

# Radiation Safety for Yttrium-90-polymer Composites (RadioGel™) in Therapy of Solid Tumors

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**Abstract**—Yttrium-90 (<sup>90</sup>Y)-polymer composite (RadioGel™) is a new cancer therapeutic agent for treating solid tumors by direct interstitial injection. The <sup>90</sup>Y-composite comprises insoluble, microscopic yttrium-phosphate particles carried by a sterile, injectable water-polymer (hydrogel) solution that can be placed directly by needle injection into solid tumors. The yttrium-90-RadioGel™ agent was designed to provide a safe, effective, localized, high-dose beta radiation for treating solid tumors. The properties of <sup>90</sup>Y-RadioGel™ also make it a relatively safe agent for health care personnel who prepare, handle, and administer the material. The purpose of this work was to demonstrate and characterize radiation safety of the injectable <sup>90</sup>Y-RadioGel™ therapeutic agent. Safety in the patient is defined by its ability to target precisely and remain confined within tumor tissue so that radiation doses are imparted to the tumor and not to normal organs and tissues. Radiation safety for health care personnel is defined by the low radiation doses received by persons who prepare and administer the agent. These safety features were demonstrated during experiments, first involving laboratory rabbits and second in cat and dog animal patients that were treated clinically for sarcoma tumors. This paper focuses mainly on the rabbit tissue biodistribution study; follow-on clinical application in cat and dog subjects confirmed the rabbit results. Implanted VX2 liver tumors in the hind limbs of 26 New Zealand White rabbits were treated using tracer amounts of either (a) <sup>90</sup>Y-RadioGel™ or (b) <sup>90</sup>Y-microparticles in phosphate-buffered saline (PBS) without the gel carrier. Tumor and margin injections were interstitial. Rabbits were euthanized at 48 h or 10 d following injection. Blood and tissues (tumor or tumor margins, liver, lymph nodes, rib bone, kidney, spleen) were collected for liquid scintillation counting using wet-ash procedures. Biodistribution was also analyzed at 10 d post-injection using micro-computed tomography. Thirteen cat and

dog subjects were also treated clinically for sarcomas. Liquid scintillation counting at 48 h post-injection of tumors or margins with <sup>90</sup>Y-RadioGel™ showed that significant radioactivity was measurable only at the site of administration and that radioactivity above detector background was not found in blood or peripheral organs and tissues. At 10 d post-injection, microCT showed that yttrium phosphate microparticles were confined to the injection site. Yttrium-90 remained where placed and did not migrate away in significant amounts from the injection site. Radiation doses were confined mainly to tumors and margin tissues. During preparation and administration, radiation doses to hands and body of study personnel were negligible. This work showed that <sup>90</sup>Y-RadioGel™ can be safely prepared and administered and that radiation doses to cancer patients are confined to tumor and margin tissues rather than to critical normal organs and tissues.

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## INTRODUCTION

MEASURES FOR radiation safety apply to the patient receiving treatment and also to the health care personnel who administer radioactive agents for treatment. Patient safety means that the radioactive agent is placed correctly and that radiation doses to non-target organs and tissues are minimized.

Personnel radiation safety means that persons who prepare and administer the radioactive agent do not themselves receive radiation doses that are harmful. Personnel administering therapy can be monitored with radiation dosimetry and protected in other ways to show that therapy is not hazardous for health care workers. Animal experiments with the radioactive agent show that radiation doses are delivered to tumor tissues without the implanted radioactive sources migrating away into normal tissues elsewhere in the body.

Radiation safety was demonstrated in two types of animal study: (1) a tracer injection in laboratory rabbits and (2) a therapy study involving pet cat and dog cancer patients treated at veterinary cancer centers. This paper focuses primarily on the tracer study in laboratory rabbits.

<sup>2</sup>KD Thrall (undated laboratory report). *Final Report: Evaluation of Migration of Y-90 in Animal Tumor Model*. Battelle, Pacific Northwest Division, Richland, WA (unpublished communication).

