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CyberKnife Frameless Radiosurgery for the Treatment of Extracranial Benign Tumors

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Limited data exists for the use of radiosurgery for benign extracranial tumors. The purpose of this study was to evaluate the feasibility, toxicity, and local control of patients with benign extracranial lesions treated with the CyberKnife Frameless Radiosurgery System. From September 2001 thru January 2004, 59 benign tumors in 44 patients were treated using the CyberKnife a frameless image-guided radiosurgery system. Of these tumors, there were 21 neurofibromas, ten schwannomas, eight meningiomas, eight hemangioblastomas, seven paragangliomas, two hemangiopericytomas, one pseudotumor, one ependymoma, and one arteriovenous malformation (AVM). The anatomic locations of these tumors were spinal (25 cervical, four thoracic, 14 lumbar, and two sacral), neck (eight), orbital (three), brainstem (one), and foramen magnum (one). All patients were treated in a single fraction except three lesions were treated in a fractionated manner. The median treatment delivery time per fraction was 59 minutes (range 11-194). Twenty three lesions initially underwent surgical resection. Ten lesions received prior external beam radiation with a median dose 48 Gy (range 40-54 Gy), and one lesion received two prior CyberKnife treatments for a total dose of 32 Gy to the 80% isodose line. The median follow-up was eight months (range 1-25 months). Acute and late toxicity was graded using the National Cancer Institute Common Toxicity Criteria (CTC) scale. Symptomatic response was documented as "improved," "stable," or "progression". The median tumor dose delivered was 16.0 Gy to the 80% isodose line (range 10-31 Gy). The median tumor volume was 4.3 cc (range 0.14-98.6 cc). The median spinal cord volume receiving more than 8 Gy was 0.035 cc (range 0-2.5 cc) and the median maximum spinal cord dose 11.5 Gy (range 0-19.8 Gy). There were no patients that suffered a significant (Grade 3, 4, or 5) acute toxicity. There was no observed late toxicity. 78% of patients experienced an improvement of their pre-treatment symptoms while only one patient experienced symptom progression. Of the 26 patients who underwent follow-up imaging, the local control rate was 96%. This study suggests that CyberKnife Radiosurgery is a safe and efficacious treatment modality for benign tumors, even for those patients with recurrent previously irradiated lesions.

Key words: CyberKnife; Extracranial; Radiosurgery; and Benign tumors.

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Introduction

Radiation therapy has been used for the treatment of numerous benign diseases since the discovery of the therapeutic potential of ionizing radiation (1-6). Frame based stereotactic radiosurgery (SRS) for the treatment of benign intracranial lesions has become widely accepted with excellent long term outcomes and minimal toxicity (7-12). There are now multiple modalities for extracranial SRS using frame based or frameless fixation for target immobilization (13-17). Extracranial SRS for the treatment of various malignancies has had encouraging early results in terms of efficacy and toxicity (18-23). However, the data for SRS

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for benign extra-cranial tumors is currently limited. We hypothesized that SRS could safely and adequately control benign extracranial lesions, including recurrent lesions previously resected or irradiated. Therefore, the objective of this study was to prospectively evaluate patients with benign extracranial lesions treated with the CyberKnife, an image-guided frameless stereotactic radiosurgery system.

Methods and Materials

This study involved the prospective evaluation of forty-four patients with fifty-nine benign lesions who were treated using the CyberKnife Image-Guided Radiosurgery System® (Accuray, Inc., Sunnyvale, CA) using the DTS (Dynamic Tracking System) 3.0 software. All patients were treated at the University of Pittsburgh Medical Center, Pittsburgh, PA, and the protocol was approved by the University of Pittsburgh's Institutional Review Board. All patients signed an informed consent and were aware that they were part of an investigational protocol. The protocol was designed as a non-randomized clinical longitudinal cohort study that would create a registry to follow up all patients treated with the CyberKnife and would allow for subsequent outcome evaluation and analysis.

The study was designed to test the hypothesis that radiosurgery is safe, feasible, and clinically effective for benign lesions. The protocol was developed as a registry as opposed to a clinical trial. Therefore, any subject undergoing CyberKnife treatment would meet the inclusion criteria and any data collected relative to that treatment would be available for subsequent evaluation. There were no exclusion criteria included in the protocol regarding prior irradiation or surgery. All patients were to be followed indefinitely as part of their clinical care. There were a variety of tumor histologies including (in chronological order) neurofibromas, schwannomas, meningiomas, hemangioblastomas, paragangliomas, hemangiopericytomas, pseudotumor, ependymoma, and arteriovenous malformation (AVM). The benign histologies of these tumors were based from the pathologic specimen of the initial surgical resection for the 23 recurrent and the radiographic appearance for the remaining tumors. The anatomic location of these tumors was spinal (42% cervical, 8% thoracic, 24% lumbar, and 3% sacral), neck (14%), orbital (5%), brainstem (2%), and foramen magnum (2%). Patient characteristics are shown in Tables I and II.

