

# Special Report

## Spinal Radiosurgery for Metastatic Disease of the Spine

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**Background:** *Metastatic tumor in the spinal column is common, causing symptomatic spinal cord compression in approximately 25,000 patients annually. Although surgical treatment of spinal metastases has become safer, less invasive, and more efficacious in recent years, there remains a subset of patients for whom other treatment modalities are needed. Stereotactic radiosurgery, which has long been used in the treatment of intracranial lesions, has recently been applied to the spine and enables the effective treatment of metastatic lesions.*

**Methods:** *We review the evolution of stereotactic radiosurgery and its applications in the spine, including a description of two commercially available systems.*

**Results:** *Although a relatively new technique, the use of stereotactic radiosurgery in the spine has advanced rapidly in the past decade. Spinal stereotactic radiosurgery is an effective and safe modality for the treatment of spinal metastatic disease.*

**Conclusions:** *Future challenges involve the refinement of noninvasive fiducial tracking systems and the discernment of optimal doses needed to treat various lesions. Additionally, dose-tolerance limits of normal structures need to be further developed. Increased experience will likely make stereotactic radiosurgery of the spine an important treatment modality for a variety of metastatic lesions.*

### Introduction

Metastatic disease in the spine is common, affecting up to 70% of cancer patients, with the vertebral column being the most frequent site of bony metastases.<sup>1-3</sup> Among patients with bony spinal metastases, 10% to 20% (or approximately 25,000 patients annually) will develop symptomatic spinal cord compression.<sup>4,6</sup> Treatment of these lesions has traditionally centered on the use of pain medications, corticosteroids, and chemotherapy. Surgical treatment was limited to cases of tumor progression associated with spinal instability, pain or neural compression with acute or progressive neurologic decline. During the last decade, however, surgery has

become safer and more feasible in this patient population because of recent advances in technique and spinal instrumentation.<sup>4,7-9</sup> Surgery is now a viable option for most patients and has a demonstrated efficacy in neural decompression and in maintaining spinal stability for the remainder of the patient's life.<sup>7</sup> However, in some patients, poor overall medical condition, limited life expectancy, or widespread spinal disease makes the surgical option inordinately risky or impractical.

External-beam radiotherapy (EBRT), used either alone or in conjunction with surgical decompression, has been a mainstay of treatment of metastatic disease for many years and can often be used to accomplish the goals of palliation and disease control.<sup>10,11</sup> However, the utility and efficacy of this modality are limited. EBRT utilizes a relatively broad, unfocused energy beam that radiates all structures in its field. This presents an obvious treatment limitation, especially in cases of relatively radioresistant tumors in which toxicity to organs at risk (OARs) may prevent the administration of doses needed for oncologic control.<sup>12-16</sup> Radiation administered in this manner affects the overlying skin and fascial layers and may impede wound healing in patients who have undergone surgical intervention.<sup>17</sup> Broad radiation fields may also affect clinically significant amounts of bone marrow and delay chemotherapy in patients with poor reserves. Although EBRT is effective in providing palliative relief in patients with significant pain, the palliative effects are often slow to be realized, with two thirds of

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**Abbreviations used in this paper:** EBRT = external-beam radiotherapy, OARs = organs at risk, LINAC = linear accelerator.

the patients experiencing pain relief at 3 months.<sup>11</sup> Finally, EBRT has significant logistical limitations. Because the spinal cord and other OARs tolerate radiation better in small, fractionated doses, EBRT is administered in daily fractions over a period of 2 to 4 weeks.<sup>18,19</sup> This presents a disadvantage for patients with a limited longevity, especially those who do not live near a center capable of providing EBRT. Although EBRT has been invaluable in the treatment of metastatic disease, its limitations are significant.

