NUCLEAR PHARMACY CONFERENCE

Saturday, October 7 – Sunday, October 8, 2023

PRIMER ON POTENTIAL THERANOSTIC AGENTS

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OBJECTIVES

1. Recall Radionuclides for therapy
2. Describe Regulations for therapy radiopharmaceuticals
3. Identify potential new radiopharmaceutical therapies

RADIATION THERAPY USE OF RADIOPHARMACEUTICALS

- RAM use in therapy is SYSTEMIC Radioimmunotherapy (RIT) or Radiopharmaceutical Therapy (RPT)
- Radiation Oncologists can be Authorized Users and receive radioactive materials, but most do not receive this training in traditional residencies
- Movement of Medical Oncologist to become AU for unit dose RPT

RADIATION THERAPY TERMINOLOGY

- External radiation therapy
  - Accelerator therapy
  - Proton therapy
  - Intensity modulated radiation therapy
  - Cyberknife-robotic accelerator
  - Gamma Knife Co-60
- Internal radiation therapy (Brackytherapy)
  - LDR-Seeds (Ir-192, I-125, Pd-103)
  - HDR (10.5 Ci Ir-192)

RADIATION BENCHMARKS (EFFECTIVE DOSE)

- X-Ray of the chest: 0.04 mSv (4 mrem)
- CT of the chest: 7.8 mSv (780 mrem)
- Barium enema including fluoroscopy: 8.7 mSv (870 mrem)
- Bone scintigraphy: 3.5 mSv (350 mrem)
- I-131 sodium iodine 10 mCi (0% uptake): 24 mSv (2400 mrem)

External Radiation Therapy

- Skin dose limit: 25 Gy (2500 rad)
- Spinal cord: 10 Gy (1000 rad)
- Kidney: 23 Gy (2300 rad)
- Marrow: 2 Gy (200 rad)

Radiopharmaceutical Treatment

RN	Emission	Half-life	Radiopharmaceutical	Indications	Avail
I-131	β	8 days	^{131}I-sodium iodide	Thyroid cancer Graves' Disease	Yes
P-32	β	14 days	^{32}P-sodium phosphate ^{32}P-chromic phosphate	Radiosynovectomy Solid tumors	Off-market
Sr-89	β	51 days	^{89}Sr-strontium chloride (Metastron®)	Skeletal metastases	FDA-1993
Sm-153	β	46 hours	^{153}Sm-lexidronam (Quadrimet®)	Skeletal metastases	FDA 1997 Off-market
I-131	β	8 days	^{131}I-Iobenguane (Azedra®)	Sympathohromaffin tumors	FDA 2018 Off-market
I-131	β	8 days	^{131}I-tositumomab (Bexaar®)	Non-Hodgkin Lymphoma	Off-market
Y-90	β	64 hours	^{90}Y-Ibritumomab tiuxetan (Zevalin®)	Non-Hodgkin Lymphoma	FDA 2002
Ra-223	α	11 days	^{223}Ra-radium chloride (Xofigo®)	Castrate-resistant prostate cancer skeletal metastases	FDA 2013
Lu-177	β	6.6 days	^{177}Lu-DOTATATE (Lutathera®)	Neuroendocrine tumors	FDA 2018
Lu-177	β	6.6 days	^{177}Lu-PSMA	Prostate Cancer	Mar 2022

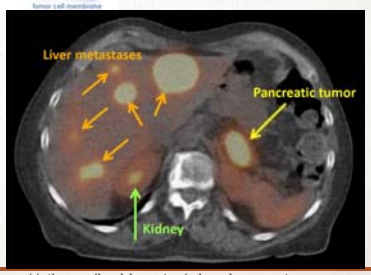
WHAT IS IMPORTANT IN CHOOSING AN ISOTOPE FOR RADIOTHERAPY?

- Type of production (reactor, cyclotron)
- Half-life (dose rate)
- Type of emissions (alpha, beta, gamma)
- Energy of the emissions (range in tissue)
- Specific Activity (% radioactive atoms)
- Availability and Cost
- "Theranostics"

WHAT IS THERANOSTICS?

- Theranostics is a combination of the terms **thera**peutics and diag**nostics**. 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.