Table I
Summary of histological tumor types.

Histologic Type	Number of Cases (%)
Neurofibroma	21 (35.6%)
Schwannoma	10 (16.9%)
Meningioma	8 (13.6%)
Hemangioblastoma	8 (13.6%)
Paraganglioma	7 (11.9%)
Hemangiopericytoma	2 (3.4%)
Pseudotumor	1 (1.7%)
Ependymoma	1 (1.7%)
Arteriovenous Malformation	1 (1.7%)
Total	**59 (100%)**

The primary indication for treatment was tumor progressions leading to symptomatic clinical presentation such as pain or progressive neurological deficits. Twenty-three (42%) lesions had previously undergone open surgical resection. Ten (20%) lesions received prior external beam radiation with a median dose 48 Gy (range 40-54 Gy), and one (2%) lesion received two prior CyberKnife treatments for a total dose of 32 Gy to the 80% isodose line.

The CyberKnife system and the treatment overview have been previously described (18, 24). This frameless image-guided radiosurgery system utilizes the coupling of an orthogonal pair of x-ray cameras to a dynamically manipulated robot-mounted 6-MV linear accelerator capable of six degrees of freedom that guides the therapy beam to the intended target without the use of frame-based fixation. Real-time image tracking allows for the tracking of patient movement with a 1 mm spatial accuracy. The CyberKnife radiosurgery treatment consists of three distinct components: (i) CT image acquisition based upon skull bony landmarks or implanted bone fiducials; (ii) treatment planning; and (iii) the treatment itself. The neck, foramen magnum, orbital, brainstem, or cervical spine lesions were tracked relative to skull bony landmarks. The thoracic, lumbar, and sacral spine lesions were tracked relative to bone fiducials placed adjacent to the lesion. Because these implanted fiducials

Table II
Pre-treatment and Treatment related data

Characteristic	Number of Cases/Value (%)	
Previous external beam irradiation	10	(17%)
Previous open surgical resection	23	(39%)
CyberKnife Treatment Locations		
Cervical spine	25	(42%)
Thoracic spine	5	(8%)
Lumbar spine	14	(24%)
Sacral spine	2	(3%)
Neck	8	(14%)
Orbit	3	(5%)
Brainstem	1	(2%)
Foramen Magnum	1	(2%)
Cranial Tracking	38	(64%)
Fiducial Tracking	21	(36%)
Median age	42 yrs	(18-75)
Median tumor volume (cc)	4.3 cc	(0.14-98.6)
Median dose to 80% isodose line (Gy)	16 Gy	(15-25)
Median volume of spinal cord/canal dose > 8 Gy (cc)	0.04 cc	(0.0-2.5)

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

All patients with neck, foramen magnum, orbital, brainstem, or cervical spine lesions were fitted with a noninvasive molded Aquaplast facemask (WRF/Aquaplast Corp., Wyckoff, NJ) that stabilized the head and neck on a radiographically transparent headrest. Computed tomography scans were acquired using 1.25 mm thick slices from the top of the skull to the bottom of the cervical spine. In the remaining cases involving the thoracic, lumbar, or sacral spine, fluoroscopy was used to guide the placement of four to six gold fiducial markers (Alpha-Omega Services, Inc., Bellflower, CA) into the pedicles immediately adjacent to the lesion using a standard Jamshidi bone marrow biopsy needle (Allegiance Healthcare Corporation, McGraw Park, IL) as described previously (18). Three fiducials are required to define a full spatial transformation in all six degrees of target translation and rotation. The fiducial placement procedure was performed in the operating room in an outpatient setting. There were no complications associated with fiducial placement. The patient then returned as an outpatient for the planning CT. The patient was placed in a supine position in a conformal alpha cradle during CT imaging 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.

In each case, the radiosurgical treatment plan was designed based on tumor geometry, proximity to spinal cord and location. Planning treatment volume (PTV) was defined as the radiographic tumor volume with no margin. Treatment planning was performed using the Accuray treatment planning system DTS 3.0 (Figure 2). The tumor dose was determined based upon the histology of the tumor, spinal cord tolerance, and previous radiation quantity. An inverse treatment planning technique was utilized 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 and kidneys. The dose limit for the spinal cord and small bowel was 8 and 6 Gy, respectively.

