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Efficacy of Re-188-labelled sulphur colloid on prolongation of survival time in melanoma-bearing animals

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Abstract

In this study, the effectiveness of a ^{188}Re labeled sulfur colloid with two particle size ranges was used to evalucate the effectiveness of this agent on melanoma tumors in mice in terms of animal lifespan.

Methods: Two separate group of animals were used for investigating biodistribution and survival time. A total of 188 B16F10-melanoma-bearing BDF_1 mice were injected intraperitoneally with 3.7 MBq (0.1mCi)/2mL of radiolabeled sulfur colloid ten days after intraperitoneal inoculation of $5x10^5$ B16F10 melanoma cells/2ml. For group 1, 30 mice were sacrificed at 1, 4, 24, 48 and 72 hours for biodistribution studies. In group 2, 158 mice were divided into 9 groups (n=16~18/groups)each receiving respectively tumor alone, tumor with normal saline, cold colloid or hot colloid with 16, 23, 31, 46, 62, or 124 MBq activity. Each of these colloid groups was further divided into two groups, one receiving smaller particle sizes ($<3\mu$m:80.4 $\pm$7.2%, colloid 1) and the other receiving larger particle sizes ($<3\mu$m:12.3$\pm$1.0%, colloid 2). The animals were checked daily until death and their survival recorded.

Results: Colloid 2 showed higher accumulation in almost all tissues, the highest accumulation organ was tumor (~ 40%), then spleen (~20%), stomach (~15%), diaphragm (~3%), and liver (~2%). There was a significant increase in survival time with increasing amount of the larger-particle-size colloid. Administered levels of 16–31 MBq/mouse were most efficacious and with higher amounts the survival times decreased significantly below that of the controls. There was a significant difference in the dose-response curves for the two preparations. Protection factors (1/Relative-risk) of nearly 5 were achieved using the larger colloid size, and nearly 30 using the smaller colloid size. An amount of 16–31 MBq of the colloid 2 was the optimal activity in these studies. On the one hand, the survival data agreed well with the biodistribution data, where higher accumulation was found in tumor with colloid 2.

Conclusion: Rhenium-188 offers on-site availability, medium half-life, higher beta-particle energy of 2.12 MeV for therapy and emission of 155keV gamma photon suitable for imaging. The present study demonstrated that ^{188}Re-sulfur colloid is an effective agent in controlling tumor cells in the abdominal cavity in animals. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Re-188-sulfur colloid; Melanoma; Biodistribution; Animal survival

1. Introduction

Rhenium-188 is of interest for a variety of therapeutic applications including radioimmunotherapy [2,3] and use Rhenium-188 aminex microspheres and colloids for potential treatment of rheumatoid arthritis of the synovial joints [23,25] and hepatoma [22,24]. Other applications which are expects to be pursued include treatment of bone pain with ^{188}Re-labeled phosphates [7,10,14,16]. Recently, an initial feasibility study with ^{188}Re-hydroxyethylidene diphosphonate (Re-188-HEDP) using different ^{188}Re sources demonstrated that application of Re-188-HEDP is safe and positive results in pain relief palliation [16]. In addition, dose esca-

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lation studied with Re-188-HEDP in prostate cancer patients showed that 3.3 GBq(~90 mCi) dose is the maximum tolerated [17].

In past years, for many years radioisotopes have been used in the treatment of ascites tumors, in particular ^{32}P-chromic phosphate in the case of disseminated ovarian cancer [8,18,26]. There have also been many trials of novel radioisotopes delivery methods using, for example, antibodies to tumor-associated antigens labeled with ^{131}I [4] or ^{90}Y [20]. In addition, more effective densely ionizing radiations have been studied in experimental systems, including the Auger-emitter ^{125}I [1] and α-emitting radioimmunoconjugates [8,15,19]. Microspheres (1.8μm) have also been studied as a delivery vehicle, and have shown promise in retaining ^{211}At, for example on the intraperitoneal surfaces [21]. The difficulty in all these studies has been delivering sufficient radionuclide selectively to the tumor while minimizing injury to normal tissue. As an example, in the studies using ^{212}Pb-labeled sulfur colloid, gastrointestinal toxicity was dose limiting.

Sulfur colloid, usually labeled with ^{99m}Tc, has been used extensively for the imaging of abdominal organs following intraperitoneal injection, and the particle size is generally less than 1μm [12]. Particle size is important, and this determines the uptake and retention by particular organs. Rhenium-188 has good characteristics for imaging and for potential therapeutic use, because of its β energy (2.1 MeV), its short physical half-life(16.9 hr) and its 155keV γ-ray emission for dosimetric and imaging purposes [11]. The short physical half-life of ^{188}Re allows for higher doses compared with long-lived radionuclides. Furthermore, the short half life reduces the problems of radioactive waste handing and storage. In particular, ^{188}Re is available from in-house generator system similar to Tc-99m generator. ^{188}Re can be obtained from a ^{188}W/^{188}Re generator, which makes it very convenient for clinical use.

Therefore, ^{188}Re deserves consideration as a potential candidate in the treatment of ascites tumors. In the present study, a ^{188}Re-labeled sulfur colloid with two particle size ranges was used to test its effect on a melanoma tumor in the mouse in terms of animal lifespan.