Improvements in cancer diagnosis and treatment have resulted in longer patient survival, and thus the treatment of metastasis is becoming a primary focus of practice. New treatments must be devised that address both tumor control and quality of life in a safe and targeted manner. Radiosurgery is one such treatment that holds significant promise for the treatment of spinal metastases. This technique is capable of accurately delivering a highly focused dose of radiation in a single session to a specified target while sparing closely surrounding structures of clinically relevant doses.<sup>20,22</sup> Single-dose radiation probably has a greater radiobiological effect than EBRT and has been shown to be superior in lesion control.<sup>23</sup> In the treatment of metastatic brain disease, it has a demonstrated efficacy and safety, with lesion control being achieved in more than 85% of cases.<sup>20,22,24</sup>

The concept of radiosurgery is ideal for the treatment of spinal metastatic disease because of its ability to accurately target areas that can be difficult or impossible to reach with surgery while sparing critical surrounding structures from the effects of radiation. The technique, however, has been hampered by problems with ensuring accurate target immobilization and localization for delivery of radiation. Because high doses are given, errors in delivery can have potentially disastrous results. The spinal column, unlike the skull, is highly mobile, and devising a means of rigid fixation has been problematic. In recent years, however, significant advances in imaging and computer technology have led to several solutions to this problem, and the use of radiosurgery in the treatment of spinal metastasis is now a practical reality. In this article, we review the evolution of spinal radiosurgery, describe current techniques and delivery systems, and discuss current indications, outcomes, and areas needing further study.

## History of Spinal Radiosurgery

The concept of stereotaxis for accurate navigation of the spine was first reported in the 1870s, when Woroschiloff<sup>25</sup> developed a rigid skeletal fixation system that allowed insertion of an electrode into the spinal cord to study neurophysiological function. Since then, others have used stereotaxy to navigate the spine and perform various procedures, including biopsies,

tractotomies, cordotomies, and the production of various spinal cord lesions.<sup>26-29</sup>

In 1951 Leksell<sup>30</sup> combined stereotactic targeting of intracranial lesions with the delivery of multiple crossed beams of radiation and thus created the concept of stereotactic radiosurgery. The cranial vault was ideal for the development of radiosurgery because it provides a rigid structure that is easily immobilized and has a constant relationship with its contents. Extracranial fiducial markers could thereby precisely localize intracranial lesions. Advances in imaging techniques, namely computed tomography (CT) and magnetic resonance imaging, combined with improvements in computer technologies, have dramatically advanced the state of radiosurgical management of intracranial lesions, making complex lesions adjacent to critical structures amenable to treatment. However, treatment remains frame-based and requires the use of a fixed cranial immobilizer and extracranial fiducial markers.

Challenges with immobilization and localization hindered the use of radiosurgery in the spine until 1995 when Hamilton et al<sup>31</sup> reported their use of the modality in the treatment of 5 patients with metastatic neoplasms of the spine. These authors developed a system in which a fiducial frame was surgically attached directly to the spinous process, providing immobilization and accurate target localization. A linear accelerator (LINAC)-based system was used to irradiate the lesion, which had been delineated on CT scanning (described below). They reported on the radiographic and clinical success of all 5 patients treated. Although all of these patients had been treated with EBRT previously and mean follow-up monitoring was only 6 months, this study was a landmark because it demonstrated the feasibility and safety of using radiosurgery in the treatment of extracranial lesions. The technique itself was still somewhat crude in that it required placement of a surgical fiducial marker under general anesthesia and prone positioning of the patient, which makes the spine more susceptible to respiratory motion.

Further efforts that focused on target tracking and radiation delivery culminated in the development of the Cyberknife system (Accuray Inc, Sunnyvale, Calif). This more practical spinal radiosurgical delivery system was described in an initial report of the treatment of 16 patients with various spinal lesions in 2001.<sup>32</sup> This system was unique in that it implemented internal fiducials that could be implanted using a minimally invasive technique instead of a fixed external frame requiring general anesthesia. Once implanted, the fiducials could be tracked in real time using x-rays. The direction of the beam is also altered in real time to account for target motion. The newest iteration of this system can track target and respiratory motion directly, thus eliminating the need for implanted fiducials in most cases. The Novalis Shaped-Beam system (BrainLAB, Ammerthalstrabe, Ger-

many) adopted some of these innovations to create an additional method for the delivery of focused radiation to the spine. These two are the primary systems available today for stereotactic radiosurgery of the entire spine and are discussed in more detail below. A third system, the Gamma Knife (Elekta AB, Stockholm, Sweden),

requires rigid cranial fixation and has been used principally in the treatment of intracranial pathology, although it is capable of treating high cervical lesions. This system is not discussed in detail in this article.