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Safety and efficacy are key determinants for regulatory approval of radiopharmaceuticals and brachytherapy for general use. It follows that high therapeutic ratios<sup>3</sup> are the objective of all cancer treatments. In high-dose radionuclide therapies, the tumor dose should be great enough for maximum tumor-control efficacy, and at the same time radiation doses to normal organs and tissues should be limited to minimize undesirable, adverse tissue reactions. The greatest therapeutic ratios can be obtained by injecting the radioactive source directly into the tumor, where it remains in place. A directly injectable radionuclide therapy can be optimized for therapeutic ratio by (1) employing a high-energy, pure beta-emitter (such as <sup>90</sup>Y), (2) confining the radioactive source to the tumor, and (3) distributing the beta-emitter as uniformly as possible within the tumor. In this strategy, we employed (a) a highly insoluble yttrium-phosphate (YPO<sub>4</sub>) crystalline matrix to tightly bind <sup>90</sup>Y and also (b) a polymer composite carrier (injection solution) that transitions from liquid to solid gel in the tumor after an elevation in temperature from a cold state to a warm body temperature; gelation serves to confine the <sup>90</sup>Y(YPO<sub>4</sub>) particles interstitially. Highly insoluble microparticles confined by in situ gelation prevent migration of the radioactive source material (<sup>90</sup>Y) away from the injection site. Thus, tumor doses are high, and normal tissue doses are comparatively small. High therapeutic ratios make it possible to administer highly efficient tumor doses without simultaneous undesirable side effects in normal organs and tissues.

To assess radiation safety as defined by the favorable therapeutic ratio, we studied the in vivo behavior of <sup>90</sup>Y-RadioGel™ in laboratory rabbits with implanted tumors, and in privately owned cat and dog cancer patients presenting at veterinary clinics with spontaneous tumors. These studies were performed to demonstrate that the administered radioactive agent <sup>90</sup>Y remained at the injection site and did not migrate via blood circulation to irradiate normal organs and tissues. We also monitored radiation doses to attending health care personnel to show the safety of the treatment procedures.

### Tumor model

The rabbit VX2 hepatic tumor model represents a common liver tumor in rabbits for studying tumor biology and response to therapy; VX2 is a fast-growing adenocarcinoma initially derived from a virus-induced papilloma specific to the rabbit (Parvinian et al. 2014). An arterial blood supply to the rabbit VX2 hepatic tumor is similar to human liver cancer, and VX2 tumor size is large enough to be observed by clinical imaging.

<sup>3</sup>Therapeutic ratio is  $D_{\text{tumor}}/D_{\text{organ}}$ , the radiation absorbed dose  $D$  to tumor tissue divided by the dose to the limiting normal organ or tissue.

### Yttrium-90

Yttrium-90 ( $T_{1/2} = 64$  h) is a well-accepted, high-energy medical isotope used in various forms for cancer treatment, such as radiolabeled monoclonal antibodies for radioimmunotherapy (Schaefer et al. 2011) and microsphere brachytherapy (Tong et al. 2016). High-energy beta-particles ( $E_{\text{max}} = 2.3$  MeV;  $E_{\text{avg}} = 0.93$  MeV) from <sup>90</sup>Y with pathlengths up to about 10 mm help to distribute spatially the energy imparted to tumor tissue. A bremsstrahlung component of <sup>90</sup>Y decay is measurable but does not represent a significant contributor to cross-organ radiation dose in the patient—or otherwise any radiation hazard to persons nearby.

### Radionuclide polymer composite

In this work, <sup>90</sup>Y was incorporated into highly insoluble yttrium-phosphate (YPO<sub>4</sub>) microparticles to prevent dissolution and migration away from the injection site. The carrier hydrogel is a non-toxic water-based polymer solution that perfuses interstitial tumor space and then gels as it warms to body temperature. Gelation helps to contain the <sup>90</sup>Y(YPO<sub>4</sub>) particles within the tumor. Pending as a commercial product, the <sup>90</sup>Y-polymer composite is designated as RadioGel™ for human cancer therapy and IsoPet® for animal therapy of solid tumors.<sup>4</sup>

### Research purpose

The purpose of this work was to assess and characterize the behavior (biodistribution after injection, retention, redistribution, and clearance, if any), safety features, radiation safety, and dosimetry of injectable <sup>90</sup>Y-RadioGel in tumors of animals as models for eventual cancer treatments in humans. This paper focused mainly on the rabbit tissue biodistribution study, although follow-on clinical application in cat and dog subjects confirmed the rabbit biodistribution results. The goal was to establish a radiological safety profile for <sup>90</sup>Y-RadioGel preparation and use.

