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ORIGINAL ARTICLE

Pain Relief Following Spinal Lesion Treatment with Stereotactic Radiosurgery: Clinical Experience in 65 Cases

Shih-Wei Hsu[1], Hsing-Lung Chao[2], Kuen-Tze Lin[2], Yu-Ching Chou[3], Cheng-Hsiang Lo[2], Shih-Yu Lee[4], Wen-Yen Huang[2], Chun-Shu Lin[2], Chien-Min Lin[5], Chao-Yueh Fan[2], Da-Tong Ju[1]

Departments of [1]Neurological Surgery and [2]Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, [3]School of Public Health, National Defense Medical Center, [4]Graduate Institute of Aerospace and Undersea Medicine, National Defense Medical Center, Taipei, [5]Department of Neurosurgery, Taipei Medical University, Shuang Ho Hospital, New Taipei City, Taiwan

Background: This study determines the pain-reducing effect of CyberKnife radiosurgery in the treatment of spinal lesions. **Materials and Methods:** We evaluated the clinical outcomes of patients treated with CyberKnife radiosurgery for spinal lesions in 65 patients with 76 spinal lesions at Tri-Service General Hospital, Taipei, Taiwan, from July 2007 to May 2013. Pre- and post-treatment visual analog scale (VAS) scores for pain were obtained. **Results:** In the benign cases, 12 patients had a pretreatment VAS score of 7 (46.2%); 12 patients, 8 (46.2%); and 2 patients, 9 (7.7%). For the posttreatment VAS scores, 10 patients had a score of 1 (38.4%); 15 patients, 2 (57.7%); and 1 patient, 4 (3.8%). In the malignant cases, 2 patients had a pretreatment VAS score of 8 (28.6%); 3 patients, 9 (42.9%); and 2 patients, 10 (28.6%). For the posttreatment VAS scores, 1 patient had a score of 2 (14.3%) and 6 patients had a score of 3 (85.7%). In the metastatic cases, 15 patients had a pretreatment VAS score of 8 (46.9%); 7 patients, 9 (21.9%); and 10 patients, 10 (31.3%). For the posttreatment VAS scores, 3 patients had a score of 1 (9.4%); 11 patients, 2 (34.4%); 16 patients, 3 (50%); and 2 patients, 4 (6.3%). Wilcoxon signed-rank tests to compare the pre- and post-treatment VAS scores in each patient group showed significant decreases in all groups ($P < 0.05$ for all comparisons). **Conclusions:** Collectively, these results show that significant pain relief without obvious adverse effects can be achieved when treating spinal lesions using stereotactic radiosurgery.

Key words: Stereotactic radiosurgery, CyberKnife, spine, pain reduction, lesion

INTRODUCTION

The use of stereotactic radiosurgery for treating both benign and malignant intracranial lesions is well-established.[1,2] It is also a practical treatment for brain metastases.[3,4] Benign lesions such as meningiomas, acoustic neuromas, pituitary adenomas, and arteriovenous malformations can be primarily treated with radiosurgery.[5-8] The main goals of radiotherapy in the treatment of spinal tumors are to relieve pain, prevent pathologic fractures, and preserve neurologic function.[9]

Drawbacks to using the conventional radiotherapy technique include the presence of large irradiated areas and overdoses in the surrounding normal organs. The tumor locations, which can often be difficult to reach surgically, and the general condition of the patients often limit the success rate of surgical tumor removal. Another treatment option is radiosurgery, a noninvasive technique that can treat the tumor more precisely. Gamma knife radiosurgery can treat intracranial, but not extracranial, tumors, and requires an additional fixed frame. CyberKnife radiosurgery (Accuray Inc., Sunnyvale, CA, USA), on the other hand, is frameless and can target both intra- and extra-cranial tumors using the intrafraction image-guided tracking technique (through fiducial marker implantation or using a bony structure as a marker).

