Stereotactic Body Radiotherapy in the Management of Painful Bone Metastases

By Pavan Jhaveri, MD [2], Bin S. Teh, MD [3], Charles Bloch, PhD [4], Robert Amato, DO [5], E. Brian Butler, MD [6], and Arnold C. Paulino, MD [7]

Bone metastases are a common feature of many solid cancers, especially those originating from the prostate, breast, lung, kidney, melanoma, and other sites. Up to 80% of patients with these cancers will develop painful bony disease during the course of their disease.

Conventional Radiotherapy

Conventional radiotherapy has a well described role in the acute treatment of metastatic disease of the bone, specifically the spine. In cases that do not involve spinal instability, previous radiotherapy, or radioresistant tumor types such as renal cell carcinoma, conventional radiation therapy has been indicated and successfully used.

Dosing schedules in conventional external-beam radiotherapy have been the subject of various randomized trials (including a phase III Radiation Therapy Oncology Group trial), all comparing the use of single-fraction regimens with multifraction regimens.[1-5] A comprehensive meta-analysis published in 2007 examined 16 randomized trials from 1986 to the present that evaluated single-fraction vs multiple-fraction treatment schedules for painful bone metastases.[6] The most common single-fraction schedule used was 8 Gy in 1 fraction. The multiple-fraction schedules varied, and included 30 Gy in 10 fractions, 24 Gy in 6 fractions, and 20 Gy in 5 fractions. The final conclusion of the meta-analysis was that there is no significant difference between single- and multiple-fractionation schedules in terms of bone pain relief. However, there is a significant difference in terms of higher retreatment rates in the single-fraction patients.

Other meta-analyses, including two Cochrane database reviews published in 2002 and 2000 on the same topic support this conclusion.[7-10] The use of conventional radiotherapy is considered effective for pain relief with these fractionation schemes, with 80% to 90% experiencing some relief and up to 33% experiencing complete resolution of pain.[11,12]

Stereotactic Body Radiotherapy

A newer alternative, SBRT has been hypothesized to provide a better local control rate and longer duration of symptom palliation in the setting of bone pain, compared to conventional radiation therapy.[13] This technique has been defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) and the American College of Radiology (ACR) as a treatment method used to deliver a high dose of radiation to a target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body.[14] Figure 1 shows a comparison between typical treatment volumes in conventional radiotherapy and SBRT.
Some unique and defining characteristics of SBRT set out in the literature include the following features and requirements\[14-16\]:

1. Secure immobilization to reduce patient movement
2. Accurate positioning from simulation scan to treatment
3. Utilization of multiple beams to reduce the dose to normal tissue
4. Accurate tracking of surrounding organ motion
5. Use of image guidance and tumor surrogates such as implanted fiducials or bony landmarks
6. Use of an ablative dose and fractionation scheme delivered with millimeter accuracy

Many consider requirement number 6 the most vital and defining characteristic of SBRT. The other characteristics are important, because they allow the delivery of an ablative dose accurately and without otherwise expected healthy tissue toxicity.\[15\] Indeed, this capability is considered to be the main reason for the hypothesis that SBRT can provide better local control and duration of pain relief in the setting of metastatic bone lesions.\[13\]

Candidate requirements for SBRT treatment, although not officially agreed on, have also been reported in the literature, as follows\[17\]:

1. Well-circumscribed lesions
2. Minimal cord compression
3. Previously irradiated lesions
4. Recurrent surgical lesions
5. Inoperable lesions
6. Lesions that do not require open spinal stabilization

**Advantages of SBRT**

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SBRT has been under increasing study because of various advantages it offers over conventional radiotherapy (Table 1). The advantages of hypofractionated radiotherapy for treating bone metastases include a shortened treatment course and the ability to irradiate a smaller normal tissue volume because of rapid dose fall-off on SBRT treatment plans when compared to standard multifractionated radiotherapy. Possibly the largest advantage is the ability to deliver an ablative dose without incurring previously dose-limiting tissue toxicity. SBRT may also provide faster and more durable pain relief.\[18,19\] The delivery of a biologically more potent dose may provide better local control. This approach is especially advantageous for patients with solitary or oligometastases after a prolonged cancer-free interval.

