J Neurooncol (2009) 94:119–127
DOI 10.1007/s11060-009-9814-7

CLINICAL STUDY - PATIENT STUDY

Assessment of image-guided CyberKnife@ radiosurgery for metastatic spine tumors

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Received: 20 January 2009 / Accepted: 16 February 2009 / Published online: 3 March 2009

Abstract Spinal metastases are associated with significant symptoms. From September 2005 to September 2007, 69 consecutive patients with 127 malignant spine metastatic lesions were treated at Wanfang Hospital with CyberKnife@ (CK) radiosurgery. The radiosurgery dose ranged from 10 to 30 Gy (mean 15.5 Gy) prescribed to the 75–85% isodose line that encompassed at least 95% of the tumor volume. We used fiducials as tracking landmarks for CK treatment of the thoracic and lumbar spine. A torso anthropomorphic phantom and GafChromic MD-55 films were used to verify the accuracy of CK radiosurgery and 2D dose distribution, demonstrated high targeting accuracy with 2% average deviation of the measured dose from the estimated dose at the set-up center and less than 5% dose deviation in 2D isodose curve. Visual Analogue Scale and Oswestry Disability Index questionnaires were used to monitor functional outcome after radiosurgery. Local tumor control at 10 months was 96.8%. Mean pain scores decreased significantly from 65 to 30 after treatment ($P = 0.001$). Functional disability was significantly improved after treatment ($P = 0.002$). The most common treatment toxicities were nausea and fatigue. In conclusion, CK radiosurgery is a well-tolerated and effective treatment for spine tumors with good local tumor control and a favorable outcome on pain and functional improvement after treatment.

Keywords CyberKnife@ radiosurgery · GafChromic films · Anthropomorphic phantom · Spinal metastases

Introduction

Spinal metastases are associated with significant symptoms such as back pain, radiculopathy, weakness of extremities, sensory deficits, and bowel and bladder changes due to epidural spinal cord or cauda equina tumor compression. They are responsible for a large part of the decrease in quality of life experienced by cancer patients with metastatic disease. Effective treatment administered when the patient is still ambulatory provides the best chance for maintenance of a good quality of life.

Unfortunately, treatment options for the spine are limited, largely due to the proximity of neighboring dose-limiting structures, including the spinal cord, nerve roots, peripheral nerves, esophagus, heart, kidneys and bowel. Standard treatment includes pain medications, external beam radiation therapy, surgical decompression, and chemotherapy. External beam radiation therapy is offered in the vast majority of patients and achieves varying degrees of pain relief [1]. Conventional radiotherapy is administered to the area of vertebral segments above and below the involved spine and uses multiple sessions of fractionated treatment over several weeks [2]. It is the low tolerance of

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the spinal cord to radiation that often limits the treatment dose to a level far below the optimal therapeutic dose. As cancer patients experience longer survival with improved therapies, the goals of treatment for spinal metastasis should be to relieve pain, preserve or restore neurologic function, and control the tumor, while remaining a convenient and non-burdensome form of therapy for the patient.

Stereotactic radiosurgery (SRS) delivers a large, highly conformal radiation dose to a localized tumor by an accurate targeting stereotactic approach. SRS is currently regarded as a standard treatment modality for a number of intracranial neurosurgical diseases. The difficulty in applying radiosurgery to extracranial sites is mainly due to organ motion and lack of immobilization techniques. Among the extracranial organs, the spine is relatively immobile and its bony structure facilitates its imaging for target confirmation [2–5]. The sub-millimeter accuracy of SRS allows the delivery of large doses of radiation in a single fraction to the target near the radiosensitive spinal cord [6–8]. Special treatment planning is used to increase the conformality of radiation to the tumor while providing concave dose distributions to wrap the dose around the spinal cord, excluding the spinal cord and other dose-limiting structures from the high-dose region. This makes the spine suitable for SRS [2–5].

CyberKnife@ (Accuray, Inc., Sunnyvale, CA) is a frameless, image-guided robotic radiosurgery delivery system. The CyberKnife@ (CK) system consists of a 6 MV linear accelerator mounted on a robotic arm that moves along 6 spatial axes [4, 9–12]. It can provide broader translational and rotational movement than a standard linear accelerator. A real-time imaging tracking system references the position of the treatment target to the fiducial markers of the spine [13–15]. It uses real-time X-ray imaging to check the position of the target during treatment by comparing it with digitally reconstructed radiographs (DRR) generated from pretreatment computed tomography (CT) scans. The calculated differences in the three translational and three rotational axes of the target position are dynamically compensated by an adaptive beam pointing at the target. The CK system provides a precise noninvasive means of radiation delivery with less than 1 mm spatial accuracy, allowing the patient to be positioned in the treatment room without rigid immobilization. In addition, CK provides high conformity of prescription isodose to the target volume and rapid dose fall off outside the target. This dosimetric distribution is accomplished using hundred of non-isocentric and non-coplanar beams spread in a large range of angles. The highly conformal and accurate radiation is delivered to the spine, minimizing irradiation to the spinal cord and other surrounding normal tissues.

