

TREATMENT OF SPINAL TUMORS USING CYBERKNIFE FRACTIONATED STEREOTACTIC RADIOSURGERY: PAIN AND QUALITY-OF-LIFE ASSESSMENT AFTER TREATMENT IN 200 PATIENTS

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OBJECTIVE: Benign and malignant tumors of the spine significantly impair the function and quality of life of many patients. Standard treatment options, including conventional radiotherapy and surgery, are often limited by anatomic constraints and previous treatment. Image-guided stereotactic radiosurgery using the CyberKnife system (Accuray, Inc., Sunnyvale, CA) is a novel approach in the multidisciplinary management of spinal tumors. The aim of this study was to evaluate the effects of CyberKnife stereotactic radiosurgery on pain and quality-of-life outcomes of patients with spinal tumors.

METHODS: We conducted a prospective study of 200 patients with benign or malignant spinal tumors treated at Georgetown University Hospital between March 2002 and September 2006. Patients were treated by means of multisession stereotactic radiosurgery using the CyberKnife as initial treatment, postoperative treatment, or retreatment. Pain scores were assessed by the Visual Analog Scale, quality of life was assessed by the SF-12 survey, and neurological examinations were conducted after treatment.

RESULTS: Mean pain scores decreased significantly from 40.1 to 28.6 after treatment ($P < 0.001$) and continued to decrease over the entire 4-year follow-up period ($P < 0.05$). SF-12 Physical Component scores demonstrated no significant change throughout the follow-up period. Mental Component scores were significantly higher after treatment ($P < 0.01$), representing a quality-of-life improvement. Early side effects of radiosurgery were mild and self-limited, and no late radiation toxicity was observed.

CONCLUSION: CyberKnife stereotactic radiosurgery is a safe and effective modality in the treatment of patients with spinal tumors. CyberKnife offers durable pain relief and maintenance of quality of life with a very favorable side effect profile.

KEY WORDS: Cancer, CyberKnife, Quality of life, Radiation, Spine, Stereotactic radiosurgery

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Benign and malignant tumors of the spinal column and spinal cord are a common and costly clinical problem, causing significant morbidity. Metastatic disease to the spine is the most common presentation; approximately 160 000 new spinal metastases are diagnosed in the United States each year, resulting in considerable pain, functional impairment, and neurological compromise (3). In addition, primary spine and spinal cord

tumors arise in 10 000 patients in the United States each year (28).

The morbidity of malignant involvement of the spinal column derives from the many functions served by the spine in its normal state: support of the trunk and appendicular skeleton, basis for attachment of ligaments and muscles, bending and rotation, protection of the spinal cord and nerve roots, hematopoiesis, and mineral storage. Spinal tumors impair

ABBREVIATIONS: CT, computed tomographic; EBRT, external beam radiation therapy; MCS, Mental Component Summary; MRI, magnetic resonance imaging; PCS, Physical Component Summary; SRS, stereotactic radiosurgery; VAS, Visual Analog Scale

these functions in addition to causing pain and decreased quality of life (4, 5, 16, 21, 29, 30).

In all cancer patients, bone pain is the most common pain syndrome requiring treatment. Survival is typically longer in patients with bone metastases than those with visceral metastases (4): approximately 29.3 months for prostate cancer and 22.6 months for breast cancer (5). Furthermore, pain from bone metastases usually becomes symptomatic earlier and lasts longer than visceral metastases alone. As a result, patients may suffer severely from inadequately palliated spinal sites and from recurrence or progression of incompletely treated sites. Our goal was to determine whether stereotactic radiosurgery (SRS) could eliminate or significantly reduce pain attributable to spinal tumors and improve the patient's quality of life. The authors believe that pain and quality of life are primary end points of great importance to both the patient and the physician.

Spinal tumors are usually managed with a multimodality approach. Surgery is primarily reserved for decompression of neurological elements and stabilization of the spinal column (12, 42, 43). In some cases, complete resection is possible (11, 22, 23, 43), although radiotherapy remains the mainstay of treatment for the majority of patients. Conventional external beam radiation therapy (EBRT) is often limited by potential toxicity to the spinal cord, brainstem, and other critical structures. Treatment with EBRT may also be limited by the relative radioresistance of some tumors as compared with the tolerance of surrounding critical structures. These limitations may lead to incomplete local control and palliation. As a result, clinical or symptomatic recurrences are frequently seen after EBRT.

SRS differs from EBRT in that it uses multiple convergent beams to accurately deliver high doses of radiation to target volumes while minimizing exposure to surrounding healthy tissues. SRS was first introduced in the treatment of intracranial and cranial base tumors using linear accelerator-based technology and gamma knife radiosurgery (6, 33, 39, 46, 47). Early attempts at spinal radiosurgery used external frame-based fixation (44). The CyberKnife (Accuray, Inc., Sunnyvale, CA) is a robotic, image-guided radiosurgery system that is able to deliver treatment without external fixation (1). Real-time image guidance allows the CyberKnife robot to accurately compensate for patient position during treatment; its geometric flexibility and mechanical accuracy are well suited for the treatment of spinal tumors. The practice, efficacy, and safety of spinal SRS have been well documented (8, 9, 13, 17–19, 26, 27, 37). In addition, CyberKnife allows for treatment delivery in multiple sessions, taking advantage of the radiobiological principles of fractionation. We believe that multisession treatment results in an excellent rate of local tumor control, while minimizing normal tissue complications.

We have previously reported our initial experience treating 51 patients with spinal tumors using the CyberKnife (13). We now prospectively report the clinical outcomes of our first 200 patients with primary and metastatic spinal tumors who underwent CyberKnife SRS as initial treatment, postoperative treatment, or salvage after previous surgery, EBRT, and/or chemotherapy (13, 16, 21).

PATIENTS AND METHODS

Patient Selection

Georgetown University Hospital initially acquired the CyberKnife system in 2002 and began treating patients with spinal tumors at that time. Each patient was prospectively evaluated by the senior author (FCH) and a radiation oncologist (GJG). From March 2002 to September 2006, patients with both primary and metastatic tumors of the spine who were candidates for spinal radiosurgery were consecutively enrolled. Two hundred patients with a total of 274 spinal tumor sites were treated with the CyberKnife.

