Original Contribution

Spinal radiosurgery for metastatic disease

Scott G. Soltys, MD, and Iris C. Gibbs, MD

Department of Radiation Oncology, Stanford University, Stanford, CA

Management of metastatic spinal disease, which affects more than 100,000 patients yearly, is a continuing challenge. Treatment of symptomatic lesions often includes radiotherapy to control pain and neurologic symptoms. Advances in the delivery of radiation have allowed the implementation of radiosurgical principles, initially developed for the treatment of intracranial disease, to extracranial sites such as the spine. The authors examine the rationale behind the increasingly common use of spinal stereotactic radiosurgery, some of the initial data supporting it, and its potential advantages over conventional fractionated radiotherapy.

The spine is the most common site of skeletal metastatic disease. Nearly 40% of bony metastases involve the vertebrae,[1] and more than 100,000 patients are affected yearly.[2] In addition, each year, more than 20,000 cancer patients with advanced disease develop epidural spinal cord compression, a medical emergency.[3] Although spinal lesions may be asymptomatic, many patients experience back pain or neurologic compromise from spinal cord or nerve root impingement. Treatment for spinal metastases may include systemic chemotherapy, surgery, or radiotherapy. Symptomatic lesions are often treated with radiotherapy to control pain or neurologic symptoms and decrease the risk of pathologic fracture.

In the United States, conventionally fractionated external-beam radiotherapy (EBRT) for skeletal metastases is typically delivered over 5–20 days to a total dose of 20–40 Gy (most commonly 30 Gy in 10 fractions); in contrast, single-fraction treatments of 8 Gy are common in Europe.[4] These doses are used to provide short-term regression of tumor-related symptoms but are often suboptimal for long-term control of extensive disease. Up to 25% of patients may experience tumor progression within 2 years of treatment with conventional radiotherapy.[5] Retreatment of these patients who have received prior radiation therapy is limited by the low tolerance of the spinal cord to irradiation. Given the low radiation tolerance of the spinal cord and the need for improved local control of disease, investigators have translated their experience with stereotactic radiosurgery of intracranial metastases to the treatment of spinal metastases.

Stereotactic radiosurgery

Radiosurgery, as conceived by Lars Leksell of the Karolinska Institute in Sweden,[6] is designed to deliver an ablative dose of radiation to a lesion, targeted by stereotactic localization, with a rapid dose falloff, minimizing irradiation of surrounding normal structures. Stereotactic radiosurgery (SRS) is a well-established, accepted standard treatment for various intracranial targets.[7] SRS for metastatic disease to the brain results in up to 85%–95% local tumor control.[8–10] The use of extracranial SRS, also known as stereotactic body radiotherapy, has been investigated for the treatment of spinal metastases.

Treatment of spinal lesions

Radiosurgical systems that use an invasive head frame for stereotactic immobilization are limited by the inability to treat the entire spine. The first report of spinal SRS in 1995 attempted to translate stereotactic principles to the treatment of spinal tumors.[11,12] Although the clinical results seemed promising, the need for general anesthesia and the invasive spinal fixation required prevented wide application of this technique. In 1994, a prototype of the CyberKnife® (Accuray, Inc., Sunnyvale, CA) radiosurgical system was developed at Stanford University,[13] and the first spinal lesion was treated with this system in 1996.

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Correspondence to: Scott G. Soltys, MD, 875 Blake Wilbur Drive, Stanford, CA 94305-5847; telephone: 650-724-1569; fax: 650-725-8231; e-mail: sgsoltys@stanford.edu.

