J of Nuclear Medicine Technology, first published online November 8, 2021 as doi:10.2967/jnmt.121.262294

Radiation Safety Considerations and Clinical Advantages of Alpha-Emitting Therapy Radionuclides

Authors: Brian Serencsits, Bae P Chu, Neeta Pandit-Taskar, Michael R McDevitt, Lawrence T Dauer

Brian Serencsits, Department of Medical Physics, Memorial Sloan Kettering Cancer Center

Bae P Chu, Department of Medical Physics, Memorial Sloan Kettering Cancer Center

Neeta Pandit-Taskar, Department of Radiology, Memorial Sloan Kettering Cancer Center

Michael R McDevitt, Department of Radiology, Memorial Sloan Kettering Cancer Center

Lawrence T Dauer, Department of Medical Physics, Memorial Sloan Kettering Cancer Center

Disclaimer

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748

Contact (and first author)

Brian Serencsits

1275 York Avenue

Schwartz-1117

New York, NY 10065

212-639-7391

Fax: 212-717-3010

Serencsb@mskcc.org

Document Word Count: 4604

Running Title: Alpha-Emitting Therapy Radionuclides

Abstract

Alpha-emitting radionuclides provide an effective means of delivering large radiation doses to targeted treatment locations. Radium-223 dichloride ($^{223}RaCl_2$) is FDA approved for treatment of metastatic castration-resistant prostate cancer (mCRPC) and Actinium-225 (^{225}Ac-Lintuzumab) radiolabeled antibodies have been shown to be beneficial for patients with acute myeloid leukemia. In recent years, there is an increasing use of alpha emitters in theranostic agents with both small and large molecule constructs. The proper precautionary means for their use and surveying documentation of these isotopes in a clinical setting are an essential accompaniment to these treatments.

Methods

Patient treatment data collected over a three-year period, as well as regulatory requirements and safety practices, are described. Commonly used radiation instrumentation was evaluated for their ability to identify potential radioactive material spills and contamination events during a clinical administration of ^{225}Ac. These instruments were placed at 0.32 cm from a 1.0 cm ^{225}Ac disk source for measurement purposes. Radiation background values, efficiencies, and minimal detectable activities were measured and calculated for each type of detector.

Results

The median external measured patient dose rate from $^{223}RaCl_2$ patients (n = 611) was 2.5 µSv hr^{-1} on contact and 0.2 µSv hr^{-1} at 1 meter immediately after administration. Similarly, ^{225}Ac-Lintuzumab (n = 19) patients had median external dose rates of 2.0 µSv hr^{-1} on contact and 0.3 µSv hr^{-1} at 1 meter. For the measurement of ^{225}Ac samples, a liquid scintillation counter was found to have the highest overall efficiency (97%), while a zinc sulfide (ZnS) alpha probe offered the lowest minimal detectable activity at 3 counts per minute.

Conclusion

In this study, we report data from 630 patients who were undergoing treatment with alpha-emitting isotopes ^{223}Ra and ^{225}Ac. While alpha emitters have ability to deliver higher internal radiation dose to the tissues exposed as compared with other unsealed radionuclides, they typically present minimal external dose rate concerns. Additionally, alpha radiation can be efficiently detected with appropriate radiation instrumentation, such as a liquid scintillation counter or ZnS probe, that should be prioritized when surveying for spills of alpha-emitters.

Key words: alpha-emitters, actinium, radium, nuclear medicine, radiation efficiency

Introduction

Alpha-Emitting Radionuclides

Alpha-emitting radionuclides offer a unique and effective way of treating various types of cancer by delivering high linear energy transfer focal radiation deposition to a treatment site. The physical characteristics of high particle energy, often 5-9 MeV, and short < 100 μm particle range in tissue makes alpha-emitting radionuclides attractive sources to deliver large radiation doses to targeted tissues (*1*). Alpha particles create dense ionization tracks that can produce multiple damages to the DNA resulting in less repairable double-strand break damage (*2*,*3*). This allows radiopharmaceutical carriers of alpha-emitting radionuclides to produce efficient cell death in targeted tumor cells while sparing untargeted normal healthy tissues beyond the range of the alpha emissions (*4*,*5*).