## METHODS AND MATERIALS

The in vivo localization and retention of injected <sup>90</sup>Y-RadioGel™ were studied in tumors of rabbits, cats, and dogs. We also looked for potential migration of free <sup>90</sup>Y or complexed (tightly bound) <sup>90</sup>Y(YPO<sub>4</sub>) via blood circulation away from the tumor to any normal organs and tissues.

### New Zealand White rabbits

This study involved male New Zealand White rabbits (3–4 kg) obtained from Covance Research Products (Denver, PA). VX2 liver tumors were grown in 12 rabbits designated as donor rabbits; tumor tissues from these donor rabbits were then implanted into 26 recipient rabbits. Rabbits were housed individually in standard wire-bottom,

<sup>4</sup>For simplicity, both products are referred to in this paper as <sup>90</sup>Y-RadioGel™.

stainless steel rabbit cages with resting boards, food (Lab Diet Laboratory Rabbit Diet High Fiber), and water ad libitum. Prior to the study, an animal use protocol was reviewed and approved by the Battelle Institutional Animal Care and Use Committee. The study was performed according to *Guide for the Care and Use of Laboratory Animals* (National Research Council 2011). The animal facility at Battelle, Pacific Northwest Division (Richland, WA) is AAALAC accredited and registered with the US Department of Agriculture as a Class R research facility (91-R-0006).

### VX2 tumor cell line

The VX2 tumor cells used in this study were grown in donor rabbits from a cell line obtained from the Division of Cancer Treatment and Diagnosis Tumor Repository at the National Cancer Institute (Bethesda, MD).

### Tumor cell harvesting and implantation

Tumor cells were harvested from among the 12 euthanized donor rabbits. A volume of VX2 carcinoma suspension (0.5 mL with approximately  $5 \times 10^7$  mL<sup>-1</sup> tumor cells) was injected into the vastus lateralis muscle of each of 26 recipient rabbit's left hind limb using aseptic techniques. Tumors in recipient rabbits developed thereafter in about 14 d and were ready for treatment.

### Yttrium-90-RadioGel™ preparation

The RadioGel™ is supplied as two separate vials, one of which contains the <sup>90</sup>Y(YPO<sub>4</sub>) microparticles in phosphate-buffered saline (PBS), and one of which contains only the polymer carrier solution. The two vials are combined and mixed prior to injection into the tumor.

Calibrated amounts of <sup>90</sup>Y were obtained from PerkinElmer (Waltham, MA) as a high-purity, radiochemical grade yttrium-90-chloride <sup>90</sup>Y(YCl<sub>3</sub>). Yttrium-phosphate <sup>90</sup>Y(YPO<sub>4</sub>) microparticles (nominally 0.5- to 2.0-μm diameter) were then synthesized, assayed, measured, and QA/QC-checked at Pacific Northwest National Laboratory (Richland, WA, rabbit study) or at IsoTherapeutics Group LLC (Angleton, TX, cat and dog studies). Briefly, insoluble <sup>90</sup>Y(YPO<sub>4</sub>) particles were prepared using solutions of stable Y(YCl<sub>3</sub>) and radioactive <sup>90</sup>Y(YCl<sub>3</sub>), H<sub>5</sub>-DTPA, Na<sub>2</sub>HPO<sub>4</sub>, and HCl as reported elsewhere (Fisher et al. 2020). The <sup>90</sup>Y(YPO<sub>4</sub>) particles were washed free of unbound <sup>90</sup>Y and suspended in phosphate-buffered saline at <sup>90</sup>Y activities and PBS concentrations pre-determined by calculation to achieve a prescribed activity on day of implant.

