Strontium-89 Therapy in Painful Bony Metastases

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This is the second article in a four-part series on nuclear medicine oncology procedures. Upon completion of this article, the technologist will be able to describe the history, pharmacology, and efficacy of strontium-89 therapy.

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Strontium-89 (^{89}Sr), a bone-seeking radiopharmaceutical, has been used successfully in recent trials to palliate bone pain secondary to metastatic disease. The use of this beta emitter in systemic radionuclide therapy should become an integral part in the management of many patients with metastatic disease to the bone. Intravenous ^{89}Sr may be used in conjunction with standard chemotherapy and external beam radiotherapy. Hematologic toxicity is less than that previously seen with phosphorus-32 (^{32}P), and other side effects are minor.

The skeleton is a common site for carcinoma metastases with the most common metastatic sites occurring in the axial skeleton. In order of frequency, the vertebra, proximal femur, pelvis, ribs, sternum, and proximal humerus are most frequently involved. Bone pain secondary to skeletal metastases is the most common intractable cancer pain syndrome (*1*). Bone pain from metastatic disease is usually caused by infiltration and expansion of periosteal membranes by tumor. It may also result from encroachment on hematopoietic tissue in the marrow, compression of the spinal cord or nerve roots and mechanical instability, or pathologic fractures secondary to tumor weakened bones. These are most commonly seen in the proximal femur and cervical and lumbo-sacral spine (*2*).

Metastases to the skeleton occur in over 50% of patients with breast, lung, or prostate cancer, in the later stages of the disease. Pain management becomes a critical issue in these patients. Treatment of metastatic bone pain may initially involve chemo-, surgical, radiation, and hormonal therapies (*3*). Radiation, in particular, may be useful in the management of bone pain, with reported efficacy in 65%–100% of patients, although the pain relief may be transitory (*4*). External beam radiotherapy helps to prevent impending pathological fractures and is a mainstay in the treatment and prevention of spinal cord compression. However, since bony metastases are usually multiple and often widespread, the administration of systemic radiation with the use of radiopharmaceuticals often extends more long-lasting relief (*5*).

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HISTORY

The use of the calcium analog, ^{89}Sr, actually preceded that of ^{32}P in the treatment of bone metastases (*6*). In the early 1940s, Pecher first demonstrated the concentration of ^{89}Sr in osteoblastic reactive bone surrounding osteogenic sarcoma. He then reported the clinical use of ^{89}Sr for pain relief in a small series of patients with carcinoma metastatic to the bone (*7,8*). In 1949, Lawrence and Wasserman reported poor response in the treatment of multiple myeloma, using ^{32}P in conjunction with ^{89}Sr. However, ^{89}Sr was given to only a limited number of their patients (7 cases) and in a dosage lower than current dosages (*9,10*).

The work of Firusian and colleagues elicited widespread interest in the use of ^{89}Sr in therapy of metastatic bone pain. In 1973, after the first European trials, they published favorable results in the use of ^{89}Sr for pain relief in 8 of 10 patients with osseous metastases and systemic disease (multiple myeloma) (*11*). Three years later, they reported long lasting pain relief (16 wk to 1 yr, or until death) in 8 of 11 patients with skeletal metastases from prostate carcinoma. No significant myelosuppression was observed (*12*).

Robinson and colleagues at the University of Kansas began clinical trials with ^{89}Sr in 1977 (*5*). This group published the first large series in the use of ^{89}Sr, with a pain response rate of 80% in 100 prostate carcinoma patients and 89% in breast cancer patients. Eighty percent of patients demonstrated mild myelosuppression, while 20% exhibited no change in hematologic counts (*13–15*).

