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Radiopharmaceutical treatments of canine skeletal conditions using ^{153}Sm, ^{90}Y, or ^{117m}Sn as the radionuclide do not require isolation of the treated animal from human beings, but the ^{90}Y and ^{117m}Sn treatments do require restrictions on prolonged, close human interaction with the animals for 3 to 4 weeks after treatment.

Radiation Safety Considerations in the Treatment of Canine Skeletal Conditions Using ^{153}Sm, ^{90}Y, and ^{117m}Sn

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Abstract: *The treatment of pets, service animals, and pre-clinical research subjects with radionuclides raises concern for the safety of the people who interact with the animals after their treatment. Three treatments of skeletal conditions in dogs are considered in this study: ^{153}Sm-1,4,7,10-tetraazacylcododecanetetramethylenephosphonic acid, which is a bone-seeking radiopharmaceutical; unencapsulated ^{90}Y permanent interstitial implants, which are sometimes called "liquid brachytherapy"; and ^{117m}Sn radiosynoviorthesis, which is also called radiosynovectomy. External exposure rate readings of the ^{153}Sm and ^{117m}Sn treatments, and Monte Carlo simulations of ^{117m}Sn at a distance of 1 m and of all three in direct contact with tissue were analyzed for doses. Dogs that have received any of these treatments using typically administered activities may be released from radiation safety isolation immediately after treatment from the standpoint of external exposure. People should avoid prolonged close proximity, such as sleeping with a treated dog, for three weeks following an ^{90}Y interstitial implant or for a month following ^{117m}Sn radiosynoviorthesis. No such avoidance is necessary after treatment with ^{153}Sm-1,4,7,10-tetraazacylcododecanetetramethylenephosphonic acid. Health Phys. 118(6):702–710; 2020*

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INTRODUCTION

The radiation safety of human beings is an important concern in the administration of radioactive materials to veterinary patients and preclinical research subjects. In veterinary treatments that employ relatively large amounts of radioactivity, a balance must be struck between the radiation absorbed dose to people after the animal is released from radiation safety isolation and the well-being of the animal, especially in the case of pets and their families, if the animal is unaccustomed to being isolated from people. The post-release instructions to the people who interact with the animal should be the least onerous that are practicable. While the protocols for handling radioiodine treatment of feline thyroid conditions are well-established and are incorporated explicitly into some states' regulations, there is no guidance for the care of dogs that have received radionuclides for the treatment of skeletal conditions.

This study investigated the radiation safety restrictions for three treatments that use radionuclides on canine skeletal conditions. The

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bone-seeking radiopharmaceutical, ^{153}Sm-1,4,7,10-tetraazacylcododecanetetramethylenephosphonic acid (^{153}Sm-DOTMP), and a form of brachytherapy that employs unencapsulated ^{90}Y in a permanent, interstitial implant are used to treat osteosarcoma. Colloidal particles labeled with ^{117m}Sn are used to treat osteoarthritis.

MATERIALS AND METHODS

Radionuclides

All three of these radionuclides emit electrons, either as conversion electrons or as beta particles, through which they deliver their therapeutic effects. Two of the three, ^{153}Sm and ^{117m}Sn, also emit photon radiation that could result in external exposure. Their most relevant characteristics are summarized in Table 1.

Treatments

Samarium-153-DOTMP is administered intravenously at dosages in the range of 37–74 MBq kg^{-1}. About 40% of the administered activity is taken up by the skeleton, and the remainder is excreted within 2 hours through the urinary system (Simon et al. 2012). There is thus the potential for radioactive contamination of a pet's household and thence internalization of ^{153}Sm by household members.

The ^{90}Y implants are formulated as an unencapsulated particulate suspension that is designed to remain at the site of implantation within a tissue. This material has been injected under very low pressure (Stearns et al. 2015) into holes that had been drilled into a bone tumor. Activities totaling between 0.0% and 0.3% of the administered amounts were observed in the excreta of eight rats that had received intramuscular implants and were observed for 6 or 10 days after implantation, while detectable activity was found in the urine of some of the treated dogs for up to 2 days.[8] The maximum activity that has been administered to a dog is 1.59 GBq.

The ^{117m}Sn radiosynoviorthesis formulation is also a particulate. This material has been used to treat osteoarthritic canine elbows. Although some dogs were treated with as much as 130 MBq per elbow during clinical trials, the current protocol is for the administered activity to be determined by a weight-based estimation of the body surface area under the constraint of a maximum dosage of 111 MBq per elbow. In a study of normal dogs, at six weeks after administration, less than 1% of the administered activity had left the joint space into which the material had been injected. About 0.7% of the administered activity was found in the liver, 0.1% in the spleen, and 0.1% in the excreta (Lattimer et al. 2016).

Dose limits

In the United States, human patients to whom radionuclides have been administered may be released from the licensee's control if the maximum likely effective dose equivalent to an individual who is exposed to the patient is less than 5 mSv (US NRC 2007a, 2008). This is higher than the annual limit of 1 mSv for the protection of the general public. The National Council on Radiation Protection and Measurements (NCRP) implies that the infrequent exposure limit of 5 mSv for the general public could be applied to veterinary treatments (NCRP 2004), but it does not explicitly recommend it.

