Society of Nuclear Medicine and Molecular Imaging/European Association of Nuclear Medicine Procedure Guideline for Palliative Nuclear Medicine Therapies of Bone Metastases

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Conflicts of Interest:
ARP reports consulting activities for GE, Blue Earth Diagnostics Ltd., and Progenics and institutional research support from Progenics – all outside the submitted work.
ME reports prior consulting activities for Blue Earth Diagnostics Ltd., Novartis, Telix, Progenics, Bayer, Point Biopharma, and Janssen and a patent application for rhPSMA – all outside the submitted work.
DDB has no conflicts of interest to disclose.
ATK has no conflicts of interest to disclose.
RL has no conflicts of interest to disclose.
IR has no conflicts of interest to disclose.
EBS has no conflicts of interest to disclose.
MPT has no conflicts of interest to disclose.

PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine.

The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service for patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI/EANM recognizes that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines 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 physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines 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 the guidelines.

The practice of medicine includes both the art and the science of 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 these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action on the basis of current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

I. PURPOSE

The purpose of this guideline is to assist nuclear medicine practitioners in treating patients with ^{89}Sr-chloride, ^{153}Sm-lexidronam (^{153}Sm-EDTMP), or ^{223}Ra-dichloride (^{223}Ra-Cl_2) for palliation of bone pain secondary to osteoblastic metastases. These guidelines provide information on (1) evaluating patients who might be candidates for radiopharmaceutical treatment, (2) performing these treatments, and (3) understanding the sequelae of therapy.

II. DEFINITIONS AND BACKGROUND INFORMATION

Please see Table 1 for a summary of indications, radiophysical data, and administered activity.

Table 1: Summary of indications, radiophysical data, and administered activity

Agent	Indication	Emission(s)	Physical Half-Life	Administered Activity
^{89}Sr-chloride	Relief of bone pain caused by osseous metastases	β, rare γ	50.5 days	148 MBq (4.0 mCi) is recommended; alternative weight-based activity of 1.5-2.2 MBq/kg (40-60

				μCi/kg) may be used
^{153}Sm-lexidronam	Pain relief in patients with osteoblastic metastases seen on radionuclide bone scan	β, γ	1.9 days	Weight-based activity of 37 MBq (1.0 mCi) per kg
^{223}Ra-dichloride	Treatment of patients with castration-resistant prostate cancer with symptomatic osseous metastases and no known visceral metastatic disease	Predominantly α, with additional β and γ	11.4 days	Weight-based activity of 55 kBq (1.49 μCi) per kg

A. Definitions

1. ^{89}Sr-chloride

   ^{89}Sr-chloride is a radiopharmaceutical indicated for relief of bone pain in patients with painful osseous metastases. Currently marketed as Strontium89, ^{89}Sr-chloride was previously marketed as Metastron. It decays through beta emissions with a maximum energy of 1.46 MeV, a mean energy of 0.58 MeV, and an average soft tissue range of 2.4 mm. ^{89}Sr-chloride has a rare gamma emission (0.01%) with an energy of 0.91 MeV (*1*). Gamma camera images may be obtained by imaging bremsstrahlung emission following administration of ^{89}Sr-chloride (*2,3*). Its physical half-life is 50.5 days (*4*). ^{89}Sr-chloride is given through an intravenous injection. A fixed activity of 148 MBq (4 mCi) is recommended, but an alternative weight-based scaling of injected activity of 1.5-2.2 MBq/kg (40-60 μCi/kg) may be used (*5*). Radiation dosimetry is provided in Table 2. ^{89}Sr-chloride is not commonly used today.

2. ^{153}Sm-lexidronam (^{153}Sm-EDTMP)

   A radiopharmaceutical for pain relief in patients with osteoblastic metastases, ^{153}Sm-EDTMP consists of radioactive ^{153}Sm complexed to a chelator, ethylenediaminetetramethylenephosphonic acid (EDTMP). ^{153}Sm-EDTMP emits multiple beta (β) particles with a maximum energy of 0.81 MeV and an average energy 0.23 MeV (*1*). The average and maximum beta particle range in water are 0.5 mm and 3.0 mm, respectively. A gamma (γ) emission with 29% abundance and an energy of 103 keV allows concomitant imaging. ^{153}Sm-EDTMP has a 1.93-day physical half-life. ^{153}Sm-EDTMP therapy is given through an intravenous injection as a weight-based scaling of activity of 37 MBq/kg (1.0 mCi/kg) (*6*). Radiation dosimetry is provided in Table 3. ^{153}Sm-EDTMP is marketed as Quadramet and is not commonly used today.

3. ^{223}Ra-dichloride (^{223}Ra-Cl_2)
   ^{223}Ra-Cl_2 is a radiopharmaceutical for the treatment of patients with castration-resistant prostate cancer (CRPC) with symptomatic osseous metastases and no known visceral metastatic disease (*7*). ^{223}Ra-Cl_2 is chemically similar to calcium (-chloride), with the Ra ion behaving similarly to the Ca ion, and is concentrated in the calcium-dense osteoblastic metastases of prostate cancer (*8*). Here, it delivers alpha (α) particles to neighboring cancer cells within the bone matrix with high linear energy transfer (*9,10*). ^{223}Ra-Cl_2 decays through a complex decay series with alpha emission predominating. Additional beta and gamma emissions result in a total energy emitted of 28.2 MeV (*7,11*). Alpha emission energy for Ra-223 and its progeny ranges from 5 to 7.5 MeV (*11*). A soft tissue range of less than 100 μm for alpha particles limits toxicity to non-target adjacent tissues. ^{223}Ra-Cl_2 has a 11.4-day physical half-life (*7*). Imaging can be performed by gamma camera (either planar or single-photon emission computed tomography) through the detection of the ~84 keV X-rays (~40%), 154 keV gamma (5.79%), and 270 keV gamma (14%) from the parent ^{223}Ra (*12*), although this is rarely performed. ^{223}Ra-Cl_2 is administered through an intravenous injection as a weight-based scaling of injected activity of 55 kBq/kg (1.49 μCi/kg). ^{223}Ra-Cl_2 is marketed as Xofigo and is usually given at 4-week intervals for 6 total injections, as tolerated (*11*). Radiation dosimetry is provided in Table 4.