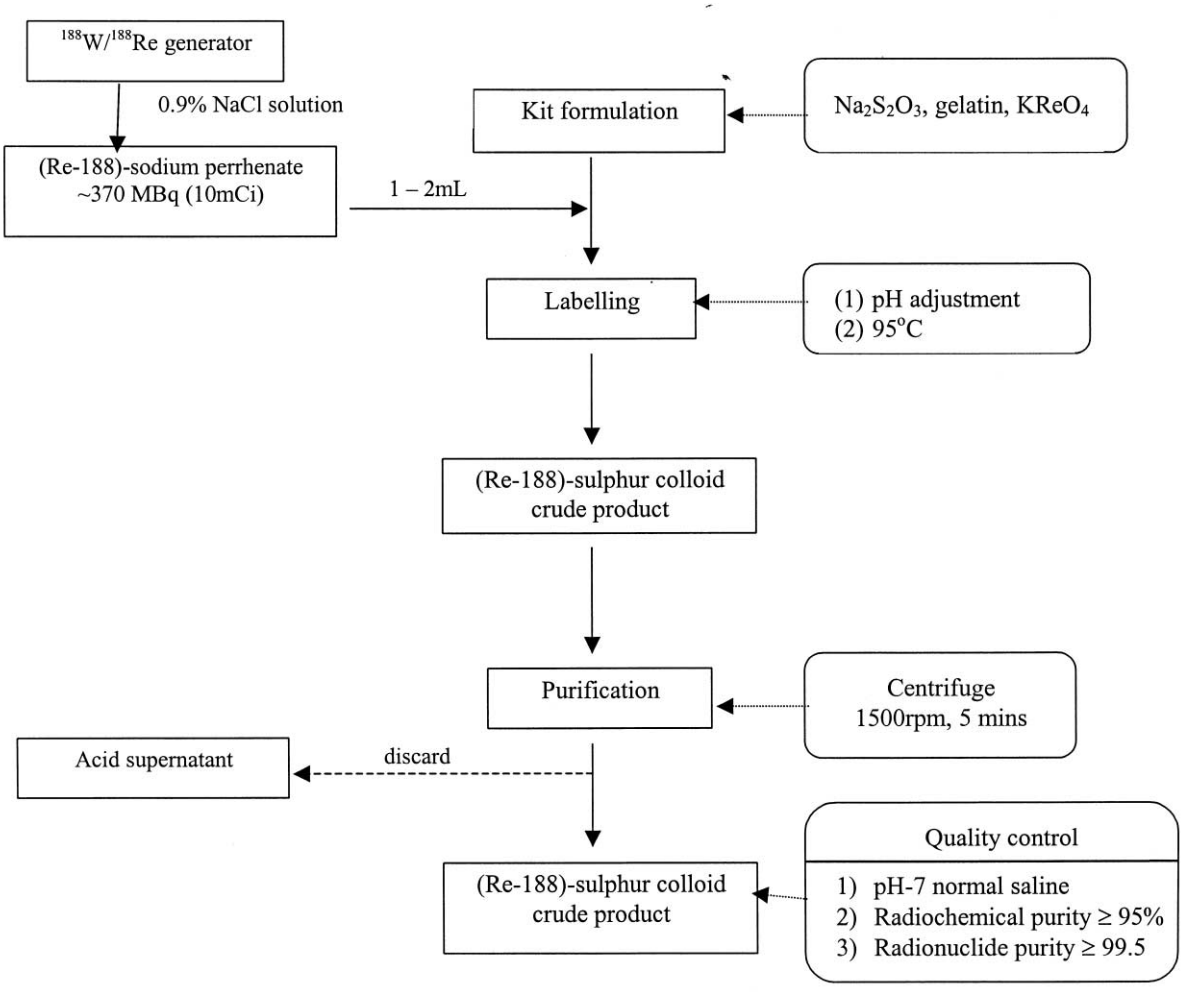

Fig. 1. Flow chart of (Re-188)-sulfur colloid preparation.

2. Materials and methods

2.1. Preparation of ^{188}Re-sulfur colloid

Rhenium-188 was obtained from an alumina-based ^{188}W/^{188}Re generator as described previously [5,6,9,13,21]. The ^{188}W was produced by double-neutron capture of ^{186}W. Elution of the ^{188}W/^{188}Re generator with normal saline provided solutions of carrier-free ^{188}Re as sodium perrhenate ($NaReO_4$). The ^{188}W/^{188}Re generators have demonstrated consistently high ^{188}Re yields and low parent breakthrough for a period of at least 3 months [6,9].

The method of preparation of ^{188}Re-sulfur colloid was a modification of our report [25]. The radiolabelling flow chart procedure for preparation of the ^{188}Re-sulfur colloid is shown on Figure 1. The optimal requirements for the preparation of the compound are:

1. Perrhenate carrier has to be present in the reaction solution,
2. Reaction temperature of 95° C and a reaction time of 30 minutes, and
3. pH of the reaction solution must be maintained at 0.5.

