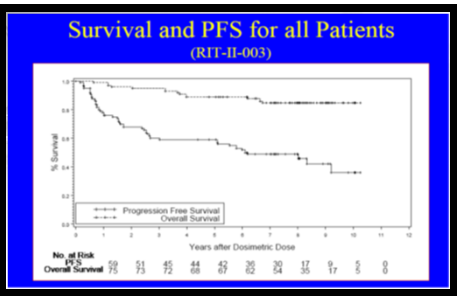
Individuals with a rapid clearance rate require a higher dose of radiation (in mCi)

Individuals with a slow clearance rate require a lower dose of radiation (in mCi)



Slide 36

Survival and PFS for all Patients (RIT-II-003)



Kaminski MS et al. N Engl J Med. 2005 Feb 3;352(5):441-9. doi: 10.1056/NEJMoa041511.

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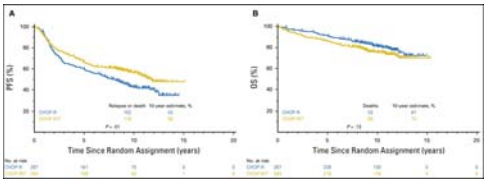


Fig 3. Comparison of (A) progression-free survival (PFS) and (B) overall survival (OS) of patients with advanced-stage follicular lymphoma who received either six cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) or six cycles of CHOP-RIT (cyclophosphamide, doxorubicin, vincristine, and prednisone followed by consolidation with iodine-133–tositumomab radioimmunotherapy).

Published in: Manyar Shadman; Hongli Li; Lisa Rimsza; John P. Leonard; Mark S. Kaminski; Rita M. Braziel; Catherine M. Spier; Ajay K. Gopal; David G. Maloney; Bruce D. Cheson; Shaker Dakhil; Michael LeBlanc; Sonali M. Smith; Richard I. Fisher; Jonathan W. Friedberg; Oliver W. Press; *JCO* **2018,** *36*, 697-703.
DOI: 10.1200/JCO.2017.74.5083

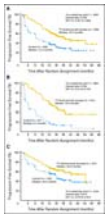
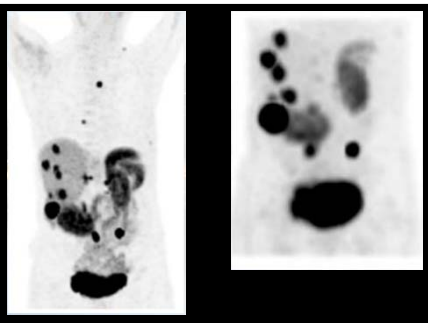


Fig 2. Kaplan-Meier plots for progression-free survival (PFS) in all patients and PFS stratified by response to first-line induction treatment. (A) PFS plot for all randomly assigned patients. (B) PFS plot for patients achieving a partial response to first-line induction treatment. (C) PFS plot for patients achieving a complete response/unconfirmed complete response to first-line induction treatment. 90Y, yttrium-90.

Published in: Franck Morschhauser; John Radford; Achiel Van Hoof; Umberto Vitolo; Pierre Soubeyran; Herve Tilly; Peter C. Hutjgens; Arne Kolstad; Francesco d'Amore; Marcos Gonzalez Diaz; Mario Petrini; Catherine Sebban; Pier Luigi Zinzani; Marinus H.J. van Oers; Wim van Putten; Angelika Bischof-Delaloye; Arna Rohatiner; Gilles Salles; Jens Kuhlmann; Anton Hagenbeek; *Journal of Clinical Oncology* 2008 26:5156-5164.
DOI: 10.1200/JCO.2008.17.2015



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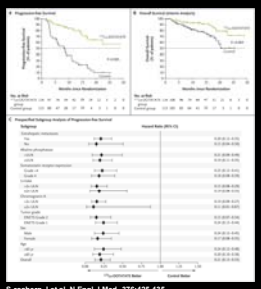
Progression-free Survival and Overall Surv val



S rosberg J et al. N Engl J Med 376:125-135

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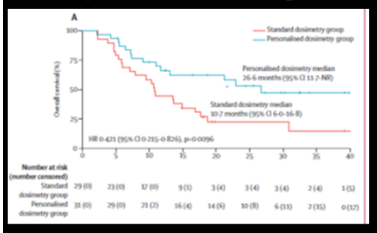
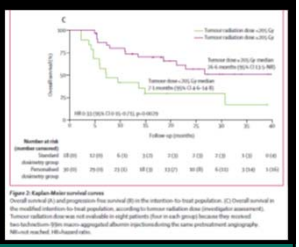
Improved Survival with Higher Patient Specific Dosing of Y-90 Theraspheres in HCC





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Garin et al ." *The Lancet Gastroenterology & Hepatology* (2021)

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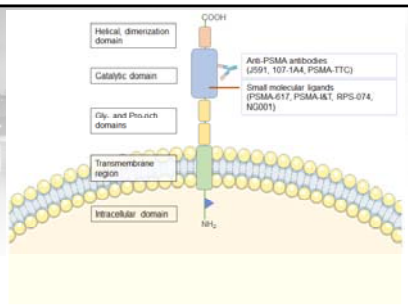
PSMA



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^{68}Ga-PSMA PET ^{177}Lu-PSMA SPECT

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European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:2536–2544
https://doi.org/10.1007/s00259-019-04485-3

GUIDELINES

Check for updates

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

Clemens Kratochwil[1] · Wolfgang Peter Fendler[2] · Matthias Eiber[3] · Richard Baum[4] · Murat Fani Bozkurt[5] · Johannes Czernin[6] · Roberto C. Delgado Bolton[7] · Samer Ezziddin[8] · Flavio Forrer[9] · Rodney J. Hicks[10] · Thomas A. Hope[11] · Levant Kabasakal[12] · Mark Konijnenberg[13] · Klaus Kopka[1] · Michael Lassmann[14] · Felix M. Mottaghy[15] · Wim Oyen[16,17,18] · Kambiz Rahbar[19] · Heiko Schöder[20] · Irene Virgolini[21] · Hans-Jürgen Wester[22] · Lisa Bodei[20] · Stefano Fanti[23] · Uwe Haberkorn[1] · Ken Herrmann[2]

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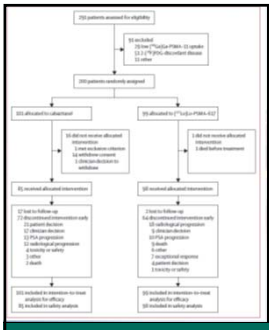

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Michael S Hofman, Louise Emmett, Shahneen Sandhu, Arne Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherfield, Andrew Weickhardt, Andrew M Scott, Sze Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Gominski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†

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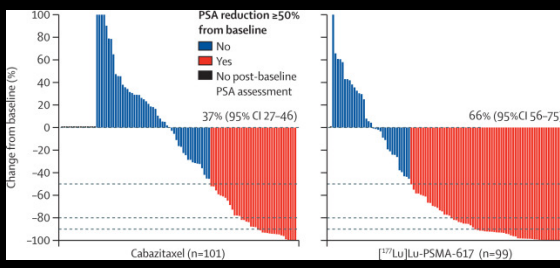

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TheraP Findings

- Randomized:
- PSA decline of >50% , 37% of carbazitaxel, 66% of LuPSMA (p<.0001)
- Longer PFS in LuPSMA group: HR .63 (p=.0028)
- Lower grade 3-4 toxicity: LuPSMA 617 vs carbazitaxel (33% vs 53%)
- Improved pain control and QOL in PSMA group vs chemotherapy

Value indicators are positive for PSMA targeted RPT.