4. Osteoblastic metastases
   Osteoblastic metastases are sites of increased radiotracer uptake demonstrated with bone scintigraphy secondary to active bone formation (*13*). Bone scintigraphy can detect an increase in focal osteoblastic activity caused by a metastasis to bone before it can be seen with anatomic imaging studies such as plain radiography or computed tomography (CT) (*14*).

5. Visceral metastases
   Visceral metastases are those to organs, such as the liver or lung, excluding osseous and lymph node metastases.

B. Osseous Metastases

For all cancers, bone is the third most common site of metastasis, only outnumbered by lung and liver metastases. Breast and prostate cancer have a particular propensity to develop osseous metastases, in part owing to the indolent clinical course of some subtypes of these malignancies (*15*). The incidence of osseous metastases in prostate cancer increases with time, approaching 30% at 10 years (*16*). In the 10%-20% of patients who develop CRPC, $\geq$ 84% have osseous metastases at the time of diagnosis (*17*). Bone is also the most common site of metastasis in breast cancer (*18*), and the incidence of osseous metastases increases over time, with over 8% of patients developing osseous disease in 10 years (16). Nevertheless, osseous disease portends a poor prognosis and the associated pain affects quality of life (*19*).

Bone metastases are rarely solitary and prefer the axial to the appendicular skeleton, likely reflecting the distribution of hematopoietic red marrow (*15*). The development of metastases requires breaking of intercellular cohesion and tissue boundaries, circulation in blood or lymph, evasion of tumor-suppressing immune response, manipulation of the cellular microenvironment of the metastatic site, and angiogenesis to promote growth. Neoplastic cells migrating to the bone may remain dormant or

quiescent for years, evading detection thresholds and treatment, only to activate and grow much later (*20*).

Osteoblastic metastases alter the regulation of the coupling of bone formation and reabsorption, allowing reactive bone mineral deposition to outpace lysis in the normal cycle of bone turnover. This process is not well understood and may vary in different cancer types (*21,22*). Osteoblastic metastases are typical of prostate cancer and can be seen in breast cancer (*15,22,23*).

Osteolytic metastases are typical of myeloma, renal cell carcinoma, non-small cell lung cancer, thyroid cancer, and non-Hodgkin lymphoma, among others (*15*). Although not a simple one-factor process, osteolysis is primarily due to misregulated osteoclast activity rather than direct destruction by growing tumor (*24*). Currently available radionuclide therapy agents target osteoblastic metastases, leaving purely osteolytic metastases outside the practice scope of this guideline.

Mixed blastic and lytic osseous metastases may be seen in gastrointestinal and squamous cell cancers, as well as in some breast cancers (*15*). Radionuclide therapy may be used for mixed blastic/lytic metastases, depending on symptoms, treatment alternatives, and the preponderance of a blastic over a lytic component. Technetium 99m-methylene diphosphonate (^{99m}Tc-MDP) or technetium 99m-hydroxymethylene diphosphonate (^{99m}Tc-HDP) bone scintigraphy should be used as a surrogate for the presence of osteoblastic uptake of bone-seeking therapeutic agents.

C. Targeted Radionuclide Therapy of Osseous Metastases

Intravenous injection of ^{89}Sr-chrloride, ^{153}Sm-EDTMP, and ^{223}Ra-Cl_2 have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of bone pain resulting from osseous metastases. ^{89}Sr-chloride and ^{153}Sm-EDTMP are indicated for pain relief from bone metastases regardless of the primary malignancy (*5,6*); on-label use of ^{223}Ra-Cl_2 is currently limited to patients with CRPC (*11*). Physicians involved in treating such patients should understand radiation safety, the pathophysiology and natural history of the disease process, the rationale for radionuclide therapy, and the limitations of radionuclide therapy. Treating physicians should collaborate closely with the other physicians and healthcare personnel involved in the overall management of metastatic disease.

The administration of these agents in the United States falls under the guidelines of the Nuclear Regulatory Commission (NRC), Title 10 CFR Part 35.300, or Agreement State Institutional License. Institutional licenses must specifically list individuals licensed to use Section 35.300 materials. In Europe, clinicians involved in treatment with radionuclide therapy must be aware of and compliant with all national and local legislation and regulations.

^{32}P-sodium phosphate was discussed in the prior version of this guideline; however, this treatment is not currently available in the United States. The discussion of ^{32}P-sodium therapy for bone metastases has therefore been eliminated. ^{32}P-sodium phosphate proved effective in treating pain from osteoblastic metastases (*25*) and had several production advantages (*26*). However, bone marrow suppression from high-energy β-emission hampered widespread clinical acceptance (*26*), and commercial manufacturing was discontinued in 2009 (*27*).

Additional radiopharmaceuticals will be added to the guideline when they are approved by the FDA for the palliative treatment of painful bone metastases. Several radiopharmaceuticals approved in countries

outside of the United States (e.g., ^{186}Re-etidronate) are not discussed in this guideline. If new indications are added to the radionuclide therapies included here, these new indications will likewise be added to the discussion.

III. INDICATIONS AND CLINICAL TRIAL EXPERIENCE

A. ^{89}Sr-chloride

^{89}Sr-chloride is a beta-emitting, bone-seeking radiopharmaceutical that localizes to foci of osteoblastic activity in a manner similar to calcium (*28*). ^{89}Sr-chloride is indicated for relief of bone pain from osseous metastases (*29*). It is used for palliation of bone pain caused by osteoblastic or mixed osteoblastic lesions from any tumor that has abnormally increased focal osteoblastic activity as seen on bone scan.

A systematic review in 2005 of clinical trials of ^{89}Sr-chloride reported a range of efficacy for relief of pain, with a mean overall response rate of 76% (32% of patients had a complete response and 44% had some response). A decrease in analgesic use was also seen. Efficacy has been demonstrated with repeat dosing. Pain relief with ^{89}Sr-chloride began between 3 days and 4 weeks after administration, with relief lasting up to 15 months (*30*). Delayed and variable onset of relief limits the utility of ^{89}Sr-chloride in patients with a short life expectancy and those in need of rapid relief.

A transient increase in pain or "flare" after therapy, usually within 72 hours (*1*), has been reported in up to 25% of patients. Although speculation exists that this may predict good clinical response, the available data do not demonstrate an association of flare with response (*31,32*). Transient variable hematologic side effects are the most common adverse event, with platelet count decreasing by ~30% and white cell count by up to 65%; these effects generally recover without intervention (*30*). ^{89}Sr-chloride is not recommended in the presence of compromised bone marrow reserve. Bone scintigraphy may help assess the extent of marrow involvement; extensive osteoblastic activity may suggest compromised marrow reserve, necessitating careful attention to blood counts preceding and following therapy.

