The Management of Painful Bone Metastases with an Emphasis on Radionuclide Therapy

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Objective: This review provides an update on the management of painful bone metastases, with an emphasis on radionuclide therapy, and introduces oligometastases and quantitative imaging evaluations for clinical trials.

Methods: The current use of radionuclides, alone and in combination with chemotherapy and radiation therapy for painful bone metastases, is discussed, including toxicity, cost and overall outcomes.

Results: Radionuclide therapy is shown to be a useful and cost-effective means of alleviating bone pain in metastatic disease and may be more effective when combined with chemotherapy, bisphosphonates and radiation therapy. Early use of radionuclides in pain therapy may limit cancer progression by inhibiting oligometastases development. Thus, radionuclides can significantly decrease patient morbidity, prolong patient survival, and may decrease the occurrence of new bone metastases.

Conclusion: Palliative pain therapy is critical for effectively managing bone metastases, with treatment options including analgesics, external beam radiotherapy, chemotherapy and radionuclides. Radionuclide therapy is underutilized. Recent studies using radionuclides with chemotherapy and bisphosponates, or using newer radionuclides or combinations of radionuclides and treatment paradigms (e.g., higher activities, repetitive or cyclic administration, chemo sensitization, chemo supplementation), are encouraging. A comprehensive, inter-disciplinary clinical approach is needed. Clinical collaborations will optimize radionuclide therapy for pain palliation and increase awareness of its benefits.

Key words: cancer ■ bone ■ metastasis ■ pain

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INTRODUCTION

Patients with bone metastasis commonly endure severe bone pain, especially in the advanced stages of breast and prostate cancer. Treatment for this pain continues to be a major therapeutic challenge, and its alleviation is crucial to improving patient quality of life.[1] Increased care requirements and treatment costs associated with bone pain also present a significantly increased financial burden for both patients and caregivers. Unfortunately, skeletal metastases are a major cause of morbidity and mortality in 65–75% of advanced breast and prostate cancer patients, and in 15–30% of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid and kidney.[2-4] Moreover, bone is commonly the first site of relapse (e.g., in ~46% of breast cancer patients)[5] and sometimes the first and only site of metastasis in patients with advanced prostate cancer.[3] Each year, about 200,000 new cases of painful metastatic bone disease are diagnosed in the United States, with 73% of these attributable to breast, prostate and lung cancers.[6,7]

Palliative treatment in cancer-induced bone disease normally progresses from nonsteroidal analgesics to opioids and chemo- or hormonal therapy, as well as radiation treatment using external-beam, sealed or unsealed sources. After the initial standard palliative treatment, about 50% of these patients continue to have substantial bone pain.[8] Bone-targeted radionuclide therapy has proven to be an effective alternative and is often less expensive and free of the side effects associated with other treatments.[9-12] However, despite proven palliative efficacy[12] (Table 1),[13-31] radionuclide therapy continues to be underutilized, being called upon only in the late phase of disease and primarily for the treatment of pain from advanced bone metastases. Reasons for this include lack of awareness about this modality, lack resources in small community hospitals as well as misconceptions about the toxicity and expense of therapeutic radionuclides.

More than 15 years ago, an improved median survival of 19 months was noted in advanced prostate and breast cancer patients due to advances in early diagnosis and better treatment options in metastatic disease.[32,33]

More recently, reported survival for breast and prostate cancer patients with bony metastasis and undergoing bisphosphonate therapy was 27 and 17 months, respectively.[34] Although limited progress has been made in treating advanced cancer in this patient population, more affordable, effective, readily available, conveniently administered and less toxic treatments such as radionuclide therapy may be beneficial. Advantages of systemic radionuclides include addressing all involved osseous sites simultaneously, while selective absorption into bone metastases limits the dose to normal tissue and increases the therapeutic ratio. This makes systemic radionuclides appealing in situations when external-beam therapy options have been exhausted and normal tissue tolerance has been reached. Administration as a single intravenous injection in an outpatient setting is a further advantage. Furthermore, use of radionuclides early in disease management can complement or delay the use of the other palliative approaches for bone pain, such as external beam radiotherapy, chemo- or hormonal therapy, bisphosphonates or analgesics, and may be tumoricidal or tumoristatic as well.

Unsealed radiotherapy, also called "systemic radiotherapy," has been used for six decades to treat painful bone metastases. Radioactive isotopes of phosphorus (^{32}P) and strontium (^{89}Sr) were the first radiopharmaceuticals approved for this purpose, since these elements preferentially incorporate into the sites of bone metastases at rates 2–25 times greater than in normal bone.[35,36] The clinical use of ^{32}P has decreased since the 1980s in favor of ^{89}Sr and newer alternatives, due in part to higher myelotoxicity from higher-energy decay and longer

Table 1. Results of clinical studies on radionuclide therapy with in the last decade

Reference	Year	Dosage MBq	Sample "n"	Relief %	Repetition
^{32}P					
Nair[13]	1999	440 (oral)	16	87.5	—
Shah Syed et al.[14**]	1999	185 (IV)	20	Not mentioned	Yes (++)
Rao and Radhamohan[15*]	2001	185 (oral)	15	80	Yes (+)
Silberstein et al.[16] (meta-analysis)	1992	Various	322 (BC) 444 (PC)	84 (BC) 77 (PC)	Yes
^{153}Sm					
Anderson et al.[17]	2002	30/kg	30	75–100	—
Dolezal[18]	2000	39/kg	33	74 (at 1 m)	
Tian et al.[19***]	1999	18.5 or 37/kg	105	84	
Serafini et al.[20***]	1998	18.5 or 37/kg	118	62-72	—
Olea et al.[21***]	2000	18.5–55.5/kg	417	73	
^{188}Re					
Palmedo et al.[22**]	2000	2,900 (Avg)	22	64	—
Zhang et al.[23**]	2003	2,875 (Avg)	30	80 (46 CR)	—
^{186}Re					
Sciuto et al.[24]	2000	1,406	60	80 (31 CR; 6m)	
Palmedo et al.[25]	1996	1,295	30	70	+++
^{89}Sr					
Quilty et al.[26]	1994	200	284	66	
Kasalicky and Krajska[27]	1998	150	118	55 (3 yr)	Yes (++++)
Kraeber-Bodere et al.[28]	2000	150	94	78 (31 CR)	Yes (+++)
Turner et al.[29]	2001	150	93	63	—
Ashayeri et al.[30]	2002	150	41	>67	—
^{117m}Sn					
Srivastava et al.[31***]	1998	2.64–10.58	47	75 (30 CR)	—