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Vision Trial: Lu-PSMA-617

Sartor, Oliver, Johann de Bono, Kim N. Chi, Karim Fizazi, Ken Herrmann, Kambiz Rahbar, Scott T. Tagawa et al. "Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer." *New England Journal of Medicine* (2021).

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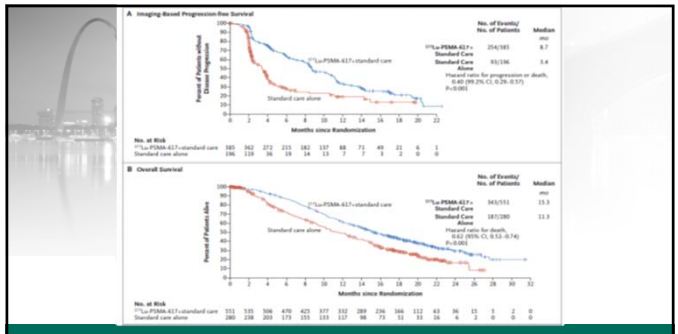

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- FDA-approved **lutetium-labeled somatostatin analog (Lu-177 DOTATATE)** therapy for neuroendocrine tumors and other tumors expressing somatostatin receptors—diagnostically paired with somatostatin receptor imaging (Currently **Ga-68 DOTATATE**, Ga-68 DOTATOC, Cu-64 DOTATATE and In-111 pentetreotide are FDA-approved for somatostatin receptor imaging).
- FDA-approved **Ra-223 dichloride therapy for symptomatic bone metastases** of prostate cancer, diagnostically paired with Tc-99m-MDP bone scan or [F-18]NaF PET scan
- FDA-approved **Samarium** (Sm-153 EDTMP) Lexidronam and **Strontium-89** (Sr-89) for bone pain of metastatic cancer, diagnostically paired with Tc-99m-MDP or [F-18]NaF images
- FDA-approved high specific activity iobenguane I-131 **(I-131 MIBG)** for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy, with the administered activity informed by a pre-therapy scan for targeting assessment with I-123 MIBG as well as dosimetry scan with low dose iobenguane I-131 MIBG.
- FDA- approved **Y-90 ibritumomab tiuxetan** previously paired with In-111 ibritumomab tiuxetan for treatment of Non-Hodgkins Lymphoma. Interestingly, the paired diagnostic agent is no longer part of the therapeutic regimen.
- FDA-approved therapy of Non-Hodgkins Lymphoma with I-131 tositumomab paired with I-131 tositumomab dosimetry scans , which is no longer commercially available.
- Lutetium-labeled **prostate specific membrane antigen** targeting **peptide (Lu-177-PSMA)** therapies for metastatic castration-resistant prostate cancer, diagnostically paired with Ga-68 or F-18 PSMA targeting imaging agents in late-phase clinical trials.
- Investigational I-131-labeled antibodies to leukemia targets such as **anti-CD-45 antibody (IOMAB-aparnistamab),** with a pre-therapy treatment planning I-131-labeled antibody diagnostic scans
- Investigational **alpha-emitting therapeutics targeting including PSMA (Ac-225 or Th-227 PSMA),** diagnostically paired with a PSMA-targeted imaging study (Ga-68 or F-18 PSMA); and
- Numerous additional RPT agents with a myriad of targets are in development, many already in early phase human trials.

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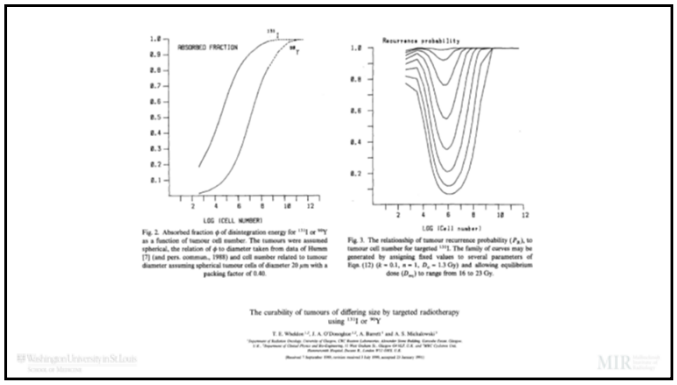
The curability of tumours of differing size by targeted radiotherapy
using ^{131}I or ^{90}Y
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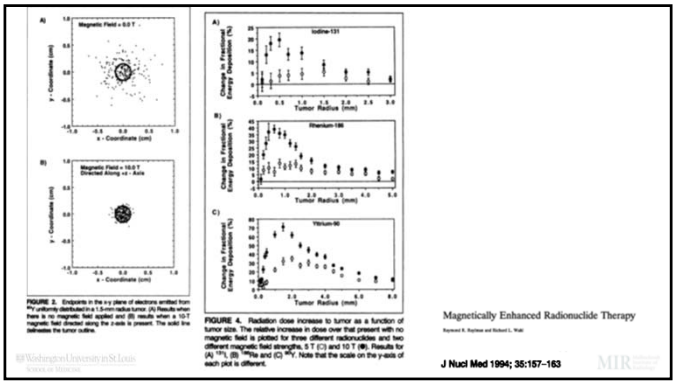
Magnetically Enhanced Radionuclide Therapy
J Nucl Med 1994; 35:157–163
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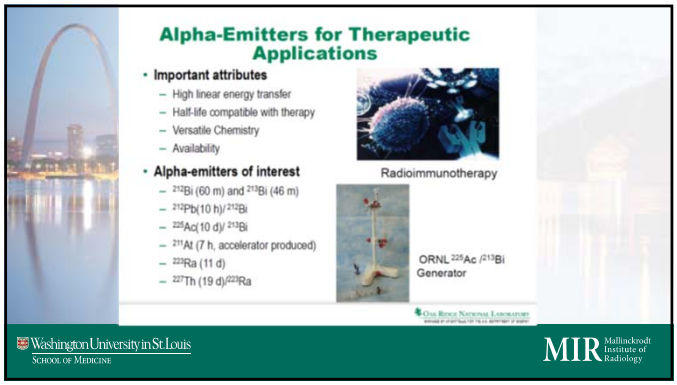
Alpha-Emitters for Therapeutic Applications
Important attributes
High linear energy transfer
Half-life compatible with therapy
Versatile Chemistry
Availability
Alpha-emitters of interest
^{212}Bi (60 m) and ^{213}Bi (46 m)
^{212}Pb(10 h)/^{212}Bi
^{225}Ac(10 d)/ ^{213}Bi
^{211}At (7 h, accelerator produced)
^{223}Ra (11 d)
^{227}Th (19 d)/^{223}Ra
Radioimmunotherapy
ORNL ^{225}Ac /^{213}Bi Generator
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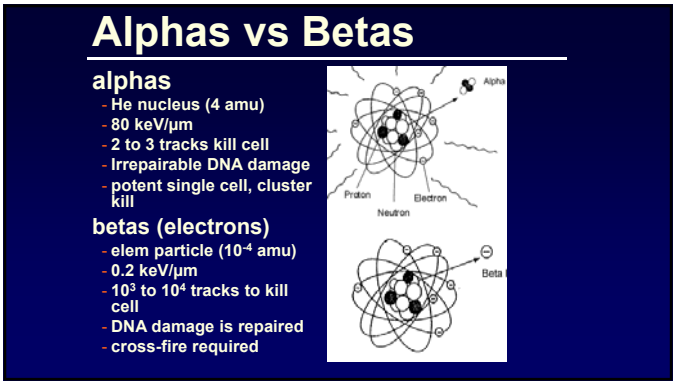
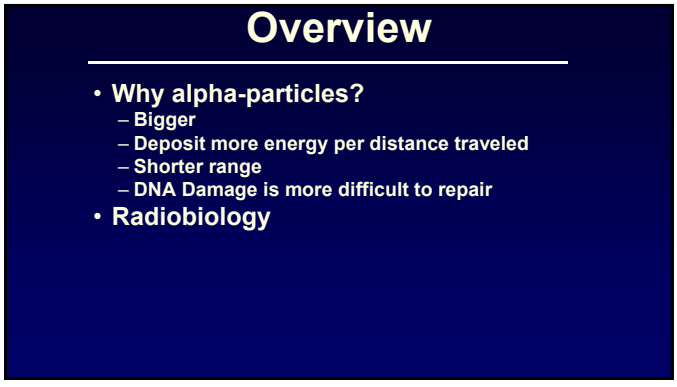
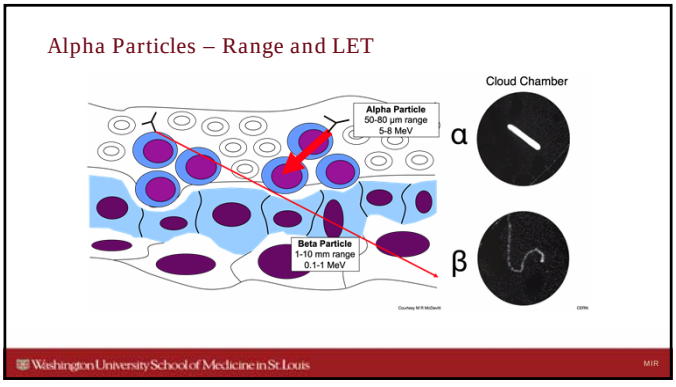

