A Review Article on
CyberKnife Stereotactic Radiosurgery for Spinal Lesions

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Abstract

The efficacy of the CyberKnife [Accuray, Inc., Sunnyvale CA], a new stereotactic radiosurgery device utilized in the treatment of benign and malignant spinal tumors, is reviewed. The study assesses the number and type of spinal tumors safely and effectively treated with CyberKnife radiosurgery.

Most reports concerning the utilization of CyberKnife stereotactic radiosurgery [CSR] for the treatment of malignant [primary, metastatic] or benign spinal lesions have been published within the last 5 years. CSR may be administered alone or in conjunction with surgery and external beam radiation therapy. A major benefit of CSR is that it can be completed within 1 week [1-5 fractions] as compared with the several weeks required for external beam radiotherapy, with limited toxicity. A frameless device, the CSR’s accuracy is +/- 1 mm. Additionally, the Xsight program now allows the cervical and lumbar spine to be treated without fiducial marker placement; however, this is still required to accurately target thoracic lesions.

CyberKnife radiosurgery is effective in treating both benign and malignant lesions. For benign tumors, the CSR successfully arrests tumor progression and minimizes pain. It is unique for the management/palliation of malignant metastatic disease where it functions as an adjunct or alternative to invasive surgery and/or routine external beam radiotherapy.

In summary, CyberKnife stereotactic radiosurgery, approved by the Federal Drug Administration [USA 2001], may be safely and effectively administered within 1 week’s time to treat both benign and malignant spinal lesions with limited toxicity.

Key words: CyberKnife, stereotactic radiosurgery, spine tumors

INTRODUCTION

Frameless stereotactic radiosurgery is increasingly utilized to treat both benign and malignant lesions of the spine. A specific frameless device approved by the Food and Drug Administration in 2001 is the CyberKnife [Accuray, Inc., Sunnyvale CA]. Without utilizing a frame, the CyberKnife delivers stereotactic radiosurgery [CSR] with pinpoint accuracy [ +/- 1 mm] in 1-5 fractions over a 1-week interval. Fiducial markers, no longer required to treat cervical or lumbar tumors, are only implanted to target thoracic lesions, and these may be placed in the neuroradiology suite under local anesthesia. CSR is particularly useful in the management of malignant metastatic spine disease, as it can supplement or
supplant primary/secondary surgery and/or routine external beam radiation therapy [RT] with limited toxicity.

**Stereotactic Radiosurgery**

The CyberKnife is utilized to administer a high dose of radiation to tumors or vascular anomalies in 1-5 fractions administered over a 1-week period. [4, 7] The short duration of therapy, particularly when administered for palliation in malignant/metastatic disease, rapidly reduces pain while avoiding daily treatments that can span several weeks duration. Furthermore, the radiation dose to adjacent structures and its inherent toxicity are kept to a minimum as compared with conventional radiotherapy.

**Treatment Planning**

The frameless CyberKnife couples an orthogonal pair of X-ray cameras to a dynamically manipulated robot-mounted linear accelerator which delivers/directs the beam to the tumor site utilizing 50-300 positions without the use of frame-based fixation [6, 12]. Beams are sequentially delivered; moving from position to position, cross-filing through the lesion to attain optimal conformality. The treatment, safely administered in an outpatient setting, utilizes structural skeletal landmarks for localization in the cervical and lumbar spine, but still requires fiducial placement for thoracic lesions [7]. CyberKnife radiosurgery may be utilized instead of or as an adjunct to prior surgery and/or routine external beam radiotherapy. It is an excellent device for the treatment of ‘unresectable tumors’ or those not amenable to or previously unsuccessfully managed with routine RT.