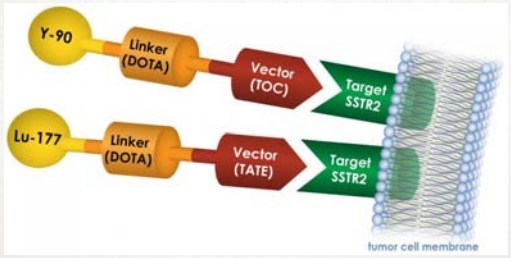
Diagnostic



No Biopsy

https://uihc.org/health-topics/what-theranostics

THERAPY



https://uihc.org/health-topics/what-theranostics

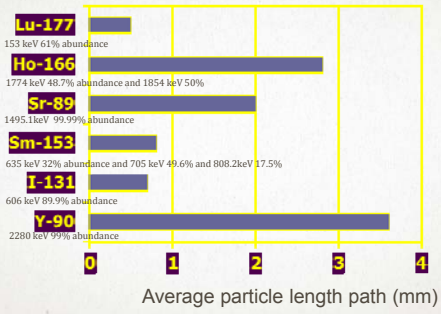
MODE OF DECAY

Travel distance (range) depends on particle energy and absorber density
Linear energy transfer (LET) = energy delivered per distance

	energy	LET	Air Distance	Soft Tissue Distance
Beta (β)	50-2300 keV	low	~10 m	<10 mm
Alpha (α, ^{4}He)	5-9 MeV	high	~50 mm	<100 μm (5-10 cells)
Auger electron	< 1keV	high	~50 mm	<0.5 μm (nucleus)
Gamma (γ)	100-900 keV	low	long-range	low attenuation
Neutron	up to 20 MeV	high	long-range	low attenuation

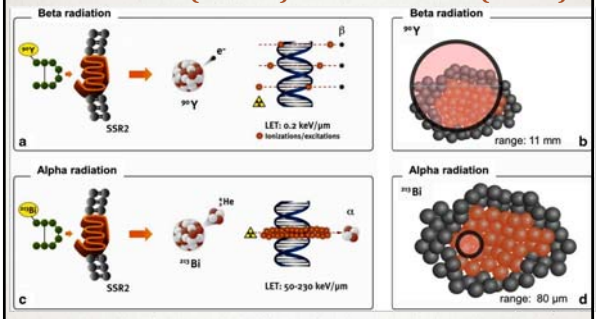
- Beta 50-250 cell diameters
- **Auger electrons**
  - Produced from electron capture and internal conversion
  - e.g. I-125, I-123, In-111
  - Very short range (<1um)
  - Must be deposited intra-nuclear

AVERAGE MM RANGE OF β-EMISSION IN WATER



(~0.25 mm= ~20 cell diameters)

BISMUTH-213 (45 MIN) VS YTTRIUM-90 (64 HR)



Kratochwil, et.al, Eur J Nucl Med Mol Imaging (2014) 41:2106–2119

THERAPY RADIONUCLIDE PROPERTIES

Radionuclide	Therapeutic emission	Approximate emission range in tissue (mm)	Radionuclide half-life
Yttrium-90	β^-	5.30	64.1 hours
Iodine-131	β^-	0.8	8.0 days
Samarium-153	β^-	0.4	46.5 hours
Lutetium-177	β^-	0.62	6.6 days
Astatine-211	α	0.05	7.2 hours
Lead-212/bismuth-212	β^-/α	<0.1/0.05	10.6 hours/1.0 hours
Radium-223	α	0.05–0.08	11.4 days
Actinium-225	α	0.05–0.08	10.0 days
Thorium-227	α	0.05–0.08	18.7 days

Sgouros. Nature Reviews 2020 vol 19

SNMMI RPT
DESIGNATED CLINICAL CENTERS OF EXCELLENCE

- ARA Theranostics Center
- ChristianaCare
- Dallas VA Medical Center
- Edward Hines VA Hospital
- Excel Diagnostics and Nuclear Oncology Center
- Hoag Memorial Hospital Presbyterian
- Intermountain Medical Center
- John Cochran VA Medical Center
- Kettering Health Main Campus
- MHP Radiation Oncology Institute part of the Genesiscare Network
- Northwell Health
- Northwestern Memorial Hospital
- Rush University Medical Center
- St. Luke's University Health Network
- Unity Point Health Des John Stoddard Cancer Center
- University Hospitals of Cleveland
- University of California Irvine
- University of Southern California Theranostics Center

https://therapy.snmmi.org/SNMMI-THERAPY/Resources/SNMMI-THERAPY/Radiopharmaceutical_Therapy_Centers_of_Excellence.aspx