TABLE 1. Radiation Dosimetry

Organ	Rad/mCi	Gy/Bq
Bone surface	59	1.6×10^{-8}
Red bone marrow	40	1.1×10^{-8}
Bladder wall	0.23	6.2×10^{-11}
Whole body	3.0	8.1×10^{-10}

PHARMACOLOGY, KINETICS, AND DOSIMETRY

Strontium-89 is produced in nuclear reactors by direct neutron activation. Strontium-89 chloride is essentially a pure beta emitter (E max: 1.46 MeV) with a physical half-life of 50.6 days. Following intravenous injection, soluble strontium, a calcium analog, is cleared rapidly from the blood and localizes selectively in bone (*16*). Uptake of ^{89}Sr by bone occurs preferentially in sites of active osteogenesis, yielding a high therapeutic ratio of metastases to normal bone (*15,17–19*). Eighty percent of the plasma clearance is renal and exhibits significant correlation with calcium clearance. The remaining 20% excretion is by the fecal route. Prolonged physical retention of ^{89}Sr in the metastatic sites, first reported by Robinson, may extend pain control (*15*). Since ^{89}Sr is a beta emitter, it delivers greater radiation dose to cortical and trabecular bone than to the more radiosensitive elements of bone marrow. It also selectively irradiates sites of metastatic involvement more than normal bone. Recent kinetic studies demonstrated uptake of strontium in osteoblastic lesions at 2 to 25 times that of normal bone (*20*).

Dosimetry is based on either the Medical Internal Radiation Dose Committee (MIRD) or the International Commission on Radiological Protection (ICRP) schema for calculating absorbed dose to bone marrow and other organs. Determination of radiation dose to the bone marrow by ^{89}Sr is complicated due to inhomogeneity of deposition. Strontium-89 retention is dependent on the renal plasma clearance rate as well as the extent of metastatic disease (*17,18*). A recent radiation dosimetry study reported absorbed doses to the red marrow of 2 to 50 times less than in prior published estimates (*20*). The presently accepted dosimetry for the major organs is summarized in Table 1. Median dose to metastatic bone sites is estimated at ~200–2500 rad/mCi, varying with the extent of disease (*17*).

CLINICAL STUDIES

In the last 15 years, numerous authors have reported on the efficacy of ^{89}Sr therapy. The results of these studies and the dosages used are summarized in Table 2. The largest patient series to date has been followed by Robinson and colleagues, who recently reported on a total of ~500 patients. They have found a response rate of 79% for patients with metastatic prostate cancer, and 83% for those with breast cancer, using a 40-μCi/kg dose (*5*). Robinson also has suggested that a dose-response relationship occurs with ^{89}Sr and that the ideal dose range may lie from 40 to 60 μCi/kg (*5*). It is important to note that although most large series report a >75% response rate, complete pain relief is achieved in <20% of patients (*15,19,21,22*). Recently published results of a Canadian study demonstrated up to 60% complete pain relief with a combination of external beam radiation therapy and ^{89}Sr systemic therapy, using a single 10.8-mCi dose (*23*).

TECHNICAL CONSIDERATIONS

Shielding for ^{89}Sr is similar to that for ^{32}P, since it is essentially a pure beta emitter. The most important shielding consideration is that of bremsstrahlung radiation, which will augment the skin dose equivalent significantly. Since the amount of bremsstrahlung photons produced is directly proportional to the square of the atomic number of the attenuating material, shielding with plastic or glass is preferable.

The optimal administration technique should provide adequate shielding for the administrator, with an appropriate glass or plastic syringe shield. Our laboratory utilizes a three-way apparatus for the injection of ^{89}Sr. We have found this procedure to be self-contained and practically spillproof. A three-way stopcock is used, with the dose syringe placed on one of the ports and a 10-ml saline syringe on the side port. As the dose is injected, intermittent flushing with a small amount (1–2 ml) of saline is performed. At completion of the injection, the dose syringe is rinsed with the remainder of the saline and injected. Syringe disposal is achieved by disposing of the entire apparatus as radioactive waste. The unit is wrapped in absorbable paper, labeled with the date, and allowed to decay the usual ten half-lives (~17 mo). The injection unit is surveyed with a beta sensitive

TABLE 2. Strontium-89 Clinical Data

Investigator (Ref. No.)	Dose (μCi/kg)	Cancer Type	Number of Patients	Efficacy: Pain Response (%)
Firusian (*12*)	30	prostate	11	72
Robinson (*15*)	40	prostate	100	80
		breast	28	89
Silberstein (*19*)	16	prostate	17	51 (overall)
	70	breast	11	
		other	9	
Kloiber (*21*)	100	prostate	9	50 (overall)
	180	renal cell	1	
	(average: 130)			
Laing (*22*)	40	prostate	83	75