Under the above conditions, the yield of Re-188 sulfur colloid was more than 85% of the particles were obtained as colloid 1, when 60 mg of gelatin was added to the reaction solution. However, without the addition of gelatin, more than 92% of the particles were obtained as colloid 2. Particle sizes were measured by a particle size analyser (FRA9200, Microtrac).

Table 1
Particle sizes of colloid 1 and colloid 2

^{188}Re-Sulphur colloid	Reactants	Particle (μm)
Colloid 1	$Na_2S_2O_3{\cdot}5H_2O$: 40 mg	<1: 55.3 ± 6.2%
	EDTA: 4.8 mg	<3: 80.4 ± 7.2%
	KReO4: 0.8 mg	<10: 93.3 ± 5.2%
	Gelatin: 60 mg	<30: 98.5 ± 1.5%
Colloid 2	$Na_2S_2O_3{\cdot}5H_2O$: 40 mg	<1: 3.9 ± 0.5%
	EDTA: 4.8 mg	<3: 12.3 ± 1.0%
	$KReO_4$: 0.8 mg	<10: 54.5 ± 1.4%
		<30: 92.3 ± 3.8%

2.2. In vitro stability studies

Rhenium-188 sulfur colloid were dispersed into 15 mL vials which containing either 5 mL of normal saline, phosphate buffer (pH=7) or feta1 bovine serum. The vials were stopped and immerred in a water bath at 37^{0}C for 72 hr. The radiochemical purity and in-vitro stability were analyzed by silica gel impregnated fiber sheets (ITLC-SG, Gelman Sciences Inc.) using acetone as developer. Rhenium-188 sulfur

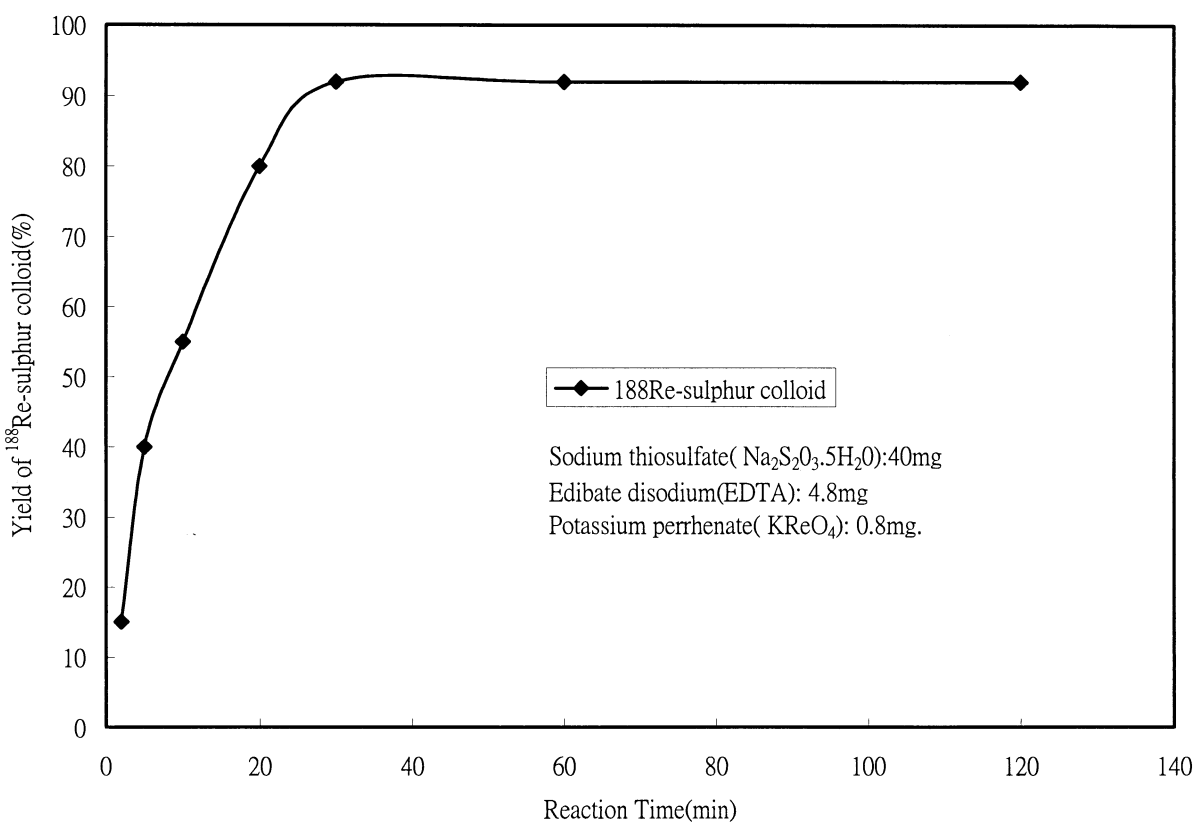

Fig. 2. Influence of pH on the yield of 188Re-sulfur colloid

Table 2
Relative risk and protection factors as a function of activity for colloid 1 and colloid 2

Activity (MBq/mouse)	Relative risk		Protection factor	
	Colloid 1	Colloid 2	Colloid 1	Colloid 2
16	0.71	0.18	1.4	5.6
23	0.21	0.42	4.8	23
31	0.23	0.034	4.4	29
46	0.24		4.2	
62	9.5		0.11	
124	38		0.026	

colloid remains at the origin ($R_f=0$) while free perrhenate will move to solvent front ($R_f=1$) in acetone. The R_f values were determined using a radio thin layer chromatography scanner (Bioscanner, System 200 Imaging Scanner and Auto Change 3000, Bioscan, Inc. U.S.A.). For obtaining the optimal yield of ^{188}Re-sulfur colloid, the influences of reaction time and pH of reaction media were also investigated.