A phase II study of prostate cancer showed a survival benefit with the addition of ^{89}Sr-chloride to doxorubicin compared with doxorubicin alone in patients with androgen-independent prostate cancer (*33*). No other data are available to support a potential survival advantage.

B. ^{153}Sm-lexidronam (^{153}Sm-EDTMP)

^{153}Sm-EDTMP is a beta-emitting radiopharmaceutical that localizes to bone and bony metastases in a manner similar to ^{99m}Tc-MDP (*34*). ^{153}Sm-EDTMP is indicated for pain relief in patients with osteoblastic metastases that demonstrate uptake on radionuclide bone scan (*6,29*).

Numerous clinical trials of ^{153}Sm-EDTMP have demonstrated efficacy in relieving the pain of osseous metastases. Patients with prostate cancer have been most extensively studied, followed by patients with breast cancer and other cancers. Pain relief has been assessed through a variety of metrics, including patient and physician assessment and decreased opiate use. Response rates have varied, but consistently over 50% of patients have received some benefit (*35-38*). Relief was attained as early as 1 week with sustained responses seen at up to 4 months (*30*). A minority of patients (variable, but reported to be up to 31%-38%) had a marked response to therapy, including resolution of pain (*36,38*).

Transient marrow toxicity, generally mild, was noted with a nadir at approximately 1 month and recovery by 2 months. No grade 4 toxicities or irreversible toxicities were observed (*35-38*).

A transient increase in pain after treatment, deemed "flare phenomenon," is seen in a small percentage of patients (up to 8% in the 1 mCi/kg group (*35*) (*36*)). In a study of 152 men with prostate cancer, the same percentage of patients, 6%, experienced flare in the ^{153}Sm-EDTMP treatment group as in the placebo groups (*38*).

Previously, concern was raised that combining bone-targeted therapies may decrease the effectiveness of pain palliation (*1*). However, more recent studies suggest possible synergy (*39*) in which ^{153}Sm-EDTMP may be safely combined with bisphosphonate therapy. Bisphosphonates do not decrease uptake of ^{153}Sm-EDTMP (*40-42*). A small study demonstrated a shorter time to pain relief after ^{153}Sm-EDTMP when zoledronic acid was given 2 to 3 days prior to ^{153}Sm-EDTMP compared with a week before or after therapy (*43*).

There is no convincing evidence of a survival benefit with ^{153}Sm-EDTMP.

C. ^{223}Radium dichloride (^{223}Ra-Cl_2)

^{223}Ra-Cl_2 is an alpha particle-emitting calcium mimetic approved by the FDA and EMA, both in 2013, for CRPC with symptomatic bone metastases and no known visceral metastatic disease (*11*).

The phase III randomized, placebo-controlled Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial demonstrated a survival benefit of 3.6 months (median survival 14.9 months in the treatment arm compared with 11.3 months in the placebo arm in an updated analysis), independent of concurrent bisphosphonate use or prior docetaxel therapy. Moreover, the time to first symptomatic skeletal events was significantly longer in the treatment group than in the control group (15.6 vs. 9.8 months), and subjects in the treatment group had improved quality-of-life scores (*44,45*). Patients with a good baseline performance status and more than 6 osseous metastases, but without extensive confluent osteoblastic metastases (often called a "superscan") on pretreatment imaging, were more likely to achieve a survival benefit (*44*).

Although the ALSYMPCA trial excluded patients with lymph node metastases measuring greater than 3 cm in the short axis, and ^{223}Ra-Cl_2 has not been validated in that population, such lymphadenopathy is not a contraindication on the FDA label. Similarly, although residual primary prostate malignancy is not an absolute contraindication to ^{223}Ra-Cl_2, a trial of 44 ^{223}Ra-Cl_2 patients observed a higher death rate in those with intact primary prostate masses than in those with radical prostatectomy (*46*). For both of these populations, we consider the occasional use of ^{223}Ra-Cl_2 for palliation of painful bony metastases with the caveat that these patients may not achieve a survival benefit. In addition, although the label indication emphasizes palliation of bone pain and deemphasizes survival benefit, a recent trial of ^{223}Ra-Cl_2 demonstrated that asymptomatic patients were more likely to complete treatment and had better overall survival, time to progression, and time to symptomatic skeletal event than did symptomatic patients (*47*), suggesting a beneficial role among asymptomatic patients and those with a smaller tumor burden.

The 2019 National Comprehensive Cancer Network (NCCN) guidelines for management of prostate cancer include ^{223}Ra-Cl_2 among the options for systemic therapy for patients with symptomatic bone metastases and no visceral metastases, with category 1 or high-quality evidence supporting its use.

According to the NCCN guideline, $^{223}Ra\text{-}Cl_2$ may be considered as first-, second-, or subsequent-line therapy in this population (*48*). The optimal timing of $^{223}Ra\text{-}Cl_2$ relative to alternative therapies is not known. Within the heavily pretreated population of Expanded Access Programs (EAPs), patients with more advanced disease and pain tended to discontinue treatment early and had a shortened life expectancy (*49*). Conversely, $^{223}Ra\text{-}Cl_2$ in patients with fewer cycles of prior systemic therapy was associated with prolonged survival (*50*). It is unclear whether this indicates greater efficacy of $^{223}Ra\text{-}Cl_2$ earlier in the therapeutic algorithm, or that patients with progression through multiple systemic therapies simply have more advanced disease.

