CyberKnife frameless single-fraction stereotactic radiosurgery for tumors of the sacrum

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Object. The role of stereotactic radiosurgery for the treatment of intracranial lesions is well established. The experience with radiosurgery for the treatment of spinal and sacral lesions is more limited. Sacral lesions should be amenable to radiosurgical treatment similar to that used for their intracranial counterparts. The authors evaluated a single-fraction radiosurgical technique performed using the CyberKnife Real-Time Image-Guided Radiosurgery System for the treatment of the sacral lesion.

Methods. The CyberKnife is a frameless radiosurgery system based on the coupling of an orthogonal pair of x-ray cameras to a dynamically manipulated robot-mounted linear accelerator possessing six degrees of freedom, which guides the therapy beam to the intended target without the need for frame-based fixation. All sacral lesions were located and tracked for radiation delivery relative to fiducial bone markers placed percutaneously. Eighteen patients were treated with single-fraction radiosurgery. Tumor histology included one benign and 17 malignant tumors.

Dose plans were calculated based on computerized tomography scans acquired using 1.25-mm slices. Planning treatment volume was defined as the radiographically documented tumor volume with no margin. Tumor dose was maintained at 12 to 20 Gy to the 80% isodose line (mean 15 Gy). Tumor volume ranged from 23.6 to 187.4 ml (mean 90 ml). The volume of the cauda equina receiving greater than 8 Gy ranged from 0 to 1 ml (mean 0.1 ml). All patients underwent the procedure in an outpatient setting. No acute radiation toxicity or new neurological deficits occurred during the mean follow-up period of 6 months. Pain improved in all 13 patients who were symptomatic prior to treatment. No tumor progression has been documented on follow-up imaging.

Conclusions. Stereotactic radiosurgery was found to be feasible, safe, and effective for the treatment of both benign and malignant sacral lesions. The major potential benefits of radiosurgical ablation of sacral lesions are relatively short treatment time in an outpatient setting and minimal or no side effects. This new technique offers a new and important therapeutic modality for the primary treatment of a variety of sacral tumors or for lesions not amenable to open surgical techniques.

KEY WORDS • CyberKnife • image-guided surgery • radiosurgery • robotic surgery • sacral tumor • stereotaxis

Stereotactic radiosurgery is currently regarded as a standard treatment modality for a number of intracranial neurosurgical disease processes. The role of stereotactic radiosurgery for the treatment of a wide variety of benign and malignant intracranial lesions is well established.^{7,8} Stereotactic radiosurgery is an effective treatment for brain metastases, with or without whole-brain radiation therapy, and produces an 85 to 95% tumor control rate.^{8,12,21,23} Its role for the primary treatment of benign lesions, including arteriovenous malformations, pituitary adenomas, acoustic neuromas, and meningiomas is well supported by the literature.^{5,10,13,19,20,29}

The role of radiotherapy in the treatment of tumors of the spine and sacrum is also well established; however,

conventional external-beam radiotherapy lacks the precision to allow delivery of large doses of radiation near radiosensitive structures such as the spinal cord and cauda equina, thus precluding spinal radiosurgery. It is the low tolerance of the spinal cord to radiation that often limits the treatment dose to a level that is far below the optimal therapeutic dose.^{11,22,28} If the radiation dose could be confined more precisely to the treatment volume, as is the case for intracranial radiosurgery, the likelihood of successful therapeutic radiobiological effect for benign lesions should increase at the same time that the risk of spinal cord injury is minimized.

Current frame-based stereotactic radiosurgery devices do not have the capability of treating lesions below the foramen magnum. Conformal radiotherapy and intensity-modulated radiotherapy are limited by problems with target immobilization. This limitation of intensity-modulated radiotherapy precludes large single-fraction treatment to

Abbreviations used in this paper: CT = computerized tomography; LINAC = linear accelerator; MR = magnetic resonance.

spinal lesions. Conventional frame-based devices used for stereotactic radiosurgery of intracranial lesions involve the use of a rigid frame to immobilize the lesion at a known location in space. The frame acts as a fiducial reference system to provide accurate targeting and delivery of the radiation dose. Intracranial radiosurgery is practical because the lesions are fixed with respect to the cranium, which can be immobilized rigidly in a stereotactic frame. Spinal lesions also have a fixed relationship to the spine; however, stereotactic radiosurgery techniques developed for spinal lesions treated by standard LINACs require the placement of an invasive rigid external frame system directly to the spine and therefore are not technically practical.¹⁷

