2019 (Resolution 39)*

ACR–ACNM–ASTRO–SNMMI PRACTICE PARAMETER FOR THE PERFORMANCE OF THERAPY WITH RADIUM-223

PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care[1]. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner in light of all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document is advised to document in the patient record information sufficient to explain the approach taken.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of this document is to assist practitioners in achieving this objective.

[1] Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing, ___ N.W.2d ___ (Iowa 2013) Iowa Supreme Court refuses to find that the *ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures* (Revised 2008) sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, Stanley v. McCarver, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.

I. INTRODUCTION

This practice parameter was developed collaboratively by the American College of Radiology (ACR), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

This practice parameter is intended to guide appropriately trained and licensed physicians performing therapy with unsealed radiopharmaceutical sources. Such therapy requires close cooperation and communication between the physicians who are responsible for the clinical management of the patient and those who administer radiopharmaceutical therapy and manage the attendant side effects. Adherence to this parameter should help to maximize the efficacious use of radium-223, maintain safe conditions, and ensure compliance with applicable regulations.

Application of this parameter should be in accordance with the ACR–SPR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals, as that standard relates to the handling of radiopharmaceuticals, radiation safety, and radiation protection of patients, personnel, and the public [1]. There must also be compliance with applicable laws and regulations.

The goal of therapy with unsealed radiopharmaceutical sources is to provide either cure or significant prolongation of disease specific survival, and effective reduction and/or prevention of adverse disease-related symptoms or untoward events while minimizing treatment-associated side effects and complications.

II. DEFINITION

Therapy with unsealed sources involves administration of radiopharmaceuticals for the treatment of medical conditions.

Radium-223 dichloride (radium-223) is an alpha particle–emitting isotope used for targeted bone therapy. It is used for the treatment of metastatic cancer to bone.

III. INDICATIONS

Radium-223 is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic metastatic to bone, and without known visceral metastatic disease. Selected patients with CRPC metastatic to bone, but with minimal visceral disease, may be appropriate candidates for treatment with radium-223.

As no widely accepted criteria to define CRPC exist outside of a clinical trial, the decision requires the clinical judgment of the treating physician. In practice, patients who have evidence of disease progression despite adequate (serum testosterone <50 ng/dL) androgen-deprivation therapy [2,3] are considered castration resistant.

Evidence of disease progression includes:

- New metastasis while on androgen-deprivation therapy.
- Progression of existing metastases while on androgen-deprivation therapy.
- A rise in serum prostate-specific antigen (PSA) while on androgen-deprivation therapy, particularly in patients without metastases, confirmed by a second PSA at least 1 week apart.

Bone metastases may be considered symptomatic for the purposes of qualification for radium-223 therapy at the discretion of the treating physician. Symptomatic bone metastases are defined as two or more metastases to the skeleton resulting in clinical signs or symptoms, including pain, decreased mobility, impaired function, or fracture. Bone metastases requiring intervention with surgery or external-beam radiation therapy are also considered to be symptomatic.

Visceral metastatic disease includes involvement of liver and other solid intra-abdominal organs, peritoneum, lung, and brain. Other soft-tissue sites of disease (eg, prostate bed or bladder wall) and lymph nodes are not considered as visceral.

Radium-223 dichloride is not currently FDA approved for use in the treatment of malignancies other than CRPC though it is anticipated that radium-223 may be of benefit in patients with other cancer types demonstrating osteoblastic metastases. Additional uses of radium-223 may occur as part of a clinical trial.

IV. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

The qualifications and responsibilities of physicians and other personnel performing these therapeutic procedures should be in accordance with the ACR–SPR Technical Standard for Diagnostic Procedures Using Radiopharmaceuticals and/or the ACR–ASTRO Practice Parameter for Radiation Oncology [1,4]. In addition, training and experience must be in compliance with the applicable laws and regulations.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

The written or electronic request for a radiopharmaceutical procedure should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). Additional information regarding the specific reason for the procedure or diagnosis would be helpful and may at times be needed to allow for the proper performance of the procedure.

