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Nuts and Bolts of ^{223}Ra-dichloride Therapy

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Running Title:
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Learning Objectives:
On successful completion of this activity, participants should be able to describe: 1) properties of ^{223}Ra-dichloride and its utility in treating osteoblastic osseous metastatic disease; 2) important components of patient work-up including needed pre-therapy laboratory analysis and imaging; 3) proper use and handling of ^{223}Ra-dichloride; 4) how to set up a successful therapy program with ^{223}Ra-dichloride; and 5) important aspects of coding and billing.

Abstract:
Radionuclide therapy with ^{223}Ra-dichloride can be helpful for patients with osteoblastic osseous metastatic disease in the setting of castration resistant prostate cancer without visceral metastases. This article reviews the indications, proper use and handling, patient work-up prior to therapy and many of the technical considerations including discussion of coding/billing along with pitfalls that have been identified.

Key words: ^{223}Ra-dichloride, radium, radionuclide therapy, CRPC, osseous metastases

Introduction:

^{223}Ra has not always been known as such, early in the time after discovery in the early 1900s, this was known as "Actinium X" or "radio-actinium" (1, 2, 3, 4, 5, 6). Much has been learned about this radionuclide since that time. ^{223}Ra-dichloride, a bone-seeking calcium mimetic, works as an alpha-particle therapy which binds to areas of increased bony turnover in osseous metastases within the hydroxyapatite matrix, like ^{99m}Tc-methlyene diphosphanate (MDP), ^{99m}Tc-hydroxydiphosphonate (HDP) or ^{18}F sodium fluoride. Once localized, the alpha-particle deposits its energy in a highly localized manner, within a range of 100 μm (7), or on the order of a few cells apart from the site of disease. The alpha-particles deposit high levels of energy that cause predominantly double-stranded DNA breaks in the treatment region leading to highly localized cell death (8, 9), and sparing adjacent normal tissues (10, 11). More than a century after discovery of ^{223}Ra, it was studied to treat osseous metastases in the setting of prostate cancer and found to demonstrate a survival benefit in the landmark trial Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study (12). It was subsequently approved by the food and drug administration (FDA) on May 15, 2013 (13) for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease (14). ALSYMPCA demonstrated not only a survival benefit, but favorable effects on patient quality of life and favorable safety profile (12).

It is important to know some background information regarding prostate cancer. In the United States, prostate cancer is the most common cancer in men after lung cancer. It effects 1 in 8 men and is the cause of death in 1 in 41 men (15). Osseous metastatic disease in the setting of prostate cancer occurs in 70-90% of patients (16, 17). Prostate cancer patients with osseous metastatic disease are known to have lower quality of life, increased cost of care and higher mortality (17,18). Because of this, radium therapy can have a clear impact on these patients. The ALSYMPCA trial demonstrated a survival benefit of 14.9 months in the treatment group versus 11.3 months in the untreated group which received best standard of care plus placebo (12). Though this seems like a short time, it does amount to 30% longer timeframe compared to those who did not receive ^{223}Ra-dichloride.

Patient Selection, Clinical Considerations & Protocol:

The FDA approved indication for ^{223}Ra-dichloride the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Castration-resistant is cancer that continues to grow even when the testosterone levels are at or below the castrate level; it is also known as "hormone refractory" or "hormone-resistant" prostate cancer (19). Careful screening of prior imaging for visceral metastatic disease in organs and lymph nodes is helpful; the package insert advises an upper limit of 3 cm for lymph nodes (14). If not already performed, clinical guidelines indicate that patients should have a CT of the chest, abdomen and pelvis prior to therapy to assess for visceral metastatic disease (20). It is notable that prostate bed disease or localized involvement of the urinary bladder is also not considered visceral disease (20). Hematologic analysis must also be performed if the patient does not have visceral metastases and is considered for therapy. Per

the package insert, prior to the first treatment, the absolute neutrophil count (ANC) should be greater than or equal to 1.5 x 10^9/L, the platelet count should be greater than or equal to 100 x 10^9/L and the hemoglobin should be greater than or equal to 10 g/dL (14). Blood work should be done within at least 30 days of the initial therapy (20). There is some expected impact on bone marrow and the patient will need follow-up blood count analysis before additional therapies. For subsequent administration of the radionuclide therapy, the patient should have an ANC of 1 x 10^9/L and a platelet count of 50 x 10^9/L; no hemoglobin limit is required for subsequent therapies (14). Please see summary Table 1.

