Guidelines for the Therapeutic Administration of Strontium-89

These guidelines have been prepared by the Radiation Safety Program and Radiation Advisory Committee following wide consultation with interested persons and organisations. The guidelines are to be used in conjunction with the licensing requirements of the regulations to ensure that therapeutic use of strontium-89 is only carried out by appropriately trained persons taking account of relevant radiation protection issues.

Introduction

The treatment of painful bony metastases with bone-seeking radiopharmaceuticals has emerged as an effective new therapy for selected patients in clinical practice. The approval by the Therapeutic Goods Administration (TGA) of [^{89}Sr] chloride (strontium-89) led to the need for guidelines for therapeutic administration to be established, particularly in view of the radiation safety issues and potential toxicity of this treatment.

Strontium-89 is a β emitting radioisotope that is a physiologic calcium analogue, with similar whole body biodistribution. It has preferential uptake and retention by osteoblastic bone metastases compared to normal bone, with whole body retention dependant on the extent of osteoblastic tumour burden (ranging from 11-88% administered dose). The mechanism of action is believed to be through the direct action of beta particles on the metastasis itself or on adjacent bone. Dose-dependent marrow toxicity is observed, and is the limiting and only major reported side effect of strontium-89 therapy.

Referring Physician/Specialist

The physician/specialist referring a patient for treatment with strontium-89 must have appropriate qualifications, training and experience in managing patients with prostate cancer. It is extremely important that the strontium-89 be given in the context of overall patient management which takes into account the current clinical picture, previous radiotherapy and alternate treatment options appropriate at that time. A multidisciplinary and consultative approach must be adopted, and the patient must be properly assessed and followed up after the strontium-89 has been given.

The referring physician/specialist must have specialist qualifications in Radiation Oncology, Medical Oncology, or Urology.

Patients should be assessed by a by a Radiation Oncologist before they undergo treatment with strontium-89.

Administering Physician/Specialist

All physicians/specialists who administer strontium-89 for the therapy of painful bone metastases must have appropriate qualifications, training and experience in the use of unsealed sources for therapy. They must satisfy the following criteria:

Criterion 1

Joint Specialist Advisory Committee (JSAC), of the Royal Australasian College

State Government Victoria Department of Human Services

of Physicians and the Royal Australian and New Zealand College of Radiologists, recognised specialist qualifications in Nuclear Medicine or Radiation Oncology; **and**

Criterion 2
adequate prior training, practical experience and a current licence for the therapeutic use of unsealed sources. The specialist must also be actively practising the use of unsealed sources for therapy.

Adequate prior training is defined as approved postgraduate study (by formal coursework and/or within accredited training programs) within the areas of:

- radiation biology;
- radiation dosimetry;
- radiation safety;
- clinical uses of radioisotopes;
- administration of radioisotopes.

The training in these areas must relate to the *therapeutic* uses of any unsealed sources.

Adequate practical experience is defined as demonstration of regular prior therapeutic treatment of patients with unsealed sources (eg I-131, P-32) over 2 or more years, and/or supervised patient evaluation and administration of strontium-89 for a minimum of three patients. An adequate understanding of the literature on the use of strontium-89 is also required.

In instances where further practical experience is required, the required supervision of strontium-89 administrations should be undertaken by a physician/specialist licensed to use strontium-89.

Specialists wanting to have strontium-89 added to their licence must contact the Radiation Safety Program.

Patient Treatment

Indications
- The indications for patient treatment should directly conform to the Therapeutic Goods Administration (TGA) approved product information for the use of strontium-89 in force at the time of patient treatment. The current TGA approved indications for strontium-89 therapy are:

As an alternative to external beam therapy for the palliation of pain from bone metastases secondary to prostatic carcinoma at the stage of hormone therapy failure.

- A bone scan performed within 4 weeks of proposed administration must show multiple intense but focal areas of increased bony uptake, which are attributable to metastases causing the patient's pain.

Contraindications
- Strontium-89 therapy performed within the last 3 months.

- Spinal cord compression. Urgent surgery or external beam radiotherapy or other appropriate therapy must be considered immediately.

- Platelet count less than 100,000/mm^3.

- Total white cell count less than 3,000/mm^3.