In each of the three canine radionuclide treatments that are analyzed in this report, there is a concentration of the radioactivity within a small volume of the overall skeletal system. There is essentially complete localization in the treated region for the ^{90}Y and ^{117m}Sn treatments, and it is unlikely that the tissues surrounding the treated area would offer more than minimal shielding, especially in the extremities. Thus, the contact dose was also considered. Although there is no regulation in the United States of the doses to the skin or to the lens of the eye of members of the public, there are annual occupational limits on these doses. The International Atomic Energy Agency (IAEA) recommends dose limits to the skin and to the lens of the eye of a member of the public that are equal in value to one-tenth of the annual limits in the United States for occupational exposure (IAEA 2009). These figures are consistent with those in Table 6 of ICRP Report 103 (ICRP 2007).

Because an elevated limit for the effective dose equivalent is not explicitly recognized for veterinary patients and there are no regulatory limits on localized exposure to members of the general public, the recommendations in this report are based upon the following limits, which were derived from the regulatory limits in the United States (US NRC 2007b) as well as the recommendations of the IAEA and the

Table 1. Relevant characteristics of the radionuclides analyzed in this investigation. The row labeled "Γ" is the published exposure rate constant for ^{153}Sm and ^{117m}Sn and the estimated exposure rate constant from bremsstrahlung radiation in bone for ^{90}Y.

	^{153}Sm[a]	^{90}Y[b]	^{117m}Sn[c]
Physical Half-life	46.3 h	64.1 h	14.0 d
Electrons (mean energy keV)	200–265	935	135
Photons (keV)	103 + others	minimal	159
"Γ" (nC kg^{-1} MBq^{-1} h^{-1} @ 1 m)	0.336	0.0105	1.18

[a]ICRP 2008; Smith and Stabin 2012.
[b]Zanzonico et al. 1999; ICRP 2008.
[c]Srivastava 2007; ICRP 2008; Smith and Stabin 2012.

[8]Unpublished data.

International Commission on Radiological Protection.

- Annual effective dose equivalent to the most exposed person: 1 mSv; and
- Annual localized dose to the surface of an exposed person: 50 mSv at a depth of 70 microns averaged over 10 cm^2 as the skin dose and 15 mSv at a depth of 3 mm averaged over 1 cm^2 as the dose to the lens of the eye.

Simulations

The dose in tissue at a distance of 1 m through air from a point source of ^{117m}Sn and the doses in tissue at various depths from a superficially located source of ^{153}Sm, ^{90}Y, or ^{117m}Sn that resembles a bone tumor or a treated joint were simulated using Monte Carlo software (GATE version 6.2, 7.2, or 8.0, Open GATE Collaboration) (Jan et al. 2004). The radionuclide sources were defined using the ICRP 107 decay scheme data (ICRP 2008). None of the tabulated emissions was excluded, regardless of energy or abundance.

For the ^{153}Sm and ^{90}Y treatment simulations, the "bone" was 30 cm in length, of which the middle 5-cm segment was a "lesion." The bone had a central core with a diameter of 1.6 cm and material properties resembling trabecular bone (using the GATE material "SpineBone") surrounded by a 2-mm-thick layer with material properties resembling cortical bone (using the GATE material "RibBone"). It had an overall diameter of 2 cm and was covered by 2.5 mm of tissue. This is shown in top and side views in Fig. 1 and Fig. 2. The tissue that was in contact with the bone is also shown.

Although ^{153}Sm-DOTMP is presumed to be taken up by and distributed on the surfaces of the trabecular and cortical bone, data on the bone surface area of the dog have not been found in the literature, so both ^{153}Sm and ^{90}Y were treated as being distributed uniformly within the entire volume of the lesion for the purpose of determining the activity in the lesion. The skeletal mass was assumed to be 14% of the total body mass of the dog. This value is higher than the 10% estimate from the University of Florida 26-kg dog model (Padilla et al. 2008) and lower than the 20.6% estimate in a literature survey (Lindstedt and Schaeffer 2002), but it is consistent with the 13–14.5% skeletal mass of adult human models (ICRP 2002) with total body masses of 60–73 kg. The lesion with a volume of 15.7 cm^3 would thus constitute 0.308% of the skeletal mass of a 70 kg dog, assuming a bone density of 1.92 g cm^{-3} (ICRU 1989).

FIG. 1. A top-down view of a cross-section through a central plane of the simulation of the treatments with ^{153}Sm and ^{90}Y. The rectangle at the top of the figure is the block of tissue, which is pressed up against the treated limb. It is 5 cm thick, 10 cm wide (in the direction of the limb) and 30 cm high (perpendicular to the direction of the limb). The inner core of the simulated bone has a radius of 8 mm and the material properties of trabecular bone while the 2-mm-thick outer sheath has the material properties of cortical bone. A 2.5-mm-thick sheath with the properties of tissue surrounds the bone. For ^{153}Sm and ^{90}Y, the radionuclide was uniformly distributed within both the trabecular and cortical portions of the central segment of the bone in order to simulate a lesion. For ^{153}Sm the portions of the bone that are adjacent to the portion simulating the lesion had one-tenth of the activity of the central portion; whereas for ^{90}Y the bone outside of the lesion contained no radioactivity.

