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

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 considering 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 variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and 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 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, 831 N.W.2d 826 (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 Radium Society (ARS), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

This practice parameter is intended to guide appropriately trained and credentialed physicians performing therapy with radium–223 dichloride (hereafter simply referred to as radium-223). Such therapy requires cooperation and communication among members of the healthcare team, to include the healthcare practitioner

involved in the clinical management of the patient, the physician consulted regarding radiopharmaceutical therapy, and those who will administer the radiopharmaceutical therapy and manage the radiation safety precautions and possible side effects. Adherence to this parameter should help 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–ACNM–ASTRO–SNMMI Practice Parameter for the Performance of Therapy with Radiopharmaceuticals [1]
and ACR–AAPM–ACNM–SNMMI–SPR Technical Standard For Therapeutic Procedures Using Radiopharmaceuticals (rev. 2022). There must also be compliance with applicable federal and state laws and regulations.
The goal of therapy with radium-223 is to provide prolongation of disease specific survival and/or effective reduction and/or prevention of adverse disease-related symptoms, while at the same time minimizing treatment-associated side effects and complications.
Therapy with radium-223 involves the intravenous administration of the agent radium-223 for the treatment of selected medical conditions.

II. PHYSICAL PROPERTIES

Radium is an alkaline earth metal with an atomic number of 88 that belongs to group 2 of the periodic table, similar to calcium. The two elements share an affinity to incorporate in bone hydroxyapatite. Radium-223 is a naturally occurring isotope in the radium decay scheme with a half-life (T ½) of 11.4 days. Radium-223 decays to radon-219 (T ½ 3.96 seconds) with 100% emission of an alpha particle with a peak energy of 5.97 MeV [2]. Although radium-223 is naturally formed in trace amounts by the decay of uranium-235, it is generally produced artificially for commercial use. Commercial production is accomplished by exposing naturally occurring radium-226 to neutrons to produce radium-227, which decays to actinium-227, which then decays to thorium-227 and then to radium-223 [3].

III. INDICATIONS

At the time of preparation of this document, radium-223 is indicated only for the treatment of patients with symptomatic, castration-resistant prostate cancer (CRPC), metastatic to bone, and without known visceral metastatic disease [4].
Selected patients with CRPC metastatic to bone, but with minimal visceral disease, may be appropriate candidates for treatment with radium-223.
The National Comprehensive Cancer Network and Prostate Cancer Writing Group 3 (PCWG3) define CRPC as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (less than 50 ng/dL. , In practice, patients who have evidence of disease progression despite adequate (serum testosterone less than 50 ng/dL) androgen-deprivation therapy [5,6] are considered castration resistant.
Evidence of disease progression to define CRPC includes:

- Development of new metastasis while undergoing androgen-deprivation therapy.
- Progression of existing metastases while undergoing androgen-deprivation therapy.
- Any rise in serum prostate-specific antigen (PSA) while on androgen-deprivation therapy, particularly in patients without known 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. Features of symptomatic bone metastases include pain, decreased mobility, impaired function, and/or fracture. Bone metastases requiring intervention with surgery and or external-beam radiation therapy (EBRT) are also considered to be symptomatic. Because of the multiple etiologies of pain, especially in patients with known malignancies, clinical suspicion of

osseous metastasis should be verified by appropriate imaging techniques, for example, radioisotope bone scan, CT scan, and/or prostate-specific membrane antigen (PSMA) PET.
Visceral metastatic disease includes the involvement of any soft tissue excluding lymph nodes or local disease of the prostate gland and prostate bed as the osseous skeleton. However, for patients with lymphadenopathy > 3 cm in short-axis measurement were not eligible for the Alpharadin Symptomatic Prostate Cancer (ALSYMPCA) trial, but this should not be considered visceral metastasis [7].