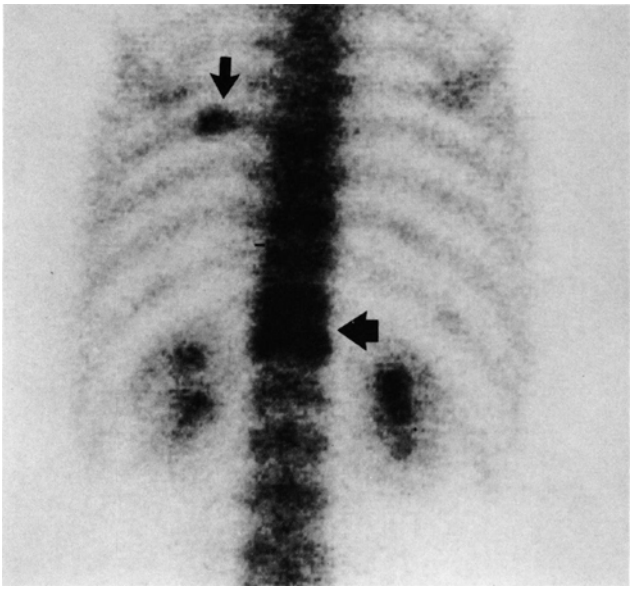

FIG. 1. Initial technetium-99m MDP bone scan of patient with carcinoma metastasized to bone. Arrows highlight areas of metastasis.

Geiger-Mueller counter and if the level is equal to background, disposed of as contaminated hospital trash.

The rules for spills with ^{89}Sr are the same as for any radionuclide: inform, contain, and decontaminate. It is important to remember that since the half-life of this radionuclide is long, storage of contaminated cleaning materials during the radionuclide's decay must be maintained over a long time period.

TREATMENT AND FOLLOW-UP GUIDELINES

Candidates for ^{89}Sr radiotherapy should have demonstrable osteoblastic metastases to the bone from primary carcinoma. A primary physician (e.g., oncologist or urologist) should be identified, with whom further patient management, including a hematologic follow-up, can be coordinated (*5*). Robinson and colleagues have proposed a platelet count of >60,000 and a white blood cell count of >2400 as the minimum levels allowable prior to treatment. A low hemoglobin level alone is not a contraindication to ^{89}Sr injection (*5*). U.S. clinical trials have required the monitoring of complete blood and platelet counts every 2 wk, although more frequent monitoring may be required, especially in those patients with initial low levels or those undergoing concomitant chemotherapy. The nadir is usually seen at 4–6 wk postinjection, with an average reduction of 20%–30% in platelet counts. Recovery, either complete or near complete, should occur by 12 wk (*5,24*).

Aside from mild myelosuppression, an occasional "flare response" in the first week posttreatment has been noted by most investigators. This phenomenon involves a transient worsening of the patient's bone pain and may signify that the patient will have a good response to treatment (*5*). No other significant side effects have been reported with ^{89}Sr therapy.