* Performed with androgen potentiation; ** Had >1 study arm; *** Study had >1 dosage group; CR: complete response; PR: partial response; BC: breast cancer primary; PC: prostate cancer primary; Avg: average; + – ++++: A relative scale used by the individual authors; Adopted from Damerla et al.[12]

range in tissue. However, ^{32}P is the only radiopharmaceutical available as an oral formulation, providing distinct advantages in cost and convenience, especially in developing nations. Newer beta-emitting isotopes for palliation of cancer-induced bone pain are administered using multidentate chelate complexes of samarium [^{153}Sm], rhenium (^{186}Re or ^{188}Re), and tin (^{117m}Sn); ^{153}Sm was approved by the FDA in 1997 for treatment of painful bone metastases, while the others remain experimental. All of the newer beta-emitting radiopharmaceuticals (including ^{89}Sr, approved by the FDA in 1995) have comparable decay energies (0.22–0.58 MeV) and maximum range in tissue (3.4–6.7 mm).[37] ^{117m}Sn is a promising therapeutic nuclide with lower maximum decay energy (see discussion below) and a maximum range in tissue of 0.3 mm, postulated to reduce bone marrow toxicity.[31,38] A variety of other experimental radionuclides, designed to relieve bone pain while minimizing marrow suppression (e.g., ^{33}P, ^{175}Yb, ^{177}Lu), are in preclinical development but have not yet been tested in humans and will not be discussed further.[39-42] Finally, a small phase-1 study of an alpha-emitting radium isotope (^{233}Ra) showed encouraging results[43] but will not be discussed further due to its limited clinical history.

Following intravenous or oral administration, these new radionuclides have preferential affinity to diseased bone sites. Bone marrow exposure dose is directly proportional to the bone-absorbed dose of the radionuclide.[44-49] Tumoricidal efficacy, duration of pain palliation, toxicities, cost and potential for repetitive administration can vary with each radionuclide.[50] Selection of a radionuclide depends on each patient's anticipated diagnostic and therapeutic need.

In this update, we will highlight uses of radionuclide therapy for the management of metastatic bone pain. In addition, we will report some of the exciting newer developments in radionuclide therapy. Optimizing the use of available radionuclide therapies could help minimize patient toxicity and maximize therapeutic benefits, thereby contributing to better patient outcomes and quality of life.

Radionuclides in Cancer Bone Pain

The responses and toxicities of radiopharmaceuticals used for pain palliation are described. Myelosuppression is the most common adverse reaction to radionuclides, as documented in both preclinical and clinical trials. Grade-2 or -3 hematological toxicity is very common, especially affecting platelets. Dafermou et al. demonstrated such toxicity in 25.5% of all cases and in 38.9% of retreatments.[10] Bleeding fatalities associated with rare life-threatening thrombocytopenia and leucopenia have also been reported.[51,52]

Phosphorus-32 Orthophosphate

Radioactive phosphorous with or without testosterone was used as early as 1958 in the treatment of metastatic breast and prostate cancers.[12,53] The ^{32}P radionuclide produces ~60–90% pain reduction.[13] Since 1939, radioactive phosphorus has been used to treat myeloproliferative and lymphoproliferative diseases.[54] However, its use has been limited due to its strong incorporation into various phosphate-containing intracellular constituents, including DNA and RNA, in addition to bone hydroxyapatite per se. Dose-limiting myelosuppression with reversible pancytopenia is the most common disadvantage, occurring maximally 5–6 weeks after administration.[55] A single death has been reported secondary to ^{32}P-related myelosuppression.[56] The consequences of its incorporation into bone marrow intracellular constituents, such as pancytopenia, are well known theoretically but are not well-substantiated by peer-reviewed data.[57,58] In a study of 31 patients with skeletal metastases, this radionuclide, administered orally, was similar in effect and far less expensive than intravenously administered ^{89}Sr.[13] Hence, in underdeveloped countries with limited resources, it is economical for enteral administration as there is no need for added sterility requirements for intravenous (IV) administration of other radionuclides. However, the total dose and kinetics of radioisotope excretion vary with oral administration, and extra care should be taken to avoid unnecessary radioactive exposure to caregivers, hospital staff and subsequent users of toilet facilities.

Strontium-89 Chloride

Due to the chemical similarity between strontium and calcium, ^{89}Sr (Metastron®) is preferentially retained in the skeleton, especially in areas of rapid osteoblastic activity and bone formation associated with tumor-mediated bone remodeling (by a factor of about 10 times versus healthy bone).[50,59] Moreover, newer therapeutic nuclides, including ^{89}Sr, do not readily incorporate into the intracellular constituents of marrow (as ^{32}P does), effectively concentrating radioactive exposure to regions immediately surrounding sites of bone formation. A review of published data over the last decade shows pain relief in 55–78% of patients receiving ≥1 IV dose of strontium-89 chloride (Table 1). In one study directly comparing the efficacy of oral ^{32}P to IV ^{89}Sr, severe myelotoxicity was not observed in any subject.[13] Serafini[56] has reported that the overall incidence of marrow depression with strontium use was ~6%, whereas the pain flare response was ~10%.[56] Myelosuppression is temporary and typically occurs <6 weeks after therapy. Recovery is slow over the next six weeks. After their evaluation of ^{89}Sr and ^{186}Re-HEDP (discussed below) in metastatic breast cancer, Sciuto et al.[60] proposed that ^{89}Sr should be the preferred radionuclide in patients with moderate pain, good performance status, longer life expectancy and higher marrow reserve.[60]

