Human Pharmacokinetics of Samarium-153 EDTMP in Metastatic Cancer

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Samarium-153 ethylenediaminetetramethylene phosphonic acid ([^{153}Sm]EDTMP) has been proposed to palliate pain resulting from osteoblastic metastatic bone cancer. Encouraging results in dogs with primary malignant bone cancer provided the catalysis for human biodistribution studies in five patients with metastatic skeletal carcinoma. The objective was to assess the preferential localization of [^{153}Sm]EDTMP in bony lesions and compare it to the ^{99m}Tc-labeled phosphonates. Blood clearance of [^{153}Sm]EDTMP was rapid with minimal accumulation in nonosseous tissues. Both radiopharmaceuticals showed identical lesion uptake in 23 paired lesions ($p > 0.05$). This indicates that the two radiopharmaceuticals concentrate in metastatic skeletal lesions by the same mechanism and since [^{153}Sm]EDTMP emits beta radiation it may be therapeutically useful in ameliorating metastatic bony cancer pain.

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To palliate intractable skeletal pain due to disseminated bony metastases, several radiotracers have been used with none achieving widespread clinical acceptance. Phosphorus-32 as $Na_3{}^{32}PO_4$, was the first and most widely employed radiotracer to treat metastatic bone cancer pain (*1–6*). Because of undesirable myelosuppression it has generally been abandoned. Recent reports have suggested an array of radiotracers to irradiate diffuse skeletal metastases such as rhenium-186 (^{186}Re) (*7*), yttrium-90 (^{90}Y) (*8*) and iodine-131- (^{131}I) labeled diphosphonates (*9–10*), and strontium-89 (^{89}Sr) chloride (*11–12*). At the University of Missouri-Columbia, in conjunction with the Dow Chemical Co., we have developed samarium-153 ethylenediaminetetramethylene phosphonic acid (EDTMP), a radiopharmaceutical that is chemically and biologically stable and preferentially concentrates in skeletal metastases (*13–15*). The short half-life of ^{153}Sm (46.3 hr) makes it suitable for repeat tumor irradiation and preliminary work has shown that the chelate is effective against primary bone neoplasm in dogs (*16*). Before instituting a dose tolerance and therapeutic efficacy clinical trial, we evaluated this agent in humans with metastatic bone cancer using a sub-therapeutic dose of [^{153}Sm]EDTMP in a pharmacokinetic trial.

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METHOD

Patient Selection

Five patients with histopathologically proven primary cancer and radiographic and/or scintigraphic bony metastases were studied under physicians IND 27865 (RAH). All subjects were male and their ages ranged from 62–85 yr (mean 67 ± 10 yr). Three patients had primary lung carcinoma and the other two prostate carcinoma.

Preparation of [^{153}Sm]EDTMP

Samarium-153 was produced at the University of Missouri Research Reactor (MURR) by thermal neutron irradiation of enriched (99.06%) [^{153}Sm]oxide. The oxide target was then dissolved in 1.0 N HCl and diluted to 0.1 N HCl with sterile water. Six milliliters of the solution were added to a lyophilized kit containing 210 mg of EDTMP and sufficient NaOH was added to bring the final product to a pH of 7.0–8.5. The yield of the [^{153}Sm]EDTMP complex was >99% determined by ion exchange chromatography (*13–14*). The chelate preparation can be stored in the formulation vial at room temperature and retains its stability for > 7 days. The primary radiation emissions of Sm-153 are shown in Table 1, and the structure of EDTMP is shown in Figure 1.

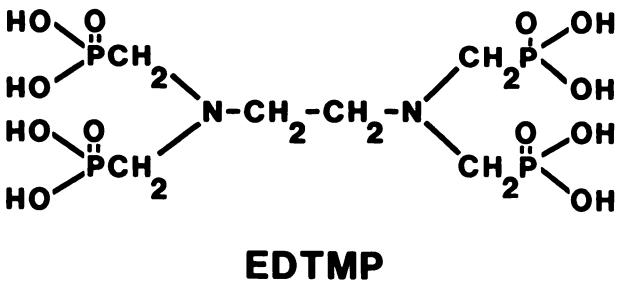
TABLE 1
Primary Radiation Emissions of ^{153}Sm

Maximum energy (keV)	Type	Abundance
810*	Beta	20%
710*	Beta	50%
640*	Beta	30%
103	Gamma	28%

* The average beta particle energy from [^{153}Sm]EDTMP is 225 keV (NCRP Report No. 58, 1985) and the average range in water is 0.83 mm (*33*).