Radiosurgery Treatment

CyberKnife Radiosurgery System

The CyberKnife is a robotic, image-guided SRS system with a 6-MV X-band linear accelerator mounted on a fully articulated robotic arm that is capable of rotational and translational movements to target tumors without rigid external fixation (1). In this study, real-time image guidance was provided by 2 orthogonal imagers, and the beam was dynamically, through the robotic gantry, brought into alignment during treatment to account for patient/target movement. Non-isocentric treatment allowed the delivery of highly conformal and homogeneous radiation doses to complex target volumes with steep dose gradients, which limited the radiation dose to surrounding normal structures. In the first 3 years of this series, patients underwent surgical implantation of stainless steel fiducials. These fiducials served to register the location of the treatment volume in Cartesian space.

Fiducial-less Spinal Tracking

Although fiducials were used in early patients, advances in CyberKnife tracking software permitted spinal tracking without fiducials in later patients by means of the XSight tracking system (Accuray, Inc.). With this technology, which has been used at Georgetown University Hospital since 2005, pretreatment digitally reconstructed x-rays were generated from computed tomographic (CT) scans. Image processing was performed to enhance visualization of skeletal structures and 3-dimensional target displacements; global translations and rotations of spinal structures were determined by comparing x-rays with digitally reconstructed x-rays (19).

Treatment Planning

For the treatment group, the irradiated volume (planning target volume) was considered to be the clinical treatment volume. The clinical treatment volume included the gross tumor volume plus a margin of tissue at risk for microscopic disease. The gross tumor volume was the tumor evident from imaging (CT scan with contrast or magnetic resonance imaging [MRI] scan). The critical structures (spinal cord, cauda equina, nerve roots, bowel) were contoured as precisely as possible. These structures, therefore, represented a small part of the entire thecal sac. Thus, on the axial view, the spinal cord contour represented a small area within the intradural (subarachnoid) space. The contouring was done in a manner to maximize the irradiation of the posterior longitudinal ligament and other epidural structures. Treatment margins placed on target volumes were determined on the basis of clinical presentation, histology, and proximity to critical structures. Treatment planning was based on the CT scan, and fused MRI was used when further visualization was necessary. Inverse treatment planning using a linear optimization algorithm was performed. Treatment doses depended on histology, but they generally ranged from 2100 to 2400 cGy in 3 fractions and up to 3750 cGy in 5 fractions.

Treatment Delivery

During treatment, ceiling-mounted x-ray units acquired real-time images, allowing real-time tracking of patient movement and positioning. The process has been described in detail previously (37). Tracking images were obtained before every beam or at less frequent intervals, depending on setup reproducibility.

Patients were treated daily, up to 5 days per week. Patients were offered mild sedation, such as benzodiazepines, during the treatment. The use of antiemetics, corticosteroids, and narcotics was determined according to each patient's pretreatment status: if the patient was in significant pain, corticosteroids and pain medications were given before each treatment. The presence of tumor near the spinal cord militated for high-dose corticosteroids (dexamethasone, 6 mg by mouth or intravenously, 4 times per day, throughout the treatment period). Corticosteroids were then tapered over several days. Pain medication included hydromorphone (Dilaudid; Abbott Laboratories, North Chicago, IL; 2–4 mg, administered intravenously) for severe pain or acetaminophen (Tylenol with codeine; McNeil Consumer Healthcare, Fort Washington, PA) for moderate pain. Usually, pain medication was tapered during treatment because of the improvement in pain each day.

Patient Evaluations

This study was conducted under a formal Institutional Review Board-approved protocol. Each patient was evaluated by a neurosurgeon and radiation oncologist. To limit the tendency of patients to report favorable results to their treating physician, data on quality of life, pain, and presence of complications were prospectively collected by the research assistant (IM). Data were collected before irradiation; at 1, 3, 6, 9, and 12 months; and at 6-month intervals thereafter. In some instances, the research assistant collected data by telephone. A small number of patients were lost to follow-up; complete data were collected on 95% of the patients enrolled.

Neurological Assessment

Patients were evaluated by a single treating neurosurgeon. Neurological deficits including paresis and paresthesias attributable to the treated lesion were assessed and followed. Follow-up imaging studies including MRI, CT, and positron emission tomographic/CT scans were obtained as clinically indicated.

Quality-of-life Survey

The SF-12 quality-of-life survey was completed by the patients before treatment and at follow-up intervals. It is a multipurpose short-form generic measure of health status, derived from the SF-36, which, in turn, includes 8 health concepts selected from 40 included in the Medical Outcomes Study, including items in use since 1970 (14, 18). The SF-12 has been extensively validated and is widely used as an instrument for monitoring the health of both general and specific populations (2, 15, 24, 34, 48, 49). It measures 8 concepts: physical functioning, role limitations attributable to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations attributable to emotional problems, and mental health (psychological distress and psychological well-being). Two summary scales representing Physical Component and Mental Components of health are generated from the SF-12 items. In the general population, each scale has a mean of 50 with a standard deviation of 10. Higher values signify better health. The SF-12 form can be completed by most patients in 2 minutes or less.

Pain

At each evaluation, pain scores were recorded using the Visual Analog Scale (VAS), one of the most frequently used health assessment

scales owing to its simplicity and efficacy. It has commonly been used to measure pain and is particularly well suited to assessing change within individuals (7, 25, 40). The scale consists of a 100-mm straight line representing a continuum of pain scores ranging from 0 to 100. The patient marks the line at a position corresponding to the state of their pain at that given evaluation time. In this study, pain at the treated CyberKnife site and overall pain were assessed. The amount of narcotic pain medication taken by each patient was also recorded.

Statistical Analysis

To analyze changes in VAS pain scores, Physical Component Summary (PCS) scores, and Mental Component Summary (MCS) scores, we used repeated-measures, mixed-effects models (48). VAS pain scores were converted to proportions, and the arcsine square root was transformed for normality before analysis (49). Models included fixed effects for treatment category (initial versus retreatment), disease type (malignant versus benign), time, and a time by disease type interaction.

