Introduction

Osseous metastases are frequently seen in cancer patients; autopsy series have noted bony metastases in up to 85% of patients dying with carcinomas of the prostate, breast, and lung.1,2 These three primary sites account for approximately 80% of patients suffering from distant cancer spread.

Therapies such as hormonal manipulation and cytotoxic chemotherapy may result in control of the disease and an overall improvement in quality of life measurements in clinical trials. The ultimate prognosis is poor, however, with most patients suffering progression and death because of this clinical scenario. Of equal concern to patients and health care providers are the pain, fracture, and loss of function that frequently accompany a diagnosis of skeletal metastases. These problems impair both the quality and quantity of remaining life, limit activities of daily living, and result in costly medical care that is often only marginally effective in returning the patient to an independent, active lifestyle.

The primary symptom of osseous metastases is pain. The pain is related in part to cytokines released at the site of the metastases and neuropeptides elaborated by or acting upon bone-associated nerves in the endosteum. Pain is also caused, in part, by stretching of the periosteum by growing tumors that deform the cortical bone.2,3 Because the skeleton provides both form and support, this sets the stage for activity-associated pain, a symptom that is often intermittent and related to weight-bearing and movement.

Because bone often functions as a conduit for peripheral nerves traveling from distal body parts to the central nervous system, neuritic pain syndromes related to radiculopathies, plexopathies, spinal cord compression resulting from tumor growth and invasion into surrounding tissues, and bone fracture may occur. These complicate both the diagnosis and treatment of metastatic bone disease. In addition, the pain syndromes mentioned encourage increasing loss of mobility and bed rest, which, in turn, may result in increasing generalized weakness.
with consequent mobilization difficulties and risk of thromboembolic disease, hypercalcemia, and atelectasis and pneumonia. The latter occur particularly in patients who also suffer from painful rib metastases.

The ultimate mechanical symptom is actual mechanical failure, or pathologic fracture, of a bone affected by metastasis. Surgical intervention may be indicated but may not be possible because of the patient’s clinical status, including general medical condition, and the condition of the affected bone.

Bone metastases are often classified by their radiologic appearance as osteolytic, osteoblastic, or mixed. Osteolytic metastases, the most common metastatic pattern, show bone destruction and are characterized by a radiolucent lesion on radiographs. Osteoblastic lesions appear more radiodense compared with surrounding bone and are the most common metastatic lesions seen in patients with disseminated prostate carcinoma. At the microscopic level, however, little qualitative difference exists between osteolytic and osteoblastic metastases. Most bone metastases induce bone destruction and new bone formation concurrently, and the predominant process results in the particular radiographic appearance.

The treatment of bone metastases requires a multidisciplinary approach to the patient that is frequently reevaluated during the clinical course of the disease. The primary goal of therapy is pain relief with improvement in quality of life. Although most of these patients do not have a curable condition, enhancement of survival, if possible, represents an obvious goal. Aside from appropriate systemic anticancer therapy (for example, total androgen ablation for prostate carcinoma and hormonal therapy or chemotherapy for breast carcinoma), several treatment options are available to palliate symptomatic disease, each with specific advantages and drawbacks. These options include the use of bone-seeking radioisotopes. In this article we review the other options briefly and discuss the experience with and future potential of radionuclide therapy in detail.

**Treatment Options for Bone Metastases**

**Analgesics**

Analgesics, including narcotics, allow the physician considerable flexibility in altering both the dose of medication and the route of delivery to control pain. Oral, transdermal, and parenteral routes of administration result in systemic distribution of the drug with consequent toxicities, such as sedation, nausea, and anorexia, that are occasionally dose-limiting. These agents are relatively inefficient therapy for patients suffering from pain arising from one or two skeletal sites or those with mechanical bone pain that is intermittently experienced, such as only with movement.

**Local Field Irradiation**

The value of local field irradiation for palliation of painful osseous metastases is well recognized. Some relief of pain is reported in approximately 80% of patients treated with this technique; up to 50% of patients have complete resolution of pain within the treated area. Unfortunately, most patients with bony metastases have multiple metastases or will develop new sites of involvement with associated pain. Consequently, patients managed solely with this modality need multiple courses of external beam irradiation, which, although usually well tolerated, are expensive and demand several visits to a treatment facility.

**Wide Field Irradiation**

Wide field irradiation delivered to one hemibody, or sequentially to both hemibodies treated at 5- to 7-week intervals, has been shown to be an effective external beam radiation strategy, with partial pain relief achieved in 55% to 100% of
subjects. In up to 80% of patients who have relief of pain, the effect lasts until death.4,8 These benefits are counterbalanced by appreciable toxicity, particularly affecting the hematopoietic, pulmonary, and gastrointestinal systems. Close sequencing of hemibody therapies is also limited by myelosuppression, which reduces the convenience and efficacy of this modality.