The polymer solution contained a dissolved, non-toxic co-polymer of PLGA [poly-(DL-lactic acid-co-glycolic acid)] and PEG [poly-(ethylene glycol)] in a sterile PBS. Yttrium-90(YPO<sub>4</sub>) particles in sterile PBS were mixed with the dissolved polymer solution immediately prior to injection into tumors or tumor margins. The mixture was cooled in crushed ice prior to injection.

### <sup>90</sup>Y(YPO<sub>4</sub>) injections

When tumors reached an appropriate size for treatment, each recipient rabbit was sedated with acepromazine and anesthetized with isoflurane. The lateral aspect of the left hind limb was clipped and aseptically prepared with a chlorhexidine scrub.

Tumors grown in recipient rabbits were treated using tracer levels of <sup>90</sup>Y(YPO<sub>4</sub>) microparticles to evaluate biodistribution of the <sup>90</sup>Y microparticles post-injection. Prior to administration, calibrated activities of <sup>90</sup>Y(YPO<sub>4</sub>) particles were added to a sterile hydrogel carrier solution or to PBS alone to facilitate intra-tumoral injection by needle and syringe.

Under ultrasound guidance, the center of each tumor was injected once with a tracer <sup>90</sup>Y level comprising 0.2 mL of either <sup>90</sup>Y-RadioGel™ or <sup>90</sup>Y(YPO<sub>4</sub>) in PBS (controls). In other rabbits, tumor margin tissues were injected with 0.2 mL <sup>90</sup>Y-RadioGel™. The administered <sup>90</sup>Y activity in each rabbit tumor and margin was 7.4 MBq of <sup>90</sup>Y(YPO<sub>4</sub>) in polymer carrier or saline carrier (controls) at particle mass concentrations of 27 to 31 mg YPO<sub>4</sub> mL<sup>-1</sup>. The number of rabbits in each treatment group is shown in Table 1.

### Tumor tissue resections

To determine the <sup>90</sup>Y(YPO<sub>4</sub>) biodistributions in rabbit tissues, the rabbits from each study group were euthanized at either 48 h (13 rabbits, Table 2) or 10 d post-injection (13 rabbits). At 48 h post-injection, blood and tissues (tumor or tumor margins, liver, lymph nodes, rib bone, kidney, spleen) were harvested, and the tissues were prepared for liquid scintillation counting using a standard wet-ash procedure. At 10 d post-injection, VX2 tumors and normal organs were surgically resected for microCT imaging.

### Post-injection assays

Rabbit tissue assays for tumor and organ tissues collected at 48 h were performed by liquid scintillation counting. Non-destructive imaging on intact tissues collected at 10 d was performed using microCT, as follows.

**Liquid scintillation counting.** Rabbit tissues collected at 48 h were weighed, digested, and counted for <sup>90</sup>Y activity. One-gram tissue specimens were placed in a beaker with concentrated nitric acid (70%, 16 M) and heated while stirring

**Table 1.** Experiment design: number of rabbits per treatment group.

Tissue analysis: Liquid scintillation counting at 48 h post-injection		
Treatment	Interstitial tumor tissue	Tumor margin tissue
<sup>90</sup> Y-RadioGel	5	3
<sup>90</sup> Y-PBS	5	0
Tissue analysis: MicroCT imaging at 10 d post-injection		
Treatment	Interstitial tumor tissue	Tumor margin tissue
<sup>90</sup> Y-RadioGel	5	3
<sup>90</sup> Y-PBS	5	0

**Table 2.** Liquid scintillation counting results for  $^{90}\text{Y}$  in rabbit tumors, tumor margins, non-target organs, and whole-animal blood for rabbits sacrificed at 48 h post-injection.