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 and/or the ACR–ARS Practice Parameter for Radiation Oncology [8]. 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)

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

1. Clinical Evaluation

Before the agent is administered, each patient should be evaluated by the authorized user (AU) for eligibility and suitability for radium-223 treatment. The evaluation may include a complete history and physical examination and a review of any prior radiotherapy or systemic therapy for prostate cancer. Any history of comorbidity that may impact radium-223 administration must be thoroughly reviewed. History of pain at bony sites, especially spine with neurological symptoms suggestive of cord compression, should be assessed. The patient's life expectancy should be >6 months with a preferred ECOG Performance Status of 0 to 2. Pain assessment and pain-reported symptoms should be documented to evaluate the quality of life before, during, and after the treatment. A radionuclide bone scan, NaF-PET-CT, contrast-enhanced CT (if the patient meets the criteria), or PSMA PET-CT should be obtained to confirm the presence of bone metastasis before the first therapeutic administration. A CT scan of the chest, abdomen, and pelvis should be performed to assess for visceral metastasis. In cases of contrast allergy, an abdominal MRI can be performed to rule out visceral metastais.
Laboratory studies including a complete blood cell count (CBC) with an absolute neutrophil count (ANC), should be obtained within 30 days before the first injection of radium-223. PSA and alkaline phosphatase (ALP) may be obtained before the first injection and preferably as close as possible to the first treatment for establishing a pretreatment baseline level. However, PSA and ALP are not required to ensure eligibility for treatment. During radium-223 therapy, changes in ALP have been shown to better correlate with response compared with changes in PSA alone.
Because myelosuppression is a side effect of radium-223, a CBC with differential should be performed before each subsequent injection. Consideration of the benefits and risks of radium-223 should be discussed with patients who may have undergone cytotoxic chemotherapy within 4 weeks before administration of radium-223, had hemibody external-beam radiation, or had systemic radionuclides within 24 weeks of therapy. If patients have been treated with radiation in the past, the dosing and extent should be reviewed; if more than 25% marrow exposure is noted, it should be carefully assessed. Epidural tumor or spinal cord compression should be managed appropriately before radium-223 therapy. Combination use of radium-223 and second-generation antiandrogen agents can lead to skeletal adverse events. Risks and benefits should be discussed, and bone protection agents used as appropriate if combination therapy is indicated.
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 g/dL.

For subsequent treatments:

- ANC > 1.0×10^9/L;
- Platelets > 50×10^9/L.

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 medical team.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

2. Quality Management

All radium-223 injections must be preceded by a completed written directive, signed and dated by the AU. specifying the , indication, prescribed administered activity, and route of administration.. The AU is responsible for confirming the patient identity using a minimum of two forms of identification (eg, name, date of birth) before radium-223 injection.

Typically, the consulting physician will be the AU supervising the radium-223. If for any reason this is not possible , a covering AU should assume responsibility for patient identification, for safe and effective injection, and for appropriate follow-up management. Reliable intravenous access must be ensured, and good blood return should be checked before delivery of the agent. A superficial upper-extremity or antecubital vein butterfly needle, three-way stopcock, and 10-mL saline flush is efficient and allows for safe and effective delivery of the agent All intravenous lines and connections used in the delivery of radium-223 should be secure. The agent should be administered using an appropriate syringe shield and disposable gloves, into a peripheral intravenous port or an arm resting comfortably on a bedside table or injection chair with at-risk surfaces covered by absorbent shielding, which should then be monitored. The syringe and treatment lines should be generously flushed with saline after the complete delivery of radium-223. Existing in-dwelling lines or ports should be used in accordance with local policies.

The activity should be measured and documented shortly before injection to confirm that the activity is within acceptable US Nuclear Regulatory Commission (NRC) or state regulatory specifications, as well as the written directive. Following administration of radium-223, the residual activity in the injection needle, and intravenous line, as well as any administration-related paraphernalia should be measured. The local site of administration should be examined for any evidence of extravasation; if present, that area should be monitored and measurements recorded. 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 included as part of the permanent record.

Radium-223 use should be included in a written Quality Management Program for Radiopharmaceutical Therapy to ensure that facility policies and procedures are followed routinely and that any unintended deviation from the written directive is detected early and appropriately managed.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

3. Informed Consent

Informed consent must be obtained and documented. See the ACR–ARS Practice Parameter on Informed Consent Radiation Oncology [9].

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

4. Procedure

The procedure and follow-up care should be performed using a standardized process established by the facility. All steps in the process should comply with appropriate jurisdictional licensure and regulations.