CyberKnife is different from the conventional linear accelerator because it has a dynamic tracking system. It consists of diagnostic-quality X-ray imaging devices with a computer-controlled robotic arm. Multiple noncoplanar and nonisocentric radiation beams can be delivered by CyberKnife. Thus, CyberKnife can send updated position information to the robot, allowing adaptive beam algorithms to adjust for patient movement, which permits accurate radiotherapy. In view of the radiation source can track the target, complete

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Corresponding Author: Dr. Da-Tong Ju, Department of Neurological Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Gong Road, Neihu, Taipei 114, Taiwan. Tel: +886-2-87923311. Fax: +886-2-66002357 E-mail: wxyz670628@yahoo.com.tw

target immobilization is unnecessary.[10-12] For spine lesions, the Xsight spine-tracking mode is useful. In addition, the average set-up error is around 0.52-0.61 mm. Use of this technique for treating spinal lesions (benign, malignant, or metastatic) can improve patients' quality of life and decrease the adverse effects of radiotherapy.[13-17]

The spine is the most common site of cancer metastasis to bone. Bone pain is a major patient concern, and the degree of bone pain is often underestimated. Spinal compression can lead to a poor quality of life, as it can significantly affect motor and sensory functions.[18,19] Breast cancer, lung cancer, and prostate cancer are easily metastatic to bone. Subsequently, metastatic bone pain, compression fractures, and spinal cord compression develop. Hence, the palliative intent of spinal metastasis treatment is to relieve pain and reduce neurologic deficits. The purpose of this study, therefore, was to determine the pain-reducing effects of CyberKnife radiosurgery in patients being treated for spinal lesions.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed the files of patients who received CyberKnife radiosurgery for spinal lesions from July 2007 to May 2013 in the stereotactic radiosurgery center of a single medical center at Tri-Service General Hospital, Taipei, Taiwan. The eligibility criteria were as follows:

1. Primary spinal lesions where surgery was not considered feasible or appropriate,
2. Spine metastases in the context of oligometastatic disease, and
3. Symptomatic spine metastases. A total of 65 patients with 76 spinal lesions treated by CyberKnife radiosurgery were identified (34 men and 31 women; mean age: 53 years; age range: 8-87 years).

The length of follow-up ranged from 3 to 61 months (median: 16 months). Tables 1-3 provide summaries of the clinical characteristics and treatment in each of the patient groups. The protocol was approved by the Institutional Review Boards of the Medical Centers in Taiwan.

Radiosurgery technique

All patients wore a custom-made aquaplast mask (WFR/Aquaplast Corp., Wyckoff, NJ, USA) and were immobilized on the treatment table. For treatment planning, before computed tomography and magnetic resonance imaging (MRI) using T1-weighted images were performed, 125 mL of omnipaque contrast (350 mg I/mL; Nycomed, Inc., Princeton, NJ, USA) was administered intravenously. The neurosurgeon offered lesion and critical organ contours and the radiation oncologist supplied the prescription dose and dose constraints for the critical organs. The CyberKnife treatment planning system (Multiplan v2.1) and Xsight spine-tracking mode were used in all patients. We evaluated each treatment plan using the tumor coverage, homogeneity index (HI), conformity index (CI), and new CI (nCI). The HI = D_{max}/prescribed dose, where D_{max} is the maximum dose, while CI = prescription isodose volume (PIV)/tumor isodose volume (TIV), where PIV is the total three-dimensional volume of the isodose line and TIV is the tumor volume covered by the isodose volume. The nCI = tumor volume (TV) × plan target volume/(target isodose volume).[2,20]

Radiation dosage and isodose lines

The doses and fractionation were different because of the different nature of each lesion. For benign cases, the average prescription dose (Gy) was 25.9 ± 7.8 (range: 12-60 Gy), and the average fraction was 4.6 ± 1 fractions (range: 1-5 fractions). For malignant cases, the average prescription dose (Gy) was 26.7 ± 6.1 (range: 21-40 Gy), and the average fraction was 4.3 ± 1 fractions (range: 3-5 fractions). For metastatic cases, the average prescription dose (Gy) was 27.7 ± 7.7 (range: 7.6-50 Gy), and the average fraction was 4.4 ± 1.2 fractions (range: 1-5 fractions). The radiation dose prescribed was between 70% and 80% of the isodose lines.