**BISPHOSPHONATES**

Recent clinical trials have expanded the indications for bisphosphonates, which effectively suppress bone resorption, to include the treatment of osseous metastases.9

Randomized trials in breast cancer and multiple myeloma patients have shown a benefit from bisphosphonates in terms of a decrease in adverse skeletal events (i.e., pathologic fracture, vertebral collapse, spinal cord compression) and the need for orthopedic surgical procedures or palliative irradiation. In addition, use of bisphosphonates results in a reduced requirement for narcotic analgesics, diminished increase in bone pain, and slower deterioration in performance status over time compared with placebo in studies employing concurrent chemotherapy or hormone therapy.10-12

The usefulness of these agents in the treatment of established pain is less certain, and conflicting evidence of their usefulness in metastatic prostate carcinoma makes blanket recommendations on the use of these drugs for osseous metastases difficult.9,13,14

**BONE-SEEKING RADIOISOTOPES**

The initial use of phosphorus 32 ($^{32}$P) in the treatment of bone metastases from both breast and prostate carcinomas opened another, potentially attractive avenue for the treatment of patients with bone metastases. Because most patients with skeletal metastases have multiple deposits, many of which are symptomatic, a radiation technique that approaches the patient’s malignancy in a “systemic” fashion (much as iodine 131 does in the treatment of disseminated thyroid carcinoma metastases) offers the opportunity to treat several symptomatic metastases simultaneously. The systemic approach also offers a therapy that may have antitumor efficacy and analgesic properties.

Currently, three radioisotopes are employed for this purpose in clinical

---

**Table 1**

**Characteristics of Radionuclides Available for Treatment of Bone Metastases**

| Radionuclide       | Half-Life | Radiation Emission | Decay Energy (MeV) | Status       |
|--------------------|-----------|---------------------|--------------------|--------------|
| Phosphorus 32 ($^{32}$P) | 14.2 days | Beta                | 1.71               | Approved     |
| Strontium 89 ($^{89}$Sr) | 50.6 days | Beta                | 1.492              | Approved     |
| Samarium 153 ($^{153}$Sm) | 46.3 hours | Beta, Gamma         | 0.81, 0.10        | Approved     |
| Rhenium 186 ($^{186}$Re) | 90.6 hours | Beta, Gamma         | 1.071, 0.137      | Investigational |
| Rhenium 188 ($^{188}$Re) | 16.7 hours | Beta                | 2.116              | Investigational |
practice: \(^{32}\)P, strontium 89 chloride (\(^{89}\)Sr), and samarium 153 (\(^{153}\)Sm) (Table 1). All three share certain characteristics. First, they are incorporated into bone by virtue of their elemental nature or through the chemical properties of an attached ligand. Next, the therapeutic radiation emitted is that of low-energy electrons (beta emissions) as opposed to gamma radiation, which is normally used in nuclear medicine imaging. Finally, they are preferentially incorporated into bony lesions undergoing repair compared with normal bone.

How these agents work to relieve pain is incompletely understood. Often patients experience dramatic pain relief within 24 to 72 hours of administration, too short a time for significant tumor shrinkage to occur as a result of radioactive isotope emissions. This suggests the involvement of other mechanisms, such as a reduction in lymphocyte-associated cytokines or alterations in the function of osteoclasts and osteoblasts.

Considerable clinical experience has accumulated in the use of these agents for osseous metastases, particularly hormone-refractory or endocrine-resistant prostate carcinoma. The reasons for this are threefold. First, until recently, no effective systemic (chemotherapeutic) regimens were available for the treatment of hormone-refractory prostate carcinoma. Second, metastatic prostate cancer predominantly affects the skeleton, and in many patients bony metastases are the only apparent manifestations of disseminated disease. Third, visceral metastases usually occur late in the course of the disease, making symptomatic systemic metastases less of a concern.

In addition, most prostate cancer metastases are osteoblastic, and it was thought that an increased amount of radioisotope would be deposited at the site of osteoblastic lesions because of apparent new bone formation. In contrast, fewer breast cancer patients have been treated because of the availability of other treatment options, the high rate of visceral metastases, and a higher rate of osteolytic or mixed metastases as seen on bone radiographs.

**Studies of Radioisotopes in Treatment of Osseous Metastases**

Many clinical reports and trials have involved the use of radioisotopes in the treatment of osseous metastases. In general, these studies have shown the usefulness of radioisotopes in controlling pain from symptomatic bony lesions. Unfortunately, most of these studies suffer from serious weaknesses both in terms of clinical trial methodology and in terms of data analysis, leading to difficulty in comparing the efficacy of the various radioisotopes versus each other and versus other modalities.

Most studies using radioisotopes have accrued small numbers of patients, making calculation of rates of pain relief problematic. Other reports are simply retrospective collections of patients treated with varying doses of radioisotope, making comparison of response rates among reports and assessment of any dose-response relationship exceedingly difficult.

Finally, the criteria for judging symptomatic relief vary widely among reports. Some papers simply note the proportion of patients obtaining “some” pain relief without further qualification or quantification of the degree of relief achieved. Others use a graduated scale for degree of pain relief that can vary in complexity from simple, unquantified descriptors (“complete,” “markedly improved,” “some,” or “no” pain relief) to complicated and often unvalidated scoring systems that assign grades based on general condition, mobility, analgesic intake, and pain analysis. Although such scales are more helpful than rates of achievement of some pain relief, their use invariably leads to difficulties in comparing rates of salutary responses among differing treatment modalities and among reports.
Further complicating assessment of the literature is the high proportion of patients registered in many clinical trials who were treated but later proved not able to be evaluated for response. The usual reasons for not being able to be evaluated are early death (often within 3 months of therapy), loss to follow-up, insufficient time elapsed after therapy before evaluation, and concomitant therapy within the posttreatment period. Patients who fall into these categories may, as a group, have higher tumor burdens, poorer performance status, and a poorer response to therapy.