Recommendations for administration may periodically change, and users should consult the most recent vendor prescribing literature for guidance [4].

Radium-223 is usually administered at 4-week intervals for a total of 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 be flushed with 10–20 mL isotonic saline after injection of the isotope.

CBC with differential should be obtained within 1 week of each radium-223 administration. Subsequent administration may be delayed up to 6–8 weeks after the last administration for recovery of treatment-related

cytopenia. If blood counts do not recover within 6–8 weeks after the last administration despite supportive care, further treatment with radium-223 should be discontinued.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

5. Radiation precautions

With each treatment in the six-part course of therapy, patients and their caregivers should receive instructions regarding standard radiation precautions to be followed for the home, relating to blood, stool, and body fluid precautions in the initial week following therapy. There are no restrictions regarding contact with other people after receiving radium-223. Patients should follow good hygiene practices while receiving radium-223 and for at least 1 week after the last injection to minimize radiation exposure from bodily fluids to household members and caregivers. Whenever possible, patients should urinate seated on the toilet and flush several times after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves should be encourarged. .haring of food or drink and sexual contact should be discouraged, as should prolonged close contact with children and pregnant patients for a period of two weeks after each injection. Patients who are sexually active should use condoms and their female partners of reproductive potential should use a highly effective method of birth control during treatment and for 6 months following completion of radium-223 treatment.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

6. Published Clinical Reports

a. Parker et al and Hoskins et al reported the 3-year safety profile of radium-223 dichloride in patients with CRPC and symptomatic bone metastases, in the ALSYMPCA trial, in 2013 [10-12]. Before randomization, 58% and 57% of patients in the radium-223 and placebo arms, respectively, had received docetaxel. During treatment and up to 12 weeks following the last injection, 564 of 600 (94%) radium-223–treated patients and 292 of 301 (97%) placebo-treated patients had treatment-emergent adverse events (TEAEs). Incidence of myelosuppression was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (6% versus 13%), neutropenia (2% versus =1%), and thrombocytopenia (3 % versus =1%). Follow-up at 3 years showed no acute myelogenous leukemia, myelodysplastic syndrome, or new primary bone cancer. Secondary non–treatment-related malignancies occurred in four (0.6%) radium-223 patients and three (0.9%) placebo patients. One radium-223 patient developed aplastic anemia 16 months after the final treatment The most common adverse reactions in patients receiving radium-223 include nausea, diarrhea, vomiting, and peripheral edema, with grade 3/4 events reaching only 2% in each. Transient increase in bone pain or "flare" has also been reported.
b. Primary endpoint of the trial was overall survival.
c. The study was stopped early following a planned interim analysis when data demonstrated a median overall survival advantage in favor of radium-223 (14.0 versus 11.2 months, *P* = .019; hazard radio 0.695).
d. Fewer skeletal-related events (SREs) were seen in the radium-223 arm. 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%).
g. Both safety and efficacy of radium-223 versus placebo were favorable even in subjects with prior docetaxel treatment.
h. Cytotoxic chemotherapy can be safely delivered to patients following radium-223 treatment.
i. Treatment with radium-223 resulted in an improvement in key quality of life measures versus placebo[13-16], although the report by Smith et al did note an increase in skeletal fractures in patients who received radium-223 plus abiraterone and prednisone [16].

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 survial compared with radium-223 alone [14], a subsequent phase III trial (ERA223) exploringradium-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.

In 2017, Sartor et al [17] reported their experience in retreatment of 44 patients who had disease progression having previously received radium-223. Twenty-nine of the 44 were able to receive a second full course of radium-223 (six administrations). In this open-label phase I/II study, retreatment with radium-223 following disease progression after a first course was both safe and effective, , with a median overall survival of 24.4 months in retreated patients [17]. No grade 4 or 5 hematologic events were noted [17]. Sartor et al subsequently confirmed the ability for a similar cohort of patients to receive systemic chemotherapy following a course of radium-223 [15]. Nilsson et al, in a follow-up study of the cohort of ALSYMPCA, reported both improved survival and quality-of-life in the study group [13].