Biodistribution

After injecting 2 mCi of [^{153}Sm]EDTMP intravenously, whole-body planar scintigraphic images, blood clearance and 24-hr urinary excretion of the radiopharmaceutical were obtained using the 103 keV (29.8%) gamma photon emission of ^{153}Sm. The images were started 2 hr following the injection of the [^{153}Sm]EDTMP and a large field-of-view (LFOV) scintillation camera equipped with a low-energy all purpose (LEAP) parallel hole collimator. The count data was digitized and computer enhanced to produce quality images for interpretation and quantification. The quantified indices included: lesion-to-normal bone ratios; lesion to soft-tissue ratios; and normal bone to soft-tissue ratios. The ratios were determined after the soft tissue background was subtracted. An experienced observer (AS) outlined lesions on the scintigrams with the computer (ADAC-3300) and the average regional counts were used to calculate the bone to nonbone ratios. Twenty-three (*23*) lesions were studied in the five patients. Each patient received a [^{99m}Tc]HDP (Osteoscan-HDP, Mallinckrodt, St. Louis, MO) bone image 2 days before the [^{153}Sm] EDTMP injection. This was done to identify the metastatic sites in the patients and generate scintigraphic images of the bony lesions so that they could be compared to the [^{153}Sm] EDTMP images. As with [^{153}Sm]EDTMP, the [^{99m}Tc]HDP images were taken 2 hr postinjection of 20 mCi in one patient, 2 mCi in a second and 5 mCi in the remaining three. The [^{99m}Tc]HDP dose was varied to adjust the dose to one which was similar to [^{153}Sm]EDTMP, minimizing variations in image quality. Twenty millicuries of [^{99m}Tc]HDP, the usual standard dose, was felt to be too large, while 2 mCi was obviously too low for an ideal comparison. Computer enhancement of the image was very helpful when the lower dose was used. Interobserver variability was eliminated since a single observer analyzed the data.



EDTMP

FIGURE 1
Structure of the EDTMP compound which complexes with ^{153}Sm to form [^{153}Sm]EDTMP.

Radiopharmaceutical Safety

The safety of [^{153}Sm]EDTMP was determined by using a sterile pyrogen free preparation, monitoring vital signs before and up to 1 hr postinjection of the [^{153}Sm]EDTMP, by performing pre- and postinjection hematologic profiles (white cell, red cell, and platelet counts), urinalyses and serum chemistries (BUN, serum creatinine, and liver function tests). All pre-injection samples were drawn 4 hr prior to the intravenous administration and all postinjection samples were obtained within the subsequent 24 hr.

Statistical Methods

Skeletal ratios of [^{153}Sm]EDTMP and [^{99m}Tc]HDP were analyzed using the matched pair group design (*17*) which determines if a significant difference existed between the lesion localization of the two agents. A probability of $p < 0.05$ was considered significant. The same lesion in each patient served as control for the comparison. All data represents the mean ± 1 s.d.

RESULTS

In the top row of Figure 2 the skeletal images (A, B, C) taken with 5 mCi of [^{99m}Tc]HDP and the same images in the lower row (D, E, F) taken with 2 mCi of [^{153}Sm]EDTMP show excellent visualization of the multiple bony metastases. The ratios of the lesion quantification are tabulated in Table 2. Lesion-to-normal bone ratios for [^{153}Sm]EDTMP and [^{99m}Tc]HDP were 4.04 ± 2.62 and 4.01 ± 1.97, respectively. Lesion-to-soft-tissue ratios were 5.98 ± 3.18 for [^{153}Sm]EDTMP and 6.87 ± 4.67 for [^{99m}Tc]HDP. Normal bone to soft tissue ratios were 2.47 ± 1.01 for [^{153}Sm]EDTMP and 2.44 ± 1.25 for [^{99m}Tc]HDP. No significant difference between the accumulation of these two agents in bone cancer lesions was observed ($p > 0.5$). The data indicates that the same mechanism of localization exists for the [^{153}Sm]EDTMP and [^{99m}Tc]HDP in skeletal metastases, and the soft-tissue localization was minimal.