Because this therapy localizes to regions of bony turnover, it is imperative that a patient have a bone scan before being considered for therapy. If the osseous metastases do not have uptake, the patient should not receive therapy as the patient would not benefit from this therapy. Pre-therapy bone scans can be done with single photon or PET bone scanning agents. Clinical guidelines indicate that there should be at least two osseous metastatic lesions (20). Please note that PET agents such as PSMA and fluciclovine are not a substitute for bone seeking tracers in this setting (21).

Increasingly, nuclear medicine professionals are seeing patients in consultation prior to therapies and utilizing evaluation and management (E&M) codes. This is beneficial for the patient so they are not seen only on the day of therapy, but rather would have some time to prepare for potentially unexpected radiation safety instructions and offers easing concerns about the therapy itself, side effects and answering questions the patient and their families or caregivers may have. This is also helpful from the point of view of having time to adequately review the patient's history, coordinate with the urologist or oncologist or other clinical colleagues who refer the patient. This also allows time for insurance pre-authorization. During the course of the consultation process, needed items could be identified like a bone scan, blood work or other items may be identified and can be obtained in a timelier manner and not delay care or result in a wasted therapy dose.

Understanding prior therapies the patient has had is also important. There has been association of combined therapy of ^{223}Ra-dichloride with abiraterone plus prednisone or prednisolone which has led to increased frequency of fractures compared with those who did not receive the therapy with ^{223}Ra-dichloride (22). This has caused the European Medicines Agency (EMA) to recommend a contraindication in this setting; it is not reflected in the FDA's package insert at this time, nonetheless current guidelines discourage this practice (20). Other recent myelosuppressive therapies the patient may have had in the 4 weeks preceding therapy may also set the patient up for more profound myelosuppression. Likewise, if patients have had external-beam hemibody radiation or other systemic radionuclides within 24 weeks of therapy, careful considerations of risk/benefits of therapy is recommended (20). If the patient has epidural tumor or spinal cord compression, they should be treated preferentially with external beam radiation therapy prior to ^{223}Ra-dichloride (20). Working together with clinical colleagues to settle on an appropriate time for ^{223}Ra-dichloride therapy is important.

Assessing performance status is recommended. This can be done with the Eastern Cooperative Oncology Group (ECOG) or Zubrod performance status criteria (23). Guidelines suggest that life expectancy should be at least greater than 6 months and an ECOG performance status of 0 to 2 is preferred (20). Guidelines also recommend documentation of pain and patient-related symptoms pre-therapy and during the course of therapy to evaluate the patient's quality of life (20, 22).

Because of the elements of therapy to track and complexity of patients, it can be helpful to employ a checklist to ensure each data element has been obtained and meets therapy parameters for each individual patient. An example of items to keep on such a checklist is in Table 2.

Providing the patient meets the laboratory parameters and functional status requirements, therapy is given intravenously every 4 weeks for a total of 6 therapies. Therapies can be delayed if there is evidence of myelosuppression; this is allowed to up to 6-8 weeks following the most recent therapy. If blood counts do not improve despite supportive care, further treatment should be discontinued (14). Table 3 reviews important clinical metrics to evaluate prior to therapy. Figure 1 describes the therapy procedure at a glance.

Radiopharmaceutical Therapy Properties & Dosimetry:

^{223}Ra is an alpha particle and has a half-life of 11.43 days. The majority of the therapy (95.6% abundance) is alpha particles which deposit high energy with very short path length. Beta particles make up 3.6% of the decay and gamma photons make up 1.1% (14). This gamma photon allows for easy measurement on standard dose calibrators and survey meters. The full decay schema is described in Figure 2 and Table 4 details the dosimetry (24). Given the dosimetric data, one can understand why gastrointestinal symptoms may occur as this is excreted predominantly via the GI-tract in normal individuals.

Radiation Safety Precautions, Patient Consent & As Needed Medications:

According to the Nuclear Regulatory Commission (NRC), all radionuclide therapies should be given under the auspices of a "quality management" program (20). A written directive is required for each ^{223}Ra-dichloride therapy for each individual (i.e. 6 written directives for an individual patient for the entire course of therapy). Written directives will include the administered activity for the radionuclide therapy which in this case is weight-based (1.49 μCi/kg) and an updated weight will be necessary for ordering doses a week prior to therapy. Once again, assessment of the CBC with differential will be necessary to assess if the patient is experiencing myelosuppression and the need to pause or discontinue therapy.