A group of practicing urologists and medical oncologists have argued that, as bone metastases most often precede visceral metastases in CRPC cases, there may be a window of eligibility for $^{223}Ra\text{-}Cl_2$ that favors use earlier in the disease course, perhaps as second-line therapy following advanced anti-androgen therapy, rather than as salvage therapy (*49*). For example, use of $^{223}Ra\text{-}Cl_2$ as second-line therapy following advanced anti-androgen therapy, rather than as salvage therapy, may capitalize on the window of opportunity; however, no trials have studied this directly. In ALSYMPCA, the survival benefit of $^{223}Ra\text{-}Cl_2$ was similar among those with or without prior docetaxel therapy (*51*). A secondary analysis of ALSYMPCA patients that evaluated outcomes of chemotherapy after $^{223}Ra\text{-}Cl_2$ (docetaxel in 70% of cases) found no difference in adverse effects or survival from the start of chemotherapy among $^{223}Ra\text{-}Cl_2$ vs. placebo arms (*52*). Patients receiving $^{223}Ra\text{-}Cl_2$ did initiate subsequent chemotherapy later than those receiving placebo, 3.8 vs. 2.6 months after completion of study treatment, in keeping with a possible progression-free survival benefit of $^{223}Ra\text{-}Cl_2$; however, the statistical significance of this 1.2-month difference was not reported. Overall survival following docetaxel therapy was similar by prior treatment with $^{223}Ra\text{-}Cl_2$ (16 months) vs. placebo (15.8 months)

Taken together, the available data indicate that $^{223}Ra\text{-}Cl_2$ is safe and effective either preceding or subsequent to systemic chemotherapy. Whether either timeline offers superior survival is unclear; however, earlier use of $^{223}Ra\text{-}Cl_2$ likely reduces the risk of losing eligibility because of the development of visceral metastases.

Whether $^{223}Ra\text{-}Cl_2$ can or should be used in combination with anti-androgen or chemotherapy is also unclear. Single-arm studies through EAPs suggested that combination therapy with abiraterone, enzalutamide, or denosumab was safe and may increase survival benefit by about 3 months over $^{223}Ra\text{-}Cl_2$ alone (*50,53*). However, the blinded, randomized, placebo-controlled ERA 223 trial of combination $^{223}Ra\text{-}Cl_2$ with abiraterone and prednisone/prednisolone raised doubts about the safety of combination therapy. The trial was unblinded prematurely because of an increased rate of fractures in the treatment arm and a nonsignificant trend for poorer survival in the treatment arm vs. the placebo arm (*54*). This prompted the EMA in 2018 to issue a formal warning, contraindicating the use of $^{223}Ra\text{-}Cl_2$ in combination with abiraterone plus these steroids (*55*). In addition, it has restricted the use of $^{223}Ra\text{-}Cl_2$ to metastatic CRPC (mCRPC), to be used only after 2 previous mCRPC treatments or when other treatments cannot be taken. Moreover, the FDA does not recommend $^{223}Ra\text{-}Cl_2$ in combination with abiraterone plus prednisone/prednisolone, citing increased fractures and mortality (*11*).

Notably, there was no appreciable difference in pathological fracture rates or progression of osseous metastases in ERA 223. The excess fractures were primarily fragility fractures at sites uninvolved by metastases. Accordingly, some experts have concluded that the excess fractures were not secondary to the combination of $^{223}Ra\text{-}Cl_2$ and abiraterone per se, but to the concomitant steroid course required to offset abiraterone's inhibition of glucocorticoid synthesis and maintain homeostasis in the adrenocorticotropic hormone-mineralocorticoid axis (*56*). Prednisone/prednisolone alters bone

turnover and suppresses osteoblast differentiation and activity (*57*), and it may have an interactive effect with $^{223}Ra\text{-}Cl_2$, which suppresses alkaline phosphatase, a marker of osteoblast activity (*58,59*). Future trials may investigate the use of smaller steroid doses or alternative combinations not requiring steroids; for the time being, no combination therapy involving $^{223}Ra\text{-}Cl_2$ is proven safe or superior to monotherapy.

Currently, retreatment following completion of $^{223}Ra\text{-}Cl_2$ is not routine. A single-arm trial of repeat treatment of up to 6 additional injections of $^{223}Ra\text{-}Cl_2$ demonstrated no new safety concerns or serious adverse events over up to 2 years of follow-up (*60*). Median overall survival was 24.4 months; no control arm was implemented to establish whether survival was prolonged by retreatment.

The approved indication for $^{223}Ra\text{-}Cl_2$ includes patients with prostate cancer only. $^{223}Ra\text{-}Cl_2$ has been studied in other malignancies in which investigators noted that the radiopharmaceutical localized to areas of bone turnover, not to the tumor itself. $^{223}Ra\text{-}Cl_2$ has been studied in breast cancer with several case reports (*61,62*) and early clinical trials in a variety of settings with encouraging results (*63,64*); additional trials are planned. Trials in different disease states in a variety of settings, including renal cell carcinoma, have also been reported (*65,66*)

Summary

In the United States, $^{223}Ra\text{-}Cl_2$ is indicated as first-, second-, or third-line/salvage treatment for patients with CRPC with osseous metastases and bone pain, but no visceral metastases. In Europe, the EMA has limited its approval to patients with mCRPC after 2 previous lines of treatment. $^{223}Ra\text{-}Cl_2$ confers a survival benefit of approximately 3 months in select populations. Current expert consensus regarding the timing of $^{223}Ra\text{-}Cl_2$ is that it should be used after progression through advanced anti-androgen therapy, but ideally early in the treatment course, as the prevalence of visceral metastases increases over time and would preclude $^{223}Ra\text{-}Cl_2$. Although studies are ongoing, there is no current role for combination therapy or retreatment with $^{223}Ra\text{-}Cl_2$. Residual primary disease and lymph node metastases > 3 cm do not absolutely contraindicate palliative use for symptomatic bone metastases, but likely reduce the survival benefit of $^{223}Ra\text{-}Cl_2$. Given the demonstrable survival benefit, and favorable effects on symptomatic skeletal events, $^{223}Ra\text{-}Cl_2$ should be considered a treatment of choice in select men with prostate cancer.

IV. PROCEDURE

A. Qualifications and Responsibilities of the Facility and Personnel

1. ^{89}Sr-chloride, ^{153}Sm-EDTMP, and $^{223}Ra\text{-}Cl_2$ may be administered only in a facility with a valid radioactive materials license incorporating NRC Section 35.300 or comparable Agreement State license in the United States, or an equivalent license in the European Union.

2. All administering physicians/staff (both the physician writing the prescription and the physician/staff injecting the therapy) must be listed on the NRC or Agreement State license or specifically designated under a broad license. A written directive must be signed by an authorized user prior to administration.

3. Patients should be seen in consultation with the administering/treating physician in collaboration with the physician assuming overall patient management. The physician directing the administration of the radionuclide therapy should participate in the care of the patient as part of the patient management

team. Discussion with the patient regarding radiation safety after administration must be completed prior to administration (outpatient instructions covered below). Written informed consent should be obtained by the treating physician following a risk-benefit discussion with the patient.