Alphas vs Betas
alphas
He nucleus (4 amu)
80 keV/μm
2 to 3 tracks kill cell
Irrepairable DNA damage
potent single cell, cluster kill
betas (electrons)
elem particle (10^{-4} amu)
0.2 keV/μm
10^3 to 10^4 tracks to kill cell
DNA damage is repaired
cross-fire required
Alpha
Proton
Electron
Neutron
Beta


Overview
Why alpha-particles?
Bigger
Deposit more energy per distance traveled
Shorter range
DNA Damage is more difficult to repair
Radiobiology


Alpha Particles – Range and LET
Cloud Chamber
Alpha Particle
50-80 μm range
5-8 MeV
Beta Particle
1-10 mm range
0.1-1 MeV
α
β
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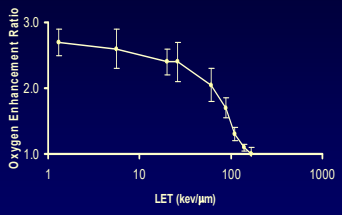
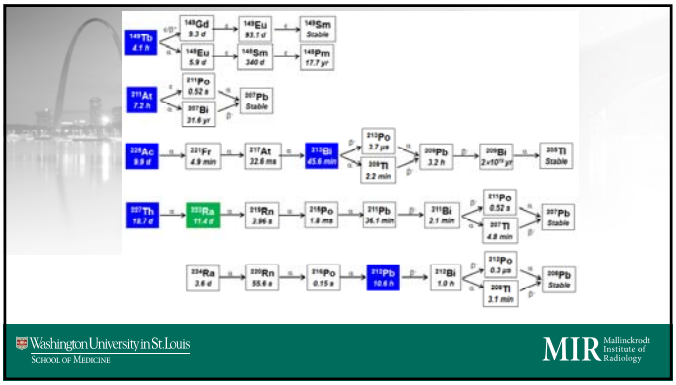
Reduced oxygen effect

$OER = D_{hypoxic}/D_{oxic}$

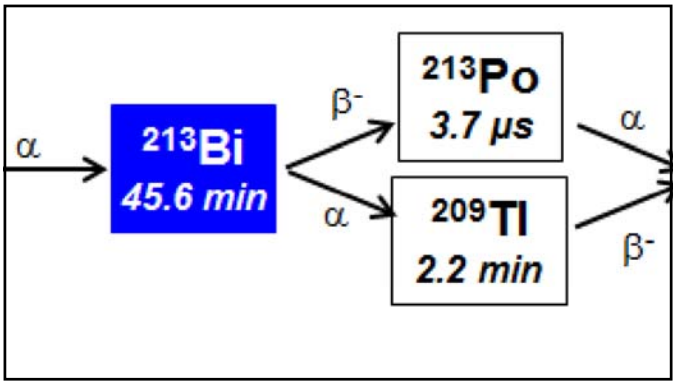


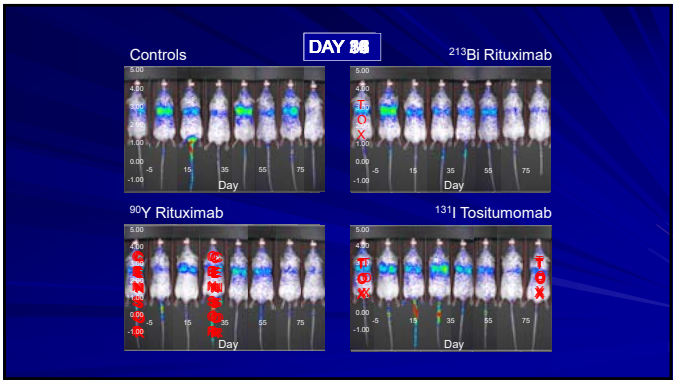
(Barendsen, et al., Int J Radiat Biol 10:317-327, 1966.)



Routes of Delivery

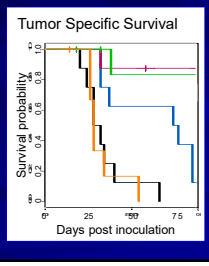
- How quickly does the therapeutic localize to the tumor?
- Small Molecules can be fast
- Intact antibodies can be very slow
- Half Life of therapy should be equivalent or longer than that of localizing molecule
- Intravenous and systemic
- Intraarterial (e.g. hepatic artery) other arterial trees
- Intracavitary: Intraperitoneal, Intrapleural,
  - Interstitial (e.g. brain tumors), intratumoral,
  - Topical?





Results: Study 3

- Kaplan-Meier survival



Survival/Tumor Progression to Day 85	% Survival	% Tumor Progression
Controls	0	100
^{213}Bi Rituximab	75	25
^{131}I Tositumomab	62.5	25
^{90}Y Rituximab	0	75*
Unlabeled Rituximab	12.5	87.5

*Remaining 25% died 2nd anesthesia

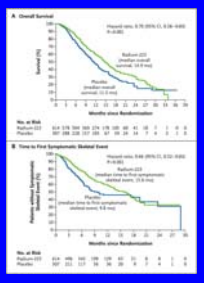
Astatine-211 conjugated to an anti-CD20 monoclonal antibody eradicates disseminated B-cell lymphoma in a mouse model

by Damian J. Green, Mazyar Shadman, Jon C. Jones, Shani L. Frayo, Aimee L. Kenoyer, Mark D. Hylarides, Donald K. Hamlin, D. Scott Wilbur, Ethan R. Balkan, Yukang Lin, Brian W. Miller, Sofia H. L. Frost, Ajay K. Gopal, Johnnie J. Orozco, Theodore A. Gooley, Kelly L. Laird, Brian G. Till, Tom Bäck, Brenda M. Sandmaier, John M. Pagel, and Oliver W. Press

Blood
Volume 125(13):2111-2119
March 26, 2015

blood

Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event



Parker C et al. N Engl J Med 2013;369:213-223.

