Published in final edited form as:

Clin Nucl Med. 2013 December ; 38(12): . doi:10.1097/RLU.0000000000000290.

Targeted α -Particle Therapy of Bone Metastases in Prostate Cancer

Hossein Jadvar, MD, PhD, MPH, MBA^{*} and David I. Quinn, MD, PhD[†]

^{*}Divisions of Nuclear Medicine, Department of Radiology, Kenneth J. Norris Jr. Comprehensive Cancer Center, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA.

[†]Divisions of Cancer Medicine, Department of Medicine, Kenneth J. Norris Jr. Comprehensive Cancer Center, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA.

Abstract

Medical oncology is moving toward personalized and precision treatments. This evolution is spearheaded by ongoing discoveries on the fundamental machinery that controls tumor and hosts microenvironment biological behavior. α -Particles with their high energy and short range had long been recognized as potentially useful in the treatment of cancer. More than a century after the discovery of radium by the Curies, ^{223}Ra dichloride is now available in the expanding armamentarium of therapies for metastatic castration-resistant prostate cancer. This advance occurs in the context of several other novel therapeutics in advanced prostate cancer that include more effective androgen receptor pathway inhibition, better chemotherapy, and immunotherapy. We present a concise review on the therapeutic use of ^{223}Ra dichloride in this clinically important setting including excerpts on the radium history, physical properties, the alphas in symptomatic prostate cancer clinical trial, and practical information on its use in the clinic. It is anticipated that, with the current emergence of ^{223}Ra as a viable form of therapy, interest in and use of α -particle therapy in the management of cancer will grow.

Keywords

radium; α ; prostate; ALSYMPCA; cancer; therapy

Targeted therapy for cancer is emerging as an important treatment option in the era of personalized and precision medicine. Such treatment, by definition, is associated with high specificity of tumor targeting and little adverse effect on nontarget healthy tissues. Targeted radionuclide therapy is particularly an attractive approach in that intense localized irradiation can be delivered to the tumor for high therapeutic effect at all tumor sites scattered in the body.

For effective targeted radionuclide therapy, several components will need to be addressed.¹ The first step is to identify the most suitable biological target(s), which are preferably expressed in abundance and are accessible in tumors, whereas they have little or no expression or are inaccessible in the healthy tissues. There may also be biological platform strategies in which the target may first be “primed” by inducing specific expression in the

tumor that would not otherwise be presented. Multispecific targets may also provide additional exclusivity of tumor localization for subsequent radionuclide therapeutic action.

The next important step in targeted radionuclide therapy is the selection of suitable radionuclide(s) that can be incorporated into an agent with chemical and physical properties (eg, half-life) that matches the biological platform (eg, turnover of the radiolabeled carrier complex). From the outset, many factors will need to be carefully considered for optimized development of such therapeutic agents. These factors may include availability and cost of raw material and manufacture, ease of radiochemical incorporation, specific activity, synthesis yields, chemical and biological stability, dosimetry, radiobiologic modeling, expected therapeutic index, potential replaceability by other readily available (and less costly) agents, ease of protocol use and patient administration, and ease of regional and worldwide distribution.¹

Suitable radioisotopes for therapy may emit Auger electrons (eg, ¹¹¹In, ¹²⁵I), β -particles (eg, ¹³¹I, ¹⁷⁷Lu, ⁹⁰Y, ¹⁸⁶Re), and α -particles (eg, ²²³Ra, ²¹¹At, ²¹²Bi, ²¹³Bi, ²²⁷Th). There are advantages and disadvantages with each of these radioisotope types. β -Particle therapy (eg, CD20 antigen directed radiotherapeutic antibody using ⁹⁰Y-ibritumomab tiuxetan) is often associated with the “cross fire” or “bystander” effect of antigen-negative tumor cells because of the longer range of the particle (several mm), but this is at the cost of normal tissue toxicity. α -Particles, on the other hand, have much higher energy and lower range than β -particles and therefore are often associated with less collateral damage to the surrounding healthy tissue.²⁻⁴