A unique image-guided frameless stereotactic radiosurgery delivery system known as the CyberKnife (Accuray, Inc., Sunnyvale, CA) has been developed that allows for the treatment of sacral lesions. The system consists of a lightweight LINAC mounted on a robotic arm. Real-time imaging tracking allows for patient movement tracking with 1 mm spatial accuracy.^{3,7,9,28} The CyberKnife was developed as a precise noninvasive means to align treatment beams with targets. It differs from conventional frame-based radiosurgery in three fundamental ways.²⁸ First, it references the position of the treatment target to internal radiographically demonstrated features such as the skull or implanted fiducials rather than to a frame. Second, it uses real-time x-ray imaging to establish the position of the lesion during treatment and then dynamically brings the radiation beam into alignment with the observed position of the target to be treated. Third, it aims each beam independently, obviating the need for a fixed isocenter. Changes in patient position during the treatment are compensated for by adaptive beam pointing rather than controlled through rigid immobilization. This allows the patient to be positioned on the treatment couch without precise reproduction of the position in the treatment planning study.^{1,3,6,28}

With the ability to treat lesions throughout the spine by using fiducial tracking, we evaluated the possibilities of treating sacral lesions with a radiosurgical technique.^{14,26,28} Sacral tumors that are not otherwise candidates for open surgical intervention or conventional external-beam irradiation might benefit from radiosurgical therapy similar to intracranial lesions of the same histologies. Because of the spatial precision with which the CyberKnife can administer radiation, it is theoretically feasible to administer a tumoricidal radiation dose in a single treatment as has been the case for intracranial disease.

CLINICAL MATERIAL AND METHODS

Patient Population

This study involved the prospective evaluation of 18 patients with sacral tumors who were treated using the CyberKnife Image-Guided Radiosurgery System running DTS (Dynamic Tracking System) 3.0 software. All patients were treated at the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, and the protocol was approved by the institutional review board. There were 11 men and seven women. Ages ranged from 47 to 72 years (mean 57 years). Tables 1 and 2 provide summaries of the

TABLE 1
Summary of histological tumor types in 18 patients

Tumor Type	No. of Cases
renal cell	3
multiple myeloma	2
prostate	2
unknown primary	2
colon	2
cervical	2
sarcoma	1
breast	1
melanoma	1
bladder	1
schwannoma	1

lesion histologies and the characteristics of the treatment group.

The CyberKnife System

The CyberKnife consists of a 6-MV compact LINAC that is smaller and lighter than LINACs used in conventional radiotherapy.^{2,16,27} The smaller size allows it to be mounted on a computer-controlled six-axis robotic manipulator that permits a much wider range of beam orientations than can be achieved with conventional radiotherapy devices. The CyberKnife system uses image-guided frameless robotic radiosurgery. Two diagnostic x-ray cameras are positioned orthogonally (90° offset) to acquire real-time images of the patient's internal anatomy during treatment. The images are processed automatically to identify radiographic features (such as skull bone landmarks or implanted fiducials) and are then automatically compared with the patient's CT treatment planning study. The precise tumor position is communicated through a real-time control loop to a robotic manipulator that aligns the radiation beam with the intended target.

The system can adapt to changes in patient position during treatment by acquiring targeting images repeatedly and then adjusting the direction of the treatment beam. The target to be treated is identified prior to treatment on planning CT images, and typically 80 to 120 beams are used to irradiate the target stereotactically. The treatment beam can be maneuvered and pointed nearly anywhere in space. Treatment beams are also not confined to isocentric geometry, so they can be arranged in complex overlapping patterns that conform to irregularly shaped tumor volumes.²⁸ An analysis of the accuracy of the CyberKnife radiosurgery system found that the machine has a clinically relevant accuracy of 1.1 ± 0.3 mm when using a 1.25-mm CT slice thickness. The accuracy of CyberKnife is comparable to published localization errors in other current frame-based radiosurgical systems.⁹

Overview of Treatment

The CyberKnife spinal radiosurgery treatment consists of three distinct components: 1) CT image acquisition based on skull bone landmarks or implanted bone fiducials; 2) treatment planning; and 3) the treatment itself. The sacral lesions in this series were tracked relative to bone fiducials placed adjacent to the lesion. Because these

TABLE 2

Pretreatment- and treatment-related data

Characteristic	No. of Cases or Value
prior external-beam radiotherapy	15
primary indications for radiosurgery	
pain	13
postirradiation tumor progression	3
primary treatment modality	2
additional characteristics	
mean tumor volume (ml)	90
mean dose to 80% isodose line (Gy)	15
mean vol of spinal canal dose >8 Gy (ml)	0.1

implanted fiducials have a fixed relationship with the bone in which they are implanted, any movement in the sacrum would be detected as movement in the fiducials, and this movement is detected and compensated for by the CyberKnife's LINAC.