No detectable dissociation of the radiolabelled sulfur colloid was observed either using normal saline, phosphate buffer or feta1 bovine serum.

2.3. Biodistribution of ^{188}Re-sulfur colloid in mice

Thirty B16F10-melanoma-bearing BDF_1 mice weighing between 25 to 30 g were used to determine the biodistribution of the ^{188}Re-sulfur colloid preparation. The animals were injected intraperitoneally with 3.7 MBq (0.1 mCi)/2mL with radio-labeled sulfur colloid 10 days after intraperitoneal innoculation of $5x10^5$ B16F10 melanoma cells/2ml. The mice were sacrificed at 1, 4, 24, 48 or 72 hours after colloid injection.

Approximate 0.1 g-samples of tumor, spleen, liver, lung, bone, blood (1 mL), kidney, stomach, small intestine, large intestine, diaphragm, skin, muscle, brain and heart were taken and weighed. Radioactivity was measured using a Beckman γ-counter, then the tissue concentrations were calculated and expressed as percentage of injected dose per gram.

2.4. Survival time of ^{188}Re-sulfur colloid treated mice

A total of 158 B16F10-melanoma-bearing BDF_1 mice were used to estimate overall survival time after intraperi-

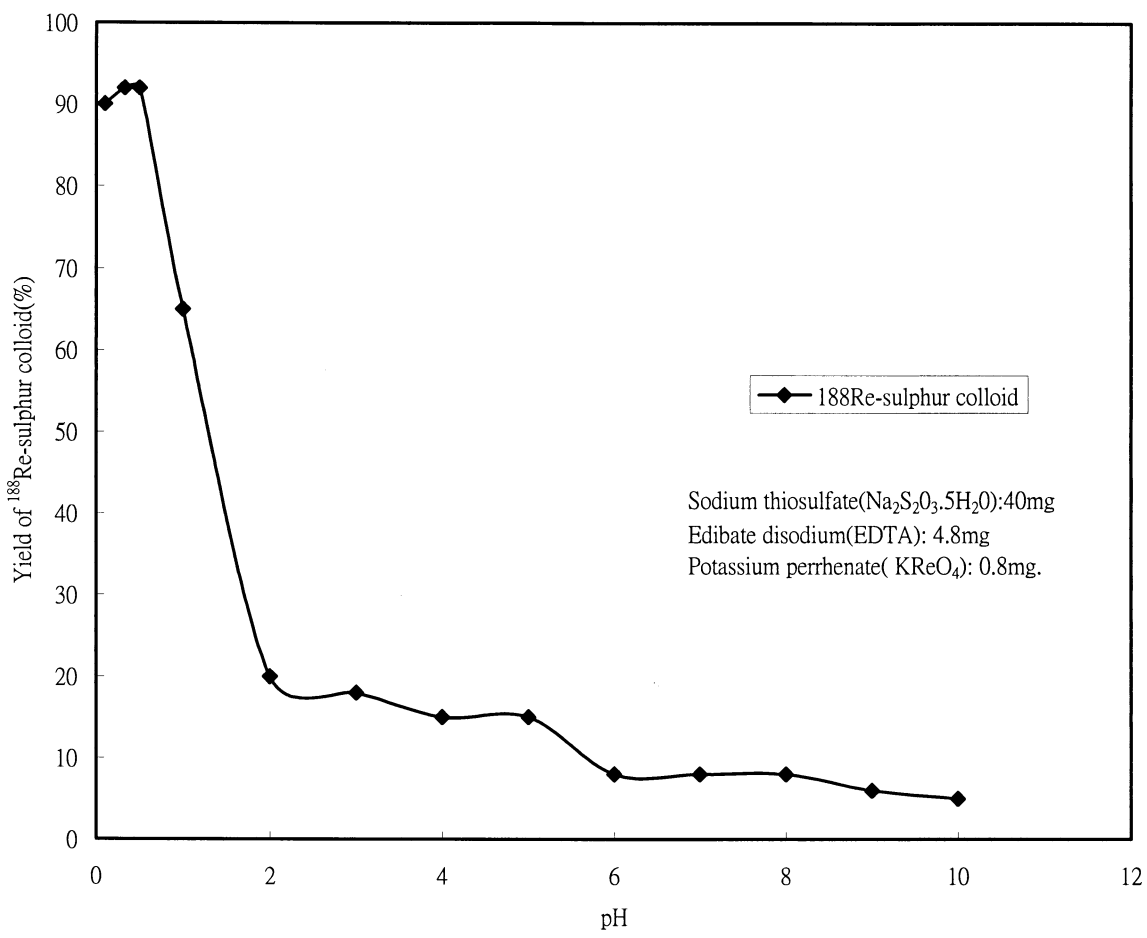

Fig. 3. Influence of pH on the yield of 188Re-sulfur colloid