SNMMI RPT DESIGNATED COMPREHENSIVE CENTERS OF EXCELLENCE

- Ahmanson Translational Theranostics Division, David Geffen School of Medicine at UCLA, UCLA Heath Medical Center
- Banner University Medical Center- Tucson. University of Arizona- Tucson
- BC Cancer - Vancouver
- CHU de Québec - Université Laval
- Cincinnati Children's Hospital Medical Center
- City of Hope
- Dana-Farber /Brigham and Women's Cancer Center
- Duke University Health
- Emory University Hospital
- H. Lee Moffitt Cancer Center and Research Institute
- Indiana University Health
- London Health Sciences Centre
- Lucile Packard Children's Hospital at Stanford
- M Health Fairview University of Minnesota Medical Center - East Bank Hospital
- Mayo Clinic
- MD Anderson Cancer Center
- Medstar Georgetown University Hospital
- Memorial Sloan Kettering Cancer Center
- Methodist Dallas Medical Center
- Mount Sinai Health System
- New York-Presbyterian Weill Cornell
- Oregon Health & Science University
- SSM Saint Louis University Hospital
- Stanford University - Stanford HealthCare
- The Ohio State University Wexner Medical Center - The James Hospital and Solove Research Institute
- UC San Diego Health
- University Health Network, Toronto, Canada
- University of California, San Francisco
- University of Colorado Anschutz Medical Center
- University of Iowa
- University of Pittsburgh Medical Center (UPMC)
- University of Washington Fred Hutchinson Cancer Center
- University of Wisconsin - Madison
- UT Southwestern Medical Center
- Vanderbilt University Medical Center

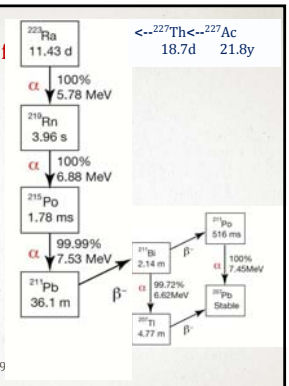
RADIUM-223

- **Chemical Symbol:** ^{223}Ra
- **Chemical Form:** Radium-223 dichloride
- **Half-life:** 11.4 day
- **Manufacturer(s):** Bayer HealthCare Pharmaceuticals Inc.
- **Trade name(s):** Xofigo®
- **Diagnostic use:** Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

RADIUM-223 DICHLORIDE (XOFIGO®)

- Indication: an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.
- Physical half-life: 11.4 days
- Target: Hydroxyapatite (bone)
- Particle range in bone and soft tissue: ~ 10 µm

Radium-223 has a complex decay scheme, with emission of four α, two β, and multiple γ



<--227Th<--227Ac
18.7d 21.8y

- alpha (95.3%)
  - 5.7 MeV
- beta (3.6%)
- gamma emission (1.1%)
  - In keV's 81 (15%), 84 (24%), 154 (5%), 269

DOSAGE (1.49 MICROCURIE/KG)

- 1 injection every 4 weeks for 6 injections
- Volume of injection determined by concentration of supplied solution
- Monitor blood counts at baseline
  - ANC ≥ 1500/μL; platelet ≥ 100,000/μL; Hgb ≥ 10 g/dL
- Monitor blood counts prior to every dose of Xofigo
  - ANC ≥ 1000/μL; platelet ≥ 50,000/μL administering
- Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care

SIDE EFFECTS

- Hematologic (57%)
- 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia
  - grade 3 & 4 anemia
  - neutropenia,
  - thrombocytopenia
- Gastrointestinal (>10%)
  - Nausea
  - Vomiting
  - Diarrhea

External radiation exposure

Time (h)	Surface	0.3 m	1 m
0	0.58	12	3
24	0.91	12	3
48	0.19	1	1
144	0.05	1	1

STABILITY AND STORAGE

- Provided to the pharmacy in a single-use vial at a concentration of 30 microcurie/mL at the reference date with a total radioactivity of 162 microcurie/vial at the reference date
- Provided to the hospital in a unit dose syringe from the pharmacy (Cardinal-Denver)
- Should not be diluted or mixed
- Storage at room temperature
- Shelf life: 48 hours
- Should be stored for 4 months and discard as nor


TRAINING

- 35.300 RAM category requiring written directive
- 35.390 Training category for nuclear medicine physicians
  - Will be listed as 35.300
- 35.396 Training route for radiation oncologists
  - On RAM license
    - Listed 35.300 and 35.400
    - Or 35.300 and 35.600

LICENSE AMENDMENTS

- Radium-223
- Atomic number 88 (atomic mass – 223)
- Most licenses will categorize possession limits to radionuclides with atomic numbers 1-83.

STRONTIUM-89

- **Chemical Symbol:** ^{89}Sr
- **Chemical Form:** Strontium-89 chloride
- **Half-life:** 50 days
- **Manufacturer(s):** BioMed through Drax 2020
- **Trade name(s):** Metastron
- **Diagnostic use:** Indicated for the relief of bone pain in patients with painful skeletal metastases that have been confirmed prior to therapy.