**Specific Radioisotopes**

**Phosphorus 32**

Radiophosphorus-labeled phosphates were the first radionuclides used to treat bone metastases. In 1950, Friedell and Storaasli reported on the use of 32P in breast cancer patients suffering from bone metastases, with marked pain improvement in 10 of 12 patients. Leukopenia was the major toxicity.

Since then, many reports have been published about the use of 32P in patients with prostate and breast carcinoma. Most patients treated by this agent received either androgen (for prostate cancer) or parathormone stimulation, or both, in an effort to increase radioisotope incorporation into osseous metastases. As Silberstein has pointed out, however, no evidence exists that supports these practices in enhancing clinical outcome, and no preclinical data exist to document increased 32P uptake. Most patients have been treated with multiple daily injections of the isotope, but, again, little evidence from clinical trials supports this approach. Indeed, no randomized trials, blinded or otherwise, have been performed that document the efficacy of these agents.

32P can cause hematologic toxicity, resulting in leukopenia and thrombocytopenia. Although its incorporation into primary tumors and other organs has been documented, no sequelae have been described. A “pain flare” similar to that seen with 89Sr has been described but may be in part related to androgen stimulation. The currently available product, 32P orthophosphate, is economically priced compared with similar beta-emitting radionuclides used for this purpose, but it has fallen into disuse because of the widely held impression that current 32P approaches are too toxic. However, as noted in recent reviews by Silberstein, only one patient fatality attributable to 32P has been reported in the literature.

**Strontium 89 Chloride**

Although 89Sr is, like 32P, a pure beta-emitting radioisotope, it has several theoretical advantages as a treatment agent for bony metastases.

Strontium is found in the same periodic table family as is calcium and is metabolized in a similar fashion, with significant concentrations found in the skeleton and small amounts elsewhere in the body. Strontium is incorporated in the skeleton rapidly, with activity reaching a maximum within hours in murine models.

Blake and colleagues have described preferential retention of radiostrongium at the sites of metastases, and this deposition has been confirmed by autoradiographs of autopsy and surgical specimens. Such deposition, combined with the long isotopic half-life (more than 50 days) of 89Sr, suggests the possibility of prolonged, low-dose irradiation of osseous metastases compared with normal bone, in which the half-life of 89Sr is approximately 14 days. However, other investigators have shown that although the ratio of 89Sr in metastatic lesions compared with normal bone is approximately 2, some metastases do not retain 89Sr for a longer time than does normal bone. This finding may explain some of the variability in treatment results.

Radiation doses to metastases have been estimated to vary between 1.5 and
15.2 cGy/MBq (220 to 2,260 cGy/mCi) of administered $^{89}$Sr, with an average of about 5.7 cGy/MBq (850 cGy/mCi).\textsuperscript{21}

Several clinical trials and retrospective reports on the use of $^{89}$Sr have appeared in the literature, most relating to the treatment of prostate cancer metastases, with a smaller number relating to the treatment of metastases from breast carcinoma.\textsuperscript{26-37} These reports have dealt with subjective effects (including pain relief and possible placebo effects), objective effects (including survival), and efficacy as an adjunctive therapy.

**Subjective Effects**

An early, small trial by Buchali and coinvestigators\textsuperscript{26} failed to find a difference between $^{89}$Sr and placebo, but the pain score employed or the actual hormonal treatment status of the patients is unknown.

In contrast, Lewington and associates\textsuperscript{27} randomly assigned 32 patients with

### Table 2

| Study            | Approximate $^{89}$Sr dose (MBq/kg)\textsuperscript{*} | Total Patients (No.) | Evaluable Patients (No.) | Pain Relief (%) Evaluable Patients |
|------------------|---------------------------------------------------------|-----------------------|--------------------------|-----------------------------------|
| Correns et al\textsuperscript{28†} | 0.5                                                     | 20                    | 17                       | 47 18 65                          |
| Firusian et al\textsuperscript{30†} | 1.1                                                     | 11                    | 11                       | 73 9 82                           |
| Silberstein & Williams\textsuperscript{31} | 0.6–2.6                                                  | 17                    | 17                       | Uncertain                         |
| Robinson et al\textsuperscript{32†} | 1.5                                                     | NS                    | 100                      | 10 29 39                          |
| Tennvall et al\textsuperscript{33} | 1.4                                                     | 8                     | 8                        | 13 37 50                          |
| Reid et al\textsuperscript{34} | 1.6                                                     | 18                    | 16                       | 6 0 6                             |
| McEwan et al\textsuperscript{35†} | 1.5                                                     | 35                    | 26                       | 27 50 77                          |
| Lewington et al\textsuperscript{27} | 2.1                                                     | 15                    | 12                       | 33 8 41                           |
| Laing et al\textsuperscript{29} | 0.7                                                     | 11                    | 5                        | 0 0 0                             |
|                  | 1.5                                                     | 78                    | 54                       | 24 35 59                          |
|                  | 2.2                                                     | 27                    | 17                       | 17 24 41                          |
|                  | 3.0                                                     | 14                    | 12                       | 0 33 33                           |

\textsuperscript{*}Many studies dosed patients with a standard dose without regard for patient weight; for comparison purposes, a rough approximation was calculated using a 70-kg patient as an example (see Mertens et al\textsuperscript{50}).