The request for the procedure must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the state's scope of practice requirements. (ACR Resolution 35, adopted in 2006 - revised in 2016, Resolution 12-b)

General Procedures

1. Clinical evaluation

   Clinical Evaluation: Radium-223 dichloride is a radiopharmaceutical delivered intravenously (monthly for six injections). It is FDA approved for the treatment of patients with symptomatic CRPC with bone-predominant metastatic disease. At least two bone metastases should be identified on imaging studies, and there should be no evidence of visceral metastases (malignant adenopathy ≤3 cm in the short axis is allowed). Before the treatment is administered, each patient should have a consultation with a radiation oncologist, nuclear medicine physician, or nuclear radiologist that includes a complete history and physical examination and a review of prior radiotherapy and systemic therapy for prostate cancer. The patient's life expectancy should be >6 months with a preferable ECOG Performance Status of 0 to 2. Pain assessment and patient-reported symptoms should be documented to evaluate the quality of life of patients before, during, and after the treatment. Laboratory studies including a complete blood count (CBC) with an absolute neutrophil count (ANC), should be obtained within 30 days prior to first injection. PSA and alkaline phosphatase (ALP) may be obtained prior to first injection. During radium-223 therapy, however, changes in ALP have been shown to correlate more with response compared with changes in PSA alone. A bone scan or NaF-PET-CT should be obtained to assess for active osteoblastic metastases prior to first therapy. A CT scan of the chest, abdomen, and pelvis should be performed to assess for visceral metastasis. Because myelosuppression is a side effect of radium-223, a CBC with differential should be performed before each subsequent injection. Special consideration of the benefits and risks of radium-223 should be given for patients with the following situations: cytotoxic chemotherapy within 4 weeks prior to administration of radium-223, external-beam hemibody radiation, and systemic radionuclides within 24 weeks of therapy. Epidural tumor or spinal cord compression should be treated with external-beam radiation therapy prior to radium-223 therapy. Currently, it is not recommended to use radium-223 in combination with abiraterone

plus prednisone/prednisolone outside a clinical trial (see below: 7j). For initial treatment with radium-223, the following hematologic parameters are recommended: ANC > 1.5×10^9/L, platelets ≥ 100×10^9/L; hemoglobin (Hgb) ≥ 10.0 g/dL. For subsequent treatments: ANC > 1.0×10^9/L, platelets > 50×10^9/L, and with no set parameters for Hgb. For patients who experience a decrease in Hgb while on radium-223 therapy, a transfusion of red blood cells may be considered at the discretion of the referring and treating physicians.

2. Quality Management

In order to use radiopharmaceuticals as unsealed sources for therapy, a "quality management" program must be in place as required by the U.S. Nuclear Regulatory Commission (NRC) or by Agreement State regulations. (An Agreement State is any state with which the NRC or the U.S. Atomic Energy Commission has entered into an effective agreement under subsection 274.b of the Atomic Energy Act of 1954 as amended, 73 Stat, 689.)

All radium-223 injections should be preceded by a written directive from the authorized user specifying radiopharmaceutical, indication, prescribed dose, and route of administration. As with any radionuclide therapy, the treating physician is responsible for confirming the patient identity using a minimum of two forms of identification (ie, name, date of birth) prior to radium-223 injection.

The radiopharmaceutical is ordered 1 week prior to therapy. The activity should be measured and documented before injection in order to confirm that the activity is within acceptable NRC or state regulatory specifications. After the patient receives the injection, the residual activity of the postinjection needle and line will be determined. The ordered and measured pre- and postinjection activities should be recorded, and the actual administered radium-223 activity with the radiopharmaceutical lot number should be made part of the permanent hospital/clinic record. Under ideal conditions, the consulting physician should be the medical professional administering the radium-223. If this is not possible because of scheduling issues, a covering physician with experience in unsealed radiopharmaceutical therapy should assume responsibility for patient identification and for safe and effective injection. Reliable intravenous access must be ensured prior to dose delivery. A procedure using a superficial upper-extremity or antecubital vein butterfly needle, three-way stopcock, and 10-ml saline flush works best and allows for safe, maximum effective delivery of the prescribed radiopharmaceutical. All intravenous lines and connections used in the delivery of radium-223 should be secure. The treatment should be administered, using an appropriate syringe shield and disposable gloves, into an intravenous port or an arm resting on a bedside table or injection chair with at-risk surfaces covered by absorbent shielding. The syringe and treatment lines should be generously flushed with saline after the complete delivery of radium-223.