Whole blood clearance of [^{153}Sm]EDTMP is shown in Figure 3. The percent dose in blood was derived from the blood volume estimates using the method of Nadler (*18*). Rapid chelate clearance results in only 5.17 ± 1.05% and 2.09 ± 0.52% of the activity remaining in whole blood at 2 and 4 hr postinjection. When the plasma is separated the percent [^{153}Sm]EDTMP remaining at 2 and 4 hr postinjection were 5.2 ± 1.09 and 2.11 ± 0.38, respectively. The complex clears through the kidneys and the amount excreted into the urine at 24 hr is shown in Figure 4. These results of the [^{153}Sm]EDTMP biodistribution are nearly identical, to the blood clearance properties of [^{99m}Tc]HDP and ^{99m}Tc methylene diphosphonate (MDP) (*19*). The pre- and postinjection hematologic profiles, serum chemistry and urinalyses demonstrated no changes in all five

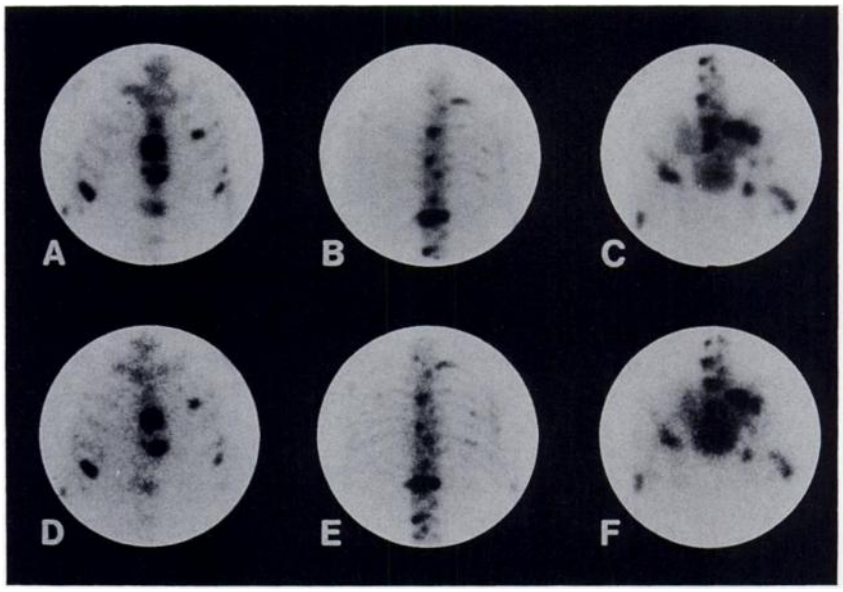


FIGURE 2
Anterior chest (A), posterior spine (B), posterior lumbosacral spine and pelvis (C) images acquired with 5 mCi of [^{99m}Tc]HDP are exhibited in the top row. Bottom row shows same projections (D, E, F) obtained using 2 mCi of [^{153}Sm]EDTMP. Both sets of images were taken 2 hr postinjection. Each revealed the identical metastatic lesions.

patients. Vital signs did not vary following the injection of [^{153}Sm]EDTMP indicating the safety of [^{153}Sm] EDTMP at the subpharmacologic doses employed in our patients.

DISCUSSION

Painful disseminated bony metastases are common with carcinomas of the lung, prostate, and breast. In lung cancer, bony metastases are found in 36% of patients undergoing metastatic skeletal surveys with bone scans, while nearly half of the patients with prostatic cancer demonstrate bony metastases at the time of their initial presentation (*20–21*). These lesions are frequently widespread and show high avidity for the ^{99m}Tc phosphonate complexes. Carcinoma of the breast is the second most common cancer in females and may be associated with bony metastases in 50% of the patients within 12 mo of its initial presentation. By 18 mo bony metastases may occur in three quarters of these patients (*22*). Approximately one- to two-thirds of these patients will develop pain (*23*). External beam irradiation is an ideal therapy to ameliorate the pain of isolated metastases. Although disseminated bony metastases have also been treated with hemibody or total-body external irradiation with some success the approach of the additional radiation burden is undesirable and potentially myelosuppressive. Analgesics used to ameliorate bone pain are frequently limited in their period of effectiveness and patients rapidly develop drug tolerance. Addiction is not an uncommon sequelae of narcotic analgesia in patients with intractable bone cancer pain. Pain relief using chemotherapeutic regimens and/or hormone therapy is a welcomed but unpredictable consequence and is limited and brief in duration.