In the case of ^{153}Sm, radioactivity was distributed along a 15-cm length of the bone with a 10:1 ratio of activity in the 5-cm-long lesion to that in the 5-cm-long adjacent segments of the normal bone. This is shown in top and oblique views in Fig. 1 and Fig. 2.

For simulation purposes, the activity in the lesion may be estimated by taking the administered activity times the skeletal uptake fraction times the fraction of the skeletal mass accounted for by the lesion times the lesion-to-normal ratio of the uptake in the lesion. An administered activity of 74 MBq kg^{-1} of ^{153}Sm-DOTMP to a 70-kg dog, which is slightly more than the highest actually administered dosage of 67.3 MBq kg^{-1} in the canine studies, would lead to 63.8 MBq in the "lesion." The two adjacent 5-cm lengths of normal bone in the simulation would contain 6.38 MBq, assuming the simplified case of instantaneous uptake by the skeleton and instantaneous clearance from the soft tissues.

In the simulation of ^{90}Y brachytherapy, which is a highly localized treatment by virtue of its administration as an implant, the radioactivity was uniformly distributed within the lesion and nowhere else in the simulated bone.

For the ^{117m}Sn radiosynoviorthesis simulation, a stylized ball and socket joint as shown in Fig. 3 and Fig. 4 was modeled. The activity was concentrated on the surfaces of the synovial membrane, which was modeled as a cylindrical surface surrounding the rest of the joint. Concentrating the activity in the synovium is consistent with measurements showing that there is negligible remaining activity in the synovial fluid within a few days after administration.[9]

The dose to tissue that is in contact with the treatment site was assessed in a block of material that had the properties of soft tissue and was 5 cm thick, 30 cm long, and 10 cm wide. It was positioned

[9]Unpublished data.

FIG. 2. An oblique view of the simulations of ^{153}Sm and ^{90}Y. The block of tissue is rendered as a wireframe of a rectangular prism that is 5 cm thick, 10 cm wide and 30 cm high. The segment of the bone simulating the lesion is the brighter area in the center of the cylinder that is in contact with the tissue block.

touching a simulated limb with its long axis parallel to the 10-cm dimension so that the source was centered on the 30 cm × 10 cm face.

Two billion events were simulated for each situation. The number of events divided by the sum of the yields or abundances of all of the emissions of the source gives the number of disintegrations, or Bq s, that were simulated. Doses in the tissue block were averaged over an area of 10 cm^2 at a depth of 70 um from the surface of the block that was touching the limb and over an area of 1 cm^2 at a depth of 3 mm from that surface of the block. Both analysis areas were centered on the peak of the dose distribution.

Exposure rate measurements

The external exposure rates from the ^{153}Sm and ^{117m}Sn treatments were measured using calibrated ionization survey meters (Model 9DP, Ludlum Measurements, Inc., Sweetwater, TX). These treatments were performed at different sites, and a different meter was used at by each site. A correction factor was determined for each of these radionuclides.

For ^{117m}Sn radiosynoviorthesis, which is typically administered into an appendicular joint with only the thin surrounding tissue to attenuate its photon emissions, the numerator of the correction factor was obtained by calculating the dose rate constant in air for each photon emission separately using the method described by Smith and Stabin (2012) and then summing them. The denominator was obtained by calculating the weighted sum of the dose rate constants of the individual photon emissions using the energy responses of the meter at each energy (Ludlum Measurements, Inc. 2017) as the weights. The correction factor for ^{117m}Sn was calculated to be 1.45.

In the case of ^{153}Sm-DOTMP, which is distributed throughout the entire skeleton, the spectrum of the emissions is modified by the attenuation of the whole body, which is akin to the beam-hardening phenomenon in x-ray imaging (Bushberg et al. 2012). Treating the skeleton as the source organ, the transmission factor for each photon energy was estimated from the absorbed fractions at each photon energy in the whole body in the

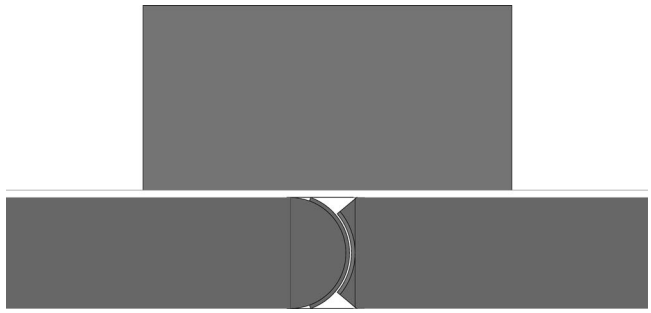

FIG. 3. A top-down view of a cross-section through the central plane of the simulation of ^{117m}Sn. The tissue block is the same as in the other simulations. The joint is a stylized ball and socket joint. Layers of cartilage lie between the ball to the left and the socket to the right in the figure. The synovium in which the radioactivity was uniformly distributed is transparent in this figure. It is a thin cylindrical layer that surrounds the joint between the solid cylinders of bone. The bone and joint are 1.5 cm in radius. The superficial tissue is 2 mm thick.