Because of this large dose delivery, radioresistant tumors such as melanoma, renal cell carcinoma, and sarcoma, which tend to metastasize to the bone, can now be investigated as viable treatment targets.\[20-24\] Similarly, the treatment of previously irradiated sites with SBRT can now be investigated due to the increased accuracy and reduced treatment volumes of SBRT over conventional therapy.\[25-27\]

**Disadvantages of SBRT**

On the other hand, SBRT comes with its own unique disadvantages as well (Table 1). To achieve the increased accuracy with the use of immobilization devices, image guidance, multiple beams, intensity-modulated beam delivery or a combination of any of these, treatment times are increased as compared to conventional treatment. In the case of painful bone metastases, this increased time and planning/delivery requirements can be difficult for the patient to bear. Some patients may require pretreatment pain medication or generalized anesthesia. In certain severe cases, patients will have to forgo treatment with SBRT because of this issue. The increased planning time requirement generally precludes SBRT from being used in the treatment of emergent cord compressions.
Additionally, if accuracy is compromised, surrounding tissues will receive high doses of radiation that could potentially lead to more severe toxicity after treatment. In the setting of spinal metastases, the surrounding critical normal tissues that can receive toxic doses include the spinal cord, small bowel, and respiratory tract structures. The doses to these serially functioning tissues are important to consider with the use of SBRT, because even if a small segment becomes damaged, the entire organ becomes nonfunctional. Some consider this to be the principle limiting factor in the use of SBRT.[15,28]

It is also not rational or feasible to use SBRT to treat extensive multilevel disease that involves the spine. Other concerns regarding the delivery of very high doses per fraction include fractures and severe skin or soft-tissue reactions for bony lesions in close proximity to the skin.

**Clinical Experience**

**TABLE 2**

Summary of Retrospective Trials Investigating SBRT

Unlike conventional radiotherapy, no randomized controlled trials have evaluated aspects of SBRT treatment for bone metastases. However, various retrospective and initial experiences have been published (Table 2).[18,19,29-32] These studies usually contain a smaller number of patients but are important because their results suggest that SBRT is effective and safe for use in the setting of bony disease. Nevertheless, they do contain flaws inherent to most retrospective studies, including nonuniform treatment regimens, small numbers of patients, and more cautious dosing regimens than might be attempted in clinical practice. These characteristics make it more difficult to draw solid conclusions from these data. There have been, to our knowledge, seven published prospective trials that address some of these issues, although not all of them specifically investigate the use of SBRT in the setting of bony metastases (Table 3).

**TABLE 3**

Summary of Prospective Trials Investigating SBRT

- **Henry Ford Hospital Trials**—The Henry Ford Hospital group published their first prospective study in 2003.[25] This initial clinical feasibility study involved 10 patients who received 25 Gy in 10 fractions prior to receiving a 6- to 8-Gy single-fraction SBRT boost to the target. All patients had one or two contiguous vertebral metastases. Disease pathology was varied. Although pain was not a primary endpoint, it was reported in the study. Nine patients had significant pain prior to radiotherapy. After SBRT, five out of nine patients had complete pain relief, and the remaining four were able to reduce their pain medication. Time to pain relief was reported as 2 to 4 weeks after SBRT completion. While the dose was less than what we currently consider appropriate for SBRT, and pain relief was not a primary endpoint, this initial study gave encouraging results to further refine the technique.

  In early 2007, the same group published preliminary results from a study that treated 196 patients with 270 spinal metastases.[33] Over the course of this trial, patients have been treated with a single fraction, with dose escalation in 2-Gy increments from 10 to 18 Gy. The authors reported on the first 49 patients to have completed treatment. Approximately 85% have experienced some pain relief without major acute toxicity. Presumably, final results of this trial are pending.
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• M.D. Anderson Cancer Center Trial—A phase I clinical trial published by Chang et al in 2004 reported on 15 patients who underwent SBRT at a dose of 30 Gy in five fractions for spinal bone metastases of varying pathologies.[27] A total of five patients had received conventional radiotherapy prior to the SBRT as part of their treatment. The efficacy of the treatment in terms of pain resolution was not reported. However, the study is included here because it reported that no neurotoxicity, grade 3/4 toxicity, radiation-induced spinal cord injury, or other myelopathy were observed during the follow-up period, which ranged from 6 to 16 months (median = 9 months). This suggests the possibility of safely using high biologic equivalent dose (BED) treatments such as SBRT without causing undue normal tissue toxicity, especially in the setting of retreatment.