\textsuperscript{†} Response criteria uncertain or not comparable to those of other reports.

CR = complete relief of pain, analgesics discontinued; NS = not stated; PR = partial relief of pain, with a reduction in analgesic use of more than 50%; RR = response rate (CR + PR).
poorly controlled pain and no change in anticancer treatment for the 3 months before treatment to 150 MBq of $^{89}$Sr or chemical strontium chloride. These investigators found a statistically significant improvement in symptoms in the active treatment group. However, six patients were considered unable to be evaluated because of death, illness, or change in treatment and were excluded from the analysis. Interestingly, one patient who received the placebo experienced a substantial improvement in pain scores, suggesting that caution is required in the interpretation of single-arm trials of these agents.

The main outcome measured in studies of these radionuclides is the degree of pain relief experienced by patients with painful metastases. One study reported a high rate of pain relief, which may have been the result of hormonal therapy that was not described in the report. $^{28}$ Other studies revealed rates of complete relief of pain ranging from 0 to 73% for patients able to be evaluated (Table 2).

As was noted earlier, quantifying less than complete pain relief for the purpose of comparison among trials is more difficult because of the variable and often poorly defined response criteria used in these trials. When “partial relief of pain” is defined as a marked reduction in pain with a consequent reduction in analgesic requirements to less than half of pretreatment dosages, the proportion of patients able to be evaluated who achieved complete or partial pain relief ranged from 0 to 82% (Table 2). Many patients experienced lesser degrees of pain relief of uncertain clinical importance.

The wide range of responses is probably related to the small number of patients treated in some trials and the large number of patients unable to be evaluated in others, combined with variable response definitions. Another source of variability is the failure of many trials to stratify patients according to tumor burden.

Laing and associates $^{29}$ noted substantial improvement in pain symptoms in 78% of patients with “light” metastases (as judged by pretreatment bone scan) who were given a variety of $^{89}$Sr doses. In comparison, 42% to 50% of those with extensive metastases experienced improvement in pain symptoms. Robinson et al $^{32}$ described the impression of a higher response rate at one contributing center, possibly because of earlier referral of patients and a consequent lower metastatic burden. This possibility must be considered when future clinical trials are planned. Table 2 reviews reports of $^{89}$Sr employed as a single agent for pain palliation in prostate cancer.

**Objective Effects**

Prostate cancer, when metastatic solely to bone, has been notoriously difficult to assess with regard to traditional parameters of objective tumor response. Investigators are limited to radionuclide bone scans, radiographs, and serum tumor markers (which are likely to continue to be produced by uncontrolled primary tumors and soft tissue metastases).

Few studies of single-agent $^{89}$Sr have addressed the issue of anticancer efficacy, especially because many early trials were conducted before the widespread use of serum prostate-specific antigen (PSA) testing. Kloiber and associates $^{38}$, for example, attempted to measure lesion to nonlesion technetium 99 ($^{99}$Tc) uptake ratios on digitalized images. They noted an average decrease after therapy, but it is not known how significant this is.

Papatheofanis $^{39}$ evaluated urinary excretion of pyridinoline and deoxypyridinoline as measures of bone resorption and found that patients who were treated with $^{89}$Sr did not have a continued increase in excretion similar to that of subjects who were not treated with the radionuclide. Others have attempted to correlate changes in bone scan appearance with clinical response but without much success.
In a randomized Canadian study, high-dose $^{89}$Sr (400 MBq) as an adjuvant to local field irradiation was compared with local field irradiation alone. Results suggested that a higher percentage of patients who received the radionuclide experienced a decrease in PSA of more than 50%. Unfortunately, relatively few patients had PSA values measured or reported, and the reporting of the results did not account for those patients who died at the time of interval reporting of results. Thus, comparison with the serum PSA response criteria currently used in systemic chemotherapy protocols is inappropriate.

The poor survival results and limited treatment options available to patients with hormone-refractory prostate cancer stimulated the hope that new beta-emitting radionuclides might favorably increase survival. Thus far, however, single-agent radionuclides have been disappointing. Buchali and colleagues treated 49 patients with either $^{89}$Sr (75 MBq monthly for 3 months) or a saline placebo. They found a statistically significant prolongation of survival in the active treatment group, although no difference in pain control was seen in the two arms. It is unclear whether patients in this trial were truly hormone refractory or whether they were on active hormone-based therapy.

A recent United Kingdom trial compared $^{88}$Sr (200 MBq) with hemibody irradiation. This study failed to find a survival benefit, as did the Canadian study of high-dose $^{89}$Sr (400 MBq) as an adjuvant to local field irradiation.

Reduction in New Symptomatic Disease

Patients suffering from osseous metastases often need repeated external beam irradiation to control painful symptoms. Any treatment that would reduce the need for additional palliative therapy could be useful in terms of both quality of life and cost.

The Canadian trial mentioned earlier randomly allocated patients with hormone-refractory prostate cancer suffering from painful bony metastases to external beam irradiation with or without adjuvant high-dose $^{89}$Sr. These patients normally would have been treated with palliative external beam irradiation to a maximum of two treatment fields. Patients receiving the radioisotope had similar pain control at the index sites of pain (which were given external beam irradiation in both treatment groups). Over time, however, those who received $^{89}$Sr experienced less pain. A higher proportion of these patients were pain free (40% versus 23%), fewer used analgesics (17.1% not taking analgesics after radioactive therapy versus 2.4% after radiotherapy only), and they had a significantly lower number of new sites of pain (0.59 versus 1.21, $P < 0.002$). Time to next external beam radiotherapy treatment was prolonged by a median of 15 weeks.