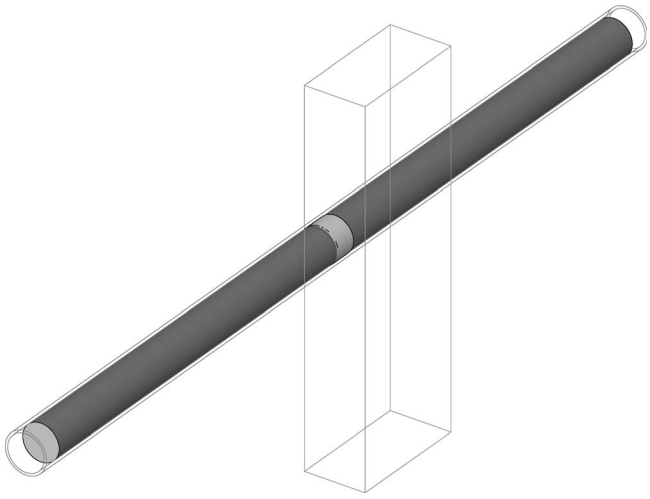

FIG. 4. An oblique view of the simulation of ^{117m}Sn. The synovium is rendered as the lighter band in the center of the limb.

University of Florida canine model (Padilla et al. 2008). The numerator of the correction factor was the sum of the dose rate constants for each emission times the corresponding transmission factor for each emission. The denominator of the correction factor was a weighted sum of those dose rate constants where the weighting factors were the products of the transmission factor and the energy response of the ionization meter for each photon emission. The correction factor was calculated to be 1.24 when the shielding effect of the whole body from the University of Florida canine model was included compared to a factor of 1.35 for a source of ^{153}Sm in air.

Animal studies

Samarium-153-DOTMP. Nine dogs were administered 37–74 MBq kg^{-1} of ^{153}Sm-DOTMP to treat spontaneous osteosarcoma. They weighed 37–62 kg and ranged in age from 3–9 y.

The external exposure rate was measured at a distance of 1 m by one of the ionization survey meters. The raw readings were corrected for the energy response of the meter by the factor of 1.24. Measurements were performed at times of 3, 24, 48, 72, and 96 h after administration. The exposure rates were normalized by the activity that had been administered and then were fit by a single exponential decay curve that was constrained to reach a final value of zero (Prism, GraphPad Software, La Jolla, CA).

In an earlier study, four dogs that had osteosarcomas and that weighed 32–55 kg had been administered 37 MBq kg^{-1} and imaged 21–24 h later using a planar gamma camera with a low-energy, parallel-hole collimator (Selting et al. 2011). Those image data were re-analyzed for the present study. Regions of interest were drawn around the bone lesions and over an area of the adjacent bone with a normal appearance and the counts per pixel in each were determined for the purpose of estimating the lesion-to-normal uptake ratio.

Yttrium-90 interstitial implants. No external exposure rate measurements that had been made shortly after treatment were recorded. Anecdotally and qualitatively, activity has been detectable in the dogs' urine for up to 2 days after treatment with some of the early formulations of the material.[10]

Tin-117m radiosynoviorthesis. Twelve adult dogs that were suffering from Grade 3 osteoarthritis of the elbow were studied. Nine received treatments of both elbows and three were treated in only one elbow. The nominal dosage to a single elbow of a 22.7 kg dog was 64.8 MBq. The nominal administered activity was scaled by a weight-based estimate of the dogs' body surface area according to a chart of fixed dosages for weight ranges in increments of 4.5 kg. The dogs' weights ranged from 22.7 to 45.9 kg. The total activity that was administered to each dog averaged 137 MBq with a range from 59.2 to 207 MBq.

The external exposure rate was measured using the other of the two ionization survey meters and was corrected for the energy response of the meter by the factor of 1.45. The exposure rate was measured at a distance of 1 m from the center of the chamber to the nearest surface of the dog's closer elbow from each side and from in front of the dog. These measurements were made as soon as the dog had recovered from the sedation of the procedure and then again the next day, nominally 24 h later.

In order to calculate the expected external exposure rate, the distance between the proximal and distal elbows is needed, but that distance had not been measured. In a separate cohort of 24 dogs of various breeds and both sexes ranging in weight from 2.5 to 44.9 kg, the distance between their elbows was measured while they were standing. On the assumption that the distance would scale roughly with the cube root of their masses, a linear fit of the cube root of their masses to their elbow-to-elbow distances subject to the constraint that it pass through the origin was performed and found to be

$$D_{elbows} = 5.68\sqrt[3]{W}, \qquad (1)$$

where D_{elbows} is the elbow-to-elbow distance in centimeters and W is the mass of the dog in kilograms. The resulting distance was used to

[10]Unpublished data.

adjust the expected exposure rate for the effect of the inverse square law on the contribution to the exposure by the distal elbow.