To justify the use of the CK image-guided SRS system in spine lesions, it was necessary to demonstrate that the system could meet the beam-targeting precision and dosimetry requirements of radiosurgery [14, 16, 17]. This report will present data that demonstrate the dose alignment precision of the system and an analysis of dose shape and conformity for spine cases.

Materials and methods

From September 2005 to September 2007, 69 consecutive patients with 127 malignant spine metastatic lesions were treated at Wanfang Hospital with CK radiosurgery. All patients had a histology diagnosis of malignant neoplasm and had metastasis involving spine segments. All spinal metastasis lesions were diagnosed by magnetic resonance imaging (MRI).

CyberKnife@ radiosurgery procedures

During treatment, cervical spine lesions were tracked relative to skull landmarks and were secured to a head mask. For all other spine lesions, six gold fiducial markers were inserted percutaneously into the pedicles adjacent to the spine lesions before planning and treatment [14]. Patients with implanted fiducials were immobilized in a vacuum bag. Simulation CT images acquired using 1.25 mm thickness were sent to the planning computer (Multiplan$^{\mathrm{TM}}$, Accuray, Sunnyvale), an inverse treatment planning system. Digital reconstruction radiographic (DRR) images were generated as reference images for position and motion tracking of the spine. Multiplan$^{\mathrm{TM}}$ generated several hundred different beams during a single treatment. Highly conformal radiation was optimized to the spine and radiation to the spinal cord and other critical structures was minimized. The involved spine and the paraspinal soft tissue of the tumor were included within the target volume of the radiosurgery treatment. Circular cones were used, ranging in diameter from 10 to 35 mm. The prescription dose to the tumor margin was based on histology of the tumor, tumor location, previous irradiated dose and the maximum dose to the spinal cord. The spinal cord constraint was 10 Gy to 1 ml of the spinal cord in a single fraction treatment. Detailed dosimetric and volumetric information was generated by the treatment planning system.

Treatment accuracy and dosimetry verification

Because many of the spine lesions were immediately adjacent to the radiation-sensitive spinal cord, evaluation of the accuracy of targeting was highly important [3, 9].

