Cancer Metastasis Rev (2006) 25:669–675
DOI 10.1007/s10555-006-9025-z

Targeted and systemic radiotherapy in the treatment of bone metastasis

Alexander Lin · Michael E. Ray

Published online: 9 December 2006

Abstract Cancer metastasis to the bone develops commonly in patients with a variety of malignancies, and is a major cause of morbidity and diminished quality of life in a significant proportion of cancer patients. The effective treatment of bone metastasis requires cooperation between medical, surgical and radiation oncologists. Radiotherapy, either in the form of targeted external beam radiation therapy, or systemic administration of radionuclides, plays a central role in treatment of symptomatic bone metastases. The appropriate external beam treatment techniques, dose and fractionation regimens for the treatment of symptomatic, localized bone metastasis have been established in prospective clinical trials. Large-field, hemi-body irradiation has been utilized for treatment of symptoms related to more widely disseminated bone metastases, but has been associated with substantial toxicity. Strontium-89 and Samarium-153 are widely available systemically administered radionuclides that are useful for the treatment of widely disseminated disease, and have largely supplanted the use of hemi-body irradiation. Combined with appropriate medical and surgical interventions, as well as the appropriate use of analgesics, radiotherapy is a well-tolerated and highly effective treatment for the palliation of symptomatic bone metastases.

Keywords Bone metastasis · Radiotherapy · Radioisotopes

A. Lin (✉) · M. E. Ray
Department of Radiation Oncology, University of Michigan,
UHB2C490 1500 East Medical Center Drive,
Ann Arbor, MI 48109-0010, USA
e-mail: alexlin@umich.edu

M. E. Ray
e-mail: mray@umich.edu

1 Introduction

Skeletal metastases are a common manifestation of disseminated disease in many types of solid cancers, and are often a source of significant morbidity. Bone metastases are most frequently found in those with breast and prostate primaries, but are also seen in those with lung, renal, thyroid, and testicular cancers [1, 2]. Pain secondary to osseous metastases is the most common cause of intractable cancer pain [3], and failure to adequately address this problem can lead to diminished mobility, anxiety, depression, and diminished quality of life. Average long-term survival of patients with bone metastases is generally poor, but superior to those with metastases to other systemic sites. Data from a Radiation Therapy Oncology Group (RTOG) trial showed that median survival with a solitary bone metastasis is 36 weeks, while survival with multiple bone metastases was 24 weeks [4]. Survival was highly variable, with patients with breast and prostate primaries (30–73 weeks) having significantly longer survival than those with lung primaries (12–14 weeks). With improvements in systemic treatment options, it is expected that the length of survival for these patients will improve in the future. Effective and durable treatment of localized, painful bone metastases is therefore important.

The goals of treating osseous metastases are manifold. Proper therapy can lead to significant improvements in pain control and function, and maintain skeletal integrity. The approach to treatment requires a multidisciplinary approach. Widespread metastatic disease necessitates systemic therapy, while a localized problem is best managed with surgery, external beam radiotherapy, or both. Treatment should be individualized, and take into account the overall prognosis of the patient. Patients with bone metastases can

have prolonged survival, and proper management can have a significant impact on their quality of life.

Although the approach to these patients requires the cooperation of medical, surgical, and radiation oncology, this review will focus mainly on the role of external beam radiotherapy and radioisotopes in the treatment of bone metastases.

2 Local field radiotherapy

Local field radiotherapy is commonly used in the treatment of localized bone metastases. The indications for its use include pain relief and control of localized disease. It is also used postoperatively after surgical fixation of impending or pathologic fractures to prevent loosening of surgical hardware secondary to disease progression. A retrospective study showed that 15% of patients treated with surgery alone developed loosening of prostheses or hardware, compared to only 3% in patients who received radiotherapy following surgery [5]. A multidisciplinary approach to these patients is important, and before radiotherapy is delivered, it is important to assess the affected bone for the risk of fracture and the potential need for surgical fixation. One study showed that the fracture rate after radiotherapy was 13% in long bones, and 6% in spinal sites [4]. If surgical fixation is indicated, it is preferable to deliver radiation postoperatively, as surgery through a previously irradiated field may carry with it an increased risk of complications [6]. For patients who are receiving radiotherapy postoperatively, treatment should start at least 7 days after surgery to allow for proper wound healing.