Rabbit ID Code	Counts (dpm) <sup>a</sup>		Percent of tumor or margin count value <sup>b</sup>				
	Tumor with $^{90}\text{Y}$ -RadioGel	Spleen	Rib bone	Nearest lymph node	Liver	Kidneys	Whole-animal blood
24	210,600	0	0.05	0.03	0	0.01	0.01
26	628,200	0	0	0	0	0	0
30	394,400	0	0	0.02	0.03	0	0
34	814,000	0	0	0	0.09	0	0
36	2,056,000	0	0	0	0	0	0
	<b>Margin with <math>^{90}\text{Y}</math>-RadioGel</b>	<b>Spleen</b>	<b>Rib bone</b>	<b>Nearest lymph node</b>	<b>Liver</b>	<b>Kidneys</b>	<b>Whole-animal blood</b>
2	224,000	0	0	0	0	0	0
3	280,000	0	0	0	0.09	0	0
4	9,850	0	0	0	0	0	0
	<b>Tumor with <math>^{90}\text{Y}</math>-PBS</b>	<b>Spleen</b>	<b>Rib bone</b>	<b>Nearest lymph node</b>	<b>Liver</b>	<b>Kidneys</b>	<b>Whole-animal blood</b>
11	754,800	0	0	0	0	0	0
16	168,100	0.04	0.03	0.41	0.03	0.08	2.65
19	498,700	0.08	0	0	0.16	0.02	0
27	334,300	0	0.01	0	0	0	0.02
35	210,000	0	0	0	0.01	0	0.01

<sup>a</sup>Whole tumor or tumor margin counts (disintegrations) per minute, decay-corrected to 48 hours post-injection.

<sup>b</sup>Percent of residual tumor counts (disintegrations) per minute, decay-corrected to time 48 hours post-injection.

at a low boil to dryness. Dilute (0.05 M) nitric acid (1.5 mL) was added to each sample residue, and the solution was transferred to a glass liquid scintillation vial. The digestion beaker was washed three times with dilute nitric acid, and the wash was added to the same liquid scintillation vial (to a total volume of 3 mL). A diluted fraction of each prepared sample solution was drawn for liquid scintillation counting (Packard/Tricarb) over the 0-2,000 keV energy region and decay-corrected to the day of administration.

**MicroCT image analysis.** MicroCT may be used to image crystalline yttrium phosphate if density and concentrations are great enough at the resolution available to distinguish colloidal yttrium phosphate from normal tissue. Rabbit tissues collected at 10 d were bonded with surgical glue to plastic for image orientation. The bonded tissues were individually imaged using a GE eXplore 120 microCT scanner at the following scan parameters: 90 kV peak tube voltage, 40 mA current, 16 msec exposure time, and 900 projections covering 360° of rotation with 0.4° angular separation. Images were reconstructed to 50 μm isotropic resolution to visualize the three-dimensional physical distribution of crystalline yttrium-phosphate in the tissues.

### Animal cancer patients

Following demonstration of tracer biodistributions in laboratory rabbits, cat and dog cancer patients were treated by intra-tumoral injection with  $^{90}\text{Y}(\text{YPO}_4)$ -RadioGel™ to evaluate  $^{90}\text{Y}$ -microparticle biodistribution and therapy effectiveness. With owner consent, 10 pet cats and three pet

dogs presenting with spontaneous or vaccine-associated soft-tissue sarcomas were treated with multiple intra-tumoral injections of  $^{90}\text{Y}$ -RadioGel™ at two university and one private veterinary cancer clinics.

Early results of the clinical treatment in eight cats and dogs were previously reported elsewhere (Fisher et al. 2020).

## RESULTS

### Rabbit tracer study

Upon injection into rabbit tumors, the polymer solution carried the suspended  $^{90}\text{Y}(\text{YPO}_4)$  particles into tumor interstitial fluid space, where the solution perfused radially within the target tissue. After warming to near body temperature (30-37 °C), the polymer solution transitioned from liquid to gel phase, which solidified the mixture within the tumor tissue interstitium and entrapped the  $^{90}\text{Y}$ -microparticles in the tumor. Liquid scintillation measurements and microCT imaging confirmed that physical sequestration of  $^{90}\text{Y}$  prevented out-migration from tumor tissue to other organs via blood circulation.