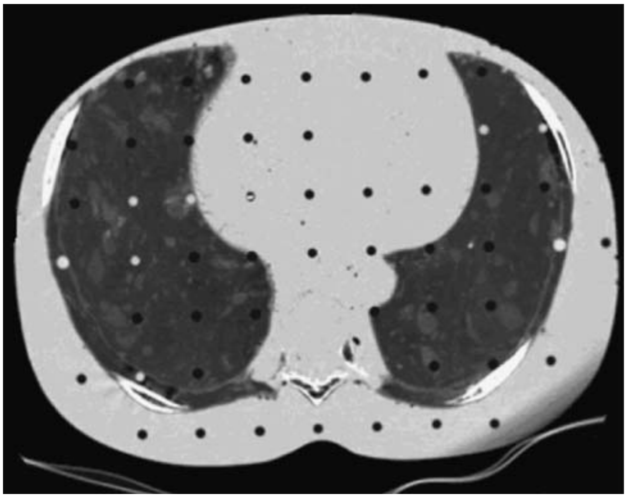


Fig. 1 Axial CT image of chest and thoracic spine of the torso phantom

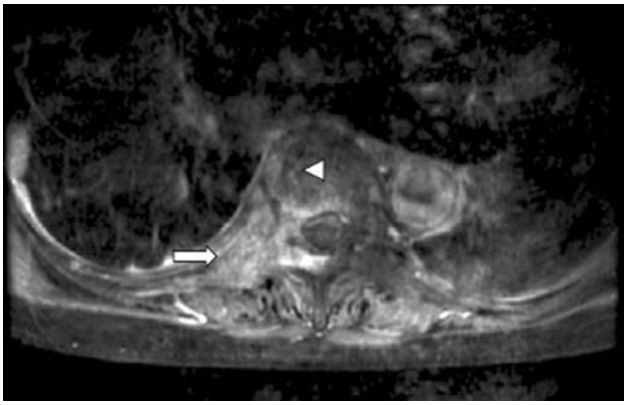
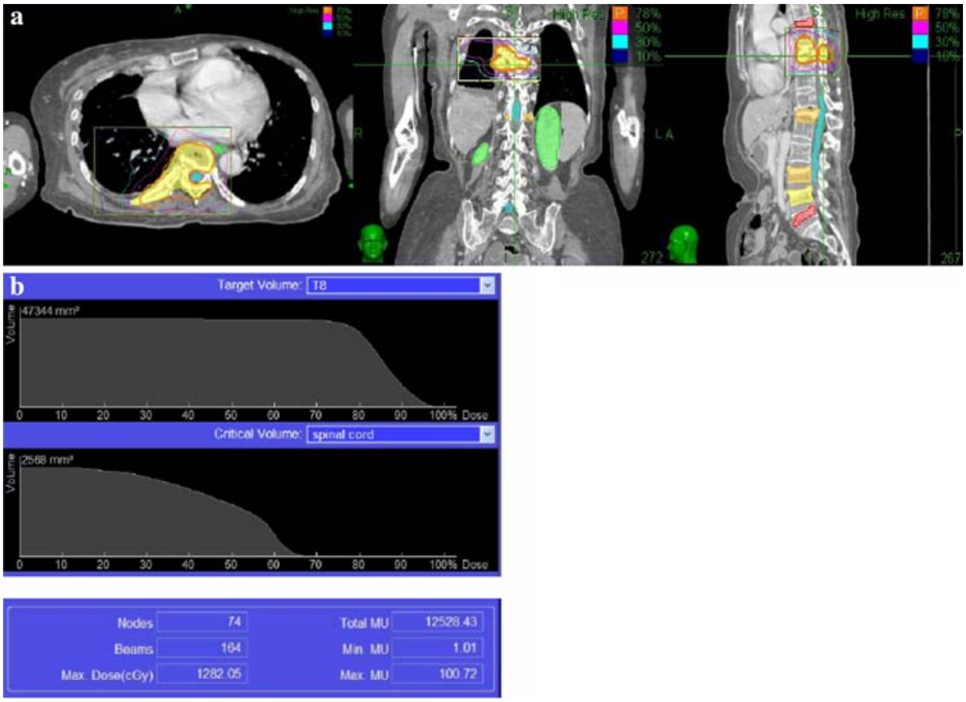


Fig. 2 Magnetic resonance imaging of a patient with metastatic lung cancer with T8 bone marrow tumor infiltration (*arrowhead*) and right side paraspinal mass (*arrow*)

Accuracy and precision of the CK system were assessed by simulating the whole treatment process, including CT scanning, treatment planning, image guidance tracking and robotic radiosurgery treatment. We used a torso anthropomorphic phantom to mimic the target of the spine and hold films for radiation dose measurements. The phantom was made of natural skeletal tissue and plastic with tissue-equivalent materials (Fig. 1). Firstly, we placed six gold fiducial markers into the target spines of the phantom for tracking purposes. The phantom was then scanned with a CT scanner using 1.25 mm slice thickness, and the images were transferred to the treatment planning system. We simulated the spine lesion of an illustrative case of lung cancer with T8 spine metastasis (Fig. 2) and generated the same treatment target and plan for dose verification (Figs. 3, 4). The torso phantom was then set up for radiosurgery according to the pre-designed plan. The main components of the CK radiosurgery fiducial tracking system of this study are shown in Fig. 5. We measured the radiation dose at the set-up center with a micro ion chamber, and radiographic film was employed as a two-dimensional dosimeter [16, 18, 19]. GafChromic MD-55 films were placed between slices of the phantom before set-up for irradiation (Fig. 6). The response of the film to dose was calibrated by a response H-D curve built from 0 to

Fig. 3 **a** CyberKnife$^{@}$ radiosurgery treatment plan for spinal metastasis. The treatment target volume includes the abnormal T8 vertebral body and the soft tissue tumor of the right side paraspinal area. The radiosurgery dose was 10 Gy prescribed to 78% isodose line. Axial (*right*), coronal (*middle*), and sagittal views (*left*) are shown. **b** Dose-volume histogram showing dose coverage to the T8 vertebral body, and sparing of the spinal cord



Target Volume: T8

Critical Volume: spinal cord

Nodes	74	Total MU	12528.43
Beams	164	Min. MU	1.01
Max. Dose(cGy)	1282.05	Max. MU	100.72

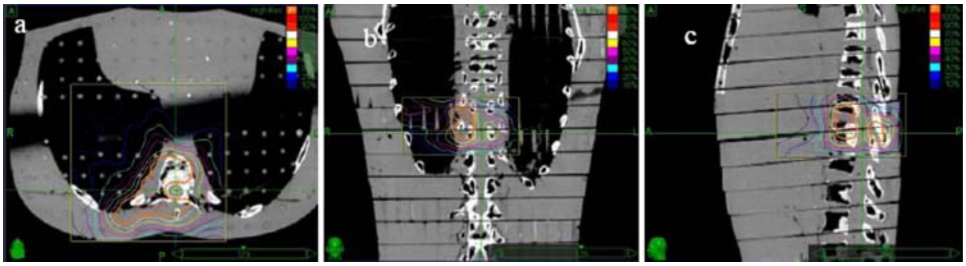


Fig. 4 CyberKnife$^{@}$ radiosurgery treatment plan for the torso phantom. **a** Axial, **b** coronal, and **c** sagittal view of isodose distribution are shown

100 Gy range. In the final step, the GafChromic films inside the phantom were scanned using an optical scanner and the targeting errors were analyzed.