McGowan reported a modeled cost-benefit analysis for the Transcanada trial that suggests an overall favorable cost-benefit ratio, supporting the addition of high-dose $^{89}$Sr to palliative radiotherapy in these patients.

The United Kingdom trial was conducted in a similar group of patients, who were initially stratified as suitable for either local field irradiation (148 patients) or hemibody irradiation (157 patients). The patients were then randomly allocated to the appropriate external beam irradiation technique or to $^{89}$Sr treatment (200 MBq).

Again, both treatments were equally effective in reducing pain at the index sites of pain, but the radionuclide-treated patients were significantly less likely to develop new sites of pain. At 12 weeks, 65% were pain free after $^{89}$Sr versus 46.5% after local field radiotherapy ($P < 0.01$), and 73.3% were pain free after $^{89}$Sr versus 54.6% after hemibody irradiation ($P < 0.05$). Toxicity was predictable for the radioisotope-treated groups, with those patients receiving $^{89}$Sr experiencing...
substantially fewer gastrointestinal side effects.

Although both randomized trials showed reduced pain or delayed time to new pain and next radiation treatment, the United Kingdom study is not an adjuvant trial; patients received either external beam radiation or $^{89}$Sr, which represents the most common clinical decision pathway for clinicians using these therapies. Furthermore, the dose of $^{89}$Sr in this trial was closer to the recommended dose of 150 MBq than was the higher dose safely administered in the Canadian study.

Toxicity

Side effects have been largely limited to a flare reaction, which may occur 24 to 48 hours after injection, and myelosuppression, particularly thrombocytopenia and leukopenia. The platelet nadir occurs 6 to 12 weeks after administration of $^{89}$Sr and represents a drop of 20% to 40% compared with pretreatment levels. Recovery occurs slowly, but pretreatment levels are usually achieved. The degree of myelosuppression rarely reaches the level of World Health Organization (WHO) or Southwest Oncology Group (SWOG) grade 3 or 4 toxicity. If severe myelosuppression develops, consideration should be given to coadministered agents, such as chemotherapy drugs, or the presence of bone marrow failure related to progressive malignancy.

SAMARIUM 153 LEXIDRONAM

The US Food and Drug Administration has recently approved samarium 153 lexidronam chelated to ethylenediaminetetramethylenephosphonic acid ($^{153}$Sm-EDTMP) for the relief of pain in patients with osteoblastic bone metastases. This radioisotope, like $^{32}$P and $^{89}$Sr, emits low-energy electrons. Unlike the other approved agents, however, $^{153}$Sm has a shorter half-life (less than 2 days) and gamma emission suitable for imaging and prospective dose estimation.

Turner and colleagues$^{42}$ reported an early phase I trial of $^{153}$Sm-EDTMP with individual beta radiation dosing based on pretreatment pharmacokinetic studies in individual patients given a 740-MBq tracer dose. The retained skeletal dose was found to vary from 40% to 95% of the administered dose.

Similar results were found in a more recent study, which determined that 54% ± 16% of the injected dose was retained in the skeleton, with a range of 15% to 85%.$^{43}$ As expected, the dose-limiting toxicity was myelosuppression. Platelet counts of less than 100 x $10^9$ per liter occurred in 42% of courses in which the bone marrow radiation-absorbed dose exceeded 200 cGy in the first trial, and the decrease in pretreatment platelet count was more than 50% for an absorbed marrow dose of more than 200 cGy in the second trial. Platelet counts began to decline 2 weeks after administration, and the platelet nadir occurred at 24 ± 5 days after administration. A pain flare was reported in 10% to 13% of patients, with self-limiting characteristics similar to those described with the other radioisotopes.

In the report by Turner et al.$^{42}$ 63% of patients experienced complete or partial pain relief; however, 83% of breast and prostate cancer patients experienced pain relief. Relief began within 2 weeks of administration and lasted 4 to 35 weeks.

Collins and coinvestigators,$^{44}$ reporting two dose levels (37 MBq/kg and 92.5 MBq/kg) in a nonrandomized phase I/II trial of hormone-refractory prostate cancer patients, found similar results. One month after therapy, 32% of patients were able to discontinue opioid use. This trial suggested a higher rate of pain improvement and more patients achieving improved performance status with the higher dose. The 92.5 MBq/kg-dose was also associated with a higher rate of modest PSA decline (a decline of more than 25% in 50% of those treated with the
higher dose compared with 10% of those treated with the lower dose at 4 weeks, $P = 0.035$). The higher dose was associated with a longer median survival (9 versus 6 months, $P = 0.03$), although it must be remembered that this was not a randomized trial.

In contrast, Alberts and associates failed to find improved results with doses higher than 55 MBq/kg.

Two randomized, placebo-controlled clinical trials, which accrued either largely or only patients with hormone-refractory prostate cancer, showed significantly improved pain relief in those who received the radioisotope. No trials have been reported comparing $^{153}$Sm-EDTMP with other radioisotopes or with radiation. Despite the theoretical advantages of employing the gamma emission in dose calculation and the modest evidence for an increased pain and tumor marker response with a higher dose of $^{153}$Sm-EDTMP, the recommended dose is 37 MBq/kg.

