Advisory Committee on the Medical Uses of Isotopes

Fall Meeting
October 4, 2021

Meeting Handout

MEETING AGENDA
ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES
October 4, 2021
Virtual Meeting

NOTE: Sessions of the meeting may be closed pursuant to 5 U.S.C. 552(b) to discuss organizational and personnel matters that relate solely to internal personnel rules and practices of the ACMUI; information the release of which would constitute a clearly unwarranted invasion of personal privacy; information the premature disclosure of which would be likely to significantly frustrate implementation of a proposed agency action; and disclosure of information which would risk circumvention of an agency regulation or statute.

Monday, October 4, 2021

OPEN SESSION

10:00 – 10:15	**1. Opening Remarks** Mr. Einberg will formally open the meeting and Mr. Williams will provide opening remarks.	**C. Einberg, NRC** **K. Williams, NRC**
10:15 – 10:30	**2. Old Business** Mr. DiMarco will review past ACMUI recommendations and provide NRC responses.	**D. DiMarco, NRC**
10:30 – 11:00	**3. Medical Events Subcommittee Report** Dr. Ennis will provide an analysis of FY20 medical events.	**R. Ennis, ACMUI**
11:00 – 11:45	**4. Radionuclide Generator Knowledge and Practice Requirements Subcommittee Report** Mr. Green will discuss the subcommittee's recommendations on the knowledge and specialized practice requirements for eluting, measuring, and testing, and processing the eluate from radionuclide generator systems	**R. Green, ACMUI**
11:45 - 12:00	**5. Open Forum** The ACMUI will identify medical topics of interest for further discussion.	**ACMUI, NRC**
12:00 - 12:45	**LUNCH**	
12:45 – 1:30	**6. Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics Subcommittee** Dr. Jadvar will discuss the subcommittee's recommendations on the knowledge and specialized practice requirements needed for the safe use and handling of emerging radionuclides in theranostics.	**H. Jadvar, ACMUI**
1:30 - 2:15	**7. Future of Personalized Dosimetry** Discuss the work of new AAPM task groups on this subject.	**R. Hobbs, AAPM**
2:15 - 3:00	**8. Production Challenges for Therapeutic Radiopharmaceuticals** Discuss production methods of emerging therapeutic radiopharmaceuticals and effects on radiation safety for end users, and the challenges of various production methods.	**M. Shober, ACMUI**

3:00 – 3:15	**BREAK**	
3:15 - 3:30	**9. Special Presentation to Mr. Michael Sheetz**	**R. Lewis, NRC**
3:30 - 3:45	**10. Open Forum** The ACMUI will continue discussion on medical topics of interest.	**ACMUI, NRC**
3:45 – 4:00	**11. Administrative Closing** Mr. DiMarco will provide a meeting summary and propose dates for the spring 2022 meeting.	**D. DiMarco, NRC**
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Open ACMUI Recommendations and Action Items

Item #	Item	Date	Status		Target Completion Date for NRC Action
2019					
17	The ACMUI endorsed the Appropriateness of Medical Event Reporting Subcommittee report and the recommendations provided therein.	09/10/2019	*Accepted*	Propose closure	Fall 2021
18	The ACMUI endorsed the Evaluation of Extravasations Subcommittee Report, as amended, to note that under future revisions to Part 35 rulemakings, extravasations be captured as a type of passive patient intervention in the definition of patient intervention.	09/10/2019	*Accepted*	Open	April 2022
2020					
4	The ACMUI endorsed the Patient Intervention subcommittee report, as presented, and the recommendations provided therein.	03/30/2020	*Accepted*	Open	April 2022
11	As part of the Non-Medical Events report, the ACMUI recommended to the NRC staff and/or NMP to evaluate the issue of detection of short-lived medical isotopes in municipal waste (waste from nuclear medicine patients that might be triggering the landfill alarms) and provide some level of guidance, best practices, or additional instructions.	09/21/2020	*Accepted*	Propose closure	Spring 2022

Open ACMUI Recommendations and Action Items

Item #	Item	Date	Status		Target Completion Date for NRC Action
2021					
1	The ACMUI tentatively scheduled the fall meeting for October 4-5, 2021. The alternate meeting date is September 13-14, 2021. A virtual or in-person meeting for fall 2021 is to be determined.	03/16/2021	*Accepted*	Propose closure	Fall 2021
2	The ACMUI endorsed the ACMUI Abnormal Occurrence Subcommittee report, and the recommendations provided therein.	05/27/2021	*Accepted*	Propose closure	Fall 2021
3	The ACMUI formed a new subcommittee on the Radionuclide Generator Knowledge and Practice Requirements. The subcommittee is expected to provide a draft report and any recommendations at the fall 2021 ACMUI meeting.	05/27/2021	*Accepted*	Propose closure	Fall 2021
4	The ACMUI formed a new subcommittee on Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics. The subcommittee is expected to provide a draft report and any recommendations at the fall 2021 ACMUI meeting.	05/27/2021	*Accepted*	Propose closure	Fall 2021
5	The ACMUI formed a new subcommittee on the Diffusing Alpha-emitter Radiation Therapy (DaRT) Manual Brachytherapy Source. The subcommittee is expected to provide a draft report and any recommendations at the spring 2022 ACMUI meeting.	09/02/2021	*Accepted*	Open	Spring 2021

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Medical Events Subcommittee Report

Ronald D. Ennis, M.D.

Advisory Committee on the Medical Uses of Isotopes

October 4, 2021

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Subcommittee Members

- Ronald D. Ennis, M.D. (Chair)
- Richard Green
- Darlene Metter, M.D.
- Zoubir Ouhib, M.S.
- Michael O'Hara, Ph.D.
- Michael Sheetz
- Harvey Wolkov, M.D.

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Summary

- Two overarching themes remain
  - Performance of a time out/use of a checklist immediately prior to administration of radioactive byproduct material, as is done in surgery and other settings, could have prevented some MEs
  - Lack of recent or frequent performance of the specific administration or inattention during performance of the procedure/treatment appear to be contributing factor(s) in a number of cases
  - NRC issued an Information Notice alerting the users to this issue in 2019. https://www.nrc.gov/docs/ML1924/ML19240A450.pdf

Summary

- Specific issues
  - Increase complexity of unsealed source administrations of newer agents may lead to more equipment related MEs in future
  - MEs involving Y90 administration continue to be the most common MEs. We propose the creation of a subcommittee to evaluate this issue in more depth and, in conjunction with the vendors, propose solutions to decrease the frequency of MEs

35.200 Use of Unsealed Byproduct Material for Imaging and Localization

Medical Events Summary

	2017	2018	2019	2020	Total
Cause					
Wrong drug	0	0	0	0	0
Wrong dosage	2	0	0	0	2
Wrong patient	1	0	0	0	1
Extravasation	1	0	0	0	1
Human error	0	0	1 (8 patients)	0	1 (8 patients)
Total	4	0	1	0	5

3/5 possibly preventable by time out

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35.300 Use of Unsealed Byproduct Material, Written Directive Required

Medical Event Summary

	2017	2018	2019	2020	Total
WD not done or incorrectly	2	1	2	0	5
Error in delivery (#capsules)	1	0	1	0	2
Wrong dose	0	0	0	0	0
Equipment	0	1	4	0	5
Human Error	0	0	1	2	3
Wrong patient	1	0	1	0	2
Total	4	2	9	2	17

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35.400 Manual Brachytherapy

Medical Event Summary

	2017	2018	2019	2020	Total
Applicator issue (e.g. jam, eye plaque dislodged)	0	0	0	2	2
Wrong site implanted (e.g. penile bulb, bladder)	1	1	1	2	5
Activity/prescription error (e.g. air kerma vs mCi, enter wrong activity in planning software)	1	0	1	0	2
Prostate Dose	5	11	3	0	19
New device	0	1	0	0	1
Wrong source	0	0	0	1	1
Patient health (?patient intervention)	0	0	0	1	1

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35.400 Manual Brachytherapy

Medical Event Summary

	2017	2018	2019	2020	Total
Total ME	7	13	5	6	31
"Time out" may have prevented	1	0	1	1	3
Lack of experience/inattention may have played a role	1	1	1	1	4

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35.400 Manual Brachytherapy

Many MEs in this category are no longer categorized as MEs due to change from dose to activity-based definition, although even in 2019 this definition continued to be used for some MEs.

Lack of experience or inattention possibly plays a role in the true MEs of this type, but hard to assess to what degree in each case.

In approximately 15% of cases, a “time out/checklist”, enhanced retraining prior to performance of an uncommon procedure or increase attention during the procedure might have prevented the ME.

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

	2017	2018	2019	2020	Total
Wrong position	2	3	4	7	16
Wrong reference length	2	1	4	2	9
Wrong plan	0	2	0	0	2
Wrong dose/source strength	0	1	0	0	1
Machin/applicator malfunction	2	3	1	1	7
Software/hardware failure	2 (9 pts)	0	1	1	4
Treatment planning	0	0	0	2	2
Total	8 (14 pts)	10	10	13	41

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

Medical Event Summary

	2017	2018	2019	2020
Location				
Breast	0	1	0	1
Gynecological	7 (14 pts)	7	8	10
Skin/neck	0	1	0	2
Bronchus	0	0	0	0
Prostate	0	0	0	0
Brain	1	1	2	0
Total	8 (14 pts)	10	10	13

GYN tumors most common site of ME

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

MEs that may have been prevented by "timeout" (wrong plan or dose)

- 2017 0/8 events
- 2018 3/10 events
- 2019 3/10 events
- 2020 10/13 events

Total 16/41 (39%)

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

MEs caused by "infrequent user/inattention"

This is difficult to determine based on information in NMED. For this assessment, assumed wrong position is a surrogate for "infrequent" user/inattention

- 2017 2/8 events
- 2018 1/10 events
- 2019 1/10 events
- 2020 9/13 events

Total 13/41 (32%)

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35.1000 Radioactive Seed Localization

Medical Events Summary

	2018	2019	2020	2021
Total Medical Events	0	1	0	1
Cause:				
Delayed seed removal (patient intervention)	0	1	0	0
Lost seed	0	0	0	0
Wrong implant site	0	0	0	0
Seed migration	0	0	0	1

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35.1000 Intravenous Cardiac Brachytherapy

- **Medical Events Summary**

	2017	2018	2019	2020	Total
Did not follow proper procedure	0	0	1	0	1
Tortuous vessel anatomy	0	1	1*	0	2
Catheter issue	0	1	0	1	2
Total	0	2	2	1	5

*AU felt this is "patient intervention"
No time out issues
Difficult to assess the unfamiliarity issue, but possibly played a role in some

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35.1000 Gamma Knife® Perfexion™ and Icon™

Medical Events Summary

	2017	2018	2019	2020
Total Medical Events	0	1	2	2
Cause:	0	0	0	0
Back-up battery power source failure	0	1	0	0
Patient setup error	0	0	0	1
Patient movement	0	0	2	0
Wrong site (treatment plan)	0	0	0	0
Pt motion management system failure	0	0	0	1

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35.1000 Y-90 Theraspheres

Medical Events Summary

	2017	2018	2019	2020	Total
Total Medical Events	15	14	15	15	59
Cause:					
> 20% residual activity remaining in delivery device	7	11	9	12	39
Delivery device setup error	2	2	1	1	6
Wrong dose (treatment plan calculation error)	4	0	1	0	5
Wrong site (catheter placement error)	2	0	0	2	4
Wrong dose vial selected	0	1	4	0	5