Samarium-153 EDTMP

^{153}Sm is administered with a large excess of a bone-targeting phosphonate-chelating agent [lexidronam or ethylenediaminetetramethylenephosphonate (EDTMP)] to enable delivery of injected ^{153}Sm to areas of bone formation. Absorption of this radiopharmaceutical is 17 times faster in lesions versus normal bone, and due to rapid renal clearance nonosseous radioactive exposure is low.[37,61] Efficient excretion of ^{153}Sm-EDTMP plus slow destruction of the complex outside the bone microenvironment prevent significant redistribution following dose, possibly explaining the apparently longer-term benefits from ^{89}Sr, which is freely redistributed at the prevailing rate of bone remodeling.[37] 153Sm-EDTMP (Quadramet®) is most widely used in the United States to relieve pain from bone metastasis, with palliation occurring in 65–80% of patients with better overall response rates at higher doses in early phase-1/2 studies.[62,63] Symptomatic response is typically rapid, occurring within one week of administration and frequently within 48 hours. Bone marrow suppression is generally mild, reversible and not associated with grade-4 toxicity. In regard to the use of the radioisotope ^{153}Sm, Collins et al.[64] have observed that its use results in a ~40–50% decrease in the white cell and platelet count by the second week posttherapy and then returns to normal by the fifth or sixth week posttherapy.[64] Myelosuppression is highly present from higher-administered activities, with no associated increases in pain relief.[64] This radionuclide has been associated with pain flare rates comparable to that of ^{89}Sr.[56] Treatment has been repeated safely for recurrent symptoms, and it appears to be well tolerated.[56]

Rhenium-186/-188 Etidronates

^{186}Re and ^{188}Re are investigational pharmaceuticals for bone pain palliation in the United States and are delivered with a stable bone avid chelate [hydroxyethylidene diphosphonate (HEDP)]. These isotopes appear to cause only minimal myelosuppression but seem to have a higher incidence of pain flare response up to 50% in one study.[22] Another study demonstrated an overall pain palliation of 92% in breast cancer patients, with significantly faster pain relief and marrow recovery for patients treated with ^{186}Re versus ^{89}Sr.[60] These results can be partially understood as the result of short physical half-life and high dose rates, which ultimately predict a rapid symptom response. Consequently, the use of ^{186}Re-HEDP may be most appropriate in patients already somewhat compromised in marrow function and life expectancy, who have an urgent need for palliation.

Tin-117m DTPA

Its modes of radioactive decay and bone deposition make the investigational radionuclide ^{117m}Sn unique among those radionuclide therapies discussed herein. The chelating complex with tin [diethylenetriaminepentaacetic acid (DTPA)] is soluble in vivo but has little affinity for bone, serving only to deliver the chelated ^{117m}Sn to bone tissue, whereupon it is released, permanently adhering to the bone surface.[37] The decay of ^{117m}Sn to the nonmetastable isomer ^{117}Sn occurs by an internal conversion process, in which the energy stored in ^{117m}Sn is released by ejection of so-called 'conversion electrons.' These ejected particles have 1.7–5.5 times lower energy than the other radiopharmaceuticals discussed, resulting in better isolation of decay energy to bone tumor areas[38] and theoretically enabling much higher administered doses due to better targeting.[65] Unfortunately, published work on this nuclide has slowed, purportedly due to "economic factors," halting developmental efforts.[58]

DISCUSSION

Advances in therapies are described, including their costs, efficacy of pain management and ability to limit the spread of disease.

Expenses and Economics

The management of cancer bone pain requires a multimodality approach. External-beam radiation is one commonly used choice. Pain relief can be achieved by both hemibody irradiation (HBR) and local-field radiotherapy. However, HBR is associated with significant myelotoxicity, involves complicated patient management and is expensive. Overall pain relief of 60–90% can be achieved with radiotherapy,[66-70] which is comparable to radionuclides. The degree of palliation achieved by external radiation therapy treatment versus radionuclide-based therapy was similar in a recent Cochrane study.[71] An earlier study by Quilty et al.[26] also demonstrated similar findings.

At initial metastatic presentation, prolongation of retreatment intervals was noted using simultaneous radionuclides and external radiation, which is cost effective.[72] Radionuclides may lower costs overall if used early for potential cure. Compared to the average monthly costs for opioid analgesics or external radiation therapy treatments, Macklis and Lasher[73] have demonstrated that the use of ^{89}Sr or ^{153}Sm-EDTMP is less expensive. A cost savings of ~$6,725 per patient per annum was achieved with the use of radionuclides instead of opioid analgesics for cancer bone pain in another study.[74]

There are several other advantages to using radionuclides instead of external radiotherapy. When using radionuclides, there is no need for special, costly equipment. Radionuclide therapy can be performed in any hospital or outpatient-based clinic following simple radioactive precautions. While treating symptomatic osteoblastic bone lesions, asymptomatic osseous metastasic lesions can be simultaneously ablated with radionuclide therapy. This results in an extra cost savings as additional radiation therapy is avoided later, since it is common for patients undergoing targeted radiotherapy to experience pain at

previously asymptomatic sites, necessitating further sessions of radiotherapy to the new sites of discomfort.

In some emergency conditions, external radiation therapy is the preferred treatment. Comparing costs is appropriate under those circumstances. Radionuclide therapy is not an effective therapy to provide relief or reduce adverse skeletal events in a timely fashion during emergencies, such as spinal cord compression by epidural masses, soft-tissue mass nerve compression or entrapment, or impending or already evident pathologic bone fractures.[58] Analgesic therapy is also not a treatment of choice for such emergencies. There is no debate regarding cost or appropriateness of the treatment where palliative external-beam radiotherapy or surgery is the best option for the patient.

Efficacy of Pain Management

Efficacy of pain management can be achieved in several ways. The aspects of care for the patient undergoing routine radionuclide therapy that include pretreatment assessment, underlying principles, procedure guidelines, practical aspects and recordkeeping have been well reviewed elsewhere.[50,58,75]

Duration of Response

After a single radionuclide dose, the duration of response was noted to be ~4–15 months for ^{89}Sr, [76] ~1–11 months for ^{153}Sm, [77] ~1–12 months for ^{186}Re [64] and ~4–12 weeks for ^{32}P.[14]

If bone marrow function and blood parameters remain within recommended guidelines, radionuclide treatments may be repeated at ~8–12 week intervals.[58] In the evaluation of retreatments, the duration of response for palliation after the third retreatment using ^{89}Sr was ~3–4.5 months and after fifth treatment it was ~4.2–5 months.[27]

Within the last decade, several published clinical studies using radionuclide therapy with typical palliative outcomes (Table 1) found excellent pain relief with unsealed source radiotherapy. However, Papatheofanis, who surveyed 100 board-certified medical oncologists, reported that medical oncologists underutilize radionuclide therapy in pain palliation compared to oral opiod analgesics.[78] Hence, systemic radionuclides are perceived as suboptimal for pain palliation, contrary to the broad-based clinical evidence. This suggests that radionuclides may offer greater palliative and cost benefits, in comparison to the other presented options, even to patients with only a few sites of bone metastases.[74,78] In contrast, opioids may improve patient quality of life but provide only temporary palliative pain relief. However, a single radionuclide dose provides long-lasting pain relief with the potential of treating the underlying disease, as described below.