**Future Research**

Although systemic radionuclides offer some patients with osteoblastic metastases substantial pain relief, additional efforts clearly must be made to improve their efficacy. Table 3 shows several strategies that could be employed with the hope of improving patient outcome, and in this section we describe some current avenues of research being pursued.

**RHENIUM 186 AND RHENIUM 188**

Rhenium 186 (Sn) hydroxyethylidene diphosphonate ($^{186}$Re-HEDP) has characteristics similar to those of $^{153}$Sm-EDTMP, with a beta emission half-life of 90.64 hours and a gamma emission suitable for imaging.

Maxon et al. reporting a double-

---

### Table 3

| Potential Strategies to Enhance Efficacy of Bone-Seeking Radionuclides |
|---|
| **New radionuclides** |
| Advantages of short half-life (combination with other agents) versus long half-life (low dose rate irradiation) |
| Dose intensity |
| Increased administered dose of radionuclide |
| Colony-stimulating factor support |
| Bone marrow/peripheral blood stem cell support |
| Bisphosphonates |
| Direct pain relief |
| Possible increased retention of isotope at site of metastases |
| Chemoradiosensitization |
| Radiosensitizing chemotherapy agents |
| Coadministered chemotherapy agents effective in hormone-refractory prostate cancer |
blind crossover comparison with placebo, found a significantly greater decrease in pain with the active agent. Another study by Maxon and colleagues showed significant pain relief in 80% of 20 patients treated with an average dose of 1,221 MBq. Toxicity was mild, but given the availability of other, similar isotopes, it is uncertain whether $^{186}$Re-HEDP will undergo further development.

The same group of investigators recently reported on the use of rhenium 188 (Sn) HEDP ($^{188}$Re-HEDP) in the treatment of osseous metastases. This isotope differs from the others in that it has a very short beta emission half-life (17 hours), beta energy (2.12 MeV) sufficient for therapy, and gamma emission suitable for imaging. The study included eight men with painful metastases from prostate cancer. Two-thirds experienced pain relief. Toxicity was mild, with expected myelosuppression; two patients had mild increases in serum creatinine levels and trace proteinuria.

This agent could prove useful in high-dose therapy, with fewer external radiation concerns because of its short half-life, and it could hold promise in combination therapies in which long beta emission half-lives would be a distinct disadvantage. These advantages have to be weighed against the inconvenience of producing this short-lived agent close to the clinical administration unit, most likely with the use of a tungsten-rhenium generator.

COMBINATION THERAPIES
The growth of new therapeutic modalities for the treatment of bone metastases, particularly metastases from prostate cancer, suggests the possibility of incorporating more than one strategy into a new approach designed to improve the efficacy of therapy.

Dose Intensity
Dose intensity remains an important, if still somewhat controversial, concept in oncology. Attempts to evaluate dose intensity in beta-emitting radioisotopic treatment of bone metastases have been frustrated by methodologic problems, such as evaluation of pain in a reproducible, graded manner; the absence of trials that randomly allocate patients to treatment groups of differing doses; and the dose-limiting toxicity of the isotopes themselves. Although some authors have noted apparent improvement in results with higher doses, others have been unable to show improvement.

Bisphosphonates have been shown to be beneficial in treatment of patients with breast cancer and multiple myeloma, but evidence of their usefulness in metastatic prostate carcinoma is conflicting.

The development of new beta-emitting isotopes of short half-lives, such as $^{188}$Re-HEDP and $^{153}$Sm-EDTMP, offers the opportunity to increase the intensity of therapy and incorporate the use of colony-stimulating factors, cytoprotective agents such as amifostine, and possibly even peripheral blood stem cell rescue and chemotherapy in aggressive strategies that would have less to do with palliation of painful metastases than with tumor control and, ultimately, prolonged survival.

Chemoradiosensitization and Combined Radioisotope/Chemotherapy Strategies
The use of chemotherapy and external beam radiation has proved useful in
many clinical situations, and many chemotherapy agents have proved to be effective radioenhancing compounds. Given the limited options for treatment of patients with osseous metastases requiring palliation, the possibility of combining anticancer agents, preferably without overlapping toxicities, is attractive.

Mertens and coinvestigators evaluated two infusions of low-dose cisplatin in conjunction with one injection of $^{89}$Sr. They found a pain relief rate at least as high as any other achieved with $^{89}$Sr and little additional toxicity, although the trial was relatively small. Nineteen percent of patients with hormone-refractory prostate cancer experienced a decrease in serum PSA of more than 50%, a result that is better than expected for either the radioisotope or the dose of cisplatin administered.

Tu et al combined repeated injections of $^{89}$Sr every 3 months with weekly 24-hour infusions of doxorubicin, a noted radioenhancing agent. They achieved a 32% rate of PSA response and a 57% pain-free palliation rate. This trial differs from the cisplatin study in that repeated $^{89}$Sr courses and long-term chemotherapy were given. Doxorubicin, in addition to being a radioenhancing agent, has also shown objective responses in hormone-refractory prostate cancer.

Early trials of estramustine and $^{89}$Sr have also been described, and this combination holds promise as a palliative regimen of improved efficacy. However, improvements in palliation, PSA-based response rates, and survival endpoints will be determined only through randomized, controlled clinical trials, which are necessary if the additional cost, inconvenience, and potential toxicity of combined therapy are to be justified to both patients and insurers.