α -PARTICLE THERAPY

There are more than 100 α -emitting radioisotopes, but most decay too fast to be useful for targeted radionuclide therapy. α -Particles are positively charged helium nuclei with a short range of about 50 to 80 μ m (vs several mm for β -particle) and high linear transfer energy of about 100 to 200 keV/ μ m (vs 0.2 keV/ μ m for β -particle) (Tables 1 and 2). The relative biologic effect of α -particles is about 3 to 7 folds of that for x-ray reference radiation for cell sterilization.⁵⁻¹⁰ The very high energy deposition of α -particles in a very small distance can cause irreversible double-strand DNA breaks. This is in contrast to β -particles that are often associated with single-strand DNA breaks. Cells are much better equipped to repair single-strand DNA breaks than double-strand DNA breaks.¹¹ Other than DNA break, the high localized irradiated energy leads to radiolysis of intracellular water that results in highly toxic radicals and chemicals that destroy the cell. Because the high energy of the α -particles is given off over a very short range, the targeted cells receive high absorbed radiation doses, whereas adjacent cells (tumor or healthy cells) may receive little or no radiation at all. The conventional Medical Internal Radiation Dose dosimetric method may therefore not be appropriate in this setting, and microdosimetric methods have been devised.¹² Of further importance in prostate cancer, and also potentially breast cancer, is that the mechanisms of action of ²²³Ra through ds-DNA breaks and radiolysis is independent of the sex steroid receptor–signaling mechanisms leveraged by most hormonal agents. This is potentially important as more exposure to androgen receptor pathway blockade pushes the cells toward an anaplastic state that may have growth kinetics independent of hormone signal and response.¹³ In this context of therapies such as ²²³Ra, which act independently of these agents, the benefit may increase as the cancer progresses through these treatments.

Although there has been much interest in the use of α -particles for targeted therapy, only lately this topic has been brought into spotlight by the recent US Food and Drug Administration (FDA) approval of ²²³Ra dichloride (Xofigo; Algeta–Bayer HealthCare

Pharmaceuticals, Wayne, NJ) for targeted therapy for bone metastases in men with castration-resistant prostate cancer.¹⁴

²²³Ra

Radium is a calcium mimetic and, along with barium and strontium, belongs to the alkali earth metals in the periodic table. On December 26, 1898, the Curies (Madame Curie and her husband, Pierre Curie) informed the *l'Académie des Sciences*, that they had come upon a very active substance that behaved chemically almost like pure barium, and they suggested the name of radium (²²⁶Ra with half-life of 1601 years) for the new element. The Curies and Henri Becquerel shared the Nobel Prize in physics in 1903 in recognition of the discovery and research on the radioactivity phenomenon. One of the radium isotopes, ²²³Ra, is the first α -emitter that has undergone formal testing for clinical use. It can be obtained from uranium mill tailings or in generator form from ²²⁷Ac (half-life, 21.8 years) parent through the reaction $^{227}\text{Ac} \Rightarrow ^{227}\text{Th} \Rightarrow ^{223}\text{Ra}$. The half-life of ²²³Ra is 11.43 days. The emitted energy distribution is 93.5% α -particle, 5.78 MeV (average), less than 3.6% as β -particle, and less than 1.1% as γ radiation with 28 MeV combined energy for complete decay including 0.9 MeV as γ radiation (Fig. 1).

²²³Ra targets the hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] matrix in the bone naturally because it simulates the stoichiometry of calcium. It is interesting that the potential use of ²²³Ra in therapy was recognized long ago as described in the following excerpt from “*Radium, A Cure For Cancer?*” written by Dr Louis Wickham, director of the Radium Institute, on December 18, 1909, “It is difficult, without exaggeration, not to recognize that radium therapy, as I have often repeated, has won its place in the therapeutic armamentarium, that the French discovery of Curie and Madame Curie has borne definite and certain fruit in the medical field.”¹⁵ It should be noted that radium was used as a source for external beam radiation therapy until the 1960s when ⁶⁰Co and other more modern techniques prevailed.^{16,17} Recently in 2013, the editorial by Vapiwala and Glatstein¹⁸ stated, “ α -Particles in medicine may be newly explored 115 years after their discovery.” Given the self-targeting of ²²³Ra to areas of active bone remodeling and formation, ²²³Ra was systematically evaluated for highly localized treatment of osteoblastic bone metastases.