Limiting Spread of Disease

Tumors with initially localized disease and low metastatic potential traverse to an advanced disease stage with highly dysregulated cells and highly probable invasion. A transitional stage of "oligometastases" lies in between these two extremes. The cancer cells escape the primary tumor site in this stage, until these metastatic cells become clinically apparent but remain in a limited scope amenable to local treatment strategies. More succinctly, the state of oligometastasis begins with an established tumor and ends with overt untreatable metastasis. Instead of considering mutually exclusive conditions of "localized primary tumor" versus "metastatic tumor," a conceptual focus on the transitional state of oligometastases is useful when considering how to optimally manage or prevent metastatic bone disease. For example, if one assumes that removal or ablation of the primary tumor is microscopically incomplete or occurs after at least some malignant cells have been released, a goal of preventing disseminated cells from becoming clinically damaging neoplasms could provide optimal clinical benefits for the majority of patients. This strategy could include targeting the circulating cancer cells, preventing abnormal bone destruction with antiresorptive agents or vitamin-D analogues, or preventing vascularization of oligometastatic lesions with angiogenesis inhibitors, to name a few options.

This focus on oligometastasis may also aid in understanding emerging concepts in cancer biology and treatment that emphasize the importance of aggressive early treatment of metastases. Hellman and Weichselbaum[79] have reported that in the presence of oligometastatic deposits, underlying disease can be aggressively approached. Patients with advanced prostate cancer and higher numbers of lesions visible on bone scans had shorter survival.[80,81] One study reported that patients with ≤5 metastatic bone lesions had significantly better long-term survival compared to those with >5 lesions.[82] Improvement in survival and quality of life can occur with decreased skeletal tumor burden by any treatment. The reasons for this sharp contrast in survival are not clear; some factors, such as TGF-β cytokine or growth factor dysregulation[83] or some other unknown disruptions, could allow the growth of more aggressive cancer cells and stop the advancement of metastatic disease to >5 metastatic lesions. Hence, early and aggressive radiation therapy of metastatic disease with additional conformal radiotherapy ideally positioned to treat any pelvic girdle- or lumbar spine-confined oligometastases in prostate cancer, with additional or conjoint surgery or radio surgery, is warranted.[82] It is also possible that patients with ≥1 identifiable lesion also have other smaller coexisting oligometastases that are not detectable by current imaging technology[84] and, hence, not treatable by surgery or external radiation therapy.

In cases of low tumor burden, we propose that radio-

nuclides may be the best available option to effectively target both gross and microscopic tumor sources, including symptomatic and nonsymptomatic metastases. Indeed, for patients with early skeletal invasion, systemic radionuclides could play a key role due to their high degree of specificity for the abnormal bone remodeling associated with osseous tumor growth. In this context, ^{89}Sr might be the ideal "early treatment" radionuclide because it alone has the capacity for redistribution following an initial dose, thus providing a longer-lasting antitumor effect while remaining highly bone specific. This hypothesis might partially explain the longer lasting palliative effects of this radionuclide.[85,86] Moreover, the measured reduction in serum prostate-specific antigen (PSA) and bone turnover biomarkers following ^{89}Sr administration is indicative of a (possibly causative) tumoricidal effect.[85,87] Of course, the benefits of faster effect and minimized toxicity in the newer radionuclides should be carefully weighed, along with the characteristic that redosing with these radiopharmaceuticals would have a similar longevity of effect (but with additional cost). Further exploration of both tumor and bone turnover markers in response to various radiopharmaceutical regimens is clearly warranted in order to elucidate the physical and cellular mechanisms of pain palliation, as well as the potential antitumor effects in vivo. Improvements in these markers and quantitative imaging techniques could ultimately provide a useful means of personalized medicine in a group of patients with an urgent need for optimally effective treatments.

According to Resche,[88] breast cancer patients with painful bone metastases treated aggressively with ^{153}Sm-EDTMP had longer survival. ^{153}Sm-EDTMP played an important role in the prolongation of life and in symptomatic relief of bone pain in prostate cancer patients as well, per Tu et al.[89] The beneficial effects of early radionuclide therapy on pain and disease progression for prostate or breast cancer patients, including patients with only a few sites of involvement, have been documented by McEwan[90] and Turner and Claringbold.[91] Thus, as a low-risk and cost-effective method for treating oligometastases, the early use of therapeutic radionuclides should be strongly considered.

The goals of further research should be improving survival and disease progression outcomes. Selection of the "ideal" radiopharmaceutical for tumoricidal or tumoristatic purposes in given individual clinical circumstances should be a priority. Another area where more research is needed is determining the "stage" or "extent/aggressiveness of disease." As an example, fluorodeoxyglucose whole-body PET scans may be used to grade the biologic activity of metastatic lesions in bone via tumor to background (T/B) ratios.[92] Alternatively, imaging studies using gamma-emitting isotopes (e.g., ^{99m}Tc bone scintigraphy) could be used to assess the extent of disease (EOD) as number of lesions[80] "percentage of positive area on a bone scan"[93] or the "bone scan index,"[94] as developed at various institutions. Uptake and distribution of isotopic tracers are also strongly reflective of EOD and the associated elevations in bone turnover,[95,96] potentially providing a path towards a clinically useful urinary test for tumor-associated changes in bone remodeling.[97] Serum and urinary markers of bone turnover are also useful in this context, provided that adequate numbers of subjects are studied to mitigate high natural intra- and intersubject variability.[98,99] Feasibly then, the biologic activity of earlier oligometastatic bone lesions can be compared to the later-appearing distant metastasis in visceral or bony tissues, especially with breast and lung cancer. These techniques could also be developed as clinical tools, where changes in EOD and isotopic markers could be used to select and optimize individual or combination radiopharmaceutical(s), or combined modality therapy(ies) for oligometastatic disease.