Differences among patients were treated as a random effect, and models were fit by restricted maximum likelihood. The response variable used in each analysis was the change in patient scores from pretreatment values. Therefore, a significant intercept was used to indicate an overall change in scores from the pretreatment values. This intercept was independent of any continued increase or decrease after treatment as represented by the fixed effect for time. Patients lacking pretreatment scores or having no follow-up scores were omitted from the analysis. These omissions were proportionately distributed among the different patient categories. Statistical significance for each parameter was evaluated at $\alpha = 0.05$, and all analyses were carried out using S-Plus software (Insight Corp., Seattle, WA).

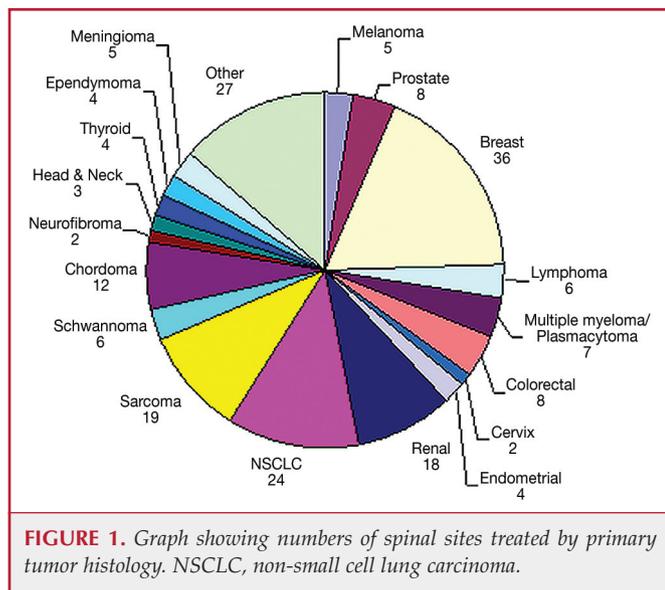
RESULTS

Patient Characteristics

Two hundred patients with a total of 274 spinal tumor sites were treated with the CyberKnife. Baseline patient characteristics are shown in Table 1. Forty-nine patients with primary spinal tumors and 151 patients with metastatic disease were treated. One hundred thirty-seven spinal sites were treated with Cyber-

TABLE 1. Patient characteristics

Patient characteristics	No.
Spinal sites	274
Patients	200
Primary spine tumor	49
Benign	36
Malignant	13
Metastatic	151
Age (y)	
Median	56
Range	3–91
Sex	
Male	101
Female	99



Knife radiosurgery as a component of the initial management of that site, either as up-front treatment (n = 118) or postoperative treatment (n = 19). A significant number of patients (n = 137) had undergone previous surgery or radiation therapy and were re-treated using the CyberKnife. In these patients, 125 sites had received previous conventional irradiation to a median dose of 3500 cGy, 20 sites had previous CyberKnife treatment, and 19 sites had previous surgical management, including corpectomy or laminectomy and stabilization. Patients with tumors at all spinal levels were treated, although thoracic tumors predominated (19% cervical, 44% thoracic, 22% lumbar, and 15% sacral). Primary histopathological diagnoses are represented in Figure 1. The most common tumor types treated were breast cancer, non-small cell lung cancer, and sarcoma. No patients were excluded on the basis of pathological subtype.

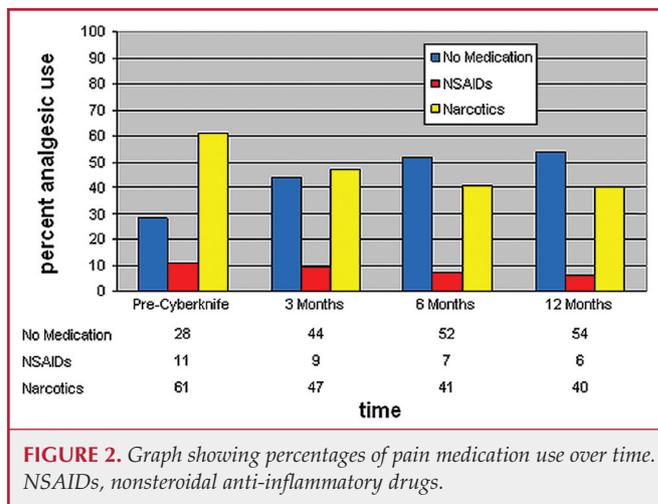
Treatment Delivery

All patients completed their prescribed treatment course. Fiducial-based tracking was used in 139 patients, and fiducial-less tracking using X-Sight or cranial tracking was used in 61 patients. All patients completed their treatment within a span of 10 days.

Lesions with no previous radiation were treated with CyberKnife/SRS to a mean dose of 2640 cGy in 3 fractions prescribed to the 75% isodose surface. The isodose surface, or isodose line on axial views, represents that region of target receiving the same dose of irradiation. In this case, the 75% isodose line receives 75% of the maximum irradiation dose. Previously irradiated lesions were retreated to a mean dose of 2105 cGy in 3 fractions to approximately the 75% isodose surface. Thirty-one patients received concurrent chemotherapy, endocrine therapy, or targeted therapy during their CyberKnife treatment course.

Pain Scores

Initial site-specific pain scores before treatment ranged from 0 to 100 (mean, 40). Seventy-six percent of patients reported some



degree of pain before treatment. Most patients were managed with narcotic analgesics and nonsteroidal anti-inflammatory drugs.

Data on the use of pain medication were available for 181 patients. Throughout the follow-up period, the use of pain medication in general, and the use of narcotic analgesics in particular, declined as a function of time (Fig. 2). Of 105 patients who were initially managed with narcotic analgesics, 48 (46%) were able to stop narcotics at some point during the follow-up period; approximately two-thirds of this latter group were able to remain off narcotics for the entire follow-up period.

Pain score assessment revealed a significant decrease between pre- and posttreatment values ($P = 0.0001$) (Fig. 3; Table 2). At the 1-month follow-up evaluation, pain scores had decreased by 19 points, and 38% of patients reported that they were pain-free at this time. In addition, there was significant continued improvement in pain over the course of the follow-up period ($P = 0.049$) (Table 2).

