

12. Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992;268:2420-2425.

A thoughtful introduction to what is meant by evidence based medicine.

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Procedure Guideline for Bone Pain Treatment: 1.0

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Key Words: strontium-89 therapy; osseous metastasis; practice guideline

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PART I: PURPOSE

The purpose of this guideline is to assist nuclear medicine practitioners in evaluating patients who might be candidates for Strontium-89 (⁸⁹Sr) treatment of bone pain due to osteoblastic metastases, to provide information for performing this treatment and to assist in understanding the sequelae of therapy.

PART II: BACKGROUND INFORMATION AND DEFINITIONS

A. Definitions

1. Strontium-89 therapy means the intravenous injection of the radionuclide ⁸⁹Sr as the soluble salt strontium chloride. Strontium-89 emits a beta particle with maximum energy 1.463 MeV, mean energy 0.58 MeV, average soft-tissue range 2.4 mm and a 0.01% abundant gamma emission with a photopeak of 0.910 MeV. It has a 50.5 day physical half-life.
2. "Osteoblastic" or "osteoblastic metastases" mean foci of increased activity on bone scintigraphy caused by osseous reaction to tumor in bone.

B. Background

Intravenous injection of ⁸⁹Sr-chloride has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of bone pain due to osteoblastic metastasis. Physicians involved in treating such patients should have an understanding of the natural history of the disease process and should be able to collaborate closely with the physician or group of physicians handling the overall management of the patient's disease.

The administration of this agent falls under the guidelines of the Nuclear Regulatory Commission (NRC), Title 10 CFR Part 35.300 or Agreement State Institutional License. Institutional licenses must specif-

ically list individuals licensed to use Section 35.300 materials.

As other radiopharmaceuticals are approved by the FDA for the treatment of bone pain due to osteoblastic metastases, they will be added to the guideline.

PART III: COMMON INDICATIONS

Strontium-89-chloride (and the other unsealed beta- or conversion electron-emitting radiopharmaceuticals under development or available commercially, i.e. ³²P-orthophosphate) is indicated for the treatment of bone pain due to a metastatic malignancy that has involved multiple skeletal sites and has evoked an osteoblastic response on bone scintigraphy. Where there is danger of either spinal cord compression from vertebral metastases or pathologic fracture in the extremities, ⁸⁹Sr therapy should only be used in conjunction with other forms of management directed at these complications.

PART IV: PROCEDURE

A. Facility/Personnel

1. Strontium-89 may only be administered in a facility with a valid radioactive materials license incorporating Section 35.300 or comparable Agreement State License.
2. All administering physicians (the physician writing the prescription and injecting the dose) must be listed on the NRC or Agreement State license or specifically designated under a broad license.
3. Patients should be seen in consultation by the administering/treating physician in collaboration with the physician assuming overall patient management.
4. The administering physician should be board certified in nuclear medicine, radiology, radiation oncology or be able to document equivalent training, competency and experience in the safe use and administration of unsealed radiotherapeutic sources.
5. The administering physician should participate in the ongoing and follow-up care of the patient as part of the patient management team.
6. The facility in which the treatment is performed must have proper radiation safety procedures, in-

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cluding waste disposal, handling of contamination of personal belongings, etc.

B. Patient Preparation

1. Prior to administration of ^{89}Sr , the patient should have had recent bone scintigraphy (4–8 wk) documenting increased osteoblastic activity in the painful sites.

Radiographs taken within 4–8 wk demonstrating osteosclerotic lesions are not adequate, since there are rare cases where the increased bone density has occurred slowly and bone scintigraphy shows little increased activity. In such cases, ^{89}Sr uptake will be inadequate.