Advances in Treatment

Autologous peripheral stem-cell infusion prior to high activities of radionuclides with rescue from myelo-suppression appears promising. ^{186}Re-HEDP (5,000 MB) in hormone-resistant prostate cancer patients[100] and ^{153}Sm-EDTMP (1,110 Mbq/kg) in bone-metastatic sarcoma patients[17] were used with this technique in phase-1 clinical trials. Using a similar technique, phase-2 clinical trails are in progress.[84] Radionuclide effectiveness can be improved significantly by this technique. However, good working cooperation between medical oncologists and nuclear medicine physicians is required.

When using gamma-emitting isotopes, a "whole-body dose," as opposed to a "fixed activity," may be prescribed in conjunction with the stem-cell infusion (as previously described) in treating refractory neuroblastoma patients with 131 I-MIBG.[101] Less bone marrow and hematological toxicity was noted with ^{186}Re-HEDP using this technique and may prove better than the "activity escalation" method.[102]

Size of metastatic lesions and radionuclide pain response are inversely proportional. However, the number of metastases and radionuclide uptake are independent.[84,103] Limited range of beta particles and the radiation dose gradient across the layers of osteoblastic tumor-infiltrated bone can explain this inverse relationship. Small lesions can be ablated better.[84] Ablation of the outermost layers of tumor in large lesions may be limited by decay of the incorporated isotope and by tumor distance from the beta particle source. In this situation, frequent renewal of the radioactive source, use of higher activities or concurrent chemosensitization is needed. Thus, fractionated repeated radionuclide doses are needed, and further evaluation in pilot studies and perhaps in randomized clinical trials, as appropriate, are also necessary.[84]

To augment uptake of ^{32}P radionuclide by bony metastases, hormonal agents such as PTH and testoster-

one have been used successfully. In patients with severe symptoms from late uncontrollable disease in metastatic prostate cancer, testosterone-primed ^{32}P administration has been found to be quite effective.[35] According to Silberstein,[57,58] use of androgens in prostate cancer is inappropriate because androgens stimulate cancer growth, and the response rates to ^{32}P administration are not different with or without androgens. In a separate small pilot study with androgen priming, Rao et al.[15] reported that 100% of a subset of breast cancer patients afflicted with painful bone metastases achieved pain relief. However, the response rate in prostate cancer patients in the same study appears to support Silberstein's assertion that androgen priming does not improve the response rate (75–80%) without androgens.[57,58] Androgens in treating bone metastases from breast, lung or other cancers may be helpful, but their use in prostate cancer metastases may be clinically questionable.

Combined radionuclide therapy and chemotherapy improves efficacy of pain management. Systemic radionuclide therapy with ^{89}Sr combined with cytotoxic drug therapy had greater efficacy than radionuclide therapy alone.[84] It was shown in a randomized trial of 70 patients with prostate cancer that patients receiving cisplatin and ^{89}Sr had 91% overall pain relief, compared to 63% in the arm with ^{89}Sr alone.[104,105] There are other studies using concurrent administration of carboplatin, doxorubicin or the estramustine/vinblastine combination with ^{89}Sr in metastatic prostate cancer patients.[89]

The role of bisphosphonates in cancer bone pain is promising. In both benign and malignant bone disease, bisphosphonates preferentially inhibit bone osteoclastic processes and reduce fracture-related skeletal events. Bisphosphonate agents have reduced skeletal events and bone pain in metastatic renal cancer, breast cancer, prostate cancer and multiple myeloma.[4,98,106-108] In addition to this, there are ongoing studies of whether bisphosphonates offer an antitumor or bone-protecting role as adjuvant therapies.[109] However, high drug costs and potentially severe side effects[110] might prevent widespread adjuvant use of this therapy without a strong protective effect. Combining bisphosphonate therapy with other modalities could provide additive benefits. This was indicated by Soerdjbalie-Maikoe et al.[111] who demonstrated a reduction in the incidence of spinal cord compression in hormone-resistant prostate cancer patients who received ^{89}Sr with the bisphosphonate olpadronate.[111] Finally, the role of bisphosphonates with radionuclides remains to be determined in regard to their optimal dose, their use before clinical metastatic disease, the appropriate combinations and dose regimens of radionuclide and bisphosphonates, etc.

SUMMARY AND CONCLUSIONS

Radionuclide therapy offers significant cost-effective palliative pain relief from metastatic bone disease. However, some areas for its use need further explanation and attention. Some of these include:

a) **Treatment response.** Researchers need to develop methods to predict responders from nonresponders prior to therapy.
b) **Selection of an agent.** ^{89}Sr, ^{153}Sm, ^{186}Re and ^{32}P appear to have comparable benefits in terms of pain palliation and so there is a need to clarify the criteria for the agent of choice in individual patients and hospital settings based on solid evidence.
c) **Need for clinical trials in the "oligometastatic" stages.** The hypothesis that administering radionuclides will improve survival if they are used in the oligometastatic stages with prophylactic stem-cell support, chemo- or hormonal therapy, or at higher dosages for patients with limited early bone metastases need to be vigorously tested in clinical trials.
d) **Need to improve underutilization of radionuclide therapy.** There is a need to improve the awareness among oncologists and other cancer caregivers of radionuclide therapy; access to clinical facilities for nuclear medicine physicians also needs to be improved. Another step that can overcome underutilization of radionuclide therapy is to encourage nuclear medicine physicians to participate in the daily clinical care of oncology patients, especially with treatment planning for pain and for pre- and posttreatment care. Through these collaborations, medical and radiation oncologists will be better exposed to the benefits of radionuclide treatments while sharing their patient care skills with nuclear medicine practitioners.
e) **Education about the toxicity profile.** As resources are limited for healthcare, the cost-effective treatment modality of radionuclides should not remain underutilized. As Damerla et al. noted,

   Prudent patient selection, vigilant patient pre-and post-treatment assessments, modest investments in added patient care training for nuclear medicine physicians, and the early publication of data from clinical studies will contribute significantly to allaying the concerns of oncologists and health care policy makers regarding radionuclide toxicity.[12]

f) **Staging and customizing treatment.** Determining the "stage" or EOD and/or aggressiveness of the disease in individual patients and then "tailoring" treatments to individual patients needs to be further investigated and developed.

