

Samarium-153-EDTMP Biodistribution and Dosimetry Estimation

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Fifty-two patients were treated with single doses of ^{153}Sm -EDTMP in a Phase I escalating dose protocol for palliation of bone pain from metastatic prostate carcinoma. Samarium-153 ($T_{1/2}$ 46.3 hr), maximum β -particle energies 810 keV (20%), 710 keV (30%), 640 keV (50%), gamma photon 103 keV (28%), was complexed to the tetraphosphonate chelate, EDTMP. Five groups of patients were treated at doses of 1.0, 1.5, 2.0, 2.5, and 3.0 mCi/kg to evaluate toxicity from treatment. Patients were screened prior to treatment and followed after treatment with $^{99\text{m}}\text{Tc}$ -MDP bone scans. Biodistribution data on this group of patients were acquired and showed rapid uptake of ^{153}Sm -EDTMP into bone with complete clearance of nonskeletal radiotoxicity by 6–8 hr. Also included are complete sets of dosimetry estimations on an additional seven patients who received 0.5 mCi/kg ^{153}Sm -EDTMP Ca^{++} as part of a multiple dose therapy trial. Estimated radiation absorbed doses to bone surfaces averaged 25,000 mrad/mCi (6686 Gy/MBq), and urinary bladder doses averaged 3600 mrad/mCi (964 Gy/MBq).

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Patients with disseminated carcinoma often have painful bone metastases. In these patients who have progressive disease despite treatment, a systemic bone-avid radiopharmaceutical for treatment of widespread bony metastases has potential benefit. This has long been a goal in nuclear medicine practice. Beginning with radiophosphorus, diverse radionuclides have been used but have not gained widespread acceptance because of myelosuppressive side effects (1–6). Patients with late stage hormone-refractory prostatic cancer are an ideal group to derive benefit from systemic treatment of osteoblastic bone lesions with bone-seeking radiopharmaceuticals. Once these patients have developed hormone-refractory disease with painful bony metastases, pain control becomes difficult and most patients die within 6–10 mo of inanition associated with narcotic use and immobility. Because of this, effective pain

palliation in this patient group might be associated with prolonged survival.

Samarium-153, a radionuclide with medium-energy beta particle emissions and a medium-energy gamma photon (103 keV), is an appropriate candidate for therapeutic use in this setting. It can be attached to multidentate chelates to yield biolocalization similar to technetium bone agents for effective delivery of beta particle energy directly to bone with little soft-tissue dose. Pre-clinical studies in dogs that received a high dose of ^{153}Sm -EDTMP showed spontaneous recovery of bone marrow function after a period of pancytopenia (7). Because of this failure to effect marrow ablation even at extremely high doses in the animal model, ^{153}Sm -EDTMP may be useful in the treatment of patients with bony metastatic disease in whom decreased bone marrow function from disease involvement and prior treatment is common.

Samarium-153-EDTMP at low doses has been used elsewhere in the treatment of metastatic carcinoma to bone (8,9). We report here the results of a Phase I trial of ^{153}Sm -EDTMP using escalating single doses in groups of four patients with hormone-refractory prostatic carcinoma metastatic to bone. Administered doses were higher than those in previous trials and were designed to define limiting toxicity in this patient population. This report details the methods of preparation, administration, and biodistribution and dosimetry estimates of therapeutic doses of ^{153}Sm -EDTMP for pain palliation in prostatic carcinoma. Specific details of the clinical parameters observed in these patients are reported elsewhere (10).