- Wide field radiotherapy within the previous 4 weeks, depending on blood count values.

Relative Contraindications
- Since the clinical benefit of strontium-89 treatment is not apparent for 3-4 weeks, a patient should not be considered for strontium-89 therapy if their life expectancy is significantly less than 3 months.

- Patients who may be incontinent. There will occasionally be instances where urinary incontinence can be overcome by urinary catheterisation, and provided that radiation safety issues can be satisfactorily addressed, there is no reason to exclude such a patient from possible treatment.

- The presence of urinary obstruction requiring catheterisation should be a relative contraindication to treatment only, and provided appropriate radiation safety precautions are observed for handling of urine, such treatment can be satisfactorily undertaken.

- The treatment of imminent pathologic fractures should take precedence over systemic therapy with strontium-89.

- The presence of a diffuse increased uptake on bone scan (super scan) should be a relative contraindication for treatment only. The implication of a diffuse increased uptake or super scan is that there may be increased toxicity from the strontium-89 therapy to bone marrow. This is an extremely variable parameter as some patients who have such a bone scan appearance can receive strontium-89 therapy with minimal toxicity, and other factors which can affect marrow reserve, eg. prior cytotoxic chemotherapy and extensive radiotherapy may have more impact on marrow toxicity following strontium-89 therapy. The likelihood of marrow toxicity following strontium-89 therapy will need to be evaluated by the treating physician/specialist after careful review of the patient's history and available investigations.

- Renal failure is a relative contraindication, as the marrow toxicity from strontium-89 can be increased in this condition. Careful evaluation of renal function and the patient's history should be undertaken prior to treatment with strontium-89.

- Recent treatment with diphosphonates or other drugs which reduce bone turnover may reduce strontium-89 uptake. Confirmation of uptake in metastases on bone scan after such therapies is required prior to treatment with strontium-89.

- Strontium closely mimics the biodistribution and metabolism of calcium in-vivo, and therefore any calcium supplements routinely administered to the patient should be withdrawn at least 1 week prior to strontium-89 therapy.

Precautions

- It should be recognised that there may be some temporary increase in pain in the days following strontium-89 therapy (due to 'flare' phenomenon) and the benefits of the therapy may not be apparent for several weeks after treatment. Appropriate medications for pain relief should therefore be made available for control of pain symptoms during this time period.

Patient Preparation

- Informed patient consent to the procedure and to the restrictions imposed by radiation safety requirements must be obtained.

- Details of treatment must be described to the patient, and details relevant to radiation protection obtained so that potential problems are solved before administration of strontium-89.

- An appropriate radiation safety adviser should be aware of all patients considered for treatment with strontium-89, and in appropriate circumstances, should be directly involved with the patient's treatment. Therapy with strontium-89 should not be undertaken in situations where radiation protection guidelines cannot be adequately adhered to.

Administration

- The administering specialist is to be present to carry out the clinical direction (and possibly the physical direction) of therapy administration.

- The dispensed activity must be checked by two persons licensed with the Department of Human Services to use unsealed radioisotopes or registered with the Medical Radiation Technologists Board as a nuclear medicine technologist

- Secure intravenous access is mandatory, given the consequences of beta-emitter extravasation. An intravenous cannula, preferably of a flexible material, must be inserted and a free flowing intravenous infusion established before injection of the strontium-89 therapy.

Facilities

- The design of specialised therapy inpatient rooms, and the procedures involved in use of strontium-89 must comply with the Australian Standard AS2243.4 –1998 *Safety in Laboratories Part 4; Ionizing Radiations*.

The necessity for isolating a patient within a single room following strontium-89 therapy should, however, be decided on a case by case basis.

Post Treatment

- The patient must be provided with an information card, which includes their personal details, radionuclide administered (i.e. strontium-89), the activity administered, date of administration, name and contact number of their doctor and / or radiation safety adviser for emergencies or other hospitalisation, duration of radiation safety restrictions and any specific advice relevant to the patient's individual circumstances. The patient information card should be carried on the patient until the date when restrictions cease. This information should also be provided to the referring doctor. A sample instruction card appears in Appendix 1.