**Federal Drug Administration Approval in the USA 2001**

The radiation therapy is administered via a mobile x-band linear accelerator placed on a robotic arm. To ensure the accuracy of treatment delivery, the Cyberknife utilizes an image guidance system, which employs an X-ray imaging source and amorphous silica detectors [9]. Therapy is delivered by integrating the image guidance system, the automated couch, and linear accelerator utilizing real-time tracking. In 2001, the CyberKnife was approved by the Federal Drug Administration to be utilized in the USA “anywhere in the body where radiation treatment is indicated”.

**Accuray**

The CyberKnife target treatment accuracy, previously utilizing spinal fiducials, was observed to be +/- 1 mm [Accuray, Inc., Sunnyvale CA] [12]. Chang, Main, Martin et. al. studied the CyberKnife’s beam delivery accuracy [robot and camera image tracking] for localizing the target [CT and treatment planning] [1]. Accuracy tests utilized head phantoms and radiochromic film, looking to confirm the adequate integration of treatment planning software, the robot, the camera, and the linear accelerator. The mean error measured was 0.7 mm when the CT slice was 0.625 mm thick compared with a mean error of 1.97 mm for slices 3.75 mm thick. For clinical purposes the accuracy was measured to 1.1 mm +/- 0.3 mm when CT thickness was 1.25 mm. When the accuracy of the CyberKnife was tested at three different sites with head and torso phantoms utilizing radiochromic film, the average error was 0.7 +/- 0.3 mm utilizing a CT slice thickness of 0.625-1.5 mm, while the average precision was 0.3 +/- 0.1 mm [15].

**Xsight Tracking System**

The Xsight tracking system presently utilizes spinal bony landmarks rather than implanted fiducial markers to effectively target CyberKnife radiosurgery to the spine [11]. However, many would still consider fiducial markers essential to target the thoracic spine, but that they are no longer warranted for cervical or lumbar spine treatment planning. In Muacevic, Stuehler, Drexler et. al. study, they ‘end to end’ tested the accuracy of the CyberKnife utilizing first a phantom of the cervical spine, and secondarily treating 50 spinal lesions in 42 patients [11]. The mean target error was 0.52 +/- 0.22 mm, treatment doses ranged from 12-25 Gy [to the median isodose of 65%], and tumor volumes varied from 1.3 cm3 - 152.8 cm3. The average spinal cord volume receiving over 8 Gy was 0.69 cm3. No complications were noted over the 1-7 month evaluation period, and pain was successfully relieved in 14 of 15 patients.
Utilizing (18)F-Fluorodeoxyglucose [FDG] Positron Emission Tomography [PET] for Planning CyberKnife Radiosurgery Treatment for Metastatic Disease

Many patients with metastatic disease are living longer due to improved surgical techniques, chemotherapeutic regimens, and radiation therapies. Stereotactic radiosurgery is in greater demand than ever to treat patients with recurrent disease who have ‘failed’ previous treatment protocols. Gwak, Youn, Chang et. al. utilized FDG-PET to better outline recurrent/residual tumor for patients slated to undergo hypofractionated stereotactic radiosurgery [10]. Three patients with recurrent metastatic spinal disease [1 sarcoma, and 2 with breast cancer] were treated with the CyberKnife. Patients received three fractions of treatment following tumor localization with FDG-PET. All 3 patients had previously received conventional external beam radiation therapy [30-45 Gy]. FDG-PET studies were performed prior to treatment, and 1 and 6 months after therapy. Standard uptake values [SUV] were appropriately calculated. Following CSR, no complications were encountered over an average of 13.3 months. The SUV at six months correlated with outcomes; 1 showed partial failure, while 2 exhibited no local regrowth of tumor.