METHODS

Radioradiopharmaceutical Preparation

Samarium-153 ($T_{1/2}$ 46.3 hr, mean β -particle energies: 810 keV, 20%, 710 keV, 50%, 640 keV, 30% and 103 keV gamma photon, 28%) was produced at the University of Missouri Research Reactor (MURR) from neutron irradiation of an enriched ^{152}Sm -oxide target (11). The target was dissolved in dilute HCl and 300–800 mCi ^{153}Sm in HCl was shipped for final preparation of the radiopharmaceutical. Samarium-153-Cl (specific activity 22–52 mCi/ml) was added by injection into a lyophilized kit containing 217.2 mg EDTMP using a manual remote labeling apparatus. The final product volume was adjusted by adding quantity

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TABLE 1
Treatment Groups

¹⁵³ Sm-EDTMP dose group	Number of patients	¹⁵³ Sm (mCi)	¹⁵³ Sm (MBq)
1.0 mCi/kg	20	53–105	1961–3885
1.5 mCi/kg	4	139–176	5143–6512
2.0 mCi/kg	4	147–219	5439–8103
2.5 mCi/kg	20	149–299	5513–11063
3.0 mCi/kg	4	224–294	8288–10878

sufficient to make 6 ml of 0.05 M phosphate-buffered saline, with the pH of the final product 7.0–8.5. Chelation yield of the kit was determined by passage of 15–20 μl of the final product over a 0.6-ml SP Sephadex C-25 (Pharmacia LKB, Pleasant Hill, CA) column, where the chelate bound radionuclide eluted and free ¹⁵³Sm was bound to the column. A 1:10 dilution of the final product was also tested for pyrogenicity using a limulus amoebocyte assay (sensitivity 0.0125 EU/ml, Pyrotell, Assoc. of Cape Cod, Woods Hole, MA).

Patients

All patients had hormone-refractory prostate carcinoma. These patients also had a Southwest Oncology Group performance status of at least 3, normal hematologic parameters and had not received maximum radiation to any local site. Any prior treatment with either radiotherapy or chemotherapy was completed 4 wk prior to admission to this study. Since ¹⁵³Sm-EDTMP has identical sensitivity for metastatic lesions as visualized by ^{99m}Tc-MDP bone scans, a positive ^{99m}Tc-MDP bone scan was required for entry into the treatment protocol.

This trial was carried out with the approval of the University of Washington Human Subjects and Radiation Safety committees. Samarium-153 doses were administered to groups of four patients at five escalating doses for determination of toxicity (20 patients total). To further define toxicity limits, an additional 16 patients were treated at the 1.0 mCi/kg and 2.5 mCi/kg dose levels (32 additional patients) (Table 1).

Treatment

Patients were treated as inpatients in standard hospital rooms. After giving signed informed consent, with special attention to the potential risks of toxicity from the treatment, patients had an intravenous line placed in each arm. One line was for infusion of the ¹⁵³Sm-EDTMP treatment dose, and the other was for serial blood sampling after dose infusion. Patients were hydrated with intravenous fluids for at least 6–8 hr prior to infusion. Just before infusion, patients had indwelling three-way Foley catheters placed with constant bladder irrigation for 8 hr after infusion. The catheter remained in place for 24–48 hr.

The ¹⁵³Sm-EDTMP therapy dose was placed in a 10-cc syringe and infused at a constant rate over 30 min by using an infusion pump (Harvard Appliances Inc., S. Natick, MA) that was housed in 1-in. thick lead shielding. Calcium gluconate for intravenous use was available at the patient bedside in case the patient exhibited signs of hypocalcemia from administration of the chelate. Vital signs were monitored every 30 min for 2 hr after the infusion, and then hourly for 4 hr. After infusion, the radiation safety officer surveyed the patient room with a handheld dose rate meter and posted a map of radiation dose rates at various positions in the patient room. Patients were discharged from the hospital when dose rates at one meter from the patient indicated a body burden of 30 mCi or less; this usually occurred 48 hr after treatment at the higher dose levels.