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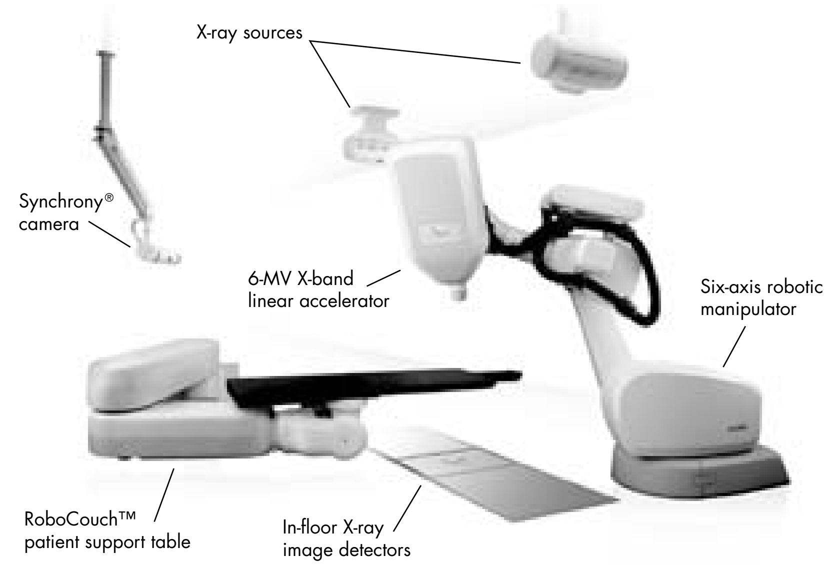

FIGURE 1 CyberKnife® image-guided robotic radiosurgery system.

With a radiographic image-guidance system coupled to a robotically controlled treatment-delivery system, the CyberKnife allows for frameless, noninvasive radiosurgery with exquisite accuracy and precision. A pair of ceiling-mounted x-ray imaging sources and two amorphous silica flat-panel detectors placed on the floor of the treatment room (Figure 1) comprise the image-guided targeting system. Treatment is delivered through a lightweight, compact 6-mV X-band linear accelerator (LINAC) mounted on a robotic manipulator. High-resolution digital images are acquired in real time and registered to digitally reconstructed radiographs by aligning implanted metal fiducials or bony anatomy, using Accuray's Xsight™ spinal tracking system, in three translational and three rotational axes. This information is sent to the treatment-delivery system, where adjustments are made by the treatment couch and the robotic manipulator to achieve accurate and precise targeting of the LINAC. This process is repeated throughout the treatment session to maintain stereotactic accuracy. Generally, patients with spinal metastases receive one to five sessions of irradiation.

The radiosurgical accuracy of the CyberKnife, when used with the Xsight system for spinal tracking, is 0.61 mm.[14] This level of accuracy compares favorably with that of systems such as the Gamma Knife® (Elekta AB, Stockholm, Sweden), which use rigid frame fixation to ensure accuracy (recently reported as ranging from 0.26 to 0.71 mm, depending upon the imaging modality used for treatment planning[15]).

A majority of early data on spinal radiosurgery stem from treatments with the Novalis® system (BrainLAB AG, Feldkirchen, Germany) or the CyberKnife. The Novalis system is similar to the CyberKnife in that it uses an image-guidance system with paired images for treatment setup and delivery to ensure accuracy. Unlike the CyberKnife, but similar to other extracranial SRS systems, the Novalis system uses a fixed gantry linear accelerator and intensity-modulated radiotherapy (IMRT) fields. Other radiation-delivery devices that have been used for spinal radiosurgery include TomoTherapy® (Madison, Wisconsin) and modified linear accelerator systems such as Trilogy® (Varian Medical Systems, Inc., Palo Alto, CA) and AXESSE™ (Elekta AB).[16]

Clinical experience with SRS for spinal lesions

Since the first published use of spinal SRS in 1995,[12] multiple institutions have reported their initial experience with this approach (Table 1).[16–21] The initial Stanford University account of spinal SRS was recently updated.[17] The new report describes the use of SRS to treat 102 spinal metastases in 74 patients, 62 of whom (84%) presented with pain. A total dose of 16–25 Gy was delivered in one to five sessions. Multiple sessions were used in this high-risk population (74% had received prior spinal radiotherapy) when the target was in intimate proximity to the spinal cord. Figure 2 shows a representative treatment plan.