Certain alpha-emitting radionuclides, such as ^{223}Ra, ^{225}Ac, and ^{227}Th, are part of a radioactive decay chain with multiple alpha particle emissions that results in a total emission energy per decay that are typically two orders of magnitude higher than conventional beta particle theranostics. This provides an advantage for clinical applications because the necessary administered activities for effective therapy are hundreds of times less than their beta particle or photon-emitting counterparts (*6*). Therefore, the radiation exposure rates due to particle and photon emissions from alpha-emitting radionuclide's progeny pose little to no external concerns and are not a safety-limiting factor at the sub-millicurie quantities used in clinical practices. This ability to deliver smaller activities, with minimal radiation exposure concerns, allows alpha-emitting radionuclides to be advantageous for radiation safety considerations, encompassing both occupational staff exposure and adhering to patient release criteria at the federal and state level.

Initially used in 1912 for the treatment of ankylosing spondylitis, ^{224}Ra was the first alpha-emitting radionuclide to be used in a clinical application (*7*). However, it was not until much later in 2013 that $^{223}RaCl_2$, now produced by Bayer Pharmaceuticals under the name Xofigo®, became the first FDA-approved alpha-emitting radionuclide therapy for the treatment of prostate cancer with metastatic bone lesions (*8*). More recently, other alpha-emitters such as ^{225}Ac and ^{227}Th have begun to see expanded use in clinical trials. ^{227}Th is produced by the decay of long-lived parent isotope ^{227}Ac, the same processes already used for its decay product, ^{223}Ra (*9*). Found naturally in the Neptunium decay series, seen in Figure 1, the current supply of ^{225}Ac comes from fissile ^{233}U, and its decay product

^{229}Th, first produced during investigation into nuclear weapons and reactors (*10*). ^{225}Ac, can be separated and purified from ^{229}Th through a combination of ion exchange and extraction chromatographic methods (*11*). Alternative methods to produce ^{225}Ac have been explored, the most promising is a ^{226}Ra(p, 2n)^{225}Ac reaction, which has not been widely used, but is being further explored (*12*).

Alpha-Emitting Radionuclide Therapies at Memorial Sloan Kettering Cancer Center (MSKCC)

Three alpha-emitting radionuclides currently in use at MSKCC under specific institutional protocols will be specifically addressed in this paper; these include $^{223}RaCl_2$ for metastatic castration resistant prostate cancer (mCRPC), ^{225}Ac monoclonal antibody Lintuzumab for acute myeloid leukemia, and a recently initiated ^{227}Th labeled antibody-chelator conjugate BAY 2701439 (Bayer) for targeting HER2-expressing tumors. $^{223}RaCl_2$ has been used for treatment of symptomatic patients with mCRPC, and its use has resulted in an overall improvement in quality of life and increased length of overall survival (*13,14*). Although ^{225}Ac, with a half-life of 10 days, is still early in research stages, ^{213}Bi, the final radioactive daughter product in the decay chain, has been used in clinical trials and shown to be safe and therapeutically efficacious in patients with acute myeloid leukemia (*15*).

The work described herein will provide an overview of our experience using alpha-emitting radionuclides in current and recently completed clinical trials, with a focus on the preparation, administrative procedures, radiation safety precautions, and regulatory requirements that must be met to safely administer alpha-emitting radionuclides in a clinical setting. In addition, radiation detection equipment is evaluated to see the varying effectiveness for monitoring the alpha-emitter ^{225}Ac in the clinical setting, which can help guide individuals on the proper selection of survey equipment.

Method:

Regulatory Framework

When preparing an institution for the administration of alpha-emitting radionuclides, there are regulatory requirements that must first be fulfilled. The Nuclear Regulatory Commission's NUREG documents offer guidance on the types of precautions and instrumentation that must be present for proper administration of alpha-emitting radionuclides. These documents will be addressed alongside perspectives from groups, including the International

Commission on Radiation Protection, National Council on Radiation Protection and Measurements, and the National Research Council.

Since many general broad scope radioactive material licenses for medical use include only materials with "Any byproduct material with atomic numbers 1 through 83" as designated by guidance of NUREG-1556 Volume 11 (*16*). Most alpha-emitting radionuclides, including all those discussed in this paper, have an atomic number greater than 83 and must be specifically documented on a radioactive material license. Estimations for the maximum possession amount should be reflected by the proposed patients load, estimated activity needed per patient, and waste storage capabilities.