For 2020: Time out 3/15 (20%),
Infrequent/inattention 12/15 (80%)

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35.1000 Y-90 SirSpheres

Medical Events Summary

	2017	2018	2019	2020	Total
Total Medical Events	8	7	11	8	34
Cause:					
> 20% residual activity remaining in delivery device not due to stasis	7	2	8	8	25
Wrong dose (treatment plan calculation error)	0	2	0	0	2
Wrong site (catheter placement error)	1	2	2	0	5
Wrong site (WD error)	0	1	1	0	2

2020: Time out: 0
Infrequent/inattention: 8/8 (100%)

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Actions to Prevent 35.1000 Y-90 Microsphere Medical Events

- Review mechanics of Y-90 microsphere delivery device and setup procedures
- Confirm all data and calculations in treatment plan
- Perform “Time Out” to assure all elements of treatment are in accordance with Written Directive

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Possible Elements of a “Time Out”

- Identity of patient via two identifiers (e.g. name and DOB)
- Procedure to be performed
- Isotope
- Activity
- Dosage –second check of dosage calculation and that the WD and dosage to be delivered are identical
- Others as applicable
  - units of activity (LDR prostate)
  - anatomic location
  - patient name on treatment plan
  - treatment plan independent second check has been performed
  - reference length (HDR)
  - Implant site location (RSL)

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Acronyms

- 10 CFR – Title 10 of the *Code of Federal Regulations*
- AUs – authorized users
- FY – Fiscal Year
- gyn – gynecological
- HDR – high dose-rate
- LDR – low dose rate
- mCi – milliCurie
- ME – Medical Event
- RSL – radioactive seed localization
- Y – Yttrium

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Nuclear Regulatory Commission (NRC)

Advisory Committee on the Medical Uses of Isotopes (ACMUI)

Subcommittee on Medical Events

Subcommittee Final Report

Submitted On: October 4, 2021

Subcommittee Members: Mr. Richard Green, Dr. Ronald D. Ennis (Chair), M.D., Dr. Darlene F. Metter, Mr. Zoubir Ouhib, Mr. Michael Sheetz, Dr. Harvey Wolkov

Charge

The specific charge of this subcommittee is to annually review the medical events (MEs) with an eye to advising the ACMUI and NRC about emerging trends needing regulatory attention.

Background

The subcommittee reviewed medical events from the Fiscal year 2020 as part of its ongoing annual or biennial review.

Findings

The Medical Events during 2020 were similarly low as in years past. This issue regarding time outs and checklists as a method to minimize MEs was again noted. In the committee's discussion regarding the category that it had previously called "infrequent/inexperience use" the point was made that some of these events may be due to inattention at the time of the procedure rather than infrequent or inexperience use. So, this category has been renamed to highlight this ambiguity. The NRC has issued an Information Notice in 2019 advising the user community about these issues.
https://www.nrc.gov/docs/ML1924/ML19240A450.pdf

The concern raised by this subcommittee last year that emerging, more complex, radiopharmaceuticals may lead to an increase in MEs was not seen. There was only one such event in 2020.

MEs involving Y-90 microspheres continue to be the most common, although as a proportion of all such procedures an ME is very rare. The MEs occur with both Therasphere and Sirsphere, although more commonly with Therasphere, despite reportedly equal market share of the two products. Because of this, the subcommittee recommends the appointment of a subcommittee specifically focused on investigating the MEs associated with this therapy and to propose, in consultation with the vendors, methods to decrease these MEs.

Concluding Remarks

The subcommittee looks forward to performing an in-depth trend analysis in 2022.

The subcommittee welcomes any comments and/or suggestions.

Respectfully Submitted,
The Medical Event Subcommittee

Radionuclide Generator Knowledge and Practice Requirements Subcommittee Report

Richard L. Green

Advisory Committee on the Medical Uses of Isotopes

October 4, 2021

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Subcommittee Members

- Vasken Dilsizian, M.D.
- Richard Green (Chair)
- Melissa Martin
- Megan Shober
- Harvey Wolkov, M.D.

- *NRC Staff Resource: Maryann Ayoade*

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Subcommittee Charge

- To review and evaluate the knowledge and practice requirements for eluting, measuring and testing, and processing the eluate from radionuclide generator systems based on the evolution of radionuclide generator distribution.
- To evaluate and determine the appropriateness of the requirements and how best to obtain the required knowledge and practice.

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Subcommittee Charge (cont'd.)

- To evaluate whether and how additional knowledge and practice should be obtained as necessary to supervise the use of ANY radionuclide generator system.
- Provide considerations and recommendations to staff.

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Introduction

In 1994, the NRC amended its commercial distribution of radioactive drugs and medical use regulations in 10 CFR Parts 32 and 35, in part, to allow properly qualified nuclear pharmacists and authorized users who are physicians with greater discretion in preparing radioactive drugs containing byproduct material for medical use.

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Introduction (cont'd.)

The rule, "Preparation, Transfer for Commercial Distribution, and Use of Byproduct Material for Medical Use," resulted in the language presently found in 10 CFR 35.290, "Training for imaging and localization studies." Specifically, 10 CFR 35.290(c)(1)(ii)(G) relative to generators reads:

- "(G) Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs;"

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Background

Over the last 27 years there has been significant change in:

- Types of radionuclide generators used in clinical nuclear medicine practice
- Location where generators are housed and used
- Individuals who handle generators

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Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators

- Prior to 1972, ^{99}Mo/^{99m}Tc generators were ubiquitous and were found in every clinical nuclear medicine facility.
- First CRP opened in 1972 and today there are approximately 300 CRPs in the United States.

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Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators (cont'd.)

- The locations of most ^{99}Mo/^{99m}Tc generators migrated from hospital nuclear medicine departments to CRPs as nuclear medicine facilities converted to patient ready unit doses and utilized the services of CRPs for the provision of radiopharmaceuticals.

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Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators (cont'd.)

- Today approximately 95% of all radiopharmaceuticals used in the United States originate from a CRP.
- As a result of the consolidation of activities, there are fewer ^{99}Mo/^{99m}Tc generators in use today than were used in the past.

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Molybdenum-99/Technetium-99m ($^{99}Mo/^{99m}Tc$) generators (cont'd.)

- It is estimated that the United States utilizes approximately 720 new $^{99}Mo/^{99m}Tc$ generators weekly, with 90% of them (~660) delivered to CRPs for use under the direction of an ANP and 10% of them (~60) delivered to hospital facilities for use under the direction of an AU physician or local ANP.

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Strontium-82/Rubidium-82 ($^{82}Sr/^{82}Rb$) generators

- Because of the 75 second half-life of $^{82}RbCl_2$ used for PET myocardial perfusion imaging, all ^{82}Rb generators are in clinical nuclear medicine facilities for use under the direction of an AU physician.

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Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generators

- It is estimated that currently in the United States, approximately 70% of ^{68}Ge/^{68}Ga generators are delivered to CRPs for use under the direction of an ANP and 30% are delivered to hospital facilities for use under the direction of an AU physician.

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Background (cont'd.)

- The evolution of where radionuclide generators are located has presented challenges for fellows-in-training in residency programs.
- Many residency programs made arrangements with commercial radiopharmacies for their fellows-in-training to attend generator training but due to COVID-19 these radiopharmacies have restricted access to their facilities.

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Background (cont'd.)

- This increased the knowledge and practice burden affecting fellows-in-training who were unable to attend commercial radiopharmacies to receive generator training due to COVID-19 closures of these facilities.

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Background (cont'd.)

- In June 2020, several professional societies (ASNC, SNMMI, ACR, and ASTRO) united to request "that the U.S. NRC consider Title 10 of the Code of Federal Regulations (10 CFR) 35.290(c)(1)(ii)(G), "Training for Imaging and Localization Studies," as a potential area for regulatory relief during the Coronavirus Disease 2019 (COVID-19) PHE".

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Background (cont'd.)

- This letter states that most of the commercial radiopharmacies that supply portions of this training are closed to visiting trainees because of the COVID-19 PHE and may not reopen for the foreseeable future.

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Background cont'd.

- This letter further states that they believe that this experience requirement can be satisfied virtually, via demonstrative educational webinars during the duration of the PHE. ([ADAMS] Accession No. ML20231A931).

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Discussion

The Subcommittee deliberated the intent of the existing Rule language, including:

- The knowledge elements necessary for AU physicians to possess with regard to generator systems
- Various methods of acquiring knowledge of these element

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Discussion (cont'd.)

- The Subcommittee recognizes the AU physician's role, as described in 10 CFR 35.27, in supervising nuclear medicine technologists who may be operating generator systems at clinical sites.
- The Subcommittee believes that AUs, whether or not they personally use radionuclide generators:
  - must be familiar with how generators work
  - how breakthrough is tested
  - how reagent kits are used to label radioactive drugs

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Discussion (cont'd.)

- The Subcommittee also believes that it is not necessary for AU physicians to have direct hands-on work experience with the generators, although the Subcommittee recognizes that direct work experience is an excellent way to fulfill the training requirements.

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Discussion (cont'd.)

- In order to facilitate learning, and to provide training programs flexibility to deliver training, the Subcommittee discussed the strengths and limitations of in-person, pre-recorded, or live virtual training opportunities.

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Discussion (cont'd.)

- The Subcommittee believes that training can incorporate any combination of these methods, but the Subcommittee believes it is essential for the training to include an opportunity for physicians to ask questions about the subject material and receive answers in real time.

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Discussion (cont'd.)

- In addition, it is important for the trainer to be able to assess physician learning as the training is progressing. If pre-recorded material is used to deliver a portion of the training, there should also be a live component (whether in-person or via virtual meeting) where trainees and trainers can directly interact.

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Discussion (cont'd.)

- Consistent with existing regulation, the Subcommittee further believes that it is not necessary to mandate training on every radionuclide generator system. Training programs should have the flexibility to modify the training curriculum as the use of generator systems evolves.

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Conclusion – Subcommittee Recommendation

- Current rule language in 10 CFR 35.290(c)(1)(ii)(G):
  - (G) "Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs; and"
- Subcommittee proposed revision:
  - (G) "Participating in educational sessions to gain knowledge and provide supervision of – (1) radionuclide generator systems and their operation;(2) the measurement of radionuclidic impurities and acceptable limits; and (3) the use of reagent kits with radionuclide eluate to prepare radioactive drugs."

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- ACR – American College of Radiology
- ADAMS - Agencywide Documents Access and Management System
- ANP – Authorized Nuclear Pharmacist
- ASNC – American Society of Nuclear Cardiology
- ASTRO – American Society for Radiation Oncology
- AU – Authorized User
- CFR – Code of Federal Regulations

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Acronyms

- CRP – Centralized Radiopharmacy
- $^{68}Ge/^{68}Ga$ – Germanium-68/Gallium-68
- $^{99}Mo/^{99m}Tc$ – Molybdenum-99/Technetium-99m
- NRC – U.S. Nuclear Regulatory Commission
- PET – Positron Emission Tomography
- PHE – Public Health Emergency
- SNMMI – Society of Nuclear Medicine and Molecular Imaging
- $^{82}Sr/^{82}Rb$ – Strontium-82/Rubidium-82

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U.S Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes

Subcommittee on Radionuclide Generator
Knowledge and Practice Requirements

Draft Report
Submitted on September 8, 2021

Subcommittee Members:
Vasken Dilsizian, M.D.
Richard Green (Chair)
Melissa Martin
Megan Shober
Harvey Wolkov, M.D.