Pre- and post-treatment pain scores and follow-up

We evaluated the patients' pretreatment pain levels on the first clinical visit before CyberKnife radiosurgery. We assessed the degree of pain using a visual analog scale (VAS) with scores ranging from 0 to 10.[21,22] The first posttreatment clinical visit was scheduled 1-month after CyberKnife radiosurgery. Each change in the prescribed analgesics was recorded. Further evaluation and MRI images were obtained at 3, 9, and 18 months after treatment. When comparing the pretreatment MRI images to the ones acquired 3 months after treatment,[23] we checked the tumor size and measured the tumor volume (Vol) with the following formula: Vol (mm^3) = Tr (a × b × c)/6, where a, b, and c are the width, height, and thickness, respectively. The World Health Organization Handbook for Reporting Results of Cancer Treatment was used to classify the response to therapy as a complete response, partial response, stable disease, or progression.

Based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0), toxicity was evaluated during and after the treatment at 1-2 month intervals for the first 6 months and then every 3 months until 18 months.

Statistical analysis

Descriptive summaries were used to describe the clinical characteristics. The Wilcoxon signed-rank test was used to

Table 1: Summary of patients with benign spine tumors

Patient and treatment characteristics	*n* (%)
Age	49.6±20.2 years (range: 21-84 years)
No previous operation to treatment site	17/26 (65.4)
Previous operation to treatment site	8/26 (30.8)
Previous operation with radiotherapy to treatment site	1/26 (3.8)
Primary indications for radiosurgery treatment	
Pain	9/26 (34.6)
Primary treatment modality	2/26 (7.7)
Progressive neurologic deficits	10/26 (38.5)
Pain and progressive neurologic deficits	5/26 (19.2)
Location of lesions: Primary disease	
Hemangioma	4/26 (15.4)
AVM	1/26 (3.8)
Cavernoma	1/26 (3.8)
Giant cell tumor	2/26 (7.7)
Chondroblastoma	1/26 (3.8)
Ependymoma	2/26 (7.7)
Hemangioblastoma	1/26 (3.8)
Meningioma	6/26 (23.1)
Neurofibroma	4/26 (15.4)
Schwannoma	4/26 (15.4)
Location of lesions: Vertebral level of lesions	
Cervical	10/26 (38.5)
Cervical and thoracic	2/26 (7.7)
Thoracic	10/26 (38.5)
Lumbar	3/26 (11.5)
Lumbar and sacrum	1/26 (3.8)
Tumor volume (mm^3)	9504.5±13984 (range: 118-61763)
Prescription isodose line (%)	77.5±6 (range: 70-89)
Tumor PIV/TIV (CI)	1.4±0.2 (range: 1.11-2.04)
Tumor volume × PIV/(TIV)^2 (nCI)	1.7±0.6 (range: 1.23-3.69)
Maximum dose/prescribed dose (HI)	1.3±0.1 (range:1.12-1.43)
Average fraction	4.6±1 (range: 1-5)
Average prescription dose (Gy)	25.9±7.8 (range: 12-60)

AVM = Arteriovenous malformation; CI = Conformity index; PIV = Prescription isodose volume; TIV = Tumor isodose volume; nCI = New conformity index; HI = Homogeneity index; Gy = Gray