- Appropriate follow-up of patients should be undertaken, and clearly scheduled prior to administration of strontium-89. Regular monitoring of blood counts to detect possible toxicity should be performed following treatment and monitoring of the patient's symptoms should also be documented on a regular basis.

- The scheduling of blood tests should be left to the discretion of the administering physicians/specialist and referring specialist, but should be performed at least at 2-3 week intervals until marrow recovery is evident, or 8 weeks have elapsed since treatment. The results of these tests should be clearly recorded in the patient's medical records.

- When administering strontium-89 to a patient remaining in hospital, careful attention should be paid to radiation safety issues, particularly in regard to urine handling and disposal (most unbound strontium will be excreted within 24-48 hours of administration in the presence of normal renal function). Provided that appropriate radiation safety precautions are observed, patients will not require a single room following treatment, although each patient should be reviewed on a case by case basis.

- When discharging a patient to another institution (eg. nursing home, hospital) details of patient therapy (eg residual activity, estimate of activity excreted in the urine) and necessary radiation protection procedures must be supplied.

- The response of the patient to strontium-89 therapy (pain control, mobility, quality of life, use of other medications) should be carefully evaluated and documented. This information will allow evaluation of the efficacy of strontium-89 therapy to be made, and guide further treatment (including possible repeat therapy with strontium-89).

Suggested check list when planning strontium-89 therapy.	
1	Patient surname.
2	Referring physician.
3	Result of bone scan date of scan.
4	Result of full blood count and biochemistry screen date of test.
5	Relevant details of any previous radionuclide therapy or other bone marrow suppressive therapy, especially hemibody radiation therapy.
6	Notification of Radiation Safety Adviser..
7	Proposed date of administration.
8	Patient's primary language. (An interpreter may need to be present when treatment is given.)
9	Details of where the patient will stay after therapy.
10	After therapy, will the patient have any contact with children or pregnant women. If so, what are the details?
11	Details of any factors likely to cause radiation protection problems during therapy (eg. incontinence, poor mobility).
12	Arrangements for follow up blood tests.

Precautions Following Death of a Patient

Post mortem, cremation and burial aspects, should the patient die with significant strontium-89 body residue, must be considered.

- The handling of any corpses containing radioactive materials should be carried out in accordance with the requirements of the NHMRC *Code of Practice for the Safe Handling of Corpses Containing Radioactive Materials* (1986)

- Hospitals are required to ensure that patients and corpses treated with radiopharmaceuticals are not released until they are considered safe for handling. On the rare occasion that a body containing radiopharmaceuticals is to be cremated and the radioactive material has not yet decayed away to an acceptable level, pathologists, funeral directors, cemetery and crematoria staff will be notified by the administering hospital.

- As a general rule, with the possible exception of 'superscan' patients, the retention data discussed in Appendix 2 would suggest that there should be no problems in handling the corpses of patients who die more than 1 month after the strontium-89 administration.

- The limitations for burial are much higher at 2000 MBq.

- Written instructions for crematorium staff on the processing of cremation ashes following treatment with strontium-89 can be obtained from the Radiation Safety Program, Department of Human Services.

Written Procedures

Each centre using strontium-89 must have written procedures for the administration of strontium-89. These procedures should include:

⇨ Contact name/number for the Radiation Safety Officer (*or appropriate radiation safety adviser*) in the event of problems developing.

⇨ Procedures for loss or spillage of strontium-89 (including excreta).

⇨ Follow up procedures for the patient.

⇨ Nursing care instructions appropriate to the patient's circumstances.

⇨ A copy of these guidelines.

Appendix 1

Sample Patient Information Card for Strontium-89 Administration

Patient Name: _____

Patient Age: _____ Patient UR Number: _____

Patient Address: _____

_____

Referring Specialist Responsible for Continuing Management: _____ Phone: _____

Administering Nuclear Medicine Specialist: _____

Date of Therapy Administration: _____

Activity of Strontium-89 Administered: _____

Specific Advice to Patient Based on Individual Circumstances:

_____

_____

General Patient Instructions After Strontium-89 Therapy

Strontium-89 is a radioisotope that is used for the treatment of bone pain in patients with metastatic prostate cancer. It is important that you are aware of the general precautions that you should undertake after receiving this treatment. Your administering specialist will explain any specific precautions to you, and can answer any questions that you may have.