Cancer-related bone pain significantly contributes to morbidity and the loss of quality of life for patients; it continues to be a major challenge in oncology and re-

quires a multidisciplinary, multimodal approach for its management, improvement and research. Use of radionuclide therapy offers a significant palliative benefit to patients with bone metastatic disease, yet remains underutilized in the management of bone metastases. More focused clinical and translational research is needed to examine the concepts of oligometastases and micro metastases, to identify optimal radiopharmaceuticals for individual patients, and to isolate newer, more effective and less toxic radionuclides and different dosage schedules. Although the understanding of cancer pain management has improved vastly during the past few years, there are significant opportunities to improve many facets of cancer pain management further and new ways of applying the concepts of radionuclide therapy. Additional clinical research can help lower morbidity and mortality, and optimize quality of life for patients.

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REFERENCES

1. Yau V, Chow E, Davis L, et al. Pain management in cancer patients with bone metastases remains a challenge. *J Pain Symptom Manage.* 2004;27:1-3.

2. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* 2001;27:165-176.

3. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;350:1655-1664.

4. Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors, *J Natl Cancer Inst.* 2005;97:59-69.

5. Solomayer EF, Diel IJ, Meyberg GC, et al. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat.* 2000;59:271-278.

6. Jemal A, Murray T, Samuels A, et al. Cancer Statistics, 2003. *CA Cancer J Clin.* 2003;53:5-26.

7. Scarantino CW, Ornitz RD, Woodard SA. Metastases and Disseminated Disease. In: Clinical Oncology: a Multi-Disciplinary Approach for Physicians & Students, 8th ed. Philadelphia, PA: W.B. Saunders; 2001;846-863.

8. Bonica JJ. Importance of effective pain control. *Acta Anaesthesiol Scand Suppl.* 1987;85:1-16.

9. Piffanelli A, Dafermou A, Giganti M, et al. Italian Association of Nuclear Medicine (AINM). Radionuclide therapy for painful bone metastases. An Italian multicentre observational study. Writing Committee of an Ad Hoc Study Group. *Q J Nucl Med.* 2001;45:100-107.

10. Dafermou A, Colamussi P, Giganti M, et al. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. *Eur J Nucl Med.* 2001;28:788-798.

11. Woo SB, Hellstein JW, Kalmar JR. Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws. *Ann Intern Med.* 2006;144:753-761.

12. Damerla V, Packianathan S, Boerner PS, et al. Recent developments in nuclear medicine in the management of bone metastases. A review and perspective. *Am J Clin Oncol.* 2005;28:513-520.

13. Nair N. Relative efficacy of ^{32}P and ^{89}Sr in palliation in skeletal metastases. *J Nucl Med.* 1999;40:256-261.

14. Shah Syed GM, Maken RN, Muzzaffar N, et al. Effective and economical option for pain palliation in prostate cancer with skeletal metastases: ^{32}P therapy revisited. *Nucl Med Commun.* 1999;20:697-702.

15. Rao DV, Radhamohan G. Pain palliation with testosterone potentiated orally administered sodium orthophosphate in patients with disseminated bone metastases: a preliminary study. *Indian J Nucl Med.* 2001;16:16-19.

16. Silberstein EB, Elgazzar AH, Kapilivsky A. ^{32}P radiopharmaceuticals for the treatment of painful osseous metastases. *Semin Nucl Med.* 1992;22:17-27.

17. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose ^{153}Sm-ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol.* 2002;20:189-196.

18. Dolezal J. Systemic radionuclide therapy with ^{153}Sm-EDTMP for painful bone metastases. *Nucl Med Rev Cent East Eur.* 2000;3:161-163.

19. Tian JH, Zhang JM, Hou QT, et al. Multicentre trial on the efficacy and toxicity of single-dose ^{153}Sm-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. *Eur J Nucl Med.* 1999;26:2-7.

20. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using ^{153}Sm lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* 1998;16:1574-1581.

21. Olea E, Riccabona G, Tian J, et al. Efficacy and toxicity of ^{153}Sm-EDTMP in the palliative treatment of painful skeleton metastases: results of an IAEA international multicenter study [abstract]. *J Nucl Med.* 2000;41(suppl):146P.

22. Palmedo H, Guhlke S, Bender H, et al. Dose escalation study with ^{188}Re-HEDP in prostate cancer patients with osseous metastases. *Eur J Nucl Med.* 2000;27:123-130.

23. Zhang H, Tian M, Li S, et al. ^{188}Re-HEDP therapy for the palliation of pain due to osseous metastases in lung cancer patients. *Cancer Biother Radiopharm.* 2003;18:719-726.

24. Sciuto R, Tofani A, Festa A, et al. Short- and long-term effects of ^{186}Re-1, 1-hydroxyethylidene diphosphonate in the treatment of painful bone metastases. *J Nucl Med.* 2000;41:647-654.

25. Palmedo H, Bender H, Schomburg A, et al. Pain therapy with ^{186}Re-HEDP in multiple bone metastases. *Nuklearmedizin.* 1996;35:63-67.

26. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of ^{89}Sr and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol.* 1994;31:33-40.

27. Kasalicky J, Krajska V. The effect of repeated ^{89}Sr chloride therapy on bone pain palliation in patients with skeletal cancer metastases. *Eur J Nucl Med.* 1998;25:1362-1367.

28. Kraeber-Bodere F, Campion L, Rousseau C, et al. Treatment of bone metastases of prostate cancer with ^{89}Sr chloride: efficacy in relation to the degree of bone involvement. *Eur J Nucl Med.* 2000;27:1487-1493.

29. Turner SL, Gruenewald S, Spry N, et al. Metastron Users Group. Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. *Br J Cancer.* 2001;84:297-302.

30. Ashayeri E, Omogbehin A, Sridhar R, et al. ^{89}Sr in the treatment of pain due to diffuse osseous metastases: a university hospital experience. *J Natl Med Assoc.* 2002;94:706-711.

31. Srivastava SC, Atkins HL, Krishnamurthy GT, *et al.* Treatment of metastatic bone pain with ^{117m}Sn-(Stannic)-diethylene triamine pentaacetic acid: a phase I/II clinical study. *Clin Cancer Res.* 1998;4:61-68.

32. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol.* 1991;9:509-524.

33. Clark GM, Sledge GW Jr, Osborne CK, et al. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol.* 1987;5:55-61.

34. Coleman RE. Should bisphosphonates be the treatment of choice for metastatic bone disease? *Semin Oncol.* 2001;28:35-41.

35. Burnet NG, Williams G, Howard N. ^{32}P for intractable bony pain from carcinoma of the prostate. *Clin Oncol (R Coll Radiol).* 1990;2:220-223.