Training required by the Nuclear Regulatory Commission for an authorized user to administer unsealed byproduct material can be found in 10 CFR 35 Subpart E and includes items related to education, training and experience, and board certification (*17*). For an individual to become an authorized user they must also be approved by an institution's internal radiation safety committee. In addition to approving authorized users for the administration of radioactive materials, the most important part of the radiation safety committee's job is to instill a proper safety culture in their staff members' daily routine and make safety a top priority over any other item (*18*). This can be accomplished through a plethora of means such as a robust radiation safety training program, proper workflow processes, and widespread monitoring and self-auditing practices.

Alpha-Emitting Radionuclide Therapy Overview

In a review of applicable alpha-emitting radionuclide protocols at MSKCC, all radionuclides were administered according to vendor or internal protocol recommendations. $^{223}RaCl_2$ was administered as a slow bolus intravenous injection over 3-5 minutes, whereas ^{225}Ac and ^{227}Th labeled antibodies were administered over a 15 to 30-minute infusion. All three protocols completed, or plan to complete, a dose escalation and/or expansion study to determine dose limiting patient toxicity levels. Results of the completed dose escalation studies are shown in Table 1. As shown, $^{223}RaCl_2$ and ^{225}Ac treatment activities were based upon patient weight, whereas planned ^{227}Th doses are based strictly on fixed activity levels.

Treatment Preparation

The requirements for the administration of radioactive materials will vary drastically depending on the type of radioactive material being administered. For staff directly handling these radionuclides, procedural items such as the use of long-handled tools or shielded syringes may be used to help minimize extremity radiation exposure but are often unnecessary for the lower activities being used. Storage of alpha-emitting radionuclides prior to treatment should be done such that both the beta and photon radiation is shielded to a reasonable extent.

Due to minimal external dose rate readings, patients may be treated in locations without lead shielding or other radiation limiting interventions. Most treatments using alpha-emitting radionuclides involve either an injection or infusion of radioactive material through a syringe, allowing for a closed system that delivers radioactive materials directly into the blood stream, which limits risk of contamination events or radiation exposure to staff members. Since alpha particles are of great concern for inhalation and ingestion, proper care should be taken to mitigate the risk of these intake pathways. Proper personal protective equipment, such as gloves (double preferred) and laboratory coats, should always be worn by staff administering alpha-emitting radionuclides. Absorbent pads should be placed around the injection or infusion site to mitigate the risk of spreading contamination in the event of a spill.

Special Considerations

Needle sticks and skin contamination that occur during treatments are considered special events and must be treated promptly and properly. For possible intake of radioactive material through a finger prick or skin contamination, rapid cleaning of the area and continual monitoring must be performed. Evaluation of radioactive material intake and the necessity for further investigation is described in NRC Regulatory Guide 8.9. In special monitoring situations, a suspected intake of material must be evaluated with scope commensurate with potential risk (*19*).

If radioactive material intake is suspected, a bioassay test is the preferred method for estimating the amount of material ingested. A single 24-hour biospecimen sample may be sufficient, but regular daily measurements could be needed for higher intakes. For alpha-emitting radionuclides, including all three reviewed herein, fecal bioassays are preferred since they contain a larger percentage of the excreta than urine (*20*). Intake retention functions can be used to estimate total intake of radioactive material, which can then determine the cumulative total internal dose, the committed effective dose equivalent (CEDE), to a staff member. This is done by using Appendix B values from 10

CFR 20 for the appropriate annual limits on intake (ALI) value for each isotope and any necessary tissue weighting factors ($w_{t.}$) from ICRP 103 (*21*,*22*). The committed effective dose equivalent, added to any external occupational exposure, is called the total effective dose equivalent for an individual, and carries a limit of 5,000 mrem annually in the United States. Equation 1 provides the calculation of occupational dose from internal exposures (CEDE). Annual limit on intake values are the amount of radioactive material that would need to be inhaled or ingested to reach the annual occupational dose limit for a radiation worker without any other exposure, with examples shown in Table 2.

$$CEDE = \text{Intake} * \frac{\text{Occupational Dose Limit}}{ALI} * w_t$$

Equation 1: Committed Effective Dose Equivalent calculation for the intake of radioactive material.