## Novalis Shaped-Beam System



Fig 1. — The Novalis Shaped-Beam system. Photo courtesy of BrainLAB AG, Ammerthalstrabe, Germany.

The Novalis Shaped-Beam system consists of a 6-MV photon energy LINAC and a micro-multileaf collimator (mMLC), which uses 26 pairs of leaves to alter the shape of the beam emitted from the LINAC (Fig 1). The system is capable of delivering radiation to uniquely shaped targets in numerous ways, including through a circular cone, a fixed-shaped conformal beam using the mMLC, fixed- or dynamic-shaped conformal arcs using the mMLC, or a fixed gantry using static or dynamic intensity-modulated beams. Intensity modulation is a technique used to increase the potency of the dose to the lesion and reduce the potency of the dose to OARs by varying the dose of the beam in real time as it moves through various planes.

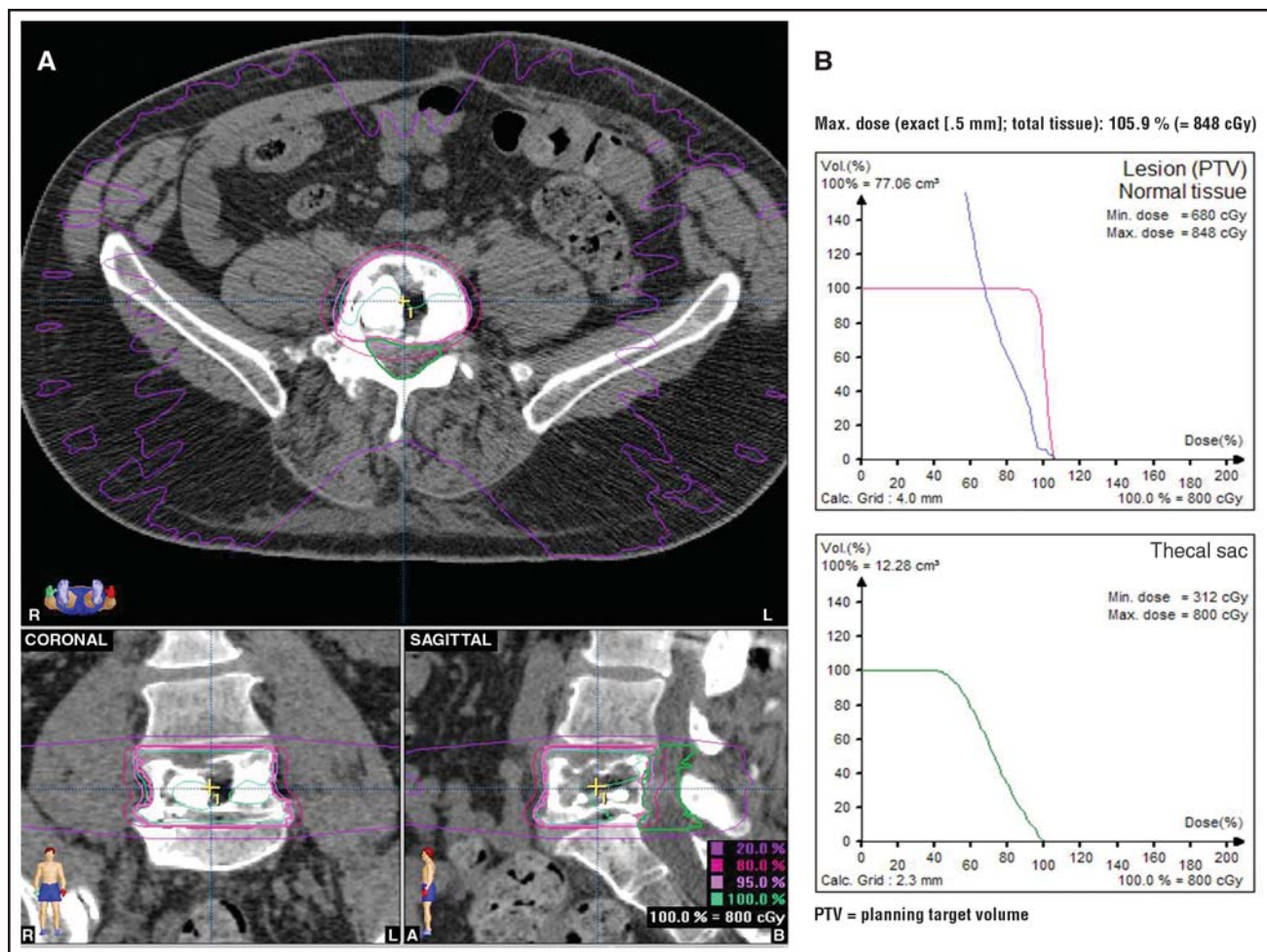


Fig 2A-B. — (A) Target planning image. The thick dark pink line surrounds the target volume. The thick dark green line represents the thecal sac (main organ at risk). The remaining lines represent isodose lines. (B) Dose-volume histograms demonstrating steep falloff of radiation, with high doses being applied to the lesion and a low volume of the thecal sac being exposed to significant dose.

Target positioning accuracy is maintained with a patient immobilization method, such as the BodyFix vacuum body-fixing device (Philips Medical Systems, Cleveland, Ohio) and two image-guided localization devices (the Novalis Body and ExacTrac systems) working in tandem. The ExacTrac is an alignment system that consists of infrared fiducial markers placed on the patient's body at the time of CT scanning. These are then registered in a computer plan and used during treatment to align the patient, and thus the target, with the LINAC beam by adjusting the position of the table. Position is fine-tuned with the Novalis Body system, which is made up of two perpendicular keV x-ray tubes that compare anatomic landmarks of the patient (eg, vertebral body anatomy) with those from the planning CT scan. Deviations in location are forwarded to the ExacTrac system, which then moves the patient to ensure accurate alignment of target with the LINAC beam.

The procedure begins with the acquisition of a CT scan with the patient in the body-fixing device and the infrared fiducial markers in place. These images are then sent to a planning station where the lesion, or clinical target volume, and the OARs are outlined. A 2- to 3-mm margin is included in the clinical target volume in most cases to account for possible positioning deviation. A treatment plan is devised using these data and an inverse planning algorithm,<sup>33</sup> the details of which are beyond the scope of this review. Dose-volume histograms are created to examine the doses to be