2. Bone scintigraphic abnormalities should be correlated with appropriate physical examination and imaging studies to ascertain that osseous or soft tissue abnormalities which might cause cord compression or pathologic fracture in an extremity are not present. Strontium-89 would be indicated in these circumstances only in conjunction with local radiation therapy or surgical intervention and only if there are other painful osteoblastic sites.
3. In general, patients should not have received long-acting myelosuppressive chemotherapy (e.g. nitrosoureas) for 6–8 wk and full doses of other forms of myelosuppressive chemotherapy or systemic radiotherapy for approximately 4 wk *prior to* administration of ^{89}Sr and for 6–12 wk *after* ^{89}Sr administration because of the potential for severe leukopenia or thrombocytopenia. Caution should be used if ^{89}Sr is used in conjunction with myelosuppressive chemotherapy.
4. The patient should not have received external beam hemibody radiation within 2–3 mo prior to administration of ^{89}Sr to reduce the probability of combined myelotoxicity from the external and internal radiation sources during this period.
5. Complete blood counts should usually be obtained within 7 days prior to administration of ^{89}Sr . The patient's platelet count should probably exceed 60,000 and preferably 100,000/ μl ; the leukocyte count should probably exceed 2400–3000 and preferably 5000/ μl ; and the absolute granulocyte count should exceed 2000/ μl to receive ^{89}Sr . Results below these blood count levels are not absolute contraindications to treatment but raise the chance of infection or bleeding.
6. The presence or absence of hormone therapy is irrelevant to administration of ^{89}Sr . Bone pain could be worsening while hormone therapy is controlling other sites of tumor, so hormone therapy need not be discontinued. Strontium-89 can be of value after failure of hormone therapy to control the pain of osseous metastases.
7. Before using ^{89}Sr , the pain usually should be severe enough to limit activity and/or require narcotic analgesia for control of symptoms.
8. Active disseminated intravascular coagulation (DIC) may be a risk factor for severe thrombocytopenia post-therapy. Deaths have been reported in patients with DIC after therapy with beta-emitting radiopharmaceuticals and this potential risk must be carefully considered before administering ^{89}Sr in the presence of DIC.

9. Hypercalcemia should not deter ^{89}Sr treatment unless accompanied by renal failure.

10. The patient need not fast before administration of the radiopharmaceutical.

11. The radiopharmaceutical should be administered slowly through an intravenous catheter or a running intravenous line to avoid infiltration, to reduce the hand dose to the injecting physician and to permit flushing of the syringe so that all of the ^{89}Sr is injected. A plastic syringe shield or equivalent is suggested for administration of the radiopharmaceutical. Flush the syringe and intravenous line from the syringe to the patient with saline from the running intravenous line or a saline filled syringe attached to a three-way stopcock.

12. Hospitalization is not required for the administration of ^{89}Sr .

13. A patient who has a life expectancy of less than 2–3 wk is unlikely to benefit from ^{89}Sr and, at his/her death, the pathologist will require certain precautions (goggles, double gloving) if an autopsy is performed less than 1 wk postadministration. There is no problem with cremation if the crematorium annually handles bodies containing less than 2 Ci of all radionuclides except ^{131}I for which there is a 200-mCi limit per year.

14. The usual administered activity of ^{89}Sr ranges from 1.5 to 2.2 MBq/kg (40–60 $\mu\text{Ci}/\text{kg}$). Some physicians calculate the activity based on lean body mass, reduce the activity given in patients with azotemia or slightly increase the administered activity with diffuse widespread metastases. There are no unequivocal data on these adjustments.

15. The procedure may be repeated 12 or more weeks after the first injection if blood counts are at the suggested levels. The response rate after the second treatment is about 50%.

C. Information Pertinent to Performing the Procedure

1. Patient demographics (age, sex, weight, height, diagnosis).
2. Indications for therapy.
3. Current medications, especially those affecting coagulation and bisphosphonates.
4. Extent of disease on bone scan obtained 4–8 wk prior to therapy.
5. CBC, prothrombin time and serum creatinine within 1 wk before therapy.
6. Relevant radiographs and/or MRI of painful sites to exclude severe lytic lesions or cord compression.
7. Life expectancy estimate.
8. Negative pregnancy test in women of childbearing age. No breastfeeding. These are absolute contraindications to therapy.

D. Instructions for Patients

1. The patient should be told that ^{89}Sr has a 60%–80% probability of reducing the bone pain due to cancer spread in bone, but that the chance of relieving pain completely is low.
2. The patient should be told that this is not a curative treatment for cancer, but a palliating treatment for pain, even though some cancer cells will be killed.
3. The patient should be told that the two major side effects are:
 - a. Possible significant increase in bone pain (“flare”) occurring within 21 days after injection.

tion and lasting 2–5 days. Flare is unusual after the second week.

- b. A possibility that the leukocyte and platelet counts may decrease by 30%–70% of baseline values or possibly to even lower levels which could lead to infection if leukocytes are too low or bleeding if the platelets are too low. Bleeding or the risk of bleeding could require platelet transfusion. Marrow replacement by tumor, ⁸⁹Sr therapy, chemotherapy and external beam radiotherapy have additive effects on myelosuppression, and the presence of two or more of these risk factors increases the possibility of clinically significant marrow suppression.