NRC Staff Resource: Maryann Ayoade

Subcommittee Charge:

- To review and evaluate the knowledge and practice requirements for eluting, measuring and testing, and processing the eluate from radionuclide generator systems based on the evolution of radionuclide generator distribution.

- To evaluate and determine the appropriateness of the requirements and how best to obtain the required knowledge and practice.

- To evaluate whether and how additional knowledge and practice should be obtained as necessary to supervise the use of any radionuclide generator system.

- Provide considerations and recommendations to staff.

Background:

In 1994, the NRC amended its commercial distribution of radioactive drugs and medical use regulations in 10 CFR Parts 32 and 35, in part, to allow properly qualified nuclear pharmacists and authorized users who are physicians with greater discretion in preparing radioactive drugs containing byproduct material for medical use. The rule, "Preparation, Transfer for Commercial Distribution, and Use of Byproduct Material for Medical Use," resulted in the language presently found in 10 CFR 35.290, "Training for imaging and localization studies." Specifically, 10 CFR 35.290(c)(1)(ii)(G) relative to generators reads:

> *"(G) Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs;"*

Over the last 27 years, the types of radionuclide generators used in clinical nuclear medicine practice, the location where they are housed and used, and the individuals who handle them have all significantly changed.

Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators

Prior to 1972, ^{99}Mo/^{99m}Tc generators were ubiquitous and were found in every clinical nuclear medicine facility. The first centralized radiopharmacy (CRP) opened in 1972 and today there are approximately 300 centralized radiopharmacies in the United States. Over the course of time, the locations of most ^{99}Mo/^{99m}Tc generators migrated from hospital nuclear medicine departments to CRPs as nuclear medicine facilities converted to patient ready unit doses and utilized the services of CRPs for the provision of radiopharmaceuticals. Today approximately 95% of all radiopharmaceuticals used in the United States originate from a CRP. As a result of the consolidation of activities, there are fewer ^{99}Mo/^{99m}Tc generators in use today than were used in the past. It is estimated that the United States utilizes approximately 720 new ^{99}Mo/^{99m}Tc generators weekly, with 90% of them (~660) delivered to CRPs for use under the direction of an authorized nuclear pharmacist (ANP) and 10% of them (~60) delivered to hospital facilities for use under the direction of an authorized user (AU) physician or local ANP.

Strontium-82/Rubidium-82 (^{82}Sr/^{82}Rb) generators

Because of the 75 second half-life of $^{82}RbCl_2$ used for PET myocardial perfusion imaging, all ^{82}Rb generators are in clinical nuclear medicine facilities for use under the direction of an AU physician.

Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generators

It is estimated that currently in the United States, approximately 70% of ^{68}Ge/^{68}Ga generators are delivered to CRPs for use under the direction of an ANP and 30% are delivered to hospital facilities for use under the direction of an AU physician.

The evolution of where radionuclide generators are located has presented challenges for fellows-in-training in residency programs. Many residency programs had made arrangements with commercial radiopharmacies for their fellows-in-training to attend generator training but due to COVID-19 these radiopharmacies have restricted access to their facilities. This increased the knowledge and practice burden affecting fellows-in-training who were unable to attend commercial radiopharmacies to receive generator training due to COVID-19 closures of these facilities.

In June 2020, several professional societies (American Society of Nuclear Cardiology, Society of Nuclear Medicine and Molecular Imaging, American College of Radiology, and the American Society for Radiation Oncology) united to request “that the U.S. Nuclear Regulatory Commission (NRC) consider Title 10 of the Code of Federal Regulations (10 CFR) 35.290(c)(1)(ii)(G), “Training for Imaging and Localization Studies,” as a potential area for regulatory relief during the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (PHE).” This letter states that most of the commercial radiopharmacies that supply portions of this training are closed to visiting trainees because of the COVID-19 PHE and may not reopen for the foreseeable future. This letter further states that they believe that this experience requirement can be satisfied virtually, via demonstrative educational webinars during the duration of the public health emergency. (Agencywide Documents Access and Management System [ADAMS] Accession No. ML20231A931).

Discussion:

The Subcommittee deliberated the intent of the existing Rule language, the knowledge elements necessary for authorized user physicians to possess with regard to generator systems, and various methods of acquiring knowledge of these elements. The Subcommittee recognizes the authorized user physician's role, as described in 10 CFR 35.27, supervising nuclear medicine technologists who may be operating generator systems at clinical sites. Consequently, the Subcommittee believes that authorized users, whether or not they personally use radionuclide generators, must be familiar with how generators work, how breakthrough is tested, and how reagent kits are used to label radioactive drugs. The Subcommittee also believes that it is not necessary for authorized user physicians to have direct hands-on work experience with the generators, although the Subcommittee recognizes that direct work experience is an excellent way to fulfill the training requirements.

In order to facilitate learning, and to provide training programs flexibility to deliver training, the Subcommittee discussed the strengths and limitations of in-person, pre-recorded, or live virtual training opportunities. The Subcommittee believes that training can incorporate any combination of these methods, but the Subcommittee believes it is essential for the training to include an opportunity for physicians to ask questions about the subject material and receive answers in real time. In addition, it is important for the trainer to be able to assess physician learning as the training is progressing. If pre-recorded material is used to deliver a portion of the training, there should also be a live component (whether in-person or via virtual meeting) where trainees and trainers can directly interact.

Consistent with existing regulation, the Subcommittee further believes that it is not necessary to mandate training on *every* radionuclide generator system. Training programs should have the flexibility to modify the training curriculum as the use of generator systems evolves.

Conclusion – Subcommittee Recommendation:

Current rule language in 10 CFR 35.290(c)(1)(ii)(G):

> *(G) "Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs; …"*

Subcommittee proposed revision:

> *(G) "Participating in educational sessions to gain knowledge and provide supervision of – (1) radionuclide generator systems and their operation; (2) the measurement of radionuclidic impurities and acceptable limits; and (3) the use of reagent kits with radionuclide eluate to prepare radioactive drugs."*

Respectfully Submitted on September 8, 2021
Radionuclide Generator Knowledge and Practice Requirements Subcommittee
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
U.S. Nuclear Regulatory Commission (NRC)

OPEN FORUM

(No Handout)

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics

Hossein Jadvar, MD, PhD, MPH, MBA

Advisory Committee on the Medical Uses of Isotopes

October 4, 2021

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Agenda

- ACMUI Subcommittee Membership
- ACMUI Subcommittee Charge
- Theranostics (Background)
- Theranostics (Emerging Agents)
- Theranostics (Challenges)
- Knowledge Requirements
- Theranostics Room Setup

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Emerging RPT Knowledge Requirements in Theranostics - ACMUI Subcommittee Membership

- Hossein Jadvar, MD, PhD (Nuclear Medicine Physician; Chair)
- Vasken Dilsizian, MD (Nuclear Cardiologist)
- Ronald Ennis, MD (Radiation Oncologist)
- Michael O'Hara, PhD (FDA Representative)
- Zoubir Ouhib (Therapy Medical Physicist)
- Josh Mailman (Patients Rights Advocate)
- Maryann Ayoade (NRC Staff Resource)

3

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ACMUI Subcommittee Charge

- To outline the knowledge and specific or specialized practice or policy requirements needed for the safe use and handling of emerging radiopharmaceuticals in theranostics.
- Provide considerations and recommendations to staff.

4

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Background

- **Definition:** Systemic integration of diagnostic tools (e.g., nuclear imaging) and therapeutic agents (e.g., radiopharmaceuticals) related to the same (or similar*) biomolecular target (or parameter*) →
  - Precision / Personalized Medicine
- **History:** 1941 with treatment of a hyperthyroid patient with radioiodine by Saul Hertz, MD, at Massachusetts General Hospital

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Background (contd.)

- **Current oncologic theranostic agents**
  - ^{123}I/^{131}I (NaI symporter; thyroid)
  - ^{111}In/^{90}Y-ibritumomab (anti-CD20; lymphoma)
  - ^{18}F-NaF/^{99m}Tc-MDP; $^{223}RaCl_2$ (osteoblastic mets; mCRPC)*
  - ^{99m}Tc-MAA; ^{90}Y-microspheres (hyperperfusion; liver tumors)*
  - ^{123}I/^{131}I-MIBG (norepinephrine transporter; pheochromocytoma, paraganglioma)
  - ^{68}Ga/^{64}Cu-DOTATATE, ^{68}Ga-DOTATOC; ^{177}Lu-DOTATATE (SSTR+ neuroendocrine tumors)

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Theranostics (Emerging Agents)

- **Within near future**
  - ^{68}Ga*/^{18}F-PSMA*; ^{177}Lu-PSMA** (mCRPC)

  (*FDA approved; ** FDA approval anticipated)

- **In the horizon**
  - ^{225}Ac/^{227}Th-PSMA (alpha RLT; mCRPC)
  - ^{68}Ga-pentixafor/^{177}Lu-, ^{90}Y-pentixather (chemokine receptor 4; multiple myeloma)
  - ^{68}Ga/^{177}Lu-NeoB (GRPR; solid tumors)
  - ^{68}Ga/^{177}Lu-FAPI (fibroblast activation protein; multiple cancers)

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Theranostics (Emerging Agents) (contd.)

- **In the horizon (contd.)**
  - ^{89}Zr/^{177}Lu-girentuximab (carbonic anhydrase IX; clear cell RCC)
  - ^{68}Ga/^{177}Lu-FF58 (integrin $\alpha_3\beta_5$; GBM)
  - ^{18}F/^{131}I-PARPi (DNA repair enzyme Poly-(ADP ribose) polymerase 1; multiple cancers)

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Theranostics (Challenges)

- **Technical**
  - Interdisciplinary teams
  - Standardized protocols
  - Radionuclide pipeline / supply chain
- **Economic**
  - Comparative cost; cost-utility
  - Reimbursement
  - R&D funding

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Theranostics (Challenges) (contd.)

- **Biomedical**
  - Basic science, pre-clinical, first-in-human, and large prospective clinical trials
  - Single, tandem, combination therapies
  - New applications

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Emerging RPT Knowledge Requirements in Theranostics

- Make up of the healthcare team at the time of administration
  - Depending upon the therapy, the team administering the dose may consist of – AU with appropriate training in theranostics, CNMT, RSO, Registered Nurse, and Medical Physicist (if available/applicable)
- AU must be present at the time of dose administration

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Emerging RPT Knowledge Requirements in Theranostics (contd.)

- Therapy should be done in a dedicated and regulatory-approved room appropriate for radioisotope administrations
- Non-radiation workers (e.g., oncology nurse) participating in the procedure may need to wear a radiation badge as determined by the RSO

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Emerging RPT Knowledge Requirements in Theranostics (contd.)

- Extravasation; patient release criteria (addressed by other ACMUI subcommittees)
- Radioactive waste management (refer to the facility established guidelines and regulations)
- The AU is responsible for patient concerns related to RPT, including radiation induced injuries
- Ensure that emerging theranostics are within the regulatory guidelines

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Emerging RPT Knowledge Requirements in Theranostics (contd.)