Biistribution Data Collection

All patients received 25 mCi of ^{99m}Tc-MDP (Medi-Physics, Emeryville, CA) for bone scanning prior to treatment for localization of bony metastases. Whole-body scans with selected spot images were obtained 3 hr after injection. A General Electric 500 gamma camera with a dedicated Starcam computer was used for image acquisition. The camera was centered over the 140 keV photopeak with a 13% window. A high-resolution collimator was used. Spot images were carefully acquired for 10⁶ counts/image to demonstrate lesional areas and normal areas for comparison. Two to three regions of interest (ROIs) were drawn around representative areas of increased bony uptake for comparison of uptake with identical normal bone sites. Uptakes were normalized to counts/pixel for each site.

Twenty-four hour whole-body retention of the ^{99m}Tc-MDP dose was also calculated by comparing whole-body counts with those of a ^{99m}Tc-liquid standard (12). These counts were obtained with a heavily shielded thyroid probe utilizing a 3-in. crystal aimed at the patient or standard 15 feet away from the crystal surface. Background-subtracted counts were obtained immediately and at 24 hr postinjection. These data were later compared with the cumulative urinary excretion of the ¹⁵³Sm-EDTMP treatment dose.

After infusion of the ¹⁵³Sm-EDTMP treatment dose, serial blood samples were withdrawn at 0.5, 1, 2, 4 and 24 hr after infusion for determination of percent injected dose/gram (%ID/g) in the serum. Aliquots of urine output in the catheter collection bag were collected periodically for 24 hr. Total urine volumes were recorded and each aliquot was counted for determination of cumulative percent injected dose excreted.

Patients were imaged just prior to hospital discharge (24–48 hr) after infusion of the ¹⁵³Sm-treatment dose. Whole-body scans were acquired with the same spot views as the previous ^{99m}Tc bone scans. The camera was peaked at the ¹⁵³Sm 103 keV photopeak using the high-resolution collimator (Fig. 1). Spot images were acquired for 10⁶ counts per image and the same ROIs were applied to lesional and nonlesional areas for determination of lesion-to-normal bone uptake. These data were compared with the lesion-to-normal bone ratios for the ^{99m}Tc bone scans acquired prior to treatment.

Bone scans were obtained at 1, 3 and 5 mo while on study. In repeat bone scans, whole-body views and repeat spot views were obtained for evaluation of disease progression. Lesion-to-normal

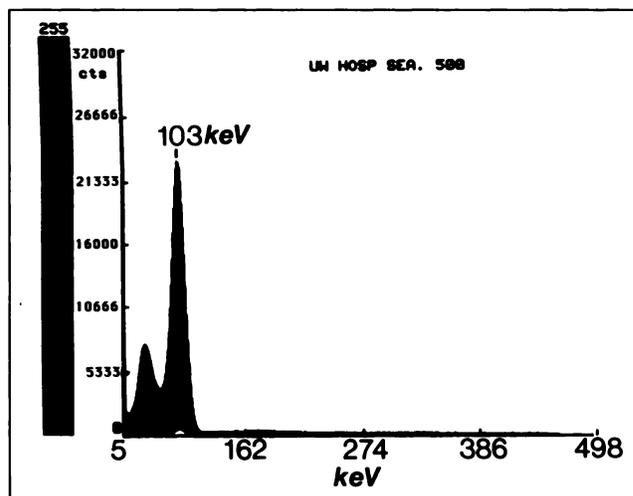


FIGURE 1. Photopeak of ¹⁵³Sm.

bone uptake ratios and 24-hr whole-body uptakes of ^{99m}Tc -MDP were also obtained for comparison with the pretreatment evaluation assay.

Dosimetry

Data for soft-tissue and skeletal dosimetry estimates in an additional seven patients were also obtained. These patients received their therapy dose while lying under the large field of view gamma camera. They received the ^{153}Sm -EDTMP radiopharmaceutical formulation with Ca^{++} added so infusion was rapid (over 1 min) with a handheld shielded syringe. Dynamic images of the chest and abdomen were acquired at a rate of 1 min/frame for 60 min, followed by planar images at 1, 2, 24 and 48 hr postinfusion using a general, all-purpose collimator. Images were accompanied by serial blood samples, complete urine collection and bone biopsy at 24 hr postinfusion. Additionally, patients were counted for whole-body retention of radioactivity daily.