4. Physicians should be aware of the wide variations that occur between jurisdictions with respect to who may administer radioisotope therapy (e.g., technologist vs. physician/authorized user).

5. The facility in which the treatment is performed must have proper radiation safety procedures, including waste disposal, handling of contamination of personal belongings, understanding what to do in case of a spill or variations during administration, etc.

6. Printed documentation regarding radiation safety should be available to patients at the time of therapy and discussed prior to therapy administration.

B. Patient Preparation

1. Prior to administration of ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2, the patient should have a recent radionuclide bone scan to demonstrate osteoblastic metastases (within 3 months is preferred, though a longer interval may be suitable in specific patient circumstances). In particular, radiotracer uptake at sites of painful metastases is important for expectation of pain relief. A bone scan must be used to verify that sclerotic lesions seen on radiograph or CT have increased radiotracer uptake, given the mechanism of radionuclide localization as discussed earlier; quiescent, treated metastases may remain sclerotic indefinitely. Similarly, osteolytic metastases seen on anatomic imaging should be further characterized with a bone scan, as increased uptake at such sites suggests utility in treating with ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2. For ^{223}Ra-Cl_2, CT of the thorax, abdomen, and pelvis should be obtained to exclude visceral disease, as discussed previously.

2. Bone scintigraphic abnormalities should be correlated with appropriate physical examination and anatomic imaging studies to evaluate for abnormalities that require attention prior to radionuclide treatment (e.g., lesions that may cause nerve/cord compression, lesions prone to pathologic fracture). In these cases, radionuclide therapies should be pursued only in conjunction with targeted therapy (local radiation or surgical treatment). Radionuclide therapies have no role in the treatment of acute presentations of these entities.

3. The presence of concomitant non-osseous abnormalities or other causes of pain may limit the extent of symptomatic relief of painful lesions from radionuclide therapy. Prior to therapy, clinicians should consider other sources of pain indicated by the patient's clinical history and physical examination.

4. Given the potential treatment myelotoxicity, clinicians should discontinue myelosuppressive chemotherapy in anticipation of ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2 treatment (6-8 weeks for long-acting myelosuppressive chemotherapy and ~4 weeks for other myelosuppressive chemotherapy), although there is a paucity of data in this area.

5. Concomitant treatment with ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2 in patients being treated with external beam hemi-body radiation should be considered with caution as data describing combined adverse effects are lacking. The potential for overlapping myelotoxicity from these treatments should be considered. In general, withholding external beam radiation for 2-4 weeks prior to radionuclide therapy is

recommended. Following radionuclide therapy, withholding hemi-body radiation until blood counts have stabilized is advised.

6. Complete blood counts should be performed within 2 weeks prior to starting ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2 therapy and for subsequent treatments with ^{223}Ra-Cl_2.

a. ^{89}Sr

Low blood counts are a relative contraindication. A complete blood count (CBC) should be obtained within 2 weeks prior to the start of therapy. The following thresholds should be considered prior to initiating therapy: hemoglobin (Hb) > 9 g/dL, white blood cell (WBC) count > 3,500/μL, platelet count > 100,000/μL. According to EANM guidelines, in select cases, more liberal thresholds of a platelet count > 60,000/μL and WBC count > 2,400/μL may be considered, provided coagulation tests exclude disseminated intravascular coagulation (DIC). Blood counts typically recover within months of treatment, either partially or completely, and should be monitored (*5,67*).

b. ^{153}Sm-EDTMP

CBC should be obtained within 2 weeks prior to the start of therapy. The following thresholds should be considered prior to initiating therapy: platelet count > 60,000/μL (preferably >100,000/μL), WBC count > 2,400/μL (preferably >5,000/μL), absolute neutrophil count (ANC) > 2000/μL, Hb > 10 g/dL (*1*). Blood counts typically recover after treatment and should be monitored.

c. ^{223}Ra-Cl_2

1. CBC should be obtained within 2 weeks prior to start of therapy. The following thresholds should be considered prior to initiating therapy: ANC ≥ 1.5 x 10^9 /L, platelet count ≥ 100 x 10^9 /L, Hb ≥ 10 g/dL.

2. Prior to subsequent treatments, ANC should be confirmed as ≥ 1 x 10^9 /L and platelet count ≥ 50 x 10^9/L (*11*).

7. Treatment with ^{223}Ra-Cl_2 concomitantly with abiraterone plus steroids is contraindicated in the treatment of prostate cancer as described earlier, and the patient's medication list should be screened for such agents. There are no known contraindications to combining hormone therapy with ^{153}Sm-EDTMP at this time. The patient's medication list may also be screened for bone health agents (e.g., denosumab or zoledronic acid) and referral may be made for consideration of such agents.

8. The approved indications for ^{89}Sr-chloride, ^{153}Sm-EDTMP, or ^{223}Ra-Cl_2 stipulate symptomatic/painful bone metastases. ^{89}Sr, ^{153}Sm-EDTMP, and ^{223}Ra-Cl_2 have demonstrated benefit in decreasing pain, with only ^{223}Ra-Cl_2 having a survival benefit (*44*).

9. Active DIC may be a risk factor for severe thrombocytopenia after therapy (*68*). Appropriate testing for this condition is important if there is any doubt as to the cause of thrombocytopenia. Moreover, if laboratory values are thought to be in flux, repeat blood work should be performed to confirm adequate counts prior to treatment.

10. Renal excretion of ^{89}Sr-chloride and ^{153}Sm-EDTMP suggests caution in dosing patients with renal dysfunction. Hence, severe renal dysfunction (glomerular filtration rate < 30 mL/min) should preclude treatment with ^{89}Sr-chloride or ^{153}Sm-EDTMP (*6,69*). ^{223}Ra-Cl_2 has only limited renal excretion. Dose adjustment is not necessary in patients with mild to moderate renal impairment (creatinine clearance < 60 mL/min). Limited data are available for patients with severe renal dysfunction (creatinine clearance < 30 mL/min) (*11*), although adequate renal function was an eligibility criterion for the ALSYMPCA trial (*44*).

11. Patients should remain well hydrated before, during, and after treatment, as ^{89}Sr-chloride and ^{153}Sm-EDTMP are renally excreted. Dehydration has also been observed in 3% of patients treated with ^{223}Ra-Cl_2 (*11*). Patients do not need to fast before or after therapy.