Contamination Survey Instrumentation

Regular surveying practices, proper radiation instrumentation, and methods for decontamination should always be present during the time of radioactive material administration. An alpha probe, such as a zinc sulfide (ZnS) scintillation detector or similar, may be preferable to a standard Geiger-Mueller (GM) detector for the detection of alpha-emitting radionuclides. Alpha probes can filter out the measurement of beta particles or photons, which allows them to have lower background levels of radiation and a subsequent lower minimal detectable activity (MDA). In addition, the mica film located on the outside of a standard GM detector makes the direct measurement of alpha particles difficult and inefficient, but still possible if the film is less than approximately 7 mg cm^{-2} (*23*). Such a film filters out most low-energy alphas and leads to a lower efficiency for those that can be measured. Coupled with a higher background reading, such filtering increases the difficulty of detecting small amounts of alpha-emitting radionuclides with a standard GM detector. Instead, GM detectors focus on measuring the associated beta particle and photon emissions from daughter nuclei. Although GM detector efficiency can reach about 33% for high energy beta particles, photon efficiencies are generally poor and often less than 1% for low-energy photons such as those produced by ^{99m}Tc or ^{125}I (*24*). A low MDA, and reasonable efficiency, is crucial for measuring the low levels of surface contamination needed to meet regulatory requirements such as the 1000 disintegrations per minute per 100 cm^{-2} combined activity for most alpha emitters (*25*).

Radiation Instrumentation Statistics

^{223}Ra efficiencies, MDA levels, dose rates, and decay pathways have been previously examined, in detail, in Dauer, et al. (*26*). ^{225}Ac has a similar decay pathway to ^{223}Ra, that contains a mixture of different decay modalities, including both alpha and beta decay (*27*). A net value of four primary alpha particle decays, two primary beta particles, and numerous gamma ray emissions are present in the decay process between radioactive ^{225}Ac and stable ^{209}Bi. Measuring the effectiveness of various radiation detection equipment for ^{225}Ac was completed experimentally by dissolving solid actinium nitrate with a 0.1 M HCl solution. The solution was then diluted and pipetted onto a 1.0 cm diameter filter disk. Prior to use, the ^{225}Ac used in this process was decayed in storage to ensure secular equilibrium with daughter products, a process that takes approximately 24 hours to complete (*28*). Portable instrumentation was placed in a repeatable geometry where the detector face was 0.32 cm from the filter disk. These radiation detectors were connected to an integrating scaler configured to accumulate counts for one minute, and the measurement was repeated ten times for both background and source counts. Stand-alone instrumentation, such as those used for wipe tests, were adjusted to count for 10 minutes for both sample and background counts. Efficiencies for each instrument was calculated by the measured count rates divided by the dose-calibrated activity. Minimum detectable activity was subsequently calculated using Equation 2 by the empirically determined efficiencies (E), background count rates (R_b), source count times (t_s), background count times (t_b) and constant value, k_1, of 1.645 representing a one-side 95% confidence interval (*29*).

$$MDA = \frac{{k_1}^2 + 2k_1\sqrt{R_b t_s(1 + \frac{t_s}{t_b})}}{t_s \, \mathrm{E} \, \mathrm{C}}$$

Equation 2. Minimal Detectable Activity

Instruments used for efficiency and MDA testing were: ZnS alpha probe (Model 43-2, Ludlum), thin windowed GM probe (Model 44-9; Ludlum, Sweetwater, TX), sodium iodide (NaI) low energy gamma probe (Model 44-3; Ludlum, Sweetwater, TX), liquid scintillation counter (Model TriCarb 2900TR, Perkin Elmer, Shelton, CT), and gamma counter (Model Wizard2, Perkin Elmer, Shelton, CT). Actinium-225, used for efficiency measurements, was supplied by the U.S Department of Energy, Oak Ridge National Laboratory (Oak Ridge, TN). Values for the efficiencies of various radiation instrumentation, and their associated MDAs, for ^{225}Ac are examined in more detail in Table 3.