Initially, gamma camera data were processed for generation of time-activity curves with ROI placement over the lungs, liver, kidneys and several skeletal sites. Soft-tissue whole organ uptake was determined using the opposing view planar quantitation technique. Since the soft-tissues were observed only anteriorly during the first hour, counts for the posterior whole organ views were estimated using correction factors derived from other imaging experience (13). After single organ time-activity curves were generated, it was noted that all sites had interference from associated skeletal structures after 20 min. For dosimetry calculations, the initial activity in an organ was assigned to be the activity measured in the 0–3-min dynamic frames, and clearance was assumed to be the same as serum clearance. Normal and disease skeletal site ROIs (humeral head, rib, sternum) were analyzed at every timepoint for generation of time-activity curves.

Kinetic data were fit to a multicompartiment model using the Simulation Analysis and Modeling (SAAM) software (14). The model contained compartments representing serum, bone, kidneys and urinary bladder. Measured kidney activity data were not fit, but assigned, as discussed above. The kidney compartment was added to provide a realistic input to the urinary bladder. Residence times (15) were estimated from results of the compartment models and entered into the MIRDOSE2 computer program (16). This program estimates radiation doses to the major organs based on absorbed fractions for the adult male phantom in the Cristy-Eckerman phantom series (17) using the standard MIRD technique (15), including the remainder of the body correction (18), the dynamic bladder model of Cloutier et al. (19) and the ICRP 30 dosimetry system for bone and marrow (20). It is important to note that the phantom employed has a red marrow mass of 1120 g, not 1500 g as in the *MIRD Pamphlet No. 5* adult male phantom (21). The urinary bladder voiding interval was 4.8 hr. Tumor activity kinetics were not included in the compartment model.

Skeletal doses were estimated from whole-body retention where skeletal retention was assumed to be the inverse of urinary clearance. Posterior iliac crest biopsies of lesional and normal bone were also obtained 24 hr postinfusion. Uptake was reported as %ID/g by counting the biopsy and comparing it to an aliquot of the injectate. Bone content was assumed to be 50% of the total biopsy weight (Appelbaum F, Bernstein I, Badger C, *personal communication*, 1989).

After counting, bone samples were embedded in methacrylate, sectioned and stained with hematoxylin and eosin. Sections were then examined for presence of tumor so that uptake of ^{153}Sm in the specimen could be assigned to lesional or normal bone. Unstained

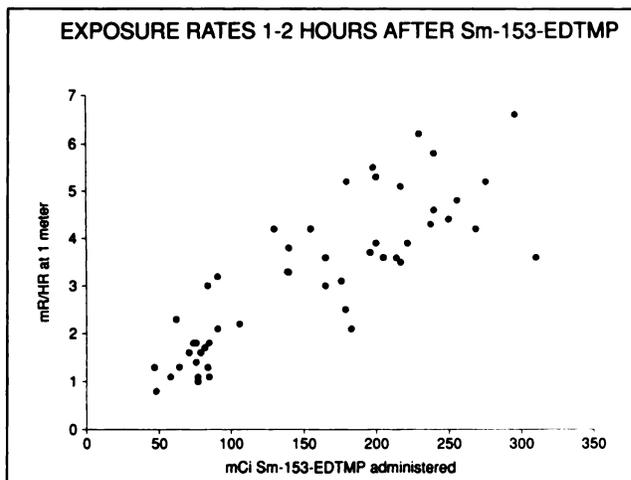


FIGURE 2. Exposure rates 1–2 hr after ^{153}Sm -EDTMP administration. Rates were measured 1 meter from the patient.

sections from each biopsy were coated with NTB-2 (Kodak, Rochester, NY) autoradiographic emulsion and exposed at 4°C in light tight boxes for 1 wk. Following standard development, slides were examined for isotope deposition in association with bone.