The CyberKnife is able to detect and track either straight gold fiducials (Alpha-Omega Services, Inc., Bellflower, CA) or stainless-steel screws (Accuray, Inc.). These fiducials are placed percutaneously with the assistance of fluoroscopic guidance. The fiducial placement procedure is performed in the operating room in an outpatient setting. Four to six fiducial markers are placed immediately adjacent to the lesion treated. Three fiducials are required to define a full spatial transformation in all six degrees of target translation and rotation. There were no complications associated with fiducial placement. The patient then returned as an outpatient for the CT treatment planning. The patient was placed supine in a conformal alpha cradle during CT scanning as well as during treatment. Scans were acquired using 1.25-mm-thick slices to include the lesion of interest as well as all fiducials.

The second component of the CyberKnife treatment is the development of the radiosurgical treatment plan. Each treatment plan was devised jointly by a team of neurosurgeons, radiation oncologists, and radiation physicists. In each case, the planning treatment volume was defined as the radiographic tumor volume, not including the margin. The tumor dose was determined based on the histological composition of the tumor, spinal canal and normal structure tolerance, and previous radiation quantity. An "inverse treatment planning" technique was often used such that the tumor received the maximum dose allowable with the restriction of the maximum spinal cord tolerance dose, as well as other critical structures such as small bowel, bladder, colon, and head of the femur.

The third component of the CyberKnife treatment is the actual treatment delivery. All treatments were performed using a single fraction in an outpatient setting. The patients were placed supine on the CyberKnife treatment couch with the appropriate immobilization device. During the treatment, real-time digital x-ray images of the patient are obtained. The location of the sacrum is established from these images and is used to determine tumor location as previously described. No intravenous sedation was used in any of these patients, and monitoring was not performed. Each patient was observed via closed circuit television throughout the treatment. Treatment duration was between 30 and 120 minutes.

RESULTS

Treatment Planning

Table 2 provides a summary of the patient characteristics and treatments. The dose to the tumor margin was based on histological composition of the tumor, location, and the patient's history of fractionated radiotherapy. Fifteen lesions had received prior external-beam irradiation. No patient had undergone prior open tumor resection. Tumor dose was maintained at 1200 to 2000 cGy to the 80% isodose line, contoured at the edge of the target volume (mean 1500 cGy). The maximum intratumor dose ranged from 1500 to 2500 cGy (mean 1800 cGy). Tumor volume ranged from 23.6 to 187.4 ml (mean 90 ml). Later in our series, the doses were escalated once safety to surrounding normal structures had been determined. A limit of 800 cGy was set as the maximum spinal canal dose for treatment planning calculations. The spinal canal (cauda equina) volume receiving greater than 800 cGy ranged from 0 to 1 ml (mean 0.1 ml), and a limit of 800 cGy was set as the maximal dose to the bowel and bladder.

Clinical Outcome

All patients successfully completed the treatment in an outpatient setting. No complications from the fiducial placement or radiosurgical treatment occurred during the follow-up period. Thirteen patients were treated for significant pain related to their lesion. At 1-month follow up axial and radicular pain improved in all 13 patients who were symptomatic prior to treatment.

Three patients underwent radiosurgery for disease progression documented on serial follow-up imaging after receiving conventional external-beam radiotherapy. The tumor types in these three patients included bladder carcinoma, colon carcinoma, and melanoma. Two patients underwent radiosurgery as their primary and only irradiation treatment for the tumors. The tumor types in these two patients were spindle cell sarcoma and an S-1 schwannoma.

Figure 1 documents the case of a 55-year-old man in whom a symptomatic left S-1 schwannoma was diagnosed. He had no history of neurofibromatosis. He suffered from numbness in an S-1 distribution. Axial MR imaging revealed a large left-sided S-1 schwannoma consistent with his complaints. The patient had no motor deficit, and tumor excision was thought to be inappropriate. A percutaneous fiducial placement procedure was performed 1 week prior to his radiosurgery. A 50-mm collimator single-fraction dose of 1800 cGy was administered, which was calculated to the 80% isodose line. The maximum dose was 2250 cGy, and the tumor volume was 98.6 ml. The dose-volume histogram showed that 81.2% of the tumor received 78.2% of the maximum dose of 2250 cGy.