- AU is encouraged to avail themselves of all the newest training information for each new theranostics as they emerge
- Patient specific dosimetry may play an important role; as relevant data becomes mature, AUs should stay abreast of developments
- Outreach to promote accurate information about safety and efficacy of theranostics

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Theranostics Room Setup

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Acronyms

- ACMUI: Advisory Committee on the Medical Uses of Isotopes
- AU: Authorized User
- CNMT: Certified Nuclear Medicine Technologist
- FDA: Food and Drug Administration
- R&D: Research and Development
- RPT: Radiopharmaceutical Therapy
- RSO: Radiation Safety Officer

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U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes

Subcommittee on Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics

Draft Report
Submitted on September 20, 2021

Subcommittee Members:
Vasken Dilsizian, M.D.
Ronald Ennis, M.D.
Hossein Jadvar, M.D., PhD (Chair)
Josh Mailman
Michael O'Hara, PhD
Zoubir Ouhib

NRC Staff Resource: Maryann Ayoade

Subcommittee Charge:

The Subcommittee was formed in May 2021, by Dr. Darlene Metter, Chair of the Advisory Committee on the Medical Uses of Isotopes (ACMUI) to:

- To outline the knowledge and specific or specialized practice or policy requirements needed for the safe use and handling of emerging radiopharmaceuticals in theranostics.

- Provide considerations and recommendations to staff.

The Subcommittee reviewed the relevant literature (see reference section) and met virtually four times in July and August 2021 to discuss the charge and propose several considerations in consultation with the NRC staff.

Introduction:

Theranostics is the systemic integration of diagnostic tools (e.g., nuclear imaging) and therapeutic agents (e.g., radiopharmaceuticals) targeted to the same (or similar*) biomolecule (or physiologic parameter*). This concept is the fundamental foundation for precision medicine that has advanced considerably in view of our enhanced understanding of biology, developments in diagnostic technologies, and expansion of therapeutic options. Precision (or personalized) medicine is hoped to improve patient outcome. While theranostics may be applied to a variety of diseases, cancer has been the primary focus in this field (1-4).

Theranostics is a recent term, but it has long been a major player in the history of nuclear medicine, and the list and interest in use of theranostics have been increasing. Early example of theranostics dates back to 1941 when Dr. Saul Hertz from Massachusetts General Hospital, in Boston, MA, treated a patient with Graves' disease realizing that radioiodine can target the thyroid tissue based on the basic knowledge that thyroid gland concentrates iodine.

The list below are the currently clinically available theranostics imaging-therapy companion agents, with the biological and disease targets shown in the parenthesis:

- ^{123}I/^{131}I (NaI symporter; thyroid)
- ^{111}In-/^{90}Y-ibritumomab (anti-CD20; lymphoma)
- ^{18}F-NaF/^{99m}Tc-MDP; $^{223}RaCl_2$ (osteoblastic metastasis; mCRPC)*
- ^{99m}Tc-MAA; ^{90}Y-microspheres (hyperperfusion; liver tumors)*
- ^{123}I-/^{131}I-MIBG (norepinephrine transporter; pheochromocytoma, paraganglioma)
- ^{68}Ga-/^{64}Cu-DOTATATE, ^{68}Ga-DOTATOC; ^{177}Lu-DOTATATE (SSTR+ neuroendocrine tumors

NaI=sodium iodide, CD20=cluster of differentiate 20, mCRPC=metastatic castration-resistant prostate cancer, NaF=sodium fluoride, MAA=macroaggregated albumin, MDP=methyl diphosphonate, MIBG=meta-iodobenzylguanidine, DOTA= 1,4,7,10-tetraazacyclododecane-N,N',N",N""-tetraacetic acid, DOTATOC=DOTA-d-Phe1-Tyr3-octreotide, DOTATATE= DOTA-DPhe1,Tyr3-octreotate

In the near future, theranostics based on prostate specific membrane antigen (PSMA) will be available clinically for the imaging evaluation of prostate cancer (initial staging, biochemical recurrence) and radioligand therapy of metastatic castration-resistant prostate cancer. The imaging agents ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (Pylarify^{TM}) were approved by the FDA in December 2020 and May 2021, respectively. The favorable results of the randomized phase III VISION clinical trial on the therapy companion – ^{177}Lu-PSMA-617 – has recently been published in the New England Journal of Medicine facilitating an anticipated FDA approval within Q1 of 2022 (5).

Additional theranostics pairs are in the horizon within the next 7 years. These include the following companion agents with the biological and disease targets shown in the parenthesis:

- ^{225}Ac-/^{227}Th-PSMA (alpha RLT; mCRPC)
- ^{68}Ga-pentixafor/^{177}Lu-, ^{90}Y-pentixather (chemokine receptor 4; multiple myeloma)
- ^{68}Ga-/^{177}Lu-NeoB (GRPR; solid tumors)
- ^{68}Ga-/^{177}Lu-FAPI (fibroblast activation protein; multiple cancers)
- ^{89}Zr-/^{177}Lu-girentuximab (carbonic anhydrase IX; clear cell RCC)
- ^{68}Ga-/^{177}Lu-FF58 (integrin a_3b_5; GBM)
- ^{18}F-/^{131}I-PARPi (DNA repair enzyme Poly-(ADP ribose) polymerase 1; multiple cancers)

RLT=radioligand therapy, GRPR=gastrin-releasing peptide receptor, FAPI=fibroblast activated protein inhibitor, RCC=renal cell carcinoma, GBM=glioblastoma multiforme

Challenges:

Despite being a rapidly developing field, theranostics faces several challenges that will need to be addressed adequately in order for it to be fully integrated into clinical medicine (3).

- Technical Challenges:
  Need for standardized and efficient protocols; formation of interdisciplinary teams; incorporation into clinical guidelines; education and training.

- Economic challenges:
  Investment into supporting the supply chain for a steady pipeline of radioisotopes relevant to theranostics; sufficient reimbursement; comparative cost-utility analysis; Research and Development funding.

- Biomedical Challenges:
  Additional basic science, pre-clinical, first-in-human, and large prospective clinical trials; evaluation of single, tandem, and combination therapies; development of new applications in oncology and non-oncology arenas.

Subcommittee Specific Comments:

1) Radiopharmaceutical (RPT) Healthcare Team:
   Depending upon the therapy, the healthcare team administrating the RPT dose may consist of the Authorized User (AU) with appropriate training in theranostics, Certified Nuclear Medicine Technologist (CNMT), Registered Nurse, Radiation Safety Officer (RSO), and Medical Physicist (if available/applicable).

2) Authorized User responsibilities:
   AU must be present at the time of dose administration; AU is responsible for patient concerns related to RPT, including radiation induced injuries; AU is encouraged to avail themselves of all the latest training information for each new theranostics as they emerge.

3) Radiation safety issues:
   Non-radiation workers of the healthcare team (e.g. oncology nurse) participating in the procedure may need to wear radiation badges for monitoring as determined by the RSO; therapy should be done in a dedicated and regulatory-approved room appropriate for radioisotope administrations (see Fig. 1); extravasation; patient release criteria (these issues are addressed by other ACMUI subcommittees).

4) Regulatory issues:
   Radioactive waste management (refer to the facility established guidelines and regulations); ensure that emerging theranostics are performed within the regulatory guidelines.

5) Dosimetry:
   Dosimetry-based (as opposed to fixed-activity) may play an increasingly important role (6-10); dosimetry-based approach may optimize patient outcome while minimizing

radiation toxicity; no randomized controlled trials to provide level 1 evidence for benefits of dosimetry-based approach; research is needed on impact of combined other nonradioactive therapy agents on RPT biodistribution and radiosensitivity, standardization across clinics, software and medical physicists, development of robust methodology for challenges of surrogate-imaging, microscale radiation effect and daughter distribution (relevant for alpha particles), and research on potential patient benefit versus cost and complexity of logistics; as relevant data becomes mature, AUs should stay abreast of developments in dosimetry.

6) Other relevant issues:
Outreach to AUs, healthcare providers, and patients to promote accurate information about safety and efficacy of theranostics (11).

Fig. 1. An illustrative example of a Radiopharmaceutical Therapy clinic room; an attached bathroom is to the left of the picture (not shown).

References:

(1) Jadvar H, et al. Radiotheranostics in Cancer Diagnosis and Management. Radiology 2018; 286:388-400.
(2) Turner JH, et al. An Introduction to the Clinical Practice of Theranostics in Oncology. Br J Radiol 2018; 91:20180440.
(3) Herrmann K, et al. Radiotheranostics: A Roadmap for Future Development. Lancet Oncol 2020; 21:e146-e156.
(4) Gomes Marin JF, et al. Theranostics in nuclear medicine: Emerging and Re-emerging Integrated Imaging and Therapies in the Era of Precision Oncology. Radiographics 2020; 40:1715-1740.
(5) Sartor O, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2021; 385:1091-1103.
(6) Sgouros G, et al. Dosimetry for Radiopharmaceutical Therapy. Semin Nucl Med 2014; 44:172-178.
(7) Lassmann M, et al. The Relevance of Dosimetry in Precision Medicine. J Nucl Med 2018; 59:1494-1499.
(8) Divgi C, et al. Overcoming Barriers to Radiopharmaceutical Therapy (RPT): and Overview from the NRG-NCI Working Group on Dosimetry of Radiopharmaceutical Therapy. Int J Radiat Biol 2021; 109:905-912.
(9) Roncali E et al. Overview of the First NRG Oncology-National Cancer Institute Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy. J Nucl Med 2021; 62:1133-1139.
(10) SNMMI ^{177}Lu Dosimetry Challenge 2021. J Nucl Med 2021; 62:10N.
(11) SNMMI Theranostics Video: https://www.youtube.com/watch?v=Bb8Ts5HWS40

Respectfully Submitted on September 20, 2021
Emerging RPT Knowledge Requirements in Theranostics Subcommittee
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
U.S. Nuclear Regulatory Commission (NRC)

FUTURE OF PERSONALIZED DOSIMETRY: AAPM PERSPECTIVE

Robert F Hobbs, Johns Hopkins

ACMUI, October 4th 2021

1

OUTLINE

1. Principles of Prospective Personalized Treatment Planning for RPT
2. Examples
3. Roadblocks
4. Bio-effect Modeling
5. Combination Therapies
6. alpha-particle RPT

2

1. RPT STANDARD TREATMENTS

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi I-131 mIBG for neuroendocrine tumours
- 200 mCi x 4 for Y-90 DOTATATE of neuroendocrine tumours
- 200 mCi x 4 for Lu-177 DOTATATE for neuroendocrine tumours
- 200 mCi x 4 for Lu-177 PSMA for bone metastases
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Credit: G. Flux Royal Marsden. EANM '18
J. Capala NCI Theranostics '18

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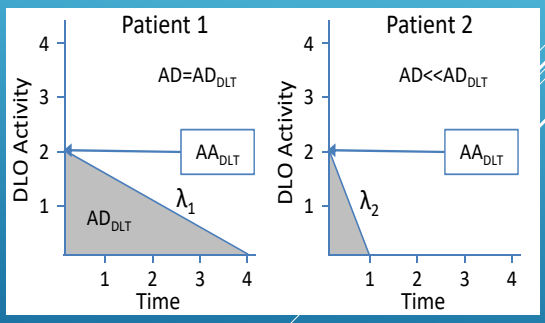
NORMAL ORGAN AD-BASED TREATMENT PLANNING FOR RPT