RESULTS

Radio pharmaceutical

Fifty-two ^{153}Sm dose aliquots were received from MURR. All doses were complexed to the EDTMP kit without problems. Complexation yields were always greater than 99%, and all final products were pyrogen-free with the limulus amoebolysate assay. Seven doses of ^{153}Sm -EDTMP Ca^{++} which were received as radiolabeled chelate had similar quality control results.

Patient Treatment

Samarium-153-EDTMP doses were administered to 59 patients without problems. Radiation dose exposures at one meter from the patient after treatment are shown in Figure 2. In two patients, significant room contamination occurred when urinals were spilled. After these occurrences, all other patients remained catheterized following treatment until discharge.

Blodistribution Data

As was previously observed (22,23), serum blood clearance half-time was rapid, with 4%–34% of the injected dose remaining in the serum 1 hr after infusion. The slow second phase of serum clearance half-time ranged from 8.1 to 17.1 hr (Table 2). Urinary excretion of ^{153}Sm was essentially complete by 6 hr after infusion. Urinary collection showed 8.7%–64% of the injected dose excreted in 10 hr without significant variation between treatment groups (Table 2). The whole-body retention averages of the ^{153}Sm -EDTMP treatment dose group (estimated as [100% – the 24-hr cumulative urinary excretion]) were comparable to those measured independently by whole-body counting, but were considered to be the most highly accurate. Whole-body retention values were comparable with those of ^{99m}Tc -MDP, ranging from 47% to 76%. Pretreatment aver-

TABLE 2
Samarium-153-EDTMP Biodistribution Data

¹⁵³ Sm-EDTMP group	Serum Clearance				Urinary/Whole-body clearance										
	%ID at 1 hr		T _{1/2} slow clearance phase (hr)		10-hr cumulative %ID in urine		% remaining in whole body at 10 hr		Pretreatment 24-hr ^{99m} Tc-MDP whole-body uptake		Lesion-to-normal bone ^{99m} Tc-MDP pre-treatment		Lesion-to-normal bone ¹⁵³ Sm-EDTMP therapy dose		
	Avg.	±s.d.	Avg.	±s.d.	Avg.	±s.d.	Avg.	±s.d.	Avg.	±s.d.	Avg.	±s.d.	Avg.	±s.d.	
1.0 mCi/kg	6.6	3.1	4.7	2.2	37.4	13.7	62.6	13.7	49.9	16.8	4.8	3.9	4.9	3.0	
1.5 mCi/kg	17.3	2.6	3.0	0.5	46.9	10.1	53.1	10.1	34.3	18.3	3.3	2.7	3.1	2.8	
2.0 mCi/kg	6.0	1.4	7.3	4.5	23.8	15.0	76.2	15.0	53.0	16.1	2.9	1.9	2.7	1.9	
2.5 mCi/kg	6.5	2.7	3.8	0.7	38.4	10.2	61.6	10.2	53.0	12.0	6.0	5.7	4.6	3.6	
3.0 mCi/kg	10.0	3.6	3.9	0.6	37.4	22.2	62.6	22.2	57.3	22.6	6.5	5.0	6.7	4.1	

Avg. is the average value for patients and s.d. is the standard deviation for the average values for each group.

age 24-hr uptakes per group on ^{99m}Tc scans ranged from 43.5% to 57.3% (Table 2). Scans of the ¹⁵³Sm-EDTMP dose obtained approximately 48 hr after treatment showed identical visualization of bony metastases (Fig. 3) compared with pretreatment ^{99m}Tc-MDP bone scans. Average uptake ratios for ^{99m}Tc-MDP and ¹⁵³Sm-EDTMP by patient group were similar (Table 2). Follow-up 24-hr ^{99m}Tc-MDP whole-body uptake values varied significantly from one patient to the next and in the same patient over time (Fig. 4). Although there was a general trend of increasing skeletal retention of ^{99m}Tc-MDP in the scans at follow-up intervals, there was a great deal of variation in these measurements. Figure 5 shows changes in lesion-to-normal bone ratios on ^{99m}Tc-MDP bone scans after treatment. As with whole-body retention values, there is a great deal of variability.