Dosimetry comparison between the CyberKnife$^{@}$ and intensity-modulated radiotherapy plan

Intensity-modulated radiotherapy (IMRT) is a three-dimensional (3-D) conformal radiotherapy technique that enables the delivery of highly conformal photon radiation to tumors in close proximity to radiation-sensitive structures [20, 21]. CK uses multiple non-isocentric, non-coplanar beams for inverse planning optimization. In this study, we made an IMRT plan using seven beams (5 posterior beams: 110°, 140°, 180°, 220°, 245°; and 2 anterior beams: 50°, 315°) to generate a steep dose gradient between the tumor and the spinal cord. Three-dimensional shaping of the radiation beam to conform the irregular tumor was achieved by computerized dynamic movement of the multi-leaf collimator. We compared the isodose profiles and dose volume histograms (DVHs) between the CK and IMRT plans.

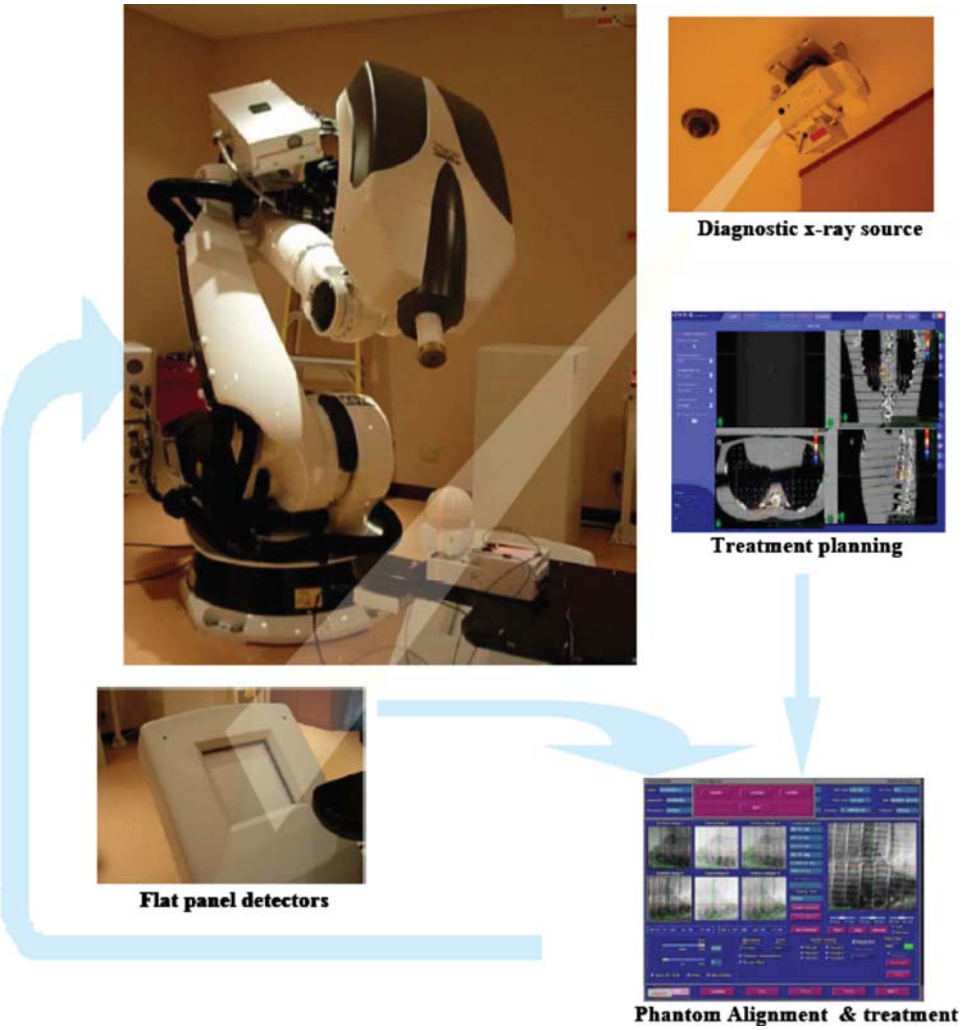


Fig. 5 Main components of the CyberKnife$^{@}$ Robotic Radiosurgery Fiducial Tracking System