Treatment of Malignant Tumors

Primary and Metastatic Malignant Lesions

CyberKnife radiosurgery was utilized to manage 72 malignant lesions in 51 patients; 58 patients had metastatic lesions, while 14 patients had primary malignant tumors [Table 1] [2]. Outcomes were assessed utilizing the Visual Analog Scale [VAS] and the Short Form-12 [SF-12]; both were obtained preoperatively, and 1, 3, 6, 8, 12, 18 and 24 months postoperatively. The average follow-up duration was 1 year. Pain improved on the VAS scale from 51.5 to 21.3 at 4 weeks, and 17.5 at one year. On the SF-12, the mean score was 50 +/- 10. Complications included dysphagia [3 patients], diarrhea [2 patients], lethargy [3 patients], paresthesias [1 patient], and wound dehiscence [1 patient].

Kyphoplasty and CyberKnife Radiosurgery for Pathological Compression Fractures Associated with Malignant Metastases

Patients with symptomatic pathological compression fractures attributed to metastatic/ malignant disease previously required surgical decompression/stabilization and external beam radiation therapy, but now may be managed less invasively with percutaneous kyphoplasty and CyberKnife radiosurgery [Table 1]. In Gerszten, Germanwala, Burton et. al. series, 26 patients presented with pathological compression fractures in the thoracic [16 patients] and lumbar spine [10 patients] [8]. Patients averaged 72 years of age. There were 6 males and 20 females. Metastatic lesions included: lung [11 patients], breast [9 patients], renal [4 patients], cholangiocarcinoma [1 patient], and ocular melanoma [1 patient]. Seven patients had received prior external beam radiation therapy. Patients underwent kyphoplasty with simultaneous fiducial placement in adjacent pedicles. They next underwent single fraction CyberKnife treatment an average of 12 days later. The average tumor dose was 18 Gy [range 12-20 Gy], and the tumor volume ranged from 12.7-37.1 cm3. Following combined percutaneous kyphoplasty and Cyberknife radiosurgery, no patients exhibited radiation related toxicity or any increase in neurological deficits over an average of 16 post treatment months [follow up range 11-24 mo]. Additionally, axial pain improved in 24 of 26 patients.

Malignant Sacral Lesions

The 18 sacral lesions included in Gerszten, Ozhasoglu, Burton et. al. series were treated with CyberKnife radiotherapy utilizing fiducial bone markers applied percutaneously [Table 1] [5]. Of note, 17 lesions were malignant, and only 1 was benign. Dose plans were based on 1.25 mm thick CT slices. All patients were treated with an average dose of 15 Gy [range 12-20 Gy] administered in a single fraction to tumor volumes which ranged from 23.6 to 187.4 cm3 [mean 90 cm3]. All patients were treated as outpatients, and none exhibited acute radiation toxicity or new neurological deficits over the mean duration of follow-up of 6 months. Furthermore, all 13 who originally presented with pain were improved.
Metastatic Melanoma

In Selvaggi and Abrahm’s case report, a 47-year-old male originally underwent resection of a shoulder melanoma in 1997 [13]. By 2004, he exhibited metastases to the brain [multiple], adrenal, lung, and bone. In 2005 a right brain lesion was removed and he had whole brain RT. Within a month, he additionally required CyberKnife therapy to the recurrent cranial lesions. Shortly thereafter, metastatic melanoma to C7 with cord compression was additionally managed with CyberKnife radiosurgery.

Combined Series of Benign and Malignant Spinal Tumors

Gerszten, Ozhasoglu, Burton et. al. treated 125 spinal tumors in 115 patients with a single fraction of CyberKnife radiosurgery [Table 1] [6, 7]. Tumors included 45 cervical, 30 thoracic, 36 lumbar, and 14 sacral lesions [2]. Seventeen tumors were benign, while 108 were malignant. Of note, 78 lesions were previously treated with routine external beam radiation. Tumor volumes ranged from 0.3-232 cm₃ [mean 27.8 cm₃]. The tumor dose averaged 14 Gy [range 12-20 Gy], with the spinal canal volume receiving an average of 8 Gy. No patients developed acute radiation toxicity, and none exhibited new neurological deficits within the post-treatment interval of 3-24 months and later 9-30 months [median 18 mo] [6, 7]. Of interest, axial pain improved in 74 of the 79 patients originally presenting with pain [6].