There was improvement in mean site-specific pain scores over time. There were no significant effects of treatment category

TABLE 2. Results of mixed-model analyses for changes in Visual Analog Scale pain scores^a

Response variables and parameters	Estimate (95% CL)	P value
VAS pain score ^b		
Change from pretreatment ^c	-0.21 (-0.31, -0.11)	0.0001
Time (after treatment)	-0.004 (-0.007, -0.00002)	0.049
Treatment history (initial versus retreatment)	0.01 (-0.07, 0.09)	0.83
Disease type (benign versus malignant)	-0.002 (-0.10, 0.11)	0.94
Time × disease type	-0.007 (-0.004, 0.003)	0.71

^a CL, confidence limits; VAS, Visual Analog Scale.

^b VAS pain scores were arcsine square root transformed for normality before analysis.

^c Overall change from pretreatment levels is represented by the intercept of the model, given that each response variable represents the change from a patient's pretreatment score.

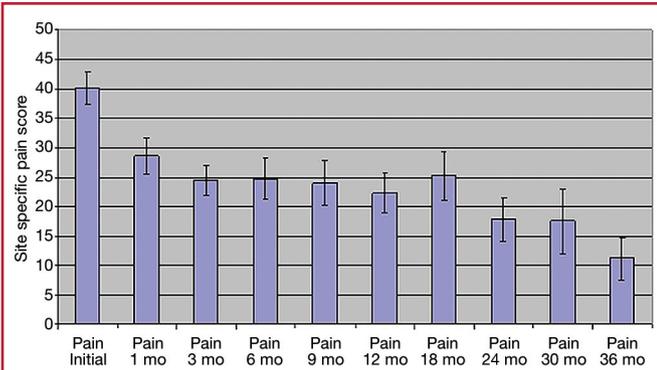


FIGURE 3. Graph showing Visual Analog Scale. Mean pain scores decreased at 1 month after CyberKnife (Accuray, Inc., Sunnyvale, CA) treatment and remained significantly decreased over time.

(initial versus retreatment, $P = 0.83$) (Table 2), disease type (malignant versus benign, $P = 0.94$) (Table 2), or the time by disease type interaction on changes in pain scores ($P = 0.71$) (Table 2). Decreases in pain were consistently observed across these patient classifications.

When patients were grouped into quartiles based on their initial pain scores, patients in the 2nd, 3rd and 4th quartiles all experienced significant improvement in pain scores ($P = 0.005$, $P = 0.002$, and $P < 0.001$, respectively). Patients with the most initial pain (4th quartile) had the most improvement, with pain decreasing from a pretreatment mean of 83 to a posttreatment mean of 35. Patients in the 1st quartile (i.e., most of whom had no pain in the initial evaluation) showed a small increase in pain scores from their baseline mean of 2 to a posttreatment mean of 10 ($P = 0.006$).

Neurological Examination

Serial neurological assessment was completed at each follow-up visit. Most patients exhibited no change in their neurological examination after treatment ($n = 131$). Forty-four patients showed neurological improvement in terms of increased strength, improved sensation or loss or paresthesias, and improved ability to walk. Five patients eventually declined neurologically as a result of widespread disease or marginal recurrence. Neurological assessment was not available in 20 patients owing to their inability to return to the clinic for follow-up.

SF-12 Survey

PCS scores showed a trend toward improvement, which did not reach statistical significance, between pretreatment and follow-up ($P = 0.46$) (Table 3). There were also no significant effects of treatment category ($P = 0.65$), disease type ($P = 0.73$), or the time by disease type interaction ($P = 0.22$) on the degree of change in PCS scores (Table 3). The mean initial PCS score was 32 (mean for the standard population, 50). Mean follow-up PCS scores increased at each follow-up interval, but this did not achieve statistical significance (1 month, 33; 12 months, 35; 24 months, 37; 36 months, 42; $P = 0.22$) (Fig. 4; Table 3).

TABLE 3. Results of mixed-model analyses for changes in SF-12 Physical Component Summary scores and SF-12 Mental Component Summary scores^a

Response variables and parameters	Estimate (95% CL)	P value
PCS score		
Change from pretreatment ^b	0.82 (-1.35, 2.99)	0.46
Time (after treatment)	-0.05 (-0.12, 0.03)	0.22
Treatment history (initial versus retreatment)	-0.41 (-2.14, 1.33)	0.65
Disease type (benign versus malignant)	-0.39 (-2.64, 1.87)	0.73
Time × disease type	-0.05 (-0.13, 0.028)	0.22
MCS score		
Change from pretreatment ^b	3.19 (0.78, 5.59)	0.01
Time (after treatment)	-0.06 (-0.13, 0.013)	0.11
Treatment history (initial versus retreatment)	-0.38 (-2.29, 1.53)	0.69
Disease type (benign versus malignant)	-1.13 (-3.62, 1.36)	0.37
Time × disease type	-0.001 (-0.08, 0.08)	0.98

^a CL, confidence limits; PCS, Physical Component Summary; MCS, Mental Component Summary.

^b Overall change from pretreatment levels is represented by the intercept of the model, given that each response variable represents the change from a patient's pretreatment score.

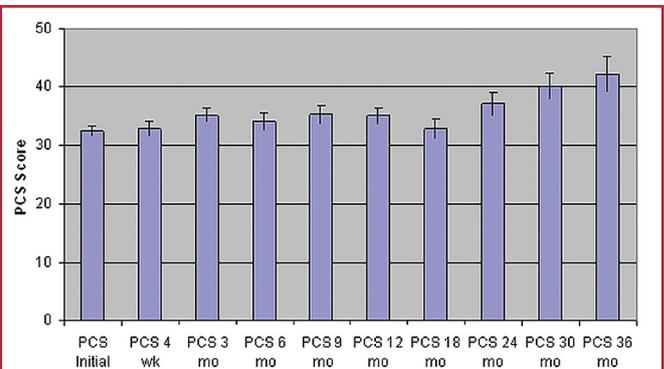


FIGURE 4. Graph showing SF-12 Physical Component Summary (PCS) scores, reflecting maintenance of the physical component of quality of life and general well-being of the patients throughout the treatment period.