All treatments were performed in an outpatient setting. All patients were treated in a single fraction but that three lesions were treated in a fractionated manner. One of these three lesions received two fractions and the remaining two lesions received five fractions The patients were placed on the CyberKnife treatment table in a supine position with the appropriate immobilization device as described above using the facemask or alpha cradle depending on location. During the treatment, real time digital x-ray images of the patient were obtained. The location of the lesion being treated is established from these images and is used to determine tumor location as previously described. No intravenous sedation was used for any of these cases, and monitoring was not performed. The patient was observed throughout the treatment by closed circuit television. The median treatment duration was 59 minutes (range 11-194 minutes).

All patients were seen in follow-up after CyberKnife to assess toxicity and clinical response. The median follow-up was eight months (range 1-25 months). Acute and late toxicity was graded using the National Cancer Institute Common Toxicity Criteria (CTC) scale. Symptomatic response was documented as "improved," "stable," or "progression". Follow-up imaging was used to assess local control.

Results

The tumor histologies and patient characteristics are shown in Tables I and II, respectively. Neurofibroma was the most common histology representing over 35% of the cases and the spine was the common location involving 80% of the cases. The extra spinal cases included paragangliomas of the neck (seven), orbital meningiomas (two), orbital pseudotumor (one), hypoglossal schwannoma of the neck (one), arteriovenous malformation of the cervical spinal cord (one), brainstem meningioma (one), and foramen magnum meningioma (one). The median age of the patients at the time of CyberKnife treatment was 42 years (range 18-75 years). The median tumor dose delivered was 16.0 Gy to the 80% isodose line (range 9-31 Gy). The median tumor volume was 4.3 cc (range 0.2-98.6 cc). For the spinal tumors, the median spinal cord volume receiving more than 8 Gy was 0.035 cc (range 0-2.5 cc) and the median maximum spinal cord dose 11.5 Gy (range 0-19.8 Gy). Thirty-eight cases (64%) were treated using skull bony landmarks for image guidance (*i.e.*, the cranial and cervical lesions), and twenty-one cases (36%) were treated using fiducial tracking.

There were no patients that suffered a significant (Grade 3, 4, or 5) acute toxicity. There was no observed late toxicity. Seventy-eight percent of patients experienced an improvement of their pre-treatment symptoms while only one patient experienced symptom progression. Of the 26 patients who underwent follow-up imaging, the local control rate was 96%.

The patient who experienced symptom progression was a young patient with Neurofibromatosis Type I with neurofibromas of the cervical spine. Despite three CyberKnife Radiosurgical treatments to the cervical spine receiving a total dose 50 Gy to the 80% isodose line, this patient still experienced neck pain as well as progressive quadraparesis requiring a cervical spine laminectomy. Of note, the patient has not experienced any sign of radiation induced spinal cord myelopathy to date one year after her last CyberKnife treatment despite the multiple radiosurgical

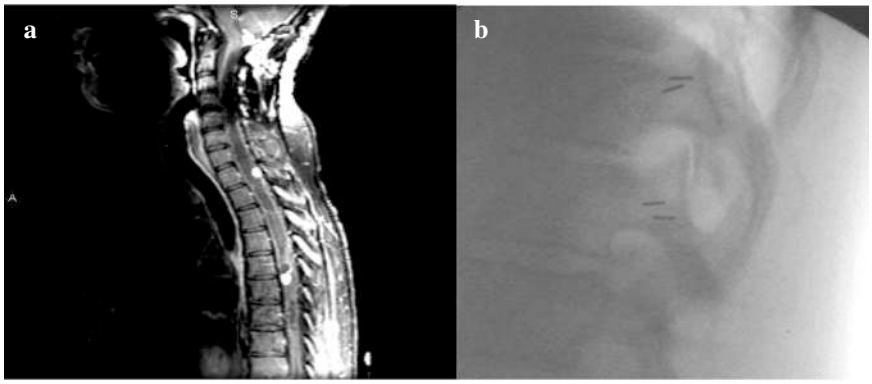

Figure 1: **a** (*left*) Sagittal image of gadolinium enhanced MRI identifying spinal hemangioblastomas. **b** (*right*) Plain radiograph showing the percutaneously placed fiducials.