YTTRIUM-90

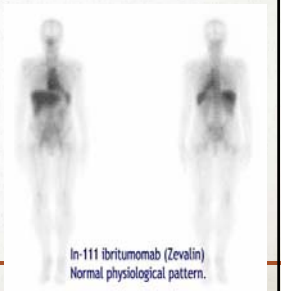
- **Chemical Symbol:** ^{90}Y
- **Chemical Form:** Yttrium-90 chloride
- **Half-life:** 64 hrs
- **Manufacturer(s):** Eckert & Ziegler, MDS Nordion
- **Trade name(s):**
- **Diagnostic use:** Indicated for radiolabeling:
- Zevalin® used for radioimmunotherapy procedures

YTTRIUM-90

- **Chemical Symbol:** ^{90}Y
- **Chemical Form:** Yttrium-90 ibritumomab tiuxetan
- **Half-life:** 64 hrs
- **Manufacturer(s):** Spectrum Pharmaceuticals
- **Trade name(s):** Zevalin
- **Diagnostic use:** Indicated for the:
- Treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)
- Treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy

- U.S. Food and Drug Administration (FDA) on November 18, 2011 removed the pre-treatment biodistribution evaluation requirement using Indium-111 ZEVALIN

^{111}In Ibritumomab Tiuxetan Imaging



ZEVALIN TX DOSAGE

- 0.4 mCi/kg in patients with a platelet count ≥150,000/µL
- 0.3 mCi/kg with a platelet count 100,000–149,000/µL
- Maximum dose is 32 mCi

Y-90 Syringe Dose Calibrator Settings

- Siegel, et al. Accurate Dose Calibrator Activity Measurement of Y-90 labeled Ibritumomab Tiuxetan. J Nuc Med March 2004
- NIST Report to IDEC Pharmaceuticals, Corp. Experimental determination of calibration factors for commercial dose calibrators for Y-90 labeled Zevalin in 10ml plastic syringe. (Needle size 25 x 0.9mm equals 20G 1")

ZEVALIN ADVERSE EVENTS

- Thrombocytopenia
- Neutropenia
- Nadir 7-9 weeks
- Median duration 30 days

ZEVALIN REQUIRES NO SPECIAL AU TRAINING REQUIREMENTS

- Must be licensed under 35.300 for unsealed therapy use
- Written directive required

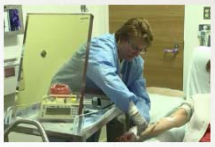
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

- Lu-177 Dotatate
- Lutathera® January 2018
- Indication: Treatment of somatostatin receptor positive GEP NET
- Phase III 79% lower risk of disease progression or death versus high dose octreotide

LUTETIUM LU-177 DOTATATE

- Tp =6.65 days
- β- emitting radionuclide
  - Beta=153keV 61% abundance
  - maximum range in tissue 2.2 mm (mean 0.67)
- Gamma 208 keV (11%) and 113 keV (6.4%)
- 10 mCi/mL
- colorless to slightly yellow solution
- pH 4.5 to 6

LU-177 DOTATATE REGIMEN



- 4 cycles (1 cycle is 8 weeks)
  - 30 min Amino Acid protectant infusion
  - 30 min 200 mCi Lu-177 dotatate
  - 3 hours of AA infusion
- Renal clearance 70% in 24 hours
- Nausea and vomiting due to amino acid infusions. Resolved upon completion of the infusions.

LU-177 DOTATATE REGIMEN

- Imaging:
  - pre-therapy staging and planning
  - May have immediate post-therapy imaging
  - ^{111}In-Octreotide, ^{68}Ga-DOTATATE
- 200 mCi (7.4 GBq) by infusion every 8 weeks x 4
- Concurrent amino acid infusion for renal protection
- Nausea/vomiting is frequent
- Post-therapy hydration is important
  - incontinence may be a radiation safety concern
- Maintain radiation safety precautions at home up to 11 days

LU-177 DOTATATE REGIMEN

- Low external radiation dose rate
  - Immediate: ~2 mR/h (1 meter)
  - 24 h: ~1 mR/h (1 meter)
- Usually discharged to home with written instructions
- Nausea/vomiting is frequent
  - likely related to amino acid infusion
- Post-therapy hydration is important
  - incontinence may be a radiation safety concern
- Maintain radiation safety precautions at home
  - Up to 11 days

LU-177 DOTATATE REGIMEN

COLD OCTREOTIDE

- Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each dose
- Do not administer long-acting octreotide within 4 weeks of each subsequent dose
- Short-acting octreotide may be given for symptomatic management during treatment, but must be withheld for at least 24 hours before each dose

DECAY IN STORAGE (10 CFR 35.92) VS *WASTE DISPOSAL* (10 CFR PART 20 SUB K)