MCS scores showed a trend toward improvement at each follow-up interval. The statistically significant difference ($P = 0.01$) between initial and 3-year follow-up reflects the death of the sickest patients. Changes in MCS scores were not associated with treatment category ($P = 0.69$), disease type ($P = 0.37$), or the time by disease type interaction ($P = 0.98$) (Table 3). The mean initial MCS score was 47. Mean follow-up MCS scores increased at each follow-up interval, although this continued increase was not statistically significant (1 month, 49; 12 months, 51; 24 months, 52; 36 months, 53; $P = 0.11$) (Fig. 5;

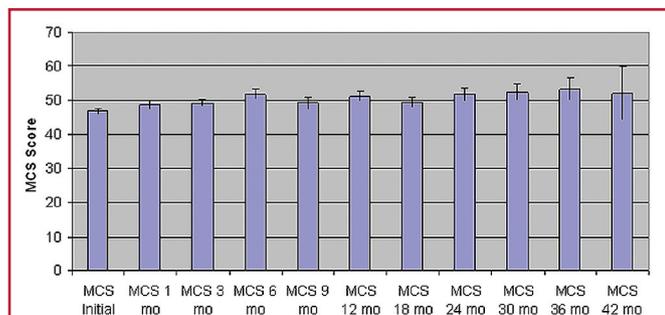


FIGURE 5. Graph showing SF-12 Mental Component Summary (MCS) scores, reflecting maintenance of the mental component of quality of life and general well-being of the patients throughout the period of treatment.

Table 3). Patients experienced durable stabilization of quality of life after treatment.

Survival

The median follow-up period was 12 months (range, 1–51 months). Eighty-two patients have been followed for at least 1 year, 40 patients have been followed for at least 2 years, and 16 patients have been followed for at least 3 years. At the time of analysis, 107 patients were still alive, and 93 patients had died. Median survival has not yet been reached in the subgroup of patients treated for benign lesions and in the subgroup of patients treated with the CyberKnife as the initial treatment of the spinal site. Median survival was 14.5 months in the subgroup of patients with malignant spinal lesions and 10.5 months in the subgroup of patients re-treated with the CyberKnife after previous radiotherapy. These survival times compare favorably with previously reported series of similar groups of patients treated with conventional external beam techniques and doses (4, 16, 30).

Toxicity and Other Outcomes

Acute Outcomes

In general, treatment was extremely well tolerated in all patients. Most patients experienced minimal or no side effects. Acute complications, when they occurred, were self-limited and mild. The most commonly reported toxicities were fatigue, nausea, esophagitis, dysphagia, and transient diarrhea.

Late Outcomes

There was no evidence of treatment-related myelitis or neurological damage in any patient, including patients with a history of previous conventional radiotherapy. Three significant complications were observed. These included a case of breakdown at a surgical site that required debridement and reclosure of the wound in a patient who had previously undergone EBRT and 2 spinal operations, and 2 patients who developed vertebral fractures in the irradiated spine. One of these patients had previously received EBRT, and both were instrumented with titanium cages; in each patient, tumor was present in the adjacent levels.



FIGURE 6. Patient 1. Sagittal T1-weighted magnetic resonance imaging scan with gadolinium contrast, showing recurrent synovial cell sarcoma at T11 after conventional radiation. The spinal cord is significantly compressed. A methylmethacrylate vertebroplasty at T11 was attempted before transfer to Georgetown University Hospital.

(Fig. 6) revealed recurrent disease at T11 with cord compression.

On transfer to Georgetown University Hospital, the authors recommended surgical resection and postoperative radiation therapy using the CyberKnife. In January 2005, he underwent an anterior thoracotomy, T11 corpectomy with fusion and stabilization with a telescopic plate spacer (TPS System; Biomet, Parsippany, NJ), and vertebroplasty at T10–T12 (Fig. 7). He underwent a completion posterior resection and stabilization (T9–L1 arthrodesis). Fiducials for SRS were placed at the time of surgery. Surgical pathology confirmed metastatic synovial sarcoma.

He was then treated with the CyberKnife in the previously irradiated T10–T12 vertebral levels to a dose of 2800 cGy in 4 fractions of 700 cGy, prescribed to the 74% isodose line (Fig. 8). He later underwent treatment with the CyberKnife to the L3 lesion to a dose of 2800 cGy in 4 fractions of 700 cGy prescribed to the 74% isodose line.

Treatment was extremely well tolerated without acute toxicity. His VAS pain score improved from 100 before treatment to 20 at 1 month after treatment and 0 at the 1-year follow-up. His SF-12 scores were 37 (MCS) and 29 (PCS) before treatment, 34 (MCS) and 32 (PCS) at 1 month after treatment, and 61 (MCS) and 42 (PCS) at the 3-year follow-up. The positron emission tomogram obtained at the time of the 3-year examination showed no evidence of recurrence. After 3 years, he remains neurologically intact, at work, and without recurrent disease.

DISCUSSION

Spinal Radiosurgery

The present series is the largest prospective series of patients who underwent radiosurgery of the spine that includes measurement of pain and quality-of-life outcomes using validated instruments. Radiosurgical treatment of spinal tumors is a relatively

ILLUSTRATIVE CASE

A 44-year-old Caucasian man (Patient 1) presented with a long history of multiply recurrent synovial sarcoma. He was initially diagnosed with synovial sarcoma of the right chest wall in 1992. He underwent resection, followed by postoperative radiation therapy. In 1995 and 2001, he developed local recurrences, which were managed with surgery and chemotherapy. The patient presented to an outside hospital in late 2003 with back pain. MRI of the spine revealed metastatic disease involving the T11 and L3 vertebral bodies. There was a compression fracture at T11 (40%) with retropulsion of the fractured vertebral elements and cord compression. Biopsy of the lesion at T11 was consistent with metastatic synovial sarcoma. He initiated a course of EBRT to T10–L4. The patient subsequently developed lower-extremity weakness and became wheelchair bound. MRI



FIGURE 7. Patient 1. Postoperative computed tomographic scan of the thoracolumbar spine, sagittal reconstruction, showing restoration of vertebral body height, alignment, and stabilization of the spine after anterior vertebrectomy and stabilization with a titanium telescopic spacer. The bright signal represents a methylmethacrylate (bone cement) vertebroplasty for the purpose of strengthening the vertebrae at the site of a second metastasis (L3).

new treatment modality. Initial studies showed that spinal radiosurgery was feasible using a rigid stereotactic frame attached to the spinous processes. The feasibility of the Novalis system (BrainLAB, Heimstetten, Germany) for spinal radiosurgery has also been reported (35, 36). More recently, authors have reported on frameless stereotactic irradiation of the spine, confirming the safety and efficacy of this approach (13, 17, 38). The current results support and extend our earlier reported experience (13). In that study, we demonstrated that staged treatments with CyberKnife radiosurgery resulted in significant, durable pain relief and maintenance of quality of life in patients with primary and metastatic spine lesions. Clinical benefits were obtained in patients who were undergoing retreatment after surgery or radiotherapy. Acute side effects were generally few, minor, and self-limited.