A qualitative assessment of the excreted activity was made by collecting 20–50 cc of the dogs' urine at each time point. The exposure rates that were measured when the meter was placed right next to the urine containers were indistinguishable from background.

Exposure models

The standard model in NUREG 1556, Volume 9, Appendix U, Revision 2 (US NRC 2008), hereinafter referred to as "NUREG-1556" or "the regulatory guidance," for estimating the dose to the most exposed person is to assume that that person spends a fraction of each day at a distance of 1 m from the patient that has received the radionuclide therapy. That fraction is typically 0.25 (i.e., 6 h a day) when the physical half-life (or the effective half-life, if it is known) of the radionuclide exceeds a day.

It is not uncommon that pets sleep with their owners. For normal interaction with a pet or a working dog during waking hours, a person could be instructed to avoid more than brief contact with the treated anatomical area of the dog, and thus prolonged contact between a particular spot on the body of that person and the highest activity area of the dog while they are awake is unlikely. However, when sleeping, it is conceivable that the point on the surface of the dog with the highest dose rate could touch a particular spot on the person for some time. The average number of times that a person shifts position while sleeping is reported to vary from 2.1 times an hour among the elderly to 4.7 times an hour for pre-teenagers (De Koninck et al. 1992). The literature documents that dogs also do not typically remain perfectly still for long times while asleep (Hansen et al. 2007; Dow et al. 2009; Patel et al. 2017).

Internalized dose

If the dog's environment were to become contaminated by the administered activity, it could be possible for people to ingest some of the radionuclide and thereby to receive an internal dose. The approach in the regulatory guidance of assuming that a fraction of the administered activity would be internalized by a person (Eckerman et al. 1988; US NRC 2008) and applying a dose conversion factor to that internalized activity is used here to estimate how significant the internalized dose might be.

RESULTS

External exposure

Samarium-153-DOTMP. The measured external exposure rate data from the dogs that were treated with ^{153}Sm-DOTMP are plotted in Fig. 5.

The effective half-life of the external exposure rate measurements was 44.6 (95% CI: 33.8–65.8) h, which is close to the physical half-life of ^{153}Sm of 46.3 h. The next-day imaging studies showed essentially only skeletal uptake. This is consistent with the rapid urinary clearance of ^{153}Sm-DOTMP that has been measured in rats (Simon et al. 2012) in which an effective half-life of 0.5 h was estimated for the urinary activity. Since the first canine measurement was taken 3 h after administration and the external exposure rate readings are fit well by a single exponential decay function, these measurements are those of the radioactivity that was taken up by the skeleton. The exposure rate per unit administered activity extrapolated back to the time of administration was 0.122 (95% CI: 0.101–0.142) nC kg^{-1} MBq^{-1} h^{-1} at 1 m.

The average ratio of the counts in the lesion and in adjacent bone in the four dogs that underwent gamma camera imaging was 12.7:1 (95%CI: 7.17:1–18.3:1). Similar radiopharmaceuticals have been reported to have tumor-to-normal background ratios of 4.0 to 11.0 in a rat model of bone tumors using mechanical trauma (Ghiron et al. 1991). One dog had more than twice the ratio of the average of the other three. Excluding the data from that dog, the average ratio was 9.5:1 (95%CI: 8.55:1–10.4:1). This is the basis of the 10:1 lesion-to-adjacent ratio that was used in the simulation of a typical lesion.

Adapting the model that is found in NUREG-1556 in which the patient spends a fraction of a day at a distance of 1 m from the most exposed person, the dose to the most exposed person would be

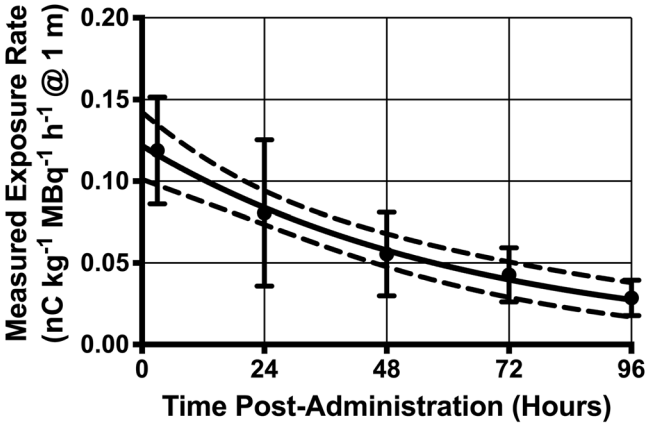

FIG. 5. Fit of a single exponential decay curve to the exposure rate measurements of ^{153}Sm-DOTMP in dogs. The fit was constrained to reach zero. The dashed lines show the 95% confidence interval of the fit. This curve is dominated by the uptake in the skeleton. The fit to the curve is $0.122e^{-\ln 2t/44.6}$ nC kg^{-1} MBq^{-1} h^{-1}. The R^2 value of the fit is 0.562.

$$D = \frac{T_{eff}}{\ln 2} \times_{meas} E = 7.14 \times 10^{-5} \text{mGy MBq}^{-1}, \quad (2)$$

where the effective half-life, T_{eff}, is 44.6 h, the measured exposure rate, X_{meas}, is 0.122 nC kg^{-1} MBq^{-1} h^{-1} at 1 m, the occupancy factor, E, is 0.25 or 6 h a day, since the effective half-life exceeds 1 d, and the f-factor of ^{153}Sm is 36.4 Gy C^{-1} kg (Smith and Stabin 2012). An administered activity of 14.0 GBq would be needed to impart 1 mSv to the most exposed person under these conditions.