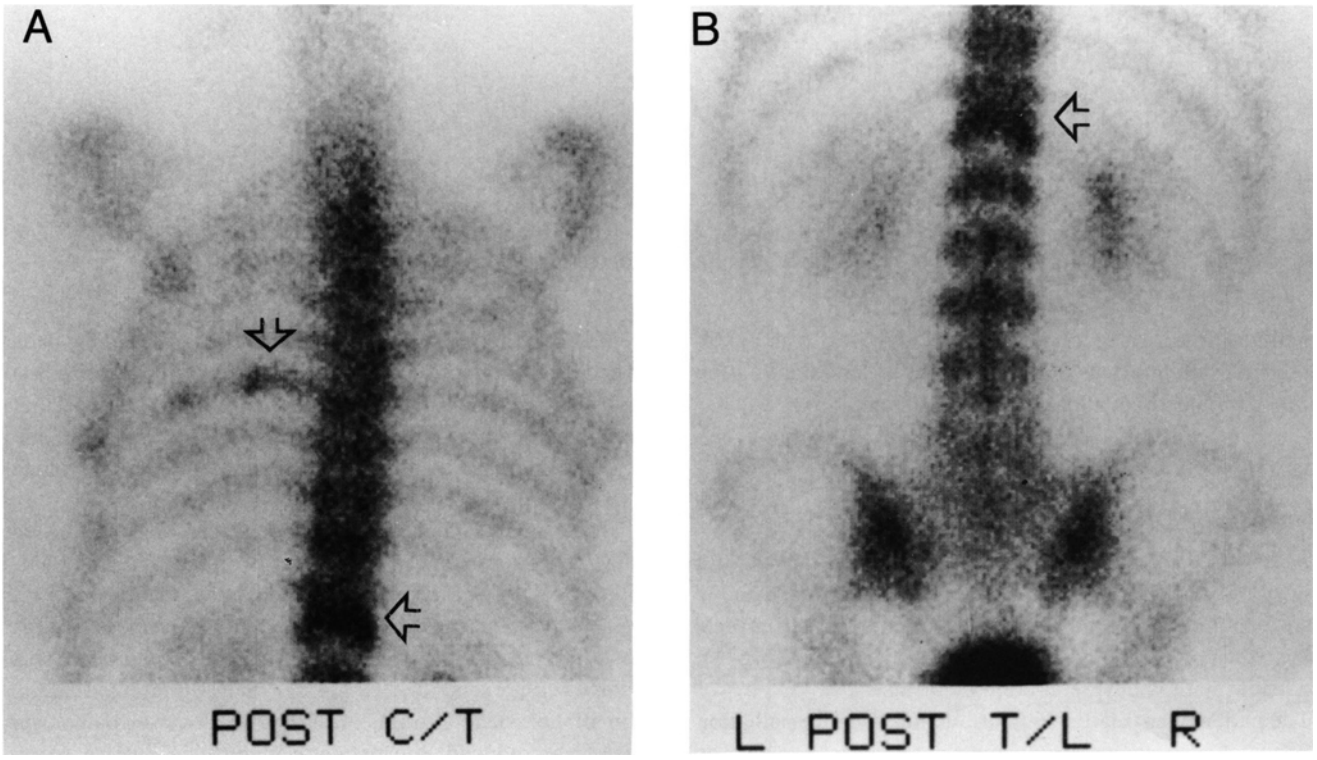

FIG. 2. Images obtained at 3 mo following ^{89}Sr treatment exhibit a decrease in uptake at the previously noted metastatic sites (open arrows). A new area of abnormal tracer uptake is seen in an adjacent area of the left posterior seventh rib.