During the course of the clinical consultation, there should be careful discussion of the radiation safety precautions, side effects, and complications. Nuclear medicine professionals should discuss precautions which primarily focus on stool and any body-fluid for the seek following therapy. Patients should be instructed to sit while urinating to minimize splatter. If a patient

has a urinary catheter, disposable gloves should be used when manipulating or changing catheters. Careful handwashing following using the restroom is imperative. Instruction on disposal of any materials which could contain body products is recommended. The patient should understand the potential side effects as part of consent for therapy. The most common side effects experienced by patients are myelosuppression, diarrhea, nausea, and peripheral edema. As needed (PRN) medications for nausea and diarrhea may prescribed or recommended over the counter. Patients should also be aware of a transient increase in bone pain, often referred to as the "flare phenomenon" (20). Because of potential flare and pain patient may have at baseline, patients should have appropriate pain medication ideally arranged by the clinician usually treating their pain and it is helpful for them to know that the patients may experience this increase in pain medication needs so they can plan appropriately. Complications that have been reported from ALSYMPCA are myelosuppression (13%), neutropenia (2%), thrombocytopenia (7%), grade 5 treatment-emergent adverse events (13%). Long term follow-up of patients from the trial yielded no findings to suggest myelodysplastic syndrome, acute myelogenous leukemia, or new primary bone cancer. Secondary non-treatment related malignancies occurred in 4 patients treated with ^{223}Ra-dichloride, while 3 occurred in placebo patients. One patient with aplastic anemia 16 months after the last injection (12).

Day of Therapy Technical Considerations:

Although external radiation exposure is quite low compared to other therapies, care in administering ^{223}Ra-dichloride is key. Care should be taken to avoid internal radiation contamination through injection, inhalation, or skin absorption. Because alpha particles deposit their energy in a highly localized range, greater damage can occur compared to beta particles or gamma photons. Because of the long half-life, spills should be avoided, but can be identified with standard survey equipment because of the gamma photon. Contamination clean-up can be performed with dilute aqueous EDTA solution and areas can be resurveyed to ensure that they are decontaminated.

Before the therapy, the therapeutic dose should be measured to ensure appropriate administered activity. Absorbent shielding should be placed under the patient's arm to prevent spill. The IV catheter should be checked for patency before initiation of therapy for each individual patient. The therapy is often given with a three-way stopcock with saline flush to ensure maximal delivery of the prescribed radiopharmaceutical. All intravenous lines and connections should be secure. Because this is an alpha particle therapy, more localized damage could occur in the event of extravasation. A dose shield is recommended for purposes to decrease dose to the individual delivering the therapy as part of an "as low as reasonably achievable" or ALARA program. Dose rates are surprisingly high near the dose itself (Table 5). Some institutions choose to use a test dose of a small amount of ^{99m}Tc-pertechnetate and acquire dynamic images to ensure a patent IV catheter. The therapy is injected by slow intravenous injection over one minute. After injection, flushing with isotonic saline is recommended (20).

Creating a Successful Radionuclide Therapy Program with ^{223}Ra-dichloride:

Technical site prerequisites for site initiation according to the company include: radioactive materials license (RML or RAM) approved for medical use of ^{223}Ra-dichloride, authorized user list for medical use of ^{223}Ra-dichloride, documentation of training on handling and use of ^{223}Ra-dichloride, and verification of calibration of dose calibrator(s) to measure ^{223}Ra-dichloride activity accurately. Dose calibrator testing with a NIST-traceable ^{223}Ra standard is provided by Cardinal Health. Additional needs which may already be established in a nuclear medicine area include: monitoring of occupational doses, securing areas for storage, waste disposal and inventory management (25).

In meeting with committees for establishing new therapies, there is data that indicates that cost effectiveness of ^{223}Ra-dichloride is cost competitive as compared to other prostate cancer therapies. In addition, ^{223}Ra-dichloride therapy results in fewer skeletal related events (SREs) than other therapies and other groups have demonstrated a slower decline of quality of life over time with meaningful improvement in patients who receive this therapy compared to placebo (12, 26).