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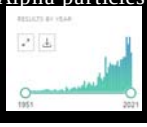
Growth in Interest in Alpha Particles esp Actinium Pub Med Search 9-19-21 :

Alpha particles: 1361 refs

Actinium: 511 refs

Actinium 225: 164 refs

Alpha particles



Actinium

Actinium 225

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Actinium: No Stable Isotopes

32 known isotopes, from 205Ac to 236Ac, and 7 isomers.

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Main Isotopes of Actinium:

Main isotopes of actinium ($_{89}$Ac)

Isotope			Decay	
	abun-dance	half-life ($t_{1/2}$)	mode	pro-duct
^{225}Ac	trace	10 d	α	^{221}Fr
^{226}Ac	syn	29.37 h	β^-	^{226}Th
			ε	^{226}Ra
			α	^{222}Fr
^{227}Ac	trace	21.772 y	β^-	^{227}Th
			α	^{223}Fr

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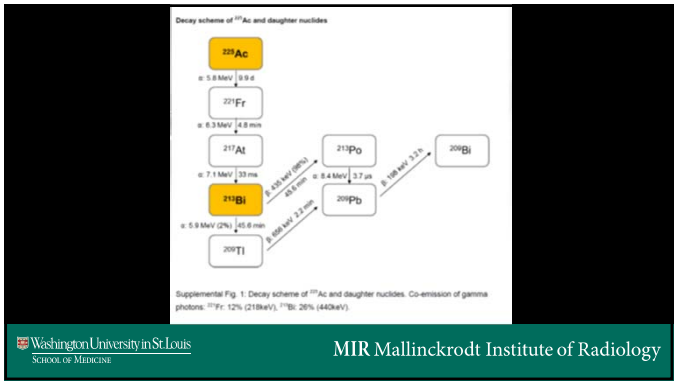
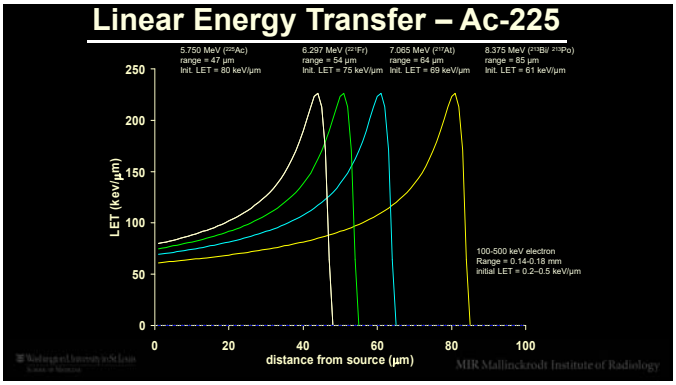




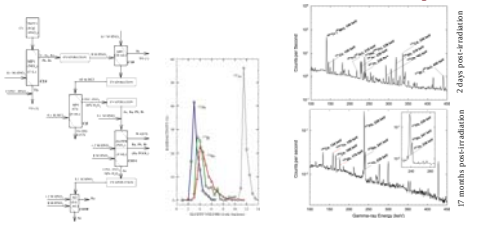
World wide Ac-225 Supply

- ^{229}Th generator (ORNL-USA)
- ^{229}Th generator (Russia)
- Proton accelerator from Thorium target
  (Tri-Lab: ORNL, LLNL, BNL & NorthStar, Wisconsin)
- Institute of Transuranium Metals (ITM; Karlsruhe, DE)
  ^{226}Ra bombardment in cyclotron and ^{229}Th-generator
- LINAC - clinical radiation oncology photon beams production (Australia)

^{225}Ac production (US)

^{229}Th generator limited in access to ^{233}U

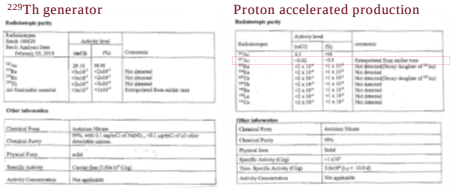
Proton accelerated production from Thorium target



Example Quality Control sheet – Oak Ridge Ac-225 supply

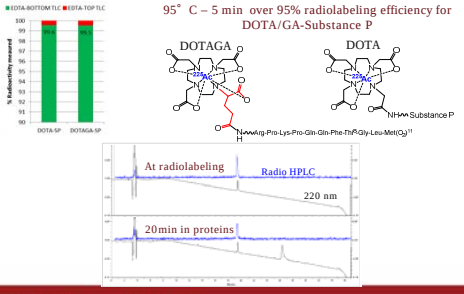
^{229}Th generator

Proton accelerated production

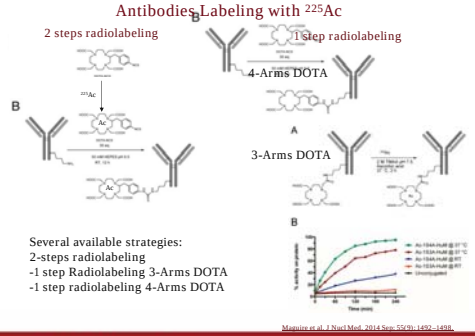


Peptide Labeling with ^{225}Ac

95° C – 5 min over 95% radiolabeling efficiency for DOTA/GA-Substance P



Antibodies Labeling with ^{225}Ac



Several available strategies:
2-steps radiolabeling
-1 step Radiolabeling 3-Arms DOTA
-1 step radiolabeling 4-Arms DOTA

Maguire et al. J Nucl Med. 2014 Sep; 55(9): 1492–1498.

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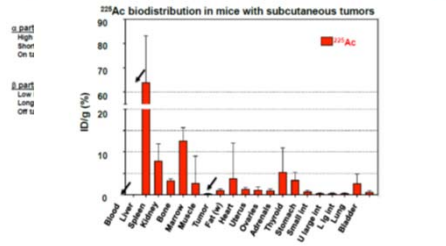
Biodistribution of free ^{225}Ac



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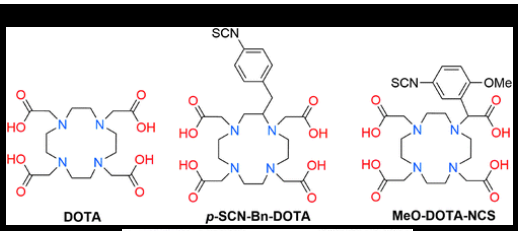
Comparative Biodistribution of ^{89}Zr-ofatumumab and ^{225}Ac-ofatumumab for Lymphoma Radioimmunotherapy Mark Longline, Mark Hoegger, Diane Abou, Kyuhwan Shim, Daniel Thorek and Richard Wahl
Journal of Nuclear Medicine May 1, 2020, 61 (supplement 1) 381;



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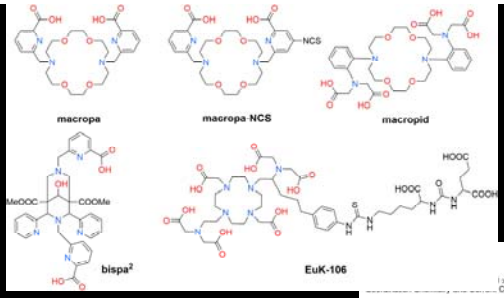