toneal innoculation with $5x10^5$ melanoma cells/2 mL, followed 10 days later by the administration of various levels of the ^{188}Re-sulfur colloid preparation. The animals were divided into nine groups, each receiving, respectively, tumor alone, tumor with normal saline, cold colloid, or hot colloid with 16, 23, 31, 46, 62, or 124 MBq activities. Each of these colloid groups was further divided into two groups, one receiving smaller particle sizes (< 3 um:80.4 ± 7.2%, colloid 1) and the other receiving larger particle sizes (< 3 um:12.3 ± 1.0%, colloid 2). The animals were checked and their survival recorded each day until death.

3. Results

3.1. Yields and partical size of ^{188}Re-sulfur colloid

The ^{188}Re-sulfur colloid was prepared with the acid reduction method. Table 1 shows the particle size formed by the addition or without addition gelatin. A smaller particle size colloid was obtained with the addition gelatin. The yields of ^{188}Re-sulfur colloid obtained were 85% without adding gelatin, called colloid 1, and 92% with adding gelatin, called colloid 2. Our results show that the yield of ^{188}Re-sulfur colloid at pH 0.5 is constant for reaction times

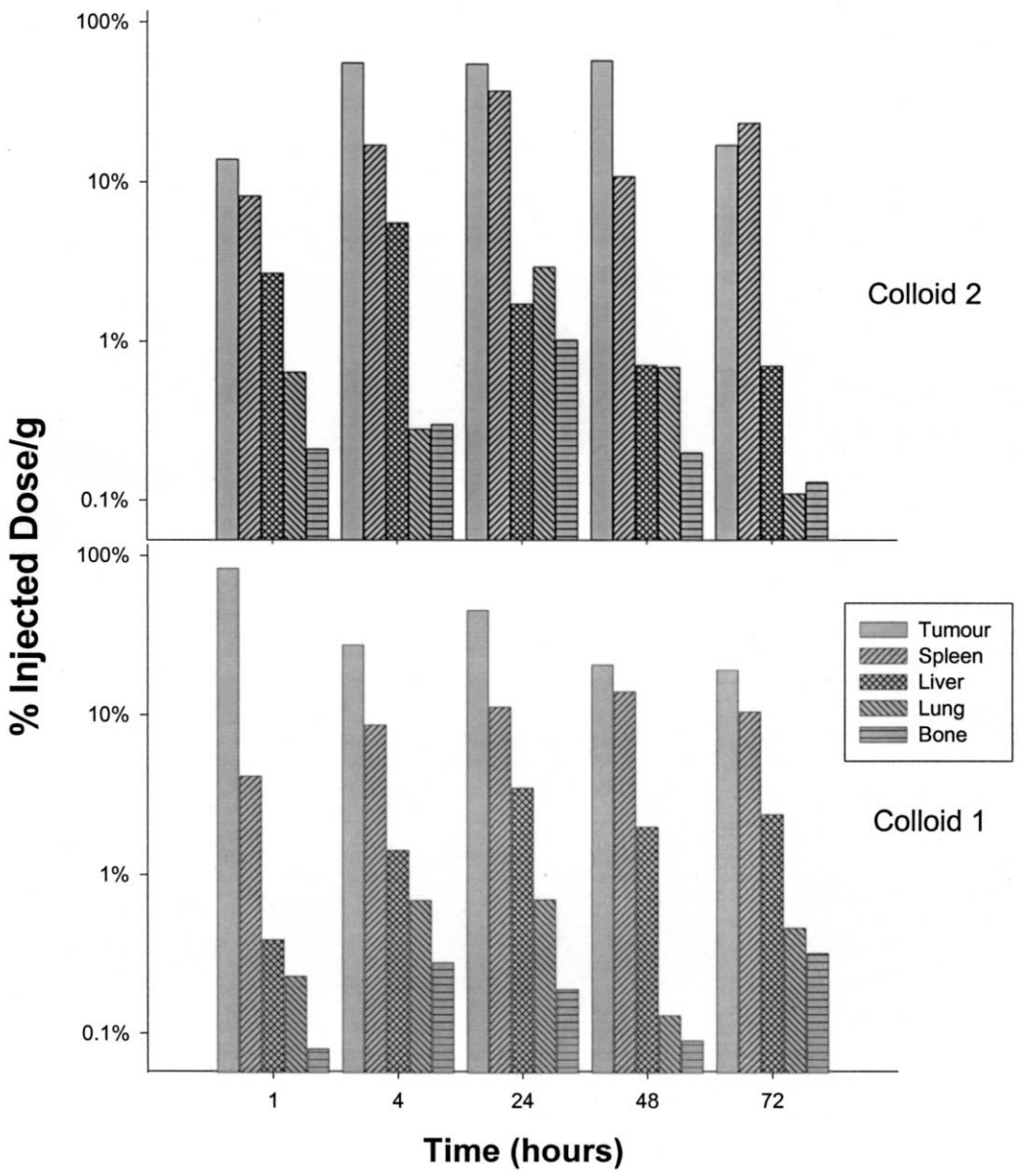

Fig. 4. Percentage of injected activity of the two colloids in some organs.