After site initiation is established, understanding of the codes involved in billing is very important. A summary of the codes needed are in Table 6. If done in a hospital setting, working closely with hospital billing offices is important as is staying tuned to potential annual changes in CMS coding practices. Both in and outside the hospital, the company offers guidance on coding (25). Prior to therapy, querying insurance companies on the need for prior authorization is recommended. The length of time needed for prior authorization to be obtained is quite variable among different insurance providers, but allowing 15 or more business days may be needed. Pitfalls of failing to use these codes can result in denial. In addition, failure to allow enough time for preauthorization or manage clinician and patient expectations can also be problematic. In order to ensure patients do not have out of pocket burden, close work with institutional billing offices and/or the company should be able to guide through issues encountered in coding and billing. In addition, the SNMMI has a “coding corner” with resources available to members (27).

In addition to these items, it is imperative to provide patients with multidisciplinary care and identify clinicians of various backgrounds who will be involved in the therapy referral and follow-up process. Follow-up practices may differ based on institutional protocols. Some practices include mid-therapy evaluation with laboratory biomarkers or imaging, however no well-defined guidelines exist as yet.

Looking Ahead:

The use of ^{223}Ra-dichloride is likely to evolve in the future considering the recent FDA approval of ^{177}Lu-vipvotide tetraxetan (also known as ^{177}Lu-PSMA-617) (28). ^{223}Ra-dichloride is a bone-based therapy while ^{177}Lu-vipvotide tetraxetan is a therapy that can also target soft tissue

lesions. Holistic evaluation and tracer uptake profile of the patient may be needed to assess which agent would be of most benefit.

Another area of interest may be repeat ^{223}Ra-dichloride therapy. Some research has already been done in this area and may suggest that this can be well tolerated and provide additional osseous metastatic disease control (28, 29). Longer term follow-up may be helpful to evaluate for continued long-term safety.

Education/Recommended Reading:

There is a good deal of helpful information available when starting a ^{223}Ra-dichloride therapy program, but these are some of the higher yield materials:

- ACR–ACNM–ASTRO–SNMMI Practice parameter for the performance of therapy with Radium-223 (20)
- ALSYMPCA Trial (12)
- Xofigo access services https://www.xofigoaccessonline.com/

Figure 1. Therapy process at a glance.