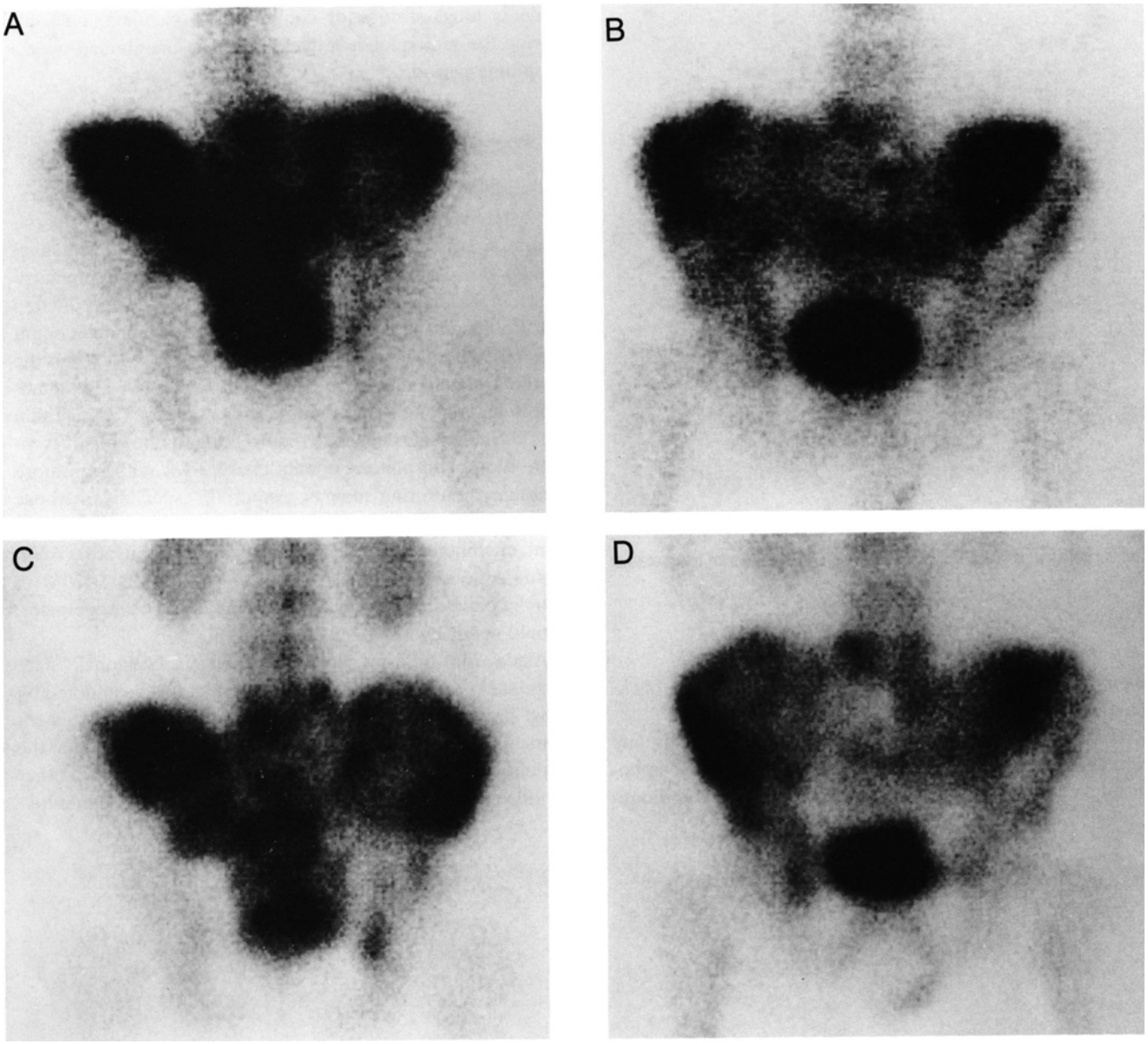

FIG. 3. (A and B) Technetium-99m MDP bone scan with anterior and posterior views of documented pelvic metastases. (C and D) A bone scan obtained at 3 mo post ^{89}Sr therapy exhibits diminished bone uptake of the radiotracer at the metastatic foci.

Treatment, performed on an outpatient basis, can be repeated at 3-mo intervals. At present, there is no limit on the number of injections allowed.

CASE STUDIES

Breast Carcinoma Patient

A 70-yr-old woman was referred for ^{89}Sr therapy with a history of breast carcinoma, metastatic to the bone. A bone scan exhibited increased radiotracer uptake in the thoracic spine, left posterior seventh rib, skull, and pelvis (Fig. 1), consistent with widespread bone metastases.

The patient was treated with intravenous ^{89}Sr for palliation of skeletal pain secondary to metastatic disease. She was followed biweekly for 3 mo. She recorded impressions of her pain pattern in a pain, sleep, and medication diary after the treatment. She reported overall improvement in low back pain as well as improvement in rib and upper back pain. She also decreased her analgesic intake and, during one period, was able to eliminate pain medication for five days. Her pain began to increase from slight to moderate at the end of the 3-month follow-up period.

Three months later, a repeat bone scan was performed (Fig. 2). Improvement in the level of uptake of radiopharmaceutical by the previously noted bone metastases was seen. A new, suspicious area of uptake was seen in the left posterior seventh rib. Eleven days later, the patient was treated with a second injection of ^{89}Sr for continued palliation of her skeletal pain. Although the overall pain level again was reduced, the patient's underlying disease worsened. She was unable to return for another follow-up bone scan and did not request a third injection.

Colonic Carcinoma Patient

A 67-yr-old man presented with a history of colonic carcinoma and metastatic bone disease. A whole-body bone scan exhibited progression of previously documented metastatic disease in the pelvis, thoracic, and lumbo-sacral spine (Fig. 3A and 3B).

The patient was treated with intravenous ^{89}Sr one week after the bone scan. He was followed biweekly after his initial injection and recorded impressions of his pain pattern in a pain, sleep, and medication diary. He reported improvement in his pain pattern, in particular, his low back pain. He progressively decreased his pain medication intake and noted improvement in sleep.