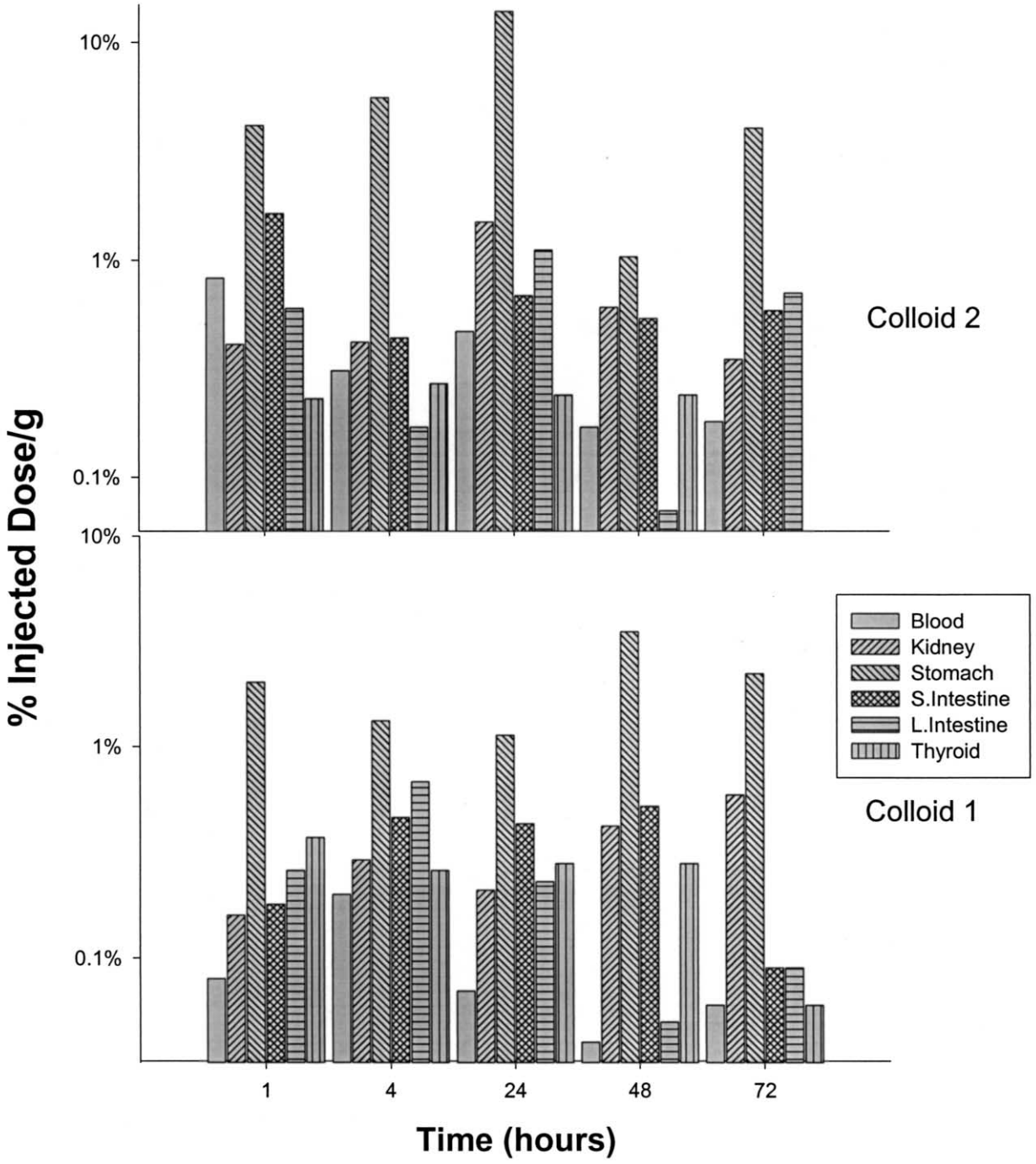

Fig. 5. Percentage of injected dose of the two colloids in other organs.

of 30 min to 120 min (Figure 2). However, the yield is reduced sharply if the reaction time is less than 20 min. The influence of pH is illustrated in Figure 3. The results showed that the yield of ^{188}Re-sulfur colloid was constant if the pH of the reaction is below 0.5. However, the yield of ^{188}Re-sulfur colloid was less than 20% if the pH is greater than 2.