Radiation treatment fields should be tailored to encompass the diseased areas with a suitable margin while minimizing the irradiation of uninvolved bone or soft tissues (Fig. 1). Minimizing the amount of bone marrow irradiated is particularly important in patients who have been heavily pre-treated with chemotherapy, or will receive additional chemotherapy in the future. In post-operative situations, enlargement of the treatment field to cover the entire bone should be considered, as tumor cell contamination may occur during the surgical procedure (Fig. 2). When designing the radiation field, it is important to define the targets carefully. Bone metastases often have associated soft tissue masses that should be included in the treatment field. The total extent of disease should be visualized and incorporated when considering field design. Optimal visualization of the total extent of disease may be facilitated by the use of computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 3).

Local radiation is effective in obtaining pain relief. Eighty to 90% of patients report at least partial pain relief, while 50 to 85% report complete resolution of pain [4, 7]. It is important to remember and counsel patients that pain relief is not instantaneous, and that the full extent of improvement may not be appreciated until 3 to 4 weeks after completion of treatment. The use and optimization of pain medications during this time is therefore important, and adjustments in analgesic doses should be tailored to the patient's pain level before, during, and after radiation.

Multiple dose and fractionation schedules are commonly used, and the optimal schedule has not been resolved. The RTOG conducted a large, national study between 1974 and 1980, comparing five different dose-fractionation schedules [4]. A total of 1,016 patients were enrolled, with patients with solitary metastases randomized to either 40.5 Gray (Gy) in 15 fractions, or 20 Gy in five fractions. Patients with multiple metastases were randomized to 30 Gy in ten fractions, 15 Gy in five fractions, 20 Gy in five fractions, or 25 Gy in five fractions. Eighty-nine percent of patients experienced minimal pain relief, 83% experienced partial relief, and 54% achieved complete relief. The median duration of minimal relief and complete relief were 20 and 12 weeks, respectively. There were no differences found in the treatment arms with respect to degree or durability of relief. The authors concluded that all the treatment dose schedules were equivalent. As a result of the findings from this trial, a schedule of delivering 30 Gy in ten fractions became a widely used regimen for treating local bone metastases.

Consideration of cost effectiveness and patient convenience has led to interest in shorter fractionation schedules. A meta-analysis of dose-fractionation radiotherapy trials for bone metastases compared the pain relief among various schedules [8]. The analyzed studies were grouped into three types: comparisons of doses given as a single fraction, of single versus multiple fractions, and comparisons of doses given in multiple fractions. The findings of this meta-analysis showed no difference between single and multiple fraction schedules with respect to overall and complete pain relief, with overall response rates of 72.7 and 72.5%, respectively. Only the re-irradiation rates were different between the treatment arms, with more frequent re-irradiation of patients originally treated with a single fraction.

The advantages of using single fractions have been reinforced by the results of three recently published randomized trials. A Dutch multicenter trial randomized 1,171 patients with painful bone metastases to either 24 Gy in six fractions, or 8 Gy in one fraction [9, 10]. The two treatment schedules were equivalent with respect to palliation, with 71 and 73% of patients experiencing a response to a single fraction and multiple fractions, respectively. There were also no differences with regards to use of pain medication, quality of life, or toxicity. More patients receiving a single fraction required re-irradiation (24 versus 6%), with overall re-treatment effective in 63%.

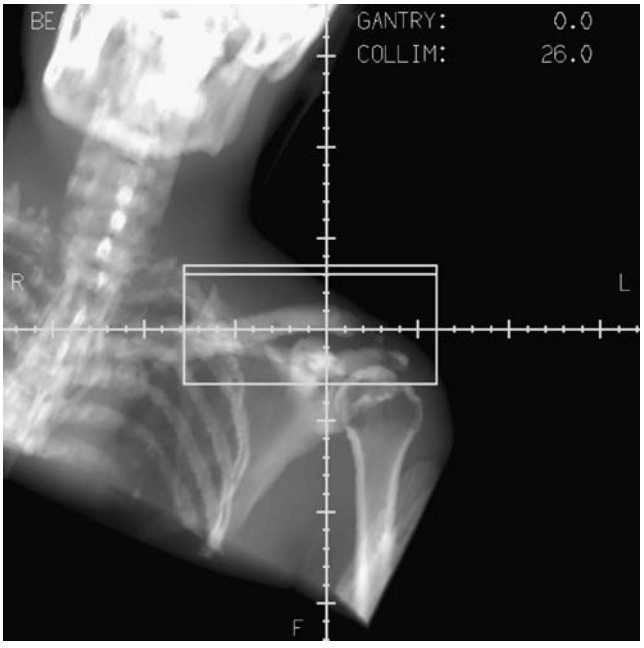

Fig. 1 Digitally reconstructed radiograph illustrating an anteroposterior field treating the left clavicle