4. A written consent form is suggested, including indications, success rate and the risks of severe infection, bleeding and death. Local hospital policies and state regulations should be followed. The patient should be told that pain reduction is unlikely before the first week, more probable in the second week and could occur as late as 25 days or longer after injection.
5. The patient should be told that he/she may continue with a normal diet, that he/she should be careful to avoid soiling underclothing or areas around toilet bowls for 1 wk postinjection and that if any underclothing is significantly soiled with urine, it should be washed separately. Sitting down to urinate will reduce the possibility of contamination. A double toilet flush should be adequate after urination. Urinary excretion is greatest (80%–90%) for the first 48 hr postinjection. Patients should wash their hands after urination.
6. If the patient is being cared for in the hospital, then his/her attendants should wear gloves and gowns if contact with urine, feces, saliva or blood is anticipated. Catheter bags should be quickly transferred to the toilet for emptying with the attendant wearing gloves. Gloves should also be worn at home if soiled garments are to be handled. (There is no significant salivary secretion of ⁸⁹Sr, so no other precautions are required).
7. In incontinent patients, a plastic mattress cover and adult urine-absorbing undergarments are recommended; condom drainage or bladder catheterization should also be considered for several days to a week.

E. Precautions

1. The degree of leukopenia and thrombocytopenia present should not be severe, as noted in IV.B.5.
2. Previous, especially recent, chemotherapy or wide-field radiation can worsen ⁸⁹Sr-induced leukopenia or thrombocytopenia.
3. Renal failure may require reducing the activity injected.
4. Exclude spinal cord compression.
5. Do not use ⁸⁹Sr alone with ≥50% destruction of an involved bone, especially of an arm or leg, or for pain due to pathologic fracture.
6. Injection technique must be used to avoid infiltration. No specific therapy is available if infiltration occurs, but local heat may increase the rate of reabsorption and therefore decrease the local radiation dose.

7. Exclude active disseminated intravascular coagulation.
8. In women of childbearing age, the pregnancy test must be negative.
9. See IV.D.5, D.6, D.7.

F. Radiopharmaceutical: Strontium-89

1. Usual therapeutic administered activity is 1.5–2.2 MBq/kg (40–60 μCi/kg)
2. Radiation Dosimetry*

Radiation Dosimetry

Organ	mGy [†]	rad/mCi	rad [‡]
Bone surface	17.0	63.0	220.5
Red bone marrow	11.0	40.7	142.5
Lower bowel wall	4.7	17.4	60.9
Bladder wall	1.3	4.8	16.8
Testes	0.8	2.9	10.2
Ovaries	0.8	2.9	10.2
Uterine wall	0.8	2.9	10.2
Kidneys	0.8	2.9	10.2

*See *ICRP 53*, p. 171.

[†]per MBq.

[‡]per mCi.

G. Guidelines for Measuring the Amount of Strontium-89 to Be Administered

Either one of the following two methods can be used to measure the amount of ⁸⁹Sr to be administered:

1. Follow the “Guidelines for the Calibration of Metastron (Strontium-89-chloride injection).” Available from Amersham Corporation: (800) 554-0157.

or

2. Use a dose calibrator specially configured to quantify beta emissions.

H. Interventions

Not applicable.

I. Processing

Not applicable.

J. Interpretation/Reporting

1. The report to the referring physician should include the fact that informed consent was obtained and that the patient is aware of leukopenia and thrombocytopenia as possibilities (this should alert the referring physician to monitor the patient). The need for leukocyte and platelet count monitoring may be mentioned on the report, usually beginning 2 wk postinjection and then every 1–3 wk for a total of 12–16 wk. The physician performing the therapy is urged to monitor the blood counts if possible.
2. The referring physician may be reminded that pain reduction does not occur until 1–3 wk have passed.
3. The physician should not assume the patient has failed ⁸⁹Sr therapy until a full 4 wk after injection.
4. A few patients who have failed to respond to the first ⁸⁹Sr injection have had pain reduction with a second injection 12 wk later.

K. Quality Control

1. The institutional Quality Management Program mandated by the Nuclear Regulatory Commission should be followed.

2. There should be close coordination in all aspects of patient work-up and follow-up with the referring physician.
 3. The relevant patient information (IV.C.) should be reviewed before ^{89}Sr injection.
- L. Sources of Error
1. Improper use of dosage calibrator. The use of the ^{32}P setting on the modern dosage calibrator approximates that of the ^{89}Sr setting. The radioactivity must be measured in geometry and in containers consistent with previous calibration of the dosage calibrator.
 2. The radiopharmaceutical should be injected through a running intravenous line or intravenous catheter to avoid infiltration of the material injected, reduce hand dose, and permit flushing of all ^{89}Sr activity out of the syringe and into the patient.

PART V: DISCLAIMER

The Society of Nuclear Medicine has developed guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

PART VI: ISSUES REQUIRING FURTHER CLARIFICATION

Relative response rates of osteoblastic metastasis from different primary cancers. Preliminary data are available on this topic (see Taylor, 1994 in bibliography).

PART VII: CONCISE BIBLIOGRAPHY

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