Several studies have been reported employing radium-223 in combination with other systemic therapies. Saad et al [14] reported on 839 patients enrolled in an international, prospective, interventional, open-label, single-arm phase IIIb study. Median overall survival was improved in patients who received radium-223 plus abiraterone, enzalutamide, or both than those who did not receive the agents and in patients who received radium-223 plus denosumab. rade 3 toxicities, primarily anemia (5%) and thrombocytopenia (2%), were uncommon [14]. An increased risk of skeletal fracture in patients receiving radium-223 in combination with abiraterone acetate and prednisone as well as when combined with enzaluatamide. The researchers did not find an improvement in skeletal event-free survival in the study cohort [16]. Other notable clinical reports in prostate cancer of the use of radium-223 before or concurrently with abiraterone, enzalutamide, and sipuleucel-T and before Lu-PSMA617. Clinical trials are ongoing in prostate cancer evaluating the combination of radium with enzalutamide, with docetaxel, with olaparib, with bipolar androgen therapy, with M3814 – DNA-PK inhibitor + avelumab, and with lutetium-177 PSMA. In addition to those, clinical trials in other tumor types are also ongoing evaluating the combination of radium with cabozantinibin in renal cell carcinoma and with paclitaxel in metastatic breast cancer.

V. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. General Procedures

7. Clinical Investigation in additional Neoplasms

Radium-223 is not currently FDA approved for use in the treatment of malignancies other than CRPC, although it is anticipated that the agent may be of benefit in patients with other cancer types demonstrating osteoblastic metastases.

Breast Cancer

A vendor-sponsored trial of radium-223 versus placebo and hormonal treatment as background therapy in subjects with bone predominant Human Epidermal Growth Factor Receptor 2negative hormone receptor positive metastatic breast cancer (NCT02258464) was initiated in 2020 but closed following lower than projected recruitment [18]. Coleman et al subsequently presented an abstract of the incomplete trial [19]. Ueno et al [20] completed a phase II study of radium-223 combined with hormonal therapy for hormone receptor-positive, bone-dominant metastatic breast cancer. Thirty-six patients were included, with a primary endpoint of disease control at 9 months. Disease control rate at 9 months was 49%. Median progression-free survival (PFS) was 7.4 months. Median bone PFS was 16 months. No grade 3/4 toxicities were reported. The authors intended to further explore the use of radium-223 in this population [20].

In 2019, a National Cancer Institute (NCI)-sponsored multicenter clinical trial (NCT04090398) investigating the addition of radium therapy (radium-223) to the usual chemotherapy treatment (paclitaxel) for advanced breast cancer that has spread to the bones was open to accrual. Target for completion of the trial with an anticipated accrual of 70 was 2023 [21].

Renal Cell Carcinoma

In 2019, an NCI-sponsored multicenter clinical trial to test the addition of radium-223 to cabozantinib for advanced renal cell cancer that has spread to bone was opened to accrual. The RadiCaL Study, a phase II, open-label, randomized trial with an accrual target of 210 participants, is scheduled for completion in 2024 (NCT04071223) [22].

Urothelial Cancer

A single-site, single-arm, phase I pilot study exploring the use of radium-223 and atezolizumab in patients with urothelial carcinoma with bone metastases who had progressed following platinum-based chemotherapy was opened to accrual in 2017. At the time the study was closed in 2018, only a single patient had been registered [23].

Thyroid Cancer

Deandreis et al reported results of an open-label, single-arm, prospective multicenter phase II trial of radium-223 for the treatment of bone metastases from radioactive iodine refractory well-differentiated thyroid cancer [24]. The RADTHYR trial was stopped early after an interim analysis demonstrated a lack of response and severe hematologic toxicity.

Osteosarcoma

Anderson et al [25] reported the use of radium-223 in combination with other systemic agents and EBRT for the management of metastatic osteosarcoma. Fifteen patients with radiographically proven bone metastases were included in the report. Systemic agents and EBRT were administered at the discretion of the attending physicians, and a variety of agents, schedules, and doses were employed. All patients had active disease at completion of their initial chemotherapy, and only 3 of 15 were able to receive the full 6 cycles intended course of radium-223, primarily because of progressive disease. Only 1 patient had a partial response, with 50% decrease in lesions measurable on PET scan. The authors suggested that radium-223 might be useful in clinical situations not amenable to surgery, perhaps in combination with stereotactic body radiation therapy [25].