A trial from the Bone Pain Trial Working Party randomized 765 patients to either 8 Gy in one fraction, 20 Gy in five fractions, or 30 Gy in ten fractions [11]. At a median follow-up of 12 months, there were no differences in time to first improvement in pain, time to complete pain relief, or in time to first increase in pain, or toxicity. Re-irradiation was twice as common after 8 Gy than after multi-fraction radiotherapy, but did not reflect a difference between the groups in the probability of pain relief.

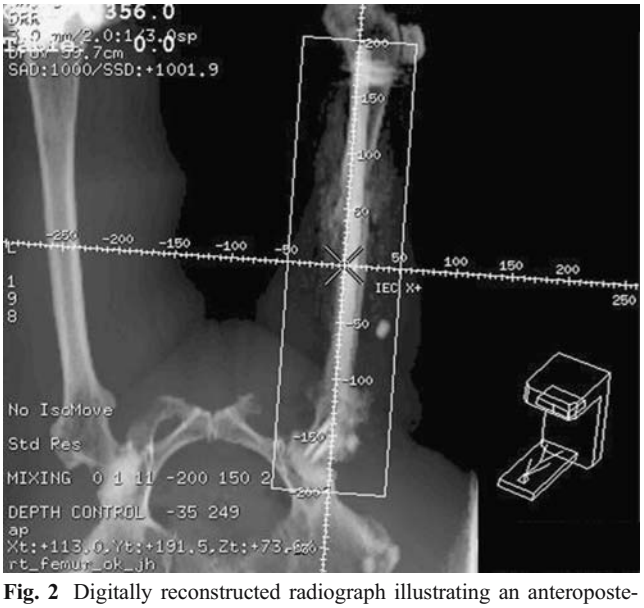

Fig. 2 Digitally reconstructed radiograph illustrating an anteroposterior field treating the right femur, status post rod placement