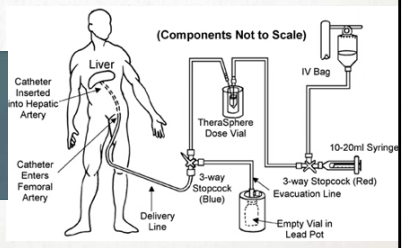
- Lu-177m T1/2p = 160.44 days
- Contaminant present in reactor-produced (Lu-176 --> Lu-177) Lu-177
- Not present in NCA Lutetium (from Yb-177)

Nucl Med Mol Imaging 2015 Jun;49(2):85-107

Y-90 MICROSPHERES SIR-SPHERES ®SIRTEX MEDICAL 2006 FDA DEVICE

- **Indication:**Metastatic liver tumors
  - Primary colorectal cancer
  - With adjuvant IHAC
- Must be no potential for resection of the tumor

THERASPHERE® Y-90 MICROSPHERES



ADMINISTRATION

- Evaluation of pulmonary shunting
  - Tc-99m macroaggregated albumin (MAA)
- Vascular status of lesions
  - CT
- Placement via hepatic artery
- Activity can be administered to localized areas
  - Altering of injection site

NRC LICENSING GUIDANCE – THERASPHERE® AND SIR-SPHERES® YTTRIUM-90 MICROSPHERES FDA DEVICE

- **REVISED DECEMBER 2007**
- Yttrium-90 (Y-90) microspheres are manual brachytherapy sources used for permanent implantation therapy. Y-90 microspheres are regulated under 10 CFR 35.1000 "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material."

TABLE 5.2 Therapeutic Radionuclides Used for Nuclear Medicine Research

Radionuclide	Description	Production
Lutetium-177	Beta emitter, 6.7-d half-life	Reactor
Astatine-211	Alpha emitter, 7.2-h half-life	Accelerator
Yttrium-90	Beta emitter, 64-h half-life	Reactor
Rhenium-186	Beta emitter, 3.7-d half-life	Reactor
Rhenium-188	Beta emitter, 17-h half-life	Reactor
Holmium-166	Beta emitter, 27-h half-life	Reactor
Iodine-131	Beta emitter, 8.0-d half-life	Reactor
Samarium-153	Beta emitter, 46-h half-life	Reactor
Bromine-77	Beta emitter, 57-h half-life	Accelerator
Copper-67	Beta emitter, 62-h half-life	Accelerator
Actinium-225	Alpha emitter, 10.0-d half-life	Accelerator
Strontium-89	Beta emitter, 50.5-d half-life	Reactor

Advancing Nuclear Medicine Through Innovation
Committee on State of the Science of Nuclear Medicine, National Research Council 2007. National Academies Press at: http://www.nap.edu/catalog/11985.html

TABLE 5.1 Reactor and Accelerator Facilities in the United States with Medical Radionuclide Production Capability

Location	Facility	Power	Medical Radionuclides Currently Produced
Reactors			
ORNL	HFIR	85 MW	^{225}Ac, ^{252}Cf, ^{43}K, ^{103}Pd, ^{188}W, ^{117m}Sn, ^{147}Pm, ^{177}Lu, ^{186}Re, ^{166}Ho, ^{194}Ir, ^{191m}Ir, and others
University of Missouri	MURR[a]	10 MW	^{32}P, ^{166}Ho, ^{192}Ir, ^{35}S, ^{186}Re, ^{90}Y, ^{51}Cr, ^{103}Pd, ^{177m}Lu, and others
Massachusetts Institute of Technology	MITR-II[a]	5 MW	^{198}Au, ^{90}Y, ^{192}Ir, and others (research quantities)
University of California at Davis	MNRC[a]	2 MW	^{123}I and others (research quantities)
Oregon State	OSTR[a]	1 MW	Variety (research quantities)
Accelerators			
LANL	LANSCE	800 MeV proton	^{26}Al, ^{67}Cu, ^{68}Ge, ^{82}Sr, ^{86}Y, ^{124}I, and others
BNL	BLIP	200 MeV proton	^{67}Cu, ^{82}Sr, ^{68}Ge, and others
Washington University	cyclotrons		^{64}Cu, ^{77}Br, ^{66}Ga, ^{124}I, ^{94m}Tc
Trace Life Sciences[b]	Various LINAC and cyclotrons		^{64}Cu, ^{67}Cu, ^{111}In, ^{123}I, ^{201}Tl

[a]Non-DOE facilities: University research reactors.
[b]Commercial production facility.

SOURCE: DOE Isotope Program.