Multiple Myeloma

Although osseous lesions from multiple myeloma (MM) are typically lytic, the use of radium-223 has been studied in the disease. A vendor-sponsored phase I trial was initiated in 2017, with a 2-phase design. Phase Ib was to consist of an open-label, dose escalation trial with bortezomib and dexamethasone in subjects with relapsed MM. The primary endpoint was to be optimal radium-223 dose. Phase II was to be an international, double-blind, randomized, placebo-controlled study to compare the study group to placebo. The study was closed to accrual in 2019, having accrued only 3 patients to phase Ib, and none to phase II [26].

VI. DOCUMENTATION

Reporting should be in accordance with the ACR–ARS Practice Parameter for Communication: Radiation Oncology [27].

The report should include , the radiopharmaceutical administered dose and route of administration. The type, dose, and route of any adjunctive pharmaceuticals used should also be documented.

VII. ACR STATEMENT ON THERAPEUTIC USE OF UNSEALED RADIOPHARMACEUTICAL SOURCES

Based on their education, training pathway(s), initial board certification(s), and clinical work experience practitioners licensed as an AU by the NRC or appropriate Agreement State must be authorized to use unsealed radiopharmaceuticals for therapy use to supervise and perform therapies using radiopharmaceuticals, including radium-223. These practitioners may include , diagnostic radiologists (DRs), nuclear radiologists (NRs), nuclear medicine physicians (NMs), and radiation oncologists (ROs). 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 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 radium-223 under the supervision of an AU. Although they may not issue written directives for the agent, 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 their NRC or Agreement State license authorizing radiopharmaceuticals for therapy use may administer the agent and may supervise other appropriate professionals in administration.

Radiologists, medical physicists, non-physician radiology providers**,** 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 who work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection, application of dose constraints and limits) and the principles of proper management of radiation dose to patients (justification, optimization including the use of dose reference levels). https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.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 in accordance with ALARA principles. 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 applicable state, local, or other relevant regulatory agencies and accrediting bodies, as appropriate. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol, using body habitus or other customized method when such guidance is available.

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

Additional information regarding patient radiation safety in imaging is available from the following websites – Image Gently® for children (www.imagegently.org) and Image Wisely® for adults (www.imagewisely.org). 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 periodically measured by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Monitoring or regular review of dose indices from patient imaging should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry and relevant publications relying on its data, applicable ACR Practice Parameters, 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; 2006, 2009, amended 2013, revised 2023 (Res. 2d).

ACKNOWLEDGEMENTS

This practice parameter was revised according to the process described under the heading *The Process for Developing ACR Practice Parameters and Technical Standards* on the ACR website (https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards) by the Committee on Practice Parameters – Nuclear Medicine and Molecular Imaging of the ACR Commissions on Nuclear Medicine and Molecular Imaging and the Committee on Practice Parameters – Radiation Oncology of the ACR Commission on Radiation Oncology, in collaboration with the ACNM, the ARS, and the SNMMI.

*Practice parameters and technical standards are published annually with an effective date of October 1 in the year in which amended, revised, or approved by the ACR Council. For practice parameters and technical standards published before 1999, the effective date was January 1 following the year in which the practice parameter or technical standard was amended, revised, or approved by the ACR Council.

Development Chronology for this Practice Parameter
2019 (Resolution 39)
Revised 2024 (Resolution 15)

Writing Committee – members represent their societies in the initial and final revision of this practice parameter

ACR
Akin, Esma A MD, Co-Chair
Wallner, Paul DO, Co-Chair
Morris, Zachary MD
Rabatic, Bryan MD

ACNM
Alexander, Sindu MD
Mulugeta, Philipose G MD
Saboury, Babak MD

ARS
Barry, Parul MD
Deville, Curtiland MD
Kishan, Amar MD
Sharma, Navesh DO

SNMMI
Colletti, Patrick M. MD
Kuo, Phillip H MD, PhD
Pandit-Taskar, Neeta MD

Committee on Practice Parameters – Nuclear Medicine and Molecular Imaging
(ACR Committee responsible for sponsoring the draft through the process)