36. Pecher C. Biological investigations with radioactive calcium and strontium: preliminary report on the use of radioactive strontium in the treatment of metastatic bone cancer. *Univ Calif Publ Pharmacol.* 1942;2:1117–1149.

37. Volkert WA, Hoffman TJ. Therapeutic Radiopharmaceuticals. *Chem Rev.* 1999;99:2269-2292.

38. Bishayee A, Rao DV, Srivastava SC, et al. Marrow-sparing effects of 117mSn(4+) diethylenetriaminepentaacetic acid for radionuclide therapy of bone cancer. *J Nucl Med.* 2000;41:2043-2050.

39. Bouchet LG, Bolch WE, Goddu SM, et al. Considerations in the selection of radiopharmaceuticals for palliation of bone pain from metastatic osseous lesions. *J Nucl Med.* 2000;41:682-687.

40. Goddu SM, Bishayee A, Bouchet LG, et al. Marrow toxicity of 33P-versus 32P-orthophosphate: implications for therapy of bone pain and bone metastases. *J Nucl Med.* 2000;41:941-951.

41. Matthew B, Chakraborty S, Das T, et al. 175Yb labeled polyaminophosphates as potential agents for bone pain palliation. *Appl Radiat Isot.* 2004;60:635-642.

42. Das T, Chakraborty S, Unni PR, et al. 177Lu-labeled cyclic polyaminophosphonates as potential agents for bone pain pallation. *Appl Radiat Isot.* 2002;57:177-184.

43. Nilsson S, Larsen RH, Fosså SD, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. *Clin Cancer Res.* 2005;11:4451-4459.

44. Turner JH, Martindale AA, Sorby P, et al. ^{153}Sm-EDTMP therapy of disseminated skeletal metastasis. *Eur J Nucl Med.* 1989;15:784-795.

45. Blake GM, Zivanovic MA, McEwan AJ, et al. ^{89}Sr therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med.* 1986;12:447–454.

46. Blake GM, Gray JM, Zivanovic MA, et al. ^{89}Sr radionuclide therapy: a dosimetric study using impulse response function analysis. *Br J Radiol.* 1987;60:685-692.

47. Breen SL, Powe JE, Porter AT. Dose estimation in ^{89}Sr radiotherapy of metastatic prostatic carcinoma. *J Nucl Med.* 1992;33:1316-1323.

48. Singh A, Holmes RA, Farhangi M, et al. Human pharmacokinetics of ^{153}Sm-EDTMP in metastatic cancer. *J Nucl Med.* 1989;30:1814-1818.

49. Maxon HR, Deutsch EA, Thomas SR, et al. 186Re-(Sn)HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology.* 1988;166:501-507.

50. Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. *J Nucl Med.* 2004;45:1358-1365.

51. Sandeman TF, Budd RS, Martin JJ. ^{153}Sm-labeled EDTMP for bone metastases from cancer of the prostate. *Clin Oncol.* 1992;4:160-164.

52. Leong C, McKenzie MR, Coupland DB, et al. Disseminated intravascular coagulation in a patient with metastatic prostate cancer: fatal outcome following ^{89}Sr therapy. *J Nucl Med.* 1994;35:1662-1664.

53. Maxfield JR Jr, Maxfield JG, Maxfield WS. The use of radioactive phosphorus and testosterone in metastatic bone lesions from breast and prostate. *South Med J.* 1958;51:320-327.

54. Silberstein EB. The treatment of painful osseous metastases with ^{32}P-labeled phosphates. *Semin Oncol.* 1993;20:10-21.

55. Silberstein EB, Elgazzar AH, Kapilivsky A. Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. *Semin Nucl Med.* 1992;22:17-27.

56. Serafini AN. Therapy of metastatic bone pain. *J Nucl Med.* 2001;42:895-906.

57. Silberstein EB. Systemic radiopharmaceutical therapy of painful osteoblastic metastases. *Semin Radiat Oncol.* 2000;10:240-249.

58. Silberstein EB. Teletherapy and radiopharmaceutical therapy of painful bone metastases. *Semin Nucl Med.* 2005;35:152-158.

59. 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.

60. Sciuto R, Festa A, Pasqualoni R, et al. Metastatic bone pain palliation with ^{89}Sr and ^{186}Re-HEDP in breast cancer patients. *Breast Cancer Res Treat.* 2001;66:101-109.

61. Brenner W, Kampen WU, Kampen AM, et al. Skeletal uptake and soft-tissue retention of ^{186}Re-HEDP and ^{153}Sm-EDTMP in patients with metastatic bone disease. *J Nucl Med.* 2001;42:230-236.

62. 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.

63. Turner JH, Claringbold PG. A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphonate. *Eur J Cancer.* 1991;27:1084-1086.

64. Collins C, Eary JF, Donaldson G, et al. ^{153}Sm-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med.* 1993;34:1839-1844.

65. Zeevaart JR, Louw WK, Kolar ZI, et al. Biodistribution and pharmacokinetics of variously molecular sized 117mSn(II)-polyethyleneiminomethyl phosphonate complexes in the normal primate model as potential selective therapeutic bone agents. *Arzneimittelforschung.* 2004;54:340-347.

66. Friedland J. Local and systemic radiation for palliation of metastatic disease. *Urol Clin North Am.* 1999;26:391-402.

67. Blitzer PH. Re-analysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer.* 1985;55:1468-1472.

68. Epstein LM, Stewart BH, Antunez AR, et al. Half and total body radiation for carcinoma of the prostate. *J Urol.* 1979;122:330-332.

69. Hoskin PJ. Radiotherapy in the management of bone pain. *Clin Orthop.* 1995;312:105-119.

70. Salazar OM, Rubin P, Hendrickson FR, et al. Single-dose half-body irradiation for palliation of multiple bone metastases from solid tumors. Final Radiation Therapy Oncology Group report. *Cancer.* 1986;58:29-36.

71. McQuay HJ, Collins SL, Carroll D, et al. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev.* 2000;CD001793.

72. Malmberg I, Persson U, Ask A, et al. Painful bone metastases in hormone-refractory prostate cancer: economic costs of ^{89}Sr and/or external radiotherapy. *Urology.* 1997;50:747-753.

73. Macklis R, Lasher J. Palliative radiotherapy for skeletal metastases: cost-substitution analyses and economic impact. *J Oncol Manag.* 1999;8:17-22.