12. ^{89}Sr-chloride, ^{153}Sm-EDTMP, and ^{223}Ra-Cl_2 should be administered by slow intravenous injection over 1 minute. An indwelling catheter should be placed for radiopharmaceutical administration and patency should be assessed through visualization of blood return and flushing. A running intravenous line may help avoid subcutaneous infiltration. A 3-way stopcock may be used to flush the syringe containing the radiopharmaceutical.

13. Patients should not be treated as inpatients.

14. Pain relief from radionuclide therapy may begin within 1 to 4 weeks of treatment, with maximum response achieved later (*38,70*). A patient with a life expectancy of less than a month is unlikely to achieve full benefit of treatment. Given the survival benefit of ^{223}Ra-Cl_2, a life expectancy of 6 months or longer is preferred prior to treatment. In addition, certain precautions at autopsy may be necessary with patients recently treated (reviewed in reference (*71*)). Cremation may also be affected.

15. Patients may be retreated with ^{89}Sr-chloride and ^{153}Sm-EDTMP if blood counts recover appropriately. ^{153}Sm-EDTMP has been readministered as soon as 8 weeks after the preceding treatment (up to 3 total administrations) without an increase in adverse events and with continued palliative benefit (*72*). Data on the efficacy of repeated treatments are sparse, but cumulative toxicity has not been apparent (*73*). Potential retreatment with ^{223}Ra-Cl_2, as discussed earlier, is not currently approved.

C. Information Pertinent to Performing the Procedure

1. Patient demographics (age, sex, weight, diagnosis).
2. Indications for therapy.
3. Current medications, especially hormonal or chemotherapy, or those affecting coagulation.
4. Extent of disease on bone scan obtained prior to initial therapy.
5. CBC and basic metabolic panel within 1-2 weeks prior to therapy.
6. Relevant radiographs or magnetic resonance imaging (MRI) of painful sites to exclude cord compression or lesions with an increased risk of pathologic fracture should be considered prior to initial treatment. CT imaging should be obtained prior to initial ^{223}Ra-Cl_2 therapy to evaluate for extraosseous metastases.
7. Life expectancy estimate.
8. Performance and pain status.
9. Pregnancy and breastfeeding are absolute contraindications to therapy with bone-seeking radionuclides.

D. Instructions for Patients

1. The following information should be discussed with patients prior to ^{89}Sr-chloride treatment:
    a. ^{89}Sr-chloride has a greater than 50% probability of achieving some element of pain relief. The chance of relieving pain completely for some period of time is real (*30*).
    b. ^{89}Sr-chloride is not a curative treatment for cancer, but a palliative treatment to relieve pain. No survival benefit has been demonstrated. Radionuclide therapy could theoretically cause a secondary cancer to develop; however, this is very unlikely for patients receiving ^{89}Sr-chloride for metastatic prostate cancer.

c. Mild and transient/reversible side effects include the following (*30*):
    i. Pain flare (~15%) 1 to 5 days after treatment, lasting up to 4 days. Pain relief may be obtained by increasing analgesia dose, if required.
    ii. Variable decrease in platelet and WBC counts, which most often normalize without intervention. A decrease in platelet and WBC counts can increase the risk of bleeding and infection, respectively. If unusual bleeding is noted, or there are signs of infection such as fever, patients should contact their doctor immediately.
d. For 2 weeks, patients should follow radiation safety precautions:
    i. Urinate while sitting and flush twice. Spilled urine should be cleaned up.
    ii. Wash hands thoroughly with soap and water after using the toilet.
    iii. Don gown and gloves when cleaning spilled body waste.
    iv. Wash soiled sheets and clothing immediately and separately from other clothes.
    v. For incontinent patients, urinary catheterization should be performed.
e. Pregnancy should be avoided for 6 months following treatment (*67*).

2. The following information should be discussed with patients prior to ^{153}Sm-EDTMP treatment:
    a. ^{153}Sm-EDTMP has a greater than 50% probability of achieving some element of pain relief. The chance of relieving pain completely for some period of time is real (*30*) (*69*). Pain reduction is not immediate, and a "flare" is possible (*30*).
    b. This is not a curative treatment for cancer, but a treatment to palliate pain and no survival benefit has been demonstrated.
    c. The following are potential side effects:
        i. Nausea/vomiting (~33% estimate) (*69*).
        ii. Weakness, constipation, anorexia (≤10%) (*69*).
        iii. Pain flare (12%-20%, depending on the study (*30*)), most often within 72 hours of injection (*6*). Pain relief may be obtained by increasing analgesia dose, if required.
        iv. Transient myelosuppression is common, with platelet and WBC counts attaining a nadir at approximately 1 month after administration. The vast majority of blood counts recover to baseline values (*69*). A decrease in platelet and WBC counts can increase the risk of bleeding and infection, respectively. If unusual bleeding is noted, or there are signs of infection such as fever, patients should contact their doctor immediately.
        v. Radionuclide therapy could theoretically cause a secondary cancer to develop.
    d. For 2 days after therapy, the following radiation safety precautions should be followed. ^{153}Sm-EDTMP can be excreted in the urine for up to 12 hours after therapy.
        i. Urinate while sitting and flush twice. Spilled urine should be cleaned up.
        ii. Wash hands thoroughly with soap and water after using the toilet.
        iii. Don gown and gloves when cleaning spilled body waste.
        iv. Do not have sexual intercourse for 2 days. An effective method of contraception should be used after receiving ^{153}Sm-EDTMP (*6*). Pregnancy should be avoided for 6 months following treatment (*67*).
        v. Wash soiled sheets separately from other clothes or store for 1-2 weeks to allow for radioactive decay.
        vi. For incontinent patients, urinary catheterization should be performed.