Results:

Therapeutic Treatment Data and Precautions

A review of patient administrations for $^{223}RaCl_2$ (n = 611) and ^{225}Ac-Lintuzumab (n = 19) was completed to provide an overview of various safety considerations during administration. The median age of $^{223}RaCl_2$ patients was 72.26 years ± 8.93 (range, 46.53 - 92.94) with administered activities of 4.81 MBq± 0.95. The median age of ^{225}Ac-Lintuzumab patients was 77.90 years ± 9.72 (range, 56.35 - 87.60) with administered activities of 3.00 Bq ±1.68. Radiation dose to members of the staff and the public were considered minimal from patients receiving both $^{223}RaCl_2$ and ^{225}Ac-Lintuzumab. $^{223}RaCl_2$ dose rate readings were minimal with a median of 2.5 μSv hr^{-1} ± 0.07 on contact. Likewise, ^{225}Ac-Lintuzumab had similar readings of 1.7 μSv hr^{-1} ± 1.2 on contact. All activity and dose rate readings were taken with ionization chambers immediately following the therapy.

Radiation Detector Measurements

Radiation detection equipment evaluations were completed to determine detector efficiency, minimal detectable activities, and the feasibility of use during administrations of ^{225}Ac. The data for an unshielded radioactive source of ^{225}Ac is summarized in Table 3. MDA values were calculated with a k_1 value of 1.645, representative of the 95% confidence level. Efficiency levels were calculated and rounded to the nearest whole percentage value.

Discussion:

External exposure rate values for patients receiving alpha-emitting radionuclides were found to be low, as expected. With median dose rate values less than 0.5 μSv hr^{-1} at a meter distance, patients may return to their regular lifestyle immediately after treatment without radiation precautions. This advantage allows for effective treatment, while avoiding some common precautions needed for other types of radiopharmaceutical treatments. Low external dose rates also allow for better patient care by staff members by removing the constraints and limitations of occupational radiation exposure. Handling of specimens containing bodily fluids should continue to be treated with care by staff members to avoid accidental intake of the radioactive material.

Due to low external dose rates, all patients under reasonable assumptions will not subject a member of the public to 1 mSv of radiation exposure, the necessary requirement as designated by Regulation Guide 8.39 (*30*). Instructions

for the proper control of bodily fluids were given to minimize the risk of dose received from accidental ingestion of material for members of the public or household members after patient release, as seen in Figure 2. The instructions include sitting while urinating or defecating, proper hand washing when encountering any bodily fluids, prompt cleanup of any vomitus or bodily fluid spills, and the use of a condom during sexual intercourse. The instructions are given for one-week post-therapy, though data suggests that most excretion of radioactive material occurs within the first 72 hours (*31*). Beyond this point the amount of radioactive material remaining is inconsequential to overall dose received by members of the public.

From a radiation detection standpoint, as shown in Table 3, there are advantages and disadvantages to different radiation detectors. Alpha probes offer the best mix of efficiency, low background, and low minimal detectable activity for surveillance purposes – due to the sulfide's ability to filter out non-alpha radiation – which allows for a near zero background. The extremely low background allows even the smallest amount of radioactive material to be detected by the scintillator which is helpful in small contamination events. Liquid scintillation counters also offer desirable results but may not offer the rapid results needed during regular administrations and surveys; they also come with both higher initial cost and upkeep expenses. The data shows that a GM detector offers higher efficiency than a ZnS alpha probe, but also a higher MDA value due to higher background radiation levels. With MDA values below that of regulatory purposes for most alpha emitters, a GM detector may be a suitable alternative for a program based on cost and availability. Larger survey areas and longer count times can always be implemented to help lower a detector's MDA, when needed. Low-energy scintillation probes and gamma counters should not be used to measure for alpha-emitting radionuclides since their MDA may be near or above the surface contamination levels that require remediation under normal circumstances.