Advancing Nuclear Medicine Through Innovation
Committee on State of the Science of Nuclear Medicine, National Research Council 2007. National Academies Press at: http://www.nap.edu/catalog/11985.html

AC-225 RADIOPHARMACEUTICALS

- 27 molecules under development
- 13 at human level
- Cover all indications that are studied with B-emitting radionuclides
- Current Lu-177 labeled drugs are being explored with Ac-225
- Zimmermann projects 3,000 Gbq (81 Ci) will be needed to treat 100,000 patients a year

Zimmermann. JNM 2023;64(10)

Ac-225 Zimmermann JNM 2023, 64 (10) 1516-1518

Technology	Source	Yearly production capacity (GBq/y/site) 2023	2032	Total (GBq/y) in 2032	Comment
A: [^{233}U→] ^{229}Th→^{225}Ac] (generator)	ORNL, United States	26	26	Up to 3,000 [80]	Highest quality of *nca* ^{225}Ac; may enter price competitively
	TerraPower, United States	>10	≤2,700		
B: [^{232}Th(p,x)^{225}Ac+^{227}Ac] (high-energy accelerator)	BNL/ORNL LANL; Tri-Lab, United States	16.7	Potential, >3,700	>9,000 [>240]	Contaminated with ^{227}Ac (0.2% EOB - ~1.5% at calibration); not suitable for large scale routine use
	CNL/TRIUMF, Canada; BWXT/ITM, United States/Germany	>1	Idem >3,700		
	SpectronRx, United States	>1	>200		
C: [→…+^{225}Ra→^{225}Ac] (as side product)	~10% of above; CNL/TRIUMF, Canada	0.3	>370 (theory)	>370 [>10]	High level of waste - expensive
D: [^{226}Ra(p,2n)^{225}Ac] (cyclotron)		First GBq		>4,500 [>120]	Additional sites under evaluation in other countries (Asia)
	SpectronRx, United States	2023	>500		
	Ionetix, United States	2023	1,900		
	Eckert&Ziegler, Germany	2024	550		
D: [^{226}Ra(d,3n)^{225}Ac] (linear accelerator)	Nusano, United States		≤160,000		Under evaluation
E: [^{226}Ra(γ,n)^{225}Ra→^{225}Ac] (photoconverter)	NorthStar, United States	2023	3,700–15,000	>37,000 [>1,000]	Rhodotron: *nca* ^{225}Ac
	TerraPower, United States	2029	3,700–5,000		
	Niowave, United States	2023	≤18,000		Linac: *nca* ^{225}Ac
F: [^{226}Ra(n,2n)^{225}Ra→^{225}Ac] (n from d on beryllium target)	Nusano, United States		≤44,000		Under evaluation

SELECTED RPT AGENTS UNDER DEVELOPMENT

Sgouros. Nature Reviews 2020 vol 19

^{177}Lu-labelled NeoBOMB1	Novartis/AAA	GRPR$^+$ tumours	GRPR binding	Phase II; completed Phase I/II; completed	NCT03724253 NCT02931929
^{166}Ho microspheres	Terumo	Hepatic malignancies	Radioembolization of liver microvasculature	Phase II; unknown recruitment status	NCT02067988
^{177}Lu-labelled DOTA-JR11	Ipsen	Neuroendocrine tumours	SSR-mediated binding and internalization	Phase I/II	NCT02592707
^{177}Lu-labelled PSMA-R2	Novartis/AAA	Prostate cancer, tumour neovasculature	PSMA-mediated binding and internalization	Phase I/II; recruiting	NCT03490838
^{225}Ac-labelled aCD38*	Actinium Pharmaceuticals	Multiple myeloma	CD38 antibody α-targeting	Phase I; recruiting	NCT02998047
^{225}Ac-labelled aCD33*	Actinium Pharmaceuticals	Leukaemia, MDS	CD33 antibody α-targeting	Phase I; withdrawn	NCT03705858
^{227}Th-labelled MSLN-TTC*	Bayer	Mesothelin$^+$ tumours	Anti-mesothelin-α-emitter immunoconjugate	Phase I; recruiting	NCT03507452
^{227}Th-labelled PSMA-TTC*	Bayer	Prostate, tumour neovasculature	PSMA-targeting α-emitter immunoconjugate; PSMA$^+$ prostate cancer targeting	Phase I; recruiting	NCT03724747
^{227}Th-labelled aCD22-TTC*	Bayer	Lymphoma	Anti-CD22–α-emitter immunoconjugate; CD22$^+$ tumours (lymphoma)	Phase I; active, not recruiting	NCT02581878
^{177}Lu-labelled CTT-1403	Cancer Targeted Technologies	Prostate, tumour neovasculature	PSMA-mediated binding	Phase I; active, not recruiting	NCT03822871
^{131}I-labelled CLR 131	Cellectar	Paediatric cancer, head and neck cancer, multiple myeloma, leukaemia, lymphoma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; recruiting Phase I; suspended (owing to COVID-19) Phase II; recruiting	NCT03478462 NCT04105543 NCT02952508
^{131}I-labelled CLR1404	Cellectar	Unresponsive solid tumour, multiple myeloma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; not recruiting Phase I; completed	NCT02278315 NCT01496663
^{225}Ac-labelled FPX-01*	J&J/Fusion Pharma	NSCLC, pan-cancer target	Insulin growth factor 1$^+$ tumours	Phase I; recruiting	NCT03746431