Dosimetry

Organ residence times observed in patients studied for dosimetry are shown in Table 3. Radiation dose estimates (Table 4) for soft tissues were similar to those estimated by Logan et al. (24) and Heggie (25), which were human doses scaled from rat biodistribution data. Skeletal doses were several fold higher, ranging from 20,000 to 32,000 mrad/mCi (5300–8800 Gy/MBq). Marrow doses ranged from 4600 to 7500 mrad/mCi (1200–2000 Gy/MBq) and urinary bladder doses ranged from 1300 to 4700 mrad/mCi (360–1300 Gy/MBq). Nonskeletal sites received negligible doses. Four bone biopsies were obtained and showed 24-hr ¹⁵³Sm content to range from 0.004 to 0.162 %ID/g bone. Autoradiographs of these specimens showed marked grain accumulation in areas of osteoblastic activity and along normal trabecular bone deposition sites (Fig. 6).

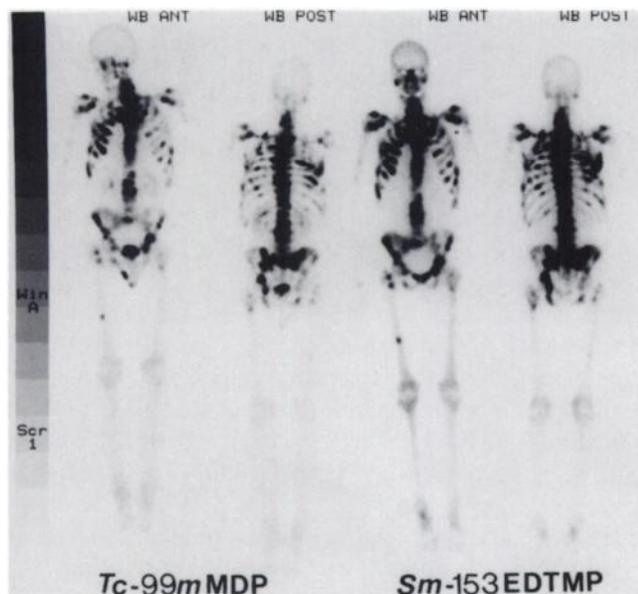


FIGURE 3. Whole-body images compare visualization of bony metastases in the ^{99m}Tc-MDP baseline scan (left) and ¹⁵³Sm-EDTMP therapy dose (right).

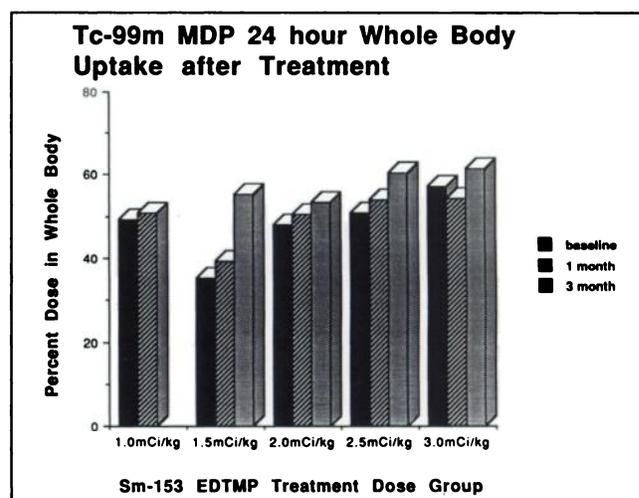


FIGURE 4. Technetium-99m-MDP 24-hr whole-body uptakes in the patients by dose group at baseline (pretreatment) and follow-up at 1 and 3 mo after EDTMP. Values displayed are averages for the four patients in each group.