• University of Pittsburgh Trials—A larger prospective evaluation from Gerszten et al, published in 2004, reported on the radiosurgical treatment of 125 lesions, the majority (86.4%) of which were metastatic to the spine, from different primary pathologies.[17] Additionally, 67.8% (78/115) of the patients received conventional radiotherapy prior to SBRT treatment. This study is important because it utilized a dose/fraction scheme that involved a single-fraction dose that, at a mean of 14 Gy to the 80% isodose line, was much higher than doses normally used in conventional therapy. Overall, 93.7% of patients experienced pain relief at 1-month follow-up, with the use of pain medication accounted for. At a median follow-up of 18 months, no acute toxicity or new neurologic deficits were noted. Although the pathologies were not uniform among all patients treated, the study did suggest that a high dose in a single fraction was safe to use for SBRT (or, in this case, stereotactic radiosurgery) in the treatment of bony disease in the spine.

In 2007, the same University of Pittsburgh group published the results of a prospective cohort trial in which 500 patients with metastatic vertebral disease were treated with a single-fraction SBRT mean dose of 20 Gy.[26] For cervical lesions, bony landmarks were used to track disease, and fiducials were used in thoracic, lumbar, and sacral lesions. To our knowledge, this is the largest clinical series to date. The primary indication for treatment in these cases was acute bone pain, with 86% of subjects achieving pain relief on long-term follow-up (median = 21 months). Pain relief was defined as a reduction of at least 3 points on a 10-point visual pain-grading system. Analgesic usage was reported as part of the results. A total of 344 patients (68.8%) had undergone prior conventional radiotherapy; even with this prior treatment, no acute spinal cord toxicity was found at follow-up visits. These results suggest that SBRT of up to 20 Gy in one fraction is effective and safe in treating bony disease from a variety of pathologies.

Specific Pathologic Types

Given that none of these trials contain only one tumor type, a logical question concerns whether there are any significant differences in results for different tumor types. Some of the more common primary site tumors from which metastases in the spine are treated include breast, lung, and prostate cancers, melanoma, and renal cell carcinoma.[34] Currently, the published literature evaluating the above question is still emerging. However, the University of Pittsburgh stereotactic radiotherapy group has published three prospective trials, and one retrospective review evaluating the use of SBRT in treating vertebral metastases from renal cell, breast, lung, and melanoma primaries.[23,24,35,36]

The outcomes were similar among all four groups. Melanoma and renal cell carcinoma, two pathologies that are traditionally deemed radioresistant, responded well to a single-fraction mean dose of 21.7 and 16 Gy, respectively. The melanoma lesions had a response rate of 96% and renal cell lesions had an 89% response rate, in terms of patients experiencing some pain relief. The lung and breast cancer groups both received a mean dose of 19 Gy, with the lung cancer patients having an 89% symptom response rate (65/73 lesions) and the breast cancer patients having a 96% symptom response rate (55/57 lesions).

Similar results were reported by Teh et al, who retrospectively reported on 23 extracranial RCC lesions treated with hypofractionated SBRT.[18,19] Fourteen patients received 24 to 40 Gy in three to six fractions. At a mean follow-up of 9 months, 93% of patients experienced some pain relief, with an overall local control rate of 87%. While these results are encouraging and suggest that similar outcomes can be obtained with hypofractionated or single-fraction therapy, it is unclear which dosing regimen is the best to use. There is a need for larger prospective, randomized trials to evaluate this clinical question.

Nonvertebral Bony Sites

The majority of SBRT data reported in the literature involve its use for bony disease in the spinal column. Two studies have reported on the use of SBRT for metastases to the sacrum.[37,38] Gibbs
et al reported retrospectively on their experience with three sacral lesions treated with single-fraction stereotactic radiosurgery.[37] All three received 18 Gy in a single fraction. No long-term side effects from the radiotherapy were reported; two of the three had undergone conventional radiotherapy prior to the stereotactic treatment. The University of Pittsburgh group gave an average dose of 15 Gy in one fraction to the target with 13 of 13 patients reporting pain relief after SBRT.[38] No neurologic toxicity was reported in the follow-up period of 6 months. Our clinical experience on the topic (unpublished) shows that SBRT can be successfully used to treat painful metastases in sites such as the ribs, pelvis, sternum, scapulae, and elsewhere. Approximately 33% of our bony disease sites have been outside of the spinal column. Overall, a 93% pain relief rate has been achieved.

Patterns of Symptomatic Failure

Because of the tight treatment margin and rapid dose fall-off involved in SBRT, recurrence adjacent to the treated segment can be a concern.[26] Ryu et al retrospectively examined failure after single-fraction radiotherapy (10–16 Gy) to the spine for pain control.[39] At the actual treated site, pain relapse was 7%. At adjacent sites, the symptomatic relapse rate was 5%. In their 500-patient prospective trial, Gerszten et al found that no patients experienced relapse at adjacent sites.[26]

Toxicity to the Spinal Cord

Toxicity to the spinal cord is a major concern in the treatment of vertebral metastases with SBRT. This is especially important in patients with solitary or oligometastases, who will survive long after treatment.