Ghesani, Munir V MD, Chair
Aboian, Mariam MD, PhD
Bartel, Twyla B DO, MBA
Gerard, Perry S MD
Marcus, Charles MD
Peacock, Justin G MD, MHPE, PhD
Surasi, Devaki Shilpa MD
Wong, Terence Z MD, PhD
Subramaniam, Rathan M MBA, MD, MPH, PhD, Chair
Akin, Esma A MD
Dibble, Elizabeth H MD
Karagulle Kendi, A. Tuba MD
Mercier, Gustavo A MD, PhD
Solnes, Lilja B MBA, MD
Trout, Andrew T MD
Zukotynski, Katherine MD, PhD

Committee on Practice Parameters – Radiation Oncology
(ACR Committee responsible for sponsoring the draft through the process)

Schechter, Naomi MD, Chair
Chao, Samuel MD
Frank, Steven J MD
Garsa, Adam MD
Morris, Zachary MD
Reilly, Michael PhD
Sio, Terence Tai-Weng MD, MS
Berkowitz, Aviva MD
Davis, Brian J MD, PhD
Freedman, Laura MD
Lo, Simon S. ChB, MB
Rabatic, Bryan MD
Saeed, Hina MD
Wallner, Paul DO

Committee on Practice Parameters and Technical Standards
(ACR Committee responsible for sponsoring the draft through the process)

Newell, Mary S MD, Chair
Caplin, Drew M MD

Committee on Practice Parameters – Radiation Oncology
(ACR Committee responsible for sponsoring the draft through the process)

Schechter, Naomi MD, Chair
Chao, Samuel MD
Frank, Steven J MD
Garsa, Adam MD
Morris, Zachary MD
Reilly, Michael PhD
Sio, Terence Tai-Weng MD, MS
Berkowitz, Aviva MD
Davis, Brian J MD, PhD
Freedman, Laura MD
Lo, Simon S. ChB, MB
Rabatic, Bryan MD
Saeed, Hina MD
Wallner, Paul DO

Larson, David B MBA, MD, Chair, Commission on Quality and Safety
Rohren, Eric MD, PhD, Chair, Commission on Nuclear Medicine & Molecular Imaging
Small, William MD, Chair, Commission on Radiation Oncology

Comments Reconciliation Committee

Akin, Esma A MD
Barry, Parul MD
Caplin, Drew M MD
Colletti, Patrick M. MD
Ghesani, Munir V MD
Kuo, Phillip H MD, PhD
Alexander, Sindu MD
Bartel, Twyla B DO, MBA
Chao, Samuel MD
Deville, Curtiland MD
Kishan, Amar MD
Larson, David B MBA, MD

Morris, Zachary MD
Newell, Mary S MD
Rabatic, Bryan MD
Saboury, Babak MD
Sharma, Navesh DO
Subramaniam, Rathan M MBA, MD, MPH, PhD
Mulugeta, Philipose G MD
Pandit-Taskar, Neeta MD
Rohren, Eric MD, PhD
Schechter, Naomi MD
Small, William MD
Wallner, Paul DO

REFERENCES

1. American College of Radiology. ACR–ACNM–ASTRO–SNMMI practice parameter for the performance of therpay with unsealed radiopharmaceutical sources. 2019; https://www.acr.org/-/media/ACR/Files/Practice-Parameters/UnsealedSources.pdf. Accessed February 15, 2023.
2. Abou D, Ulmert D, Doucet M, Hobbs R, Riddle R, Thorek D. Whole-Body and Microenvironmental Localization of Radium-223 in Naïve and Mouse Models of Prostate Cancer Metastasis. *Journal of the National Cancer Institute.* 2015;108.
3. Brunland OSF, T. *Targeted cancer therapy - an odyssey* Copenhagen, Denmark: Ravnetrykk; 2003.
4. Xofigo (radium-223 dichloride) prescribing indications. 2022; https://www.xofigohcp.com/. Accessed February 28, 2023.
5. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol.* 2014;65(2):467-479.
6. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26(7):1148-1159.
7. Institute NC. Castrate Resistant Prostate Cancer. 2023; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/castrate-resistant-prostate-cancer. Accessed February 28, 2023.
8. American College of Radiology. ACR–ASTRO practice parameter for radiation oncolog. 2018; Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RadOnc.pdf. Accessed May 15, 2018.
9. American College of Radiology. ACR–ARS practice parameter on informed consent - radiation oncology. 2022; Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/InformedConsent-RO.pdf. Accessed March 1, 2023.
10. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol.* 2014;15(12):1397-1406.
11. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.
12. Parker CC, Coleman RE, Sartor O, et al. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial. *Eur Urol.* 2017.
13. Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol.* 2016;27(5):868-874.
14. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol.* 2016;17(9):1306-1316.
15. Sartor O, Hoskin P, Coleman RE, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. *Prostate.* 2016;76(10):905-916.
16. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(3):408-419.
17. Sartor O, Heinrich D, Mariados N, et al. Re-treatment with radium-223: first experience from an international, open-label, phase I/II study in patients with castration-resistant prostate cancer and bone metastases. *Ann Oncol.* 2017;28(10):2464-2471.