Conclusion:

There is a growth of interest and usage of alpha-emitting radionuclides in the treatment of cancer because of their higher radiotoxicity per unit administered activity relative to beta, gamma and X-ray emitting radionuclides. With robust administrative and engineering controls, alpha-emitting radionuclides can be handled and administered safely for clinical use. Proper personal protective equipment, training techniques, and radiation detection instrumentation are crucial for the reduction of contamination events and continued protection of clinical staff and members of the public. Patient release instructions for alpha-emitters can be limited to only hygiene precautions to prevent against

the accidental inhalation or ingestion of radioactive material by another individual. This allows patients to resume their everyday lives free of external radiation restrictions that may accompany other radionuclide therapies. With all their advantages, alpha-emitting radionuclides continue to be a leading option in the use of radionuclide therapy and can be safety administered.

Disclaimer

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748

Key Points

Question

Are current patient precautions and radiation survey equipment sufficient for safe and compliant radionuclide therapies containing alpha-emitting radionuclides?

Pertinent Findings

External dose rate readings from patients receiving radioactive materials continue to be low in clinical trials and FDA approved treatments. Radiation detection equipment such as Zinc-Sulfide detectors and liquid scintillation detectors are preferable to the more commonly used Geiger Mueller counter.

Implications for Patient Care

Radiation safety precautions for patients receiving alpha-emitting radionuclide therapy can continue to include only hygiene-related precautions for Ac-225 and Th-227 while maintaining compliance with federal guidance and regulation.

References

1. Humm JL. Dosimetric aspects of radiolabeled antibodies for tumor therapy. *J Nucl Med.* 1986;27:1490-1497.

2. Graf F, Fahrer J, Maus S, et al. DNA double strand breaks as predictor of efficacy of the alpha-particle emitter Ac-225 and the electron emitter Lu-177 for somatostatin receptor targeted radiotherapy. *PLoS One.* 2014;9:e88239.

3. Nikula TK, McDevitt MR, Finn RD, et al. Alpha-emitting bismuth cyclohexylbenzyl DTPA constructs of recombinant humanized anti-CD33 antibodies: pharmacokinetics, bioactivity, toxicity and chemistry. *J Nucl Med.* 1999;40:166-176.

4. Jurcic JG, Rosenblat TL. Targeted alpha-particle immunotherapy for acute myeloid leukemia. *Am Soc Clin Oncol Educ Book.* 2014:e126-131.

5. Humm JL, Sartor O, Parker C, Bruland OS, Macklis R. Radium-223 in the Treatment of Osteoblastic Metastases: A Critical Clinical Review. *International Journal of Radiation Oncology, Biology, Physics.* 2015;91:898-906.

6. Sgouros G. Dosimetry of internal emitters. *J Nucl Med.* 2005;46 Suppl 1:18S-27S.

7. Fisher DR. Alpha Particle Emitters in Medicine. In: DOE, ed. United States; 1989.

8. Makvandi M, Dupis E, Engle JW, et al. Alpha-Emitters and Targeted Alpha Therapy in Oncology: from Basic Science to Clinical Investigations. *Target Oncol.* 2018;13:189-203.

9. Abou DS, Pickett J, Mattson JE, Thorek DLJ. A Radium-223 microgenerator from cyclotron-produced trace Actinium-227. *Appl Radiat Isot.* 2017;119:36-42.

10. Alvarez R. Managing the Uranium-233 Stockpile of the United States. *Science and Global Security.* 2013;21:53-69.

11. Scheinberg DA, McDevitt MR. Actinium-225 in targeted alpha-particle therapeutic applications. *Current radiopharmaceuticals.* 2011;4:306-320.

12. Apostolidis C, Molinet R, McGinley J, Abbas K, Mollenbeck J, Morgenstern A. Cyclotron production of Ac-225 for targeted alpha therapy. *Appl Radiat Isot.* 2005;62:383-387.

13. Terrisse S, Karamouza E, Parker CC, et al. Overall Survival in Men With Bone Metastases From Castration-Resistant Prostate Cancer Treated With Bone-Targeting Radioisotopes: A Meta-analysis of Individual Patient Data From Randomized Clinical Trials. *JAMA Oncol.* 2019.

14. Dizdarevic S, Jessop M, Begley P, Main S, Robinson A. (223)Ra-Dichloride in castration-resistant metastatic prostate cancer: improving outcomes and identifying predictors of survival in clinical practice. *Eur J Nucl Med Mol Imaging.* 2018;45:2264-2273.