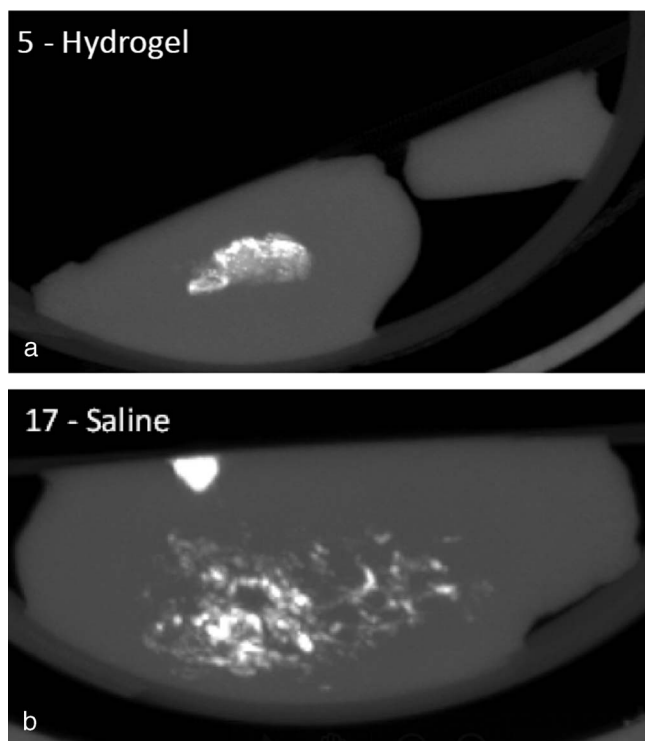
**Liquid scintillation counting.** Beta-particle liquid scintillation counting of rabbit tissue samples at 48 h post-administration showed that significant radioactivity was measurable only at the tumor site of administration. Table 2 shows measurement results for tissues obtained at 48 h post-administration (dpm g<sup>-1</sup> sample).<sup>5</sup> At 48 h

<sup>5</sup> $^{90}\text{Y}$  count rate in disintegrations per minute per gram of tissue.

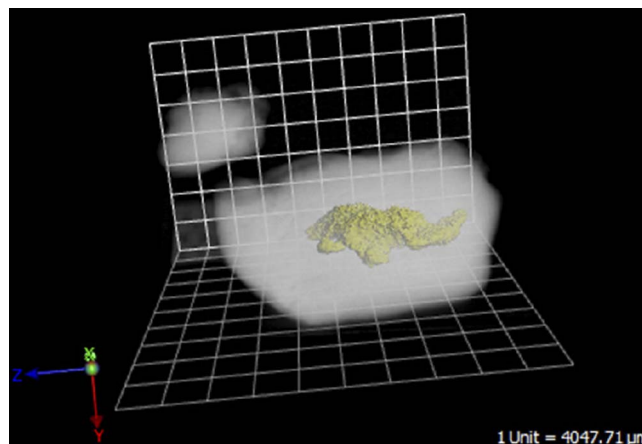
post-injection, radioactivity was confined to the tumor and tumor margins; very little radioactivity above detector background (fractions of percent tumor activity) was evident in blood or any other peripheral tissues. Similar results were obtained for  $^{90}\text{Y}(\text{YPO}_4)$ -microparticles administered using PBS but not combined with the hydrogel; highly insoluble  $^{90}\text{Y}(\text{YPO}_4)$ -microparticles remained within the injected tumor tissue (tumors and margins). One rabbit showed slight uptakes (0.03 to 0.41% of tumor uptakes) in organ tissues and blood uptake (2.65% relative to the tumor tissue). Only negligible blood uptake was observed in one rabbit (No. 24) administered  $^{90}\text{Y}$ -RadioGel.