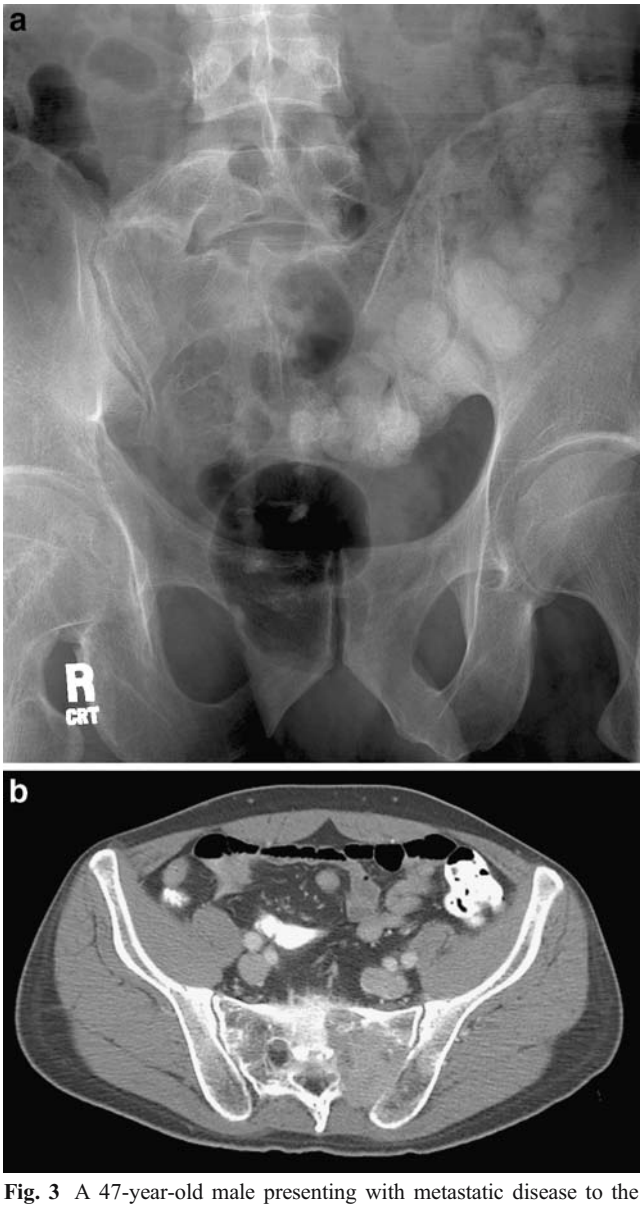

Fig. 3 A 47-year-old male presenting with metastatic disease to the sacrum on bone scan. Plain film of the sacrum (a) and axial CT image demonstrating soft tissue component of disease in the left sacrum (b)

RTOG 9714 randomized 949 patients with prostate or breast cancer and painful bony metastases to either 8 Gy in a single fraction or 30 Gy in ten fractions [12]. Patients with evidence of cauda equina syndrome or spinal cord compression were excluded. There were no significant differences in pain response between the arms. The overall response rate was 66%. Complete and partial response rates were 15 and 50%, respectively, in the 8-Gy arm compared with 18 and 48% in the 30-Gy arm. Grade 2 up to 4 acute toxicity was more frequent in the 30-Gy arm (17%) than in the 8-Gy arm (10%), with late toxicity rare (4%) in both arms. The incidence of subsequent pathologic fracture was 5% for the 8-Gy arm and 4% for the 30-Gy arm. A significantly higher

proportion of patients in the 8 Gy arm (18%) required re-irradiation compared to the 30 Gy arm (9%).

When considering dose and fractionation schedules for patients with bone metastases, a single fraction of 8 Gy is equivalent to a more protracted course with respect to efficacy and toxicity. Although there may be a higher likelihood for the need of re-treatment in those receiving a single fraction, re-irradiation is generally effective. Alternatively, the difference in the rate of re-treatment observed in previous studies may simply reflect a greater readiness on the part of physicians to prescribe re-irradiation after a single fraction, rather than a greater need. In any case, the use of single fraction radiotherapy is a cost-effective and patient-convenient option that should be considered.

Local radiotherapy is generally well-tolerated. Commonly seen acute side effects include fatigue, skin erythema, nausea and diarrhea in fields including the upper abdomen, esophagitis in thoracic fields, and myelosuppression, especially with wider radiation fields or in those heavily pretreated with chemotherapy. Late complications are relatively uncommon, due to the low doses delivered and to the limited survival of the patient population. Radiation can further weaken bone and increase the risk of a future fracture. The risk of a post-treatment fracture ranges from 4 to 18% [4].

3 Hemibody irradiation (HBI)

Patients with bone metastases often will have multiple areas of involvement. After completion of a course of localized radiotherapy, most will require additional treatment to other sites, with as many as 76% of patients requiring treatment of an additional site within 1 year [13]. The use of hemibody irradiation has been used to address this problem, where either the upper or lower half of the body is treated with external beam radiotherapy.

The potential advantages of such treatment include the ability to treat multiple lesions simultaneously, to treat asymptomatic sites, and in so doing, to prevent disease progression at these sites. HBI is effective for pain relief, and response rates are similar to focal irradiation, with 70 to 90% of patients experiencing some pain relief, and up to 45% with complete pain resolution. The onset of relief is rapid, often occurring within 24 h of treatment. HBI is associated with substantial morbidity: hospitalization may be required for hydration and administration of antiemetics. Most patients experience significant gastrointestinal toxicity with nausea, vomiting, and diarrhea in the first 24 to 48 h. Myelosuppression is also a common side effect, but rarely of clinical significance.