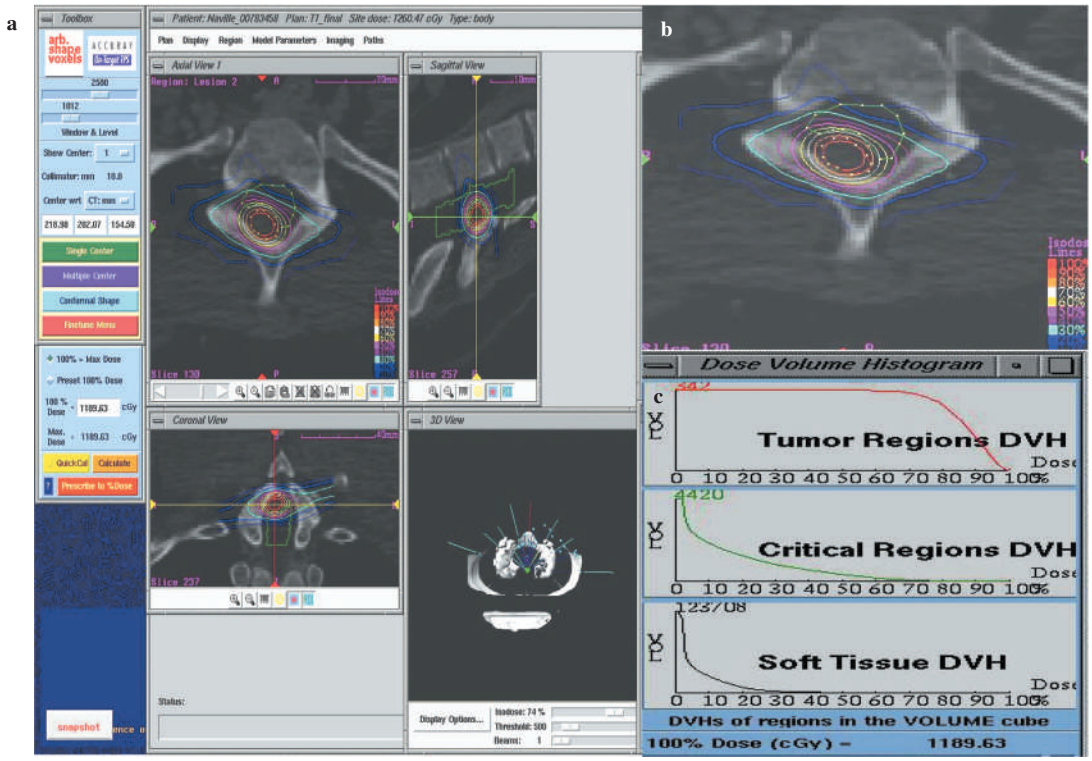

Figure 2: **a** (*left*) The treatment plan overlayed on axial, sagittal, and coronal CT reconstructions. **b** (*upper right*) Magnified image of treatment plan on axial CT image. 80% isodose represents prescribed dose of 1000cGy. **c** (*bottom right*) Dose Volume Histogram reveals 83% of the tumor received 80% of the maximum dose of 1250 cGy.

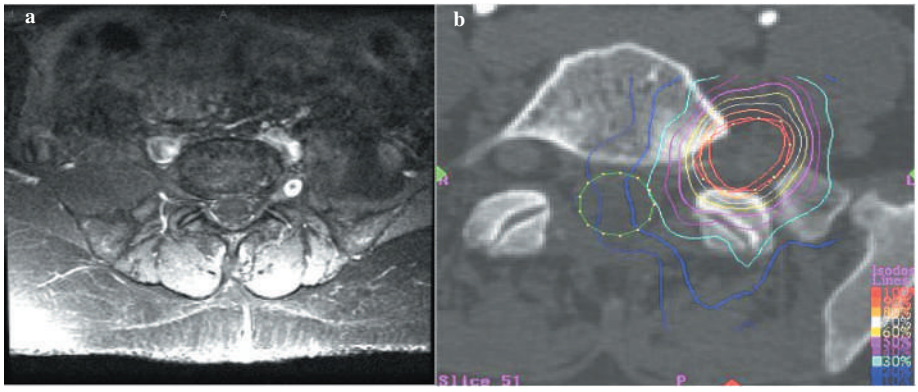

Figure 3: **a** (*left*) Axial image of gadolinium-enhanced MRI identifying neurofibroma on left pedicle of L5. **b** (*right*) The CyberKnife radiosurgery treatment plan shows the left L5 neurofibroma target. 80% isodose line represents prescribed dose of 2000 cGy. The lesion volume is 3.2 cc. The maximum dose to the thecal sac is 660 cGy.

treatments. The spinal cord volume receiving greater than 8 Gy was 0.1 cc, 0.3 cc, 0.1 cc, respectively for each of the patient's CyberKnife treatments.