**MicroCT image analysis.** At 10 d post-administration, yttrium phosphate was visualized within the tumor and margin tissues (Fig. 1) but was not visible in normal organs and tissues outside the injection site. Fig. 1 also shows differences between yttrium-phosphate biodistributions observed by microCT in tumor specimens after a single injection of (a)  $^{90}\text{Y}(\text{YPO}_4)$ -RadioGel™ and (b)  $^{90}\text{Y}(\text{YPO}_4)$ -PBS (saline).

Carrier gelation provided increased sequestration of yttrium phosphate in tumor tissue compared to yttrium phosphate in saline alone (without interstitial gelation). A three-dimensional reconstructed image of yttrium phosphate in one tumor at 10 d post-injection confirmed interstitial



**Fig. 1.** MicroCT image of yttrium phosphate within tumor interstitial space at 10 d post-injection, administered as (a)  $^{90}\text{Y}(\text{YPO}_4)$ -RadioGel™ and (b)  $^{90}\text{Y}(\text{YPO}_4)$ -saline.



**Fig. 2.** 3D-reconstructed microCT image showing colloidal yttrium phosphate within a tumor specimen at 10 d post-injection.

perfusion and gelation in tumor tissue after a single-point injection (Fig. 2).

### Results in cat and dog cancer patients

Clinical application of  $^{90}\text{Y}$ -RadioGel™ was tested at Washington State University (Pullman), the University of Missouri (Columbia), and at Vista Veterinary Hospital (Kennewick, WA) for treating cat and dog subjects presenting with inoperable sarcomas. To achieve uniform placement of  $^{90}\text{Y}$ -RadioGel™ in tumors of various sizes, therapy was administered using multiple, spaced needle injections, as described previously (Fisher et al. 2020). These studies confirmed the tumor-retention property of  $^{90}\text{Y}$ -RadioGel™ that was previously observed in rabbits. Post-injection imaging (CT or PET/CT, where available) confirmed that  $^{90}\text{Y}$ -RadioGel™ perfused interstitial fluid spaces and that  $^{90}\text{Y}$  remained within treated tumor tissues. No  $^{90}\text{Y}$  was detected using portable instruments in urine or feces of any cat or dog subject post-injection. On follow-up, complete and partial responses to treatment were observed with better therapy response resulting at higher tumor absorbed doses (Fisher et al. 2020).

**Tumor absorbed doses.** Cats and dogs were treated with escalating amounts of  $^{90}\text{Y}$ -RadioGel™ needed to achieve tumor absorbed doses of 100 to 400 Gy. In three dog subjects, the planned therapy doses were confirmed post-treatment using quantitative PET/CT imaging (Fisher et al. 2020). Tumor volumes were highly variable (1.3 to 233 g) from one subject to another. For tumor target doses of 300 Gy, the  $^{90}\text{Y}(\text{YPO}_4)$  activity administered was about  $7.4 \text{ MBq g}^{-1}$  tumor. For target doses of 400 Gy, the  $^{90}\text{Y}(\text{YPO}_4)$  activity administered was about  $9.2 \text{ MBq g}^{-1}$  tumor.

### DISCUSSION

Radiation safety is important for therapies involving radioactive material. The  $^{90}\text{Y}$ -RadioGel™ was designed

with safety in mind for both the patient and the supporting medical personnel. The high-energy, short-range beta-particle emissions from  $^{90}\text{Y}$  are favorable for localized treatment of non-resectable solid tumors; the lack of emission photons from  $^{90}\text{Y}$  helps to minimize radiation dose to persons who prepare and administer the treatment.

Cancer treatment is optimized by achieving a desired tumor dose without adverse radiation-associated effects in normal organs and tissues. This aspect of patient safety may be evaluated by comparing tumor absorbed doses with normal organ and tissue doses. Since the  $^{90}\text{Y}(\text{YPO}_4)$  remained implanted in tumors and did not migrate to normal organs or tissues, radiation doses to all normal tissues were negligible or not measurable. The best tumor retention and lowest uptake in non-target tissues was observed with  $^{90}\text{Y}(\text{YPO}_4)$ -RadioGel compared to  $^{90}\text{Y}(\text{YPO}_4)$ -PBS.