For several years particulate emitting radionuclides such as ^{32}P ($T\frac{1}{2}$ = 14d; a pure beta emitter) as either the anionic phosphate or as a ligand (HEDP), has been used to treat metastatic bone cancer. The use of this radionuclide is complicated by excessive myelosuppres-

TABLE 2
Comparison of Skeletal Localization of [^{153}Sm]EDTMP and [^{99m}Tc]HDP

Ratio	[^{153}Sm]EDTMP	[^{99m}Tc]HDP	P*
Lesion to bone†	4.04 ± 2.62	4.01 ± 1.97	>0.05
Lesion to soft tissue	5.98 ± 3.18	6.87 ± 4.67	>0.05
Bone to soft tissue	2.47 ± 1.01	2.44 ± 1.25	>0.05

All data is mean ± 1 s.d., n = 23.
* Matched pair two group design.
† Soft-tissue background corrected.

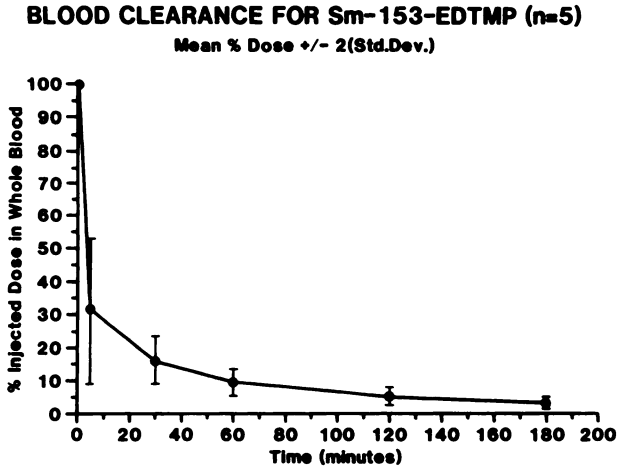


FIGURE 3
Blood clearance of [^{153}Sm]EDTMP. The plasma clearance curve (not shown) was identical.

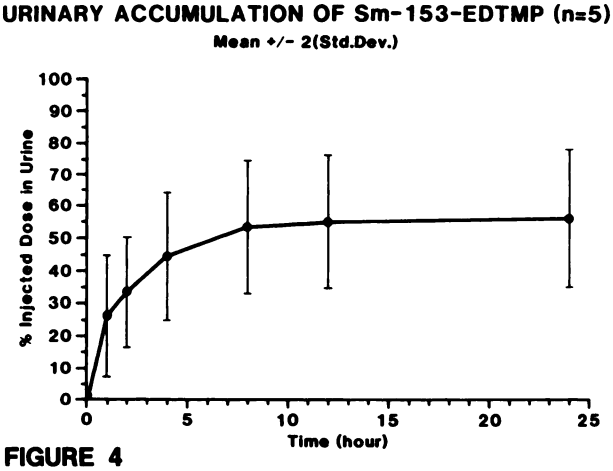


FIGURE 4
Cumulative 24-hr urinary excretion of [^{153}Sm]EDTMP.

sion (*1–6*). More recently, alpha amino-(3-[I-131] iodo-4-hydroxygenzylidene)-diphosphonate ([^{131}I]BDP3) has been used in limited clinical trials and was reported to effectively relieve bone pain in patients with bony metastases (*9–10*). Yttrium-90 EDTA has been used experimentally and has not advanced to clinical application because of high liver uptake (~10%) (*8*). Studies with [^{186}Re]HEDP in animals have shown excessive irradiation to the kidney because of high kidney uptake (*7,24,25*), however, this diminishes significantly if the ^{186}Re complex is purified and only the pure complex is used (*24*). Limited clinical trials indicate its effectiveness for pain palliation (*24*). Reddy and Robinson reported on the palliation of bone cancer pain using ^{89}Sr (*11*). Complete or marked relief of bone pain was observed in 38% of their patients, with 53% admitting to pain reduction (mild response) and 9% experiencing no relief or increase in the pain. Pain palliation with ^{89}Sr has been widely studied and the most encouraging results are reported for breast and prostate carcinoma metastases to bone (*11,12,26–28*).