74. Papatheofonis FJ. Short term reduction in pain medication costs following systemic radionuclide therapy in prostate cancer patients. *Veterans Health Syst J.* 1998;3:63-66.

75. Silberstein EB, Taylor Jr A. Procedure guideline for bone pain treatment 1.0. *J Nucl Med.* 1995;37:881-884.

76. Laing AH, Ackery DM, Bayly RJ, et al. ^{89}Sr chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol.* 1991;64:816-822.

77. Podoloff DA, Kasi LP, Kim EE, et al. Evaluation of ^{153}Sm-EDTMP as a bone imaging agent during a therapeutic trial [abstract]. *J Nucl Med.* 1991;32:918P.

78. Papatheofanis FJ. Variation in oncologic opinion regarding management of metastatic bone pain with systemic radionuclide therapy. *J Nucl Med.* 1999;40:1420-1423.

79. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13:8-10.

80. Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer.* 1998;61:195-202.

81. Kosuda S, Yoshimura I, Aizawa T, et al. Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma? A multicenter retrospective study in Japan. *Cancer.* 2002;94:964-972.

82. Singh D, Yi WS, Brasacchio RA, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys.* 2004;58:3-10.

83. Tang B, Vu M, Booker T, et al. TGF-β switches from tumor suppressor to prometastatic factor in a model of breast cancer progression. *J Clin Invest.* 2003;112:1116-1124.

84. McCready VR, O'Sullivan JM. Future directions for unsealed source radionuclide therapy for bone metastases. *Eur J Nucl Med Mol Imaging.* 2002;29:1271-1275.

85. 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.

86. Papatheofanis FJ. Serum PICP as a bone formation marker in 89Sr and external beam radiotherapy of prostatic bony metastases. *Br J Radiol.* 1997;70:594-598.

87. Papatheofanis FJ. Quantitation of biochemical markers of bone resorption following strontium-89-chloride therapy for metastatic prostatic carcinoma. *J Nucl Med.* 1997;38:1175-1179.

88. Resche I, Chatal JF, Pecking A, et al. A dose-controlled study of ^{153}Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. *Eur J Cancer.* 1997;33:1583-1591.

89. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for

advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet.* 2001;357:336-341.

90. McEwan AJ. Use of radionuclides for the palliation of bone metastases. *Semin Radiat Oncol.* 2000;10:103-114.

91. Turner JH, Claringbold PG. A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose ^{153}Sm-ethylene diamine tetramethylene phosphonate. *Eur J Cancer.* 1991;27:1084-1086.

92. Schulte M, Brecht-Krauss D, Heymer B, et al. Grading of tumors and tumor like lesions of bone: evaluation by FDG PET. *J Nucl Med.* 2000;41:1695-1701.

93. Sabbatini P, Larson SM, Kremer A, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol.* 1999;17:948-957.

94. Noguchi M, Kikuchi H, Ishibashi M, et al. Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. *Br J Cancer.* 2003;88:195-201.

95. Blake GM, Zivanovic MA, MeEwan AJ, et al. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med.* 1986;12:447-454.

96. Fitzgerald RL, Hillegonds DJ, Burton DW, et al. ^{41}Ca and accelerator mass spectrometry to monitor calcium metabolism in end stage renal disease patients. *Clin Chem.* 2005;51:2095-2102.

97. Hillegonds DJ, Burton DW, Fitzgerald RL, et al. ^{41}Ca on the horizon of individual bone turnover assessment: preclinical results and bisphosphonate response in osteopenic postmenopausal women (abstract). *Cancer Treat Rev.* 2005;31:S51-S52.

98. Kanis JA, McCloskey EV. Bone turnover and biochemical markers in malignancy. *Cancer.* 1997;80:1538-1545.

99. Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol.* 2005;23:4925-4935.

100. O'Sullivan JM, McCready VR, Flux G, et al. High activity ^{186}Re-HEDP with autologous peripheral blood stem cell rescue: a phase I study in progressive hormone refractory prostate cancer metastatic to bone. *Br J Cancer.* 2002;86:1715-1720.

101. Matthay KK, Panina C, Huberty J, et al. Correlation of tumor and whole-body dosimetry with tumor response and toxicity in refractory neuroblastoma treated with ^{131}I-MIBG. *J Nucl Med.* 2001;42:1713-1721.

102. Buffa FM, Flux GD, Guy MJ, et al. A model-based method for the predict ion of whole-body absorbed dose and bone marrow toxicity for ^{186}Re-HEDP treatment of skeletal metastases from prostate cancer. *Eur J Nucl Med Mol Imaging.* 2003;30:1114-1124.

103. McCready VR, O'Sullivan J, Dearnaley D, et al. Quantitative analysis of bone scans to determine if the dose to individual metastases from high activity ^{186}Re-HEDP therapy depends on the number of metastases. *Radiology.* 2001;221:344 (Abstract).

104. Gunawardana DH, Lichtenstein M, Better N, et al. Results of ^{89}Sr therapy in patients with prostate cancer resistant to chemotherapy. *Clin Nucl Med.* 2004;29:81-85.

105. Sciuto R, Festa A, Rea S, et al. Effects of low-dose cisplatin on ^{89}Sr therapy for painful bone metastases from prostate cancer: a randomized clinical trial. *J Nucl Med.* 2002;43:79-86.

106. Michaelson MD, Smith MR. Genitourinary malignancies. In: Giaccone G, Schilsky R, Sondel P, eds. Cancer Chemotherapy and Biological Response Modifiers, Elsevier BV, The Netherlands;2003:547-564.

107. Body JJ, Bartl R, Burckhardt P, et al. Current use of bisphosphonates in oncology: International Bone and Cancer Study Group. *J Clin Oncol.* 1998;16:3890-3899.

108. Hamdy NA, Papapoulos SE. The palliative management of skeletal metastases in prostate cancer: use of bone-seeking radionuclides and bisphosphonates. *Semin Nucl Med.* 2001;31:62-68.

109. Coleman RE. Bisphosphonates in breast cancer. *Ann Oncol.* 2005;16:687-695.

110. Ruggiero S, Gralow J, Marx RE, et al. Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients with Cancer. *J Oncol Prac.* 2006;2:7-14.

111. Soerdjbalie-Maikoe V, Pelger RC, Lycklama a Nijeholt GA, et al. ^{89}Sr (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton. *Eur J Nucl Med Mol Imaging.* 2002;29:494-498. ■