**Bisphosphonates**

Combinations of bone-seeking radionuclides and bisphosphonates are attractive in that both agents appear to improve pain and delay the onset of new overtly symptomatic osseous disease. Moreover, these agents have no overlapping toxicity. Thus far, no trial using only beta-emitting radionuclides and bisphosphonates has been published.

**Conclusion**

The addition of systemic radionuclides to the therapeutic armamentarium of multidisciplinary cancer care has been useful, with some patients achieving clear benefit from these modalities.

However, although almost 50 years have elapsed since the first report of $^{32}$P usage in the palliation of osseous metastases, the overall importance and ultimate place of systemic radionuclides in the treatment of these patients remains uncertain. The uncertainty is partly the result of the methodologic flaws of past reports and the obvious difficulties in conducting clinical trials in this area and partly because of the proliferation of other treatment modalities, particularly bisphosphonate therapy and new chemotherapy regimens for patients with hormone-refractory prostate cancer.

Palliation for most patients remains incomplete, and this problem, coupled with the need for better strategies to improve survival and diminish the morbidity of progressive disease, will provide the impetus for new experimental approaches. Undoubtedly, systemic radionuclides for the treatment or palliation of bony metastases will play a prominent role in these new treatment configurations.
References

1. Lote K, Walloe A, Bjersand A: Bone metastases. Prognosis, diagnosis, and treatment. Acta Radiologica Oncology 1986;25:227-232.
2. Garrett IR: Bone destruction in cancer. Semin Oncol 1993;20(3 Suppl 2):4-9.
3. Nielsen OS, Munro AJ, Tannock IF: Bone metastases: Pathophysiology and management policy. J Clin Oncol 1991;9:509-524.
4. Tong D, Gillick L, Hendrickson FR: The palliation of symptomatic osseous metastases: Final results of the Radiation Therapy Oncology Group. Cancer 1982;50:893-899.
5. Delcos L: New and old concepts in radiotherapeutic treatment. Int J Radiat Oncol Biol Phys 1976;1:1217-1220.
6. Garments CJ, Chu FC: The effectiveness of radiation therapy in the treatment of bone metastases from breast cancer. Radiology 1978;126:235-237.
7. Allen KL, Johnson TW, Hibbs GG: Effective bone palliation as related to various treatment regimens. Cancer 1976;37:984-987.
8. Hoskin PJ: Scientific and clinical aspects of radiotherapy in the relief of bone pain. Cancer Surv 1988;7:69-86.
9. Rogers MJ, Watts DJ, Russell RG: Overview of bisphosphonates. Cancer 1997;80(Suppl 8):1652-1657.
10. Hortobagyi GN, Theriault RL, Porter L, et al: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases: Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 1996;335:1785-1791.
11. Leurs K: Bisphosphonates and breast carcinoma. Cancer 1997;80(Suppl 8):1668-1673.
12. Berenson J, Lichtenstein A, Porter L, et al: Long-term pamidronate disodium therapy leads to a reduction in skeletal related episodes (SREs) in stage III multiple myeloma patients and an improvement in survival in those on salvage therapy. Blood 1999;89:442a.
13. Adamis P, Salvagno G, Guarrera G, et al: Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. J Urol 1985;134:1152-1154.
14. Smith JA Jr: Palliation of painful bone metastases from prostate cancer using sodium etidronate: Results of a randomized, prospective, double-blind, placebo-controlled study. J Urol 1989;141:85-87.
15. Tannock IF, Osoba D, Stockler MR, et al: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: A Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-1764.
16. Mertens WC, Reid RH, Porter AT, et al: Recent advances in radionuclide therapy of bone metastases, in Freeman LM (ed): Nuclear Medicine Annual 1992. New York, Raven Press, 1992, pp 69-89.
17. Mertens WC: Radionuclide therapy of bone metastases: Prospects for enhancement of therapeutic efficacy. Semin Oncol 1993;20(3 Suppl 2):49-55.
18. Friedell HL, Storaasli JP: The use of radioactive phosphorus in the treatment of carcinoma of the breast with widespread metastases to the bone. Am J Radiol 1950;64:559-575.
19. Silberstein EB: The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. Semin Oncol 1993;20(3 Suppl 2):10-21.
20. Van Nostrand D, Silberstein EB: Therapeutic uses of 32P, in Freeman LM, Weissman HS (eds): Nuclear Medicine Annual 1985. New York, Raven Press, 1985, pp 289-344.
21. Blake GM, Gray JM, Zivanovic MA, et al: Strontium-89 radionuclide therapy: A dosimetric study using impulse response function analysis. Br J Radiol 1987;60:685-692.
22. 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.
23. Schraml FV, Parr LF, Ghurani S, et al: Autopsy of a cadaver containing strontium-89-chloride. J Nucl Med 1997;38:380-382.
24. Ben-Josef E, Lucas DR, Vasan S, et al: Selective accumulation of strontium-89 in metastatic deposits in bone: Radio-histological correlation. Nucl Med Commun 1985;16:457-463.