18. National Institute of Health USNLoM. Study of radium-223 dichloride versus placebo and hormonal treatment as background therapy in subjects with bone predominant HER2 (human epidermal growth factor receptor 2) negative hormone receptor positive metastatic breast cancer. 2020; https://clinicaltrials.gov/ct2/home. Accessed March 1, 2023.
19. Coleman R, Aksnes AK, Naume B, et al. A phase IIa, nonrandomized study of radium-223 dichloride in advanced breast cancer patients with bone-dominant disease. *Breast Cancer Res Treat.* 2014;145(2):411-418.
20. Ueno NT, Tahara RK, Fujii T, et al. Phase II study of Radium-223 dichloride combined with hormonal therapy for hormone receptor-positive, bone-dominant metastatic breast cancer. *Cancer Med.* 2020;9(3):1025-1032.
21. National Institute of Health USNLoM. Testing the addition of radium therapy (radium-223 dichloride) to the usual chemotherapy treatment (paclitaxel) for advanced breast cancer that has spread to the bones. 2023; https://clinicaltrials.gov/ct2/show/NCT04090398. Accessed March 1, 2023.
22. National Institute of Health USNLoM. Testing the addition of a new anti-cancer drug, radium-223 dichloride, to the usual reatment (cabozantinib) for advanced renal cell cancer that has spread to the bone, the radiCaL study. 2023; https://clinicaltrials.gov/ct2/show/NCT04071223. Accessed March 2, 2023.
23. National Institute of Health USNLoM. Radium-223 and atezolizumab in patients with urothelial carcinoma with bone metastases who have had disease progression after platinum-based chemotherapy. 2018; https://www.clinicaltrials.gov/ct2/show/NCT03208712. Accessed March 1, 2023.
24. Deandreis D, Maillard A, Zerdoud S, et al. RADTHYR: an open-label, single-arm, prospective multicenter phase II trial of Radium-223 for the treatment of bone metastases from radioactive iodine refractory differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2021;48(10):3238-3249.
25. Anderson PM, Scott J, Parsai S, et al. 223-Radium for metastatic osteosarcoma: combination therapy with other agents and external beam radiotherapy. *ESMO Open.* 2020;5(2).
26. National Institute of Health USNLoM. Study testing radium-223 dichloride in relapsed multiple myeloma. 2020; https://clinicaltrials.gov/ct2/show/NCT02928029. Accessed March 1, 2023.
27. American College of Radiology. ACR–ASTRO practice parameter for communication: radiation oncology. 2019; Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Communication-RO.pdf. Accessed March 1, 2023.
28. American College of Radiology. ACR–AAPM technical standard for medical nuclear physics performance monitoring of gamma cameras. 2018; Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Gamma-Cam.pdf. Accessed May 15, 2018.
29. Morote J, Aguilar A, Planas J, Trilla E. Definition of castrate resistant prostate cancer: new insights. Biomedicines. 2022 Mar 17;10(3):689.
30. Tombal BF, Loriot Y, Saad F, McDermott RS, Elliott T, Rodriguez-Vida A, et al. Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: an interim safety analysis. J Clin Oncol. 2019;37(15_suppl):5007.
31. Silke Gilleseen et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis.. *JCO* 39, 5002-5002(2021).
32. Maughaun BL, Kessel A, McFarland TR, et al. Radium-223 plus enzalutamide versus enzalutamide in metastatic castration-refractory prostate cancer: final safety and efficacy results. Oncologist. 2021;26(12):1006-e2129.
33. McDermott RS, Greene, McCaffrey J, et al. Radium-223 in combination with enzalutamide in metastatic castration-resistant prostate cancer: a multi-centre, phase II open-label study. Ther Adv Med Oncol. 2021;13:1-10.
34. Greene JP, Jui Lim MC, Baird A-M, et al. An updated analysis evaluating skeletal related events (SREs) in CTRIAL-IE 13-21: phase II trial of radium-223 (R223) in combination with enzalutamide (ENZA) for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. J Clin Oncol. 2019;37(7_suppl):215-215.
35. Shore ND, Schellhammer PF, Tutrone RF, et al. Open label phase II study of enzalutamide with concurrent administration of radium 223 dichloride in patients with castration-resistant prostate cancer. Clin Genitourin Cancer. 2020;18(5):416-422.
36. Petrylak DP, Vaishampayan UN, Patel KR, et al. A randomized phase IIa study of quantified bone scan