Standard is the chemotherapy paradigm of dose escalation

AA limit is set by patients with maximum retention

BUT great inter-patient variability – Xbeam is limited by NO toxicity

RPT is radiation just as Xbeam



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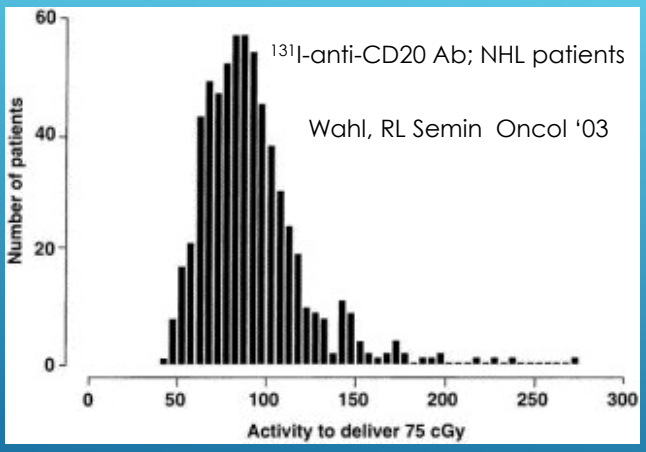
Admin Activity (AA) vs Abs Dose



Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

Increasing database shows consistent large disparities in NO dose up to an order of magnitude – current state of dosimetry

5

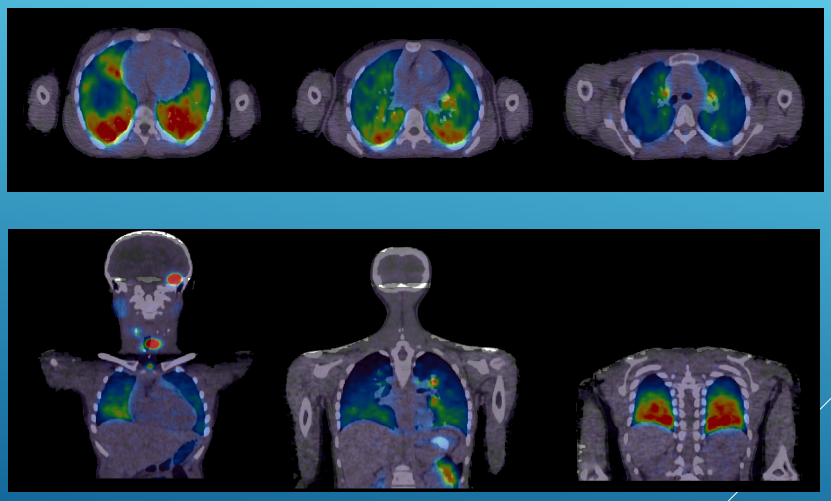
2. PEDIATRIC THYROID CANCER PATIENT: REAL-TIME TREATMENT PLANNING

- Real time (1 week) ^{131}I treatment planning for an 11 year-old girl with metastatic differentiated papillary thyroid cancer using 3D-RD.
- Heavy lung involvement meant concern about pulmonary toxicity and concern for overdosing
- Used ^{124}I and PET/CT for dosimetric assessment - Whole body PET/CT scans were performed at 1, 24, 48, 72, and 96 h

Hobbs *et al.* JNM '09

6

^{124}I PET/CT IMAGE (24 H)



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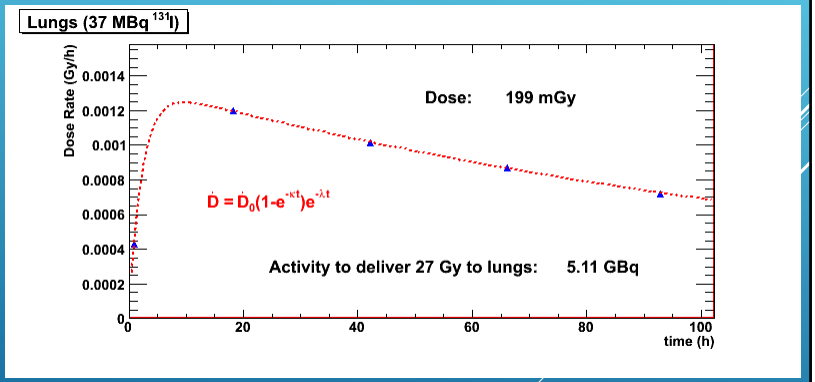
3D-RD ESTIMATION

- Activity converted to I-131
- Monte Carlo for each time point
- Plot dose rate in lungs
- Functional Fit
- Integrate for absorbed dose
- Scale to 27 Gy [a]
- **AA: 5.1 GBq**



[a] Press *et al.* N Eng J Med '93

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2. CONCLUSIONS

Feasibility of real time treatment planning using 3D-RD, patient-specific dosimetry.

A higher recommended AA (60 % more) than by an S-value based method (with a highly favorable clinical outcome) was obtained.

Re-visitation of methods led to convergence –

QA: do both methods (much misunderstanding about relative merits of MIRD (absorbed fraction) versus voxelized dosimetry

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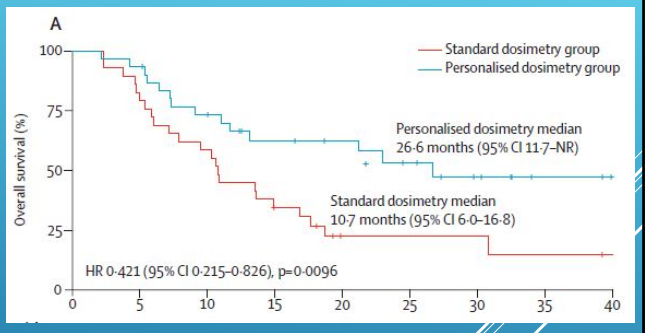
MICROSPHERES

Increased survival in Y-90 microspheres treated using combination of Normal Organ toxicity threshold (120 Gy) and lesion dosimetry objectives (min 205 Gy, max 250 Gy) **using pre-therapeutic Tc99m-MAA dosimetry**



AAA (Lu-177-DOTATATE) will not sell doses of greater than 200 mCi

Garin et al, Lancet Gastroenterol Hepatol 2020

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3. ROADBLOCKS

- Huge interest of companies, Nuke Med physicians, but still reluctant to use dosimetry.
- A large fraction of nuclear medicine physicians, med oncs do not understand the point of dosimetry
- **Standardization** and QA
- Lack of qualified physicians and physicists
- Reimbursement
- **lack of understanding of importance of RPT historically. New Grant for ^{90}Y-microspheres using Tc99m-MAA as surrogate – first submitted in 2011!**

Mantra is that the onus is on dosimetry to prove it is necessary for each and every modality

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REASONS FOR HOPE

Interest by Radiation Oncology, who understand dosimetry, therapy, uncertainty analysis, dose reporting and QA

SNMMI have engaged in a number of projects: Challenge, Registry, Education..

NCI proposes many RPT-based initiatives (often led by Med Oncs..)

Imaging software companies providing software to make dosimetry more accessible

NCI, ICRU, IAEA, ASTRO, MIRD, SNMMI advocate dosimetry-based treatment planning

Education of physicians and physicists Standardization and QA – AAPM, NIST, IROC

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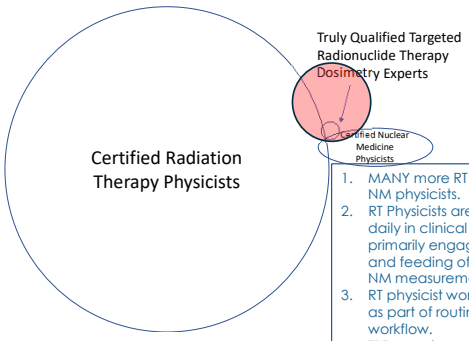
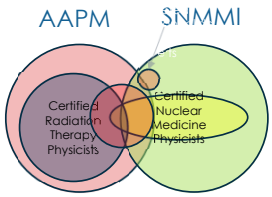
Education Expertise

Distribution and Overlap of Specialty Certified Medical Physicists ***AND*** Actually Qualified TRT Dosimetry Physicists



1. MANY more RT physicists than NM physicists.
2. RT Physicists are engaged daily in clinical workflow, NM primarily engaged in care and feeding of imaging and NM measurement equipment
3. RT physicist work **reimbursed** as part of routine clinical workflow.
4. TRT experienced physicists are currently operating in a niche specialty.

Professional Society Home for Physicists



1. AAPM is primary home to RT Physicists
2. SNMMI is primary home to NM Physicists.
3. TRT Dosimetry physicists primarily (not exclusively) are SNMMI members (MIRD, RADAR).

Credit: J. Sunderland U Iowa. SNMMI/NCI Theranostics '18

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COLLABORATION/COOPERATION ?

ASTRO/SNMMI met several times at leadership level to propose collaboration and recognized complementary expertise

Pathway of Care document was breaking point, has become more of a turf war

AAPM oversees all Medical physicists, both Nuclear Medicine and Radiation Oncology (ABR Nuclear Medicine and Radiation Therapy). Neither are ideally suited for RPT, given current training requirements. Further education for retrospective training is needed in both fields and Integrating RPT-specific training in current curricula is necessary for prospective MPs. (SNMMI also has ABNM certification).

ACR_AAPM_SNMMI Technical Standards document is case in point

Nuke Med uses technologists for administrations, concern over lack of physicists and push to ue technologist/physician combo for dosimetry as well

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AAPM EFFORTS

AAPM has RPT sub-committee under Therapy Physics (since March) and a Nuclear Medicine sub-committee under Imaging Physics. Collaboration as been mediocre. Decision was to form a separate committee given the large interest in the field. Grid strategy.

TG proposals: Y-90 microsphere dosimetry update to TG144, Lu-177 dosimetry (with SNMMI, EANM, NCI), dose calibrator standardization and traceability of standards (EPC, NIST).

WG proposals: I-131 therapies (TGs to follow), Alpha-RPT, radioactive microspheres.

MPPG: Y-90 microsphere utilization, (RPT to follow)

Education: proposal of Summer School 2023, RPT Track at annual meeting, collaborations with SNMMI and ASTRO annual meetings

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MPPG/TG ON Y-90 MICROSPHERES

Non-standardization of dosimetry – modality has evolved separately from RPT, such that nomenclature, formalism are modality-specific, very confused and confusing.

Activity specification is not very precise – within 10 %, pushing for 5 %.

Lung shunt fraction is non-uniform and generally not very precise; Tc99m site not necessarily correlating with microsphere administration .

Thresholds for toxicity really not known.

Segmentectomy prescription uses lobar dosimetry as workaround.