Radium-223 use should be included in a written Quality Management Program for Radiopharmaceutical Therapy to ensure the above considerations are routinely addressed and that any unintended deviation from the written directive is detected early and appropriately managed. A written report is required annually, but a more frequent review of individual written records is encouraged.

3. Informed consent

Informed consent must be obtained and documented. See the ACR Practice Parameter on Informed Consent – Radiation Oncology [5].

4. Treatment

The procedure and follow-up should be performed per an established system of procedural steps in a facility that is appropriately licensed for and by staff who comply with local, state, and national rules for the administration of radiopharmaceuticals.

Radium-223 is usually administered once every 4 weeks for six injections.

The standard administered activity of radium-223 is 55 kBq (1.49 μCi) per kilogram of body weight, given by slow intravenous injection over 1 minute. The intravenous access line should be well-established and flushed with isotonic saline before injection of radium-223 to ensure patency and avoid extravasation. The intravenous access line should also be flushed with isotonic saline after injection of radium-223.

Administration of radium-223 may be delayed up to 6 to 8 weeks after the last administration of radium-223 for recovery of treatment-related cytopenias. If blood counts do not recover within 6 to 8 weeks after the last radium-223 administration despite supportive care, further treatment with radium-223 should be discontinued.

5. Radiation precautions

With each treatment in the six-part therapy, patients should receive instructions regarding limited radiation precautions for the home, largely relating to blood, stool, and body fluid precautions in the initial week following therapy. Patients should be advised to sit when urinating, to use disposable gloves to manage catheters conveying urine or other bodily fluids, and to clean spilled urine or other soiled surfaces or garments. Heavily contaminated or soiled garments should be washed separately. Fluid intake and bathroom usage should be encouraged. Sharing of food or drink and sexual contact should be discouraged along with prolonged close contact with children or pregnant women for a period of 2 weeks after injection.

6. Complications

The 3-year safety profile of radium-223 dichloride in patients with CRPC and symptomatic bone metastases, in Alpharadin Symptomatic Prostate Cancer trial (ALSYMPCA), has been recently published [6]. During treatment to 12 weeks following the last injection, 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had treatment-emergent adverse events (TEAEs). Myelosuppression incidence was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (13% versus 13%), neutropenia (2% versus 1%), and thrombocytopenia (7% versus 2%). Ninety-eight of 600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs. Long-term follow-up showed no acute myelogenous leukemia, myelodysplastic syndrome, or new primary bone cancer. Secondary non–treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 months after the last injection. The most common adverse reactions in patients receiving radium-223 include nausea, diarrhea, vomiting, and peripheral edema. Transient increase in bone pain or "flare" has also been reported.

7. Published data, background, and trials

Radium-223 dichloride has primarily been investigated for the treatment of CRPC with symptomatic skeletal metastases [6-8].

a. A multinational phase III randomized (2:1) double-blind controlled trial (ALSYMPCA) of 922 men with CRPC and symptomatic bone metastases was performed to test radium-223 (given intravenously at 50 kBq/kg) versus placebo for up to six cycles at 4-week intervals.
b. Overall survival was the primary endpoint.
c. The study was stopped early following a planned interim analysis when data showed a median overall survival advantage in favor of radium-223 (14.0 versus 11.2 months, $p = .019$; hazard radio (HR) 0.695).
d. Fewer skeletal-related events (SREs) were seen in the radium-223 arm. In particular, radium-223 resulted in a significant reduction in epidural spinal cord compression events (3% versus 6%, $p = .016$). Also, the time to first SRE was extended for subjects in the radium-223 arm (13.6 versus 8.4 months, $p = .0005$).
e. There were no differences in adverse events or serious adverse events between the arms.