3.2. Biodistribution data

The highest accumulation of ^{188}Re-sulfur colloid was observed in the tumor (~ 40%), followed by the spleen (~20%), stomach (~15%), diaphragm (~3%), liver (~2%) and the rest of the sampled organs were relatively very low in amounts (Figures 4, 5, 6). Also colloid 2 showed higher

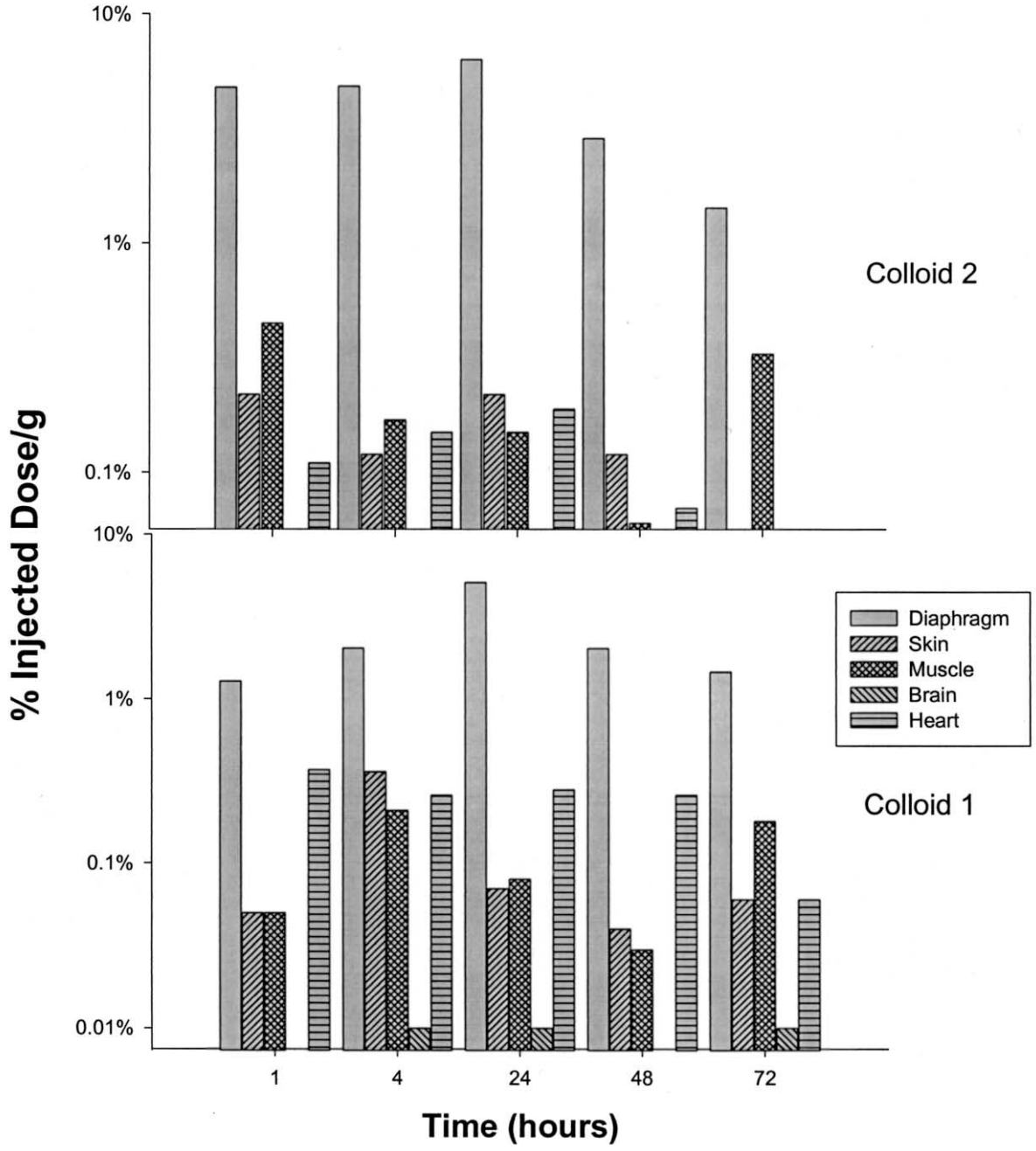

Fig. 6. Percentage of injected activity of the two colloids in various other organs.

accumulation in almost all tissues, including the tumor. However, thyroid gland up-take were also very low (Fig. 5). This can be explained ^{188}Re-sulfur colloid was stable in vivo.

3.3. Animal survival data

The survival curve for each group of animals was computed using Kaplan-Meier methods, and the mean survival time was calculated with its associated 95% confidence limits. A log-rank test was performed to compare each dose group with its zero-dose control, and significant differences ($p < 0.05$) are shown by the solid symbols in Figure 7. Although here was no significant difference between the control groups, there was a significant increase in survival time with an increasing amount of colloid 2. Amounts of 16 to 31 MBq/mouse were most efficacious, although with higher amounts the survival times decreased significantly below that of the controls.