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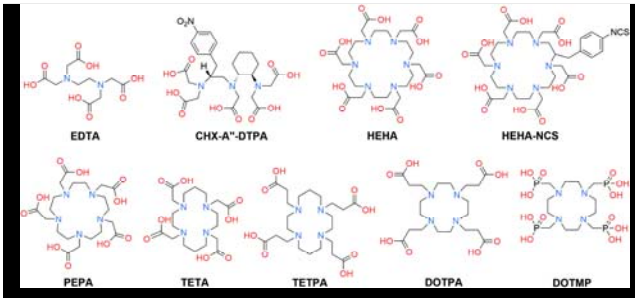

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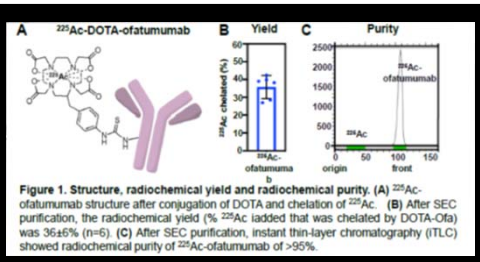

Figure 1. Structure, radiochemical yield and radiochemical purity. (A) ^{225}Ac-ofatumumab structure after conjugation of DOTA and chelation of ^{225}Ac. **(B)** After SEC purification, the radiochemical yield (% ^{225}Ac iadded that was chelated by DOTA-Ofa) was 36±6% (n=6). **(C)** After SEC purification, instant thin-layer chromatography (iTLC) showed radiochemical purity of ^{225}Ac-ofatumumab of >95%.

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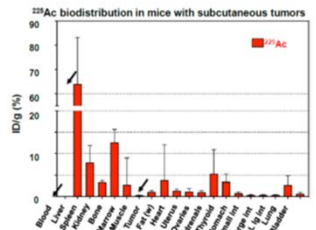
Biodistribution of free ^{225}Ac



Comparative Biodistribution of ^{89}Zr-ofatumumab and ^{225}Ac-ofatumumab for Lymphoma RadioimmunotherapyMark Longtine, Mark Hoegger, Diane Abou, Kyuhwan Shim, Daniel Thorek and Richard Wahl
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Biodistribution of ^{225}Ac-Ofa and ^{89}Zr-Ofa

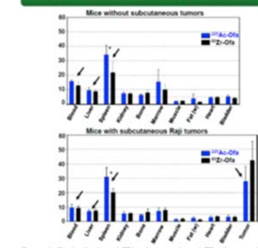

Figure 4. Biodistribution of ^{225}Ac-ofatumumab and ^{89}Zr-ofatumumab. R2G2 mice without or with Raji tumors were injected with ^{225}Ac-ofatumumab (n=4) or ^{89}Zr-ofatumumab (n=3) and biodistribution assayed 7 days later. Splenic ^{225}Ac-ofatumumab uptake was higher than ^{89}Zr-ofatumumab, $p < 0.05$, student's t-test.

Comparative Biodistribution of ^{89}Zr-ofatumumab and ^{225}Ac-ofatumumab for Lymphoma RadioimmunotherapyMark Longtine, Mark Hoegger, Diane Abou, Kyuhwan Shim, Daniel Thorek and Richard Wahl
Journal of Nuclear Medicine May 1, 2020, 61 (supplement 1) 381;

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Why alpha particles? What are the choices?

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Actinium-225-Based Antibody Radio-Conjugates (ARCs)

- Actinium 225-based ARCs have desirable characteristics for industry development
- High Energy = High Potency
  - 5-8 MeV via emission of 4 α-particles
  - Cell kill possible with 1 α particle hit to DNA
- Short Pathlength Safety Potential
  - Approximately 4 cell lengths (50-80 microns)
  - Hit what you aim at and little else
- 10 day half-life provides time for manufacturing and distribution
- Lack of restrictions on patients after administration
  - Can go to the mall

- Actimab-A is an example of industry development of ARCs
  - Actimab-A refers to the anti-CD33 antibody lintuzumab labeled with Actinium 225
    - Distinguish from earlier use of lintuzumab labeled with Bismuth-213
  - Actimab A was first Actinium 225 labeled agent in clinical trials
    - Largest clinical experience of Actinium-225 labeled agents

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Basic Considerations

- Is there a companion diagnostic (e.g. SSTR2 targeting)
- Is the same agent used for imaging and Rx? I-131
- Is there a need for an imaging dose at all?
- Is the therapeutic margin large or small?
- Is there heterogeneity in the drug delivery in vivo or in systemic clearance
- Can the therapy be given more than once?

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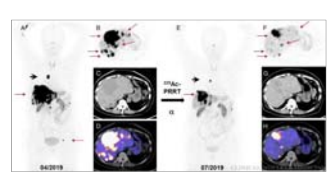
FIGURE 1



Peptide Receptor Radionuclide Therapy Using 225Ac-DOTATOC Achieves Partial Remission in a Patient With Progressive Neuroendocrine Liver Metastases After Repeated β-Emitter Peptide Receptor Radionuclide Therapy

Zhang, Jingjing; Kulkarni, Harshad R.; Baum, Richard P.
Clinical Nuclear Medicine45(3):241-243, March 2020.
doi: 10.1097/RLU.0000000000002915

A 76-year-old woman was diagnosed in 1998 with a well-differentiated functional pancreatic neuroendocrine tumor (NET) and hepatic metastases. The Ki-67 proliferation index was 7% to 10% for the primary tumor and 5% for the hepatic metastases. Immunostains for chromogranin A and synaptophysin were positive. The patient underwent resection of primary tumor in the tail of the pancreas, splenectomy, and hepatectomy (segment 5). Recurrence with multiple hepatic metastases occurred in 2005. This patient was treated with 4 cycles of peptide receptor radionuclide therapy (PRRT)1–4 using 177Lu-DOTATATE in 2005 and 2006, achieving partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.5 The relapse-free interval was approximately 4 years, after which progression occurred in 2009. The patient received 1 more cycle of 177Lu-DOTATATE, followed by a relapse-free interval of 32 months. After the sixth cycle of PRRT performed with 90Y-DOTATOC administered intra-arterially, there was again partial remission and stable disease for approximately 39 months. Disease progression occurred in 2014. The patient underwent the fourth and fifth phase of PRRT using 1 cycle of 177Lu-HA-DOTATATE (A, 68Ga-DOTATOC PET/CT after the seventh cycle) and 2 cycles of 177Lu-DOTATOC (B, 68Ga-DOTATOC PET/CT before the eighth cycle; C, 68Ga-DOTATOC PET/CT after the ninth cycle). 68Ga-DOTATOC PET/CT (D) showed progressive disease in May 2018. The 10th cycle of PRRT was performed IV with 90Y-DOTATOC. 68Ga-DOTATOC PET/CT (E) in April 2019 showed significant progression of the disease with extensive hepatic, lymph node, and bone metastases. Because of resistance to PRRT with the β-emitters 177Lu and 90Y, the multidisciplinary tumor board decision was to apply the α-emitter 225Ac bound to the peptide DOTATOC.6–13

Wolters Kluwer
 60

- 82 patients were treated with a median of five ^{225}Ac-DOTATATE TAT cycles.
- 26 (32%) patients did not receive prior PRRT,
- 25 (30%) demonstrated stable disease after completing ^{177}Lu-DOTATATE therapy,
- 31 (38%) patients progressed on ^{177}Lu-DOTATATE therapy were included in the study.