The dose fractionation schemes that are used with HBI are variable. A recently published phase III trial from the International Atomic Energy Agency sought to find the most effective and efficient method to deliver HBI [14]. A total of 156 patients with widespread, symptomatic bone metastases were randomized to one of three dose and fractionation schedules: a control arm, delivering 15 Gy in five fractions over 5 days, another delivering 8 Gy in two fractions over 1 day, and another delivering 12 Gy in four fractions over 2 days. Pain relief was seen in 91% of patients, with an equal number achieving partial or complete response within 3 to 8 days of treatment, with an average pain-free survival of 122 days. Toxicity was acceptable, with severe toxicity in 12%, mild/moderate toxicity in 50%, and no toxicity in 41%. With respect to pain relief, durability of relief, and toxicity, there was no difference between delivering 15 Gy in five daily fractions versus delivering 12 Gy in four twice-daily fractions, for all but prostate primaries, in which case 15 Gy given over 5 days was the most effective regimen. Delivering 8 Gy in two fractions in 1 day delivered the lowest biologic dose in the shortest time, and resulted in inferior pain relief and durability of relief.

Another important issue to consider is the long-term effectiveness of HBI and whether HBI might delay the onset of metastases in the areas of the body treated, and decrease the need for additional future treatment. The RTOG conducted a phase III study evaluating the efficacy of adding HBI to local-field irradiation [13]. Four hundred ninety-nine patients were randomized to receive either HBI (8 Gy in one fraction) or no further treatment following completion of palliative local irradiation (3 Gy×ten fractions to the symptomatic site). HBI was generally well-tolerated, with a 5 to 15% incidence of toxicity. Delivery of HBI did yield improvements in time-to-disease progression in the target areas. At 1 year, 50% of patients on the HBI arm showed new disease compared to 68% on the local-only arm. Time-to-retreatment within the hemibody was also delayed, but the long-term benefits of HBI are probably small. Progression rates are similar with or without HBI, and by 1 year, 60% of patients receiving HBI needed re-irradiation within the hemibody.

Hemibody irradiation offers the advantages of treating multiple metastases, and provides rapid onset pain relief. However, the morbidity associated with treatment can be significant, and long term benefits are small, with a majority of patients still requiring re-treatment at 1 year. It is for these reasons that hemibody irradiation is infrequently used in current practice, and has been largely replaced by the use of systemic radiopharmaceuticals.

4 Systemic radionuclides

The administration of systemic radioisotopes is being utilized in the treatment of patients with diffuse osseous

Table 1 Physical properties of various radionuclides

Radionuclide	Physical half-life	Maximum beta energy (MeV)	Average beta energy (MeV)	Gamma energy (keV)	Average soft tissue penetration (mm)
Phosphorus-32	14.3 days	1.71	0.7	–	3.0
Samarium-153	46.3 h	0.81	0.22	103	0.6
Strontium-89	50.6 days	1.46	0.58	–	2.4

metastases. These radioactive agents function as "radiopharmaceuticals" by localizing selectively to bone sites and delivering ionizing radiation to sites of metastasis in a focal manner. The advantages of this treatment include the ability to address all osseous sites simultaneously, the selective uptake of radionuclide by bone, thereby minimizing the dose delivered to normal soft tissues, as well as the ease of treatment delivery in a single intravenous injection in the outpatient setting. Systemic radionuclide treatment is indicated in the presence of widespread painful bony metastases, particularly in the absence of a predominant site of bony pain or if there is contraindication to further external beam radiotherapy such as when normal tissue tolerance has been reached. Systemic radionuclide treatment is less appropriate in the presence of purely lytic disease, pathologic fracture or impending fracture, spinal cord compression or pending spinal cord compression, significant renal insufficiency, or compromised bone marrow function. Patients under consideration should have a life expectancy of at least 3 months, as well as correlation of pain to the presence of lesions which show uptake on bone scans.

Currently in the United States, three radioisotopes are available for treatment of bone metastases: Phosphorus-32, Strontium-89, and Samarium-153 (Table 1). Phosphorus-32 was the first to be widely used, but its higher maximum beta energy (1.71 MeV) resulted in significant bone marrow toxicity. Phosphorus-32 has largely been replaced by Strontium-89 and Samarium-153, which have lower energies, and produce less hematologic toxicity.