given to the target and each OAR (Fig 2). Most treatments in the spine require five to nine intensity-modulated beams to accomplish safe delivery of effective doses to the target. Once an acceptable plan is devised, the data are transferred to the ExacTrac and Novalis Body system, and a test using a verification phantom is completed to confirm isocenter. The treatment is carried out as described above, with the patient immobilized in the BodyFix device and alignment ensured by using the ExacTrac and Novalis Body systems.

The accuracy and precision of the Novalis Body system have been verified with delivery of the radiation dose to be within  $1.36 \pm 0.11$  mm of the planned isocenter.<sup>34-36</sup> Fall-off is steep, with only approximately 10% of the anterior spinal cord receiving 80% of the prescribed dose.

## Cyberknife System

The Cyberknife system was developed at Stanford University and has been used in the treatment of intracranial lesions since 1994 (Fig 3).<sup>37,38</sup> The system consists of a lightweight 6-MV LINAC attached to the end of a robotic arm that has six axes of freedom. The beam can be aimed in a broad array of directions and the target is not confined to isocenter geometry, thus enabling bet-

ter conformation to irregularly shaped targets.<sup>32</sup> Target positioning is continuously updated via two perpendicular, ceiling-mounted x-ray cameras that compare anatomic data from the planning CT scan with the patient's anatomy. Adjustments in position are relayed in real time, and the beam trajectory is adjusted accordingly. Thus, the patient does not need to be rigidly immobilized. The Cyberknife delivers approximately 100 to 150 beams to the target in this fashion with an accuracy of  $1.1 \pm 0.3$  mm accuracy.<sup>39</sup>

Treatment begins with the placement of fiducial markers, which are small gold or stainless steel screws or rods. These may be placed percutaneously under fluoroscopic guidance as an outpatient procedure or at the time of surgery if the patient is undergoing partial debulking with planned postoperative radiosurgery. Typically, four to five fiducial markers are placed, although multiple lesions may necessitate the placement of additional markers. Newer real-time target and respiratory tracking technology has enabled the implementation of accurate fiducial-free target registration and dose administration; it has also broadened the range of treatment applications to lesions in the lungs and abdomen.<sup>40,41</sup> A CT scan is then performed with 1.25-mm cuts, and the resulting studies are used to create a plan in the same way as with the Novalis system. Both the clinical target volume and OARs are outlined. An inverse treatment planning technique is used. The patient is then placed in the Cyberknife machine and treated as described above.