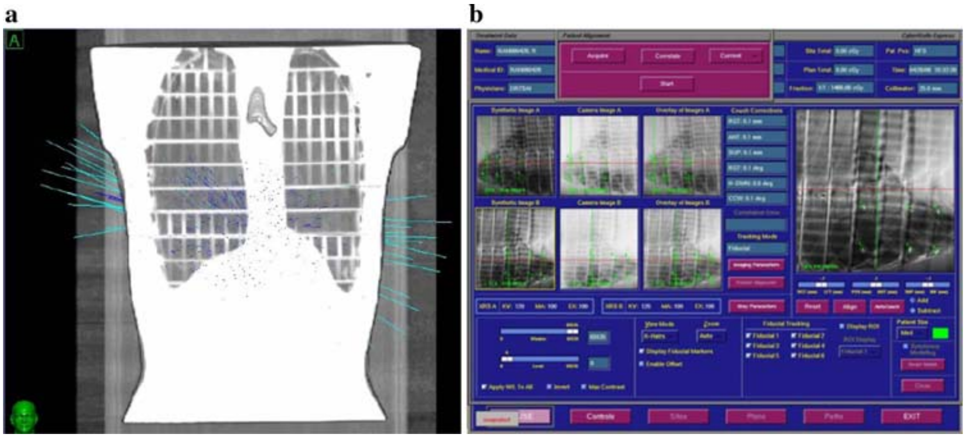


Fig. 6 **a** CyberKnife$^{@}$ radiosurgery treatment for the torso phantom. **b** Six fiducial markers were inserted into the spine structure of the torso phantom for treatment set-up and image-guided radiosurgery treatment

Patient evaluation

Before CK treatment, all patients were asked to complete the Visual Analogue Scale (VAS) questionnaire and Oswestry Disability Index (ODI) questionnaire to assess any spine symptoms and dysfunction [22]. These two questionnaires were used to measure and monitor changes in symptoms and functional outcome after treatment. A VAS usually consists of a single 100 mm line, ranging from ‘no pain’ (0 mm) to ‘very severe pain’ (100 mm). The ODI functional questionnaire measures 50 activity limitations with the sum score ranging from 0% (no disability) to 100% (maximum disability).

After CK treatment, clinical follow-up was performed at 1 week, one month, and every 3 months thereafter to determine any immediate adverse effects of therapy and changes in symptoms. Patients were asked to rate their pain and functional status with the same questionnaires. Patients were also scheduled for MRI study every 3 months in the first year for tumor response evaluation.

Results

Patient characteristics

Sixty-nine patients with a total of 127 malignant spine metastasis lesions were treated with CK. There were 34 men and 35 women. Their median age was 54 years (range 24–76 years). The baseline median Karnofsky Performance Status was 80 (range, 60–100). Table 1 summarizes the clinical characteristics of the patients. Median follow-up time was 10 months (range, 3–21 months).

Treatment dosimetric statistics

The prescribed tumor dose covered the margin of the target (mean, 15.5 Gy; range 10–30 Gy). The dose was prescribed to the 75–85% isodose line (mean 80%) that encompassed

Table 1 Characteristics of 69 patients treated with the CyberKnife$^{@}$ for spinal tumor

Characteristic	
Primary tumor	
Lung	21%
Liver	11%
Breast	18%
Colorectal	9%
Prostate	22%
Kidney	8%
Other	11%
Age	
Median	54 years
Sex	
Male	49%
Female	51%
Karnofsky performance status	
≥70	63%
<70	37%
Multiple spine lesions treated	
Present	38%
Absent	62%
Previous external beam radiotherapy	
Present	21%
Absent	79%
Primary symptoms before CK	
VAS pain score before CK	
Mild (10–30)	13%
Moderate (40–60)	68%
Severe (70–100)	18%
Motor deficit	
Present	24%
Absent	76%
Sensory deficit	
Present	28%
Absent	72%

Table 2 CyberKnife@ treatment parameters

Treatment parameters	
Radiosurgery spine lesion	
Cervical	12%
Thoracic	59%
Lumbar	26%
Sacral	3%
Treated tumor volume	
Mean	32 cm^3
Range	0.6–126 cm^3
Prescribed isodose line	
Mean	80%
Range	75–85%
Dose (Gy) to prescribed isodose line	
Mean	15.5 Gy
Range	10–30 Gy
Fraction no.	
Mean	2
Range	1–5
Collimator size (mm)	
Mean	15 mm
Range	10–30 mm
Tumor BED	
Mean	41.6
Range	26.4–60.0
Coverage	
Mean	94.5%
Range	91–97%
Conformity index	
Mean	1.32
Range	1.22–2.31
Homogeneity index	
Mean	1.2
Range	1.15–1.25

Table 3 Patient assessment based on improvement in Oswestry Disability Index

Reduction in ODI	Number of site-specific disabilities
<25% reduction	28 (22%)
25–50% reduction	80 (63%)
>50% reduction	19 (15%)

ODI Oswestry Disability Index

at least 95% of the tumor volume. Tumor volume ranged from 0.6 to 126 cm^3 (mean 32 cm^3). The spinal cord volume receiving greater than 10 Gy ranged from 0 to 1 ml (mean 0.2 ml). All patients received 1–5 fractions of radiosurgery to the involved spine (mean 2 fractions). A summary of treatment parameters and dosimetric indices for the CK plans are shown in Table 2.