The current series includes patients with a broad cross-section of metastatic and primary (benign and malignant)

tumors. Taken as a whole, the series is weighted with tumors that are generally considered to be relatively resistant to irradiation. For instance, there were 70 patients with renal cell, melanoma, thyroid, sarcoma, non-small cell lung carcinoma, and chordomas, as opposed to only 57 patients with breast, prostate, lymphoma, and myeloma lesions. In addition, many patients were referred for CyberKnife after failure of other treatment regimens. Of the 274 lesions treated with CyberKnife, 137 (50%) had recurred after previous irradiation in which the spinal cord received a tolerance dose. The smaller than expected number of patients with breast and prostate tumors in this series reflects the referral patterns for CyberKnife radiosurgery at our institution. We found that durability of pain relief and maintenance of quality of life after CyberKnife were unrelated to tumor histology. This appears to reflect more uniform sensitivity of different tumor types to hypofractionated radiation.

Our average spinal lesion volume was an order of magnitude larger than those of intracranial lesions reported in the literature (39, 44). The CyberKnife accommodates larger tumors

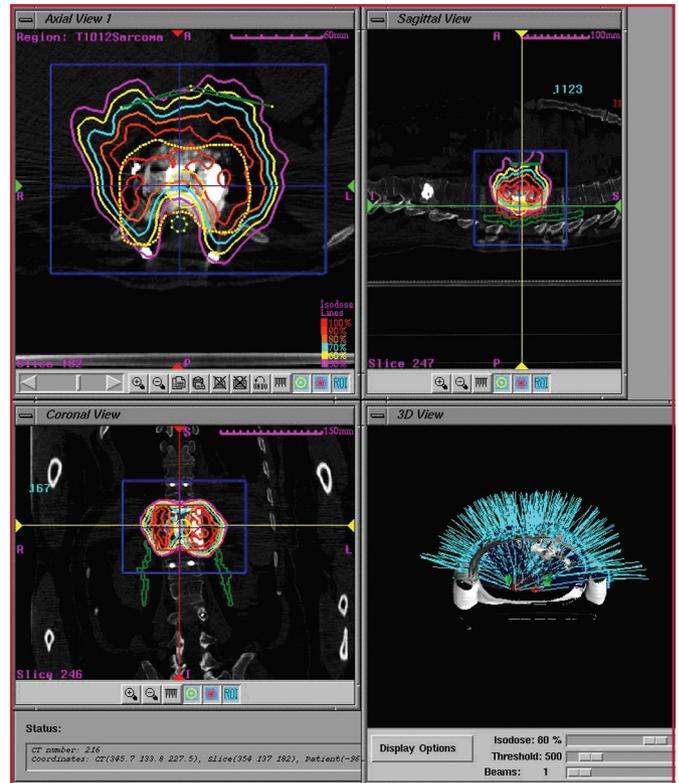


FIGURE 8. Patient 1. CyberKnife treatment plan to T10–T12 postoperative bed.

without loss of efficacy. For instance, in this series, a sacral leiomyosarcoma (839 cm³ in volume), which had been refractory to conventional EBRT, was not visible on MRI at 3 months. Despite inherent flexibility and motion of the spine owing to pain, movement has not posed a significant problem. The CyberKnife uses an adaptive beam-pointing algorithm that accommodates up to 1 cm of patient movement, verifying treatment location and correcting for submillimeter displacements at specified intervals during treatment. Movements larger than 1 cm are detected and cause cessation of treatment until the patient is repositioned.

Pain

There was a robust and statistically significant improvement in pain throughout the 48 months of follow-up. Initial site-specific pain scores before treatment were an average of 44 (range, 0–100). The improvement was statistically significant at 1, 12, 24, and 36 months. These results compare favorably with those of other spine SRS series, which reported recurrence of pain at intervals of 6 to 12 months (4, 5, 16, 20, 30). Patients with the worst initial pain (mean, 85/100) showed the most improvement, whereas patients in the intermediate quartiles had variable but durable improvement in pain. Those with no initial pain (mean, 0/100) showed a slight increase in pain over time, which is not surprising given the advanced stage of most

patients, the nature of metastatic disease, and the various reasons for pain. Of note, most patients experienced some pain relief within the first week of treatment.

Quality of Life

The SF-12 used in this study is a widely approved instrument for measurement of physical functioning, bodily pain, general health, vitality, social functioning, and mental health. The SF-12 is valid when tested against outcome instruments (14, 32, 35). PCS and MCS scores improved after CyberKnife SRS, and this change was statistically significant for MCS scores. The mean PCS score (34 and 40 at 1 and 36 months, respectively) was maintained at a level close to the measured standard of a healthy population (50 ± 10). Those patients ($n = 16$) who were followed for 36 months reported a physical quality of life that was within the normal range, reflecting, in part, the increased proportion of patients with benign tumors in this group. Mean MCS scores increased after treatment and were generally similar to those observed in the general population (mean, 49–51 at 1 and 36 months, respectively). Lack of significant differences among patients with different types of disease and different treatment histories implies that these results are largely consistent across patient classifications.

Complications

There were 2 cases (1%) of vertebral fracture in sites irradiated with CyberKnife; 1 of these had been previously irradiated with EBRT. In both cases, the fractures were most likely the result of placing hardware into osteoporotic bone; titanium cages were used to replace the resected vertebrae. Reinforcement of the adjacent osteoporotic vertebrae with polymethylmethacrylate might have avoided this complication. Other series using hypofractionation report incidences of vertebral fracture of 5 to 10% (16, 30).