CASTRATION-RESISTANT PROSTATE CANCER

The lifetime risk of prostate cancer in developed countries is about 1 in 6 men.¹⁹ In the post-prostate-specific antigen (PSA) screening era, most patients (about 93%) present with locoregional disease, whereas metastatic disease is the initial presentation in only about 4% of patients, with the remaining 3% categorized as of unknown stage.¹⁹ Men with localized prostate cancer are often treated with curative intent through use of radical prostatectomy or external beam radiation therapy. However, about 30% of men will eventually develop biochemical recurrence (PSA relapse) within the first decade of initial treatment.²⁰ Localization of disease at PSA relapse is of critical importance because it directs subsequent management, which may include active surveillance, systemic therapy, localized salvage therapy, or both systemic and localized treatments. Most men with metastatic prostate cancer are typically first treated with androgen deprivation therapy (castration or its medical equivalent) often with initial favorable response.²¹ However, most patients eventually develop a castration-resistant state with the hallmark of tumor growth despite castrate levels of serum androgens.²² Castration-resistant metastatic prostate cancer is incurable with an untreated survival of approximately 12 months and is the main cause of disease-related morbidity and mortality. At this phase of the disease, treatment is directed toward attempts to enhance survival and comfort.²³

In more than 90% of patients with castration-resistant prostate cancer, bone is the site of metastatic involvement. Bone metastasis is a major cause of death, disability, decreased quality of life, and increased treatment cost. This is due to skeletal-related events (SREs), which may include spinal cord compression and pathological fractures.^{24,25} There has been great strides over the past decade after the FDA approval of docetaxel in combination with prednisone in 2004 for the treatment of metastatic castration-resistant prostate cancer. Much of this accelerated drug development has been due to improved understanding of the complex biology of prostate cancer. These treatments have included other novel taxanes such as cabazitaxel, the active cellular immunotherapy sipuleucel-T, abiraterone acetate that inhibits the key enzyme, CYP17 (cytochrome P450 α -hydroxylase/17,20 lyase) in androgen biosynthesis, and the androgen receptor antagonist, enzalutamide.²⁶⁻³⁹ Although the new options have provided unprecedented opportunities, more studies will be needed to define potential combinations and optimal sequencing of these new therapeutics.

There have also been significant efforts in developing treatments that are specific for bone metastases.⁴⁰⁻⁴⁴ The primary objective of these therapies was aimed at alleviating pain and complications that are associated with such metastases. Bone seeking radioisotopes, such as ¹⁵³Sm ethylene diamine tetramethylene phosphonate and ⁸⁹Sr chloride, have been used successfully for palliation of pain from bone metastases in prostate cancer.^{45,46} In the recent wave of novel therapies for castration-resistant metastatic prostate cancer, renewed attention was directed toward potential role of α -particle bone-seeking radionuclides such as ²²³Ra.⁴⁷⁻⁵¹ This effort led to a formal clinical trial of ²²³Ra dichloride to establish its safety and efficacy in treating osseous metastases of patients with castration-resistant prostate cancer.

ALPHARADIN IN SYMPTOMATIC PROSTATE CANCER CLINICAL TRIAL

The alpharadin in symptomatic prostate cancer (ALSYMPCA) clinical trial was a randomized, double-blind, multinational investigation of ²²³Ra dichloride versus placebo (saline) in men with castration-resistant prostate cancer who had symptomatic bone metastases and no visceral metastases (lymph nodes up to 3 cm in short axis were acceptable) and who had adequate bone marrow reserve (www.clinicaltrials.gov, identifier: NCT00699751).⁵²⁻⁶⁰ Parker et al⁶⁰ reported on the details and the results of the phase 3 clinical trial. The patient data were collected from 136 participating centers in 19 countries from June 2008 to February 2011. There were 2 study arms in the clinical trial, 614 patients in ²²³Ra treatment arm, and 307 patients in the placebo arm (ie, 2:1 treatment-to-placebo ratio, randomized double-blind study design; Fig. 2).