Treatment accuracy and dosimetry verification

Gadolinium-enhanced MRI of the illustrative case revealed a destructive lesion over the right side of T8 vertebrae and paravertebral soft tissue compressing the spinal cord. The treatment plan was designed to achieve dose distribution for the T8 spine with 78% isodose surface (Fig. 3). The maximum tumor dose was 12.8 Gy and the spinal cord received a maximum point dose of 8.8 Gy.

The average deviation of the measured dose from the estimated dose at the set-up center was 2%. The results of 2D dose measurement demonstrated a good isodose curve alignment between the treatment plan and the measured film. The planned dose never deviated more than 5% from the measured dose (Fig. 7).

Dosimetry comparison between the CyberKnife and intensity-modulated radiotherapy plan

Comparison of the DVHs between the CK and IMRT plans are shown in Fig. 8. The gross tumor volume coverage was similar for both IMRT and CK. The spinal cord DVHs showed better sparing of high-radiation dose with the CK as compared to the IMRT plan. CK also provided better protection of surrounding normal tissues (esophagus and heart) than IMRT (Fig. 9).

Clinical outcome

Tumor control

Local treatment failures were observed in 3 patients with recurrence tumors over 3 thoracic and 1 lumbar vertebras. Local tumor control at 10 months was 96.8%. There were no significant effects of histology type ($P = 0.65$), spine location ($P = 0.73$), tumor volume ($P = 0.09$) or prescribed radiation dose ($P = 0.16$) on local tumor control. MRI of the illustrative case at 3-month follow-up is shown in Fig. 10.

Pain scores

Nearly all the patients had varying degrees of site-specific pain before CK treatment (Table 1). The majority (86%) presented with moderate to severe pain before CK treatment, with a mean VAS of 65 (range, 40–100). Pain scores decreased significantly ($P = 0.001$) one month after CK treatment to a mean VAS of 30 (range, 0–90). Seventy-nine percent of the patients described more than 50% reduction in VAS at 1-month follow-up. Overall VAS improvement after CK was found in 110 treatment sites (87%). Six patients experienced persistent or increase pain intensity during the follow-up period. There were no significant

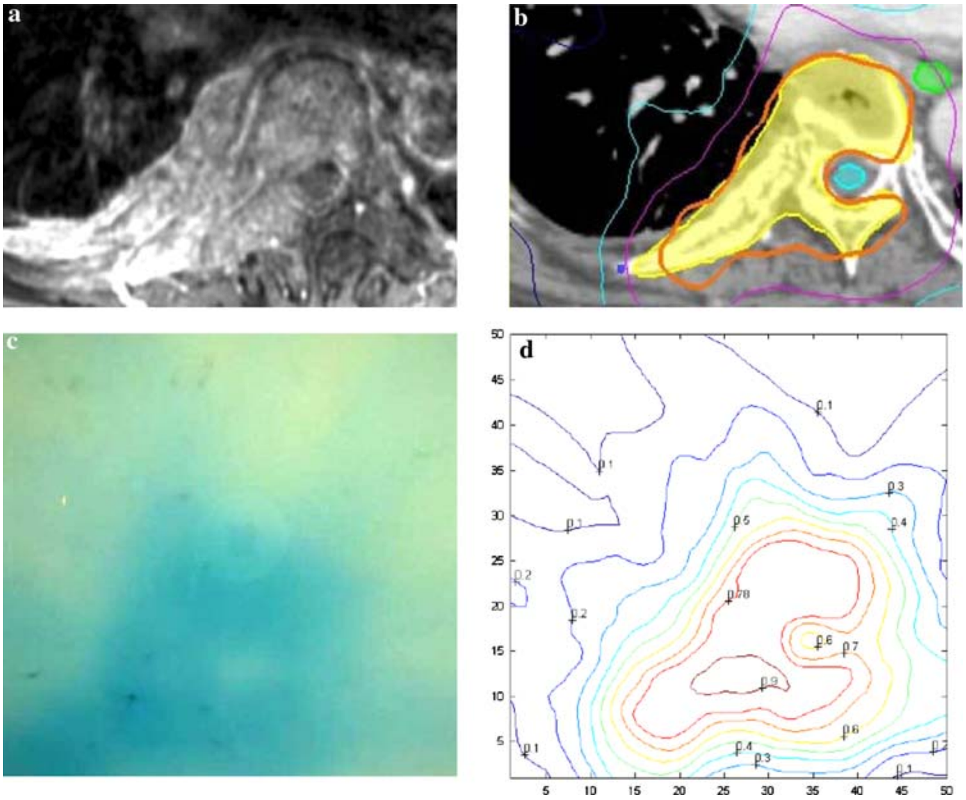


Fig. 7 **a** Axial magnetic resonance imaging scan, T1-weighted with gadolinium contrast, showing metastasis lung cancer at T8 spine. The spinal cord is significantly compressed from the right. **b**The CyberKnife@ treatment plan to T8, displayed in computed tomographic scan. **c**The appearance of GafChromic MD-55 film post CyberKnife@ irradiation shows the configuration of the T8 irradiation target. **d** The isodose curve plotted by GafChromic film measurement results