Many patients were irradiated within 2 weeks of surgery. Although the treatment course was uneventful for most of them, 1 patient who had undergone previous EBRT (the same patient who had a vertebral fracture) developed a draining back wound requiring a wound revision. Skin dose was not calculated; however, there were no complaints of skin disorders and no complications related to the skin.

In this study, long-term complications or late central nervous system effects were not observed in any patients. Late effects to the central nervous system, such as myelitis or neurological damage, typically occur after 6 to 60 months. Over the 5-year follow-up period, these changes were not evident. The investigators believe that the absence of myelitis in these patients, many of whom had been irradiated to tolerance level before undergoing CyberKnife treatment, can be explained by the staging of treatments and the reported accuracy of 0.5 millimeter with the CyberKnife technology (9).

Radiobiological Considerations

CyberKnife treatments may be administered as a single dose or in several fractions or stages (8, 10, 17, 30). There are benefits of single, higher doses, as already demonstrated in

the intracranial radiosurgery literature. Hypofractionated regimens have been demonstrated to be efficacious in the management of bone metastases (31, 41, 43, 45). At the Georgetown University Hospital Radiosurgery Center, the authors fractionate or “stage” spinal radiosurgery treatments, a procedure that is now referred to as multisession treatment. The radiobiological reasons for fractionation are well known to radiation oncologists.

Therapeutic gains are achieved by increasing the tolerance of the dose-limiting adjacent normal tissue and increasing the sensitivity of the target tissue. Staging treatments exploits the differential repair between normal tissue and tumor (normal cells undergo more efficient deoxyribonucleic acid repair); staging allows redistribution of cells within the cell cycle (irradiated cells are held up in the G_2 and mitosis phases and are, thus, more susceptible to further irradiation); and staging allows reoxygenation (tumors become hyperemic after the first irradiation; the subsequent increase in oxygenation of tumor cells confers increased sensitivity to irradiation). However, this is undoubtedly a simplification of more complex and heterogeneous phenomena (19).

A large body of radiobiological literature and empirical experience attests to the benefits of fractionation, sufficing to persuade the physician to strongly consider fractionation in any radiation delivery strategy. Although single large doses may possibly overwhelm repair, reoxygenation, and reassortment effects, we feel that multisession radiosurgery combines surgically ablative radiation doses with modest fractionation to improve the sparing of adjacent normal tissues. This allows delivery of high radiation doses to difficult, formerly untreatable lesions. We reserve single-fraction treatments for small tumors that are relatively distant from critical structures, particularly if the patient has not been previously irradiated (13).

Most benign tumors, such as neuromas and meningiomas, are thought to have a lower α/β ratio and to be “late-responding.” As such, one would generally predict that hypofractionation in 1 to 3 sessions would be more biologically effective than multisession treatment of 5 or more sessions. The radiobiological efficacy of a single large dose, however, must be weighed against the theoretical safety of delivering an equivalent dose in 5 sessions. Conversely, “early-responding” tumors with a high α/β ratio, such as neuroblastoma and lymphoma, should theoretically be more responsive to multisession treatments (45).

Surgical Considerations

The surgeon is best equipped to perform the contouring of the tumor and probable margin of disease growth. Contour of critical structures, such as the spinal cord, is also performed by the surgeon, who should be more acquainted with the intraoperative findings and also the size, shape, and position of the spinal cord within the spinal canal. The surgeon should extend the margin of tumor to include probable areas of microscopic growth that might not be evident on imaging. CyberKnife SRS has necessarily resulted in a close partnership between neurosurgery and radiation oncology.

CONCLUSIONS

SRS of metastatic and primary spinal tumors with the CyberKnife results in robust and durable improvement in pain and maintenance of the physical and mental quality of life. These improvements are seen even in those cases in which the maximum tolerated dose of irradiation has been administered to the adjacent spine. Treatment is well tolerated and has not been associated with significant early morbidity or late complications. Further studies are warranted to determine the optimum strategy for incorporating spinal SRS in the multidisciplinary management of spinal tumors, including investigations in dose escalation, different fractionation schema, incorporation of chemotherapy, and use of biological agents.

Disclosure

The senior author (FCH) received research funds to pay for data collection. He was a member of the clinical advisory board and has limited stock. The other authors have no personal financial or institutional interest in any of the drugs, materials or devices described in this article.

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COMMENTS

The present study by Gagnon et al. addresses the application of radiosurgery techniques to diseases of the spine. This cohort of patients represents a very broad spectrum of disease processes and demonstrates the potential uses of spinal radiosurgery for palliative and definitive management. The results are notable for the great safety of the technique as well as the impressive improvements in quality of life from the aspect of pain control. As a proof of concept, this article certainly is helpful in supplementing the emerging literature regarding the use of frameless image-guided methods for spinal indications. I look forward to additional reports that may refine for us the proper indications and expected outcomes for this technique, which will likely revolutionize the surgical treatment of many extracranial diseases well beyond those within the traditional practice scope of neurosurgeons.

Joseph C.T. Chen
Los Angeles, California

The authors have provided a detailed report regarding improvement of pain and quality of life in patients with spinal tumors treated with stereotactic radiosurgery. This article is important, since it looks beyond the standard follow-up radiographic studies and neurologic examinations of this patient population to assess whether radiosurgery actually improves quality of life. This type of analysis requires dedicated evaluations of patient pain and quality of life both before treat-

ment and throughout each of the follow-up periods, not just at last follow-up. The authors have shown that improvements in pain and quality of life occur fairly quickly after radiosurgery treatment, with these improvements being maintained throughout the follow-up period. The issue of rapid improvement is important, because many of the patients who are treated have metastatic disease to the spine and may have limited survival periods. Furthermore, the fact that these improvements are maintained through the follow-up period has important implications for patients with benign tumors, as it shows that quality-of-life gains are durable. This article provides solid evidence of the clinical benefits of spine radiosurgery.