Table 2: Summary of patients with malignant spine tumors

Patient and treatment characteristics	*n* (%)
Age	37.9±28 years (range: 8-74 years)
Previous chemotherapy to treatment site	1/7 (14.3)
Previous operation to treatment site	5/7 (71.4)
Previous operation with chemotherapy to treatment site	1/7 (14.3)
Primary indications for radiosurgery treatment	
Pain	7/7 (100)
Location of lesions: Primary disease	
Adenoid cystic carcinoma	1/7 (14.3)
Fibrosarcoma	1/7 (14.3)
Malignant fibrous histiocytoma	1/7 (14.3)
Myeloma	1/7 (14.3)
PNET	1/7 (14.3)
Rhabdomyosarcoma	1/7 (14.3)
Sarcoma	1/7 (14.3)
Location of lesions: Vertebral level of lesions	
Cervical	1/7 (14.3)
Cervical and thoracic	2/7 (28.6)
Thoracic	1/7 (14.3)
Lumbar	3/7 (42.9)
Tumor volume (mm^3)	120547.3±154027.6 (range: 2736-423349)
Prescription isodose line (%)	73.4±3 (range: 70-77)
Tumor PIV/TIV (CI)	1.3±0.1 (range: 1.11-1.57)
Tumor volume × PIV/(TIV)^2 (nCI)	1.6±0.3 (range: 1.27-1.95)
Maximum dose/prescribed dose (HI)	1.4±0.1 (range: 1.30-1.43)
Average fraction	4.3±1 (range: 3-5)
Average prescription dose (Gy)	26.7±6.1 (range: 21-40)

PNET = Primitive neuroectodermal tumor; CI = Conformity index; PIV = Prescription isodose volume; TIV = Tumor isodose volume; nCI = New conformity index; HI = Homogeneity index; Gy = Gray

compare the VAS scores and tumor volumes before and after radiosurgery between groups. We used Spearman correlation coefficients to clarify the correlation between the observed pain reduction effect and other related factors, such as the dose, prescribed isodose lines, tumor percentage covered, and the difference in tumor volume before and after radiosurgery. All statistical tests were two-tailed, and $P < 0.05$ was considered as statistically significant. Data analyses were performed using SPSS Statistics version 22 (IBM®, SPSS®, Statistics 22, Chicago, IL, USA).

RESULTS

Patient demographics

We identified 65 patients with 76 spinal lesions treated by CyberKnife radiosurgery between July 2007 and May 2013 at Tri-Service General Hospital, Taipei, Taiwan. Of these

Table 3: Summary of patients with metastatic spine tumors

Patient and treatment characteristics	*n* (%)
Age	59.8±11.2 years (range: 40-87 years)
No previous operation to treatment site	14/32 (43.8)
Previous chemotherapy to treatment site	13/32 (40.6)
Previous operation to treatment site	3/32 (9.4)
Previous operation with chemotherapy to treatment site	2/32 (6.3)
Primary indications for radiosurgery treatment	
Pain	15/32 (46.9)
Progressive neurologic deficit	6/32 (18.7)
Pain and progressive neurologic deficit	11/32 (34.4)
Location of lesions: Primary disease	
Colon cancer	1/32 (3.1)
Breast cancer	6/32 (18.8)
HCC	5/32 (15.6)
Hypopharynx cancer	1/32 (3.1)
Lung cancer	10/32 (31.3)
NPC	1/32 (3.1)
Prostate cancer	1/32 (3.1)
RCC	5/32 (15.6)
Oral cavity cancer	1/32 (3.1)
Uterine cervix	1/32 (3.1)
Location of lesions: Vertebral level of lesions	
Cervical	4/32 (12.5)
Cervical and thoracic	2/32 (6.3)
Thoracic	10/32 (31.3)
Thoracic and lumbar	1/32 (3.1)
Lumbar	10/32 (31.3)
Lumbar and sacrum	2/32 (6.3)
Sacrum	3/32 (9.4)
Tumor volume (mm^3)	58667.4±83703.9 (range: 682-454,678)
Prescription isodose line (%)	76.5±4.8 (range: 70-93)
Tumor PIV/TIV (CI)	1.4±0.2 (range: 1.02-1.73)
Tumor volume × PIV/$(TIV)^2$ (nCI)	1.6±0.3 (range: 1.21-2.50)
Maximum dose/prescribed dose (HI)	1.3±0.1 (range: 1.08-1.43)
Average fraction	4.4±1.2 (range: 1-5)
Average prescription dose (Gy)	27.7±7.7 (range: 7.6-50)

HCC = Hepatocellular carcinoma; NPC = Nasopharyngeal cancer; RCC = Renal cell carcinoma; CI = Conformity index; PIV = Prescription isodose volume; TIV = Tumor isodose volume; nCI = New conformity index; HI = Homogeneity index; Gy = Gray

patients, 26 patients had benign spinal lesions, 7 patients had primary malignant spinal lesions, and 32 patients had metastatic spinal lesions. Tables 1-3 provide summaries of the clinical characteristics and treatment in each patient group.