25. Breen SL, Powe JE, Porter AT: Dose estimation in strontium-89 radiotherapy of metastatic prostate carcinoma. J Nucl Med 1992;33:1316-1322.
26. Buchali K, Correns HJ, Schuerer M, et al: Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. Eur J Nucl Med 1988;14:349-351.
27. 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.
28. Correns HJ, Mebel M, Buchali K, et al: Strontium 89 therapy of bone metastases of carcinoma of the prostate gland. Eur J Nucl Med 1979;4:33-35.
29. 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.
30. Firisian N, Mellin P, 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.
31. Silverstein EB, Williams C: Strontium-89 therapy for the pain of osseous metastases. J Nucl Med 1985;26:340-348.
32. Robinson RG, Spicer JA, Preston DF, et al: Treatment of metastatic bone pain with strontium-89. International Journal of Radiation Applications and Instrumentation. Part B. Nuclear Medicine and Biology 1987;14:219-222.
33. Tennvall J, Darte L, Lundgren R, et al: Palliation of multiple bone metastases from prostatic carcinoma with strontium-89. Acta Oncol
34. Reid RH, Powe JE, Porter AT, et al: Strontium-89 therapy of multiple painful bone metastases in prostatic and breast carcinoma. J Nucl Med 1990;31:804. Abstract.
35. McEwan AJB, Porter AT, Venner PM, et al: An evaluation of the safety and efficacy of treatment with strontium-89 in patients who have previously received wide field radiotherapy. Antibody Immunoconjugates and Radiopharmaceuticals 1990;3:91-98.
36. 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.
37. Quilty PM, Kirk D, Bolger JJ, et al: A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol 1994;31:33-40.
38. Kloiber R, Molnar CP, Barnes M: Sr-89 therapy for metastatic bone disease: Scintigraphic and radiographic follow-up. Radiology 1987;163:719-723.
39. Papaefofanis FJ: Quantitation of biochemical markers of bone resorption following strontium-89-chloride therapy for metastatic prostatic carcinoma. J Nucl Med 1997;38:1175-1179.
40. Kelly WK, Scher HI, Mazumdar M, et al: Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. J Clin Oncol 1993;11:607-615.
41. McGowan D: Metastatic prostate cancer: Quality of life and cost considerations. Oncology 1994;8(Suppl):30-32.
42. Turner JH, Claringbold PG, Hetherington EL, et al: A phase I study of samarium-153 ethylenediaminetetramethylene phosphonate therapy for disseminated skeletal metastases. J Clin Oncol 1989;7:1926-1931.
43. Bayouth JE, Macey DJ, Kasi LP, et al: Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. J Nucl Med 1994;35:63-69.
44. Collins C, Eary JF, Donaldson G, et al: Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: A phase II trial. J Nucl Med 1993;34:1839-1844.
45. Alberts AS, Smit BJ, Louw WK, et al: Dose response relationship and multiple dose efficacy and toxicity of samarium-153-EDTMP in metastatic cancer to bone. Radiother Oncol 1997;43:175-179.
46. Samarium-153 lexidronam for painful bone metastases. Med Lett Drugs Ther 1997;39:83-84.
47. Maxon HR 3d, Schroder LE, Hertzberg VS, et al: Rhenium-188(Sn)HEDP for treatment of pain in patients with prostatic carcinoma metastatic to bone: A dose-response relationship? Am J Clin Oncol 1993;16:238-242.
48. Maxon HR 3d, Schroder LE, Thomas SR, et al: Rhenium-188(Sn)HEDP for treatment of painful bone metastases: Initial clinical experience in 20 patients with hormone-resistant prostate cancer. Radiology 1990;176:155-159.
49. Mertens WC, Porter AT, Reid RH, et al: Rhenium-188(Sn)HEDP for treatment of painful osseous metastases. J Nucl Med 1998;39:659-663.
50. Mertens WC, Stitt L, Porter AT: Strontium 89 therapy and relief of pain in patients with prostatic carcinoma metastatic to bone: A dose-response relationship? Am J Clin Oncol 1993;16:238-242.
51. Turner JH, Claringbold PG, Manning LS, et al: Radiopharmaceutical therapy of 5733 murine myeloma by sequential treatment with samarium-153 ethylenediaminetetramethylene phosphonate, melphalan, and bone marrow transplantation. J Natl Cancer Inst 1993;85:1508-1513.
52. Mertens WC, Porter AT, Reid RH, et al: Strontium-89 and low-dose infusion cisplatin for patients with hormone refractory prostate carcinoma metastatic to bone: A preliminary report. J Nucl Med 1992;33:1437-1443.
53. Tu SM, Delpassand ES, Jones D, et al: Strontium-89 combined with doxorubicin in the treatment of patients with androgen-independent prostate cancer. Urol Oncol 1996;2:191-197.
54. Torti FM, Aston D, Lum BL, et al: Weekly doxorubicin in endocrine-refractory carcinoma of the prostate. J Clin Oncol 1983;1:477-482.
55. Dahut W, Hoffmeister K, Chen A, et al: Weekly doxorubicin in hormone-refractory carcinoma of the prostate after hormone-refractory prostate cancer. Proc Annu Meet Am Soc Clin Oncol 1998;17:A329. Abstract.
56. Wehbe T, Akerley W, Stein B, et al: Strontium-89, estramustine, and vinblastine (SEV) in hormone refractory prostate carcinoma (HRPC): Concurrent chemoradiotherapy. Proc Annu Meet Am Soc Clin Oncol 1997;16: A1110. Abstract.