Figures 1 through 3 refer to representative case examples in this series. Figure 1a shows an MRI of a spine of a patient with Von Hippel-Lindau Syndrome with multiple symptomatic spinal hemangioblastomas who underwent CyberKnife radiosurgery. The percutaneously implanted fiducial markers in the thoracic spine pedicles are shown in a lateral radiograph in Figure 1b. The CyberKnife treatment plan including the isodose curves and dose volume histogram are also shown (Figures 2a-c). The 80% isodose line represents the prescribed dose of 1000 cGy. The tumor volume is 0.34 cc, and only 0.02 cc of the spinal cord received > 800 cGy. The dose volume histogram reveals 83% of the tumor volume received 80% maximum dose of 1250 cGy.

Case example 2 refers to a patient with Neurofibromatosis Type I. She suffered from severe left L5 radicular pain. Figure 3a refers to an axial image of a spine MRI revealing an enhancing neurofibroma on the left pedicle of L5. The treatment plan in Figure 3b shows the 80% isodose line which represents the prescribed dose of 2000 cGy. The tumor volume is 3.2 cc. The maximum dose to the thecal sac is 660 cGy. The patient had excellent pain relief within one month.

Discussion

The purpose of this preliminary study was to examine the feasibility, efficacy, and potential toxicity of CyberKnife radiosurgery for the treatment of extracranial benign tumors. Even though radiosurgery is considered one of the standard treatment options for various benign intracranial lesions based on data for over fifty years, this study is the first report on the use of radiosurgery for benign tumors outside of the skull (7-12, 25-28). Seventy-eight percent of the patients reported an improvement in the pre-treatment symptoms, and the local control rate was 96%. There was no severe or fatal toxicity in our series which included a patient with a benign spinal lesion which received three CyberKnife treatments. The outcomes of this study suggest that CyberKnife radiosurgery is a reasonable treatment option for extracranial benign lesions especially for tumor previously irradiated or resected. Further follow-up is needed to confirm this data.

In this series, the majority of the lesions were spinal (47 of 59, 80%) and ten of these lesions already received external beam irradiation and at the upper limit of tolerable spinal cord dose. Previous reports have shown excellent results for malignant spinal lesions treated with CyberKnife Radiosurgery (18-20). Gerszten *et al*. recently reported the largest series to date with 125 cases of which 78 had prior external beam irradiation who then subsequently received CyberKnife Radiosurgery with no severe toxicity and a 94% response rate (18). This study validates the safety and efficacy of CyberKnife Radiosurgery for benign spinal lesions.

This study also suggests CyberKnife Radiosurgery as a useful modality for other extra-cranial lesions in addition to spinal tumors. This treatment method was useful for treating benign tumors of the orbit and neck with minimal toxicity due to the highly conformal treatment plan. Using external beam irradiation for these tumors would most likely induce significant toxicity with possible permanent organ dysfunction because of the large treatment fields required with this modality. However, with modern treatment techniques for external beam irradiation such as intensity modulated radiation therapy (IMRT), conformal treatment plans with highly localized dose can be safely delivered that would significantly reduce such toxicity (29-32). In a phase I trial reported by Chang *et al*. using IMRT with near simultaneous CT guidance to treat spinal metastases to a dose of 30 Gy in 6 fractions using stereotactic body frame fixation, none of the fifteen patients experienced severe neurotoxicity or signs of spinal cord myelopathy after completion of their treatment with a median follow up of nine months (32). Therefore, a prospective trial comparing IMRT with CyberKnife Radiosurgery for treating these extracranial lesions is warranted.

Another advantage of CyberKnife over external beam irradiation, including IMRT, is the ability to safely deliver a large dose in a single fraction. This radiobiological advantage may help explain the 96% control rate in our series which included aggressive benign lesions with 20% of the cases being radioresistant, since they did not respond to the previous external beam irradiation, and 40% of the tumors having undergone previous surgical resection. This single fraction delivery also allows for the convenience of a single outpatient visit compared to weeks of daily treatment with external beam irradiation, thus improving the quality of life for these patients.

Conclusion

This study suggests that CyberKnife Radiosurgery is a safe and efficacious treatment modality for benign tumors, including those patients with recurrent previously irradiated lesions. There is significant symptom relief with minimal acute toxicity from extracranial radiosurgery. Local control rate thus far is encouraging, but further follow-up is needed to assess long-term control rates as well as late effects. The major potential benefits of radiosurgical ablation of spinal lesions are short treatment time in an outpatient setting with rapid recovery and symptomatic response. This technique offers a successful alternative therapeutic modality for the treatment of a variety of benign lesions not amenable to open surgical techniques, in medically inoperable patients, lesions located in previously irradiated sites, or as an adjunct to surgery.

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