dichloride alone or in combination with abiraterone acetate/prednisone or enzalutamide. ESMO Open. 2021;6(2):100082.

37. Zang PD, Zhang-Xu L, Tsao-Wei DD, et al. Immune Activation and Clinical Response From Enzalutamide (enza) Alone or with Radium 223 (Ra223) In Metastatic Castration-Resistant Prostate Cancer (mCRPC). Poster presented at: the 37th Annual Meeting of the Society for Immunotherapy of Cancer's (SITC); 08-12 November, 2022; Boston, MA.
38. European Organisation for Research and Treatment of Cancer - EORTC. A randomized multicenter phase III trial comparing enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 April 03]. Available from: https://clinicaltrials.gov/ct2/show/NCT02194842. NLM Identifier: NCT02194842.
39. Ahmed ME, Joshi VB, Badawy M, et al. Radium-223 in the third-line setting in metastatic castration-resistant prostate cancer: impact of concomitant use of enzalutamide on overall survival (OS) and predictors of improved OS [published online ahead of print January 07, 2021]. Clin Genitourin Cancer. doi: 10.1016/j.clgc.2020.12.009.
40. Vogelzang NJ, Fernandez DC, Morris MJ, et al. Radium 223 dichloride in US expanded access program (EAP) [Abs 247]. Presented at the 2015 Genitourinary Cancers (ASCO GU) Symposium; February 26-28, 2015; Orlando, FL.
41. Sartor O, Fernandez DC, Morris MJ, et al. Prior and concurrent use of abiraterone and enzalutamide with radium 223 in an expanded access setting [Abs 253]. Presented at the 2015 Genitourinary Cancers (ASCO GU) Symposium; February 26-28, 2015; Orlando, FL.
42. Shore N, Vogelzang N, Fernandez D, et al. Radium-223 dichloride in expanded-access setting in the United States: overall and concurrent experience with abiraterone or enzalutamide [MP87-12]. Presented at the 2015 American Urological Association (AUA) Annual Meeting; May 15-19, 2015; New Orleans, LA.
43. Shore ND, Sartor O, Sternberg CN, et al. Concurrent or layered treatment with radium-223 (Ra-223) and enzalutamide (enza) or abiraterone + prednisone/prednisolone (abi/pred): a retrospective study of real-world clinical outcomes in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [Abs 5026].
44. Dizdarevic S, Sternberg C, Saad F, et al. Co-treatment with radium-223 and enzalutamide: outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) from a prospective multicenter observational study [abstract]. J Nuclear Med. 2019;60(suppl 1):467.
45. Liaw B, Tsao C-K, Glasky MD, et al. PRINT: prostate cancer intensive, non-cross reactive therapy for CRP – early observations of efficacy [abstract]. J Clin Oncol. 2020;38(6_suppl):89-89.
46. American College of Radiology. ACR-AAPM-ACNM-SNMMI Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals. Available at https://www.acr.org/-/media/ACR/Files/Practice-Parameters/radiopharm.pdf.