In one dog, a small amount of  $^{90}\text{Y}$  activity was observed after drainage from the tumor to the nearest lymph node (Fisher et al. 2020), as anticipated for activity placed within tumor interstitial spaces, whereas no  $^{90}\text{Y}$  activity was found in circulating blood or in excreta. Despite multiple needle injections into cat and dog tumors, no activity was introduced into blood vessels for any of the cat and dog subjects. The results of this study showed efficient use of the beta emissions from  $^{90}\text{Y}$  to treat cancer and to avoid undesirable irradiation of normal organs and tissues.

Solid gel in the tumor dissolves over time (about 60 d) by natural biodegradation into non-toxic breakdown products and disappears, leaving only indiscernible (trace) amounts of non-toxic yttrium phosphate. Tumors destroyed by radiation resorbed by natural processes during normal healing.

### Radiation safety practices

Standard and customary health physics good practices were employed during each of the animal procedures, and monitoring results were unremarkable. Scientific and medical personnel handling the injection solutions or persons assisting in the surgical suite wore protective clothing (eye protection, surgical gowns or lab coats, latex gloves, and shoe covers). Work areas were covered with absorbent, plastic-lined paper, and were marked with safety tape to distinguish potentially contaminated areas from contamination-free (clean) areas. Yttrium-90 sources were shielded when not in use. Yellow plastic bags and sharps containers were provided for  $^{90}\text{Y}$ -contaminated needles, syringes, wipes, gauzes, latex gloves, and paper absorbents used during injection procedures. Animal subjects were surveyed after injections to check for any potential skin-surface contaminations. Detected activity was wiped with cotton gauze and isopropyl alcohol and disposed as radioactive waste. Radioactive waste was labeled and marked as radioactive, segregated, and held for 10 physical half-lives (to complete decay, or approximately 30 d), and then disposed of as unmarked regular trash.

Radiation exposures to health care personnel were monitored using personnel dosimeters and portable instruments. Health physics technicians using portable survey instruments monitored work areas, surgical table surfaces, floors, and protective clothing (hands and shoes), and survey exits were performed at the conclusion of each procedure. All radiological practices and results were ordinary and uneventful. Personnel dosimetry included commercially available lapel dosimeters and TLD-finger rings; however, no significant radiation doses were recorded for finger rings or lapel dosimeters.

Since  $^{90}\text{Y}$  is a pure beta-emitting radionuclide, it is not physically possible for persons in the immediate vicinity of a cancer patient, including pet owner families or other members of the public, to receive radiation doses approaching the annual public dose limits (1 mSv or 5 mSv) from activity placed into a released patient. Although bremsstrahlung radiation from internally placed  $^{90}\text{Y}$  may be detected externally, measured dose rates are very low (fractions of natural background), depending on activity administered, shielding, and distance.

### CONCLUSION

Liquid scintillation counting at 48 h post-injection and microCT imaging at 10 d post-injection in rabbits showed that  $^{90}\text{Y}(\text{YPO}_4)$  microparticles remained where placed and did not migrate from the tumor or margin injection sites. These results showed that:

- $^{90}\text{Y}$  activity did not redistribute to normal organs and tissues in significant amounts via circulating blood. In-situ containment was achieved using a highly insoluble chemical form of  $^{90}\text{Y}$  and by effectively restraining the microparticles within interstitial space using the polymer composite carrier (hydrogel) solution compared to PBS alone;
- Consequently, radiation doses from  $^{90}\text{Y}$  were mainly confined to tumors and margin tissues, resulting in highly favorable therapeutic ratios; and
- Since the therapeutic  $^{90}\text{Y}$  radiation dose was constrained to tumor tissue and not to the animal normal organs and tissues, these results confirm the  $^{90}\text{Y}$ -RadioGel™ should represent a radiologically safe approach for treating non-resectable solid tumors as part of overall cancer management in human subjects.

During preparation and administration, radiation doses to hands and body of study personnel were monitored and were found to be negligible (not measurable above detection limits) and unremarkable. This experience showed that  $^{90}\text{Y}$ -RadioGel™ can be safely prepared and administered.

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