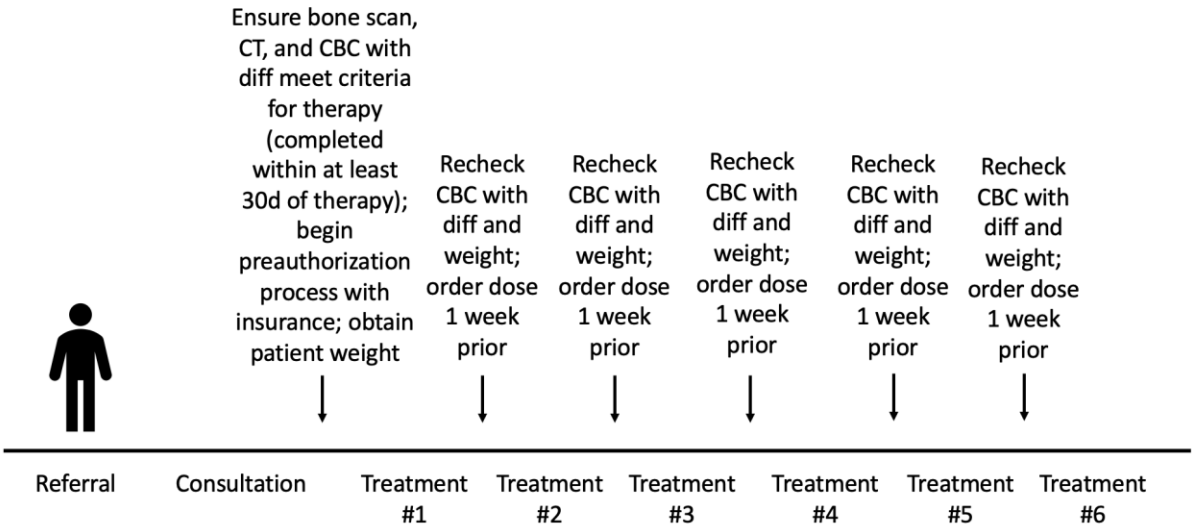

Figure 2. Decay Schema for ^{223}Ra-dichloride

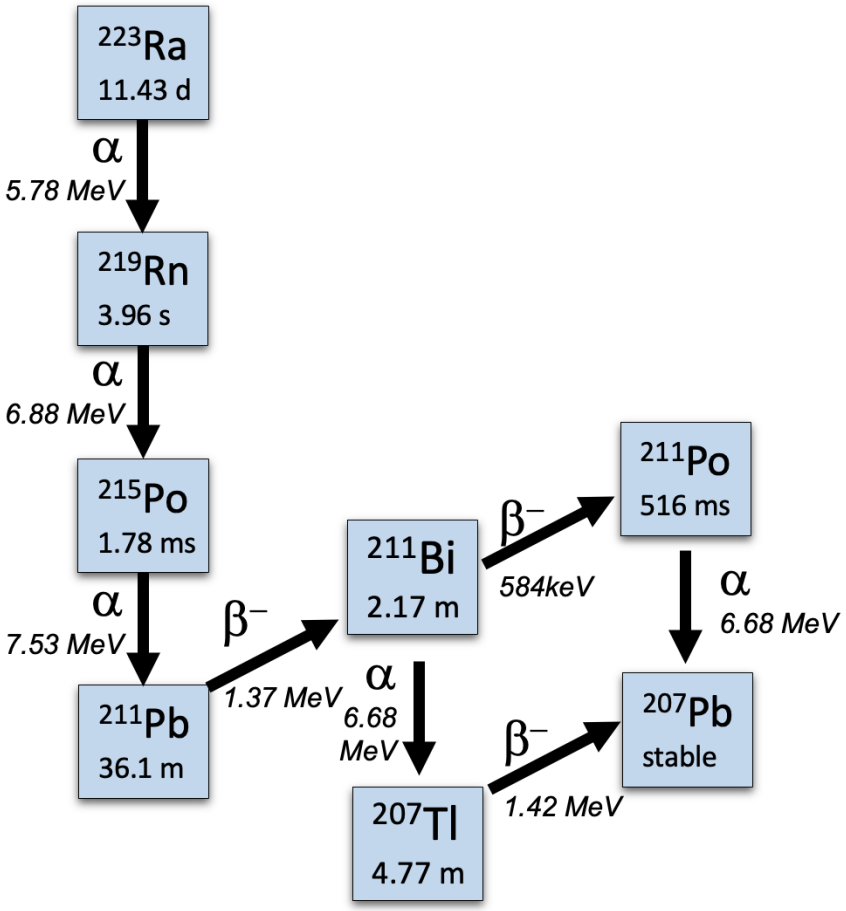

Table 1. Clinical eligibility criteria for therapy (14).

Clinical metric	**Requirement**
Castration-resistant prostate cancer metastatic to bone	Symptomatic No visceral metastatic disease Whole body bone scan with at least 2 lesions
CBC with differential	Prior to first treatment: ANC >/= to 1.5 x 10^9/L Platelet count >/= to 100 x 10^9/L Hemoglobin >/= to 10 g/dL For subsequent administration: ANC of 1 x 10^9/L Platelet count of 50 x 10^9/L No hemoglobin requirement

Table 2. Items to include in a ^{223}Ra-dichloride therapy checklist and consult note.

Data point	Reasoning/example
Documentation of bone scan demonstrating uptake in osseous metastatic disease	Required by package insert; if there is no uptake on bone scan, the therapeutic radionuclide will not localize in suspected areas of metastatic disease.
Documentation of no visceral metastatic disease	Required by package insert; the therapeutic radionuclide would not treat visceral metastatic disease – only osseous metastatic disease given its mechanism of localization; guidelines suggest CT chest, abdomen, and pelvis pre-therapy
Documentation of complete blood count with differential counts ("CBC with diff")	Required by package insert and serves as baseline prior to other therapies given potential myelosuppression of this therapy.
Plan or order for follow-up laboratory analysis prior to planned upcoming therapies	Required by package insert. Some labs may be organized by the clinician referring the patient but should know where to find this information prior to ordering upcoming doses. These labs are needed at least 1 week before each planned treatment.
Documentation of performance status	ECOG or Zubrod performance status. It is good to understand the patient's functional status prior to starting therapy for reference in future.
Review of patient continence of urine and stool	Most of this therapy will be excreted via the GI tract and to a lesser degree the urinary tract. This is helpful to give directed radiation safety instructions.
Review of home situation, travel, occupational considerations, etc.	This is helpful to give directed radiation safety instructions.
Review of side effects with recommendation for relevant PRN medications	This should be done for any medical therapy as part of consent.
Plan for follow-up weight measurements and documentation of patient weight	As doses are weight-based and the patient weight may vary due to a variety of circumstances during the therapy, good to know how this information will be obtained ahead of time.
Signed consent form	This should be done for any medical therapy as part of consent and understanding of potential risks, benefits.
Radiation safety instructions	This should be done for any radionuclide therapy.
Completed written directive for therapy #/6	This should be done for any medical therapy; ensure the updated weight is used for calculation.