## Radiosurgical Treatment of Metastatic Lesions

The indications for the treatment of spinal metastatic disease with stereotactic radiosurgery are not rigidly defined and continue to evolve as experience accrues. Common goals of treatment include pain elimination, tumor control, prevention or reversal of neurologic deficit, and treatment of residual tumor after surgery.



Fig 3. — The Cyberknife system. Photo used with permission from Accuray International, Accuray Inc, Sunnyvale, Calif.

The use of stereotactic radiosurgery must be tailored to each patient on the basis of the individual's prognosis, overall health, and ability or desire to undergo surgery or other treatments.

Pain is the most common indication for the radiosurgical treatment of spinal lesions, and the efficacy for this indication has been well documented in the literature. Several studies have demonstrated significant pain relief in more than 90% of patients with vertebral metastases.<sup>32,42-47</sup> Pain relief has been rapid, with reports of relief being obtained as early as 24 hours.<sup>48</sup> One report noted that all 26 patients experienced pain relief within 72 hours of treatment using the Novalis system.<sup>43</sup> Rapid responses may be proportionate to dose, with one author reporting a trend towards more rapid response with higher doses of radiation.<sup>43</sup> Finally, radiosurgery likely alleviates pain more quickly and in more patients than does EBRT, which is effective in two thirds of patients at 3 months.<sup>11</sup> Pain relief has also proven to be durable; in a report of 135 patients treated with the Novalis unit, 84% experienced continued relief at 1 year,<sup>49</sup> and 86% of 336 patients undergoing Cyberknife treatment experienced long-term relief.<sup>42</sup> Radiosurgery can thus be considered a treatment of choice for neurologically intact patients with metastatic disease and pain.

Although a randomized, controlled trial has not yet been completed, radiosurgery appears to be at least as efficacious as EBRT in achieving lesion control. Complete tumor regression has been reported, and control of tumor growth in most series has been reported in 75% to 100% of cases for which this was the indication to treat and for more than 95% of all patients.<sup>42,45,46,50</sup> There is likely a dose-response effect for tumor control; De Salles et al<sup>47</sup> noted a 36% rate of tumor progression at an average follow-up of 6.1 months in their series of 22 lesions treated with the Novalis unit and a mean dose of 12 Gy. In those studies with better control rates, higher doses (approximately 20 Gy) were used, similar to those used for cranial procedures. When recurrence does happen, it occurs at the margin of the treated volume and tends to occur in larger tumors.<sup>46,48</sup> Future strategies aimed at preventing such failures might include increasing the volume of normal tissue treated and using functional imaging to aim treatment at hypoxic areas of actively growing tumor.<sup>46</sup>

Radiosurgery is ideally suited to treat well-circumscribed spinal metastases in a variety of situations. First, tumors that are relatively radioresistant, such as renal cell carcinoma and melanoma, often progress after treatment with EBRT alone.<sup>12-16</sup> Radiosurgery has shown utility in both palliation and tumor control for these tumor types in retrospective series.<sup>45,46</sup> This added efficacy is likely secondary to the advantageous radiobiological effects of a single high dose of radiation.<sup>23</sup>

Radiosurgery may also be well suited for lesions that are difficult to access surgically. This is extremely

relevant in the treatment of spinal metastatic disease, which frequently affects the vertebral bodies of the thoracic spine.<sup>10</sup> Surgical access to this region often involves sternotomy, thoracotomy, or a thoracoscopic approach with significant morbidity and recovery time. In some cases, not all of the tumor may be amenable to resection, even with extensive approaches. In these circumstances, the surgeon can place fiducial markers intraoperatively and plan for radiosurgery shortly postoperatively. Because the field is focused and the overlying tissues are exposed to minimal radiation, wound healing is not a major concern. This strategy may also be useful in patients presenting with myelopathy secondary to tumor compression. Instead of subjecting the patient to a major anterior-posterior decompression, resection, and instrumentation and the attendant morbidity, a simple posterior decompression and stabilization can be performed together with postoperative radiosurgery. Additionally, certain metastatic lesions, such as melanoma and renal cell carcinoma, tend to be vascular, and attempts at surgical excision are often complicated by significant blood loss and increased morbidity.<sup>51-54</sup>