Treatment of Benign Spinal Tumors

Intradural Extramedullary Benign Tumors

Although resection of intradural extramedullary lesions may be successful in a large number of patients, a subset with neurofibromatosis, residual/recurrent lesions, multiple lesions, or prohibitive medical comorbidities excluding surgical intervention as a treatment option, may be considered candidates for CyberKnife radiosurgery [Table 1] [3]. Beginning in 1999, in Dodd et. al. series, 51 patients averaging 46 years of age [range 12-86 years old] with 55 benign spinal lesions were treated [3]. Tumors included 30 schwannomas, 9 neurofibromas, and 16 meningiomas. CyberKnife radiation doses varied from 16-30 Gy delivered in 1-5 fractions to tumor volumes ranging from 0.136-24.6 cm₃. Less than one year following treatment, only 3 patients [1 schwannoma, 1 neurofibroma, 1 meningioma] exhibited persistence or worsening of symptoms. Nevertheless, the lesion had expanded in only 1 of the 3 patients. After 3 years in data based on 28 remaining patients, 61% of lesions had remained the same size and 39% were smaller, while 2 deaths that had occurred were unrelated to the tumors. Of interest, only 1 patient developed radiation related myelopathy 8 months following treatment.

In another series, 15 patients with benign spinal lesions were treated with the CyberKnife [5]. These tumors included 5 neurofibromas, 3 parangangiomas, 2 schwannomas, 2 meningiomas, 2 chordomas, and 1 hemangioma. They were located in the cervical [12 cases], thoracic [1 case], and lumbar spine [2 cases]. Treatment, based on 1.25 mm CT slices, included average doses of 16 Gy [range 12-20 Gy] to the 80% isodose line. The average tumor volume was 6.4 cm₃ [range 0.3-29.3 cm₃]. All were treated as out patients, none developed acute radiation induced toxicity, and none exhibited new neurological deficits. Pain was improved for all of those originally exhibiting pain. No tumor progression was seen on 1-year post-operative neurodiagnostic imaging studies.

Preliminary Data For CyberKnife Radiosurgery of 40 Spinal Lesions at Winthrop University Hospital

Between August of 2005 and February of 2007, 40 patients with spinal lesions were treated at Winthrop University Hospital [Mineola, NY 11501]. Of these, 7 tumors were benign, and included 5 meningiomas, and 2 neurofibromas. Thirty-three tumors were malignant and metastasized mostly from the lung [8 patients], breast [7 patients], kidney [7 patients], and colon [4 patients] primary cancer sites. Metastatic lesions were localized to the cervical [5 patients], thoracic [16 patients], lumbar [5 patients], and sacral [7 patients] spinal regions. Patients were managed with an average of 4.1 fractions; 3 fractions on average for benign disease [total 18 Gy], and between 4-5 fractions for metastatic tumors [between 20-25 Gy]. The average follow-up duration for spine lesions
Table 1: Review of Series Utilizing CyberKnife Radiosurgery for Spinal Lesions