Table 3. Elements to review prior to treatment on day of therapy.

Data point	Reasoning
Review consultation	Gain a better understanding if a patient is new to you or refresh your memory of the patient.
Review CBC with diff	Ensure CBC parameters are within appropriate range for therapy
Confirm weight and administered activity calculation is correct	Ensure the correct dose for the patient
Verify patient identity per institutional protocol	Ensure the correct patient receives therapy
Confirm patient has pre-therapy and post-therapy medications as needed	Ensures patient comfort in the event of side effects.
Radiation safety instructions	Ensure the patient has instructions and the opportunity to ask any questions
PRN medications	Ensure the patient has the PRN medications and associated instructions on when to use.
How patient is tolerating therapy	If this is not the first therapy, you can inquire how they did with the therapy and it is an opportunity to review needs for pain medications and other symptoms as well as give a preview of current therapy (e.g. if pain medications are less and the patient is no longer constipated, there could be a higher risk of soft stools or diarrhea on subsequent therapies)

Table 4. ^{223}Ra-dichloride Dosimetry (adapted from Lassman, et al.). (24)

Organ	Absorbed dose for alpha particles (high LET) Gy/Bq	Absorbed beta/gamma dose (low LET) Gy/Bq	Dose coefficients Gy/Bq	Relative contribution of the absorbed beta/gamma dose to the total dose %
Adrenals	3.2E-09	2.4E-10	1.6E-08	7
Bladder wall	3.3E-09	4.1E-10	1.7E-08	11
Bone endosteum	3.3E-09	1.1E-10	3.8E-06	1
Brain	3.2E-09	1.8E-10	1.6E-08	5
Breast	3.2E-09	1.6-10	1.6E-08	5
GI tract				
Esophagus	3.2E-09	1.7E-10	1.6E-08	5
Stomach wall	3.2E-09	3.9E-10	1.6E-08	6
Small intestine wall	3.2E-09	3.9E-10	1.7E-08	11
Upper large intestine wall	6.8E-09	1.4E-08	4.8E-08	67
Lower large intestine wall	1.3E-08	4.0E-08	1.1E-07	75
Colon	9.5E-09	2.5E-08	7.3E-08	72
Kidneys	3.4E-09	2.4E-10	1.7E-08	7
Liver	3.6E-09	1.5E-10	1.8E-08	4
Muscle	3.2E-09	2.0E-10	1.6E-08	6
Pancreas	3.2E-09	2.2E-10	1.6E-08	6
Red marrow	7.2E-08	5.5E-09	3.7E-07	7
Respiratory tract				
Airways	3.2E-09	1.7E-10	1.6E-08	5
Lungs	3.2E-09	1.9E-10	1.6E-08	6
Skin	3.2E-09	1.6E-10	1.6E-08	5
Spleen	3.2E-09	1.9E-10	1.6E-08	6
Testes	3.2E-09	1.8E-10	1.6E-08	5
Thymus	3.2E-09	1.7E-10	1.6E-08	5
Thyroid	3.2E-09	1.7E-10	1.6E-08	8

Table 5. Dose Rates Comparing ^{99m}Tc versus ^{223}Ra derived from exposure rate constants [uSv/h per MBq] (31)

Distance from point source	Tc-99m	Ra-223	Ra-223 + progeny
1 m	0.02	~0.02	0.047
10 cm	2	~2	4.7
1 cm	200	~200	470

Table 6. Current codes Involved in ^{223}Ra-dichloride therapy (27).

Code	Purpose
CPT code 99242 (New, outpatient, problem focused 30 min)	Evaluation & Management (so called "E&M codes") are dependent on type and length of consultation
CPT code 79101	Radiopharmaceutical therapy by intravenous administration
Radiopharmaceutical code A9606	Radiopharmaceutical code: Radium Ra 223 dichloride, therapeutic, per microcurie
JW modifier	Report wasted product to ensure able to report full costs of the ordered dose (given long half-life, may not be needed, but SNMMI supports use of this modifier)
Relevant ICD-10-CM Codes: C61 – Malignant neoplasm of prostate C79.51 – Secondary malignant neoplasm of bone	Needed for supporting the use of the above codes; ensures correct indication

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