The primary end point was the overall survival that was defined as time from randomization to death from any cause. The secondary end points were time to first SRE, time to total alkaline phosphatase (ALP) progression, time to total ALP response, time to total ALP normalization, time to PSA progression, and assessment of quality of life. The treatment arm involved best supportive care plus a total of 6 IV injections of ²²³Ra (50 kBq/kg IV), with each injection spaced 4 weeks from each other. The placebo arm included best supportive care plus a total of 6 IV injections of saline with each injection spaced 4 weeks from each other. The main inclusion criteria were men with progressive symptomatic castration-resistant metastatic prostate cancer on docetaxel, those who were docetaxel ineligible, or those who refused docetaxel. The major exclusion criteria were chemotherapy within previous 4 weeks, prior hemibody external beam radiation therapy, previous systemic radioisotope therapy within 24 weeks, previous blood transfusion or erythropoietin within 4 weeks, and spinal cord compression. Castrate state was declared when serum testosterone was less than 50 ng/dL after bilateral orchiectomy or during androgen deprivation therapy with luteinizing hormone–releasing hormone agonist.

The updated analysis of all 921 patients demonstrated a 3.6-month survival benefit with ^{223}Ra in comparison with the placebo (median, 14.9 months vs 11.3 months; hazards ratio, 0.70; 95% confidence interval, 0.58–0.83; $P < 0.001$). When stratified for prior use of docetaxel, statistically significant survival benefit with ^{223}Ra versus placebo was again demonstrated (3.1-month survival benefit with prior docetaxel use vs 4.6-month survival benefit without prior docetaxel use). Similarly, the median time to first symptomatic SRE was significantly longer by 5.8 months with ^{223}Ra in comparison with placebo (median, 15.6 months vs 9.8 months; hazards ratio, 0.66; 95% confidence interval, 0.52–0.83; $P < 0.001$). With regards to SRE components, ^{223}Ra was associated with significantly fewer incidences of spinal cord compression and cases requiring external beam radiation therapy. When compared with the placebo arm, the ^{223}Ra treatment arm also showed statistically significant benefit in terms of longer median time to increase in total alkaline phosphatase (^{223}Ra , 7.4 months; placebo, 3.8 months), median time to PSA increase (^{223}Ra , 3.6 months; placebo, 3.4 months), percentage of patients with greater than or equal to 30% reduction in total alkaline phosphatase (^{223}Ra , 47%; placebo, 3%), and percentage of patients with normalization of total alkaline phosphatase (^{223}Ra , 34%; placebo, 1%).⁶⁰

Both hematologic and nonhematologic adverse events were similar between the 2 arms of the clinical trial with specifically no clinically meaningful differences in the frequency of grade 3 and 4 adverse events. ^{223}Ra was generally associated with low-grade myelosuppression in the form of neutropenia and thrombocytopenia. The major nonhematologic adverse events included bone pain, nausea, vomiting, and diarrhea, but the incidence of these events was relatively similar to those that occurred in the placebo arm. No secondary induced cancers were noted during the clinical trial period.⁶⁰ A recent report using phantoms and medium energy collimators has shown that despite low injected activity and less than 2% emission of γ photons (82, 154, 270 keV), there may be sufficient and clinically relevant information that can be obtained with imaging.⁶¹ Moreover, imaging (eg, ^{18}F -NaF PET/CT) may be used to assess response in bone metastases treated with ^{223}Ra .⁶²

In summary, within the design parameters of the ALSYMPCA clinical trial, there was clear benefit with ^{223}Ra in comparison with the placebo without an untoward toxicity profile. The encouraging outcome of this clinical trial resulted in the FDA approval and the recent incorporation of ^{223}Ra in the updated National Comprehensive Cancer Network guideline (v3.2013). Currently, there are other active clinical trials with ^{223}Ra in assessing the use in breast cancer (www.clinicaltrials.gov, identifier: NCT00070485) and in comparing docetaxel treatment and docetaxel in combination with ^{223}Ra treatment in men with castration-resistant metastatic prostate cancer (NCT01106352). Other trials examining the combination or sequencing of ^{223}Ra with abiraterone acetate and enzalutamide are planned.