Steven D. Chang
Stanford, California

Gagnon et al. report 200 patients with benign and malignant spinal tumors treated with fractionated stereotactic radiosurgery using the CyberKnife. Mean pain scores decreased significantly after treatment. Quality of life, as measured by the SF-12 survey, seemed to improve. An illustrative case example is included. The authors' careful and detailed description of their pioneering experience with spinal radiosurgery will go far toward helping establish its place as a valued treatment tool for spinal tumors.

William A. Friedman
Gainesville, Florida

The authors add to the expanding literature on spinal radiosurgery, detailing pain and functional outcomes for patients with benign and malignant tumors. This field continues to change our approaches to the care of spinal tumors, and I believe it will radically affect the role of irradiation in spinal disease. Care can be delivered faster and more effectively with radiosurgery in properly selected patients.

The authors discuss several radiobiological concepts that remain theoretical. These include the "advantages of hypofractionation," and that such concepts are "well known" to radiation oncologists. Such concepts may be known because they have been taught, but evaluations in vivo using tumor models have rarely been conducted. Again much of the dogma is theoretical or based on in vitro work. How well these concepts hold in the human setting is unclear. Radiosurgery has changed our understanding of radiobiology. Some tumors respond well, even when mathematical calculations had predicted they would not. Fractionation, which allows repair of sublethal deoxyribonucleic acid injury, likely occurs well when radiation is delivered over a period of weeks. Whether any such repair is meaningful after 3 or 5 days is not known. In addition, changes in tumor oxygenation or other metabolic responses may or may not be affected in any positive way by limited staging, such as that performed here. At our center, we focus on radiosurgery, in 1 session, whenever possible. In summary, although this report does not put forth any new concept, the findings are valuable, as they can be used as a benchmark for others.

Douglas Kondziolka
Pittsburgh, Pennsylvania

Gagnon et al. have published one of the largest and most thorough clinical assessments of patients undergoing radiosurgery for spinal tumors. A total of 200 patients were prospectively evaluated using validated outcomes instruments to measure changes in pain and quality of life after treatment. The authors selected a fractionated (3 to 5 treatments) schedule using fractional doses of between 7 and 8 Gy. A significant improvement in pain was noted in this cohort of patients; it lasted

throughout the 48 months of follow-up. Interestingly, patients with the greatest initial pain showed the most dramatic improvements. Mental Component scores of the SF-12 were significantly higher after radiosurgery treatment. Furthermore, early side effects of radiosurgery were mild and self-limited. In addition, there was no late radiation toxicity noted in the series.

The importance of this publication cannot be overstated. Not only is the degree of pain improvement documented in this study impressive, but it appears to be more durable than that achieved by using conventional fractionated radiotherapy techniques alone. It is important to note that the fractionated dose schedule used in this series may be considered a lower biologically equivalent dose than the higher single-fraction dose used at our institution and in other series. Despite this potentially lower overall dose, the outcomes reported in this study are impressive.

Similar to the widespread acceptance of intracranial radiosurgery as an essential treatment modality for a variety of intracranial pathologies, spine radiosurgery has now matured into an accepted treatment modality for both primary as well as metastatic spine and paraspinous lesions. At some time in the future, spine radiosurgery may replace conventional fractionated techniques as the primary treatment modality for certain spinal pathologies.

Peter C. Gerszten
Pittsburgh, Pennsylvania

The authors describe the Georgetown University experience with CyberKnife radiosurgery for patients with spinal tumors, specifically examining the impact of treatment on pain relief and quality of life. There were 274 tumors treated in 200 patients. Tumors were primary and benign in 36 patients, primary and malignant in 13, and metastatic in 151. Fractionated radiation therapy, to a dose of 35 Gy, had been administered previously to 125 patients, and 20 patients had had a prior CyberKnife radiosurgery treatment. A plurality of tumors were in the thoracic spine, but they were located throughout the spine. Treatments were given either in 3 or 5 fractions (for a total prescription dose of 21 Gy to 24 Gy, or 37.5 Gy, respectively). Patients with prior radiation therapy tended to have a lower total dose. Fiducial-based CyberKnife radiosurgery was performed in 139 patients, while, more recently, newer software was used, obviating the need for fiducial placement, in 61 patients.

Complete data were available for 95% of patients. Pain relief was assessed using a Visual Analog Scale (VAS) and quality-of-life assessment using the Physical and Mental Components of the SF-12 scale. Neurological examinations were performed by the treating neurosurgeon.

Overall, pain was reduced as a result of CyberKnife radiosurgery. This decrease continued over a 4-year period. Patients with the worst pain before treatment tended to benefit the most (mean VAS decreasing from 83 to 35 of 100), although patients with the least amount of pain had a slight increase in their pain (mean VAS increasing from 2 to 10). Pain medication intake was reduced, including narcotic usage. Regarding quality-of-life measures, there was no significant change in the Physical Component of the SF-12 scale, while the Mental Component improved from a mean of 49 to 53. The neurological examinations were not quantitatively assessed but were unchanged in most patients; 44 patients had improved examinations, whereas 5 patients declined neurologically. No follow-up examinations were available in 20 patients.

Patients were followed for a median period of 12 months. As 56 patients have been followed for at least 2 years, the median survival was 17 months (with the median not yet reached for patients with benign tumors). Side effects were infrequent and usually mild and self-limiting, although the authors report wound breakdown in 1 patient who had had prior radiation therapy and 2 operations, as well as vertebral body fractures in 2 other patients. There were no reported neurological side effects.

In general, disease type and treatment history had no effect on any of the above outcomes. The only exceptions were that survival was longer for patients with metastatic tumors who did not have prior radiation therapy, and, of course, for those with benign tumors, as noted.

This is a valuable report that attempts to analyze, as objectively as possible, the outcomes from a large series of patients treated with CyberKnife radiosurgery for spinal tumors, focusing mainly on functional results. The prospective follow-up is commendable, and any neurosurgeons who are beginning to use the new technology should take heed and try to do the same. Ideally, the findings of follow-up imaging would have been available to correlate with the degree of pain relief. Nonetheless, the results indicate that patients can expect adequate and sustained pain relief, with maintained quality of life, after CyberKnife radiosurgery for treatment of spinal tumors.

Michael Scholder
Manhasset, New York

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