Pain evaluation

We used the VAS to assess the degree of pain before and after radiosurgery [Table 4]. The Wilcoxon signed-rank test and a nonparametric group comparison test were used to examine the differences between the VAS scores assessed before and after radiosurgery in the benign, malignant, and metastatic groups. All three groups showed significant decreases in the VAS scores after radiosurgery ($P < 0.001$, $P = 0.017$, and $P < 0.001$, respectively) [Table 5].

However, it is possible that the observed pain relief was secondary to the effect of radiotherapy on the tumors. Indeed, tumor volume significantly decreased after radiosurgery in both the benign and metastatic groups ($P = 0.005$ and 0.015, respectively) [Table 5]. To determine the associations between the obtained outcomes (pain) and potential confounders, we performed Spearman correlation analyses. Spearman correlation analyses of the associations between the VAS differences and the clinical parameters, including the dose, prescription isodose lines, tumor percentage covered, and tumor volume differences revealed no significant correlations (P values were 0.930, 0.965, 0.301, and 0.058, respectively) [Table 6].

Treatment-related toxicities

No radiation-induced myelopathy or radiculopathy was noted at the 1-month follow-up examination. Furthermore, there were no clinically detectable neurologic signs caused by radiation-induced spinal cord injury. Only 5 patients experienced Grade 1 nausea during treatment.

DISCUSSION

The results of the present study show that a significant pain-relieving effect occurs after CyberKnife radiosurgery in patients with benign, malignant, and metastatic spinal lesions. Furthermore, we showed for the 1st time that this pain-relieving effect was not associated with the treatment dose, prescription isodose line, tumor percentage covered, or reduction in tumor volume.

According to a recent survey, up to 40% of practicing oncologists in the United States routinely use this procedure.[24] Treating spinal cord associated lesions is one of the four primary uses of this technique outlined by the National Library of Medicine. Although a number of large-scale clinical trials have used this approach to treat pain associated malignancies,[25-28] and the use of low-dosage radiation and radiosurgery for pain relief in bone metastasis is also reasonably well-established,[29] our study still provides some new and interesting findings.

Table 4: Cross-table list of the pre- and post-treatment VAS scores of patients with benign, malignant, and metastatic spine tumors

Pretreatment VAS score	Posttreatment VAS score				
	1 (%)	2 (%)	3 (%)	4 (%)	Total (%)
7	5 (7.7)	7 (10.8)	0 (0)	0 (0)	12 (18.5)
8	8 (12.3)	14 (21.5)	6 (9.2)	1 (1.5)	29 (44.5)
9	0 (0)	4 (6.2)	8 (12.3)	0 (0)	12 (18.5)
10	0 (0)	2 (3.1)	8 (12.3)	2 (3.1)	12 (18.5)
Total	13 (20)	27 (41.6)	22 (33.8)	3 (4.6)	65 (100)

VAS = Visual analog scale

Table 5: Differences in the VAS score and tumor volume between before and after radiosurgery

Group	*n*	Before surgery	After surgery	*P**
		VAS tumor volume	VAS tumor volume	
Benign	26	7.62±0.12	1.69±0.13	<0.001
		9504.50±2742.56	8299.54±3180.88	0.005
Malignant	7	8.71±0.29	2.86±0.14	0.017
		12,0547.29±58,216.94	77,623.43±32,060.98	0.063
Metastatic	32	8.84±0.16	2.53±0.13	<0.001
		58,667.38±14,796.91	46,345.09±12,684.67	0.015

*Assessed by Wilcoxon signed-rank test, data are shown as the mean ± SEM; VAS = Visual analog scale; SEM = Standard error of mean

Table 6: Spearman correlation coefficients between the ΔVAS and related factors in all patient groups