^{223}Ra LICENSING AND DOSIMETRY

In spring 2013, the US Nuclear Regulatory Commission stated that, “based on available information, the Nuclear Regulatory Commission staff agreed with the Advisory Committee on the Medical Uses of Isotopes recommendation and determined that licensing under 10 CFR Part 35, Subpart E is appropriate because the medical use of ^{223}Ra is similar to other commonly used β - and photon-emitting therapeutic radiopharmaceuticals. The staff also has determined that under current regulations, physicians authorized under 10 CFR 35.390, training for use of unsealed byproduct material for which a written directive is required, or 10 CFR 35.396, training for the parenteral administration of unsealed byproduct material requiring a written directive, can be authorized for medical use of ^{223}Ra .”⁶³

^{223}Ra is easy to shield in view of its heavy mass and limited range. It can be transported worldwide in shielded vials. It decays to stable compounds and can be disposed in clinical waste stream after decay in storage (10 CFR 35.92). Lassmann et al⁶⁴ reported on the dosimetry of ^{223}Ra in normal organs and tissues. The bone endosteum and red bone marrow received the highest dose followed by the liver, colon, and intestine (Table 3). However, given the very short range of α -particles, cell level-based dosimetry (microdosimetry) has been found to be more applicable for understanding absorbed dose values and potential toxicity in bone marrow.⁶⁵⁻⁶⁷

^{223}Ra DICHLORIDE AND PATIENT MANAGEMENT

Before considering a patient for ^{223}Ra dichloride therapy, it is imperative to check eligibility for treatment, confirm osseous metastases on a recent bone scan, and assess the initial laboratory workup data. Before the first injection, the absolute neutrophil count should be greater than or equal to $1.5 \times 10^9/\text{L}$, platelet count greater than or equal to $100 \times 10^9/\text{L}$, and hemoglobin level greater than or equal to 10 g/dL. For subsequent treatments, the laboratory data will need to be reexamined, the absolute neutrophil count should be greater than or equal to $1 \times 10^9/\text{L}$, and the platelet count should be greater than or equal to $50 \times 10^9/\text{L}$. ^{223}Ra treatment should be discontinued if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care.

Before administration, signed patient consent form should be obtained after describing the procedure to the patient or patient's caregiver and answering all the patient's questions. Direct dose calibrator measurement of the dose is not required for patient-ready doses. Packaging should be surveyed after the vial removal. Double gloves should be worn. Blue chux will be placed on the floor, on the chair without arms, and on the table. Saline flushes, double-bagged red biohazard bag, and an IV pole with 500 mL saline and primed tubing should be available. The saline flow connected through a 3-way stopcock should be stopped, and ^{223}Ra (50 kBq/kg or 1.35 $\mu\text{Ci/kg}$) should be administered as a 1-minute injection by the physician (Table 3). Then saline flushes are connected and pushed. Then all the tubing and the radioisotope syringe are placed in a Nalgene (Nunc International Corporation, Rochester, NY) container or latex glove and tape-shut then left in a red biohazard bag and measured for residual using standard meter. The technologist's and physician's hands and feet are also surveyed for potential contamination. Before patient release, the heart rate and blood pressure are checked. A report is made indicating the number in cycle and amount of the administered radioisotope along with basic information on clinical indication and laboratory data. The patient is scheduled for the next dose 28 days later. It is generally our practice to have the patient reviewed by their oncologist or urologist either on the day of therapy or a week before infusion is scheduled to occur. At that time, it is customary to obtain a complete blood cell count with white blood cell differential and metabolic panel including serum alkaline phosphatase for assessment. Other potential markers of disease state, such as serum PSA, lactate dehydrogenase, and bone-specific alkaline phosphatase, may also be obtained. We reserve imaging/restaging until after the completion of 6 cycles of ^{223}Ra unless clinical symptoms dictate earlier reassessment.

In general, there is minimal exposure to others from ^{223}Ra injection, which is below regulatory limit ($0.007 \text{ mrem/h} < 0.5 \text{ mrem/h}$). The patient is instructed to drink plenty of fluids before and after each injection. They should be instructed to use medical gloves when wiping up blood, urine, stool, or vomit and when touching or washing dirty clothes. They should urinate (while sitting) as frequently as possible to keep the bladder empty. The toilet should be flushed twice after each use. If urine is splattered, it should be wiped with a sheet of toilet paper and flushed. If the patient has diarrhea or urinary incontinence, disposable underwear or diaper pants should be used during the first week after each injection of ^{223}Ra .

Underwear worn during the first week after each injection of ^{223}Ra and any clothing soiled with urine, stool, or blood should be washed separately. The patient should avoid close and/or prolonged contact with pregnant women and small children during the first week after each injection. They should also avoid fathering a child until 6 month after the completion of therapy.