Yttrium-90 interstitial implant. The external exposure from ^{90}Y interstitial implants was assumed to arise only from bremsstrahlung x rays that are generated in bone, which have been estimated to have an exposure rate constant of 10.5 pC kg^{-1} MBq^{-1} h^{-1} at 1 m (Zanzonico et al. 1999). The maximum administered activity to date of 1.59 GBq would deliver a negligible whole body dose of 14.0 μSv using the NUREG-1556 approach.

Tin-117m radiosynoviorthesis. No significant difference was observed in the initial and next day readings from the dogs that were treated with ^{117m}Sn radiosynoviorthesis, which implies that most of the administered activity was retained in the joint and little, if any, of it either had leaked out of the injection tract or had already been transported into the lymphatic system. This agrees with another study that showed 99.1% retention in the joint at 42 d (Lattimer et al. 2016).

The dose rate constant from the simulation of a point source in air was 1.22×10^{-17} Gy m^2 Bq^{-1} s^{-1}. This falls between the published values of 1.20×10^{-17} Gy m^2 Bq^{-1} s^{-1} (Smith and Stabin 2012) and 1.89×10^{-17} Gy m^2 Bq^{-1} s^{-1} (Shleien et al. 1998). The external exposure rate readings were compared to the exposure rates that were expected, given the dose rate constant from the simulation at 1 m, the activity that was administered to each elbow, and the distance-correction of the contribution of the farther elbow. The linear fits of these data, which were constrained to pass through the origin, were

- Left Lateral: $X_{meas} = 0.703\ X_{exp}$;
- Right Lateral: $X_{meas} = 0.704\ X_{exp}$; and
- Cranial: $X_{meas} = 0.680\ X_{exp}$.

where X_{meas} is the measured exposure rate at 1 m and X_{exp} is the expected exposure rate of a bare source in air. Thus, for protection purposes, the dose rate constant of 8.54×10^{-18} Gy m^{-2} Bq^{-1} s^{-1} at 1 m is used. This is derived from the lateral measurements, which are 70% of the dose rate constant of a bare source in air.

The total dose at a distance of 1 m from a dog that has received the maximum treatment to both elbows, which would total 222 MBq, can be estimated using eqn (2) above, assuming an occupancy factor of 0.25 and an effective half-life of 14 d, and replacing the exposure rate, X_{meas}, by the product of the dose rate constant and the administered activity. In this scenario, it is 0.827 mSv. The maximum measured exposure rate, 152 nC kg^{-1} h^{-1} at 1 m from a dog that had received 206 MBq, gives a total dose of 0.671 mSv using eqn (2) with these assumptions.

Contact doses

The contact doses that are based upon the simulations of the three radionuclides are given in Table 2.

One can calculate the total dose to a patch of skin or to the lens based upon these contact doses, D_c, the activity in the lesion or joint, A_L, the occupancy factor (i.e., the fractional duration) of the contact, E, and the delay between treatment and the first such contact, Δ, according to the expression

$$D = \frac{T_{eff}}{\ln 2} D_C A_L E e^{-\frac{\ln 2 \Delta}{T_{eff}}}, \quad (3)$$

where T_{eff} is the effective half-life. There are many combinations of the values of these parameters that can satisfy the dose limits of 50 mSv to the skin and of 15 mSv to the lens of the eye. Table 3 shows just one such set of values for each treatment.

Internalized dose

The maximum administered activities, dose conversion factors, and estimated internalized doses based upon a 10 ppm internalization are shown in Table 4.

DISCUSSION

The dose limits that were employed in this study are quite conservative. The annual total effective dose equivalent of 1 mSv is that which is allowed in the United States for a member of the general public, even though a pet dog's family members could be presumed to derive a compensatory benefit from a higher exposure to the treated pet in a similar argument to the rationale for allowing a 5 mSv dose limit to the person receiving the most exposure from a human patient. None of these three treatments typically requires that the treated dog be quarantined for safety reasons based upon the total dose to a person who spends 6 hours a day at a distance of 1 m from the dog. Such exposure to the dog may commence immediately after treatment without exceeding the limit.

Table 2. The contact doses for skin and the lens of the eye from each of the three treatments based upon Monte Carlo simulations.