<table>
<thead>
<tr>
<th>References</th>
<th>Tumors</th>
<th>Location of Lesions</th>
<th>Mean Dose [Gray [Gy]]</th>
<th>Mean Tumor Volume/Range</th>
<th>Follow-Up Pain Control</th>
<th>Complications Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerszten 2</td>
<td>17 B</td>
<td>45 Cervical</td>
<td>14 Gy [12-20]</td>
<td>27.8 cm³ [0.3-232]</td>
<td>18 mo</td>
<td>None</td>
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<tr>
<td>108 M</td>
<td>30 Thoracic</td>
<td>1 Fraction</td>
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<tr>
<td>78 Prior RT</td>
<td>36 Lumbar</td>
<td>14 Sacral</td>
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<tr>
<td>Gerszten 12</td>
<td>1 B</td>
<td>18 Sacral</td>
<td>15 Gy [12-20]</td>
<td>90 cm³ [23.6-187.4]</td>
<td>6 mo</td>
<td>None</td>
</tr>
<tr>
<td>17 M</td>
<td></td>
<td></td>
<td>1 Fraction</td>
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<tr>
<td>Gerszten 11</td>
<td>26 M</td>
<td>16 Thoracic</td>
<td>18 Gy [16-20]</td>
<td>Range</td>
<td>16 mo</td>
<td>None</td>
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<tr>
<td>7 Prior RT</td>
<td>10 Lumbar</td>
<td>1 Fraction</td>
<td></td>
<td>12.7-37.1 cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dodd 14</td>
<td>55 B</td>
<td>38 Cervical</td>
<td>Range</td>
<td>Mean 0.136-24.6 cm³</td>
<td>36 mo</td>
<td>3 at 12 mo [at 8 Months;</td>
</tr>
<tr>
<td>7 Thoracic</td>
<td>8 Lumbar</td>
<td>2 Sacral</td>
<td>1-5 Fractions</td>
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<td>1 Radiation Myelopathy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 Unrelated Deaths</td>
</tr>
<tr>
<td>Sinclair 15</td>
<td>15 AVM</td>
<td>9 Cervical</td>
<td>Mean 20.5 Gy</td>
<td>Not Applicable</td>
<td>27.9 mo</td>
<td>7 MR Scans</td>
</tr>
<tr>
<td>3 Thoracic</td>
<td>3 Conus</td>
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<td>2-5 Fractions</td>
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<td>3 Years</td>
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<td>6 Stable</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Obliterated</td>
</tr>
<tr>
<td>Epstein 7B</td>
<td>33 M</td>
<td>Malignant: 5 Cervical</td>
<td>Mean 18 Gy for Benign</td>
<td>NA</td>
<td>9 mo</td>
<td>2 Deaths Due to</td>
</tr>
<tr>
<td>16 Thoracic</td>
<td>5 Lumbar</td>
<td>7 Sacral</td>
<td>Mean 20-25 Gy for Malignant</td>
<td></td>
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<td>Overall Metastatic</td>
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<td>Disease</td>
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</table>

AVM*=Arteriovenous Malformation, RT=Prior External Beam Radiation Therapy
now averages 9 mo. The majority of patients exhibited marked improvement regarding pain symptoms and experienced no significant deterioration. Two deaths unrelated to CyberKnife radiosurgery occurred during the follow-up period, and were attributed to the overall severity of the patients’ metastatic disease. A formal longer-term follow-up study will be performed in the future for these patients.

**Treatment of Vascular Malformations with the CyberKnife**

*CyberKnife for Intramedullary Arteriovenous Malformations [AVM]*

Recurrent bleeding leading to progressive myelopathy characterizes the symptomatic progression for patients with intramedullary spinal cord AVMs. Although successful embolization and surgical extirpation may be technically feasible, endovascular and/or surgical morbidity often preclude utilizing these treatment modalities. In Sinclair, Chang, Gibbs et. al. study, 15 patients with intramedullary spinal cord AVMs were treated with CyberKnife radiosurgery [14]. Spinal vascular malformations were localized to the cervical [9 patients], thoracic [3 patients], and conus regions [3 patients]. An average dose of 20.5 Gy was administered in 5 fractions. Patients were followed an average of 27.9 mo [range 3-59 mo]. Clinical and MR studies were performed yearly, while spinal angiograms were completed 3 years after treatment. Three years following treatment, MR examinations in 6 of 7 patients showed significant reduction in the size of the AVMs. Spinal angiograms, also performed 3 years later, revealed a reduction in the size of the AVM in 4 of 5 patients, while 1 showed full obliteration of the lesion. Most importantly, there were no episodes of rebleeding following CyberKnife radiosurgery, and none exhibited new and/or increased neurological deterioration.