CONCLUSIONS

The first α -particle therapy with ^{223}Ra dichloride is now available after more than a century from the first description of its potential use in cancer. The self-targeting of ^{223}Ra as calcium mimetic allows for highly localized deposition of high radiation energy at sites of active bone turnover adjacent to metastatic tumors, a common feature with many cancers including prostate cancer. The ALSYMPCA clinical trial of ^{223}Ra clearly demonstrated the increased overall survival and decreased time to skeletal-related events with ^{223}Ra dichloride in comparison with placebo in men with castration-resistant prostate cancer and symptomatic bone metastases. It is anticipated that the use of α -particles in the design of new treatments will continue in the future as medicine proceeds further toward personalized and precision health care.

Acknowledgments

The authors thank Dr Andrei Iagaru of Stanford University for his helpful consult and information on patient management during ^{223}Ra dichloride therapy.

Conflicts of interest and sources of funding: Supported by the National Institutes of Health, National Cancer Institute, grants R01-CA111613 and R21-142426. Dr David I. Quinn is on the Scientific Advisory Board of Bayer Healthcare/Algeta.

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FIGURE 1.

Decay scheme of ^{223}Ra . Adapted from Hooper⁶⁸ with permission. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

FIGURE 2.
ALSYMPCA clinical trial study design.

TABLE 1

 α -Emitting Radioisotopes

Isotope	Particle(s) Emitted	Half-Life	Energy of α -Particle, MeV
^{211}At	1 α	7.2 h	6
^{225}Ac	4 α , 2 β	10 d	6–8
^{212}Bi	1 α , 1 β	60.6 min	6
^{213}Bi	1 α , 2 β	46 min	6
^{223}Ra	4 α , 2 β	11.4 d	6–7
^{212}Pb	1 α , 2 β	10.6 h	7.8
^{149}Tb	1 α	4.2 h	4

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TABLE 2**Physical Characteristics of Radionuclides for Bone Therapy**

Radionuclide	Half-Life	Maximum Energy, MeV	Mean Energy, MeV	Maximum Range	γ -Emission, keV
^{32}P	14.3 d	1.7 (β)	0.695 (β)	8.5 mm	None
^{89}Sr	50.5 d	1.4 (β)	0.583 (β)	7 mm	None
^{186}Re	3.7 d	1.07 (β)	0.362 (β)	5 mm	137
^{188}Re	16.9 h	2.1 (β)	0.764 (β)	10 mm	155
^{153}Sm	1.9 d	0.81 (β)	0.229 (β)	4 mm	103
$^{177\text{m}}\text{Sn}$	13.6 d	0.13 and 0.16 conversion electrons		<1 μm	159
^{223}Ra	11.4 d	5.78 (α) (average)		<10 μm	154

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TABLE 3Estimated Equivalent Dose After IV Injection of 50 kBq/kg of ^{223}Ra Dichloride

Target Organs	Dose Equivalent, Sv
Adrenals	5.60×10^{-2}
Urinary bladder	5.70×10^{-2}
Brain	5.55×10^{-2}
Breast	5.55×10^{-2}
Gallbladder	5.60×10^{-2}
Heart wall	5.55×10^{-2}
Kidneys	5.60×10^{-2}
Liver	6.35×10^{-1}
Muscle	5.60×10^{-2}
Ovaries	5.65×10^{-2}
Pancreas	5.60×10^{-2}
Testes	5.55×10^{-2}
Thyroid	5.55×10^{-2}
Bone surface	13.05
Stomach	5.60×10^{-2}
Small intestine	5.65×10^{-2}
Upper large intestine	1.68×10^{-1}
Lower large intestine	3.67×10^{-1}
Skin	5.55×10^{-2}
Spleen	5.55×10^{-2}
Thymus	5.55×10^{-2}
Uterus	5.60×10^{-2}
Expiratory tract	5.55×10^{-2}
Lung	5.55×10^{-2}
Colon	2.54×10^{-1}
Thoracic lymph node	5.55×10^{-2}
Esophagus	5.55×10^{-2}
Gonads	5.65×10^{-2}
Remainder	5.60×10^{-2}

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