3. The following information should be discussed with patients prior to ^{223}Ra-Cl_2 treatment.

a. Patients receiving $^{223}Ra\text{-}Cl_2$ have an approximately 60% chance of pain reduction (*74,75*) and may benefit from an extension of life expectancy by approximately 3-4 months (*44*). Patients may also see a delay in bone-related complications such as pathologic fracture.
b. Early side effects may include the following:
    i. Nausea (38%)
    ii. Diarrhea (27%)
    iii. Vomiting (21%)
    iv. Peripheral edema (15%)
    v. Renal impairment (4%)
    vi. Dehydration (3%)
    vii. Injection site reactions (1%)
    viii. These are usually mild and self-limited but may be more severe in <5% of patients.
c. Late side effects include the following:
    i. Anemia is common, and affected 90% or more of patients receiving $^{223}Ra\text{-}Cl_2$ and their control group receiving placebo in the largest clinical trial. This was usually mild and self-limited, but more severe in 6% of both treatment and placebo groups. Anemia may cause light-headedness, racing heartbeat, or fatigue and is most likely due to disease progression.
    ii. Lymphocytopenia affected up to 92% of treated patients in a trial and was moderate to severe in 20%. Neutropenia affected 20%. These conditions were usually self-limited, and although they could increase infection risk, the rate of infections was not different between treatment and placebo groups in the ALSYMPCA trial.
    iii. Low platelets affected 34% of patients, increasing the risk of bleeding. This was usually mild and self-limited.
    iv. Bone marrow failure resulting in pancytopenia is estimated to affect 2% of patients.
    v. Radionuclide therapy could theoretically cause a secondary cancer to develop. Available data are insufficient to estimate this risk precisely; it is likely less than 1% and usually takes years to occur. This is unlikely to affect the length or quality of life of patients with mCRPC.
d. Radiation safety precautions include the following:
    i. For 2 days, use a separate bathroom when possible. Wipe yourself dry to avoid contaminating clothing. Wipe toilet seat with dampened toilet paper after use and throw in toilet to dispose.
    ii. For 1 week after each treatment, sit when voiding and avoid using a urinal. Flush the toilet twice and close the lid prior to flushing.
    iii. Follow good hygiene practices and wash hands thoroughly after voiding while receiving treatment and for 1 week after final treatment. Use of your own towel is advised. If you are incontinent, gloves should be worn when handling pads; hands should be washed thoroughly afterward.
    iv. Clothing soiled with urine or fecal material should be washed promptly and separately from other clothing.
    v. Your caregivers should use universal precautions when handling bodily fluids or handling materials contaminated with bodily fluids. This includes use of disposable gloves and barrier gowns. Caregivers should wash their hands thoroughly with soap and water after providing care.

vi. If sexually active, a condom should be used while receiving treatment and for 1 month after the last treatment. Do not father a child while receiving treatment or for at least 6 months after the last treatment. A female partner who can have children must use highly effective birth control.

e. Patients should stay well-hydrated while undergoing therapy. For 2 days, drinking 8 glasses of water or other non-alcoholic beverage per day is advised.

4. The following instructions pertain to ^{89}Sr, ^{153}Sm-EDTMP, and ^{223}Ra-Cl_2 treatment.
   a. A written consent form is strongly suggested and should include indications, expected outcomes, risks (including infection, bleeding, and death), and alternatives to treatment. Local hospital policies and state regulations should be followed.
   b. All questions should be answered prior to therapy.
   c. Expected follow-up should be reiterated to patients, including laboratory tests and clinic visits. A contact phone number should be given in the event that patients need to discuss their care with a treating physician.
   d. Patients should be provided with written outpatient instructions.
   e. Patients may continue a normal diet.
   f. Patients should be advised to contact their health care provider if they have any of the following signs or symptoms: temperature 100.4 °F (38°F) or higher; chills; difficulty urinating; diarrhea, nausea, or vomiting; pain not relieved by medication; bruising; blood in urine, semen, or stool; shortness of breath; lethargy; swelling of extremities.

E. Precautions

1. The degree of leukopenia and thrombocytopenia present should not be severe, as noted earlier. CBCs should be obtained as detailed earlier. Disseminated, confluent disease in the bones as seen on a bone scan (often referred to as a "superscan") indicates higher risk of bone marrow involvement.
2. Renal failure may require a reduction in the activity injected; no definite guidelines are available for specific recommendations.
3. Previous (especially recent) chemotherapy or wide-field radiation may decrease marrow reserve and possibly lead to treatment-induced leukopenia or thrombocytopenia.
4. Exclude spinal cord compression or soft-tissue tumor as the cause of the pain that is being treated. Lesions with a Mirel's score ≥ 8 may be referred for orthopedic evaluation for appropriateness of prophylactic fixation prior to therapy (*76*).
5. A careful injection technique must be used to avoid infiltration. No specific therapy is available if infiltration occurs, but local heat may increase the rate of reabsorption and therefore decrease the local radiation dose.
6. DIC should be excluded prior to treatment.
7. In women of childbearing potential, a pregnancy test within 2 days prior to treatment must have a negative result.
8. Patient and caregivers should be educated on radiation safety precautions and how to minimize contamination. Written instructions should also be provided.

F. Radiopharmaceuticals

1. ^{89}Sr-chloride
   Recommended activity of 148 MBq. Alternatively, 1.5-2.2 MBq/kg body weight (*5*).
2. ^{153}Sm-EDTMP
   Recommended activity of 37 MBq/kg (1.0 mCi/kg).
3. ^{223}Ra-Cl_2
   Recommended activity of 55 kBq/kg body weight administered every 4 weeks for 6 total injections.

G. Guidelines for Measuring the Activity

Both ^{153}Sm-EDTMP and ^{223}Ra-Cl_2 should be measured in a properly calibrated radioisotope dose calibrator (activity calibrator). The residual activity in the syringe must be measured to know the precise activity administered.

H. Interventions

Not applicable.

I. Processing

Not applicable.

J. Interpretation Criteria

^{153}Sm-EDTMP and ^{223}Ra-Cl_2 are not routinely imaged after treatment, but both have gamma emissions that could be imaged. Some centers acquire images regularly and dosimetry applications have been proposed and published for ^{153}Sm-EDTMP and ^{223}Ra-Cl_2 (*77-81*).

K. Reporting

After treatment, a report should be generated that includes the following items:

1. History and indication.
2. Correlative imaging (e.g., bone scan, radiographs, CT, positron emission tomography (PET)/CT) that was reviewed.
3. That informed consent was obtained and the patient was aware of the major associated risks, including leukopenia and thrombocytopenia. Pretherapy blood counts and date may be mentioned. The need for blood monitoring should be mentioned, as described earlier. The delay in pain reduction (1-3 weeks) and possibility of a pain flare may also be mentioned.
4. A sentence stating that all patient questions were answered to the patient's apparent satisfaction prior to therapy.
5. A record of the activity administered.
6. The status of the patient prior to leaving the department (e.g., the patient left the department in stable condition).
7. For multiple treatments, the number of the current treatment and total planned treatments should be mentioned (e.g., This was the Xth of 6 planned ^{223}Ra-Cl_2 treatments).