We believe [^{153}Sm]EDTMP has several distinct advantages as a radiopharmaceutical to palliate metastatic bone cancer pain. First, the medium energy of ^{153}Sm beta emissions (avg E_{avg} = 225 keV) are sufficiently energetic to deposit a high radiation dose to the tumor with less damage to the bone marrow due to its short range in tissue. The physical half-life of ^{153}Sm (46.3 hr) is relatively short and should permit it to be administered in either a single or multiple doses. It is present as a single chemical entity that exhibits excellent in vitro stability (*15*). Its rate of decay and economy of production should allow its delivery to most clinical facilitates throughout the country. Finally, it has a 103 keV (29.8%) gamma-ray emission that allows one to image the photon scintigraphically. Not only can this be used to monitor its body distribution but it can also be used to perform dosimetry of individual lesions for each patient. A dosimetric assessment of [^{153}Sm] EDTMP has recently been reported using rat model determinations (*29*). The pharmacokinetic data obtained in this human study provided the base to calculate a better estimate of dosimetry for the patients receiving [^{153}Sm]EDTMP therapy (*30*). Recent data from a safety study in humans performed in our laboratory (*31*) and in a high dose study in dogs (*32*) provides evidence that this agent will be able to produce desirable therapeutic effects at doses producing well tolerated transient myelosuppression. Quantitative image results demonstrated high lesion uptake with mean lesion to bone ratios of 4.04 ± 2.62 and lesion to soft-tissue ratios of 5.98 ± 3.18. The chelate clears rapidly from the plasma through the kidneys into the urine. Approximately half of the administered dose is excreted into the urine by 6–7 hr. The remaining dose (~45%) is deposited in the skeleton with little soft-tissue uptake such as the liver.

In conclusion, this study demonstrates that [^{153}Sm] EDTMP is a suitable radiopharmaceutical to initiate therapeutic trials in patients with bone pain resulting from skeletal metastases. Its physical and biokinetics properties appear optimum and its propensity to localize in bony metastatic sites that are osteoblastic in nature has been established. Neoplastic bone disease associated with lytic-type of bony metastases such as multiple myeloma may not be treatable with [^{153}Sm] EDTMP.

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REFERENCES

1. Cheung A, Driedger AA. Evaluation of radioactive phosphorus in the palliation of metastatic bone lesions from carcinoma of the breast and prostate. *Radiology* 1980; 134:209–212.
2. Johnson DE, Haynie TP. Phosphorous-32 for untreatable pain in carcinoma of prostate. Analysis of androgen primary, parathormone, rebound and combination therapy. *J Urol* 1977; 9:137–139.
3. Joshi DP, Seery WH, Goldberg LG, et al. Evaluation of phosphorus-32 for intractable pain secondary to prostate carcinoma metastasis. *JAMA* 1965; 193:621–623.
4. Kaplan E. Historical development of P-32 in bony therapy. In: Spencer RP, ed. *Therapy in nuclear medicine.* New York: Grune and Stratton, 1978:237.
5. Merrin C, Bakshi S. Treatment of metastatic carcinoma of the prostate to bone with parathormone and radioactive phosphorus. *J Surg Oncol* 1974; 6:67–72.
6. O'Mara RE. New P-32 compounds in therapy for bone lesions. In: Spencer RP, ed. *Therapy in nuclear medicine.* New York: Grune and Stratton, 1978:257.
7. Mathieu L, Chavalier P, Galy G, et al. Preparation of rhenium-186 labelled EDMP and its possible use in