Related factors	Benign (*n* = 26)		Malignant (*n* = 7)		Metastatic (*n* = 32)		Total (*n* = 65)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Dose	0.317	0.114	−0.104	0.824	−0.118	0.519	−0.011	0.930
Prescription isodose lines	−0.171	0.404	0.366	0.420	0.055	0.765	0.006	0.965
Tumor percentage covered	−0.090	0.660	0.869	0.011	0.153	0.405	0.130	0.301
ΔTumor volume	−0.001	0.996	0.945	0.001	0.220	0.227	0.236	0.058

VAS = Visual analog scale

First, we showed that the pain-relieving effect was not associated with the treatment dose, prescription isodose line, tumor percentage covered, or reduction in tumor volume, which has not been reported previously. Furthermore, our clinical data suggest the possibility of a radiotherapy-related mechanism of bone pain reduction.

The mechanism for reducing bone pain using conventional radiotherapy or radiosurgery is still controversial. Some preclinical studies confirmed that the effect may be caused by reduced cancer burden, reduced osteolysis, or alterations in nociceptive transmission in the central nervous system.[30-32] In our study, we used Spearman correlation analyses to show that the pain-reducing effect has little correlation with the dose, prescription isodose line, tumor percentage covered, and reduced tumor volume. These findings echo the above preclinical data.

Compared to conventionally fractionated radiotherapy for spinal lesions, CyberKnife technology can shorten the total treatment time, improve the treatment accuracy, and increase patient comfort during treatment. However, it is expensive and the National Health Insurance does not pay for this technique in Taiwan. Thus, the availability and feasibility of using CyberKnife radiosurgery to treat spinal lesions are still restricted. Our data show that most patients with spinal tumors suffer from pain rather than from progressive neurologic deficits. The life span of these patients is limited by systemic disease rather than by spinal metastasis. Therefore, pain control is the most important treatment goal for patients with spinal tumors. Several studies have demonstrated the feasibility and safety of delivering radiation doses to the spine using CyberKnife technology.[1,10,33-36] In our study, significant pain relief was achieved in all patient groups without obvious adverse effects by using stereotactic radiosurgery.

In a retrospective study conducted by Chang *et al.*,[37] 30 benign spinal tumors in 20 patients were treated with CyberKnife radiosurgery from 2002 to 2008. Significant relief of radicular and myelopathic pain was achieved after radiosurgery in most cases (94%). These findings suggest that CyberKnife has the ability to control benign spinal tumors without complications in most cases.[37]

A prospective case-series study conducted by Wowra *et al.*[38] offered clinical results of CyberKnife spinal radiosurgery without fiducial implantation. A total of 134 malignant spinal tumors in 102 patients were evaluated. Patients were only included if they had metastatic spinal lesions and not more than two tumors. The spinal pain was scored using the VAS. Within 1-week of CyberKnife radiosurgery, the pretreatment VAS score of 7 was dramatically reduced to 1. The authors concluded that CyberKnife radiosurgery for spinal lesions was a noninvasive, safe, and effective radiotherapeutic treatment method for patients with severe pain and 1 or 2 small spinal malignant tumors.[38]

Although we believe that the results presented here are compelling, we cannot exclude potential effects related to the heterogeneity of treatment regiments and the variety of confounding factors related to prior pain management. We did not observe correlations between the radiation dosage and VAS differences; nevertheless, additional trials with larger groups treated with consistent dosages of radiation would improve the treatment protocols with respect to pain management. The consistent pain relief that we observed in this study indicates that stereotactic radiosurgery is a feasible and effective approach for improving the quality of life in patients with spinal tumors compared with the traditional fractionated radiotherapy.

In the present study, we focused on the pain relief after radiosurgery, which were obtained from the medical records. In addition, we found that 15 patients of benign cases and 17 patients with metastatic cases were treated with CyberKnife radiosurgery because of muscle weakness and numbness. However, the detailed neurological function is lacking in the medical records. The assessment, such as 36-item or 12-item Short Form Health Survey, to evaluate the recovery of neurological function is definitely needed in the future study.

To summarize, CyberKnife radiosurgery is an effective method for relieving pain in patients with spinal lesions. This technique is underused and needs to be promoted in Taiwan.

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