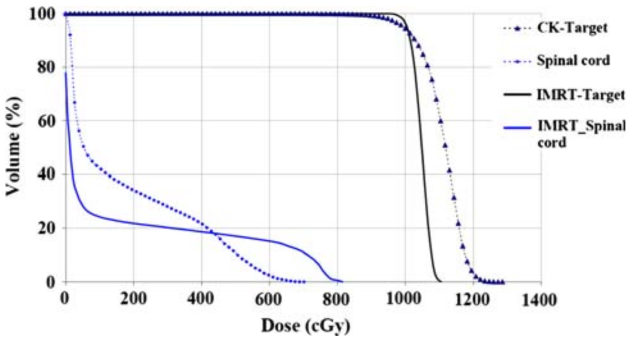


Fig. 8 Cumulative-dose volume histogram (DVH) comparison between the CyberKnife@ and IMRT plans for the same patient for the target organ (T8) and normal tissues (spinal cord). The dashed curves indicate the CyberKnife@ plan and the solid curves indicate the IMRT plan. Both plans were normalized to deliver 10 Gy via the isodose that completely encompassed the target organ

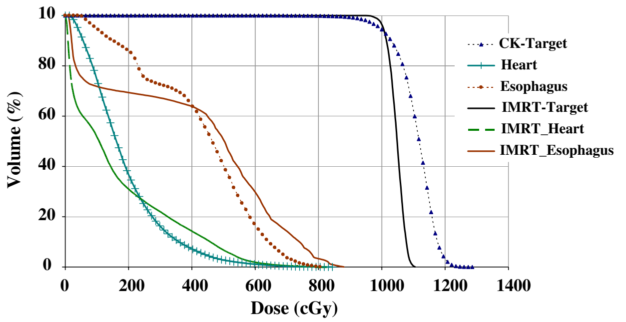


Fig. 9 Cumulative-dose volume histogram (DVH) comparison between the CyberKnife@ and IMRT plans for the same patient for the target organ (T8) and surrounding normal tissues (esophagus and heart). The dashed curves indicate the CyberKnife@ plan and the solid curves indicate the IMRT plan. Both plans were normalized to deliver 10 Gy via the isodose that completely encompassed the target organ

effects of histology type ($P = 0.94$), tumor volume ($P = 0.12$) or prescribed radiation dose ($P = 0.26$) on the changes in pain scores.

Functional disability

Patients had ODI scores ranging from 38–86% (mean 53%) before CK treatment. Post-treatment reductions of 25–50% and >50% in ODI scores were found in 63% and 15% of site-specific disabilities, respectively (Table 3). The improvement in ODI was statistically significant ($P = 0.002$). Neither histology type ($P = 0.87$) nor prescribed radiation dose ($P = 0.42$) were significantly related to changes in the disability index.

Treatment side effects

The most common acute toxicities after CK treatment were fatigue (50%), nausea (27%), vomiting (16%), esophagitis (11%), diarrhea (3%), sore throat (5%), anemia (1%), thrombocytopenia (2%) and neutropenia (4%). All toxicities were RTOG Grade 1–2. Follow-up was not long enough to detect late spinal cord toxicity.