Relative dosimetry is used, but rarely validated – pushing for post-therapy imaging for QA check a la brachytherapy

Precision of voxelized dosimetry poorly understood

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4. RADIOBIOLOGY OR BIO-EFFECT MODELING

Many modifiers of Biological Response:

- Repair – single/double strand DNA breaks, different types of repair. Different types of damage direct vs. indirect damage. **Affected by dose rate**.
- Reassortment – sensitivity depending on the life cycle of the cell. Different types of cell death.
- Reoxygenation – more oxygen has potential for free radicals. Hypoxic versus normoxic cells,
- Repopulation – tumor cell proliferation

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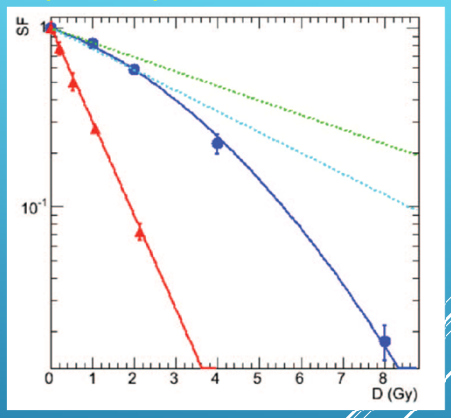
BIOLOGICAL EFFECTIVE DOSE (BED)

Nomenclature from shape of surviving fraction of cells from single bolus of radiation on a log-linear plot (blue line)

$$SF = e^{-\alpha D - \beta D^2}$$

Different dose rates give different responses – standardize/normalize dose (account for/eliminate dose rate effect) - green line

$$e^{-\alpha BED} = e^{-\alpha D - \beta D^2}$$



Equivalent linear dose compared to the linear-quadratic absorbed dose with a repair term [a]

Effectively Accounts for dose rate variations

For exponential decay, G is given by:

$$G(\infty) = \frac{\lambda}{\lambda + \mu}$$

$$BED = D\left(1 + \frac{G(\infty)}{\alpha/\beta} D\right)$$

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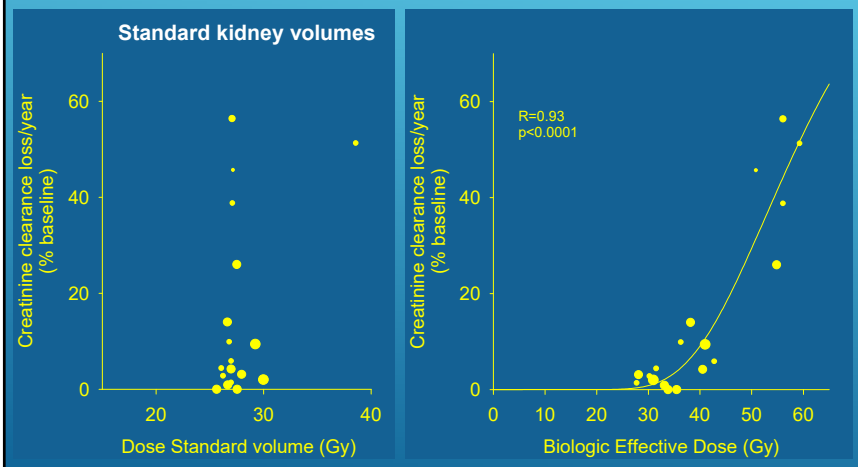
BED for Normal Organ Correlation with Toxicity

Correlation between kidney dose (Gy) and creatinine clearance loss/year (% baseline) N=18



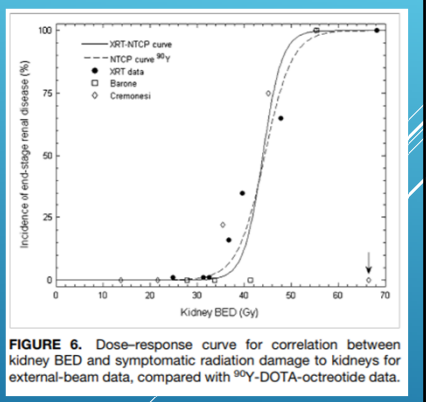


FIGURE 6. Dose–response curve for correlation between kidney BED and symptomatic radiation damage to kidneys for external-beam data, compared with ^{90}Y-DOTA-octreotide data.

Barone *et al*, JNM 2005

MIRD Pamphlet 20, Wessels *et al*. J Nucl Med '08

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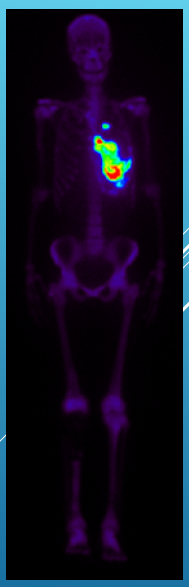
5. COMBINED ^{153}SM-EDTMP RPT WITH EBRT

Chelate is bone seeking calcium mimetic – treat pediatric metastatic osteosarcoma

- EBRT can deliver precise amounts of radiation dose to tumors but limited by adjacent normal tissues (e.g. spinal cord)
- RPT delivers radiation dose to all tumor sites including micro-metastases very conformal but can not escalate radiation dose to tumor limit and treats systemic disease, limited by uptake in normal organs



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RPT-EBRT AD EQUIVALENCE

- AD from EBRT fractionated
- AD from RPT over time
- What about biological equivalence?
- Use BED as a bridge
- Equivalence depends on dose per fraction, *d*

RPT

$$BED_i = D_i\left(1+\frac{D_i}{\alpha_i/\beta_i}\cdot G_i(\infty)\right)$$

EBRT

$$BED_i = D_i\left(1+\frac{d}{\alpha_i/\beta_i}\right)$$

$$EQD2 = \frac{D_{RPT}\left(\alpha/\beta + D_{RPT}\cdot G_i(\infty)\right)}{\alpha/\beta + 2}$$

Bodey *et al.* Cancer Biother Radiopharm '03
Bodey *et al.* IJROBP '04

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PROCEDURE (2013-2016)

a. Stem cell collection for autologous transplant
b. CTsim used for both EBRT and RPT treatment planning
c. Low dose ^{153}Sm-EDTMP (1 mCi/kg)
d. SPECT/CT imaging at 4, 24 and 48 h, image reconstruction and combined EBRT-RPT treatment plan.
e. High dose ^{153}Sm-EDTMP determined from plan (max 20 mCi/kg)
f. High dose imaging at 4, 24 and 48 h (dead-time correction), image reconstruction and EBRT plan adjustments
g. IMRT (SBRT) treatment
h. Autologous stem cell transplant when permissible from bone marrow absorbed dose (recovery)

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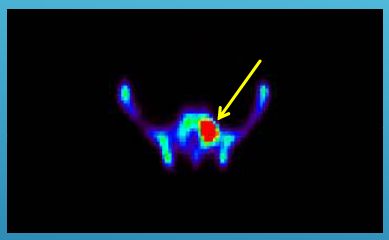
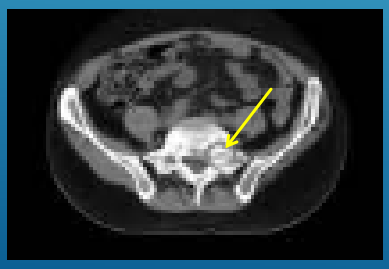
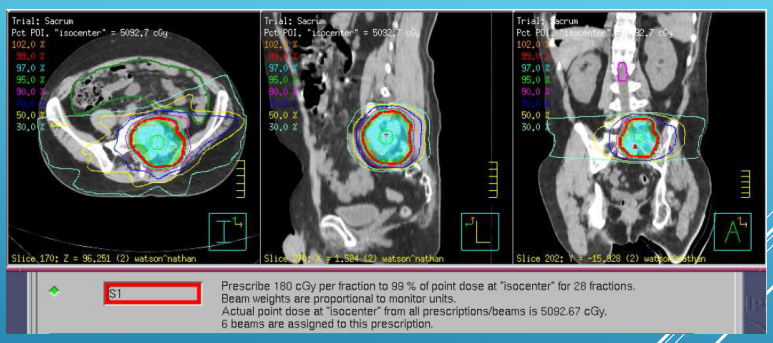
EBRT - Treatment plan







Pelvic Tumor

50.9 Gy (EBRT)
19.9 Gy (RPT)

Spinal cord

46 Gy (EBRT)
2.4 Gy (RPT)

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EBRT-RPT CONCLUSIONS

- The created treatment planning protocol combining RPT and EBRT for metastatic osteosarcoma in pediatric patients showed potential. Targeted tumors received a prescribed tumoricidal absorbed dose (> 70 Gy) due to the RPT boost

- Not a clinical success. Only 4 patients treated, diseases were not stayed. Choice of tumors and location, can't treat the tumors around the trachea/heart/major vessels, which were life threatening and were the cause of death. In future be more selective of the patients and tumor location and burden. Need to combine with chemotherapy.

- **Importance of standardized dose from bio-effect modeling general poorly understood in RPT. Often EBRT MTDs are used without converting, AD is cumulated over fractions regardless of kinetics, non-standard bio-effect modeling even less understood (Y-90 microsphere BED, e.g.)**

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5. COMBINATION ^{131}I-TOSITUMOMAB AND ^{90}Y-IBRITUMOMAB TIUXETAN

Different isotopes have different emission characteristics, idealized for different range of metastatic tumor sizes

Normal organ toxicities may be orthogonal – increase activity and dose. Application to myeloablative Bexxar and Zevalin therapy of lymphoma

Hobbs *et al.* JNM '13

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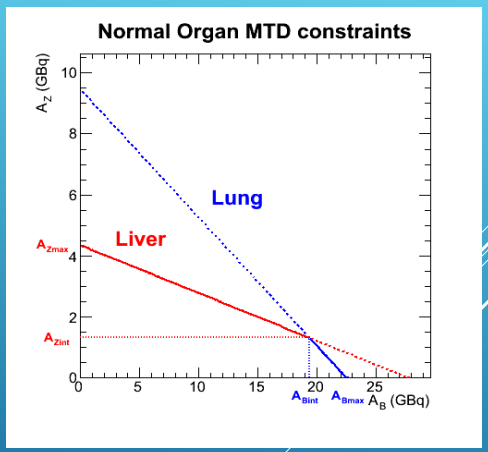
COMBINING NORMAL ORGAN MTDS

At myeloablative regimes, ^{131}I-tositumomab is limited by lung toxicity, ^{90}Y is limited by liver. [a]

Measure kinetics in patient and establish $d_{i,j}$, solve for A_B.

$$\begin{cases} MTD_{lu} = A_Z d_{Z,lu} + A_B d_{B,lu} \\ MTD_{li} = A_Z d_{Z,li} + A_B d_{B,li} \end{cases}$$



Madsen *et al.* J Nucl Med '06
[a] Song et al. J Nucl Med '07
[a] Wiseman et al. Eur J Nucl Med '00

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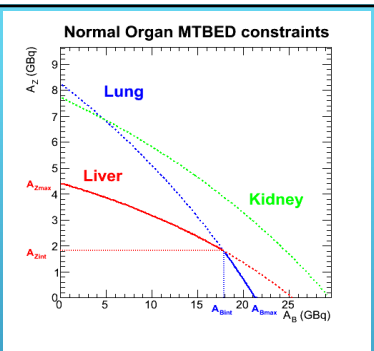
OPTIMIZE TO NO/TUMOR BED

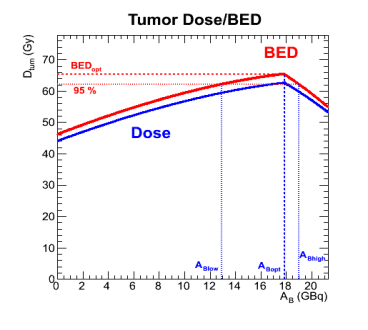
Intersection is MTBED to both organs (30 Gy for lungs, 35 Gy for liver)

Kinetics from patient data

BUT target is tumor, not Normal Organs. Tumor BED as a function of AB

Company withdrew support because of dosimetry





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CONSIDERATIONS FOR RPT ?