the treatment of osseous neoplasms. *Int J Appl Isot* 1979; 30:725–727.
8. Kutzner J, Dahnert W, Schreyer T, et al. Yttrium-90 zur schmerztherapie von knochenmetastasen. *Nucl Med 1981;* 20:229–235.
9. Eisenhut M. Iodine-131-labeled disphosphonates for the palliative treatment of bone metastases: organ distribution and kinetics of I-131-BDP3 in rats. *J Nucl Med* 1984; 25:1356–1361.
10. Eisenhut M, Berberich R, Kimmig B, Oberhausen E. Iodine-131-labeled diphosphonates for palliative treatment of bone metastases: II. Preliminary clinical results with Iodine-131 BDP3. *J Nucl Med* 1986; 27: 1255–1261.
11. Reddy EK, Robinson RG, Mansfield CM. Strontium-89 for palliation of bone metastases. *J Natl Med Assoc* 1986; 78:27–32.
12. Robinson RG, Spicer JA, Preston DF, et al. Treatment of metastatic bone pain with strontium-^{89}. *Nucl Med Biol* 1987; 14:219–222.
13. Goeckler WF, Edwards B, Volkert WA, et al. Skeletal localization of Sm-153 chelates: potential therapeutic bone agents. *J Nucl Med* 1987; 28:495–504.
14. Goeckler WF, Troutner DE, Edwards B, et al. Sm-153-radiotherapeutic bone agents. *Nucl Med Biol* 1986; 13:479–482.
15. Ketring A. Sm-153-EDTMP and Re-186-HEDP as bone therapeutic radiopharmaceutical. *Nucl Med Biol* 1987; 14:223–232.
16. Corwin LA, Lattimer JC, Goeckler WF, et al. Sm-153-EDTMP treatment of spontaneous canine bone tumors. *J Nucl Med* 1986; 27:986–987.
17. Schefler WC. Matched pair two group designs. Statistics for health professionals. Reading, MA: Addison-Wesley, 1984:169–173.
18. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; 51:22–29.
19. Littlefield JL, Rudd TG. Tc-99m-hydroxymethylene-disphosphonate and Tc-99m-methylenediphosphonate: biological and clinical comparison. *J Nucl Med* 1983; 24:463–466.
20. Hooper RJ, Beechler CR, Johnson MC. Radioisotope scanning in the initial staging of bronchogenic carcinoma. *Am Rev Respir Dis* 1978; 118:279–286.
21. Langhammer H, Sintermann R, Hor G, et al. Serial bone scintigraphy for assessing the effectiveness of treatment of osseous metastasis from prostate cancer. *Nuklear Medizin* 1978; 17:87–91.
22. McNeil BJ, Pace PD, Gray EB, et al. Preoperative and follow-up of bone scans in patients with primary carcinoma of the breast. *Surg Gynecol Obstet* 1978; 147:745–749.
23. Front D, Schneck SO, Frankel A, et al. Bone metastases and bone pain in breast cancer. Are they closely associated? *JAMA* 1979; 39:2904–2915.
24. Maxon HR, Deutsch EA, Thomas SR, et al. ^{186}Re(Sn)-HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology* 1988; 166:501–507.
25. Weininger J, Ketring A, Deutsch E. ^{186}Re-HEDP: a potential therapeutic bone agent. *Nucl Med* 1984; 23:81–82.
26. Silberstein EB, Williams C. ^{89}Sr-therapy for pain of osseous metastases. *J Nucl Med* 1985; 26:345–348.
27. Firusian N, Mellin P, Schmidt CG. Results of ^{89}Sr therapy in patients with carcinoma of the prostate and incurable pain from bone metastases. *J Urol* 1976; 116:764–768.
28. Blake GM, Zivanovic MA, McEwan AJ, et al. ^{89}Sr radionuclide therapy: dosimetry and hematological toxicity in two patients with metastasizing prostatic carcinoma. *Eur J Nucl Med* 1987; 13:41–46.
29. Logan KW, Volkert WA, Holmes RA. Radiation dose calculations in persons receiving injection of Sm-153-EDTMP. *J Nucl Med* 1987; 28:505–509.
30. Volkert WA, Simon J, Ketring, et al. Radiolabled phosphonic acid chelates: potential therapeutic agents for treatment of skeletal metastases. *Drugs of the Future* 1989: in press.
31. Holmes RA, Farhangi M. Dose tolerance of ^{153}Sm-EDTMP in metastatic bone cancer. [Astract]. *J Nucl Med* 1988; 29:775.
32. Appelbaum FR, Sandmaier B, Brown P, et al. Myelosuppression and mechanism of recovery following administration of ^{153}Sm-EDTMP. *Antibody, Immunoconj Radiopharm* 1988; 1:263–270.
33. Attix FH, Roesch WC, Tochlin E. Radiation dosimetry. New York: Academic Press, 1968:190.