Personal hygiene and laundering instruction for the first week after Strontium-89 therapy:

- Where a normal toilet is available it should be used in preference to a urinal. The sitting posture should be used in preference to the standing posture.
- Wipe up any spilled urine with a tissue and flush it away.
- Ensure that you always wash your hands after using the toilet.
- Immediately wash any linen or clothes, which become stained with urine. Wash them separately from other clothes and rinse thoroughly.

Please keep this information card with you and bring it to the attention of your medical advisers should you require medical care such as operation or hospital admission within the next 3 months.

Specifically, please bring this notice to the attention of your medical adviser should you develop obstruction to urine flow or incontinence of urine so they may contact appropriate radiation safety support for advice on management of potentially radioactive urine.

Make sure to keep appointments for follow-up blood tests.

Date of First Appointment: _____ Doctor: _____

Telephone Number for Follow-up Advice During Normal Office Hours: _____

(Person to ask for: _____)

Telephone Number for Follow-up Advice Out of Normal Hours: _____

(Person to ask for: _____)

Name of person responsible for radiation safety advice: _____

Telephone and Fax Numbers for Follow-up Radiation Safety Advice:

Phone: _____ Fax: _____

Appendix 2

Dosimetry and Whole Body Retention of Strontium-89

- Half-life = 50.5 days
- Decay = 100% beta
- Mean Energy of Betas = 583 keV

The methodology of the ICRP[2] may be used to estimate the doses to the particular organs in the body. Values of some organ doses for normal adults are listed in Table 1 below. The effective dose is estimated as 310 mSv/100 MBq. For patients suffering from bone disease the absorbed dose to metastases may be expected to be substantially higher and the absorbed dose to other organs very much less. For example, Blake et al[3] have estimated the mean absorbed dose to vertebral metastases as 23 Gy/100 MBq administered.

Table 1
Organ Absorbed Doses Following Administration of Strontium-89 chloride

Organ	mGy/100MBq
Bone surfaces	1700
Red Bone Marrow	1100
Lower Large Intestine	470
Bladder Wall	130

In developing guidelines for safe practice the following information on the uptake and clearance of strontium-89 may be helpful. Based on the work of Blake et al[4] who used strontium-85 to follow the retention of strontium, the patients can be subdivided into three categories, depending on the extent of their metastases.

- For patients with a relatively light degree of metastatic bone involvement (defined as fewer than six discrete lesions) the clearance is relatively fast with a relatively low percentage of the strontium retained after 10 days. Typically, at 100 days the retained activity is about 5% of the injected dose.

- Patients with extensive metastases in the pelvis and axial skeleton but few in the extremities have an elevated retention pattern with approximately 10% of the injected activity remaining after 100 days.

- Patients with almost complete skeletal involvement (superscan) have high retention with minimal excretion and the 100 day retention is dictated largely by the physical half-life of the isotope.

A more complete summary of these findings is included in Table 2 where the amount of activity remaining as a function of time is tabulated for each of these scenarios. In all cases the administered dose is assumed to be 150 MBq of strontium-89.

Table 2
Retention as a Function of Time Following Administration of 150 MBq Strontium-89 Chloride

Extent of Bone Disease	Activity Remaining (MBq) at Specified Time			
	Day 3	Day 10	Day 30	Day 100
Few Metastases	95	45	25	7.5
Widespread Metastases	120	85	50	17
Total Skeletal Involvement	135	120	85	32

References

1. Cooper JR, Walmsley A & Charles D. *Individual and Collective Doses from the Release of Sr-89 into the Environment Following Medical Administration.* NRPB-M193 (1989).

2. International Commission on Radiological Protection *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53 (1987).

3. Blake GM, Zivanovic MA, Blaquiere RM, Fine DR, McEwan AJ & Ackery DM. *Strontium-89 Therapy: Measurement of Absorbed Dose to Skeletal Metastases.* J Nucl Med 29 (1988) 549-557.

4. Blake GM, Zivanovic MA, McEwan AJ & Ackery DM. *Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate.* Eur J Nucl Med 12 (1986) 447-454.