DISCUSSION

Standard treatments for sacral tumors include radiotherapy alone, radiotherapy plus systemic chemotherapy, hormonal therapy, or surgical decompression and/or stabilization followed by radiotherapy.¹⁵ The goals of local radiotherapy in the treatment of sacral tumors have been

Fig. 1. This 55-year-old man presented with a symptomatic left S-1 schwannoma. *Upper Left:* Axial T_2 -weighted MR image demonstrating the lesion (arrow). *Upper Right:* An anteroposterior radiograph showing the implanted fiducial markers around the lesion. The bone erosion of the left S-1 sacral foramen is apparent. *Lower Left:* Isodose lines shown on an MR image obtained for treatment planning (large arrow). Notice the dose homogeneity. The small arrow demonstrates an implanted fiducial. *Lower Right:* Dose-volume histograms (DVHs) showing that 81.2% of the tumor received 78.2% of the maximum dose of 2250 cGy.

palliation of pain, prevention of pathological fractures, and halting progression of or reversing neurological compromise. When a sacral tumor causes compression of neural elements, surgical decompression is often necessary with or without spinal fixation based on the extent of bone destruction and instability. In the past, the role of radiosurgery for the treatment of these lesions has been limited.¹⁴

The use of multiple beams of radiation requires extremely precise control of position and movement of the LINAC. Stereotactic radiosurgery techniques such as the GammaKnife and LINAC-based systems are limited to intracranial disease because precise localization can be achieved only by fixation of stereotactic frames to the patient's skull. Most of these techniques involve a head frame device that is attached by four screws to the patient's skull. This device ensures precise targeting of the radiation to the tumor. As a corollary, therapy is typically limited to single-fraction treatments. Radiosurgery has been used to treat many different intracranial lesions, both benign and malignant, and is widely accepted as both safe and effective.^{4,6,18,24,25,29} There is reason to believe that radiosurgery in which similar doses are used would be equally efficacious in the treatment of sacral lesions.

Few authors have published large series of spinal and sacral single-fraction radiosurgery. In the Stanford University experience, 16 patients with a variety of spinal le-

sions including vascular malformations were treated using both stereotactic radiosurgery and hypofractionated stereotactic radiotherapy.²⁸ There were no sacral lesions reported in this series. These lesions were all thought to be surgically inaccessible. No patient experienced complications as a result of the procedure or progression of disease after at least 6 months of follow up. The technique used at our institution is adapted from the Stanford experience.

There has been no large-scale study in which optimal radiation doses have been established using this radiosurgery technique, and there has been no published experience regarding the tolerance of the human spinal cord and cauda equina to such single-fraction doses. In our own series of more than 150 spine radiosurgery cases, we have not had a single case of spinal cord toxicity.¹⁴ Researchers at Stanford University have reported using the CyberKnife to deliver total treatment doses of 1100 to 2500 cGy in one to five fractions.² In the present series, we used similar total treatment doses, all of which were delivered in a single fraction.

Unlike conventional radiotherapy in which a full dose is delivered to both the vertebral body and the spinal cord or cauda equina, the CyberKnife can deliver a high-dose single fraction to the target tissue while sparing most of the adjacent neural elements. The treatment plan can create a high gradient dose falloff to the target tissue that should significantly reduce the possibility of radiation-induced

myelopathy or injury to the nerve roots. This is the main advantage of stereotactic radiosurgery for treatment of many spinal and sacral tumors.

Our findings confirmed that, similar to the established stereotactic radiosurgery treatment of intracranial lesions, it is now feasible and effective to treat sacral tumors with this new modality. Stereotactic radiosurgery may now be added to the armamentarium for the treatment of various sacral lesions that in the past were not amenable to open resection or conventional external-beam radiotherapy techniques.

CONCLUSIONS

Stereotactic radiosurgery involving the CyberKnife was found to be feasible, safe, and effective for the treatment of sacral tumors. The major potential benefits of radiosurgical ablation of sacral lesions are relatively short treatment time in an outpatient setting and minimal risk of side effects or surgical complications. This new technique offers an alternative therapy for various sacral neoplasms in place of open surgery for lesions not amenable to open surgical techniques or as an adjunct to surgery.