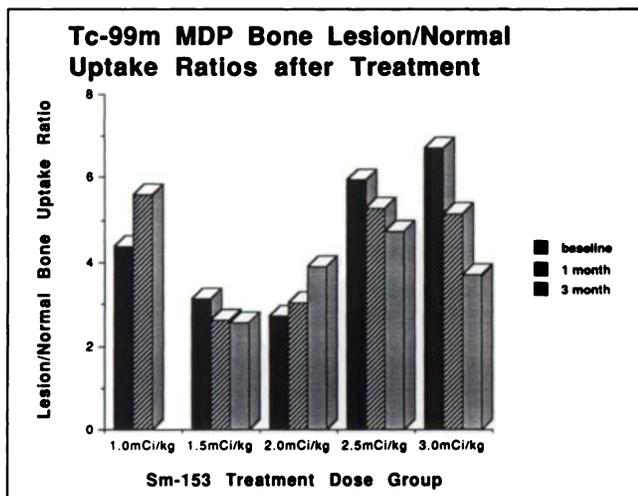


FIGURE 5. Lesion-to-normal bone ratios before and after treatment. Values are averages for each group.

DISCUSSION

In this study, we demonstrated by imaging that the bio-distributions of $^{153}\text{Sm-EDTMP}$ and $^{99\text{m}}\text{Tc-MDP}$ are very similar in lesional and nonlesional bone. Samarium-153 is as sensitive as the $^{99\text{m}}\text{Tc}$ agent for visually identifying bony lesions. Whole-body uptakes and lesion-to-normal bone ratios indicate that ^{153}Sm labels normal and lesional bone to a similar degree and implies that patient selection for treatment and follow-up by bone scanning with $^{99\text{m}}\text{Tc-MDP}$ are appropriate and relevant with respect to ^{153}Sm distribution.

Radiation absorbed doses estimated in a subset of these patients were similar to those estimated previously. Bone surface doses were substantially higher than those predicted by extrapolation of the rat data, as were the marrow doses. The primary reason for this difference is that the patients with prostate cancer allowed in the study were those with advanced hormone refractory disease. Overall, they had high skeletal retention of the administered activity because their multiple metastatic sites had exuberant osteoblastic activity. Skeletal radiation dose estimates were based on whole-body retention, which reflects the contribution in uptake from both blastic metastases and normal bone. The active marrow dose was also higher than that predicted by the animal data. Soft-tissue doses were considerably lower.

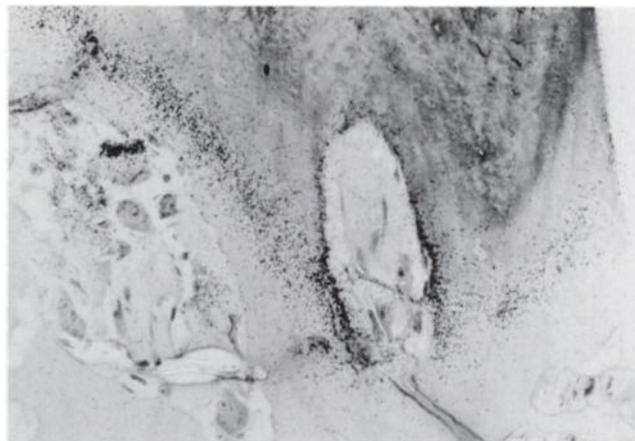


FIGURE 6. Twenty-four hour post-treatment bone biopsy autoradiograph from a patient who received $^{153}\text{Sm-EDTMP}$. Marked grain accumulation around sites of bone deposition along bony trabeculae is present.