Long-term outcome of ^{225}Ac-DOTATATE Targeted Alpha Therapy in Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumors

Chandrasekhar Bal, Sanjana Ballal and Madhav Yadav
Journal of Nuclear Medicine May 2021, 62 (supplement 1) 19

- During the median follow-up duration of 17 months, 10 patients experienced disease progression and 20 patients died.
- Median PFS and OS were not reached with a 24-month PFS and OS probability of 80.7% and 67.3%,
- Complete response (CR) was attained in 1 (1.2%) patient, partial response in 33 (43%), stable disease in 35 (45.4%), and progressive disease in 6 (8%) patients.
- 2 patients experienced grade III anemia and two patients experienced grade II thrombocytopenia. No grade 3 renal or hepatotoxicities were observed. No other unexpected longer-term adverse events were observed with ^{225}Ac-DOTATATE therapy.

Long-term outcome of ^{225}Ac-DOTATATE Targeted Alpha Therapy in Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumors

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ORIGINAL ARTICLE

^{225}Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study

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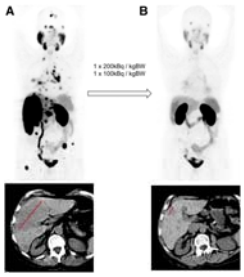
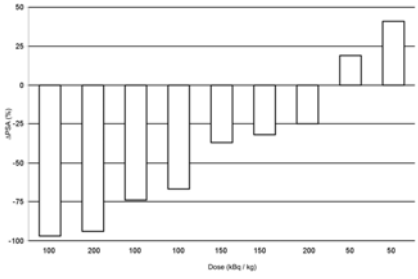


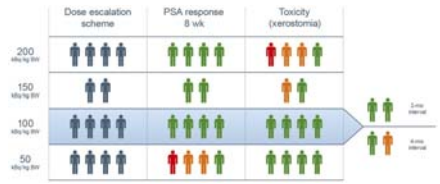
Baseline (A) and restaging (B) for a PSA-negative patient with histologically proven lung and liver metastases of prostate cancer was done with 68Ga-PSMA-11 PET (maximum-intensity projection, top) and CT (bottom), respectively. Clemens Kratochwil et al. J Nucl Med 2017;58:1624-1631

JNM The Journal of Nuclear Medicine



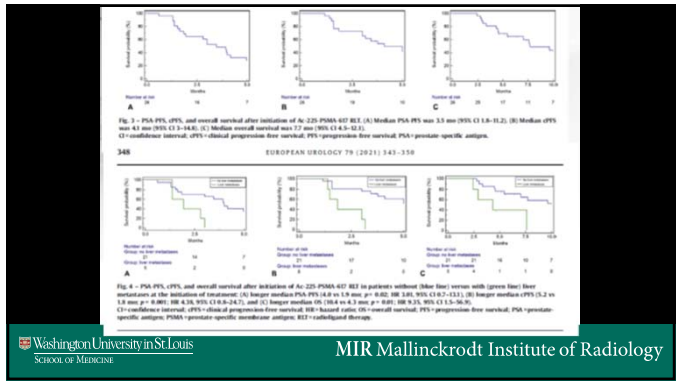
Waterfall graph of PSA response in evaluable patients. Clemens Kratochwil et al. J Nucl Med 2017;58:1624-1631

JNM The Journal of Nuclear Medicine



Reasonable treatment corridor between insufficient treatment response (red: patient died before reevaluation; orange: PSA progression; green: imaging or PSA response) and intolerable toxicity (red: xerophthalmia; orange: xerostomia G2; green: no or only G1 xerostomia). Clemens Kratochwil et al. J Nucl Med 2017;58:1624-1631

JNM The Journal of Nuclear Medicine


EUROPEAN UROLOGY 79 (2021) 343–350
348
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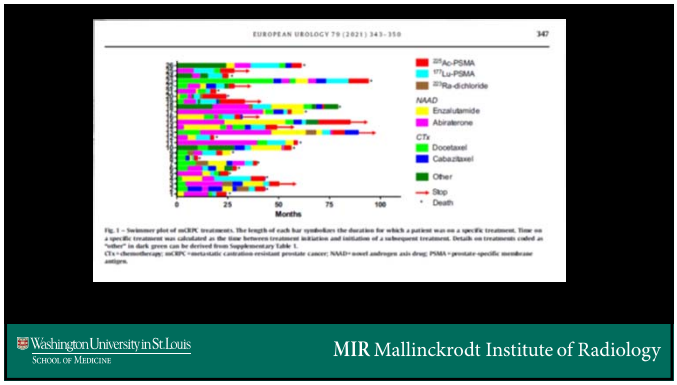
EUROPEAN UROLOGY 79 (2021) 343–350
347
225Ac-PSMA
177Lu-PSMA
223Ra-dichloride
NAAD
Enzalutamide
Abiraterone
CTx
Docetaxel
Cabazitaxel
Other
Stop
Death
0
25
50
75
100
Months
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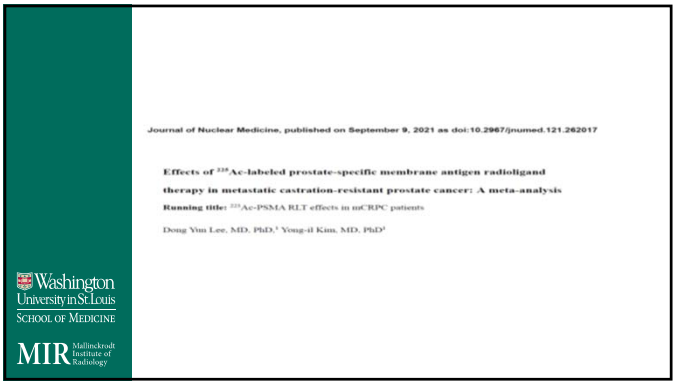
Journal of Nuclear Medicine, published on September 9, 2021 as doi:10.2967/jnumed.121.262017
Effects of 225Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis
Running title: 225Ac-PSMA RLT effects in mCRPC patients
Doug Yun Lee, MD, PhD,1 Yong-il Kim, MD, PhD2
Washington University in St. Louis
School of Medicine
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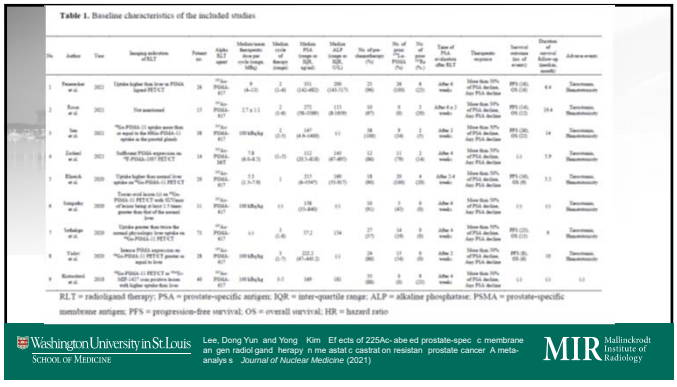
Table 1. Baseline characteristics of the included studies
RLT = radioligand therapy; PSA = prostate-specific antigen; IQR = inter-quartile range; ALP = alkaline phosphatase; PSMA = prostate-specific membrane antigen; PFS = progression-free survival; OS = overall survival; HR = hazard ratio
Washington University in St. Louis
School of Medicine
Lee, Dong Yun, and Yong Kim. Effects of 225Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis. Journal of Nuclear Medicine (2021)
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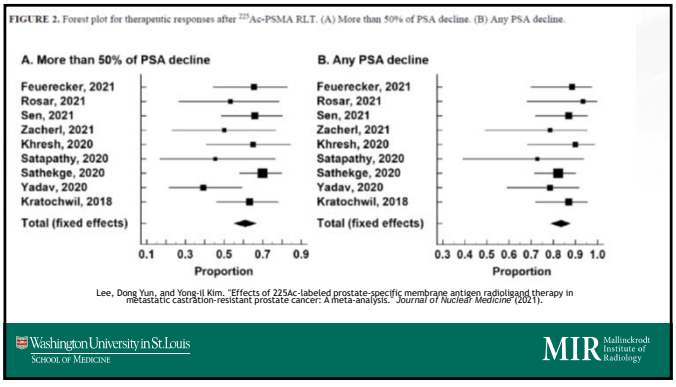
FIGURE 2. Forest plot for therapeutic responses after 225Ac-PSMA RLT. (A) More than 50% of PSA decline. (B) Any PSA decline.
A. More than 50% of PSA decline
B. Any PSA decline
Feuerecker, 2021
Rosar, 2021
Sen, 2021
Zacherl, 2021
Khresh, 2020
Satapathy, 2020
Sathekge, 2020
Yadav, 2020
Kratochwil, 2018
Total (fixed effects)
0.1
0.3
0.5
0.7
0.9
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Proportion
Lee, Dong Yun, and Yong-il Kim. "Effects of 225Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis." Journal of Nuclear Medicine (2021).
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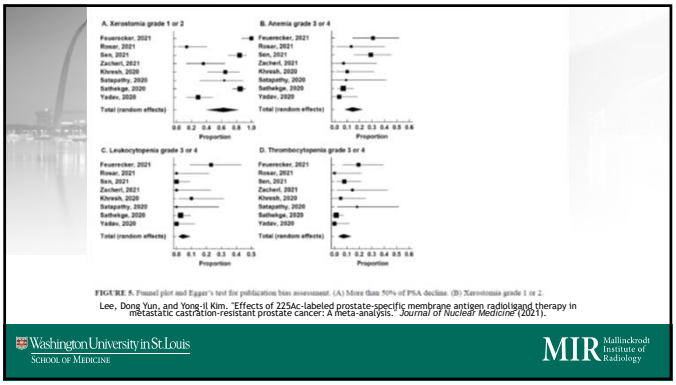