The patient's bone scan at the end of the 3-mo follow-up period exhibited improvement in the level of tracer uptake by the metabolically active pelvic metastases noted previously (Fig. 3C and 3D). There were no new areas of abnormal radioisotope uptake. The patient was injected with a second ^{89}Sr dose 3 mo later. However, his illness progressed, requiring hospice care. He developed recurrent lower extremity thrombophlebitis and became too ill to return for a follow-up bone scan.

REFERENCES

1. Wilson JD and Braunwald E. *Harrison's principles of internal medicine.* New York: McGraw-Hill; 1991:1945.
2. Campa JA and Payne R. The management of intractable bone pain: a clinician's perspective. *Semin Nucl Med* 1992;22:3–10.
3. Hosain F and Spencer RP. Radiopharmaceuticals for palliation of metastatic osseous lesions: biologic and physical background. *Semin Nucl Med* 1992;12:11–16.
4. Hoskin PJ. Scientific and clinical aspects of radiotherapy in the relief of bone pain. *Cancer Surv* 1988;7:69–86.
5. Robinson RG, Preston DF, Spicer JA, et al. Radionuclide therapy of intractable bone pain: emphasis on strontium-89. *Semin Nucl Med* 1992; 12:28–32.
6. Spencer RP. Applied principles of radiopharmaceutical use in therapy. *Nucl Med Biol* 1986;13:461–463.
7. Pecher C. Biological investigations with radioactive calcium and strontium. *Proc Soc Exp Biol Med* 1941;46:86–91.
8. Pecher C. Biological investigations with radioactive calcium and strontium: preliminary report on the use of radioactive strontium in treatment of metastatic bone cancer. (Berkeley: Univ. of Cal. Publications.) *Pharmacol* 1942;11:117–149.
9. Lawrence JH and Wasserman LR. Multiple myeloma: a study of 24 patients treated with radioactive isotopes (P-32 and Sr-89). *Ann Intern Med* 1950;33:41.
10. Lawrence JH and Tobias CA. Radioactive isotopes and nuclear radiations in the treatment of cancer. Symposium on Radioactive Isotopes and Cancer at the American Association for Cancer Research meeting, San Francisco, CA, April 16, 1955.
11. Schmidt CG and Firusian N. 89-Sr for the treatment of incurable pain in patient with neoplastic osseous infiltrations. *Int J Clin Pharmacol* 1974; 9:199–205.
12. Firusian N, Mellin P, and Schmidt CG. Results of strontium-89 therapy in patients with carcinoma of the prostate and incurable pain from bone metastases: a preliminary report. *J Urol* 1976;116:764–768.
13. Robinson RG. Radionuclides for the alleviation of bone pain in advanced malignancy. *Clin Oncol* 1986;5:39–49.
14. Robinson RG, Spicer JA, and Preston DF. Treatment of metastatic bone pain with strontium-89. *Nucl Med Biol* 1987;14:219–222.
15. Robinson RG, Blake GM, Preston DF, et al. Strontium-89: treatment results and kinetics in patients with painful metastatic prostate and breast cancer in bone. *Radiographics* 1989;9:271–281.
16. Volkert WA, Goeckeler WF, and Ehrhardt GJ. Therapeutic radionuclides: production and decay property considerations. *J Nucl Med* 1991; 32:174–185.
17. Blake GM, Zivanovic MA, Blaquiere RM, et al. Strontium-89 therapy: Measurement of absorbed dose to skeletal metastases. *J Nucl Med* 1988; 29:549–557.
18. Blake GM, Zivanovic MA, McEwan AJ, et al. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med* 1986;12:447–454.
19. Silberstein EB and Williams C. Strontium-89 therapy for the pain of osseous metastases. *J Nucl Med* 1985;26:345–348.
20. Breen SL, Powe JE, and Porter AT. Dose estimation in strontium-89 radiotherapy of metastatic prostatic carcinoma. *J Nucl Med* 1992;33: 1316–1323.
21. Kloiber R, Moinar CP, Barnes M. Sr-89 therapy for metastatic bone disease: scintigraphic and radiographic follow-up. *Radiology* 1987;163: 719–723.
22. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol* 1991;64:816–822.
23. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993;25:805–813.
24. Lewington VJ, McEwan AJ, Ackery DM, et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer* 1991;27:954–958.