4.1 Strontium-89

Strontium 89 decays by beta emission, with a maximum beta energy of 1.46 MeV, an average soft-tissue penetration of 2.4 mm, and a half-life of 50.6 days. After administration, it is taken up into the mineral matrix of bone and is selectively concentrated at areas of osteoblastic activity in diseased-affected bone, with biological behavior resembling that of calcium. The fraction that is retained is proportional to the tumor burden at the site, ranging from 20 to 80% of the administered dose, with retention lasting up to 100 days [15]. A temporary flare of pain may occur within the initial 2 to 3 days after administration, so attention to analgesia is important during this time. Pain relief occurs approximately 1 to 3 weeks after injection. Strontium-89 is eliminated mainly via the kidneys, and patients are advised to carefully dispose of urine for the first 10 days after administration. Due to negligible gamma ray emission, administration of strontium-89 is not a radiation hazard to hospital staff or family members in close contact to the patient.

The usefulness of strontium-89 has been well studied. Four randomized controlled trials have compared strontium-89 with either placebo or local external beam radiation in men with symptomatic, metastatic prostate cancer. Lewington et al. performed a prospective double-blind crossover study comparing strontium-89 with stable strontium as placebo [16]. Thirty-two patients with bone-scan positive, hormone refractory prostate cancer were enrolled and randomly assigned to receive a single injection of strontium-89 (4.0 mCi) or placebo. Response was assessed at 5 weeks. Non-responders received a second injection at 6 weeks, with another response assessment 5 weeks later. Combining the results of the first and second evaluation, those receiving strontium-89 had statistically significant ($p<0.01$) higher rates of pain relief. Four and 10 out of 20 patients receiving strontium-89 reported dramatic and any relief of pain, respectively, compared to only 4 and 0 out of 18 patients receiving placebo.

The Trans-Canada study was a phase-III, multi-center, randomized placebo control trial that evaluated the efficacy of strontium-89 given as an adjunct after external beam radiotherapy in patients with hormone-refractory, metastatic prostate cancer [17]. A total of 126 patients were randomized to receive either a single injection of strontium-89 (10.8 mCi, given within the first week after EBRT) or placebo after completion of local-field external beam radiotherapy. Overall and complete responses were greater in the treatment arm, but did not reach statistical significance. There were no differences in overall survival. Strontium-89 was associated with superior freedom from new painful metastatic lesions (59 vs. 34%), longer time to re-treatment with radiotherapy (35 vs. 20 weeks), and a greater proportion of patients who discontinued analgesic use at 3 months (17 vs. 2%). A multivariate quality-of-life (QOL) analysis showed a statistically significant improve-

ment in alleviation of pain and improvement of physical activity.

Buchali et al. reported the results of a trial of 49 patients with hormone-refractory metastatic prostate cancer, who were randomly assigned to receive strontium-89 (2 mCi) or placebo, given monthly for 3 months [18]. Analysis of results at 1–3 years after therapy failed to detect a difference in pain relief between the two groups. An unexpected result was a noted difference in survival at 2 years, favoring patients receiving strontium-89 (46 vs. 4%), which has not been shown in other studies.

The UK Metastron Investigators' Group Study compared pain relief from external beam radiotherapy to strontium-89 [19]. A total of 284 prostate cancer patients with painful bone metastases were randomly assigned to receive either external beam radiation (patients were stratified to receive either local field or hemibody radiation) or strontium-89 (5.4 mCi). All treatments provided effective overall and dramatic pain relief, with similar results for strontium-89 (61 and 44.1%, respectively), local radiotherapy (65.9 and 36.4%, respectively), and hemibody radiation (63.6 and 43.2%, respectively). Significantly fewer patients receiving strontium-89 reported new pain sites. Compared to local radiotherapy, fewer patients receiving strontium-89 required subsequent radiation (2 vs. 12 patients). There was no significant difference in survival.

The issue of optimal dosing of strontium-89 has been studied and reported by Laing et al. [20]. This multi-center study assessed 83 prostate cancer patients following the administration of at least 1.5 MBq/kg (0.4 mCi/kg). Of these patients, 75% had some pain relief, with 22% reporting complete pain relief. Pain relief began within 10 to 20 days, peaked at 6 weeks, and continued for an average of 6 months. Severe toxicity was rare, provided that patients had adequate bone marrow reserve. Based on these results, the authors recommended 1.5 MBq/kg (0.4 mCi/kg) as the optimal dose.