Ryu et al examined post-SBRT toxicity retrospectively in 230 lesions treated with single-fraction SBRT (8–18 Gy, mean = 14.3 Gy).[40] None of the patients had been treated with spinal radiotherapy prior to SBRT. Among those who were treated at a dose of 18 Gy, the highest point dose to the spinal cord was 19.2 Gy (in one patient). The average dose to 10% of the spinal cord volume in this 18-Gy cohort was 9.8 ± 1.5 Gy. None of these patients developed spinal cord toxicity. From the cumulated dose-volume histogram of all 230 lesions, the average dose to the 10% spinal cord volume was 9.2 ± 2.3 Gy. One patient developed a radiation-induced myelopathy 13 months after a single fraction of 16-Gy radiotherapy. In this patient, the highest spinal cord point dose was 14.6 Gy.

Given these results, the study concluded that the partial-volume tolerance of the spinal cord is at least 10 Gy to 10% of the spinal cord volume 5 mm above and below the target. This suggestion of 10% of the restricted cord volume receiving 10 Gy or less has been followed in both the University of Pittsburgh and Henry Ford Hospital groups’ prospective trials, with minimal to no spinal cord toxicity being reported.[17,23-26,35,36]

Survival Benefit

Patient survival outcome was not reported in the majority of studies reviewed here. The major endpoints were pain or symptom relief as well as side effects. One retrospective study found that 4 of 14 patients eventually died from disease, at an average follow-up of 6 months. Three of those patients died of systemic disease, and one died of local progression.[31] One prospective study reported that 2 of 15 patients died at an average follow-up of 9 months, but no specific cause of death was given.[27]

With such a heterogeneous group of studies, it is difficult to make a definitive claim about the survival benefit of SBRT. Patient-, disease-, and treatment-related factors (including performance status, tumor type and radioresistance, tumor burden and number of metastatic lesions, treatment response, and many others) will have an effect on survival in patients receiving SBRT. Additionally, to the best of our knowledge, no studies have compared SBRT and conventional radiotherapy head-to-head for the treatment of bony metastases with survival as a primary endpoint. The need for a well-organized study to examine the potential survival benefit of this technology and how it compares to conventional radiotherapy in this patient setting is warranted.

Cost-Benefit Analysis

A cost-effectiveness analysis is very important in the evaluation of a new treatment approach such as SBRT. This can be performed by collecting and comparing cost and outcome data (symptom or pain relief, use of medications, survival, side effects, symptom-free duration, frequency of retreatment, and many others) for patients undergoing SBRT or conventional radiotherapy in
randomized trials. Various randomized trials have compared a conventional single-fraction regimen with a conventional multifraction regimen.[1-5] To date, no reported randomized trial has compared SBRT and conventional radiotherapy in patients with painful bone metastases. SBRT may benefit most patients with isolated or oligometastases and more radioresistant tumors. However, SBRT is more expensive than conventional radiotherapy. A cost-benefit analysis is needed in future studies.

Summary and Conclusions

The use of SBRT has been shown to be safe and effective in relieving bone pain from metastatic disease. Current published results suggest that we can use single-fraction stereotactic radiosurgery at up to 20 Gy for relief of acute bone pain. Importantly, this is true even for radioresistant tumor types such as melanoma and renal cell carcinoma. However, the optimal dose schedule for specific tumor types is not known. Spinal cord toxicity is minimal when 10% of the restricted spinal cord volume (encompassing 5 mm above and below the target) receives 10 Gy or less. Overall pain relief with this technique is around 90%. Symptomatic relapse rates can range from 5% to 12% (unpublished data), depending on treatment dose and tumor pathology. It is difficult to draw specific conclusions concerning what factors may necessitate a higher dose per fraction or what other factors influence outcomes. Additionally, no trials have investigated hypofractionation, as opposed to single fractionation, in the treatment of bony metastases. Such evaluations have been performed in the conventional radiotherapy literature, and it would make sense for the SBRT literature to follow suit. Furthermore, the reporting of degree of pain relief would further elucidate the usefulness of this therapy. Large well-designed prospective trials of SBRT with long-term follow-up are warranted. In addition, various tumor pathologies and their respective outcomes need to be evaluated in separate studies. Level 1 evidence can then be used to make specific conclusions regarding SBRT and its clinical utility.

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