SELECTED RPT AGENTS UNDER DEVELOPMENT

RPT agent	Company	Indication	Properties	Development phase	NCT number
[^{153}Sm]CycloSam	Oncolix/ Isotherapeutics	Osteosarcoma	Binding to hydroxyapatite matrix	Phase I; not yet recruiting	NCT03612466
^{212}Pb-labelled DOTAMTATE*	OranoMed/ Radiomedix	SSR$^+$ tumours	SSR-mediated binding	Phase I; active, not recruiting	NCT03466216
^{177}Lu-labelled RM2	ABX GmbH	GRPR$^+$ tumours	GRPR binding	First in human	–
^{227}Th-labelled HER2-TTC*	Bayer	HER2$^+$ tumours	Anti-HER2–α-emitter immunoconjugate	Preclinical	–
^{212}Pb-labelled PLE*	OranoMed/ Cellectar	Solid tumours	–	Preclinical	–
^{212}Pb-labelled aTEM1*	OranoMed/ Morphotek	TEM1$^+$ tumours	–	Preclinical	–
^{212}Pb-labelled aCD37*	OranoMed/ NordicNanovector	Leukaemia/ lymphoma	CD37 antibody α-targeting	Preclinical	–
^{211}At-labelled aLAT-1*	Telix Pharma	Multiple myeloma	–	Preclinical	–

The list is not exhaustive and includes only agents that are being developed by a commercial sponsor. *α-Emitter-based radiopharmaceutical therapy (RPT) agents. MDS, myelodysplastic syndrome; mIBG, meta-iodobenzylguanidine; NSCLC, non-small-cell lung cancer; PSMA, prostate-specific membrane antigen; SSR, somatostatin receptor.

Sgouros. Nature Reviews 2020 vol 19

RPT SAFETY CONCERNS

- Written directive specifics
- Inventory
- 10 CFR Part 35, "Medical Use of Byproduct Material," includes requirements and provisions for the radiation safety of workers, the public, patients, and human research subjects.
- o 10 CFR 35.75(a) permits the licensee to authorize the release of any individual from its control who has been administered unsealed byproduct material or implants containing byproduct material if the total effective dose equivalent (TEDE) to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (mSv) (0.5 rem). The 5 mSv release limit applies per administration to the patient and is not a yearly limit.
- Records of the basis for authorizing patient release be maintained for 3 years if the bases of the release was other than the activity administered

RELEASE OF PATIENTS ADMINISTERED RADIOACTIVE MATERIAL
DRAFT REGULATORY GUIDE DG-8061
Proposed Revision 2 to Regulatory Guide 8.39 Issue Date: April 2023

RADIONUCLIDE-SPECIFIC (NRC REGULATORY GUIDE 8.39 REV 2)

- Estimated radiation dose not likely to exceed
  - 500 mrem (5mSv) per treatment to ANY person
  - 100 mrem (1mSv) per year to any:
    - Child
    - Breastfeeding infant
    - Any other uninvolved individual
- Administered activity (e.g. $^{131}I \leq 8.6$ mCi)
  - Can be calculated residual based on activity

OR

- Dose rate at 1 meter (e.g. ≤ 1.8 mrem/h for ^{131}I)

NRC 8.39 rev 2 (April 2023) Table 1. Basic Activity Thresholds for Radionuclides

RADIONUCLIDE	COLUMN 1 (0.5 rem) Patient Release Threshold Q-release (mCi)	COLUMN 2 (0.1 rem) Instruction Threshold Q-instructions (mCi)
At-211	460	89
Bi-213	5700	1100
Cu-67	100	20
I-131	8.6	1.7
Lu-177	110	22
Ra-223	7.3	1.5
Sm-153	180	38
Sr-89	89	18
Y-90	920	180
Zr-89	5.7	1.1

ESTIMATING POTENTIAL EXPOSURE TO OTHER INDIVIDUALS AFTER RADIONUCLIDE THERAPY

- Radionuclide-Specific
  - Half-life, Exposure rate (Γ)
- Radionuclide-Specific (Not Radiopharmaceutical-Specific)
  - Administered Activity, Time since administration
- Standard Patient-Specific
  - Occupancy Factor, Distance from Patient

POLICY ISSUE
(Information)