L. Follow-up

1. Follow-up can be performed either by the treating nuclear medicine physician (preferred) or the referring physician (e.g., urologist, oncologist). If the nuclear medicine physician will not be following the patient, it should be confirmed that the patient will receive adequate follow-up elsewhere before leaving the treating facility.
2. ^{89}Sr

Monitor blood counts at least bimonthly, continuing until recovery, noting the recovery may take greater than 3 months (*82*).

3. ^{153}Sm-EDTMP

Weekly CBC starting 2 weeks after therapy and continuing for 8 weeks or until recovery from nadir is achieved.

4. ^{223}Ra-Cl_2
    a. CBC should be repeated within 2 weeks prior to the next scheduled treatment. Treatment may continue if the following laboratory values are met: ANC ≥ 1 x 10^9/L and

platelet count ≥ 50 x 10^9/L. If these laboratory values do not normalize within 6-8 weeks, future treatments are generally discontinued. Blood counts should be monitored after completion of therapy until recovery as well. Supportive care—including colony-stimulating factor administration—may be considered if clinically indicated.

b. If the patient's general condition deteriorates significantly (decrease in Karnofsky index to <50% or increase in Eastern Clinical Oncology Group [ECOG] performance status to > 2), additional imaging may be appropriate (e.g., bone scan, PET/CT, CT, MRI). In the event of clear progression (appearance of new metastases), treatment should be continued only after careful risk-benefit assessment.
c. Monitoring of common biomarkers (e.g., prostate-specific antigen [PSA], lactate dehydrogenase, C-reactive protein, alkaline phosphatase) after several cycles (e.g., before the fourth therapy cycle) is preferable. However, fluctuations of biomarkers are not uncommon during therapy. Increasing biomarkers do not necessarily represent a lack of therapy response. There is growing evidence that alkaline phosphatase can better predict response compared with PSA (*74*). A comparison with findings from imaging (e.g., bone scan, PET/CT, CT, MRI) is advisable in order to objectify increasing biomarkers. In the event of clear disease progression (appearance of new metastases), the treatment should be continued only after careful risk-benefit assessment.
d. Continued monitoring of common biomarkers after therapy should depend on the duration of the disease, tumor biology, and previous course (if biomarkers were increased pre-therapeutically). Common intervals are 3 to 6 months at the beginning and yearly thereafter.
e. Timing of follow-up imaging (e.g., bone scan, PET/CT, PET/MRI) should depend on symptoms, duration of illness, and tumor biology. Imaging should be performed 3-6 months after the last treatment, or earlier as symptoms dictate. Patients should be advised that anatomic improvement on imaging takes time and that reactive osseous remodeling may lead to new sclerosis on CT.

M. Quality Control

1. The Institutional Quality Management Program mandated by the NRC should be followed. In Europe, similar programs are required for implementation by the EU Basic Safety Standards Directive.
2. Close communication and coordination between the referring physicians and treating physicians is recommended in all aspects of patient workup, treatment, and follow-up. Multidisciplinary conferences may be used to facilitate in-depth discussion.
3. Relevant patient information should be reviewed prior to treatment.

N. Sources of Error

1. Improper use of the dose calibrator: The activity must be measured in a geometry and a container consistent with previous calibration of the dose calibrator.
2. The radiopharmaceutical should be injected though an intravenous line, as described, with proper radiation precautions and with adequate flushing of the administered activity.

O. Future Outlook

Treatment of bone pain with radionuclide therapy has the potential to improve the quality of life of patients with osseous metastases. Treatment with ^{89}Sr-chrloride, ^{153}Sm-EDTMP, and ^{223}Ra-Cl_2 has a proven role for patients, the latter approved only for metastatic prostate cancer and the only agent with a demonstrable but small survival benefit. The integration of these therapies into clinical care should continue

to evolve as experience and research efforts continue. New agents will also become available in the future. Most notably, ^{177}Lu-prostate-specific membrane antigen radionuclide therapy for mCRPC has demonstrated encouraging results for efficacy and partly for bone pain palliation with a favorable safety profile (*83,84*). This agent has recently been granted FDA approval. Compared with the bone-seeking agents described herein, new oncotropic therapies with specific tumor targeting may offer greater benefit in patients with bone metastases. New agents and expanded indications for current agents should continue to improve and expand the treatment armamentarium.

LIABILITY STATEMENT

This guideline summarizes the views of the EANM Bone & Joint Committee, the EANM Dosimetry Committee, the EANM Radiation Protection Committee, and the SNMMI. It reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

ACKNOWLEDGEMENTS

The guidelines were brought to the attention of the relevant EANM Committees and the National Societies of Nuclear Medicine. The comments and suggestions from the EANM Bone & Joint Committee, the EANM Dosimetry Committee, the EANM Radiation Protection Committee, and the SNMMI are highly appreciated and have been considered for this guideline.

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Table 2: ^{89}Sr-chloride radiation absorbed doses (*1*)

Organ	mGy/MBq	rad/mCi
Bone surface	17.0	63.0
Red bone marrow	11.0	40.7
Lower bowel wall	4.7	17.4
Bladder wall	1.3	4.8
Testes	0.8	2.9
Ovaries	0.8	2.9
Uterine wall	0.8	2.9
Kidneys	0.8	2.9

Table 3: ^{153}Sm-lexidronam radiation absorbed doses (*6,34*)

Organ	mGy/MBq	rad/mCi
Bone surface	6.8	25.0
Red bone marrow	1.5	5.7
Lower bowel wall	0.01	0.04
Bladder wall	1.0	3.60
Testes	0.01	0.02
Ovaries	0.01	0.03
Kidneys	0.02	0.07

Table 4: ^{223}Ra-dichloride radiation absorbed doses (*11*)

Organ	mGy/MBq	rad/mCi
Osteogenic cells	1152	4263
Red bone marrow	139	514
Lower large intestine wall	46	172
Colon	38	142
Upper large intestine wall	32	120
Urinary bladder wall	4.0	15
Kidneys	3.2	12
Testes	0.08	0.31
Ovaries	0.49	1.8