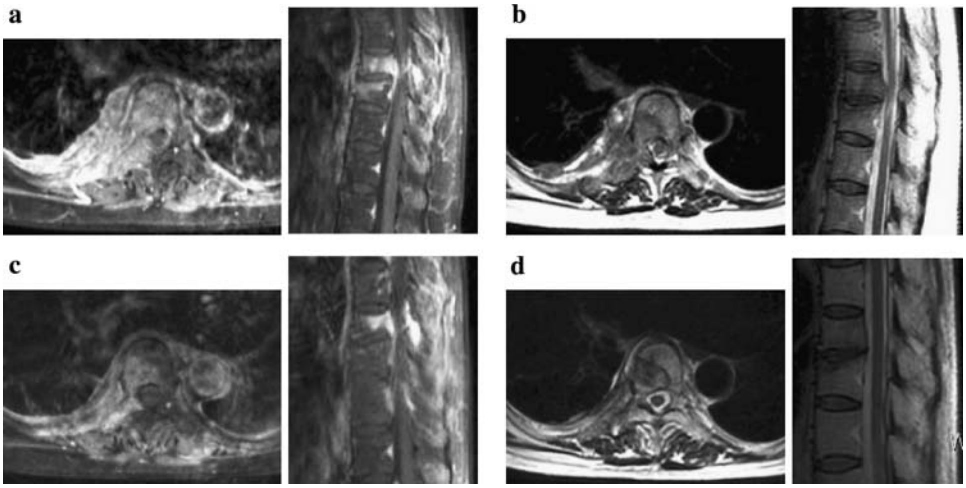


Fig. 10 **a** Pre-treatment gadolinium-enhanced T1-weighted axial and sagittal images revealed a metastasis cancer at T8 spine. **b** Pre-treatment T2-weighted axial and sagittal images, showing significant spinal canal compromise. Follow-up imaging 3 months after CyberKnife$^{@}$ treatment revealed tumor regression and relief of spinal cord compression. **c** Post-CK gadolinium-enhanced T1-weighted axial and sagittal images. **d** Post-CK T2-weighted axial and sagittal images

Discussion

Since the survival time of patients with bone metastases only is relatively long, these patients are at high risk of spine metastases and subsequent compression of the spinal cord and spinal instability. Patients with intractable pain, spinal instability, or progressive neurologic dysfunction secondary to spinal cord compression are treated with surgical decompression and stabilization.

The goals of local radiation therapy of these spinal tumors have been palliation of pain, prevention of pathologic fractures, and spinal cord compression. Spine lesions are a challenge to treat with radiation for many reasons, including inaccessibility of tumors to conventional therapy and limitations of local radiosensitive structures. Although standard palliative external beam radiation therapy may be effective in patients with a limited life expectancy, these data raise the concern that they may be inadequate for patients with expected longer median survival.

SRS delivers high dose of radiation in a single fraction to the well-defined intracranial or extracranial targets. SRS has been demonstrated to be effective for brain metastases with an 85–95% control rate [23]. The development of sophisticated image guidance technology provides real-time localization of the tumor and delivery of radiation, expanding radiosurgery applications to treat malignant vertebral body lesions. SRS has been demonstrated to be accurate, safe, and efficacious treatment alternative for malignant tumors involving the spine.

The CyberKnife$^{@}$ was first developed for the treatment of intracranial lesions. Treatment outcome has been similar to the results of conventional frame-based radiosurgery [24]. With the ability to treat extracranial lesions using fiducial tracking, a growing experience in the treatment of spinal lesions using CK has emerged. Unlike conventional radiation therapy that delivers a full dose to large segments of the spinal column (vertebral body and spinal cord), CK can deliver a high-dose of radiation to the target tissue while limiting the dose to the spinal cord [3, 9, 14]. In addition, CK can be used for cases that have previously undergone conventional external beam irradiation. The treatment plan can create a high gradient dose falloff to the target tissue that should significantly reduce the possibility of radiation-induced myelopathy of the previously irradiated spinal cord. Therefore, CK has the potential to significantly improve the quality of life of patients and local control of spine lesions.

In this study, pain was the primary indication for radiosurgery treatment. Eighty-six percent of patients reported improvement in their pain after CK treatment. Both mean pain scores and functional disability index were significantly improved. In the three patients who failed to achieve local tumor control after treatment, the lesions were recurrent tumors after conventional radiotherapy.

A Radiation Therapy Oncology Group randomized phase III clinical trial [25] comparing 8 Gy in 1 fraction to 30 Gy in 10 fractions in breast or prostate cancer patients with painful bone metastases. There was no difference in response rates between the two arms, but significantly higher retreatment rates were observed in the 8 Gy arm. Both arms had a highly significant pain improvement at 3 months, with ambulation level improvement higher in the 8 Gy arm. The prescribed doses that were delivered in our series were greater than 8 Gy (mean, 15.5 Gy), therefore we expected a more durable symptomatic response as well as local control in our patients. In addition, there was no clinically or radiographically identifiable acute or subacute spinal cord damage attributed to CK treatment in our patients. Longer follow-up will be necessary to monitor the occurrence of late spinal cord events.

Another advantage to the patient of using CK hypofractionated radiosurgery is that the treatment can be completed within 5 days rather than over a course of several weeks. The CK treatment procedure is minimally invasive compared with open surgery. Clinical response such as pain or functional disability improvement was shown to be more rapid with radiosurgery treatment.

CK is able to target the dose distribution to millimeter-level precision. The use of fiducials inserted in the spines that act as tracking landmarks presents a well-tolerated and highly accurate solution to targeting lesions in the thoracic and lumbar spine. Considering the improved normal-tissue sparing and accurate localization of the CK compared to IMRT, CK could allow for further dose-escalation to achieve better tumor control.

In conclusion, this study demonstrated that hypofractionated spinal CK treatment for malignant spine metastases is safe and clinically effective. The major benefits are relatively short treatment time in an outpatient setting and potentially better local control of the tumor with minimal risk of side effects. Furthermore, carefully delivery of higher radiation doses should be tested for better clinical outcomes.

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