4.2 Samarium-153

Samarium-153 is a synthetic radionuclide that emits beta particles, with a maximum energy of 0.81 MeV and a half-life of 46.3 h. The beta-decay is accompanied by 28% emission of 103 keV gamma rays. The samarium is chelated to a phosphonate, ethylenediaminetetramethylene (EDTMP), to produce a complex that localizes to areas of osteoblastic activity in bone. Samarium-153-EDTMP distributes to bone in a manner similar to Technecium-99 m methylene diphosphonate, the radiopharmaceutical utilized for bone scans. Bone scanning may be performed after Samarium-153 administration, to confirm uptake at sites of metastasis. Compared to strontium-89, samarium-153 has a shorter physical half-life and a higher dose rate. As a result, samarium-153 has the advantage of shorter dose delivery time, with 75% of total dose delivered over approximately 4 days, compared to 101 days for strontium-89. In addition, pain relief and recovery of blood counts occur sooner with samarium-153. Another advantage lies in the fact that samarium-153 is a gamma emitter, with a gamma energy of 103 keV. The gamma emission can be used for imaging purposes, making samarium-153 the only bone-seeking radioisotope that can be used for therapeutic and diagnostic purposes.

Two prospective, randomized phase III trials have looked at the effectiveness of samarium-153. Serafini and associates randomized 118 patients with painful bone metastases from a variety of primary malignancies to receive either samarium-153 (0.5 or 1.0 mCi/kg) or placebo [21]. Patients who had not responded by the fourth week were unblinded, and those receiving placebo were allowed to crossover to receive samarium-153 at 1.0 mCi/kg, thus limiting statistical analysis to the first 4 weeks after treatment. A significant improvement in pain relief was found for the 1.0 mCi/kg dose only, with pain relief observed in 72% of these patients during the first 4 weeks, and with 31% reporting marked or complete relief. The persistence of pain relief was seen in 43% at 16 weeks. Those receiving 1.0 mCi/kg were observed to have significantly decreased opioid analgesic use compared to the placebo group. Treatment was well tolerated, and not associated with grade 4 toxicity.

The second trial was reported by Sartor et al., and was designed to assess efficacy of samarium-153 for pain relief in patients hormone-refractory prostate cancer and concurrent painful bone metastases [22]. A total of 152 were randomized to receive either samarium-153 or placebo. Again, those who received placebo and were non-responders at week 4 were allowed to crossover and receive samarium-153. The results from this trial showed that when compared to placebo, samarium-153 gave significantly better pain relief within 1 to 2 weeks, with reduction in opioid use seen at weeks 3–4. Followup past week 4 was not possible due to the crossover at that time. Treatment was well tolerated, with mild, transient bone marrow suppression being the only adverse event, with no grade 4 hematologic toxicity.

4.3 Complications

Hematologic toxicity is the most common side effect, with most patients having a drop of 20 to 50% in blood counts after doses of 3 to 4 mCi. Although grade III toxicity is uncommon, blood counts should be monitored weekly for at least 2 months. Other side effects include a transient increase in bone pain in up to 10% of patients. Although this pain flare can be severe and last a few days, it usually predicts an eventual favorable response to treatment.

5 Conclusions

Metastatic disease to the bone is a common problem that remains a significant cause of cancer-related morbidity. Effective and durable pain relief and minimizing requirements for opioid analgesics are important endpoints, especially in patients who may have prolonged survival. Local external beam radiotherapy has an important role for patients with a localized, painful lesion. Localized treatment is effective, well-tolerated, and convenient, with courses that can be completed in 1 day with one single fraction. For patients with disseminated bony disease, radioisotopes such as strontium-89 and samarium-153 can be given systemically, and have been shown to provide durable pain relief, with minimal side effects. The use of external beam radiotherapy and radioisotopes are part of a multidisciplinary approach that should be taken for these patients, with care individualized and tailored to the clinical situation.