Pain control was achieved in 62 patients (84%).[17] Three patients (4%)

TABLE 1

Selected spinal radiosurgery series

Reference	Radiosurgery/ radiotherapy device	Number of patients (targets)	Median follow-up, mo	Prior radiation therapy, %	Pain relief, %
Rock et al[16]	Novalis	49 (61)	13	0%	84%
Degen et al[18]	CyberKnife®	38 (58)	12	53%	97%
Gibbs et al[17]	CyberKnife	74 (102)	9	74%	84%
Gerszten et al[19]	CyberKnife	393 (500)	21	87%	86%
Chang et al[20]	Varian IMRT	63 (74)	21	56%	NR
Yamada et al[21]	Varian IMRT	45 (45)	9	0%	91%

IMRT = intensity-modulated radiotherapy; NR = not reported developed symptoms attributable to radiation toxicity following SRS. All three patients had epidural spinal cord compression and had previously received full-dose radiotherapy or antiangiogenic therapy.

Degen and colleagues[18] examined pain intensity and quality of life (QOL) of 51 patients who underwent CyberKnife radiosurgery for spinal lesions at Georgetown University Hospital. In all, 14 patients with primary tumors and 38 patients with a total of 58 spinal metastases were treated. After treatment (total dose of 10–37.5 Gy in 1–5 fractions), pain was evaluated using a visual analog scale, and QOL was computed using the 12-item Short Form Health Survey (SF-12) at 1, 3, 6, 9, 12, 18, and 24 months. This study demonstrated not only rapid pain relief—with 84% of patients reporting improvement by the first follow-up visit—but also durable relief beyond 1 year. Patient QOL was maintained throughout the study period, with no significant differences from baseline in either physical or mental well-being 18 months after SRS. Adverse events following radiosurgery were infrequent and minor (three cases each of dysphagia and lethargy, two cases of diarrhea, and one instance each of paresthesia and wound dehiscence).

Gerszten and coworkers[19] published an update of the largest spinal SRS series yet reported, comprising 500 treated tumors in 393 patients. Pain was the indication for SRS in 67% of the patients. Long-term pain improvement was seen in 86% of all patients, and long-term radiographic local control was achieved in 88%. No radiation-associated spinal cord injury was observed.

Ryu et al treated 61 metastases in 49 patients with single-fraction SRS using the Novalis system.[16,22] Similar to the results reported in other series, 84% of patients had durable palliation of pain at 1 year. One case of radiation myelopathy was encountered in a patient with extensive base-of-skull involvement in 230 total targets.[23]

In a recent report of a phase I/II study of near-simultaneous IMRT of the spine, 63 patients with 74 spinal and paraspinal metastases were treated with 27 Gy in 3 fractions or 30 Gy in 5 fractions.[20] Treatment was delivered using a BodyFIX® body frame (Elekta AB) and the EXaCT Targeting™ system (Varian Medical Systems, Inc.), which integrate a CT scanner on rails with a conventional linear accelerator. Although the percentage of patients achieving pain relief was not reported, a Brief Pain Inventory (BPI) of the patients' worst pain level at 2, 4, 8, 12, and 24 weeks after treatment showed significant improvement at 2 weeks, which was maintained at 24 weeks.

Finally, Yamada et al[21] reported, in abstract form, the use of IMRT with an immobilization body cradle to treat 45 patients with spinal tumors. Local tumor progression and symptoms were seen in 9% of the patients.

Potential advantages of spinal SRS

Initial studies of SRS for spinal metastatic disease were performed primarily in patients who had received prior radiotherapy to the spinal cord for recurrent spinal disease or following primary treatment of thoracic, head and neck, or gastrointestinal malignancies. Before the advent of spinal radiosurgery, these patients were typically not offered further radiotherapy because of the high risk of inducing radiation myelopathy. SRS in these patients, who had already received radiotherapy up to the accepted full tolerance of the spinal cord, allows retreatment while minimizing the dose delivered to the spinal cord.

Given the success of the initial experience with SRS, the use of spinal radiosurgery as a primary treatment modality is increasing, likely because it offers a number of potential advantages (Table 2). In general, radiosurgery, delivered in a single session or over a course of up to 5 days, is more convenient for the patient than the typical 10–20 days needed for conventional fractionated radiotherapy. Each radiosurgical treatment, however, takes up to 60–90 minutes, rather than 15 minutes for EBRT, an issue with patients who have difficulty lying immobile or controlling their pain. The short length of treatment with SRS minimizes any delay in delivering systemic chemotherapy, which often is postponed during fractionated treatment to avoid the increased toxicity of concurrent therapy. The rapid dose fall off associated with radiosurgery minimizes the radiation dose delivered to the spinal cord as well as structures anterior to the spine, such as the bowel, lungs, heart, esophagus, and larynx; therefore, acute reactions, such as nausea, diarrhea, and esophagitis, generally are less frequent than with the use of EBRT.