FIGURE 5. Funnel plot and Egger's test for publication bias assessment. (A) More than 50% of PSA decline. (B) Xerostomia grade 1 or 2.

Lee, Dong Yun, and Yong-il Kim. "Effects of 225Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis." *Journal of Nuclear Medicine* (2021).

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Ac225 PSMA Meta Analysis

>50% decline in PSA seen in 61% of patients (55-67% CI)

84% of patients had decline in PSA

Mean PFS 9 months (7-11 mo CI)

Mean OS 12 months (10-13 mo CI)

Xerostomia most common AE, 63% (CI 39-83%)

Severe anemia, 14% (6-23% CI)

Severe leukopenia 4% (1-9% CI)

Severe Thrombocytopenia 7% (3-14% CI)

Lee, Dong Yun, and Yong-il Kim. "Effects of 225Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis." *Journal of Nuclear Medicine* (2021).

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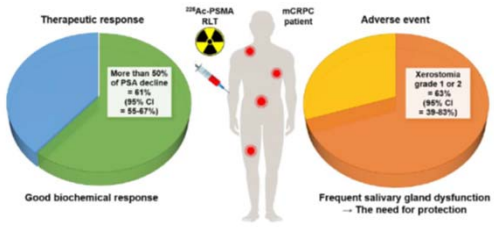
GRAPHICAL ABSTRACT



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Randomized Trials of RPT

Why alpha particles? What are the choices?

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Clinical Trials Open in US

6 trials are listed as recruiting

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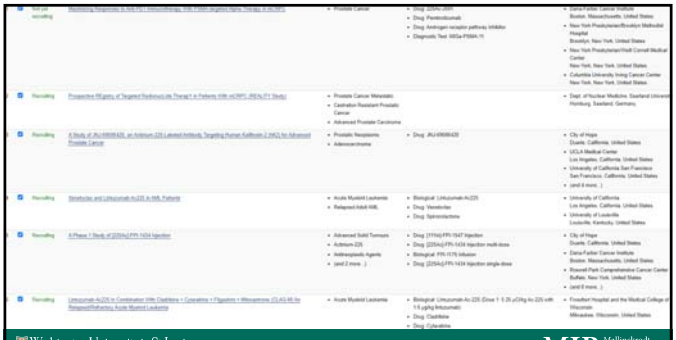

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Dickson *et al. EJNMMI Physics* (2019) 6:4
https://doi.org/10.1186/s40658-019-0241-3

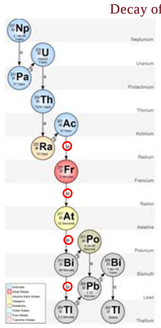
EJNMMI Physics

OPINION ARTICLE Open Access

Quantitative SPECT: the time is now

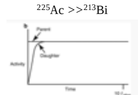
John Dickson*, James Ross and Stefan Vöö

Decay of ^{225}Ac and Detection Methods



^{225}Ac (10 d): no detectable gammas
^{221}Fr (5 min) : 218 KeV – 11% gamma ray
^{213}Bi (45min): 440 KeV – 26% gamma ray

1/2 Life:
^{225}Ac >>^{213}Bi



Secular Equilibrium

Gamma reading:
1- within 1h post separation => ^{221}Fr and ^{213}Bi
2- At secular equilibrium
4 h post separation => ^{213}Bi =^{225}Ac

Knapp F.F.., Dash A. (2016) Radionuclide Generator Systems Represent Convenient Production Systems to Provide Therapeutic Radionuclides. In: Radiopharmaceuticals for Therapy. Springer, New Delhi

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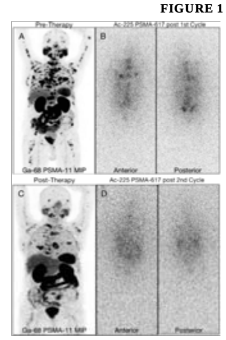
FIGURE 1



225Ac-PSMA-617 Radioligand Posttherapy Imaging in Metastatic Castrate-Resistant Prostate Cancer Patient Using 3 Photopeaks