15. Rosenblat TL, McDevitt MR, Mulford DA, et al. Sequential cytarabine and alpha-particle immunotherapy with bismuth-213-lintuzumab (HuM195) for acute myeloid leukemia. *Clin Cancer Res.* 2010;16:5303-5311.

16. USNRC. Consolidated Guidance About Materials Licenses. Program-Specific Guidance About Licenses of Broad Scope. Final Report. NUREG-1556 Vol.11 Rev.1. Washington, DC: Office of Nuclear Material Safety and Safeguards; 2017.

17. USNRC. Medical uses of byproduct material. Title 10 Code of Federal Regulations Part 35. Vol 10 Code of Federal Regulations Part 35: United States Nuclear Regulatory Commission; 2008.

18. Yonekura Y, Mattsson S, Flux G, et al. ICRP Publication 140: Radiological Protection in Therapy with Radiopharmaceuticals. *Ann ICRP.* 2019;48:5-95.

19. USNRC. Regulatory Guide 8.9 Acceptable Concepts, Models, Equations, and Asumptions for a Bioassay Program. 1993.

20. USNRC. *Interpretation of bioassay measurements. NUREG/CR-4884.* Washington, D.C.: U.S. Nuclear Regulatory Commission; 1987.

21. USNRC. Standards for protection against radiation. 10 CFR Part 20. http://www.nrc.gov/reading-rm/doc-collections/cfr/part020. Accessed March 15, 2020.

22. ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. *Ann ICRP.* 2007;37:1-332.

23. Steinmeyer P. G-M Pancake Detectors: Everything You've Wanted to Know (But Were Afraid to Ask). *RSO Magazine.* Vol 10; 2005.

24. Knoll G. *Radiation Detection and Measurement*. Hoboken, NJ: Wiley; 2010.

25. USNRC. *Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses (NUREG-1556, Volume 9, Revision 2.* Washington, DC: United States Nuclear Regulatory Commission; 2008.

26. Dauer LT, Williamson MJ, Humm J, et al. Radiation safety considerations for the use of 223RaCl(2) DE in men with castration-resistant prostate cancer. *Health Phys.* 2014;106:494-504.

27. Robertson AKH, Ramogida CF, Schaffer P, Radchenko V. Development of (225)Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences. *Curr Radiopharm.* 2018;11:156-172.

28. Pandya DN, Hantgan R, Budzevich MM, et al. Preliminary Therapy Evaluation of (225)Ac-DOTA-c(RGDyK) Demonstrates that Cerenkov Radiation Derived from (225)Ac Daughter Decay Can Be Detected by Optical Imaging for In Vivo Tumor Visualization. *Theranostics.* 2016;6:698-709.

29. Radiation Safety Associates I. Attachment I: Counting Statistics for Laboratory and Portable Instruments. Nuclear Regulatory Commission; 2011.

30. NRC. Regulatory Guide 8.39 Release of Patients Administered Radioactive Materials. 1997.

31. Yoshida K, Kaneta T, Takano S, et al. Pharmacokinetics of single dose radium-223 dichloride (BAY 88-8223) in Japanese patients with castration-resistant prostate cancer and bone metastases. *Ann Nucl Med.* 2016;30:453-460.

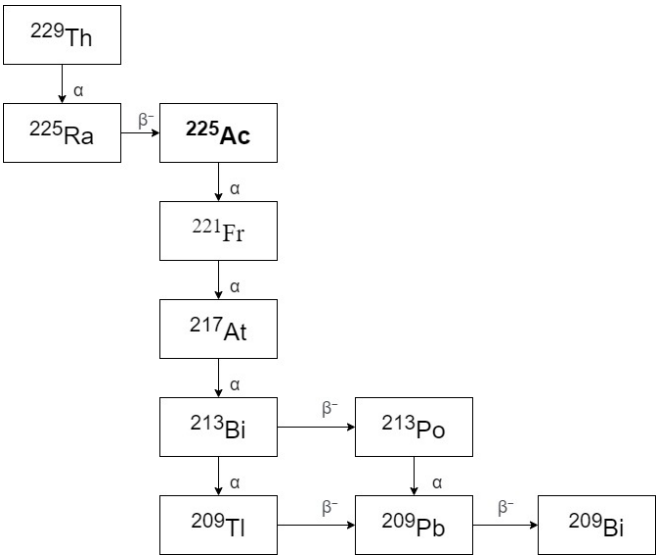

Figure 1: Decay of ^{225}Ac via the Neptunium Series

Radiation Safety After Your Alpha-Emitting Radionuclide Therapy

This information explains what you need to do to keep yourself and those around you safe after getting an alpha-emitting radionuclide therapy.