Given the necessity of a margin with EBRT, the target volume usually includes at least one vertebral body both above and below the vertebra involved with tumor. The targeting of only the tumor within the vertebra with spinal SRS minimizes the dose to normal bone marrow, potentially decreasing the risk of hematologic toxicity with future

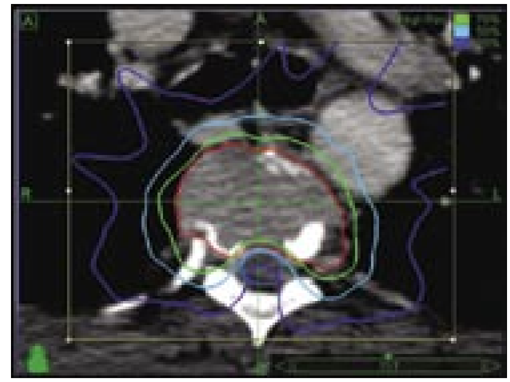

FIGURE 2 A representative radiosurgery treatment plan in a patient with a spinal metastasis and mild epidural compression. The spinal tumor target (red contour) is covered by the 70% isodose line (green contour) prescribed to deliver 24 Gy in three sessions. The 50% (cyan) and 25% (dark blue) isodose lines are shown, displaying the relative sparing of the spinal cord and surrounding structures.

TABLE 2

Potential advantages and disadvantages of spinal radiosurgery compared with conventional radiotherapy

Potential advantages of spinal radiosurgery over conventionally fractionated radiotherapy

- Convenience for patient: 1–5 days of treatment rather than 10–20 days
- Minimization of delay of systemic chemotherapy while receiving radiosurgery
- Less irradiated bone marrow, given smaller margin on tumor
- Ability to treat tumors to radiobiologically higher doses, with possibly improved local control rates
- Radiosurgical dosing may overcome the relative radioresistance of histologies such as melanoma, prostate cancer, and renal cell carcinoma
- Minimization of spinal cord dose, allowing re-irradiation over the spinal cord if necessary
- Less acute toxicity, depending upon target size and location

Potential disadvantages of spinal radiosurgery vs conventionally fractionated radiotherapy

- Not ideal for large targets over multiple vertebral body levels
- Subclinical disease may exist beyond the radiosurgical target as outlined by imaging
- Data regarding tolerance dose of spinal cord are evolving
- Accessibility for patient: technique available only at specialized radiation oncology centers

myelosuppressive chemotherapy.

Another advantage of SRS over EBRT is that the large radiation doses typically delivered with SRS allow radiobiologic tumor dose escalation. For example, using a generalized linear quadratic formula to predict the cell-killing efficiency of radiotherapy,[24] 20 Gy of radiosurgery given in 1 day is equivalent to approximately 50 Gy delivered in 2-Gy fractions over 25 days. For tumor histologies traditionally thought to be relatively radioresistant, such as renal cell carcinoma, prostate adenocarcinoma, and melanoma, the radiobiologic dose escalation may be even greater.

Summary

Initial studies of the application of SRS to treat metastatic spinal tumors demonstrate a high degree of efficacy and safety. Durable pain relief, as well as long-term local tumor control, is achieved in over 85% of patients. Moreover, spinal SRS is often the only available treatment option for individuals who have received prior radiotherapy. As outlined in this article, spinal SRS may become the preferred and definitive treatment approach for patients upon the initial diagnosis of metastatic disease, similar to the evolution and now routine use of SRS for brain metastases.

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ABOUT THE AUTHORS

Affiliations: Dr. Soltys is Clinical Instructor and Dr. Gibbs is Associate Professor, Department of Radiation Oncology, Stanford University, Stanford, CA.

Conflicts of interest: Dr. Soltys has received honoraria for clinical presentations from Accuray, Inc. Dr. Gibbs has received honoraria for clinical presentations and is a member of the Clinical Advisory Board of Accuray, Inc., the manufacturer of CyberKnife.