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A 76-year-old man with mCRPC having histopathology of adenocarcinoma, after chemotherapy and radiotherapy, was planned for 225Ac-PSMA-617 radioligand therapy (RLT) due to disease progression (with severe bony pains and rising PSA from 40.1 to 75.4 ng/mL). Pretherapy 68Ga-PSMA-11 PET/CT scan using ~111 MBq of radiotracer was done to look for disease extent and feasibility of 225Ac-PSMA-617 RLT. The MIP image showed widespread lymph nodal and skeletal metastatic disease (A). 225Ac-PSMA-617 (5.55 MBq) was administered intravenously as per existing literature,1 and posttherapy whole-body images with speed of 6 cm/min on dual-head gamma camera using high-energy general-purpose collimator and 3 different photopeaks (78, 218, and 440 keV) were acquired at 24 hours. The whole-body anterior and posterior images revealed radiopharmaceutical localization in the lesions (B). The patient had significant relief in pain with fall in serum PSA levels and was retreated with second dose of 225Ac-PSMA-617 (~5.55 MBq) after an interval of 2 months. Repeat posttherapy whole-body anterior and posterior images showed significant resolution of lesions (C). Follow-up examinations revealed only grade 2 to 3 dryness of mouth suggesting that the RLT was well-tolerated by the patient. The follow-up 68Ga-PSMA-11 PET/CT scan at 7 weeks after second cycle of 225Ac-PSMA RLT showed significant reduction in number of lesions, correlating with pain relief to patient (MIP image; D) along with stabilization in serum PSA levels. Now patient is being planned for third cycle of 225Ac-PSMA RLT. 225Ac-PSMA appears to be more effective radiopharmaceutical because of 4 α-particles per decay and very short range resulting in double-strand DNA breaks with sparing of adjacent normal cells.2 Sathekge et al in their recent study have shown durable response and tolerable adverse effects in 73 mCRPC patients treated with 225Ac-PSMA-617 after failing to other therapies including 177Lu-PSMA therapy.3 In another pilot study, chemotherapy-naive patients with advanced prostate cancer treated with 225Ac-PSMA-617 showed significant PSA decline and resolution of lesions.4 However, posttherapy imaging was not done after 225Ac-PSMA-617 administration for tracer localization. Currently, use of 2 photopeaks (218 and 440 keV) has been suggested for clinical images.5 Although Rasheed et al6 studying gamma-ray spectrum for 225Ac-PSMA-617 showed an additional third photopeak (a prominent 78 keV with higher counting statistics), it was useful for imaging with potential of quality control for tracer localization in the lesions. Literature is limited to only a clinical case report showing the feasibility of imaging using the 3 photopeaks of 225Ac, as 78 keV with higher count density in addition to 2 photopeaks (218 and 440 keV) led to higher counts, better image, and more lesions' delineation.7 Till now, posttherapy imaging after alpha therapy is usually not done, leaving the patients for clinical and biochemical follow-up apart from early functional/anatomical imaging. 225Ac-PSMA RLT posttherapy images done twice in this index case using 3 major photopeaks resulted in better lesions delineation in first image followed by response to treatment in second image confirming its efficacy.

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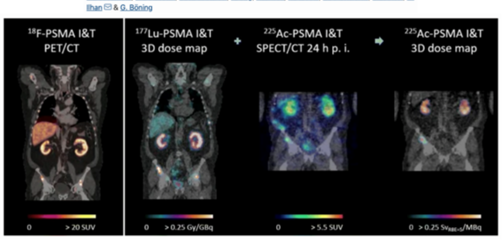
Image-based dosimetry for ^{225}Ac-PSMA-I&T therapy using quantitative SPECT

A. Gosewisch, M. Schleske, F. J. Gildehaus, I. Berg, L. Kaiser, J. Brosch, P. Bartenstein, A. Todica, H. Ilhan & G. Böning



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Research Square

Development of Alpha-emitting radioembolization for Hepatocellular Carcinoma: Longitudinal Monitoring of Actinium-225's Daughters Through SPECT Imaging

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Original research

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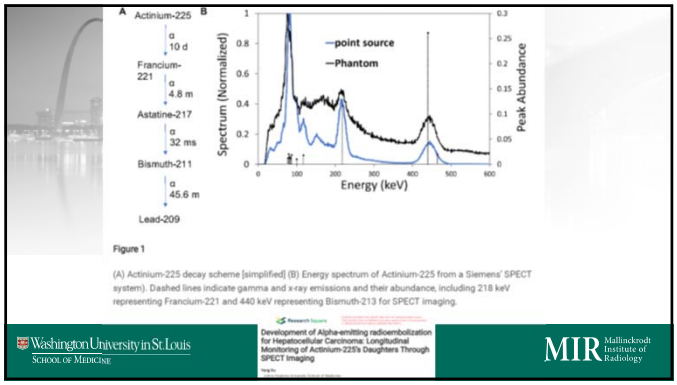

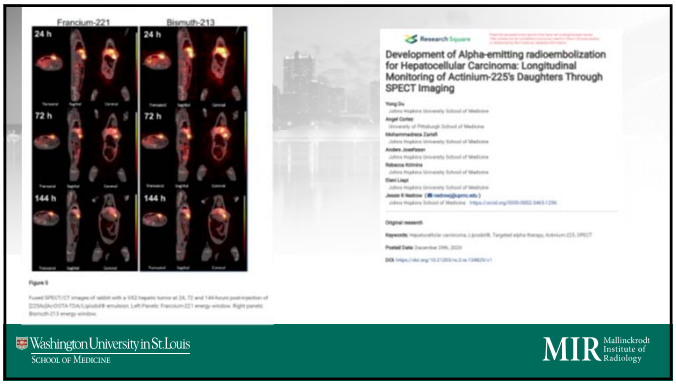

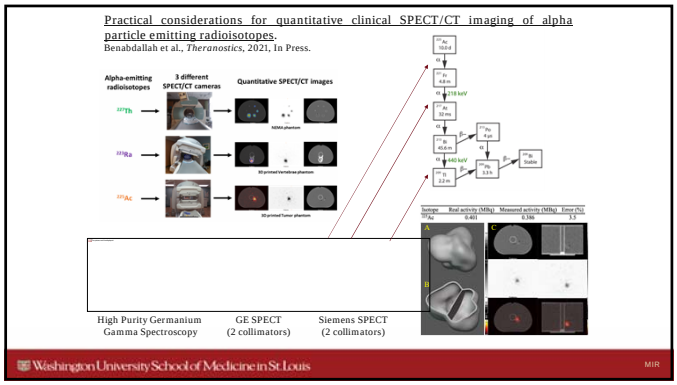

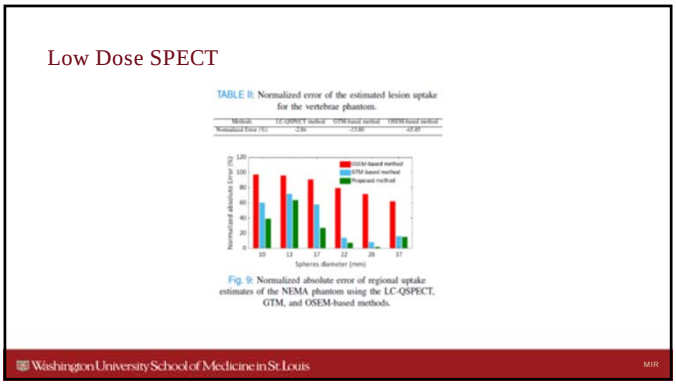

Cautions on Dosimetry:

- "this case exquisitely illustrates the methodical limitations of dosimetry and warns about an uncritical reliance on dosimetry estimates of dose-limiting organs "
- Clemens Kratochwil et al. J Nucl Med 2017;58:1624-1631
- "Patient as the dosimeter" may be the most facile approach to moving Ac225 therapies forward----RLW

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Summary

- Multiple randomized trials show benefit of radiopharmaceutical therapies but cures are elusive
- Ac225 with 10 day half life is very attractive as a general alpha therapy agent
- Supply of high quality Ac225 PSMA is currently limiting
- Ac225 PSMA targeting and very early data with NET targeting are encouraging
- Dosimetry with Ac225 PSMA is very challenging and empirical dosing is currently suggested.
- New approaches to low count dosimetry are promising but not yet validated.
- Many opportunities exist for Ac225 therapies—with or without a theranostic pairing

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