**Acknowledgement**

I would like to thank the Joseph A. Epstein Neurosurgical Education Foundation for its support of this work and the editorial assistance of Ms. Sherry Grimm, administrator of Long Island Neurosurgical Associates PC.

**REFERENCES**

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Reviewer's comment: Akira Matsumura M.D., PhD.  
Department of Neurosurgery, University of Tsukuba, Ibaraki, Japan

The meticulous review article by Dr. Nancy Epstein regarding the application of Cyberknife Stereotactic Radiosurgery (CSR) for spinal lesion is highly informative and provides useful information to the readers of this journal.

CSR is highly recommended for metastatic spinal tumors for relief of the pain and suppression of the tumor growth or shrinkage of the tumor for a certain period. The CSR for metastatic spinal tumor may be the best palliative treatment method for the patients with limited life expectancy.

The application of CSR for benign tumors should be very cautious. Since the spinal cord is a serial organ, once the radiation injury occurs even in a small portion of the spinal cord, the neurological deficit will appear in all distal portion to the injured spinal cord level. CSR of the spinal cord should be separately considered from the stereotactic radiosurgery (SRS) in the brain, since brain is a parallel organ so that a focused radiation injury may not always cause severe neurological deficit.

In fact, in the CSR series of Dodd et al., one patient developed radiation related myelopathy with a dose ranging from 16-30Gy. The dose re-calculated for 2Gy-Eq fractionated dose depend on the $a/\beta$ ratio for the spinal cord so that one should always think of the normal spinal cord tolerance dose, which is usually lower than the brain.

The CSR application to the intramedullary lesion is also of highly interesting topic. Dr. Epstein introduced the result of the application of CSR to intramedullary spinal AVMs. It is worth knowing that the patients receiving 20.5Gy (in five fractions) had so far no neurological deterioration. Since the follow-up period ranges from 3-59 months in the series of Sinclair et al, the result of longer follow-up is important because delayed radiation damage may occur several years after radiation therapy and once it occurs, it may cause a severe damage to the patient. I would like again stress the importance of the key phrase “Spinal cord should be regarded as a serial organ in radiation therapy”.

I congratulate the informative review article of Dr. Epstein concerning CSR for spinal disease and I expect expansion of application of modern radiation techniques such as CSR, Linac based intensity modulated radiation therapy (IMRT), tomotherapy and other modern irradiation techniques for the benefit of the patients suffering from spinal disorders.

Reviewer's comment: Masanori Ito, M.D.  
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Conventional external beam radiotherapy lacks the precision to allow delivery of large doses of radiation near radiosensitive structures such as the spinal cord. The use of radiosurgery for the treatment of spinal lesions has been limited by the availability of effective target immobilization and localization technologies. The CyberKnife is an image guided frameless stereotactic radiosurgery system that allows for the radiosurgical treatment of spinal lesions. The author reviewed the efficacy of CyberKnife for the treatment of spine and spinal cord tumors including intramedullary arteriovenous malformations. The review is concise and comprehensive. The promising efficacy and few postoperative complications during the follow-up period lead us to promote the spread of this technology throughout our country. However, in our country, we have just started to use CyberKnife only for the treatment of intracranial and cervical lesions, and head and neck tumors as well. It is also used for trigeminal neuralgia. Japanese Health Insurance covers the CyberKnife radiosurgery. The fixed and uniform reimbursement price is 630,000 yen. The patient's own expense is much more less because there is catastrophic coverage for high-cost care or a cap on monthly co-payment spending (High-Priced Medical Fee system: Kogaku Ryouyouhi Seido). Nevertheless, it is unfortunate that The Ministry of Health, Labor and Welfare do not allow CyberKnife to be indicated for the treatment of the lesions caudal to cervical area including those of the thoracic, lumbar and sacral spine and spinal cord. The Japanese patients do not seem to benefit from this technique for the time being.