Treatment	Skin dose (10 cm² @ 70 μm)	Lens dose (1 cm² @ 3 mm)
^{153}Sm-DOTMP (Gy Bq^{-1} s^{-1})	7.24×10^{-15}	7.64×10^{-15}
^{90}Y Interstitial Implant (Gy Bq^{-1} s^{-1})	2.61×10^{-13}	2.01×10^{-14}
^{117m}Sn Radiosynoviorthesis (Gy Bq^{-1} s^{-1})	2.76×10^{-14}	2.80×10^{-14}

In considering contact doses, the assumption that the same precise patch of skin of a person would be in direct contact with the point on the dog that has the highest dose rate for an hour a day is conservative, given that both the person and the dog are likely to move about. The assumption that a person's eye, even closed, would be touching the highest dose rate point on the dog for any length of time that even approaches an hour a day is unrealistic, given the discomfort to the person in such a scenario. It should be noted that if a dog's coat has not been clipped for the treatment, even compressed fur would offer an additional separation of the person and the treated area and thus lead to a lower skin or lens dose than that from direct contact with the dog's skin.

The estimated maximum internalized doses to people that are shown in Table 4, which are based upon the 10 ppm assumption in NUREG-1556 for human patients, are negligible for all three treatments. To reduce the potential internalized dose from excreted radioactivity further, one could isolate a treated dog until it has voided most of the administered activity that is likely to be excreted. To this end, it would be prudent to quarantine dogs that have been treated with ^{153}Sm-DOTMP for 4 h, which was eight effective half-lives of the activity in the urine in a preclinical murine study (Simon et al. 2012). Based upon the authors' clinical observation of slight ^{90}Y excretion for up to 2 days[11] one might quarantine dogs that have been treated with ^{90}Y interstitial implants for 2 days. Future improvements in liquid brachytherapy technology could reduce the duration of this quarantine. It should be ensured that the treated dogs have actually voided before their release, as, on rare occasions, dogs have been known to retain their urine for as long as 4 days when boarded in a strange kennel.[11] No quarantine for excretory reasons is warranted for ^{117m}Sn radiosynoviorthesis.

The dog's owner should be given instructions for how the dog should be allowed to interact with people and with the home or work environment in order to make it unlikely that the dose limits would be exceeded. If there is the potential for retreatment during the period covered by the annual dose limit, the instructions for each treatment should be designed to reflect the total annual dose.

[11]Unpublished data.

Table 4. The internalized dose estimates for each of the three treatments assuming the given maximum administered activities and 10 ppm internalization.

	^{153}Sm-DOTMP	^{90}Y Interstitial implant	^{117m}Sn Radiosynoviorthesis
Maximum Administered Activity (GBq)	5.18	1.59	0.222
10 ppm Internalized Activity (kBq)	51.8	15.9	2.22
Dose Conversion Factor[a] (Sv Bq^{-1})	8.07×10^{-10}	2.91×10^{-9}	7.97×10^{-10}
Internalized Dose (μSv)	41.8	46.3	1.77

[a]Eckerman et al. 1988.

Table 3. The restrictions on more than incidental touching of dogs that have received each of the three treatments. The activity A_L is that in the treatment area (or lesion), not necessarily the entire administered activity. Δ is the number of days before prolonged touching can resume and E is the number of hours a day that that touching may occur during the period of restricted touching. To obtain these values, Eq. 3 may be solved either for the occupancy, E, given the duration of no-touching, Δ, or for the duration of no-touching, Δ, given the occupancy factor, E, subject in either case to the dose limit constraint.

		Skin dose limit (50 mSv)		Lens dose limit (15 mSv)	
Treatment	A_L (MBq)	Δ (d)	E (h d^{-1})	Δ (d)	E (h d^{-1})
^{153}Sm-DOTMP	63.6	0	10.8	0	3.07
^{90}Y Interstitial Implant	1,591	19	1.21	15	1.65
^{117m}Sn Radiosynoviorthesis	111	30.2	1	54.8	1

CONCLUSION

It is compliant with the US regulatory limit on the annual dose to a member of the general public to release to their owners immediately after treatment dogs that have received any of these radionuclide treatments in commonly administered activities. People should avoid prolonged touching of the treated region and should not sleep with the treated dog for three weeks following an interstitial implant of ^{90}Y or for a month following ^{117m}Sn radiosynoviorthesis. No such avoidance of direct contact is necessary for ^{153}Sm-DOTMP.

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REFERENCES

Bushberg JT, Seibert JA, Leidholdt EM Jr, Boone JM. The essential physics of medical imaging. Philadelphia, PA: Lippincott Williams & WIlkins; 2012.

De Koninck J, Lorrain D, Gagnon P. Sleep positions and position shifts in five age groups: an ontogenetic picture. Sleep 15:143–149; 1992.

Dow C, Michel KE, Love M, Brown DC. Evaluation of optimal sampling interval for activity monitoring in companion dogs. Am J Vet Res 70:444–448; 2009. DOI 10.2460/ajvr.70.4.444.

Eckerman KF, Wolbarst AB, Richardson CB. Limiting values of radionuclide intake and air concentration and dose conversion factors for inhalation, submersion and ingestion. Washington, DC: US Environmental Protection Agency; EPA-520/1-88-020; 1988.

Ghiron J, Volkert WA, Garlich J, Holmes RA. Determination of lesion to normal bone uptake ratios of skeletal radiopharmaceuticals by QARG. Nucl Med Biol 18: 235–240; 1991.