f. Radium-223 was associated with modest effects on Grade 3/4 neutropenia (1.8% versus 0.8%) and thrombocytopenia (4% versus 2%) [8].
g. Both safety and efficacy of radium-223 versus placebo were favorable even in subjects with prior docetaxel treatment [7].
h. Cytotoxic chemotherapy can be safely delivered to patients following radium-223 treatment [9].
i. Treatment with radium-223 resulted in an improvement in key quality of life measures versus placebo [10].
j. Although an early phase trial suggested concomitant use of radium-223 with abiraterone, enzalutamide or denosumab were safe and resulted in an improved median overall survival compared with radium-223 alone [11], a subsequent phase III trial (ERA223) exploring radium-223 plus abiraterone in patients with asymptomatic or mildly symptomatic chemotherapy-naïve metastatic CRPC was unblinded early after more fractures and deaths were observed in patients receiving both radium-223 and abiraterone acetate compared with patients receiving abiraterone alone. The package insert for radium-223 was updated to state that its use in combination with abiraterone plus prednisone/prednisolone is not recommended outside a clinical trial.
k. Retreatment with radium-223 following disease progression after a first course was both safe and effective in a phase I/II study, with a median overall survival of 24.4 months in retreated patients [12].

Clinical trials for radium-223 for patients with cancers of the prostate, breast, thyroid, bladder, kidney, osteosarcoma, and multiple myeloma are ongoing.

VI. DOCUMENTATION

Reporting should be in accordance with the ACR–ASTRO Practice Parameter for Communication: Radiation Oncology [13].

The report should include the radiopharmaceutical used, the dose and route of administration, as well as any other pharmaceuticals administered, also with dose and route of administration.

VII. ACR STATEMENT ON THERAPEUTIC USE OF UNSEALED RADIOPHARMACEUTICAL SOURCES

On the basis of their education, training pathway(s), initial board certification(s), and maintenance of certification(s), NRC Authorized User (AU) status, and clinical work experience, diagnostic radiologists (DRs), nuclear radiologists (NRs), nuclear medicine physicians (NMs), and radiation oncologists (ROs) may have the qualifications to supervise and perform therapies using unsealed radioisotopes. Although it is recognized that individual physician variations and state and federal regulatory requirements may, of necessity, dictate site-specific practice patterns, these physicians may best participate in the practice according to their special interests and qualifications. In most clinical settings, one of the following common practice paradigms generally applies:

- Physicians who are board-eligible or board-certified in DR, NR, NM, or RO but do not hold AU status: These physicians may participate in the practice of therapy with specific unsealed radiopharmaceuticals under the supervision of an AU for the specific therapeutic radiopharmaceutical. Although they may not issue written directives for those specific radiopharmaceuticals, they may administer such a dosage as designated by an AU.

- Physicians who are board-certified in DR, NR, NM, or RO and hold AU status based on that certification and site-specific credentialing.

VIII. RADIATION SAFETY

Radiologists, medical physicists, registered radiologist assistants, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, “as low as reasonably achievable” (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality

necessary to achieve the clinical objective. All personnel that work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection and application of dose limits) and the principles of proper management of radiation dose to patients (justification, optimization and the use of dose reference levels)http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1578_web-57265295.pdf.

Facilities and their responsible staff should consult with the radiation safety officer to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals and that they are adhered to in accordance with ALARA. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the Nuclear Regulatory Commission (NRC) and by state and/or other regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol.

Nationally developed guidelines, such as the ACR's Appropriateness Criteria®, should be used to help choose the most appropriate imaging procedures to prevent unwarranted radiation exposure.

Additional information regarding patient radiation safety in imaging is available at the Image Gently® for children (www.imagegently.org) and Image Wisely® for adults (www.imagewisely.org) websites. These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).

Radiation exposures or other dose indices should be measured and patient radiation dose estimated for representative examinations and types of patients by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Regular auditing of patient dose indices should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry, the NCRP Report No. 172, Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director's National Evaluation of X-ray Trends. (ACR Resolution 17 adopted in 2006 – revised in 2009, 2013, Resolution 52).

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality control and improvement, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education* on the ACR website (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement).

Equipment performance monitoring should be in accordance with the ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras [14].

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Development Chronology for this Practice Parameter
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