In addition to this handout, you will be given a card that informs people you have received radioactive medicine. **Carry this card with you at all times for 1 month after each injection.**

It is safe to be in close contact with people after receiving an alpha-emitting radionuclide. There are no restrictions.

The First Week after Your Injection

For 1 week after your injection there may be some radioactivity, mostly in your blood, stool, or vomit. Even smaller amounts may be in your urine, saliva, or semen. During this time, take the following steps to protect other people from radiation:

- Use disposable gloves when wiping up spills of blood, urine, stool, vomit, saliva, or semen. Wipe small spills with toilet paper and flush it down the toilet. If you use paper towels to clean up the mess, throw them right away in the regular trash.
- Clean any area that has been spilled on with a disinfectant.
- Wash your hands with soap and water after wiping up any spills, and after using the toilet.
- Sit when using the toilet. Use a toilet, not a urinal.
- Use disposable gloves when handling clothes, towels, and bed sheets that have been touched by spills. Wash this laundry separately from other clothes. Use an extra rinse cycle if possible.
- If you are having sex, use a condom. There may be a little bit of radioactivity in all body fluids, including semen.
- If you need to give a sample of blood, urine, or stool, tell your healthcare provider that you have been treated with an alpha-emitting radionuclide.
- If you need medical care, such as visit to a doctor or a hospital, tell your healthcare provider that you have been treated with an alpha-emitting radionuclide. Your healthcare provider can call with any questions or concerns.

Figure 2: Example of radiation safety precautions for patients receiving alpha-emitting therapies

Table 1: MSKCC alpha-emitting radionuclide dose escalation and expansion clinical protocols

	Activity Administered (kBq kg^{-1})	Total Treatment Cycles	Period Between Cycles (Weeks)
^{223}Ra			
Phase 1.1	50	1	N/A
Phase 1.2	100	1	N/A
Phase 1.3	200	1	N/A
Phase 2	50	6	4
Phase 3	50	6	4
NIST-Adjusted Xofigo®	55	6	4
^{225}Ac			
Phase 1.1	18.5	1	N/A
Phase 1.2	37	1	N/A
Phase 1.3	74	1	N/A
Phase 1.4	148*	1	N/A
Phase 1.5	111	1	N/A
^{227}Th (In Progress)			
Phase 1.1	1,500 kBq †	4	6
Phase 1.2	2,500 kBq †	4	6
Phase 1.3	3,500 kBq †	4	6
Phase 1.4	4,500 kB †	4	6
Phase 1.5	6,000 kBq †	2	6
	Additional 25% increase	2	6

* Dose limiting toxicity seen at Phase 1.4

† Patients receiving ^{227}Th receive fixed dose values instead of weight-based doses.

Table 2: Restrictive Annual Limit on Intake values for select alpha-emitting radionuclides and common medical use radionuclides.

Radionuclide	Decay Mode	Restrictive Annual Limit on Intake (MBq)
^{18}F	β	1,850
^{99m}Tc	IT	2,960
^{131}I	β	1.11
^{223}Ra	α	0.026
^{225}Ac	α	0.011
^{227}Th	α	0.011

Table 3: Removable contamination efficiencies and minimal detectable activities (MDA) for commonly used radiation detection equipment integrated over a 1-minute count time for ^{225}Ac.

Instrument	Background (cpm)	Efficiency (cpm/dpm)	MDA (dpm)	MDA (Bq)
Alpha Probe (ZnS)	0	0.07	3	0.05
Thin Window Beta/Gamma Probe (GM)	33	0.18	147	2.47
Low Energy Gamma Probe (NaI)	234	0.06	1128	18.82
Liquid Scintillation Counter	36	0.97	13	0.22
Gamma Counter	288	0.13	547	9.13

Graphical Abstract