References

1. Plunkett, T. A., & Rubens, R. D. (1999). The biology and management of bone metastases. *Critical Reviews in Oncology/ Hematology, 31*, 89–96.
2. Tubiana-Hulin, M. (1991). Incidence, prevalence and distribution of bone metastases. *Bone, 12*(Suppl 1), S9–S10.
3. Foley, K. M. (1985) The treatment of cancer pain. *New England Journal of Medicine, 313*, 84–95.
4. Tong, D., Gillick, L., & Hendrickson, F. R. (1982). The palliation of symptomatic osseous metastases: Final results of the Study by the Radiation Therapy Oncology Group. *Cancer, 50*, 893–899.
5. Townsend, P. W., Rosenthal, H. G., Smalley, S. R., Cozad, S. C., & Hassanein, R. E. (1994). Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease. *Journal of Clinical Oncology, 12*, 2345–2350.
6. O'Sullivan, B., Davis, A. M., Turcotte, R., Bell, R., Catton, C., Chabot, P., et al. (2002). Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomised trial. *Lancet, 359*, 2235–2241.
7. Vargha, Z. O., Glicksman, A. S., & Boland, J. (1969). Single-dose radiation therapy in the palliation of metastatic disease. *Radiology, 93*, 1181–1184.
8. Wu, J. S., Wong, R., Johnston, M., Bezjak, A., & Whelan, T. (2003). Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *International Journal of Radiation Oncology, Biology, Physics, 55*, 594–605.
9. Steenland, E., Leer, J. W., van Houwelingen, H., Post, W. J., van den Hout, W. B., Kievit, J., et al. (1999). The effect of a single fraction compared to multiple fractions on painful bone metastases: A global analysis of the Dutch Bone Metastasis Study. *Radiotherapy and Oncology, 52*, 101–109.
10. van der Linden, Y. M., Lok, J. J., Steenland, E., Martijn, H., van Houwelingen, H., Marijnen, C. A., et al. (2004). Single fraction radiotherapy is efficacious: A further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *International Journal of Radiation Oncology, Biology, Physics, 59*, 528–537.
11. Bone Pain Trial Working Party (1999). 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: Randomised comparison with a multifraction schedule over 12 months of patient follow-up. *Radiotherapy and Oncology, 52*, 111–121.
12. Hartsell, W. F., Scott, C. B., Bruner, D. W., Scarantino, C. W., Ivker, R. A., Roach, M., et al. (2005). Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *Journal of the National Cancer Institute, 97*, 798–804.
13. Poulter, C. A., Cosmatos, D., Rubin, P., Urtasun, R., Cooper, J. S., Kuske, R. R., et al. (1992). A report of RTOG 8206: A phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *International Journal of Radiation Oncology, Biology, Physics, 23*, 207–214.
14. Salazar, O. M., Sandhu, T., da Motta, N. W., Escutia, M. A., Lanzos-Gonzales, E., Mouelle-Sone, A., et al. (2001). Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: A randomized Phase III trial of the International Atomic Energy Agency (IAEA). *International Journal of Radiation Oncology, Biology, Physics, 50*, 765–775.
15. Blake, G. M., Zivanovic, M. A., McEwan, A. J., & Ackery, D. M. (1986). Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate. *European Journal of Nuclear Medicine, 12*, 447–454.
16. Lewington, V. J., McEwan, A. J., Ackery, D. M., Bayly, R. J., Keeling, D. H., Macleod, P. M., et al. (1991). 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. *European Journal of Cancer, 27*, 954–958.
17. Porter, A. T., McEwan, A. J., Powe, J. E., Reid, R., McGowan, D. G., Lukka, H., et al. (1993). 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. *International Journal of Radiation Oncology, Biology, Physics, 25*, 805–813.
18. Buchali, K., Correns, H. J., Schuerer, M., Schnorr, D., Lips, H., & Sydow, K. (1988). Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *European Journal of Nuclear Medicine, 14*, 349–351.
19. Quilty, P. M., Kirk, D., Bolger, J. J., Dearnaley, D. P., Lewington, V. J., Mason, M. D., et al. (1994). A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiotherapy and Oncology, 31*: 33–40.
20. Laing, A. H., Ackery, D. M., Bayly, R. J., Buchanan, R. B., Lewington, V. J., & McEwan A. J. (1991). Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *British Journal of Radiology, 64*, 816–822.
21. Serafini, A. N., Houston, S. J., Resche, I., Quick, D. P., Grund, F. M., Ell, P. J., et al. (1998). Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: A double-blind placebo-controlled clinical trial. *Journal of Clinical Oncology, 16*, 1574–1581.
22. Sartor, O., Reid, R. H., Hoskin, P. J., Quick, D. P., Ell, P. J., Coleman, R.E, et al. (2004). Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology, 63*, 940–945.