The use of radiosurgery to treat patients with neural compression syndromes (ie, myelopathy and radiculopathy) is controversial. Traditionally, these problems have been treated surgically, which has been viewed as providing the quickest means of decompressing the neural elements and providing the greatest chance of recovery. However, several authors have reported on the treatment of patients with neurologic compromise with good, and sometimes remarkable, results.<sup>36,44</sup> One general exception to the use of radiosurgery in this situation is the presence of bony compression secondary to a pathologic fracture. These cases are unlikely to be helped by radiosurgery and are best treated with surgical decompression. It remains to be determined which treatment, radiosurgery or surgery, will provide optimal outcome in cases of neural compression caused by tumor growth. We favor the use of urgent surgical decompression for acute and progressive neurologic decline because this likely provides the best chance of improvement. This indication might change as a better understanding of radiation dose-response behaviors for different tumor types is gained.

Finally, spinal instability has been treated traditionally with surgery. Rao et al<sup>55</sup> recently demonstrated bony reconstitution in select patients with multiple myeloma and pathologic instability following treatment with EBRT and a cervical collar.<sup>55</sup> Whether use of radiosurgery for more radioresistant tumors will have similar results is unknown, but future investigation is warranted.

A current limitation of this application that needs further consideration is in the area of dose optimization for the treatment of specific lesions. This concept involves determining the amount of single-dose radiation necessary to control a specific lesion as well as the

amount of single-dose radiation nearby OARs can withstand without toxicity. The spinal cord has been the cause of most trepidation because it is susceptible to both early and late effects of radiation including L'Hermite's sign, acute paralysis, lower motor neuron disease, and radiation necrosis.<sup>56-58</sup> No good data are currently available on the tolerance of the spinal cord to single-dose radiation.<sup>34</sup> A figure of 800 Gy has been used by several authors, who extrapolated from safety data of radiation to the optic nerve in cranial radiosurgery.<sup>36,59</sup> This number is likely to be liberalized with additional experience because deleterious effects to the cord have yet to be realized in most series with follow-up of 2 years or more.<sup>60</sup> One group suggested that radiating <10% of the volume of the cord over <2 spinal segments with 10 Gy may be safely tolerated.<sup>60</sup> The dose tolerance of the cauda equina is also undefined but appears to be higher than that of the cord, with doses of up to 14 Gy being tolerated without obvious side effect.<sup>46</sup> Factors known to affect the radiation tolerance of the spinal cord include the fractionation scheme, the volume of cord irradiated, patient age, and chemotherapy.<sup>61</sup> Other organs with known radiation sensitivity that might be at risk with stereotactic techniques include the larynx, heart, lungs, kidneys, esophagus, and gastrointestinal tract.<sup>43</sup> Dose escalation studies and close follow-up monitoring will be needed to determine the ideal compromise between dose and efficacy. Additionally, tolerance of OARs in the setting of chemotherapy, diabetes, and prior radiation treatments must be elucidated.

## Conclusions

Stereotactic radiosurgery is a treatment modality long utilized in the treatment of brain metastases that has only recently been applied to the treatment of spinal metastases. Numerous series and case reports have demonstrated its efficacy and safety in lesion control and palliation. Continued research is needed to determine optimal doses for lesion treatment, to avoid toxicities, to refine patient selection criteria, and to elucidate long-term outcomes. Ultimately, randomized, controlled trials will need to be implemented to demonstrate any superiority to surgical treatment or radiation therapy. Results thus far are promising and the technique offers significant theoretical advantages. With additional experience, it is likely that stereotactic radiosurgery of the spine will become an additional treatment modality for patients with symptomatic and asymptomatic spinal metastases.

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