Where are Bexxar and Zevalin now ? Dosimetry is often blamed (Bexxar had basic dosimetry, but Zevalin did not). **Territorialism (oncologists vs. nuclear medicine), lack of support by drug companies for personalized quantitative medicine**

Is this relevant to current situation ? **Fixed activity at fractionated regimens for class-based therapies from chemo are still the norm. Dosimetry is being forced to adapt to this paradigm (single/reduced time point dosimetry) rather than leading changed to personalized reduced fraction/single fraction therapy.**

Compromise on precision of dosimetry leads to poor correlations, cannot be used for personalized dosimetry-based treatment planning – consider ATA recommendations in 2006 based on non-standardized dosimetry.

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SINGLE TIME POINT DOSIMETRY

Driven by a desire to reduce cost and patient inconvenience

Chemo paradigm: Dosimetry is primarily retrospective and toxicity is determined empirically. Driven by multi-fraction paradigm.

Studies are optimized for a single organ. Best results assume mono-exponential fits.

For single modality compromise between organs/tumor best times. Uncertainty is given as 10 %, but that is mean uncertainty, individual uncertainty is 2-3 times higher.

Compromise is to have no information on kinetics, so uncertainty on BED is ??? Cumulative AD is typically used instead of cumulated BED. What would Barone result look like ?

Decades of EBRT show the need and benefits for high precision in radiation therapy. Cost and inconvenience should be measured against EBRT (5-8 weeks of daily therapy) rather than nuclear medicine diagnostic procedures.

Highly precise multi-time point pre-therapeutic dosimetry could lead to reduction in number of fraction for safer, more effective, less inconvenient and less expensive therapies.

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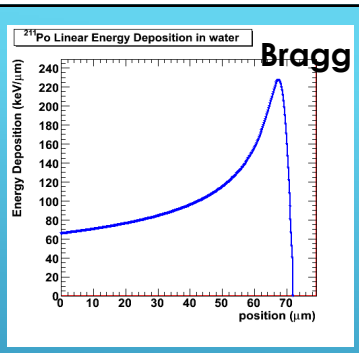
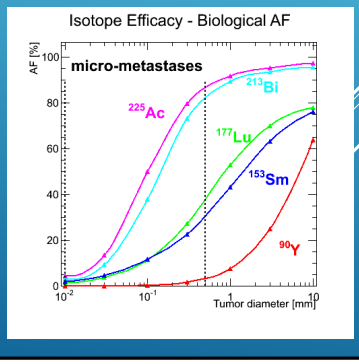
6. α-PARTICLE THERAPY

Massive particles, He nuclei (~ 8000 times electron), deposit greater energy - high Linear Energy Transfer (LET) and RBE

Very short range – 50 –100 microns for 5 -10 MeV alphas ideal for micrometastases



Bragg peak



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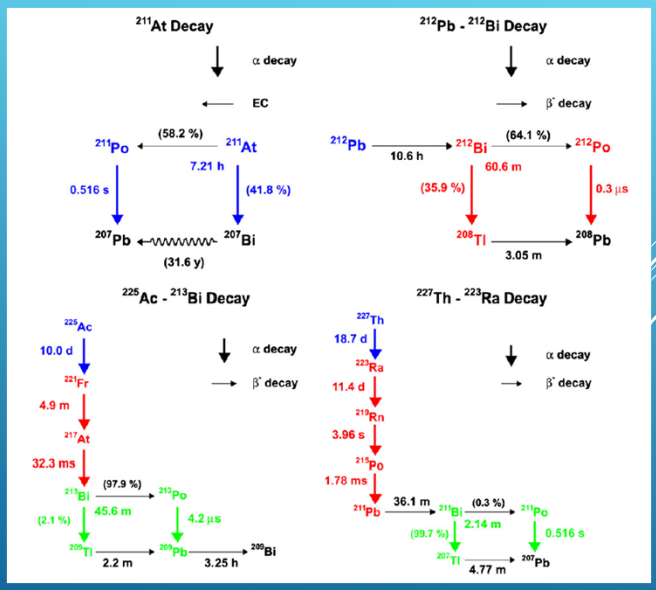
Which α-particles for RPT ?

Currently only Ra-223 is FDA-approved

Clinical trials and pre-clinical studies with:

- Pb-212
- At-211
- Ac-225 (has been used with peptides and PSMA)
- Th-227
- Bi-213



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αRPT used in NET

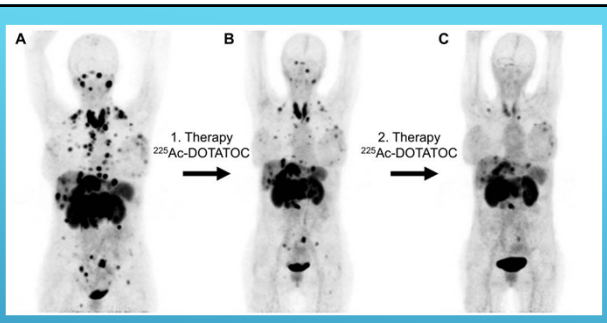
Remarkable results with Ac-225-peptide sometimes after unsuccessful Lu-177-peptide

(N.B. Bi-213 peptides also used)

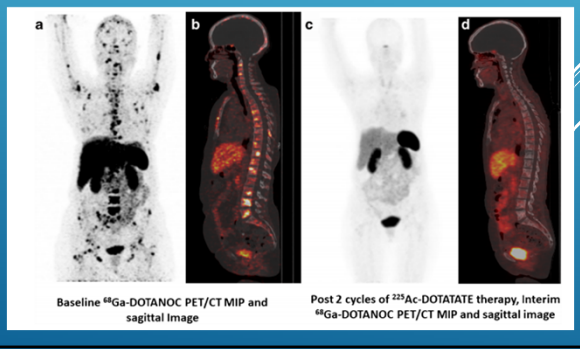
2 questions:

- **why is this not ubiquitous ?**
- **why is this working at all ?**

Ballal *et al.* EJNMMI '20



Kratochwil *et al.* Curr Radiopharm '18
Kratochwil *et al.* EJNMMI '15



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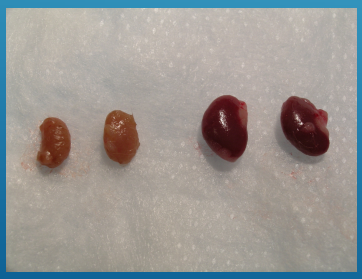
CAN WE USE RPT DOSIMETRY FOR ALPHAS ?

^{225}Ac-7.16.4 treatment of pulmonary metastases from breast cancer

Murine tail vein injection, 10^5 NT2 cells, lung metastasis, 5 wks, 100%. [a]

Therapy: effective BUT renal toxicity despite "low" dose [b]

Calculated 2+ Gy to kidneys (typical toxicity thresholds ~40 Gy BED)



[a] Song *et al.* Clin Cancer Res '08
[b] Song *et al.* Cancer Res '09

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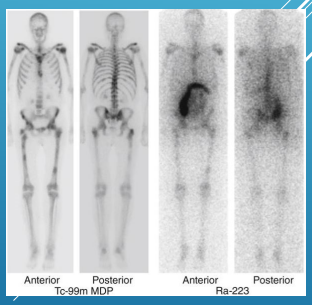
ALPHA-PARTICLE DOSIMETRY

Can we apply RPT dosimetry paradigms to αRPT?

4 Challenges:

1. RBE (standardization, variability of parametrization) value of ~5, but could vary
2. sub-organ localization of activity – short range means higher dose concentration
3. re-localization of daughters (^{225}Ac chain has 4 α-emissions, with ^{213}Bi 45 min HL)
4. low count rate for imaging (typical therapeutic activity is 100 μCi – few mCi)



Carrasquillo *et al.* EJNMMI'13

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RBE

RBE definition:

$$RBE = \left.\frac{D_L}{D_H}\right|_{SF}$$

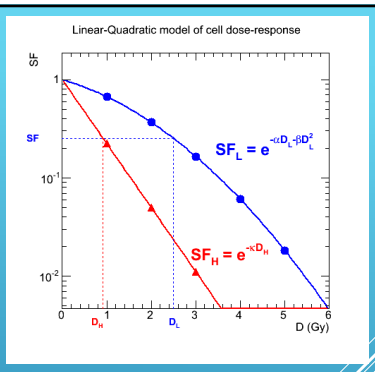
EQD2 reference dose [a]

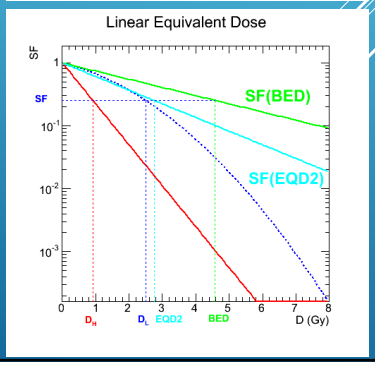
$$EQDX = D_L \frac{\alpha_L + \beta_L d_L}{\alpha_L + \beta_L X}$$

Ratio is now called RBE2 [b]:

$$RBE\,2 = \frac{\kappa}{\alpha_L + 2\beta_L}$$

[a] Bentzen *et al.* Radiother Oncol '12
[b] Hobbs *et al.* Radiation Res '14





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APPLICATION

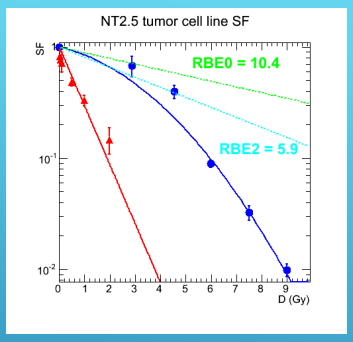
2 different cell lines:

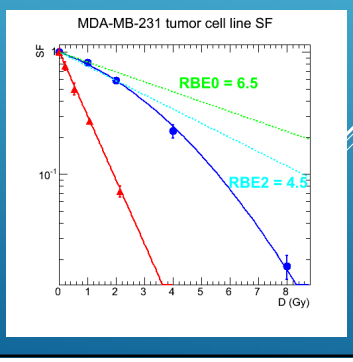
- murine breast cancer: NT2.5 (RBE = 2.4 -9.0, RBE2 = 5.9)
- human breast cancer: MDA-MB-231 (RBE = 2.4 – 6.0, RBE2 = 4.5)

Report raw data as well as derived quantities !