January 29, 2018 SECY-18-0015

FOR: The Commissioners

FROM: Marc L. Dapas, Director
Office of Nuclear Material Safety and Safeguards

SUBJECT: STAFF EVALUATION OF THE U.S. NUCLEAR REGULATORY COMMISSION'S PROGRAM REGULATING PATIENT RELEASE AFTER RADIOISOTOPE THERAPY

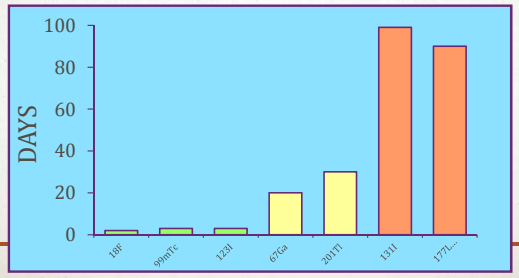
Hotel Worker Models:

- To exceed an external dose of 1 mSv (0.1 rem), the hotel check-in staff would need to be exposed to a newly released thyroid cancer patient at 1 meter for approximately 4 hours.
- To exceed the patient release dose limit of 5 mSv (0.5 rem), the hotel check-in staff would need to be exposed to a newly released thyroid cancer patient at 1 meter for approximately 23 hours.
- The internal dose received by a hotel cleaning staff person would be approximately 1.5 microsievert (μSv) (0.15 mrem) for cleaning a newly released I-131 thyroid cancer patient's room and 0.7 μSv (0.07 mrem) for cleaning a newly released I-131 hyperthyroidism patient's room.

Consequently, the NRC staff concluded that a hotel cleaning staff person would need to clean approximately 670 rooms of newly released thyroid cancer patients to exceed 1 mSv (0.1 rem), and 3,300 rooms of newly released patients to exceed the patient release limit of 5 mSv (0.5 rem).

SENSITIVITY OF HOMELAND SECURITY RADIATION DETECTORS TO MEDICAL RADIONUCLIDES IN PATIENTS:

This is to certify that _____ (Patient Name) was administered ____ mCi radioactive material (_____) for medical purposes on _____ (Date). This individual poses no health hazard to others so long as they follow the instructions given them upon their release from the hospital. This individual is expected to remain measurably radioactive until approximately _____ (Date).
(Name of Author Physician)



NUREG 1556 vol. 9 rev. 3

Emergency Surgery of Patients Who Have Received Therapeutic Amounts of Radionuclides

For emergency surgery or autopsy of patients administered byproduct material, National Council on Radiation Protection and Measurements (NCRP) Report No. 111, "Developing Radiation Emergency Plans for Academic, Medical, or Industrial Facilities," 1991, may contain helpful information.

Autopsy of Patients Who Have Received Therapeutic Amounts of Radionuclides

- Immediately notify the authorized user (AU) in charge of the patient and the RSO upon death of a therapy patient.
- An autopsy will be performed only after consultation and permission from the RSO. Radiation safety staff should evaluate the radiation hazard(s), direct personnel in safety and protection, and suggest suitable procedures to keep doses ALARA during the autopsy.
- Protective eyewear should be worn by the pathologist and assisting staff for protection from possible splashing of radioactive material. Consider the need for protection against exposure from high-energy beta rays in cases involving therapy with phosphorus-32 and yttrium-90.

NUREG 1556 VOL. 9 REV. 3

If an autopsy or cremation is to be performed

- Immediately notify the AU in charge of the patient and the RSO upon death of a therapy patient.
- Consult and get permission from the RSO.
- Instruct pathologist to excise tissue containing radioactive seeds.
  - Make pathologist aware seeds may have migrated and additional tissue may need to be removed.
  - Instruct pathologist to consult with RSO about the possibility of slicing through a seed and contaminating the facility.
- Seek municipal approval, if required, because the very high temperatures used in modern crematoria may cause seeds to burst, releasing radioactivity into the plume.

RPT CONTRAINDICATIONS

- Category X
- Contraindicated in women who are pregnant or women who are continuing to breast feed
- **Relative contraindications:**
  - use in children under ten remains a subject of debate
  - patients who require nursing care because of physical debility, mental instability.

CLOSING

- Billions of dollars in radiopharmaceutical acquisitions and licensing
  - Many ongoing trials
  - Dominated by PSMA
- Virtual Biopsy with RPT
  - Large gap between biopsy-based tumor characterization and what is actually happening in the various tumor lesions in a single patient and between patients
  - Genomics, immunohistochemistry, PK/PD data, standard tumor assessment criteria by themselves are not enough to meet the goals of Precision Medicine
  - Choosing a dosing strategy for RPT
- Choosing a dosing strategy for RPT
  - Flat or weight based dosing is simple and easy
  - It works (possibly suboptimally)
  - It's a shame to not utilize the theranostic capacity
  - Need to prove it is better