References

- Adler JR, Cox RS, Kaplan I, et al: Stereotactic radiosurgical treatment of brain metastases. **J Neurosurg** 76:444–449, 1992
- Adler JR Jr, Chang SD, Murphy MJ, et al: The Cyberknife: a frameless robotic system for radiosurgery. **Stereotact Funct Neurosurg** 69:124–128, 1997
- Adler JR Jr, Murphy MJ, Chang SD, et al: Image-guided robotic radiosurgery. **Neurosurgery** 44:1299–1307, 1999
- Alexander E III, Loeffler JS, Lunsford LD (eds): **Stereotactic Radiosurgery**. New York: McGraw-Hill, 1993
- Backlund EO, Ganz JC: Pituitary adenomas: gamma knife, in Alexander E III, Loeffler JS, Lunsford LD (eds): **Stereotactic Radiosurgery**. New York: McGraw-Hill, 1993, pp 167–173
- Chang SD, Adler JR Jr: Current status and optimal use of radiosurgery. **Oncology** 15:209–216; 219–221, 2001
- Chang SD, Adler JR Jr, Hancock SL: **The clinical uses of radiosurgery**. **Oncology** 12:1181–1188; 1191–1192, 1998
- Chang SD, Main W, Martin DP, et al: An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. **Neurosurgery** 52:140–147, 2003
- Chang SD, Murphy MI, Martin DP, et al: Image-guided robotic radiosurgery: clinical and radiographic results with the CyberKnife, in Kondziolka D (ed): **Radiosurgery 1999**. Basel: Karger, 2000, Vol 3, pp 23–33
- Colombo F, Pozza F, Chierigo G, et al: Linear accelerator radiosurgery of cerebral arteriovenous malformations: an update. **Neurosurgery** 34:14–21, 1994
- Faul CM, Flickinger JC: The use of radiation in the management of spinal metastases. **J Neurooncol** 23:149–161, 1995
- Flickinger JC, Kondziolka D, Lunsford LD, et al: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. **Int J Radiat Oncol Biol Phys** 28:797–802, 1994
- Friedman WA, Bova FJ, Mendenhall WM: Linear accelerator radiosurgery for arteriovenous malformations: the relationship of size to outcome. **J Neurosurg** 82:180–189, 1995
- Gerszten PC, Ozhasoglu C, Burton SA, et al: Feasibility of frameless single-fraction stereotactic radiosurgery for spinal lesions. **Neurosurg Focus** 13 (4):Article 2, 2002
- Gerszten PC, Welch WC: Current surgical management of metastatic spinal disease. **Oncology** 14:1013–1024, 2000
- Guthrie BL, Adler JR Jr: Computer-assisted preoperative planning, interactive surgery, and frameless stereotaxy. **Clin Neurosurg** 38:112–131, 1992
- Hamilton AJ, Lulu BA, Fosmire H, et al: Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. **Neurosurgery** 36:311–319, 1995
- Kaplan ID, Adler JR, Hicks WL Jr, et al: Radiosurgery for palliation of base of skull recurrences from head and neck cancers. **Cancer** 70:1980–1984, 1992
- Kondziolka D, Lunsford LD, McLaughlin MR, et al: Long-term outcomes after radiosurgery for acoustic neuromas. **N Engl J Med** 339:1426–1433, 1998
- Kondziolka D, Niranjan A, Lunsford LD, et al: Stereotactic radiosurgery for meningiomas. **Neurosurg Clin N Am** 10:317–325, 1999
- Kondziolka D, Patel A, Lunsford LD, et al: Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. **Int J Radiat Oncol Biol Phys** 45:427–434, 1999
- Loblaw DA, Laperriere NJ: Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. **J Clin Oncol** 16:1613–1624, 1998
- Loeffler JS, Alexander E III: Radiosurgery for the treatment of intracranial metastasis, in Alexander E III, Loeffler JS, Lunsford LD (eds): **Stereotactic Radiosurgery**. New York: McGraw-Hill, 1993, pp 197–206
- Loeffler JS, Kooy HM, Wen PY, et al: The treatment of recurrent brain metastases with stereotactic radiosurgery. **J Clin Oncol** 8:576–582, 1990
- Lunsford LD, Flickinger J, Coffey RJ: Stereotactic gamma knife radiosurgery. Initial North American experience in 207 patients. **Arch Neurol** 47:169–175, 1990
- Murphy MJ, Chang S, Gibbs I, et al: Image-guided radiosurgery in the treatment of spinal metastases. **Neurosurg Focus** 11 (6):Article 6, 2001
- Murphy MJ, Cox RS: The accuracy of dose localization for an image-guided frameless radiosurgery system. **Med Phys** 23:2043–2049, 1996
- Ryu SI, Chang SD, Kim DH, et al: Image-guided hypofractionated stereotactic radiosurgery to spinal lesions. **Neurosurgery** 49:838–846, 2001
- Steiner L, Lindquist C, Adler JR, et al: Clinical outcome of radiosurgery for cerebral arteriovenous malformations. **J Neurosurg** 77:1–8, 1992

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