The smaller particle size was less efficacious, causing a decrease in survival times. Cox regression was used to show that there was a significant difference between the two

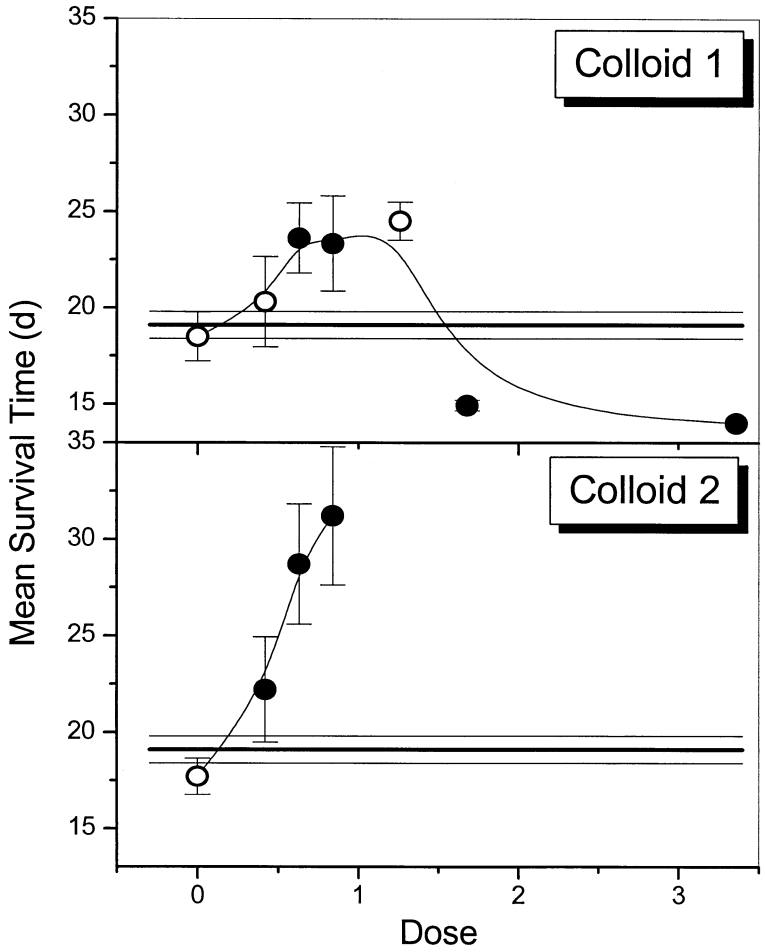

Fig. 7. Mean survival times versus injected activity (mCi) of colloid 1 and colloid 2. Error bars are 95% confidence intervals on the mean values. Horizontal lines show the mean and a 95% CI for the control group. Solid symbols indicate those groups, which show a significant difference from the zero-dose control in a log-rank test.

preparations after allowing for dosage ($p = 0.15$). Also, the use of a more complex Cox model to include the dose/colloid-type interaction indicated that there was a significant difference in the dose-response curves for the two preparations. The effect of dose was expressed as Relative Risk (<1 indicated decreased risk of death) and the reciprocal (Protection Factors) compared to the zero-dose groups. Protection Factors of nearly 5 were achieved using the larger colloid size, and nearly 30 using the smaller colloid size (see Table 2).

4. Discussion

The larger particle size (Colloid 2) shows higher accumulation in tumors and normal tissues such as spleen and stomach. Almost 40% or more of the activity is accumulated in the tumors, and this results in an increase in the overall survival of the animals.

The reason why accumulation of the ^{188}Re-sulfur colloid was higher in the spleen was possibly because it contains more fixed macrophages. In the liver, which also part of the reticuloendothelial system containing phagocytic Kupfer cells, the reason for a lower uptake could be that IP rather than intravenous injection was used, and Kupfer cells represent only a small proportion of the whole cell population within the liver.

An amount of 16 to 31 MBq of the ^{188}Re-sulfur colloid with an average particle size greater than 3 μm seemed to be an optimal activity and colloid preparation. On the one hand, the survival data agree well with the biodistribution data, where higher accumulation is found in the tumor with Colloid 2. This suggests that the radiation dose contribution from the 16 to 31 MBq activities to the critical normal tissues such as the intestine and perhaps the stomach were tolerable and that longer survival was due primarily to the higher dose to the tumors cells. The cause of death was not ascertained, and this would be particularly problematic in cases where damage to both the tumor and normal tissue is evident.

Larger particles produce a better uptake by the tumor and the reticuloendothelial system (e.g., macrophages). This

provides new knowledge of the particle size in relation to the efficiency of the uptake by macrophages. Hence, it is not necessarily the case that the smaller the particle, the better the uptake will be in terms of benefits to diagnostic imaging or tumors therapy in the reticuloendothelial system.

The animals died at 4 to 5 days after intraperitoneal administration of the higher amounts of 62 to 124 MBq of the colloid, resulting from characteristic severe intestinal damage. This is likely related to the fact that ^{188}Re has a high beta-particle energy of 2.12 MeV, which has a longe range in tissue. The injected ^{188}Re-sulfur colloid is likely to be in very close contact with the small and large intestines, therefore delivering high radiation doses to these tissues. Hence the prescription of activity for ascites tumor therapy needs to be accurately chosen.

5. Conclusion

Rhenium-188 offers on-site availability, medium half-life, beta-particle energy of 2.12 MeV and lower gamma energy of 155 KeV, the advantage, which are both suitable for therapy as well as for nuclear medicine imaging. The present study demonstrated that larger particle size of ^{188}Re sulfur colloid (>1 μm, 96%) and an amount of 16 to 31 MBq activities seemed to be appropriate for controlling tumor cells in the abdominal cavity.

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