Total absorbed marrow doses estimated by this method ranged from 1277 to 2250 rad in the 3.0 mCi/kg patient group. Two of four patients in this group experienced mild hematotoxicity (10). In canine and primate models, an external beam total body irradiation dose of 200 rad results in severe myelosuppression and doses above 400 rad result in lethal myelosuppression (26). With ^{131}I -labeled antibody, the dose of radiation required to ablate marrow appears to be slightly higher, but doses of 200–400 rad delivered to red marrow result in severe myelosuppression (27). This discrepancy between biological response and estimated marrow absorbed dose from $^{153}\text{Sm-EDTMP}$ in the patients presented here can be resolved by understanding the assumptions made by the bone dosimetry model and considering bone marrow microscopic anatomy. The ICRP-30 dosimetry model estimates dose to marrow from the source distributed on bone surfaces and assumes that all bone surfaces are in contact with marrow. The bone dose in our studies was estimated from the whole skeletal radioactive content. In reality, the active marrow cell populations are heterogeneously distributed with respect to bone surfaces and fatty infiltration. In these patients with extensive, exuberant osteoblastic disease, marrow in these metastatic areas may have received these high doses. However, marrow in normal bone, and particularly in areas of nontrabe-

TABLE 3
Organ Residence Times Observed in Patients Studied for Radiation Dosimetry

Source Organ	Mean	Residence time (hr) standard deviation
Kidneys (n = 6)	0.029	±0.026
Liver (n = 7)	0.021	±0.010
Lungs (n = 6)	0.020	±0.010
Skeleton (n = 7)*	41.6	±12.6
Urinary bladder contents (n = 7)†	2.56	±1.10

*Activity in skeleton equally divided between cortical and cancellous bone for dosimetry calculations.

†Bladder voiding interval 4.8 hr.

TABLE 4
Samarium-153-EDTMP Radiation Absorbed Doses

Target organ	Patient no.													
	m rad/mCi (Gy/MBq)		1	2	3	4	5	6	7					
Kidney	150	(41)	63	(17)	21	(6)	48	(13)	40	(11)	16	(4)	120	(34)
Liver	21	(6)	27	(7)	19	(5)	16	(4)	20	(6)	16	(4)	16	(4)
Lungs	36	(10)	26	(7)	36	(10)	38	(10)	30	(8)	22	(6)	30	(8)
Ovaries	29	(8)	37	(10)	33	(9)	35	(9)	27	(7)	32	(8)	34	(9)
Red marrow	7500	(2000)	6000	(1600)	5500	(1500)	5000	(1400)	6900	(1900)	4700	(1300)	4600	(1200)
Bone surfaces	32000	(8800)	26000	(7000)	24000	(6400)	22000	(5800)	30000	(8100)	20000	(5400)	20000	(5300)
Testes	16	(4)	23	(6)	20	(6)	22	(6)	15	(4)	21	(6)	22	(6)
Urinary bladder wall	1400	(390)	4700	(1300)	4000	(1100)	4500	(1200)	1300	(360)	4600	(1200)	4600	(1200)

Target Organ	Estimated radiation dose m rad/mCi		Gy/MBq	
	Mean	Standard deviation	Mean	Standard deviation
Kidneys	65	±52	18	±14.1
Liver	19	±4	5	±1.1
Lungs	31	±6	8	±1.6
Ovaries	32	±4	9	±0.9
Red marrow	5700	±1100	1514	±261
Bone surfaces	25000	±4700	6686	±1354
Testes	20	±3	5	±0.8
Urinary bladder wall	3600	±1500	964	±407

cular bone away from the bone surfaces likely received far less radiation, which can account for the mild toxicity observed in patients in this study. The findings in this study suggest that much higher doses of ¹⁵³Sm-EDTMP are tolerable than predicted by conventional dosimetric estimates. As the role of ¹⁵³Sm in the treatment of bony metastases is defined, this agent may have a great deal of potential benefit in cancer patient management.

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