Remaining variability reflect true biological effect

Hobbs *et al.* Radiation Res '14





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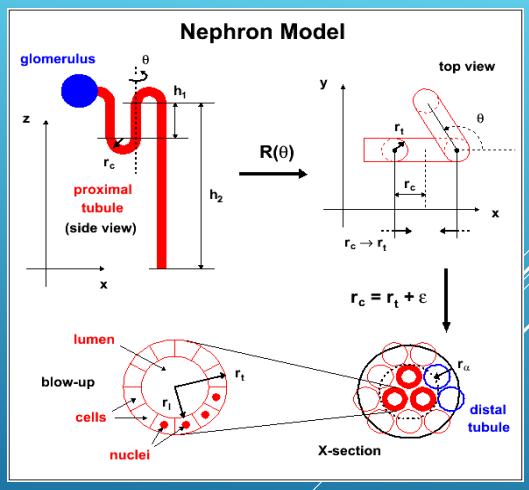
MIRD MODEL AT SMALL SCALE - NEPHRON MODEL

Use simple geometrical shapes (spheres, toroids cylinders) for S-values

1. Fold tubules to simulate proximity
2. Discriminate between tubule cells (simple cuboidal epithelials) and lumina
3. Consider range of α's and ratios of proximal/distal neighbors
4. Parameterize from ex vivo data/cadavers



Hobbs *et al.* Phys Med Biol '12

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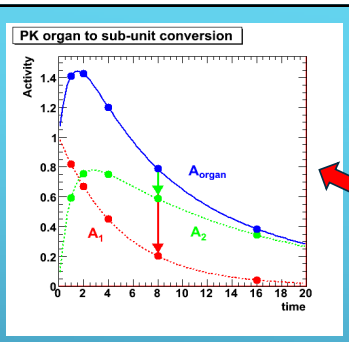
MACRO TO MICRO CONVERSION

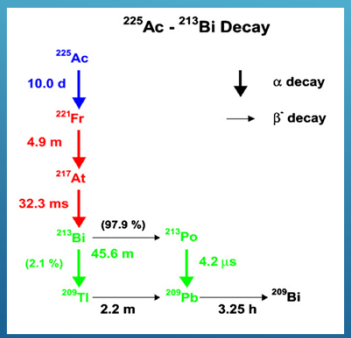
Measure (isotope) activity conc $a_{ij}(t)$ in compartments AND whole organ

Multiply by fraction of occupancy f_i to apportion fraction of activity g_i to compartments

Free ^{213}Bi

Human translation





$$A_i = g(SC) \cdot \tilde{A}_j$$

$$D_i = \sum_j S_{i \leftarrow j} \cdot \tilde{A}_j$$

Hobbs *et al.* Phys Med Biol '12

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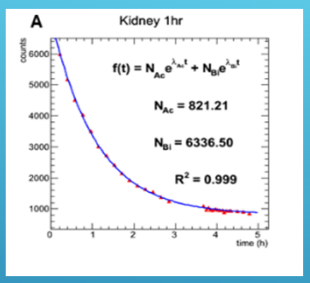
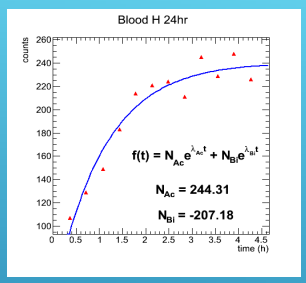
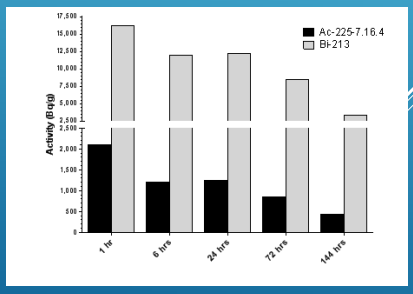
ACTIVITY QUANTIFICATION ORGAN

- Measure in γ – counter
- Only ^{213}Bi emits photons
- Fit to double exponential to quantify activities at time sacrifice
- Daughters in tumors tend to stay in tumors
- Daughters in normal organs tend to be voided (often caught in kidneys)







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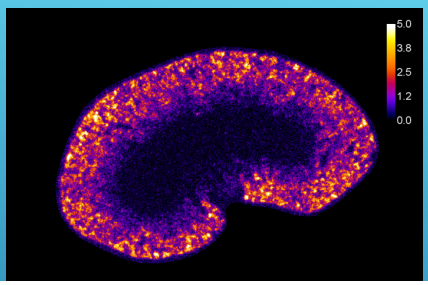
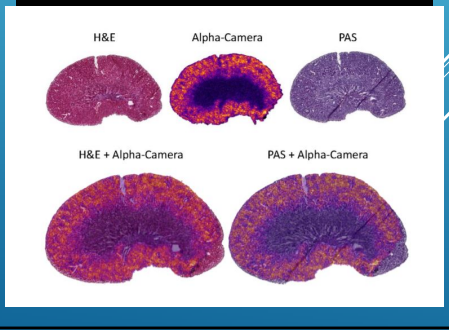
APPLICATION – ^{213}BI IMAGING

- Kidneys collected from her2-neu mice at 5, 15, 60 min p.i. of ^{213}Bi
- Frozen and cryo-sectioned in 8 µm thin slices for staining and imaging with Alpha-Camera. Imaging time between 30 and 60 min.
- Focalized Activity Uptake
- RPT - specific
- Translate to Human





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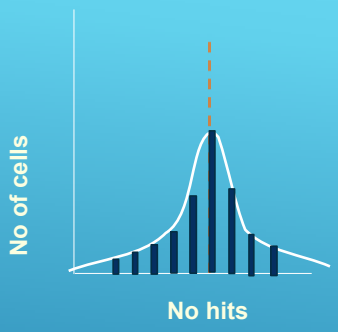
MICRODOSIMETRY

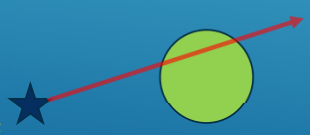
Non – uniform dose distribution at the cellular level from statistics

Consideration of nuclear/DNA target – cross-section, cellular localization of decay, cord length of potential interaction

Alpha-particles have fewer hits per cell kill on average, but low average hits means potential for Poisson Distribution – probabilistic.

Can there be other mechanisms of radiation induced cell death ?





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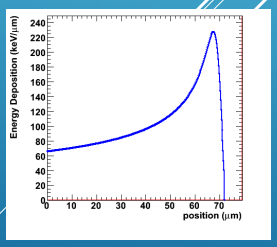

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BYSTANDER EFFECT – IMMUNE RESPONSE

Relates to αRPT effectiveness:

- bystander effect(s): cells release chemicals that cause death in neighboring cells

- immune response (likely linked to abscopal effect):

  a. cells die a more dramatic death than by low LET radiation and dead cells are "presented " to immune system that generate reaction.

  b. short range and high conformality means tumor microenvironment is much less irradiated than by standard RPT or EBRT

Chouin *et al.* Radiat Res '09
Howell *et al.* Int J Radiat Biol '12

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6. CONCLUSIONS

αRPT dosimetry much more complex than traditional RPT – not ready for general use

Currently underdosing by a far greater ratio than RPT

Small scale dosimetry (MIRD/AF method) fundamental for understanding and quantifying dosimetry

More site/cell type-specific RBE, RPT apportionment factors needed

Bio-effect modeling at cellular level/TME still in infancy need to converge approaches

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GENERAL CONCLUSIONS

Dosimetry-based Treatment Planning is catching on. (Only in microspheres for now)

Chemo paradigm still dominates – territorialism and big pharma are obstacles

Standardization, Education, Guidelines still needed (AAPM plays a role here)

Radiobiology and Bio-effect Modeling will drive further developments – extend common language to other non-radiation modalities

AlphaRPT will play an increasing role

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THANK YOU FOR YOUR ATTENTION!

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U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Production Challenges for Novel Therapy Radionuclides

Megan Shober

Advisory Committee on the Medical Uses of Isotopes

October 4, 2021

1

Overview

- Production methods
- Physics challenges
- Chemistry challenges
- Radiation safety challenges

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Copper-67

- ~2.5 day half-life, beta decays to stable zinc-67
- Accelerator-produced from stable target:

  $^{68}Zn(\gamma,p)^{67}Cu$
- Known target separation chemistry
- Paired with copper-64 diagnostic agent

3

Copper-67

- Chelators have not held the copper in place.

  ➡ Increased radiation dose to liver
- Production is adequate to meet current demand.

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Lutetium-177

- 6.6 day half-life, beta decays to stable hafnium-177
- Two production methods

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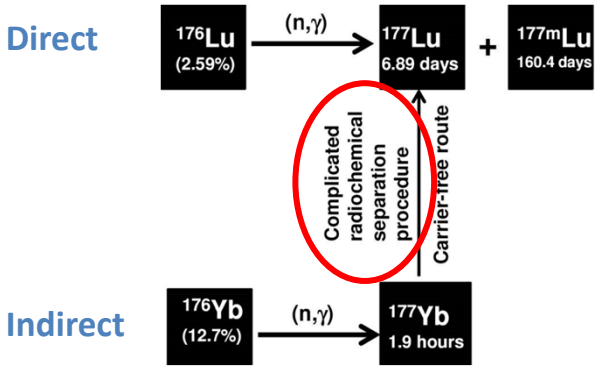
Lutetium-177

Direct

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463871/, accessed 1/20/2021

6

Lutetium-177



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463871/, accessed 1/20/2021

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Lutetium-177

- Radiation safety challenges (direct method)
  - Impurity is not eligible for disposal via decay-in-storage.
- Chemical challenges (indirect method)
  - Ytterbium and lutetium are very difficult to chemically separate.
  - Ytterbium is difficult to source.

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Actinium-225

- 10 day half-life, decay chain of four alphas and two betas to bismuth-209
- Extremely limited supply cannot support research demand.

Actinium-225

National Isotope Development Center

- Producing 40-50 mCi every six weeks from thorium-229 stock.
- Providing ~100 mCi every other month from accelerator produced Ac-225.

Accelerator Produced Actinium-225

- Thorium target irradiation produces actinium-227 as a trace contaminant.
  - Minimal effect on patient dosimetry
  - Huge radiation safety challenges for facility
- Actinium-227
  - 22 year half-life
  - Extremely difficult to detect, 44 keV beta

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Accelerator Produced Ac-225

Safety area	Ac-225	Ac-227
Annual limit on intake	3E-1 microcuries	4E-4 microcuries
Reportable spill (5 x ALI)	1.5 microcuries	0.002 microcuries
Financial assurance	Not required	10 microcuries

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Accelerator Produced Actinium-225

- To avoid co-producing actinium-227, use a radium-226 target.
  - Highly radioactive target, which must be recovered and re-used
  - Radon gas production
  - Must limit accelerator beam strength to reduce production of impurities
  - Maintenance concerns

Thorium-227

- 18.7 day half life, decay chain of five alphas and two betas to stable lead-207
- Produced by beta decay from actinium-227
- Supply chain already in place to support production of radium-223

Thorium-227

- Waste management
  - Can't use "ten half-life" rule of thumb due to ingrowth of daughter products.
- Concerns about migration of daughter products within body

Conclusions

- There is rising interest in production via accelerators and generators.
- Reducing impurities is paramount.
- Radiation safety concerns are driving decision-making for both producers and end users.

Questions?

Abbreviations

- Ac: actinium
- ALI: annual limit on intake
- Cu: copper
- keV: kiloelectron volts
- Lu: lutetium
- mCi: millicuries
- Zn: zinc

OPEN FORUM

(No Handout)

March 2022

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
27	28	1	2	3	4	5
6	7	8 NRC RIC	9 NRC RIC	10 NRC RIC	11 NRC RIC	12
13	14	15	16	17	18 APhA Annual Meeting	19 APhA Annual Meeting
20 APhA Annual Meeting	21 APhA Annual Meeting	22	23	24	25	26 AAPM Spring Clinical
27 AAPM Spring Clinical	28 AAPM Spring Clinical NCRP	29 AAPM Spring Clinical NCRP	30	31	1	2
3	4	Notes NRC's Regulatory Information Conference - March 8-11 American Pharmacists Association (APhA) Annual Mtg. - March 18-21 American Association of Physicists in Medicine (AAPM) Spring Clinical Meeting – March 26-29 National Council on Radiation Protection & Measurements (NCRP) Annual Meeting – March 28-29				

April 2022

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
27	28	29	30	31	1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16 PESACH
17 EASTER	18	19	20	21	22	23 PESACH
24 ACR	25 ACR	26 ACR	27 ACR	28 ACR	29	30
1	2	Notes Passover (Pesach) begins April 15 – April 23 (work permitted April 18-22 with restrictions) American College of Radiology (ACR) Annual Meeting – April 24-28				