Hansen BD, Lascelles BDX, Keene BW, Adams AK, Thomson AE. Evaluation of an accelerometer for at-home monitoring of spontaneous activity in dogs. Am J Vet Res 68: 468–475; 2007. DOI 10.2460/ajvr.68.5.468.

International Atomic Energy Agency. Release of patients after radionuclide therapy. Vienna: IAEA; Report 63; 2009.

International Commission on Radiation Units and Measurements. Tissue substitutes in radiation dosimetry and measurement. Bethesda, MD: ICRU; Report 44; 1989.

International Commission on Radiological Protection. Basic anatomical and physiological data for use in radiological protection: reference values. Oxford: Pergamon Press; ICRP Publication 89; 2002.

International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press; ICRP Publication 103; 2007.

International Commission on Radiological Protection. Nuclear decay data for dosimetric calculations. Oxford: Pergamon Press; ICRP Publication 107; 2008.

Jan S, Santin G, Strut D, Staelens S, Assie K, Autret D, Avner S, Barbier R, Bardies M, Bloomfield PM, Brasse D, Breton V, Bruyndonckx P, Buvat I, Chatziioannou AF, Choi Y, Chung YH, Comtat C, Donnarieix D, Ferrer L, Glick SJ, Groiselle CJ, Guez D, Honore P-F, Kerhoas-Cavata S, Kirov AS, Kohli V, Koole M, Krieguer M, van der Llaan DJ, Lamare F, Largeron G, Lartizien C, Lazaro D, Maas MC, Maigne L, Mayet F, Melot F, Merheb C, Pennacchio E, Perez J, Pietrzyk U, Rannou FR, Rey M, Schaart DR, Schmidtlein CR, Simon L, Song TY, Vieira J-M, Visvikis D, Van de Walle R, Wieers E, Morel C. GATE: a simulation toolkit for PET and SPECT. Phys Med Biol 49: 4543–4561; 2004. DOI 10.1088/0031-9155/49/19/007.

Lattimer J, Selting K, Simon J, Stevenson N, Ketring A, Manson L, Doerr C. Retention and biodistribution of Sn-117m colloid in intra-articular injections. J Nucl Med 57:322; 2016.

Lindstedt SL, Schaeffer PJ. Use of allometry in predicting anatomical and physiological parameters of mammals. Lab Anim 36:1–19; 2002.

Ludlum Measurements, Inc. Model 9DP Pressurized Ion Chamber; 2017. Available at ***https://ludlums.com/images/data_sheets/M9DP.pdf***. Accessed 21 September 2018.

National Council on Radiation Protection and Measurements. Radiation protection in veterinary medicine. Bethesda, MD: NCRP; NCRP Report No. 148; 2004.

Padilla L, Lee C, Milner R, Shahlaee A, Bolch WE. Canine anatomic phantom for preclinical dosimetry in internal emitter therapy. J Nucl Med 49:446–452; 2008. DOI 10.2967/jnumed.107.046722.

Patel SI, Miller BW, Kosiorek HE, Parish JM, Lyng PJ, Krahn LE. The effect of dogs on human sleep in the home sleep environment. Mayo Clin Proc 92:1368–1372; 2017. DOI 10.1016/j.mayocp.2017.06.014.

Selting K, Lattimer J, Ketring A, Crump D, Simon J, Frank R, Henry C. Samarium-153-DOTMP treatment of spontaneously-occurring bone cancer in dogs as a proof-of-concept model. J Nucl Med 52: 1747; 2011.

Shleien B, Slaback LA Jr., Birky BK. Handbook of health physics and radiological health. Baltimore, MD: Williams and Wilkins; 1998.

Simon J, Frank RK, Crump DK, Erwin WD, Ueno NT, Wendt RE III. A preclinical investigation of the saturation and dosimetry of ^{153}Sm-DOTMP as a bone-seeking radiopharmaceutical. Nucl Med Biol 39:770–776; 2012. DOI 10.1016/j.nucmedbio.2011.12.015.

Smith DS, Stabin MG. Exposure rate constants and lead shielding values for over 1,100 radionuclides. Health Phys 102:271–291; 2012. DOI 10.1097/HP.0b013e318235153a.

Stearns SD, Loy HM Jr., Davis DG. Delivery system for injection through zone of body. US Patent 9022987; 2015.

US Nuclear Regulatory Commission. Release of individuals containing unsealed byproduct material or implants containing byproduct material. Washington, DC: US Nuclear Regulatory Commission; 10 CFR 35.75. 2007a.

US Nuclear Regulatory Commission. Occupational dose limits for adults. Washington, DC: US Nuclear Regulatory Commission; 10 CFR 20. 1201. 2007b.

US Nuclear Regulatory Commission. Model procedure for release of patients or human research subjects administered radioactive materials. In: Consolidated guidance about materials licenses: program-specific guidance about medical use licenses, NUREG-1556, Volume 9, Appendix U, Revision 2. Washington, DC: US Nuclear Regulatory Commission; 2008.

Zanzonico PB, Binkert BL, Goldsmith SJ. Bremsstrahlung radiation exposure from pure beta-ray emitters. J Nucl Med 40:1024–1028; 1999.